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Preparation and evaluation of flurbiprofen dry elixir as a novel dosage form using a spray-drying technique

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Abstract

A dry elixir containing drug elixir in wall-forming materials as a novel oral dosage form was developed using the spray-drying technique. Poorly water-soluble flurbiprofen (FP) was used as a model compound. The dry elixir was produced when a solution of water-soluble dextrin and drug dissolved in an ethanol-water cosolvent system was spray-dried. The resulting dry elixir was spherical in shape with a geometric mean diameter of about 13 μm and small pieces of broken shells adhered to large spherical particles. A cross-sectional view of the dry elixir indicates a large inner cavity containing ethanolic drug solution in the dextrin shell. The ethanol contents in the dry elixir were highly dependent on dextrin concentration and inlet air temperatures. As the dextrin concentration increased, the ethanol contents also increased due to the rapid formation of a semipermeable dextrin membrane at the drying particle surface. The ethanol content in the dry elixir was greatest at an inlet air temperature of 90–100°C. The dissolution rate of FP in the dry elixirs within the first 5 min increased markedly compared to FP fine powder and appeared to be proportional to the ethanol content in the dry elixirs. The C_{max} and absolute bioavailability of FP powder, well-dispersed FP suspension and FP dry elixir were 14.6, 17.2 and 31.3 μg/ml; 43.6, 45.1 and 66.5%, respectively. There was no change in the T_{max} among the three products. Although the effective surface area and dispersability of the well-dispersed FP suspension increased, the $AUC_{0-6\,h}$ and C_{max} were not significantly changed compared to FP powder. However, the $AUC_{0-6\,h}$ and C_{max} of FP in the dry elixir were increased about 1.5- and 2-fold compared to FP powder. The enhanced bioavailability of FP in the dry elixir resulted from the increased dissolution rates of poorly water-soluble FP in aqueous media as a result of the cosolvent effect of ethanol and rapid dispersion of precipitated FP due to the fast dissolution of the dextrin shell. The current spray-drying technique for the preparation of dry elixir may provide a new approach to the solubilization of poorly water-soluble FP for dosage form design. As a result, it was obvious that the dry elixir might be a useful oral dosage form to improve the dissolution rate and bioavailability of poorly water-soluble FP.

Keywords: Dry elixir; Flurbiprofen; Poorly water-soluble drug; Dextrin; Ethanol; Spray-drying technique; Dissolution rate; Bioavailability

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1. Introduction

The solubilization of poorly water-soluble drugs is a widespread practice in developing pharmaceutical dosage forms for oral delivery in order to improve the dissolution rate in the gastrointestinal tract and bioavailability. Several solubilization methods by cosolvent, molecular complexation, crystal modification, prodrug formation and spray-drying technique have been reported as useful means of solubilizing poorly water-soluble drugs (Chiou and Riegelman, 1971; Corrigan and Timoney, 1975; Kawashima et al., 1975; Corrigan et al., 1980; Yalkowsky, 1981; Otagiri et al., 1982; Uekama et al., 1985; Kedzierewicz et al., 1990). The spray-drying technique was previously applied for the preparation of powder alcohol which is a microcapsule containing alcohol in wall-forming materials (Sato et al., 1974, 1982; McCormick, 1977; Sato and Kurusu, 1986). Alcohol or volatile aroma is held in water-soluble materials such as gelatin, dextrin or the like 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).

This information enabled us to produce a novel oral dosage form termed a 'dry elixir' using a spray-drying technique to improve the solubility and dissolution rate of poorly water-soluble drugs (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 enhancing bioavailability (Yoon, 1994).

Flurbiprofen (FP), a phenylpropionic acid derivative which has analgesic, anti-inflammatory and antipyretic actions, was employed as a model compound. While FP is widely used in the treatment of rheumatoid arthritis and other rheumatic disorders, the bioavailability of FP is relatively low due to its limited solubility in water (Uekama et al., 1985). The solubility of FP is very low in acidic media and water, but relatively high in alkaline media.

The purpose of the present work was: (1) to prepare the FP dry elixir varying manufacturing parameters such as dextrin concentration and inlet air temperature; (2) to elucidate the physicochemical properties of the dry elixir such as shape and dissolution rate; and (3) finally to compare the bioavailability of FP encapsulated in the dry elixir with the powder form of FP in rats.

