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# Application of Dry Elixir System to Oriental Traditional Medicine: Taste Masking of Peonjahwan by Coated Dry Elixir

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Peonjahwan, an oriental traditional medicine composed of crude herbal drugs and animal tissues is bitter and poorly water-soluble. To mask the bitterness of peonjahwan and enhance the release of bilirubin, one of the crude active ingredients of peonjahwan, peonja dry elixir (PDE), was prepared using a spray-dryer after extracting the crude materials in ethanol-water solution. Coated peonja dry elixir (CPDE) was then prepared by coating the PDE with Eudragit acrylic resin. Panel assessed bitterness and release test of bilirubin from PDE and CPDE were carried out and compared with peonjahwan alone. PDE was found to have little effect upon the reduction of the bitterness of peonjahwan. However, the bitterness of CPDE was found to reduce to 1/4 of that of peonjahwan due to the encapsulation of crude active ingredients by the dextrin and Eudragit shell ($P<0.05$). The release rate of bilirubin from PDE and CPDE for 60 min increased about 3.5- and 2.5- fold, respectively, compared to peonjahwan at pH 1.2. It is concluded that CPDE, which masked the bitterness of peonjahwan and enhanced the release of bilirubin, is a preferable delivery system for peonjahwan.

**Key words:** Peonjahwan, Bilirubin, Eudragit acrylic resin, Coated dry elixir, Bitterness test, Release

## INTRODUCTION

Oriental medicines composed of crude herbal drugs and animal tissues have been traditionally used in oriental countries due to their efficacies and low levels of side effects (Kim *et al.*, 1991). However, when orally administered as liquids or pills, they often give the patient a feeling of discomfort due to their strong intrinsic tastes and bitterness, moreover, their effects are often protracted due to poor water-solubility. Nevertheless, there has been a notable lack of the pharmaceutical development of alternative dosage forms to overcome these problems.

Recently, we developed a new oral dosage form termed dry elixir, which increased the dissolution rate of drugs with poor water solubility, which involved encapsulation with water-soluble polymers that are readily soluble or dispersible in the gastrointestinal tract after oral administration, leading to enhanced bioavailability (Ahn *et al.*, 1998; Kim *et al.*, 1994; Kim *et al.*, 1995; Kim and Yoon, 1995).

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We have tried to apply this dry elixir system to oriental traditional medicines to mask their bitterness and enhance their bioavailability. In this particular study, peonjahwan was selected as a model of oriental traditional medicines. Peonjahwan, a large pill composed of 2.55 g Notoginseng Radix, 0.15 g Bezoar Bovis, 0.21 g Serpentis Fel and 0.09 g Moschus, has been used for the treatment of hepatitis in the oriental countries (Kim *et al.*, 1991). It was reported that the bilirubin of Bezoar Bovis (Kimura *et al.*, 1968; Tanaka *et al.*, 1987; Tanaka *et al.*, 1991) and muscone of Moschus (Hashi-moto *et al.*, 1994; Kimura *et al.*, 1981; Takahashi *et al.*, 1989) have strong effects on the hepatic organs. Like other oriental traditional medicines, peonjahwan also gives the patient a feeling of discomfort due to its bitterness and its effect is delayed because of the poor water-solubility of Bezoar Bovis, Serpentis Fel and Moschus. Furthermore, it is difficult to administer at the correct usage, because it is orally administered with warm water after cutting the pills to 1/20 and $1/10^{th}$ for infants and to $1/5^{th}$ for adults (Kim *et al.*, 1991).

In this study, to mask the bitterness of peonjahwan and improve the release of bilirubin, one of the crude active ingredients of peonjahwan, peonja dry elixir (PDE) was prepared using a spray-dryer after extracting the crude materials in ethanol-water solution. Coated peonja

dry elixir (CPDE) was then prepared by coating the PDE with Eudragit acrylic resin. Finally, the panel bitterness and release test of PDE and CPDE were carried out and compared with peonjahwan alone.

## MATERIALS AND METHODS

### Materials

Acrylic acid-methacrylic acid copolymer (Eudragit S 100) and dextrin (TK-16) were purchased from Rohm Pharmaceutical Co. (Weiterstadt, Germany) and Matzdani Chemical Co. (Tokyo, Japan), respectively. Notoginseng Radix, Bezoar Bovis, Serpentis Fel, Moschus and honey were kindly supplied by Dong-Kook Pharmaceutical Co. (Jinchon, Korea). Ethanol and sodium laurylsulfate were of USP grade. All other chemicals were of reagent grade.

