Drug Development and Industrial Pharmacy, 31:747–756, 2005
Copyright © 2005 Taylor & Francis Inc.
ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500216220

Taylor & Francis
Taylor & Francis Group

The Physicochemical Characteristics of Freeze-Dried Scutellarin-Cyclodextrin Tetracomponent Complexes

Feng Cao, Jianxin Guo, and Qineng Ping
Department of Pharmaceutics, China Pharmaceutical University, Nanjing, P.R. China

ABSTRACT In an effort to improve the solubility of the insoluble drug scutellarin, a novel complexation of scutellarin with β-cyclodextrin (β-CD) was studied. Tetracomponent freeze-dried complex was prepared with scutellarin, β-CD, Hydroxypropyl Methylcellulose (HPMC), and triethanolamine. To confirm complex formation, complex was characterized by Fourier transform infrared spectroscopy (FT-IR), powder X-ray diffraction, and differential scanning calorimetry (DSC). Phase-solubility analysis suggested the soluble complexes having 1:1 stoichiometry. The β-CD solubilization of scutellarin could be improved significantly by combining water-soluble polymer and pH adjuster. Comparing the binary, ternary solid systems with tetrary systems, tetracomponent freeze-dried complex showed the best effect of solubilization. A maximal solubility of scutellarin (23.65 mg/ml) was achieved with tetracomponent freeze-dried complex, up to 148-fold increase over scutellarin solubility in water, and the solubility of scutellarin is 15.35 ug/ml (up to 6-fold) in simulated gastric fluid.

KEYWORDS Scutellarin, β-cyclodextrin, Tetracomponent complexes, Fourier transform infrared spectroscopy, Powder X-ray diffraction, Differential scanning calorimetry, Phase solubility, Solubility

INTRODUCTION

Scutellarin is the major flavonoid component of traditional Chinese medicine *Erigeron breviscapus*. It has been proven to be effective in dilating blood vessels, improving homodynamics, decreasing the viscosity of blood, reducing the blood platelet count, and preventing platelet conglomeration (Chen & He, 1998; Liu et al., 2003a; Xu & Li, 1995). The structure of scutellarin is 4′, 5, 6-trihydroxyflavone-7-glucuronide (Fig. 1). Despite its prominent advantage in therapy, scutellarin is sparingly soluble in water. The solubility of scutellarin in water was determined to be 0.16 mg/ml. This poor aqueous solubility of the drug may give rise to poor oral absorption. In order

Address correspondence to Qineng Ping, Department of Pharmaceutics, China Pharmaceutical University, No. 24 Tong Jia Xiang, Nanjing 210009, P.R. China; E-mail: pingqn@cpu.edu.cn

Order reprints of this article at www.copyright.rightslink.com

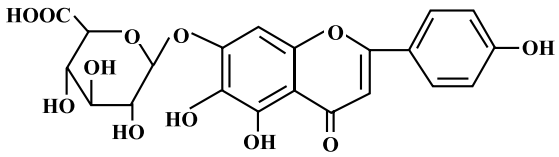

FIGURE 1 Structure of Scutellarin.

to increase the solubility of scutellarin, a novel complexation of scutellarin with β-cyclodextrin (β-CD) was developed and characterized in this study.

Cyclodextrins (CDs) are cyclic oligosaccharides used in pharmaceutical formulations to enhance solubility by means of the formation of inclusion complexes (Ficarra et al., 2000; Kim et al., 2004; Liu et al., 2003b). However, the efficiency of complexation and the solubility enhancement of a drug are usually rather limited. Therefore, relatively large amounts of cyclodextrin had to be added to complex small amounts of the drug. Nowadays, much attention has been attracted to adjust cyclodextrin system. The addition of a third component, such as alcohol, alkylsufates, amino acids, or water-soluble polymers, can enhance the effect of CDs (Loftsson et al., 1994), thus allowing reduction of the CD amount required for drug solubilization, and dramatically alter the apparent association constants and solubility (Davis & Brewster, 2004; Gladys et al., 2003; Mura et al., 2001; Valero et al., 2003; Van Stam et al., 1996; Yang & Bohne, 1996).

To overcome the solubility problem of the drug, a new method, presented in this work, was applied to explore the inclusion complex formation. The tetracomponent complex systems of β-CD, scutellarin water-soluble polymer, and pH adjuster was incorporated. The solid tetracomponent complex system was obtained by using the freeze-drying method and characterized by differential scanning calorimetry (DSC), powder X-ray diffractometry, infrared spectroscopy, and phase-solubility techniques.

MATERIALS AND METHODS

Materials

Scutellarin, 4′, 5, 6-trihydroxyflavone-7-glucuronide (purity >90%, lot number: HB 20031203) was purchased from Yunnan phytopharmaceutical CO., LTD (China). β-cyclodextrin (β-CD) was obtained from China National Medicine Group Shanghai Chemical Reagent Company (China). HPMC (K4M CR Premium grade) and K-25 Polyvinylpyrrolidone (PVP) were kindly presented by Colorcon Co. All other reagents and solvents used were of analytical grade.