2. Materials and methods

2.1. Materials

Flurbiprofen (FP) and dextrin of different grades were kindly supplied by Samil Pharm. Co. (Seoul, Korea) and Matsdani Chemical Co. (Tokyo, Japan), respectively. Ethanol (94.6 v/v%) and sodium lauryl sulfate (SLS) were obtained from Ducksan Chemical (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 FP dry elixir

A Büchi 190 nozzle type minispray dryer (Flawil, Switzerland) was used for the preparation of dry elixir. FP (2 g) was dissolved in 45 g of ethanol-water cosolvent (20:25 w/w). The resulting FP solution was prewarmed to 70°C and blended with SLS (0.2 g) and various amounts of dextrin (0–20 g). 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 90 and 55°C, respectively, except when inlet air temperatures were varied to decide maximum contents of ethanol as a function of temperature. The pressure of the spray air was 3 kg/cm^2 and the flow rate of dry air was maintained at the aspirator setting of 10. The direction of air flow was the same as that of sprayed product. The sodium lauryl sulfate was used to avoid attaching dry elixir to the inner wall of spray-drying chamber and to produce free-flowing powder. The dry elixir formulations were designated as DE-I, DE-II, DE-III and DE-IV in

Table 1
Constituents of spraying solutions for the preparation of FP dry elixirs

Ingredients	Weight of each ingredient (g)			
	DE-I	DE-II	DE-III	DE-IV
FP	2	2	2	2
Dextrin	5	10	15	20
SLS [a]	0.2	0.2	0.2	0.2
Ethanol	20	20	20	20
Water	25	25	25	25

[a] Sodium lauryl sulfate.

Table 1 according to the amounts of dextrin used of 5, 10, 15 and 20 g, respectively.

2.3. Shape and size distribution of dry elixir

The shape and surface of dry elixir were examined using a scanning electron microscope (JEOL, JJM-35, Tokyo, Japan). Dry elixir was loaded on the specimen stub via double-sided sticky tape and coated with gold (JEOL Fine Coater, Tokyo, Japan) for 20 min at 100–200 mTorr in a shutter coater before taking photograph at an accelerating voltage of 2.4 kV. The size distribution of dry elixir was also measured using a laser particle analyzer (Fritch Co., Ider-Oberstein, Germany).

2.4. Determination of ethanol and FP contents in the dry elixir

Absolute ethanol (2 ml) and acetonitrile (2 ml) as an internal standard were mixed and adjusted to 50 ml with purified water in 50 ml volumetric flask for the preparation of standard solutions. About 5 g of dry elixir accurately weighed and acetonitrile (2 ml) were dissolved in purified water in 50 ml volumetric flask and adjusted to 50 ml with purified water for the preparation of sample solutions. The concentration of ethanol in the dry elixir was determined using a gas chromatography with a Porapak Q, Chromosorb 101 column. Nitrogen was used as a carrier gas. The temperatures of the column, detector and injector were 150, 170 and 170°C, respectively.

The dry elixir was completely dissolved in 100 ml of methanol-water cosolvent solution (50%, v/v). The concentration of FP was determined using a UV/Vis spectrophotometer (Hewlett Packard 8452A, CA, USA) at a wavelength of 247 nm.

2.5. Dissolution studies

Dissolution testing was performed using the USP XXII dissolution apparatus II (paddle method). The paddle was placed 2.5 cm from the bottom of the vessel. FP powder or dry elixir equivalent to 30 mg of FP was dispersed in 900 ml of deionized water, pH 1.2 HCl solution and pH 7.2 phosphate buffer (1/15 M) at 37 ± 0.5°C at a paddle stirring speed of 100 rpm. Samples (3 ml) were withdrawn at 5, 10, 20, 30, 45 and 60 min with replacement by an equal volume of temperature equilibrated medium and filtered through a membrane filter (0.45 μm). The concentration of FP was determined spectrophotometrically.

2.6. Animal studies

Adult, albino, male Sprague-Dawley rats weighing between 250 and 300 g were used. After anesthesia with diethyl ether during surgery, the femoral vein and artery were cannulated with a 23 gauge polyethylene cannula. All of the incisions were covered with wet cotton and the cannula was flushed with 0.2 ml of heparinized normal saline (80 U/ml) to prevent blood clotting. After recovering from anesthesia, FP powder, FP suspension and dry elixir equivalent to 5 mg of FP per kg of body weight were orally administered to rats using oral sonde. FP powder and dry elixir (equivalent to 5 mg of FP) were dispersed in 1 ml of 0.5% aqueous carboxymethylcellulose (CMC) solution by simply vortexing for 10 s immediately prior to dosing. The well-dispersed FP suspension was prepared by continuous sonication and stirring in 0.5% CMC solution. On the other hand, 2.5 mg of FP was dissolved in 1 ml of pH 7.2 phosphate buffer (1/15 M) for intravenous administration and 2.5 mg of FP per kg of body weight was given intravenously to rats via the femoral vein. Blood samples (300 μl) were withdrawn at designated time intervals and cen-

trifuged at 5000 rpm for 10 min. Plasma (100 μl) was thereafter obtained and frozen under −20°C until HPLC analysis.