### Preparation of peonjahwan, peonja dry elixir (PDE) and coated peonja dry elixir (CPDE)

*Peonjahwan* Notoginseng Radix (20.4 g), 1.2 g Bezoar Bovis, 1.68 g Serpentis Fel and 0.72 g Moschus (equivalent to 8 pills of peonjahwan) were milled using a pulverizer (Tokushu Kika Kogyo/M-type, Japan) and sieved with 200 mesh. They were agglomerated with honey and divided into $1/10^{th}$ pill quantity (0.3 g) of peonjahwan.

*Peonja dry elixir (PDE)* Notoginseng Radix (20.4 g) was milled, sieved with 200 mesh, and refluxed in 200 ml of ethanol-water solution (1:1, volume ratio) at 80-90°C for 2 h. After cooling, the extract was centrifuged at 1500 rpm using a centrifuge Sorvall RC5C (Dupont, USA). The volume of the extract was then determined and, the extract equivalent of one pill of peonjahwan was evaporated at 90°C and the dried amount of extract weighed. Twenty grams of dextrin and 1 g of sodium laurylsulfate were dissolved in 200 ml of extract. Bezoar Bovis (1.2 g), Serpentis Fel (1.68 g) and Moschus (0.72 g) were milled, sieved with 200 mesh and dispersed homogeneously in this extract for 2 h and then sonicated for 10 min. The resulting solution was delivered to a nozzle at a flow rate of 5 ml/min using a peristaltic pump and spray-dried at 130-135°C inlet and 80-85°C outlet temperatures using a Buchi mini-spray dryer (Buchi, Germany). The pressure of spray air was 3 $kg/cm^2$ and the flow rate of dry air was maintained at an aspirator setting of 10. The direction of airflow was the same as that of the sprayed product (Choi *et al.*, 1999).

*Coated peonja dry elixir (CPDE)* Thirty-four grams of PDE were dispersed homogeneously in 1 L of 1-% Eudragit S 100 alcoholic solution. The PDE suspension was delivered to the nozzle at a flow rate of 5 ml/min using a peristaltic pump and thereafter, spray-dried at 130°C inlet and 80°C outlet temperatures (Choi *et al.*, 1999). The shape and surface of CPDE were examined using a scanning electron microscope (JEOL, JJM-35, Japan).

### Determination of bilirubin contents in peonja powder, PDE and CPDE

About 4.8 mg of bilirubin was dissolved in 1 L of chloroform for the preparation of the standard solution. About 1.2 g of peonjahwan, 1.7 g of PDE and 2.2 g of CPDE were refluxed in 60 ml of chloroform-0.1 N HCl (5:1, volume ratio) at 60-65°C for 1 h, respectively. After cooling, the chloroform layer was separated and adjusted to 200 ml with chloroform. These solutions were directly injected (5 μl) onto a Lichrosorb RP-18 column (Waters, 0.5 um, 25 cm × 0.46 cm i.d.). The chromatograph consisted of a high-performance chromatograph (Waters, Model TM 717) and a variable ultraviolet spectrophotometric detector (Model SPD-6A). The mobile phase consisted of methanol and 2% acetic acid (97:3, volume ratio). The eluent was monitored with an UV/vis detector set at 436 nm with a flow rate of 1.0 ml/min (Kim *et al.*, 1991).

### Determination of ethanol in PDE and CPDE

Absolute ethanol (1 g) was added to 100 ml of acetone-water solution (1:1, volume ratio) for the preparation of standard solution. About 50 g of PDE and CPDE were dissolved or dispersed in 100 ml of methanol-water solution (1:1, volume ratio), and filtered, for the preparation of test solutions. About 5 ml of each sample was diluted with 45 ml of methanol-water solution. The concentration of ethanol in the samples was determined by gas chromatography with a Porapak Q, chromosorb 101 column. Nitrogen was used as the carrier gas. The temperatures of column, detector and injector were 120, 230 and 230°C, respectively (Choi *et al.*, 1999).

### Panel bitterness test

The panel bitterness test was performed in eleven male and eleven female volunteers separately. Test materials for bitterness were 0.3 g peonjahwan, 0.425 g PDE and 0.55 g CPDE (equivalent to 1/10 pill of peonjahwan). Furthermore, 0.1-1% caffeine solutions were used as the bitterness control and scored 10-100 for degree of bitterness. Before each test, each volunteers mouth was moistened with a few mL of distilled water. Volunteers were then asked to take the test materials with 15 ml. of distilled water and to hold the mix in their mouths for 10 sec prior to swallowing. Thereafter, they were asked to sample the caffeine solutions and select the one closest to the test material for bitterness. After each experiment, volunteers removed the bitter taste from their mouths with distilled water

and cheese, prior to continuing with the experiment (Hall *et al.*, 1975; Katsuragi *et al.*, 1995; Kim and Choi, 1987).

