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Research Paper

Development of an itraconazole-loaded gelatin microcapsule with enhanced oral bioavailability: physicochemical characterization and in-vivo evaluation

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Abstract

Objectives The aim of this study was to develop a novel itraconazole-loaded gelatin microcapsule without ethanol with enhanced oral bioavailability.

Methods Various gelatin microcapsules were prepared using a spray-drying technique. Their physicochemical properties, dissolution, characteristics and pharmacokinetics in rats were evaluated and compared with those of a commercial product.

Key findings The gelatin microcapsule at a weight ratio for itraconazole/gelatin/citric acid of 1 : 3 : 0.3 was spherical in shape with a smooth surface and inner hole, and gave a maximum drug solubility of about 700 μg/ml. The gelatin microcapsule dramatically increased the initial dissolution rate of itraconazole compared with a commercial product in simulated gastric fluids (pH 1.2). Moreover, at the same dose as the commercial product, it gave significantly higher initial plasma concentrations, C_{max} and AUC of itraconazole in rats than did the commercial product, indicating that providing the drug in the gelatin microcapsule caused enhanced absorption in rats. At half dose, it gave similar AUC, C_{max} and T_{max} values to the commercial product, suggesting that it was bioequivalent to the commercial product in rats.

Conclusions The itraconazole-loaded gelatin microcapsule without ethanol developed using a spray-drying technique at half the dose of the commercial product can deliver itraconazole in a pattern that allows fast absorption in the initial phase, making it bioequivalent to the commercial product.

Keywords gelatin microcapsule without ethanol; itraconazole; rats; spray drying

Introduction

Itraconazole, an antifungal agent, is usually administered orally for the treatment of mycotic infections such as aspergillosis and candidiasis.[1] According to the biopharmaceutical classification system, it is a class II drug, being characterized by low water solubility and high permeability.[2] Various oral formulations, such as solid dispersions,[3,4] hot-melt extrusions,[5] micellar formulations[6,7] and inclusion complexes,[8–10] have been developed to improve the solubility and enhance the oral bioavailability of itraconazole.

Recently, we developed a 'gelatin microcapsule' as a method of oral dosage. This encapsulated ethanol and the drug, which was formulated using gelatin as a water-soluble polymer shell.[11] Poorly water-soluble drugs encapsulated in gelatin microcapsules are easily soluble or dispersed in the gastrointestinal tract after oral administration, which enhances the oral bioavailability of drugs such as ibuprofen[12] and piroxicam.[13] However, when the gelatin microcapsules are stored for a long period of time, ethanol leaks out from the gelatin shell and they become attached to each other, resulting in agglomeration. From the industrial viewpoint, it is not possible to develop a practical commercial product, since it is physically unstable. Thus, a new gelatin microcapsule without ethanol is required to develop a physically stable pharmaceutical product.

In this study, with the aim of developing an itraconazole-loaded gelatin microcapsule without ethanol but with enhanced oral bioavailability, various gelatin microcapsules were

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prepared using a spray-drying technique. Their physicochemical properties, dissolution characteristics and pharmacokinetics in rats were evaluated and compared with those of a commercial product.

Materials and Methods

Materials

Itraconazole and gelatin (USP grade, type A) were purchased from Hanmi Pharm. Co. (Suwon, South Korea) and Sammi Co. (Anyang, South Korea), respectively. Ethanol (94.6%, v/v) and citric acid were obtained from Ducksan Chemical Co. (Seoul, South Korea) and Shino Pure Chemical Co. (Osaka, Japan), respectively. The commercial product (Sporanox; in a capsule form) was purchased from Korea-Janssen Pharm. Co. (Hwaseong, South Korea). All other chemicals were of reagent grade and were used without further purification.

Animals

All animal care and procedures were conducted according to the Guiding Principles in the Use of Animals in Toxicology, as adopted in 1989 and revised in 1999 by the Society of Toxicology.[14] Furthermore, the protocols for the animal studies were approved by the Institute of Laboratory Animal Resources of Yeungnam University. Male Sprague–Dawley rats, 7–9 weeks old, 250–310 g, were purchased from Charles River Company Korea (Orient, Seoul, South Korea). The rats were fasted for 24–36 h before the experiments, but allowed free access to water, at a temperature of 20–23°C and a relative humidity of 50 ± 5%. The rats, divided into three groups, were administered a commercial product (45 mg/kg, equivalent to itraconazole 10 mg/kg) or gelatin microcapsules (46 mg/kg, equivalent to itraconazole 10 mg/kg, or 23 mg/kg, equivalent to itraconazole 5 mg/kg), respectively.