Preparation of Solid Inclusion Complexes

The solid-state inclusion complexes of scutellarin with β-CD in 1:1 molar ratio were developed by the method reported and prepared by Amin Kreaz et al. (1999). Simply, scutellarin (0.1 g) was accurately weighed and dissolved in 2.5 ml (0.1 Mol/L) $NaHCO_3$ aqueous solution. Added were 0.2452 g β-CD and 1 ml 1.1% (w/v) HPMC or 1.1% (w/v) PVP. After β-CD had dissolved, 0.9 ml hydrochloric acid (0.1 Mol/L) and 0.030 ml triethanolamine (TEA) or 0.021 ml diethanolamine (DEA) were added to make up a brown solution with a final concentration of 0.5% (w/v) TEA or DEA and 0.25% (w/v) HPMC. These polymer concentrations were indicated as optimal in aqueous cyclodextrin solutions (Cappello et al., 2001). This solution was stirred on magnetic stirrer (500 rpm) at 40°C for 2 h. The solution was frozen at −80°C overnight and then subjected to lyophilization in a freeze-drier (ALPHA 1–2 freeze dry system, Marin Christ, Germany). The dried cake was passed through sieve (mesh #120) to get powder and stored in a dessicator until further evaluation. The binary solid systems with β-CD and ternary systems with β-CD and water-soluble polymer or pH adjuster were prepared similarly.

Preparation of Physical Mixtures

Physical mixtures (PM) were obtained by pulverizing in a glass mortar and carefully mixing accurately weighed amount of scutellarin, β-CD, HPMC, and TEA.

Differential Scanning Calorimetry (DSC)

A NETZSCH DSC 204 was used for recording the thermograms of scutellarin raw material, β-CD, freeze-dried inclusion complexes, as well as the physical

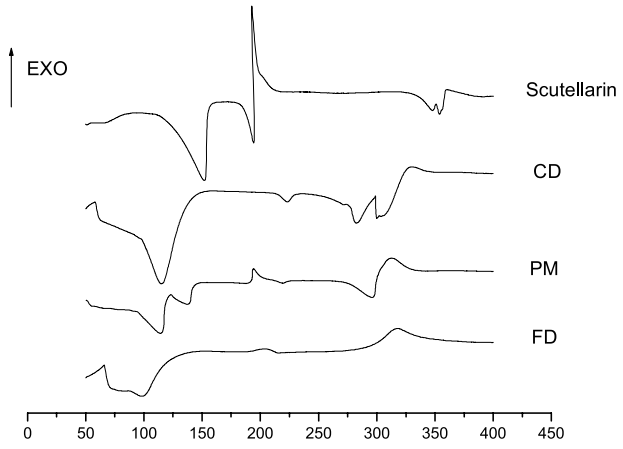

FIGURE 2 **DSC Thermograms of Scutellarin; β-CD (CD); Physical Mixture (PM); Tetracomponent Freeze-Dried Complex (FD).**

mixtures. Samples (2–8 mg) were accurately weighed and heated in closed aluminium crimped cells at a rate of 8°C min^{-1} from 40 to 400°C.

Fourier Transform Infrared (FT-IR) Spectroscopy

Fourier transform IR spectra were recorded on a Nicolet Impact 410 spectrophotometer for scutellarin, β-CD, physical mixtures and their freeze-dried complexes. The samples were prepared in KBr disks under a hydrostatic pressure of 5.2 T cm^{-2} for 3 min. The scanning range was 400–4000 cm^{-1} and the resolution was 1 cm^{-1}.

X-Ray Powder Diffractometry

X-ray powder diffraction patterns were recorded on a D/max2rc powder X-ray diffractometer (Japan) using Ni-filtered, Cu Kα radiation, a voltage of 40 kV, and a 25 mA current. The scanning rate employed was 1° min^{-1} over the 0–40° 2θ range. The X-ray diffraction (XRD) patterns of scutellarin raw material, β-CD, inclusion complexes, as well as the physical mixtures, were recorded.

Solubility Studies

Phase-Solubility Analysis

The phase-solubility experiment was performed by the reported method (Higuchi & Connors, 1965). The samples were prepared by adding 2 ml of distilled water to a series of 10 ml glass tubes containing successively increasing quantities of β-CD. Then an excess amount of scutellarin (20 mg) was added into each tube to maintain saturated conditions. The tubes were capped and rotated for 7 days in water bath kept at 25±1°C. Following equilibrium, each supernatant phase was removed, filtered, diluted, and assayed for the total dissolved scutellarin content by HPLC method. The same experiments were carried out with 2 ml, pH 3.0 or 8.0 phosphate buffer instead of distilled water. The phase-solubility diagrams were constructed by plotting the total dissolved scutellarin concentrations against the total β-CD concentrations. The binding constant ($K_{1:1}$) was calculated as the equation:

$$K_{1:1} = \text{Slope}/[So(1 - \text{Slope})]$$

The term "Slope" indicates the phase-solubility profile slope and "*So*" is the solubility of scutellarin in the absence of β-CD.