### Release test

Three grams of peonjahwan (equivalent to one pill of peonjahwan), 4.25 g of PDE and 5.5 g of CPDE were placed in a basket covered with the single fold gauze, respectively. The release studies on the bilirubin from the peonjahwan, PDE and CPDE were performed at 36.5°C using the basket method at 50 rpm with 500 ml of pH 1.2 as a release medium. At the predetermined time, 10 ml of the medium was sampled, this was then added to 30 ml of chloroform-0.1 N HCl (5:1, volume ratio) and refluxed at 60 ± 2°C for 1 h. After cooling, the chloroform layer was separated, adjusted to 50 ml with chloroform, and then analyzed by HPLC as described.

## RESULTS AND DISCUSSION

### Preparation of peonja dry elixir (PDE) and coated peonja dry elixir (CPDE)

On drying the dextrin dissolved in the ethanol-water cosolvent system on a rotary evaporator, the ethanol and water were evaporated simultaneously and the dextrin is finally dried. However, microcapsules containing ethanol in the dextrin shells were produced by spray-drying the above solution. Spraying the above solution through a fluid pressure nozzle into the drying chamber at the appropriate temperature, ethanol and water are simultaneously evaporated within the chamber of spray dryer at the first time. However, if the atomized liquid droplets contact the hot dry air for a little longer, the dextrin begins to increase near the surface of liquid droplet. As a result, a concentrated dextrin layer is formed on the surface of droplet. Water is continuously lost through this concentrated dextrin layer, but ethanol scarcely passes through this layer due to the extremely low diffusion coefficient of ethanol through the concentrated dextrin layer (Menting and Hoogstad, 1967; Menting *et al.*, 1970; Sato and Kurusu, 1974; Sato *et al.*, 1982). This concentrated dextrin wall acts as a semi-permeable membrane, permitting continual water loss by diffusion but effectively retaining the ethanol. Finally, the dextrin solidifies and the ethanol is captured inside the dextrin shell (Ahn *et al.*, 1998; Kim *et al.*, 1994; Kim *et al.*, 1995; Kim and Yoon, 1995).

In this study, the extract was prepared by refluxing Notoginseng Radix in ethanol-water solution, with the result that 25 ml of the extract (equivalent to one pill of peonjahwan) contained about 1.175 g of the dried material. Furthermore, micronized Bezoar Bovis, Serpentis Fel and Moschus were dispersed in this extract for 2 h and sonicated for 10 min. This refluxing, stirring and sonication in ethanol-water solution produced wet, soft and colloidal crude materials. Dextrin and sodium laurylsulfate were then dissolved in the extract. Sodium laurylsulfate was added to prevent dry elixir attaching to the inner wall of spray-drying chamber and to produce a free-flowing powder (Lee *et al.*, 1999). Employing the same principle of encapsulating the alcohol, microcapsules containing crude active materials of peonjahwan termed peonja dry elixir (PDE) could also be prepared by spray drying. PDE is, therefore, a solid form of microcapsule containing ethanol and crude materials of peonjahwan in dextrin shells. In this case, the ethanol-soluble crude active materials were dissolved in ethanol, while the ethanol-insoluble crude active materials were dispersed in ethanol or precipitated inside the dextrin shells.

**Table I.** Property of peonjahwan, peonja dry elixir (PDE) and coated peonja dry elixir (CPDE).

| | Peonjahwan | PDE | CPDE |
|---|---|---|---|
| Theoretical amounts (g)* | 3.00 | 4.25 | 5.50 |
| Bilirubin contents (%) | 0.82±0.36 | 0.52 ± 0.35 | 0.43 ± 0.27 |
| Ethanol contents (%) | - | 1.75 ± 0.63 | 1.32 ± 0.67 |

* equivalent to 1 pill peonjahwan.