2.7. HPLC analysis of plasma FP

Plasma samples were deproteinized with 2.5 volumes of acetonitrile, vortexed and then centrifuged at 5000 rpm for 10 min. The supernatant (20 μl) was withdrawn for HPLC analysis according to a modified method of Albert et al. (1984). The plasma FP concentration was then determined using HPLC systems (Waters Associates Inc., Milford, MA, USA) consisting of a solvent delivery system, reverse-phase chromatography column (4.6 × 150 mm, C_{18} Novopak, 5 μm), fluorescence detector and integrator. The excitation and emission wavelengths of the fluorescence detector were 250 and 315 nm, respectively. The mobile phase consisted of acetonitrile, water and phosphoric acid (65:35:0.5% v/v) was degassed under vacuum for 1 h and delivered at a flow rate of 1.5 ml/min. Peak areas of FP as a function of FP concentration over the range 0.5–50 μg/ml were plotted for construction of a standard calibration curve.

2.8. Pharmacokinetic data analysis

The noncompartmental pharmacokinetic parameters including the area under the drug concentration-time curve (AUC) and area under the moment of the concentration-time curve (AUMC) from zero to 6 h and infinity were calculated using the RSTRIP II program (Salt Lake City, UT, USA). The maximal plasma concentration of drug (C_{max}) and time to reach maximum plasma concentration (T_{max}) were also obtained from plasma data. The following standard methods were used to calculate mean residence time (MRT), total clearance (Cl_t) and apparent volume of distribution at steady state (V_{ss}) and absolute bioavailability (F) (Gibaldi and Perrier, 1982).

$$\mathrm{AUC} = \int_0^\infty C_p \mathrm{d}t = \int_0^T C_p \mathrm{d}t + \left[\frac{C_*}{\lambda}\right]$$

$$\mathrm{AUMC} = \int_0^\infty C_p t \mathrm{d}t = \int_0^T C_p t \mathrm{d}t + \left[\frac{TC_*}{\lambda}\right] + \left[\frac{C_*}{\lambda^2}\right]$$

$$\mathrm{MRT} = \mathrm{AUMC} \div \mathrm{AUC}$$

$$Cl_t = \mathrm{dose} \div \mathrm{AUC}$$

$$V_{ss} = \mathrm{MRT} \times Cl_t$$

$$F = \left[\frac{\mathrm{AUC}_{oral}}{\mathrm{dose}_{oral}}\right] \div \left[\frac{\mathrm{AUC}_{i.v.}}{\mathrm{dose}_{i.v.}}\right]$$

where C_* and T indicate last sampling concentration and time, respectively. C_p is the plasma concentration of drug at time t. The absolute bioavailability (F) of oral dosage forms was obtained based on the intravenous data. The data from different formulations were compared for statistical significance by analysis of variance (ANOVA). All results were expressed as means ± standard deviation (S.D.).

3. Results and discussion

3.1. Preparation of dry elixir

Generally, on drying the dextrin dissolved in an ethanol-water cosolvent system on a rotary evaporator, ethanol and water evaporate simultaneously and dextrin is finally dried. However, microcapsules containing ethanol in the dextrin shells are produced by spray-drying the above solution as follows. Spraying the dextrin dissolved in ethanol-water mixture through a fluid pressure nozzle into the drying chamber at the 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 dextrin 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 dextrin layer is formed on the surface of droplets. Water is continuously dried through the concentrated dextrin layer, but ethanol scarcely passes through this layer due to the extremely low diffusion coefficient of ethanol in concentrated dextrin layer.

(Menting and Hoogstad, 1967; Menting et al., 1970). Therefore, this concentrated dextrin wall acts as a semipermeable membrane, permitting continual water loss by diffusion but effectively retaining ethanol. Finally, the dextrin is solidified and ethanol is captured inside the dextrin shell and powder alcohol is produced. Employing the same principle of producing the powder alcohol, dry elixir can be prepared by spray-drying of the drug and dextrin dissolved in ethanol-water mixture.