Preparation of itraconazole-loaded gelatin microcapsules

Various amounts of gelatin and citric acid were dissolved in 50 ml water to obtain an aqueous gelatin solution. Itraconazole (1 g) was dissolved in 30 ml of a methylene chloride–ethanol mixture (2 : 1, w/w) and added to an aqueous gelatin solution. The exact composition of the itraconazole-loaded gelatin microcapsules is given in Table 1. The resulting solution 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 temperature using a Büchi 190 nozzle type mini spray dryer (Flawil, Switzerland). The air pressure of the spray was 4 kg/cm^2. The flow-rate of the drying air was maintained at the aspirator setting of 10, which was equivalent to a pressure in the aspirator filter vessel of −30 mbar.[15,16]

Table 1 Composition of itraconazole-loaded gelatin microcapsules

	Formula ingredients (g)						
	I	II	III	IV	V	VI	VII
Itraconazole	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Gelatin	1.0	2.0	3.0	4.0	3.0	3.0	3.0
Citric acid	0.6	0.6	0.6	0.6	0	0.3	0.9

Ethanol content of itraconazole-loaded gelatin microcapsules

Various volumes (0.5, 1, 2, 4 and 8 ml) of ethanol stock solution (0.1 g/ml) and acetonitrile (150 μl; internal standard) were mixed and adjusted to 100 ml with distilled water for the preparation of standard solutions. About 250 mg of each alcoholic microcapsule was accurately weighed and dissolved in 10 ml of an acetonitrile–water mixture (1.5 μl/ml) in an Eppendorf tube. The ethanol content in the microcapsules was determined using gas chromatography with a Porapak Q, Chromosorb 101 column.[17] Nitrogen gas was used as the carrier. The temperature of the column, detector and injector was 80, 160 and 130°C, respectively.

Aqueous solubility of itraconazole-loaded gelatin microcapsules

The gelatin microcapsules were added to 15 ml of simulated gastric fluids (pH 1.2), vortexed for 1 min and shaken in a water bath for 24 h. A sample of the solution (2 ml) was taken, centrifuged at 13 000*g* for 15 min and filtered through a membrane filter (0.45 μm).[11] The concentration of itraconazole in the resulting solution was then analysed by the HPLC method as described below.

Shape of itraconazole-loaded gelatin microcapsules

The shape of the itraconazole powder and an itraconazole-loaded gelatin microcapsule was examined using a scanning electron microscope (S-4100; Hitachi, Tokyo, Japan). The powder was loaded onto the specimen stub via double-sided sticky tape and coated with gold (Hitachi Iron sputter; E-1030) for 30 min at 100–200 mTorr in a sputter coater before taking photographs at an accelerating voltage of 2.4 kV.[11,16]

Thermal characteristics and crystallinity of itraconazole-loaded gelatin microcapsules

The thermal characteristics of the gelatin microcapsules were investigated using a differential scanning calorimeter (DSC 823, Mettler Toledo; Imlangacher, Greifensee, Toledo, Switzerland). About 5 mg of each sample was placed in sealed aluminium pans, before heating under a nitrogen flow (20 ml/min) at a heating rate of 10°C/min from 40 to 300°C. Furthermore, the powder crystallinity was assessed by X-ray powder diffraction (D/MAX-2500; Rigaku, Tokyo, Japan) conducted at room temperature using Ni-filtered Cutarget at 15 mA and 30 kV in the region of $10^o \leq 2\theta \leq 70^o$ with an angular increment of 0.02° per second.[18]

Dissolution of itraconazole-loaded gelatin microcapsules

The gelatin microcapsule, commercial product or itraconazole powder was inserted into a basket for the dissolution test. The basket was then placed in a dissolution tester (Shinseang Instrument Co., Hwasung, South Korea). The dissolution test was performed at 36.5°C using the basket method at 100 rev/min with 900 ml of simulated gastric fluid (pH 1.2) as a dissolution medium. At designated time intervals, 3 ml of the medium was sampled and filtered through a membrane filter

(0.45 μm).[19,20] The concentration of drug in the supernatant layer was analysed by the HPLC method, as described below.