pH Uncorrected Solubility

The pH uncorrected solubility of scutellarin was determined in simulated gastric fluid without enzymes and in distilled water, respectively. Equilibrium solubility was measured in the dissolution medium. Samples were prepared in triplicate by adding 2 ml of test fluid and excess solid powder into 10 ml glass tubes. The tubes were capped and rotated in a constant temperature water bath at 37±1°C for 1 day. Following equilibrium, samples were filtered, and the filtrates were collected and assayed quantitatively for scutellarin by a HPLC method as following.

Analytical Methods

A high performance liquid chromatographic (HPLC) assay method was developed to determine the concentration of scutellarin. The HPLC system consisted of a pump (Model LC-10A, Shimadzu, Japan), a shim-pack CLC-ODS column (150 mm × 6 mm i.d., Shimadzu) maintained at 30°C, a UV detector (Model SPD-10A, Shimadzu) at 334 nm, and a data station (Model SCL-10A, Shimadzu). The composition of the mobile phase was methanol-water-phosphoric acid (50:50:0.5, V: V: V). The mobile phase was delivered at a flow rate of 1 ml/min. The

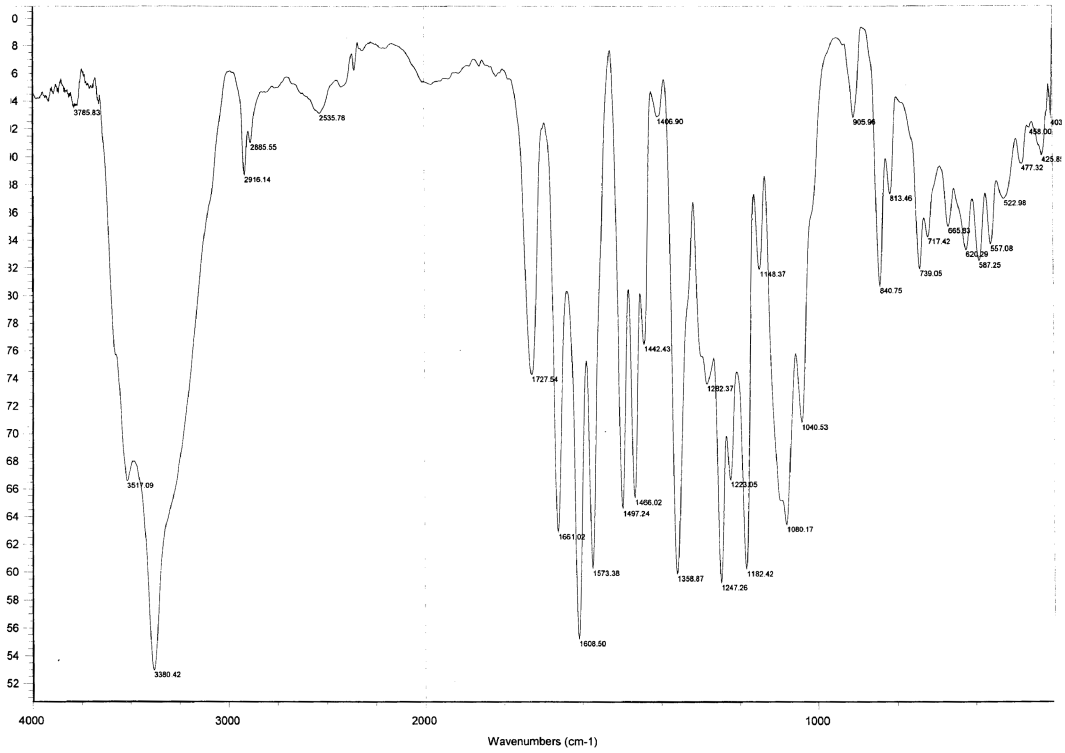

FIGURE 3 **The Infrared Spectrum of Scutellarin.**

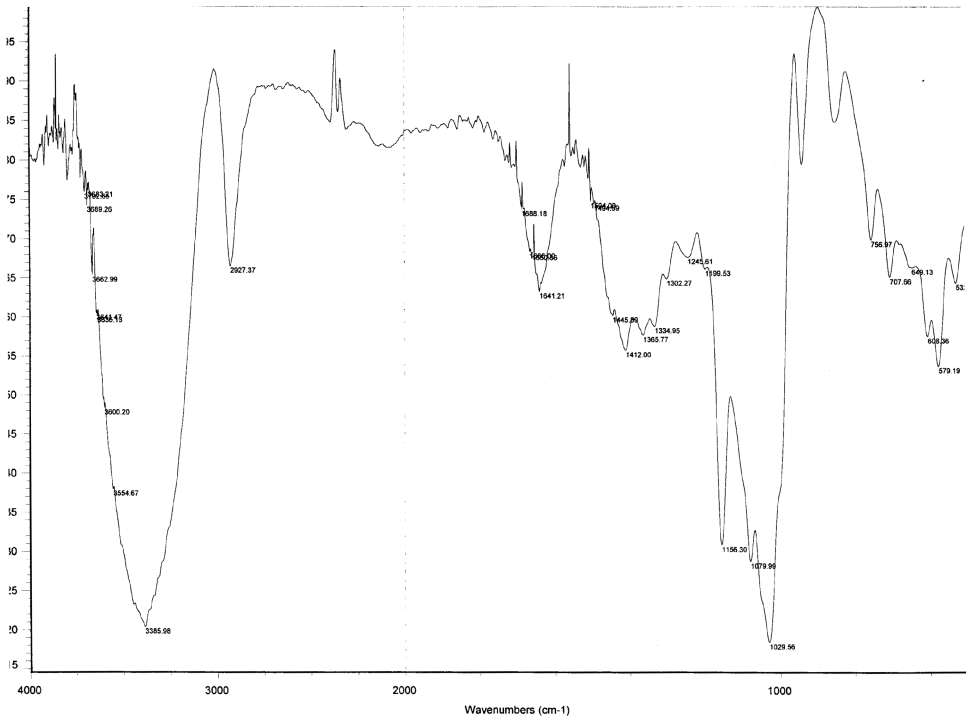

FIGURE 4 **The Infrared Spectrum of β-Cyclodextrin.**

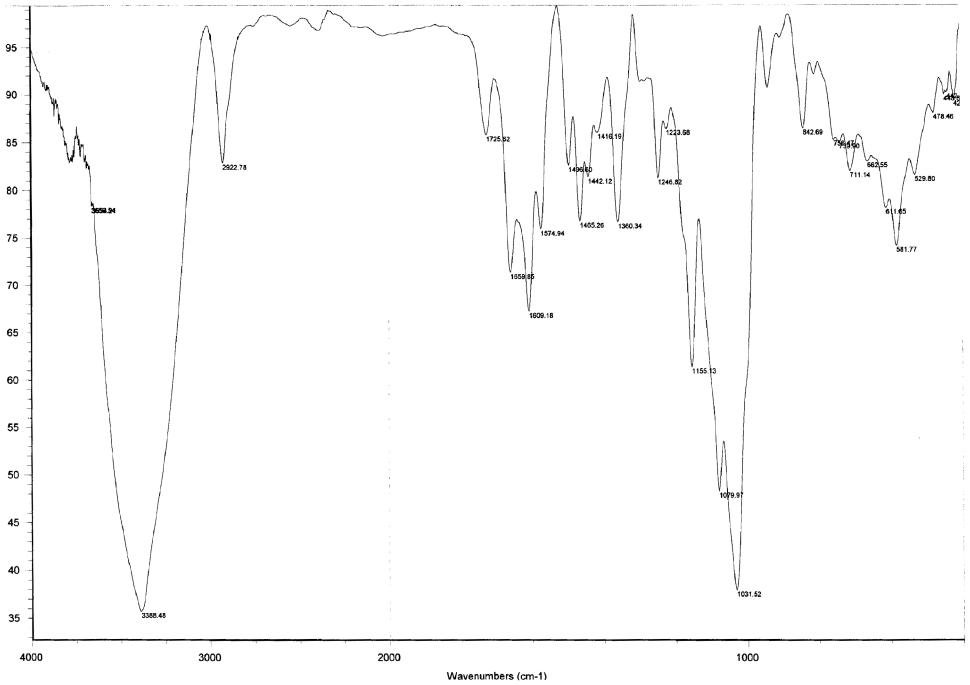

FIGURE 5 **The Infrared Spectrum of Physical Mixture.**