It is desirable to maximize ethanol contents in the dry elixir to improve the solubility and dissolution rate of poorly water-soluble drugs in aqueous media as a result of the cosolvent effects of ethanol. The ethanol contents in the dry elixir can be affected by various formulation and manufacturing conditions such as the type and concentration of water-soluble wall materials, inlet and outlet air temperature, air velocity and pressure of atomizing air. Most of all, selection of the type and concentration of dextrin as a wall material and inlet air temperature were primarily important to maximize the ethanol contents in the dry elixir. Among the wall-forming materials, the dextrin having a dextrose equivalence of 16–19 led to greater ethanol contents in the dry elixir compared to other grades of dextrin due to its high solubility in ethanol-water cosolvent (Yoon, 1994). After the type of dextrin was selected as a wall-forming material, the optimal concentration of dextrin was determined. Fig. 1 shows that the amounts of ethanol and drug encapsulated in the dry elixir are highly dependent on the dextrin concentration in the spraying solution. As the dextrin concentration increased, a greater amount of ethanol was encapsulated due to the rapid formation of a semipermeable dextrin membrane at the surface of the droplets. However, although the data were not shown, an optimal dextrin concentration may exist because the excess amount of dextrin at high concentrations does not provide any effective wall-forming capability for the drying process. On the other hand, the more the diluted dextrin solution was spray-dried, the smaller was the amount of ethanol that became encapsulated as a result of the longer period required to form the dextrin outer layer. As

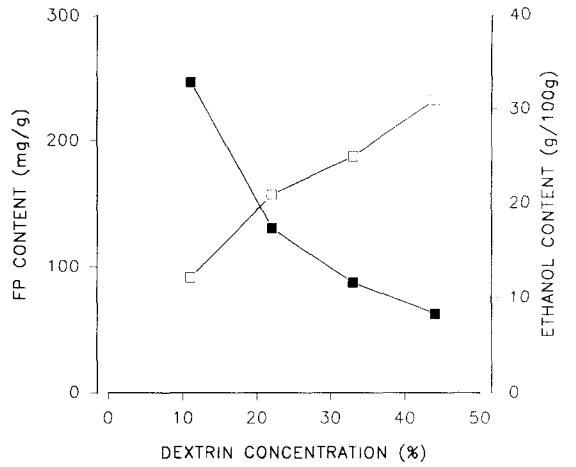


Fig. 1. Effect of dextrin concentration on the amounts of ethanol and FP encapsulated in the dry elixir. FP (2 g), SLS (0.2 g) and various amounts of dextrin (0–20 g) were dissolved in 45 g of ethanol-water cosolvent (20:25 w/w) for the preparation of spraying solutions. (□) Ethanol content, (■) FP content.

the dextrin concentration increased, the FP contents per g of dry elixir decreased and the ethanol contents increased

It is desirable to use a high enough inlet air temperature for the rapid formation of a semipermeable dextrin wall on the surface of droplets. However, a high inlet temperature reduces the ethanol content due to heat damage and a ballooning effect on the drying product, resulting in a low extent of encapsulation of ethanol into the dextrin shell. The ballooning effect occurs when the vapor pressure of ethanol inside drying droplets increases rapidly. Fig. 2 shows the amounts of ethanol and FP in the dry elixir governed by the inlet air temperatures. The ethanol contents in the dry elixirs were greatest around 90–100°C inlet air temperature during the drying process. Inlet air temperatures above 100°C have been found to decrease ethanol retention during drying, but the FP contents per g of dry elixir increased. Inlet air temperature below 90°C is undesirable due to poor drying and encapsulation efficiencies.

The influence of outlet air temperature on ethanol retention is not clear. Outlet air temperature might be controlled by the feeding rate of