Stability of itraconazole-loaded gelatin microcapsules

The itraconazole-loaded solid dispersion was stored for six months at 25°C and 40°C.[11,21] At two-month intervals, any crystals of itraconazole in the solid dispersion were examined by differential scanning calorimetry (DSC) and X-ray diffraction, and the content of itraconazole in the solid dispersion was analysed by HPLC as described below.

Oral administration

Each rat, anaesthetized in an ether-saturated chamber, was secured on a surgical board in the supine position with a thread. A polyethylene tube (PE 20; Becton Dickinson, Franklin Lakes, USA) was inserted into the right femoral artery. Three preparations were filled in small hard capsules (#9; Suheung Capsule Co., Seoul, South Korea), respectively, and orally administered to each group of rats. About 0.5 ml of blood was collected from the right femoral artery at 0, 1, 3, 4, 6, 8, 12, 24 and 48 h. Then, 0.5 ml of blood from untreated rats was replaced. To prevent blood clotting, the cannula was immediately flushed with 0.3 ml of heparinized 0.9% NaCl injectable solution (20 U/ml) after each blood sampling. These samples were immediately centrifuged at 3000*g* for 10 min using a centrifuge (5415C; Eppendorf, Hamburg, Germany).[1,8,22]

HPLC analysis of itraconazole

Plasma (0.2 ml) was mixed with 15 μl of methanol containing ketoconazole (0.6 μg/ml; internal standard). Then, 200 μl of carbonate buffer (pH 10) and 1.5 ml of *t*-butyl methyl ether were added, vortexed for 2 min and centrifuged at 4000*g* for 10 min. The supernatant layer (0.4 ml) was evaporated under nitrogen gas. The residue was reconstituted in 100 μl of the mobile phase. The resulting solution (30 μl) was analysed by an HPLC system (Varian ProStar 210/215; Varian, Chicago, USA) equipped with an Inertsil ODS-3 C_{18} column (0.5 μm, 15 cm × 0.46 cm i.d.; GL science, Tokyo, Japan) and a UV detector (Model L-7450). The mobile phase consisted of acetonitrile and distilled water containing 0.05% diethylamine (7 : 3, v/v), the pH of which was adjusted to pH 6.0 with 30% acetic acid. The eluent was monitored at 254 nm with a flow rate of 1.2 ml/min.[10,23]

Pharmacokinetic data analysis

The area under the drug concentration–time curve from zero to infinity (AUC), the elimination constant (K_{el}) and half-life (t½) were calculated using a non-compartmental anaylsis (WinNonlin professional edition, version 2.1; Pharsight, Mountain View, USA). The maximum plasma concentration of drug (C_{max}) and the time taken to reach the maximum plasma concentration (T_{max}) were obtained directly from the plasma data.[24]

Statistical analysis

$P < 0.05$ was considered to be statistically significant using a Duncan's multiple range test in the Social Package of Statistical Sciences (SPSS) posteriori analysis of variance among the three means for the unpaired data. All data are expressed as mean ± standard deviation (SD) or as the median (ranges) for T_{max}.

Results

Before preparing the itraconazole-loaded gelatin microcapsule without ethanol, the effect of inlet temperature on the ethanol content in the gelatin microcapsule was investigated. Gelatin, itraconazole and citric acid were dissolved and spray-dried using various spray-drying conditions. Apart from inlet temperature, no other conditions (air pressure, flow-rate or aspirator pressure) have been reported to influence the amount of ethanol in the gelatin microcapsules.[11] As the inlet temperature increased to 105°C, the ethanol content increased, followed by a rapid decrease at higher temperatures, although the differences were not significant (Figure 1). In particular, the gelatin microcapsule prepared at the inlet temperature of 130°C contained virtually no ethanol. At inlet temperatures below 105°C, ethanol might not penetrate during preparation of the gelatin microcapsule. However, at inlet temperatures above 105°C, ethanol in the gelatin microcapsule might evaporate.[17] The itraconazole-loaded gelatin microcapsule was not sticky and formed few agglomerations over the six months of storage (see the stability test). Thus, an inlet temperature of 130°C was chosen for the preparation of itraconazole-loaded gelatin microcapsules without ethanol.