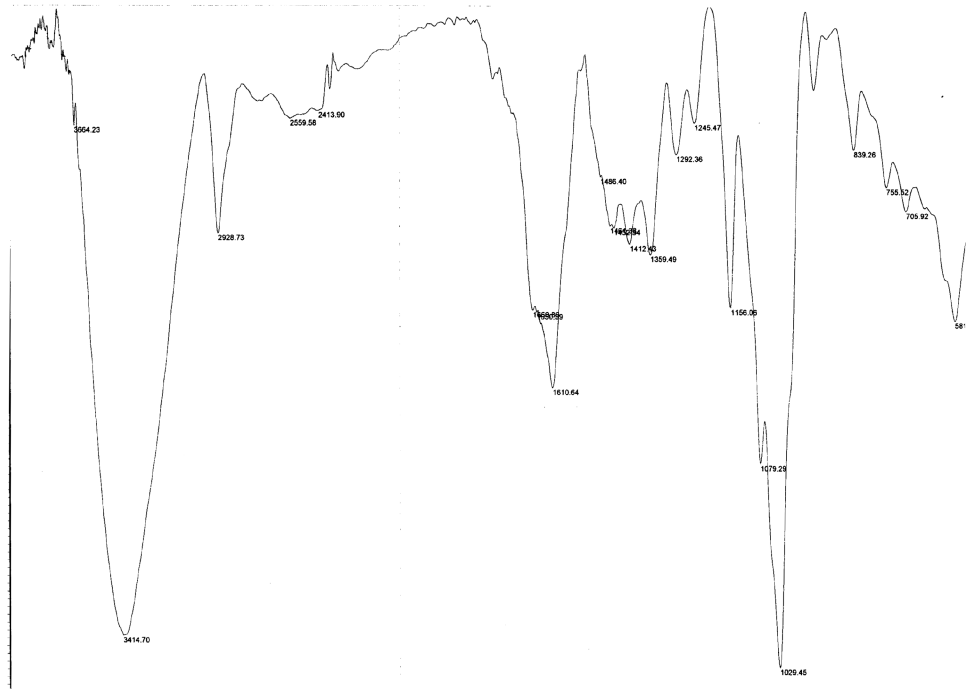

FIGURE 6 **The Infrared Spectrum of Tetracomponent Freeze-Dried Complex.**

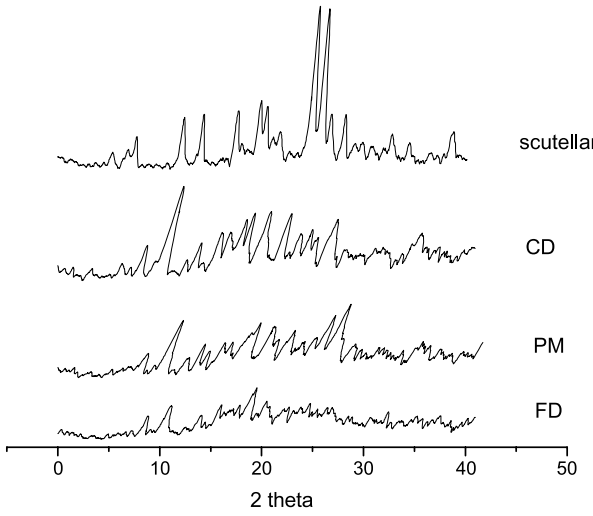

FIGURE 7 **The XRD Spectra of Scutellarin, β-CD (CD), Physical Mixture (PM), and Tetracomponent Freeze-Dried Complex (FD).**

injection volume was 20 μl and the relative retention time was found to be 11.0 min.

RESULTS AND DISCUSSION

Differential Scanning Calorimetry (DSC)

Figure 2 shows the DSC thermograms of scutellarin, β-CD, physical mixture, and the cyclodextrin complexes. The peak shift occurred in the large, broad endotherm at about 100–120°C (T_{peak} = 119.5), which was attributed to the liberation of crystal water from β-CD (14.5% as mass fraction). A phase transition and decomposition were observed at 223.3°C and the higher temperature, respectively. The DSC thermogram of scutellarin showed an endothermic melting peak at 189.7°C, and an exothermic peak assigned to the decomposition at approximately 192.5°C. HPMC in the physical mixture display an endotherm at 130.3°C, corresponding to moisture loss (Ford, 1999), but it disappeared in the tetracomponent complexes. This change was possibly attributed to the interaction between HPMC and β-CD complexes. The physical mixture showed the decomposing peak (T_{peak} = 194.2) assigned to scutellarin. However, this peak disappeared in the case of the solid tetracomponent complexes prepared by freeze-drying. These results can be explained on the basis of the interaction and complexion between the drug and β-CD.