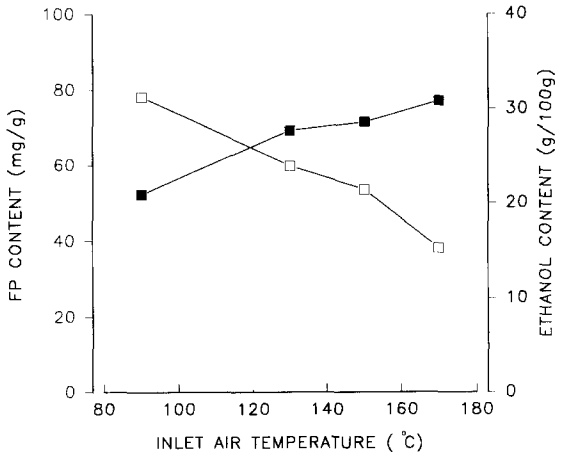
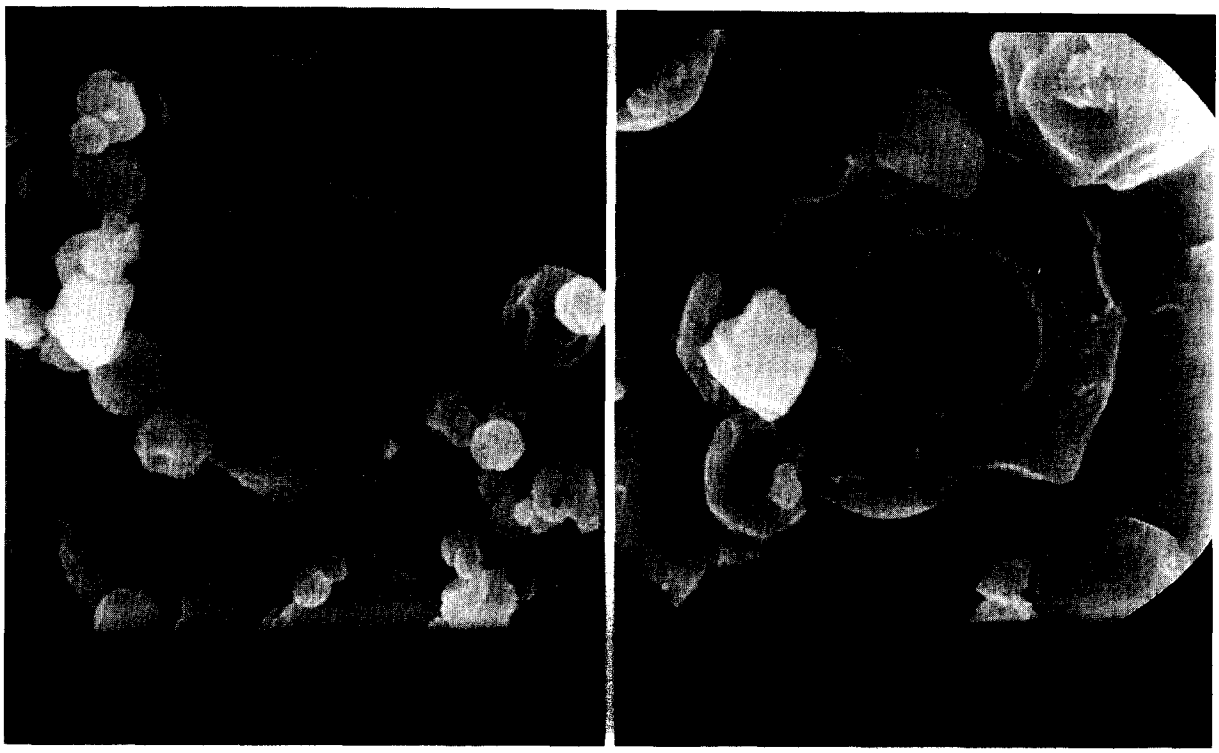


Fig. 2. Effect of inlet air temperature on the amounts of ethanol and FP encapsulated in the dry elixir (DE-IV). (□) Ethanol content, (■) FP content.

the solution and the air velocity when the inlet air temperature was held constant. In this work, the temperature difference between the inlet and outlet air temperatures was maintained at 40–45°C. High air velocity is known to improve the drying efficiency due to the more rapid heat and mass transfer associated with the drying process. However, air velocity is largely controlled by dryer design and cannot be changed to a significant degree as a dryer operating variable. In this experiment, the drying air velocity was held constant at an aspirator setting of 10. We also studied the role of the particle size of atomized droplets in determining the encapsulation of FP elixir. Others reported that large particle size resulted in improved flavor retention and flowing properties (Menting et al., 1970). Moreover, it is desirable to produce a large particle size. Small



(A) (B)

Fig. 3. Scanning electron micrographs of FP dry elixirs (DE-IV). (A) Surface; (B) cross-sectional view.

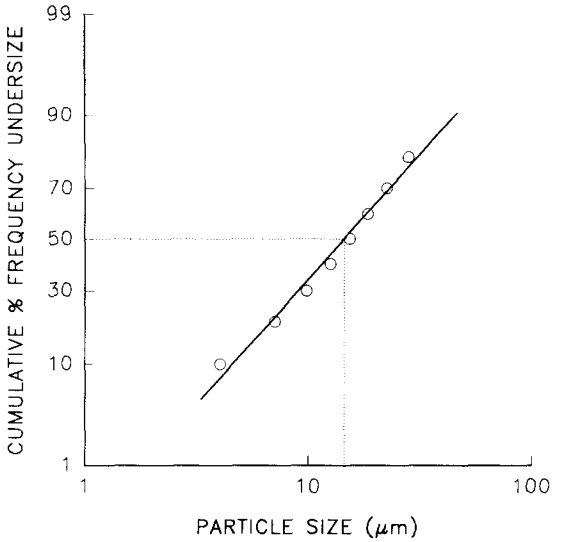


Fig. 4. Log-probability plot of volume-based size distribution of FP dry elixir (DE-IV). The geometric mean diameter is the logarithm of particle size equivalent to 50% on the probability scale.

particles tend to disperse very poorly, especially in cold water, and form lumps on the liquid surface. The spray dryer used in this work could control the particle size of atomized droplet by spray flow, pressure of atomized air and size of the nozzle orifice. Theoretically, a large particle size can be achieved through the judicious selection of these variables. However, practically, there is no difference in particle size and ethanol retention of dry elixir prepared by changing these variables. Therefore, we selected these variables as 800 NI/h of spray flow, 3 kg/cm^2 of air pressure and 0.7 mm nozzle orifice in considering the yield of dry elixir.