The effect of gelatin on drug solubility was investigated (Figure 2; Table 1, formulae I–IV). Solubility abruptly increased as the gelatin concentration increased to 3 g, followed by no significant change. Our results suggested that, at a gelatin concentration below 3 g, the amount of gelatin microcapsules prepared by the spray-drying process might increase as the gelatin concentration increased. However, at a gelatin concentration above 5 g, the amount of gelatin microcapsules prepared by the spray-drying process might not increase but the gelatin shell of gelatin microcapsules might become thicker.[15,16]

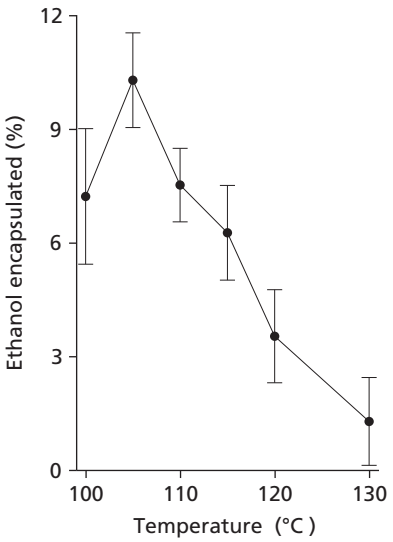

Figure 1 Effect of inlet temperature on the amount of ethanol in the gelatin microcapsules. Each value represents the mean ± SD $n = 5$

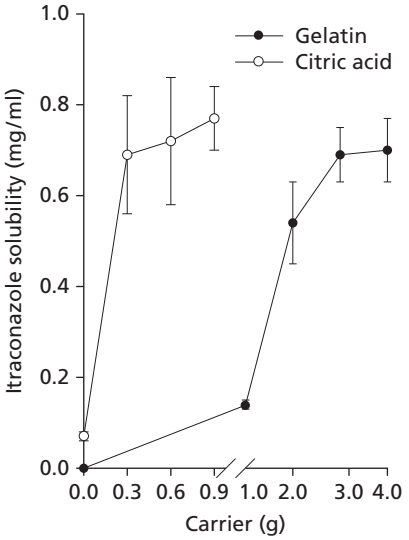

Figure 2 Effect of carriers on drug solubility. Each value represents the mean ± SD, $n = 5$

The effect of citric acid on drug solubility was investigated (Figure 2; Table 1, formulae III, V–VII). Citric acid was used as a solubilizing agent in the development of conventional itraconazole-loaded pharmaceutical dosage forms.[3,4] Gelatin microcapsules with citric acid (formulae III, VI–VII) showed significantly higher drug solubility than those without citric acid (formula V). However, there were no significant differences in the drug solubility among the gelatin microcapsules containing different amounts of citric acid (formulae III, VI–VII). In this study, citric acid played an important role as a solubilizer because it provided an acidic microenvironment for itraconazole.[25] Based on these findings, a gelatin microcapsule with a weight ratio for itraconazole/gelatin/citric acid of 1 : 3 : 0.3 and a maximum drug solubility of about 700 μg/ml was chosen for further study.

The scanning electron micrographs of itraconazole powder and an itraconazole-loaded gelatin microcapsule are shown in Figure 3. Itraconazole powder (Figure 3a) was smooth-surfaced and rectangular crystalline in shape.[16] However, the gelatin microcapsule (Figure 3b) was spherical in shape with a smooth surface. A view of a fractured microcapsule with an inner hole (Figure 3b; arrow) showed a large inner cavity within the gelatin shell.

The thermal behaviour of the drug powder, gelatin, physical mixture and gelatin microcapsule is shown in Figure 4. The physical mixture was prepared by physically mixing itraconazole, gelatin and citric acid at a weight ratio of 1 : 3 : 0.3. Itraconazole and citric acid produced a sharp endothermic peak at about 170 and 150°C, respectively, corresponding to their respective melting points, indicating their crystalline nature (Figure 4A, B). The broad endothermic peak of gelatin was observed at about 85°C (Figure 4C). The physical mixture showed a broad endothermic peak at about 170°C due to the interaction of the polymer and drug (Figure 4D). However, the sharp peak corresponding to the drug had disappeared and no peak was observed in the gelatin microcapsule (Figure 4E), suggesting that the drug was present in an amorphous state.[26]

The powder X-ray diffractometry patterns are shown in Figure 5. Itraconazole gave sharp peaks at diffraction angles that showed a typical crystalline pattern (Figure 5B). However, all major characteristic crystalline peaks for the drug were observed in the physical mixture (Figure 5A) but were barely visible in the gelatin microcapsule (Figure 5D). As with the DSC results, this indicated that itraconazole was present in an amorphous form in the gelatin microcapsule.