Infrared Spectroscopy

Fourier transform infrared spectroscopy (FT-IR) has also been used to assess the interaction between β-CD and guest molecules in the solid state. Upon complexion, the peak band of the guest shifts in the absorption spectrum. However, some of the changes are very subtle requiring careful interpretation of the spectrum (Hedges, 1998).

Infrared spectra of scutellarin, β-CD, PM, and complex system, are presented in Figs. 3–6. Drug crystals show absorption band at 1727.54 cm^{-1} (C=O stretch); 3380 cm^{-1} (OH stretch); 1608.50, 1573.38, and 1497.24 (aromatic C=C stretch). The FT-IR spectra of tetracomponent complex were compared to the physical mixtures and pure drug. PM shows a characteristic carbonyl absorption band at 1725.62 cm^{-1} along with reduced intensity of the same band. In the case of freeze-dried tetracomponent complex, in particular, the bands at 1727.54, 1573.38, and 1497.24 cm^{-1} had been totally disappeared. This can be probably due to inclusion of scutellarin into the β-CD cavity even in the presence of TEA and HPMC. These changes may suggest that the phenyl ring and the carbonyl group of the drug were involved in the cyclodextrin-ring cavity. Changes in the characteristic bands of pure drug confirm the existence of the complex as a new compound with different spectroscopic bands (Ficarra, 2002).