3.2. Shape and size distribution of dry elixir

The scanning electron micrographs of dry elixir are illustrated in Fig. 3. The dry elixir was spherical in shape with a smooth surface and very small pieces of broken shells were found to adhere to large spherical particles (Fig. 3A). Fig. 3B also demonstrates that a cross-sectional view of dry elixir shows the large inner cavity containing ethanolic drug solution in a dextrin shell. The dextrin shell is sufficiently thick to retain ethanolic drug solution during storage until the dry elixir is dissolved in aqueous medium.

The particle size and size distribution of FP dry elixir were determined using a laser particle analyzer. The volume percent data over particle diameters ranging from 1 to 250 μm were recorded. The arithmetic mean diameter was about 19.7 μm The log normal number or volume distribution of particle size is commonly used to predict the geometric mean diameter and geometric standard deviation from a linear relationship between the logarithm of particle size and cumulative percent frequency on a probability scale (Martin et al., 1983). The geometric mean diameter (12.7 μm) on a volume-basis size distribution was obtained from the log-probability plot of volume percent data shown in Fig. 4. The specific surface area (the surface area per unit volume; 0.819 m^2/cm^3) of FP dry elixir was calculated.

3.3. Dissolution of FP in dry elixir

The dissolution profiles of FP in four different dry elixirs and FP powder in distilled water at

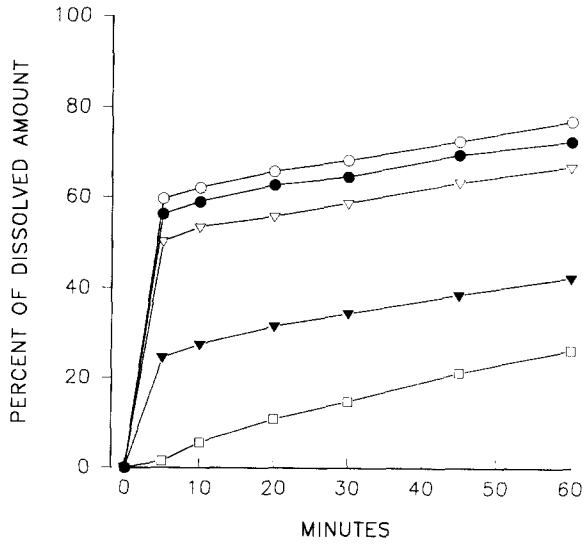


Fig. 5. Dissolution profiles of FP in four different dry elixirs and FP powder in distilled water at 37°C. (□) FP fine powder, (▼) DE-I, (▷) DE-II, (●) DE-III, (○) DE-IV.

37°C are shown in Fig. 5. FP in the dry elixirs dissolved very rapidly within the first 5 min, thereafter dissolving very slowly. The initial dissolution rates (IDRs) of FP encapsulated in DE-I, DE-II, DE-III and DE-IV within the initial 5 min increased 15–40-fold compared to that of FP fine powder (1.48, 3.01, 3.38, 3.58 vs 0.09 mg/ml min^{-1}). The amounts of FP dissolved during 5 and 60 min were related to the ratio of ethanol to FP encapsulated in dry elixir (Table 2). As the ethanol to FP ratios increased from 0.5 (DE-I) to 5 (DE-IV), IDR increased 2.4-fold and the percentages of FP dissolved for 5 and 60 min increased from 24.6 and 42.3% to 59.7 and 76.8%, respectively. Therefore, increasing IDR with respect to increasing the ratio of ethanol to FP might be caused by increasing amount of FP dissolved in ethanol in the dry elixir. As soon as the dry elixir was dispersed into the dissolution medium, a large proportion of dry elixir immediately dissolved. This phenomenon could be explained based on microenvironmental solubilization. Microenvironmental solubilization may be caused by ethanol directly as a result of the cosolvent effect, and by dextrin and SLS as a consequence of the effective surface area of FP increasing. Fig. 5 demonstrates two different dissolution steps: firstly, drug dissolved in ethanol in the dry elixir is dispersed immediately into the dissolution medium, and secondly, undissolved drug dissolves slowly according to second-order dissolution kinetics (Kim et al., 1994). Fig. 6 shows