The dissolution test on the gelatin microcapsule was performed and compared with the commercial product and itraconazole powder (Figure 6). The gelatin microcapsule gave significantly faster dissolution of itraconazole than the drug powder. Furthermore, the initial dissolution rate of itraconazole in the gelatin microcapsule was much faster than that of the commercial product. In particular, the amount of itraconazole released from the gelatin microcapsule over 5 min was about 10-fold higher than that from the commercial product. However, there was no significant difference between the

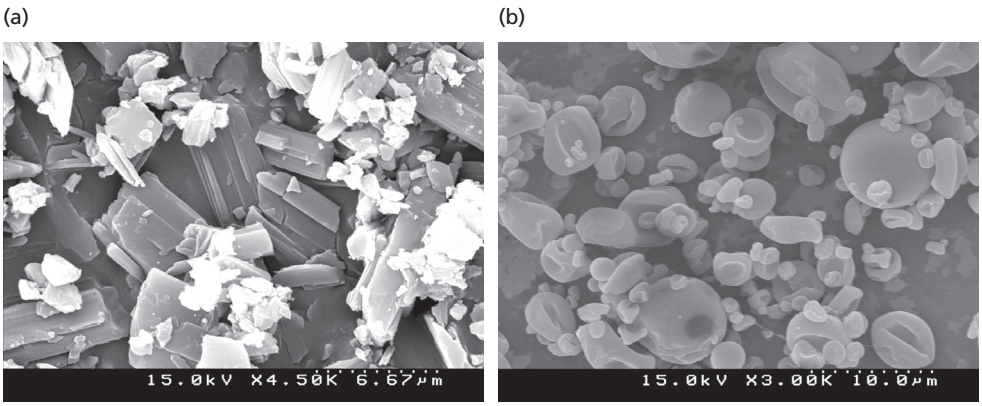

Figure 3 Scanning electron micrographs of itraconazole powder and itraconazole-loaded gelatin microcapsule. (a) Itraconazole powder (× 4500). (b) Itraconazole-loaded gelatin microcapsule (× 3000). The itraconazole-loaded gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3

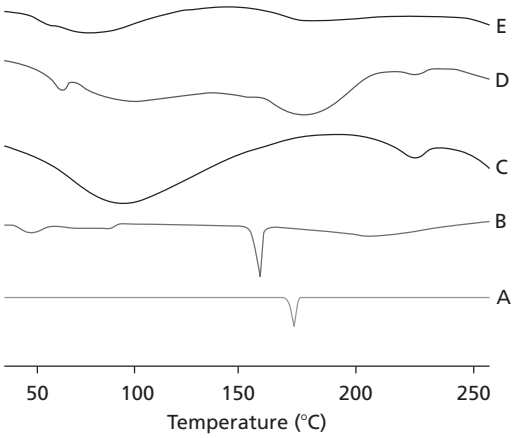

Figure 4 Differential scanning calorimetric thermograms of drug powder, citric acid, gelatin, physical mixture and gelatin microcapsule. DSC thermograms are: A, drug powder; B, citric acid; C, gelatin; D, physical mixture; and E, gelatin microcapsule. The physical mixture was prepared by physically mixing itraconazole, gelatin and citric acid at a weight ratio of 1 : 3 : 0.3. The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3

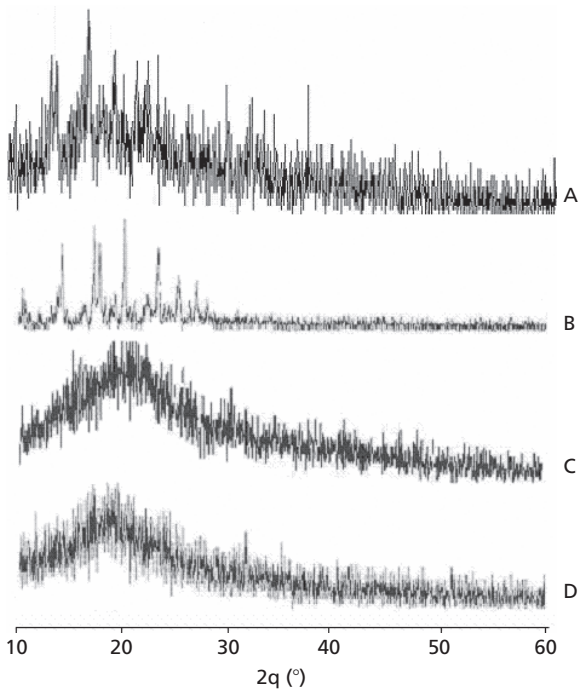

Figure 5 X-ray powder diffraction of physical mixture, drug powder, gelatin and gelatin microcapsule. The diffraction patterns are: A, physical mixture; B, drug powder; C, gelatin; and D, gelatin microcapsule. The physical mixture was prepared by physically mixing itraconazole, gelatin and citric acid at a weight ratio of 1 : 3 : 0.3. The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3

amounts of drug released from the gelatin microcapsule and commercial product over 2 h.