As it is shown in Fig. 4, characteristic bands of β-CD were found at 3385.98 cm^{-1} (OH stretch), 2927.37 cm^{-1} (C–H aliphatic stretch), 1641.21 cm^{-1} (O–H bend H_2O), 1156.3 cm^{-1} (CO stretching glucosidic bond), 1079.99 cm^{-1} (CO stretching secondary OH), and 1029.56 cm^{-1} (CO stretching primary OH). The β-CD complex showed a broad peak at 1640 cm^{-1} when compared to the corresponding peak β-CD at about 1630–1660 cm^{-1}. The broadening of the 1640 cm^{-1} peak was attributed to a change in the hydrated bonds within β-CD. The changes in the water absorbance at 1640 cm^{-1} were found as another evidence of complex formation (Jambhekar et al., 2004).

The main absorbance band of HPMC was at 1045 cm^{-1} (C–O stretch), and several smaller peaks were found between 1200 and 1500 cm^{-1} (Weerd & Kazarian, 2004). It is inconvenient to study the interaction between HPMC and complex in detail

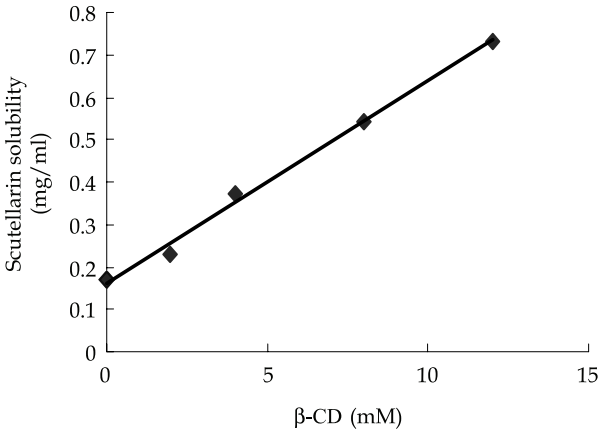

FIGURE 8 **Phase-Solubility Diagrams of the Binary System: β-CD in Water.**

because the absorbance bands of HPMC are overlapped by those of β-CD.

X-Ray Diffractometry

Figure 7 shows the X-ray diffraction patterns. In the X-ray diffractogram of scutellarin powder, sharp peaks at a diffraction angle of 2θ 19.08, 21.08, 21.72, 25.84, and 26.72° were present. It indicated that the drug was present as a crystalline material. Crystallinity peaks of β-CD were shown at a diffraction angle of 2θ 12.40, 18.90, 19.44, 20.82, 22.70, and 27.00°. The crystallinity peaks of drug and β-CD were still detectable in the respective physical mixtures. The diffractogram of HPMC in the PM showed a weak crystalline signal between angles of 17° to 22° (Wolf, 1997), which was largely superimposed by β-CD signals at 18.90, 19.44, 20.82, and 22.70°. An amorphous drug was thus produced by freeze-drying since it was impossible to

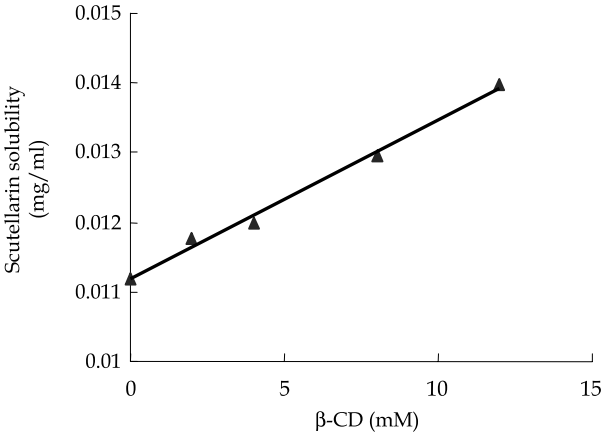

FIGURE 9 **Phase-Solubility Diagrams of the Binary System: β-CD in Buffer pH 3.0.**

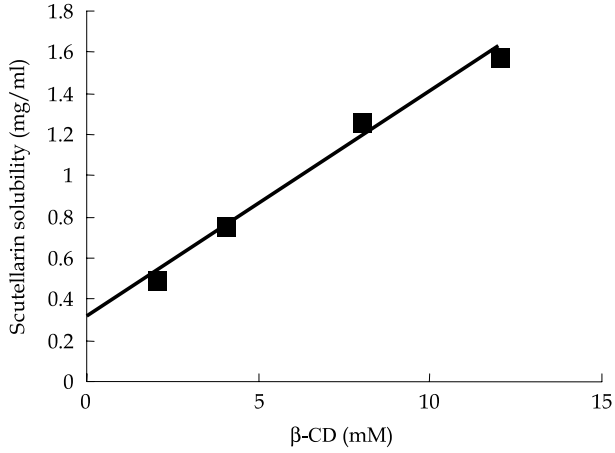

FIGURE 10 **Phase-Solubility Diagrams of the Binary System: β-CD in Buffer pH 8.0.**

distinguish the characteristic peaks of scutellarin from the X-ray diffraction patterns of tetracomponent systems. These results confirm that scutellarin is no longer present as a crystalline material and its β-CD solid complexes exist in an amorphous state.