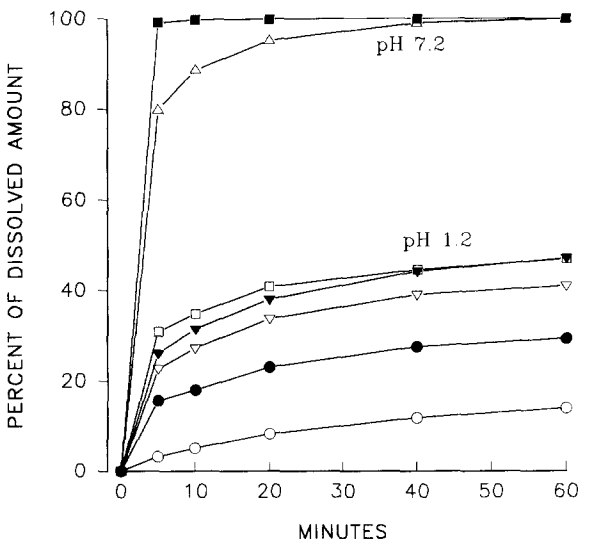


Fig. 6. Dissolution profiles of FP in four different dry elixirs and FP powder in pH 1.2 HCl solution and pH 7.2 phosphate buffer at 37°C. (1) pH 1.2: (○) FP fine powder, (●) DE-I, (▽) DE-II, (▼) DE-III, (□) DE-IV. (2) pH 7.2: (△) FP fine powder, (■) DE-I.

the FP dissolution patterns in acidic (pH 1.2) and alkaline (pH 7.2) media. The dissolution profile of FP fine powder in acidic medium is similar to those in water in Fig. 5, but FP dissolved rapidly in the alkaline phase. However, IDR of FP in the dry elixirs markedly increased irrespective of the dissolution medium.

These findings suggest that dry elixirs simultaneously containing ethanol and FP are useful for

Table 2
Percentages of ethanol and FP encapsulated in the dry elixir and the initial dissolution rates of FP in various formulations in distilled water at 37°C

Formulation	Amounts (w/w %) [a]%		Dissolved		IDR [b]
	Ethanol	FP	5 min	60 min	(mg/min per min)
FP fine powder	–	–	1.5	26.3	0.09
DE-I (2:0.2:5) [c]	12.2	24.7	24.6	42.3	1.48
DE-II (2:0.5:10)	20.9	13.0	50.2	66.7	3.01
DE-III (2:0.2:1.5)	25.0	8.7	56.3	72.3	3.38
DE-IV (2:0.2:20)	31.0	6.2	59.7	76.8	3.58

[a] Percentages of ethanol and FP per g of dry elixir formulations.
[b] Initial dissolution rate within first 5 min.
[c] Numbers in parentheses indicate the weight ratios of FP, SLS, and dextrin for the preparation of spraying solutions. The FP dry elixir formulations were designated as DE-I, DE-II, DE-III, and DE-IV when the amounts of dextrin used were 5, 10, 15 and 20 g, respectively.

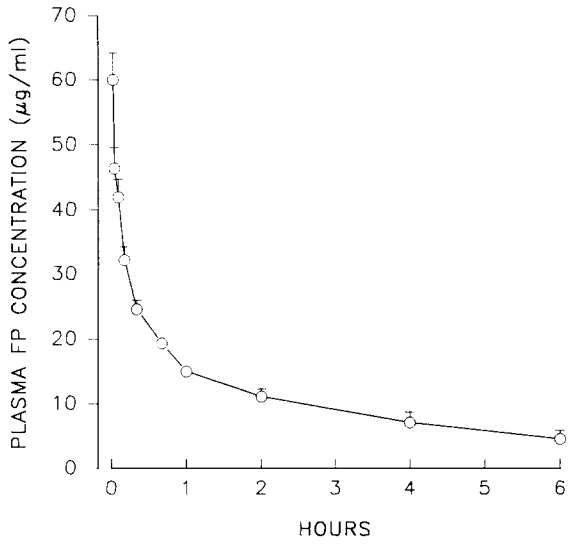


Fig. 7. Plasma concentration-time profile of FP after intravenous administration of FP dissolved in pH 7.2 phosphate buffer to rats. Bars represent standard deviation.