The effect of citric acid on the dissolution from gelatin capsules was also investigated (Figure 6). Gelatin microcapsules without citric acid showed significantly slower

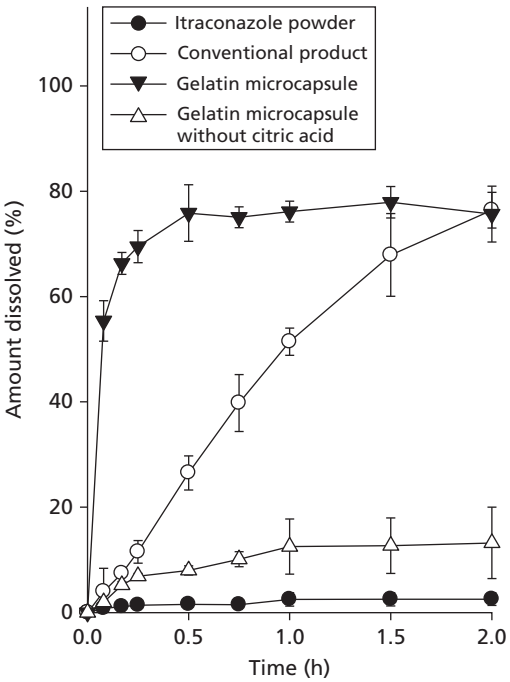

Figure 6 Dissolution profile of drug from powder, commercial product and gelatin microcapsule. The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3. The gelatin microcapsule without citric acid was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0. Each value represents the mean ± SD, $n = 6$

dissolution of itraconazole than those with citric acid, but significantly faster dissolution of itraconazole than that from powder. Thus, citric acid played the role of solubilizer by providing an acidic microenvironment for itraconazole.[25] Based on these findings, a gelatin microcapsule at the weight ratio for itraconazole/gelatin/citric acid of 1 : 3 : 0.3, with a maximum drug solubility of about 700 μg/ml, was chosen for further study.

To understand the dissolution mechanisms of itraconazole from the gelatin microcapsule, we described the dissolution rate using the following equations:

$$Mt/M = Kt^n \quad (1)$$

$$\log(Mt/M) = \log k + n\log(t) \quad (2)$$

where Mt/M is the fraction of dissolved drug at time t, k is a characteristic constant of the gelatin microcapsule and n is indicative of the dissolution mechanism. The n value of 1 corresponds to zero-order release kinetics, $0.5 < n < 1$ means a non-Fickian dissolution model and n = 0.5 indicates Fickian diffusion.[27] From the plot of log (Mt/M) versus log (t) (Figure 7), the kinetic parameter (n) was 0.087 ($r^2 = 0.953$). Our result suggests that itraconazole might be dissolved from the gelatin microcapsule by non-Fickian diffusion.

The stability of the drug in the gelatin microcapsule was evaluated by observation of the crystallinity and content of itraconazole in the solid dispersion during storage for six

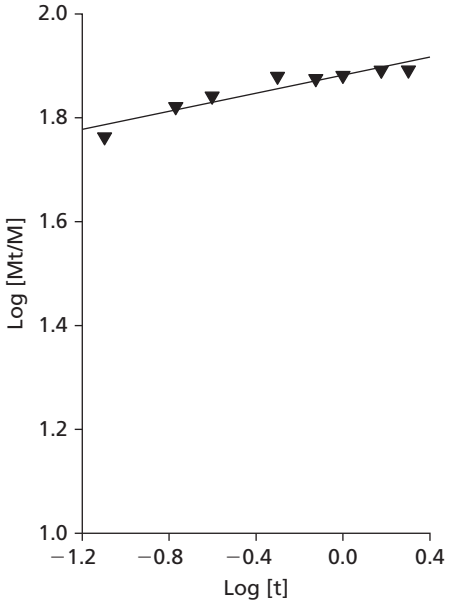

Figure 7 Dissolution kinetics of itraconazole from gelatin microcapsule. The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3. Logarithm of dissolved fractions of itraconazole was plotted against logarithm of time