Table I shows the theoretical amounts (equivalent to 1 pill peonjahwan) of bilirubin and the ethanol content of peonjahwan, PDE and CPDE. The bilirubin percentage in PDE decreased compared with peonjahwan (0.52 ± 0.35 *vs.* 0.82 ± 0.36%). This decreased bilirubin percentage might be due to the mass increase caused by the addition of dextrin (4.25 *vs.* 3 g). It is desirable to maximize the ethanol content in the dry elixir to improve the release rate of poorly water-soluble materials in aqueous media, with the result that 15% of ethanol was encapsulated in the dry elixir (Kim *et al.*, 1995). However, in the case of PDE increasing ethanol content increased both the hygroscopic nature and reduced the flow. It was reported that the amounts of ethanol in the dry elixir were governed by the concentration of wall-forming materials and the manufacturing conditions for the dry elixir (Choi *et al.*, 1999; Kim *et al.*, 1995). Thus, to prepare PDE which is less hygroscopic and with improved flow, the inlet (130-135°C) and outlet temperatures (80-85°C) were increased, with the result that the ethanol content in the PDE (1.75 ± 0.63%) was lowered considerably compared to the other dry elixirs (Choi *et al.*, 1999; Kim *et al.*, 1995).

In spite of the very low ethanol level, PDE was still hygroscopic and poorly flowing, because the surface of the PDE was composed of the dextrin, water-soluble polymer. To improve these properties, coated peonja dry elixir (CPDE) was prepared by coating the PDE with another polymer, Eudragit acrylic resin. The theoretical amounts of CPDE increased 1.3-fold compared

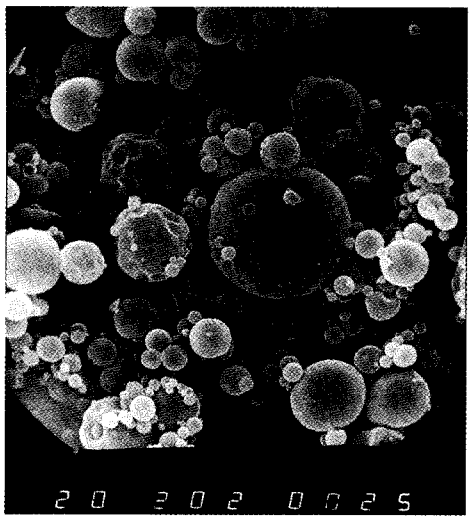

**Fig. 1.** Scanning electron micrograph of coated peonja dry elixir.

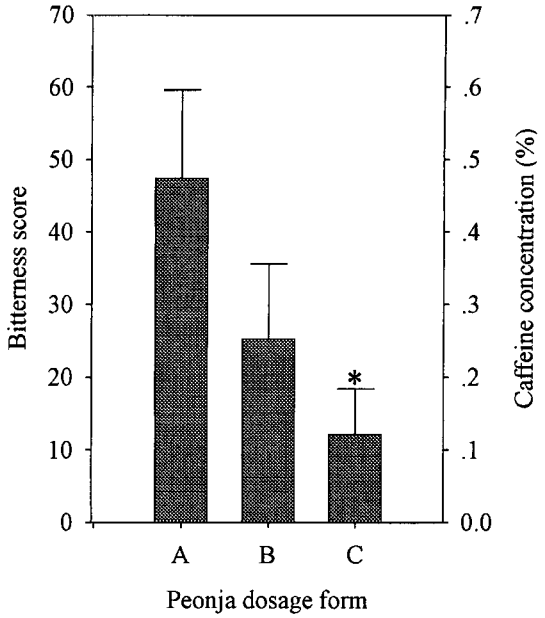


**Fig. 2.** Bitterness of three dosage forms: (A) Peonjahwan, (B) Peonja dry elixir, (C) Peonja coated dry elixir. (*) $P<0.05$ compared to peonjahwan. Each value represents the mean ± S.D. (n=22).

with PDE (5.5 *vs.* 4.25 g), indicating that the coating amount of Eudragit acrylic resin was about 30% against PDE. In the coating of conventional solid dosage form with polymers, the coating amounts were usually below 5% against naked dosage form (Lieberman and Lachman, 1980). However, in the coating of dry elixir with polymers, less than 25% of coating materials hardly improved the hygroscopic and poorly flowing properties of PDE (Choi *et al.*, 1999). The bilirubin percentage in CPDE decreased compared with peonjahwan (0.43 ± 0.27 *vs.* 0.82 ± 0.36%). The decrease in bilirubin percentage was due to the mass increase caused by the addition of dextrin and Eudragit (5.5 *vs.* 3 g). Our results indicated that the PDE and CPDE were prepared without loss of bilirubin. The ethanol content in CPDE decreased compared to PDE (1.32 ± 0.67 *vs.* 1.75 ± 0.63%). It was reported that on coating the dry elixir at elevated inlet air temperature, the decrease in ethanol content occurred at the expense of heat damage and a ballooning effect on the coated products (Kim *et al.*, 1994; Choi *et al.*, 1999; Kim and Yoon, 1995). However, on preparing the CPDE, the ballooning effect hardly occurred, because the ethanol content in the PDE was very low and the PDE was coated at the same inlet air temperature to the preparation of PDE. Ethanol percentage could only be caused by the Eudragit acrylic resin coating. As shown in Fig. 1, the scanning electron micrograph indicated that the majority of microcapsules were spherical in shape that had smooth surfaces.