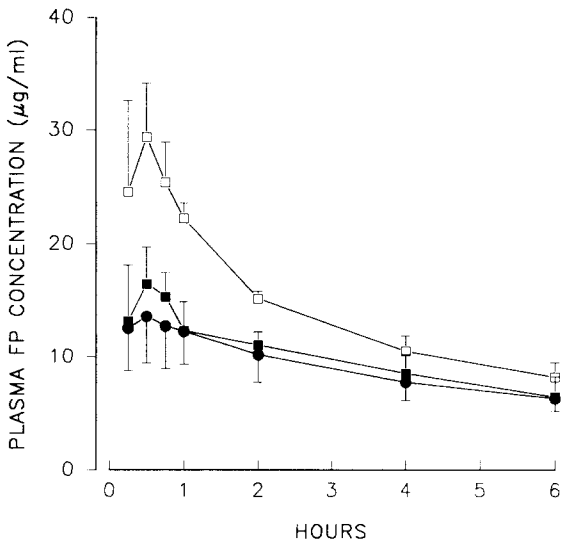


Fig. 8. Plasma concentration-time profiles of FP after oral administration of three different products to rats. Bars represent standard deviation. (●) FP fine powder; (■) well-dispersed suspension, (□) DE-IV.

improving the dissolution rate of poorly water-soluble FP.

3.4. Pharmacokinetic analysis

The plasma concentration-time profiles of FP from various FP dosage forms after intravenous and oral administration to rats are compared in Fig. 7 and 8. The noncompartmental pharmacokinetic parameters in Table 3 were calculated based on the observed plasma data. The C_{max} and absolute bioavailability (F) of FP fine powder, well-dispersed FP suspension in 0.5% CMC solution and FP dry elixir were 15, 17 and 31 μg/ml; 44, 45 and 67%, respectively. There is no significant change in T_{max} among the three products (0.5, 0.54, 0.5 h). Although the effective surface area and dispersability of well-dispersed FP suspension in 0.5% CMC solution increased, the $AUC_{0-6\,h}$ and C_{max} remained unchanged compared to FP fine powder. However, the $AUC_{0-6\,h}$ and C_{max} of FP encapsulated in the dry elixir increased about 1.5- and 2-fold compared to FP

Table 3
Analysis of noncompartmental pharmacokinetic parameters after oral administration of FP formulations to rats

Pharmacokinetic parameters	Intravenous	Oral		
		Powder	Suspension	DE-IV
C_{max} (μg ml^{-1})	–	14.6 ± 4.28	17.2 ± 3.85	31.3 ± 4.92 [a]
T_{max} (h)	–	0.50 ± 0.27	0.54 ± 0.19	0.5 ± 0.16
$AUC_{0-6\,h}$ (μg h ml^{-1})	65.9 ± 8.5	56.1 ± 13.3	59.5 ± 9.8	87.7 ± 5.9 [a]
$AUMC_{0-6\,h}$ (μg h^2 ml^{-1})	129.0 ± 32.7	145.0 ± 31.2	150.0 ± 29.0	197.0 ± 27.1 [a]
MRT (h)	1.92 ± 0.27	2.60 ± 0.12	2.52 ± 0.21	2.24 ± 0.22
Cl_t (ml h^{-1} kg^{-1})	0.038 ± 0.005	0.093 ± 0.022	0.086 ± 0.017	0.057 ± 0.004 [a]
V_{ss} (ml kg^{-1})	0.073 ± 0.003	0.24 ± 0.068	0.22 ± 0.043	0.13 ± 0.012 [a]
F		0.436	0.451	0.665

[a] $p < 0.05$ by the ANOVA test (suspension and DE-IV vs FP powder).

powder. The enhanced bioavailability of FP in the dry elixir (DE-IV) resulted from the increased solubility and dissolution rate of poorly water-soluble FP as a result of cosolvent effect of ethanol, and rapid dispersion of solid FP due to the fast dissolution of dextrin shell. The absolute bioavailability of FP in the dry elixir was the greatest and statistically significant ($p < 0.05$) compared to other FP products although it may be noted that intersubject variations were relatively large in the small study group. As a result, it was obvious that the FP dry elixir simultaneously containing ethanol and FP in a water-soluble polymer such as dextrin might be a useful dosage form to the improve dissolution rate and bioavailability of poorly water-soluble FP.

4. Conclusions

The FP dry elixir prepared by the spray-drying technique showed good flowability and was spherical in shape, having a geometric mean diameter of about 13 μm. The ethanol contents were highly dependent on the dextrin concentration and inlet air temperature. The initial dissolution rate of FP in the dry elixir increased dramatically compared to the FP powder form and appeared to be proportional to the ethanol content in the dry elixir. The $AUC_{0-6\ h}$ and C_{max} of FP encapsulated in the dry elixir were the greatest compared to FP fine powder and suspension, however, T_{max} was not changed. As a result, the current spray-drying technique for the preparation of dry elixir may provide a new approach to the solubilization of poorly water-soluble FP, and the dry elixir might be a useful dosage form to improve the dissolution rate and bioavailability of poorly water-soluble FP.

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