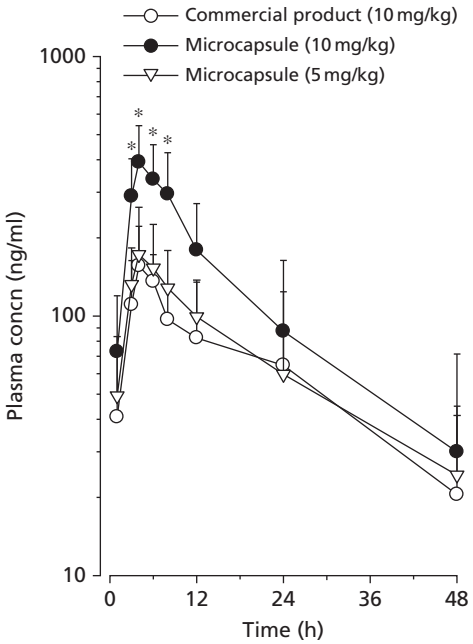

Figure 8 Plasma concentration–time profiles of drug after oral administration of the commercial product and gelatin microcapsule to rats. The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3. Each value represents the mean ± SD, $n = 8$. $^{*}P < 0.05$ compared with the commercial product

months at two different temperatures.[11,21] There was no noticeable change in the crystallinity of itraconazole in the gelatin microcapsule during this period (data not shown). Furthermore, it was not sticky and formed few agglomerations over the six months of storage. The drug content decreased by less than 3% even at 40°C (data not shown). Thus, the itraconazole-loaded gelatin microcapsule was stable for at least six months.

Figure 8 shows the mean plasma plasma concentration–time profiles of itraconazole after oral administration of the commercial product at a dose of 10 mg/kg itraconazole, and the gelatin microcapsule at a dose of 5 or 10 mg/kg itraconazole in rats. At the same dose of 10 mg/kg, the gelatin microcapsule gave higher plasma concentrations than the commercial product. In particular, the plasma concentrations of drug from the gelatin microcapsule, from 3 h to 8 h, were significantly higher than those from the commercial product ($P < 0.05$). Our results suggest that the higher initial plasma concentrations of itraconazole in the gelatin microcapsule were due to the faster initial dissolution of the drug from the gelatin microcapsule in rats.[11,16] However, the plasma concentrations of itraconazole in the gelatin microcapsule at the dose of 5 mg/kg were no different from those in the commercial product at the dose of 10 mg/kg.

The corresponding pharmacokinetic parameters are listed in Table 2. At the same dose of 10 mg/kg, the gelatin microcapsule gave significantly higher AUC and C_{max} than the commercial product ($P < 0.05$). However, the T_{max}, K_{el} and t½ values of itraconazole from the gelatin microcapsule did not significantly differ to those from the commercial product.

Interestingly, there were no significant differences in the AUC, C_{max} and T_{max} values of itraconazole between the gelatin microcapsule at a dose of 5 mg/kg and the commercial product at a dose of 10 mg/kg in rats. Our results suggest that the gelatin microcapsule at a dose of 5 mg/kg might be bioequivalent to the commercial product at a dose of 10 mg/kg in rats. Thus, it could deliver itraconazole in a pattern that allows fast absorption in the initial phase, leading to absorption that is bioequivalent to that of the commercial product.

Discussion

After drying the gelatin that was dissolved in the ethanol–water cosolvent on a rotary evaporator, the ethanol and water evaporated simultaneously, and the gelatin was eventually dried. However, microcapsules containing ethanol in the gelatin shells were produced by spray-drying. By spraying the gelatin dissolved in an ethanol–water mixture through a fluid pressure nozzle into the drying chamber at an appropriate temperature, methylene chloride, ethanol and water were initially evaporated within the chamber of the spray dryer at the same time. However, as the atomized liquid droplets came into contact with the hot dry air for a little longer, the concentration of gelatin began to increase near the surface of the liquid droplets and the water content on the surface of the droplets decreased very rapidly as the water and ethanol evaporated. As a result, a concentrated gelatin layer was formed on the surface of the droplets. Water passed continuously through the concentrated gelatin layer, but very little ethanol passed through due to the extremely low diffusion coefficient of ethanol in the concentrated gelatin layer. Thus, the concentrated gelatin acted as a semipermeable membrane, permitting continuous water loss