Phase-Solubility Analysis

The phase-solubility diagrams of scutellarin with β-CD in water and in buffer solutions at pH 3.0 and pH 8.0 at 25°C are shown in Figs. 8–10. The diagrams show that the solubility increased proportionally to the β-CD concentration. The curves obtained were of A_L-type, which demonstrated that soluble complexes with 1:1 stoichiometry were formed according to Higuchi and Connors theory (Higuchi & Connors, 1965). Stability constants for the complexes calculated from the slope of the initial straight portion of the solubility diagrams were 22,32 M^{-1} at pH 3.0, 0.29 M-1 in water, and 0.38 M-1 at pH 8.0. From these values, a different interaction in the three media between the drug and CD could be deduced. The ionization of scutellarin increased with pH increase and, as a result, the interaction of scutellarin with β-CD was preferable at pH 3.0. However, despite the fact that much stronger drug-CD complexion was found with the unionized drug (Zia et al., 2001), the achieved total solubility significantly increased at pH 8.0 (Table 1) when the scutellarin was ionized.

According to these results, it was possible to obtain a higher overall solubility by using a combined approach of pH adjustment and complexion with β-CD. When the basic compound TEA or DEA was

TABLE 1 Data of the Phase-Solubility Curves of Scutellarin with β-CD at Different pH Values

Solvent	β-CD (mM)	Final pH	Solubility (mg/ml)	Type of curse	$K_{1:1}$ (M^{-1})
Water	12	4.6	0.73±0.05	A_L	0.29
Buffer pH 3.0	12	2.9	0.0139±0.0004	A_L	22.32
Buffer pH 8.0	12	7.9	1.58±0.10	A_L	0.38

added as a third component, a larger enhancement compared to binary complexes in the solubility of scutellarin was obtained.

pH Uncorrected Solubility

Scutellarin solubility was increased significantly in distilled water and simulated gastric fluid when complexes were formed within binary, ternary, or tetrary solid systems, as shown in Table 2.

A modest increase in solubility was achieved in water when complex was formed only with β-CD. However, the solubility of such a complex decreased in simulated gastric fluid. A greater increase in solubility was obtained in both media with four ternary solid systems, especially the systems with TEA or DEA. The results showed that TEA was always superior to DEA in increasing the water solubility of scutellarin.

With lower temperature (at 40°C for 2 h) in our work, ternary solid systems with polymer gained no advantage over binary systems in increasing water-solubility. According to the reports (Cappello et al., 2001; Loftsson & Jarvinen, 1999), water-soluble polymers at low concentrations, when activated by heating (at 120°C for 20 min), may enhance drug solubilization induced by CDs. It is worth noting that these heating conditions are usually employed to sterilize pharmaceutical preparations, however it is not expected for the unstable drug scutellarin. On the other hand, comparing with binary systems, ternary solid systems with HPMC and PVP modestly increased the solubility in simulated gastric fluid. According to Loftsson and Jarvinen (1999), these polymers may interact with drug-CD complexes in a similar way as with micelles, forming drug–CD–polymer aggregates or a co-complex, which accounts for the higher drug solubility.

Comparing the solubility of scutellarin in simulated gastric fluid with that in distilled water, it is clearly observed that the solid systems with HPMC are better than that with PVP for increasing the solubility of scutellarin in water. On the contrary, the solid systems with PVP are better than that with HPMC for improving the solubility of scutellarin in simulated gastric fluid. The ionization of N atoms of PVP in simulated gastric fluid is beneficial to increase the solubility. Taken together, these data suggest that it is helpful to use the solid systems with PVP to increase solubility of a drug that is mainly absorbed in the stomach. Otherwise, using the solid systems with HPMC or other water-soluble polymers, which can not ionize, may be a better choice.

TABLE 2 Scutellarin (D), Complexes and Their Solubility in Distilled Water or in Simulated Gastric Fluid and the Fold of Solubilization (S/S_1, S'/S_2)

Sample	Solubility in distilled water (S/S_1±SD, mg/ml)[a]		Solubility in simulated gastric fluid (S'±SD, S'/S_2 μg/ml)[b]	
D	0.16±0.01		2.58±0.02	
D+β-CD	9.46±0.02	59.13	1.83±0.05	0.71
D+β-CD+TEA	16.32±0.21	102.19	5.56±0.06	2.16
D+β-CD+DEA	14.35±0.10	89.69	7.26±0.10	2.81
D+β-CD+HPMC	5.53±0.04	34.56	3.68±0.08	1.43
D+β-CD+PVP	4.42±0.10	27.63	3.76±0.07	1.46
D+β-CD+PVP+TEA	20.69±0.20	129.31	26.26±0.22	10.18
D+β-CD+HPMC+DEA	16.95±0.25	105.94	14.04±0.20	5.44
D+β-CD+HPMC+TEA	23.65±0.23	147.81	15.35±0.28	5.95

[a]The fold of solubilization in distilled water.
[b]The fold of solubilization in simulated gastric fluid.