### Panel bitterness test

Fig. 2 shows the bitterness of PDE and CPDE compared with peonjahwan using caffeine solutions as bitterness control (Emmons *et al.*, 1963; Horio and Kawamura, 1998). The panel bitterness test was performed with many volunteers, because this test showed wide deviations. The bitterness of PDE reduced to 1/2 of peonjahwan (12.12 ± 6.30 *vs.* 25.24 ± 10.29) but there was no significant difference ($P>0.05$). CPDE reduced the bitterness of peonjahwan, because the bitter crude active ingredients of peonjahwan were encapsulated in the dextrin shell. Furthermore, our results suggest that PDE could not significantly reduce the bitterness of peonjahwan, because the PDE shell was composed of water-soluble dextrin, which was easily destroyed in the human oral cavity. However, the bitterness of CPDE reduced to 1/4 of peonjahwan (12.12 ± 6.30 *vs.* 47.38 ± 12.20) ($P<0.05$). Such a reduced bitterness of CPDE also appears to have been caused by the encapsulation of the bitter crude active ingredients in the dextrin and Eudragit shell. Furthermore, CPDE had less bitterness than the PDE, because the CPDE shell was composed of water insoluble Eudragit acrylic resin, which was not easily destroyed in human oral cavity.

### Release of bilirubin from peonjahwan, PDE and CPDE

The release profiles of bilirubin from the peonjahwan, PDE and CPDE are illustrated in Fig. 3. The initial release rate of bilirubin from PDE and CPDE increased com-

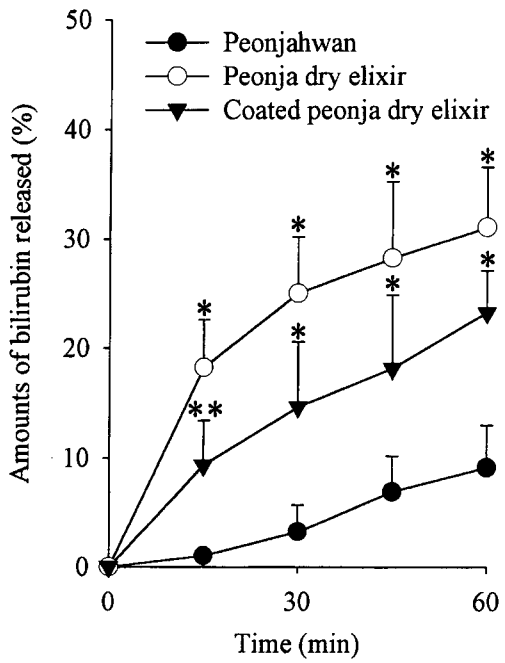


**Fig. 3.** Release profiles of bilirubin from three dosage forms in pH 1.2. (*) $P<0.05$ compared to peonjahwan. (**) $P<0.05$ compared to peonjahwan and peonja dry elixir. Each value represents the mean ± S.D. (n=6).

pared to peojahwan at pH 1.2. The amount of bilirubin released from PDE and CPDE in 60 min increased about 3.5- and 2.5-fold compared to peonjahwan at pH 1.2, respectively (31.0 ± 5.50; 23.2 ± 3.91 *vs.* 9.1 ± 3.83%). Such effects of PDE and CPDE on the release of bilirubin were attributed to the wetting, softening and colloidalization of crude materials as a result of extracting, stirring and sonication in ethanol-water solution. The bilirubin in the wet, soft and colloidal Bezoar Bovis of PDE and CPDE was released more rapidly than that in the crude Bezoar Bovis of peonjahwan. It was also thought that the bilirubin encapsulated in the PDE was released more rapidly as a result of the cosolvent effect of ethanol, because the dextrin shell was water soluble (Ahn *et al.*, 1998; Kim *et al.*, 1994; Kim *et al.*, 1995; Kim and Yoon, 1995). The amounts of bilirubin released from CPDE in 60 min was lower than that from PDE, because the Eudragit acrylic resin coating of the dry elixir retarded its release (Choi *et al.*, 1999).

It is concluded that CPDE, which masked the bitterness of peonjahwan and enhanced the release of bilirubin, is a preferable delivery system for peonjahwan.

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