Table 2 Pharmacokinetic parameters of itraconazole

Parameter	Commercial product (10 mg/kg)	Gelatin microcapsule (10 mg/kg)	Gelatin microcapsule (5 mg/kg)
AUC (h · μg/ml)	3.11 ± 1.72	5.95 ± 2.91*	3.49 ± 1.48
T_{max} (h)	5.86 ± 2.97	5.00 ± 2.14	5.60 ± 2.51
C_{max} (ng/ml)	163.12 ± 60.19	410.83 ± 147.14*	172.61 ± 89.93
K_{el} ($h^{(-1)}$)	0.04 ± 0.02	0.05 ± 0.04	0.04 ± 0.01
t½ (h)	21.15 ± 10.07	19.02 ± 11.19	21.86 ± 11.31
Ka (h^{-1})	0.74 ± 0.23	0.86 ± 0.35	0.79 ± 0.34

The gelatin microcapsule was composed of itraconazole/gelatin/citric acid at a weight ratio of 1 : 3 : 0.3. Each value represents the mean ± SD, $n = 8$. *$P < 0.05$ compared with the commercial product.

by diffusion but effectively retaining the ethanol. Finally, the gelatin was solidified and the ethanol was trapped inside the gelatin shell, leading to the production of the gelatin microcapsule. This improves the solubility and bioavailability of poorly water-soluble drugs.[11,13,28] However, when the gelatin microcapsules are stored for a long period of time, ethanol leaks out from the gelatin shell and the microcapsules become attached to each other, resulting in agglomeration. From the industrial viewpoint, this makes it impossible to develop a commercial product, since it is physically unstable.

In this study, gelatin, citric acid and itraconazole dissolved in a methylene chloride–ethanol–water cosolvent were dried on a spray dryer, the methylene chloride and water were evaporated, and microcapsules containing ethanol in the gelatin shells were produced. In addition, itraconazole and citric acid were dissolved in ethanol in the inner hole of the microcapsule. However, during spray-drying at the relatively high inlet temperature of 130°C, ethanol evaporated along with the other solvents, and microcapsules with an inner hole, without ethanol but containing itraconazole and citric acid, were produced. Unlike conventional microcapsules and solid dispersion, microcapsules with an inner hole containing the drug could only be produced with polymers such as gelatin, dextrin and polyvinyl alcohol using spray-drying.[11,16,28] At the weight ratio for itraconazole/gelatin/citric acid of 1 : 3 : 0.3 the drug in the gelatin microcapsule was present in an amorphous state.[26] During preparation of the itraconazole-loaded gelatin microcapsule, the drug was dissolved in the solvents and changed to an amorphous form as it would during conventional solvent evaporation. However, like conventional microcapsule and solid dispersion, the drug chiefly existed in the inner hole of the gelatin microcapsule. In other words, it was dissolved in ethanol in the inner cavity formed during the spray-drying procedure and remained in the inner cavity after evaporation of the ethanol.

This gelatin microcapsule gave a maximum drug solubility of about 700 μg/ml and dissolution of the drug was about 10-fold higher than that of the commercial product. The enhanced solubility and dissolution of the drug was due to the change from the crystalline form to an amorphous state,[19,28] the reduced particle size[30,31] and the effect of the acidic microenvironment on itraconazole.[25] The microcapsules were not sticky and formed few agglomerations after preparation. Furthermore, unlike previous gelatin microcapsules, they could be a practical commercial product, because they were physically and chemically stable for at least six months.[11,21] A tablet or hard capsule form could also be developed by tableting or filling with other ingredients such as lactose and microcrystalline. At the same dose, the gelatin microcapsule had a significantly higher AUC and C_{max} than the commercial product ($P < 0.05$). The enhanced oral bioavailability of the drug in the gelatin microcapsule was due to faster absorption, following the faster initial dissolution of itraconazole in the gelatin microcapsule.[3,4,11,32]

Conclusions

It was concluded that the itraconazole-loaded gelatin microcapsule gave a maximum itraconazole solubility of about 700 μg/ml at a weight ratio for itraconazole/gelatin/citric acid of 1 : 3 : 0.3. At the same dose the gelatin microcapsule enhanced the oral bioavailability of itraconazole compared with the commercial product, and at half dose it was bioequivalent to the commercial product in rats. Thus, it could be recommended for delivering itraconazole in a pattern that allows fast absorption in the initial phase, leading to absorption that is bioequivalent to that of the commercial product.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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