For a tetrary solid system with the presence of 0.5% TEA and 0.25% (w/v) HPMC, the solubility of scutellarin was 23.65 mg/ml in water (147.81 times) and 15.35 ug/ml in simulated gastric fluid. Cyclodextrin (CD), HPMC, and TEA were not only simple additives for the solubilizing scutellarin, the synergistic effect was achieved when they were used together. On the basis of the experimental FT-IR data, we suggest that scutellarin is partially immersed in the β-CD's cavity with a preferential inclusion of the phenyl ring of the drug. Considering that the acidic center of scutellarin is indeed located outside the cavity, it is postulated that in the presence of TEA, the enhancement in solubility may be contributed to a concerted mechanism that involves the complexion of the hydrophobic part of the drug into the β-CD, and the interaction of the counter ions with the hydrogen-bond system of the CD, analogously to what has been reported with basic drugs in the presence of hydroxyl acids (Redenti et al., 2000). In the tetrary system, HPMC may coat the other ternary complex and interacts with them by means of multiple intermolecular hydrogen bonds (Valero et al., 2003).

CONCLUSIONS

The aqueous solubility of β-CD in pure water is only 18.6 mg/ml. However, its solubility in aqueous drug formulations increases significantly upon formation of inclusion complexes with drugs or water-soluble polymers. The polymers not only solubilize β-CD and its complexes, but also enhance the formation of complexes between drugs and β-CD. Thus, it should be possible to form aqueous drug formulations containing a water-soluble polymer. Then, addition of a water-soluble polymer could also enhance the efficiency of the complexion. Finally, pH adjustment is also important for the ionizing drug systems.

Phase solubility study reflects the formation of 1:1 stoichiometric complexes between scutellarin and β-CD. The apparent stability constants were influenced by pH variations. The β-CD solubilization of scutellarin in aqueous solutions can be improved by addition of the basic substance TEA or DEA to the complexion medium.

The use of DSC, XRD, and FT-IR enabled us to thoroughly elucidate the solid-state interactions of the tetrary systems and suggested the formation of new solid phases. The amorphous state of scutellarin demonstrates the complex formation among scutellarin, β-CD, TEA, and water-soluble polymers.

When β-CD was combined with HPMC and TEA to form tetrary freeze-dried systems, the aqueous solubility of scutellarin has been improved substantially (up to 148-fold) in distilled water and 15-fold in simulated gastric fluid. The remarkable increase in solubility may lead to important modifications on the physicochemical and biological properties of the guest molecule, such as the improvement on bioavailability, which might eventually have relevant pharmaceutical potential.

ACKNOWLEDGMENT

This research work was granted by the National Natural Science Foundation of China with a key project number of 30300440.

REFERENCES

Amin Kreaz, R. M., Abu-Eida, E. Y., & Carmignani Kata, M. (1999). Freeze-dried complexes of furosemide with β-cyclodextrin derivatives. *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, *34*, 39–48.

Cappello, B. C., Iervolino, M., La Rotonda, M. I., & Fabrizio Saettone, M. (2001). Solubilization of tropicamide by hydroxypropyl-β-cyclodextrin and water-soluble polymers: in vitro:in vivo studies. *International Journal of Pharmaceutics*, *213*, 75–81.

Chen, X. X., & He, B. (1998). Effects of breviscapine on the changes in antioxidant enzyme activity induced by cerebral ischemia reperfusion in rats. *Journal of Chinese Pharmaceutical Sciences*, *7*, 91–93.

Davis, M. E., & Brewster, M. E. (2004). Cyclodextrin-based pharmaceutics: past, present and future. *Nature Reviews, Drug Discovery*, *3*, 1023–1035.

Ficarra, P. (2002). Study of flavonoids/β-cyclodextrins inclusion complexes by NMR, FT-IR, DSC, x-ray investigation. *Journal of Pharmaceutical and Biomedical Analysis*, *29*, 1005–1014.

Ficarra, R., Ficarra, P., Di Bella, M. R., Raneri, D., Tommasini, S., Calabró, M. L., Villari, A., & Coppolino, S. (2000). Study of the inclusion complex of atenolol with β-cyclodextrins. *Journal of Pharmaceutical and Biomedical Analysis*, *23*, 231–236.

Ford, J. L. (1999). Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: powders, gels, and matrix tablets. *International Journal of Pharmaceutics*, *179*, 209–228.

Gladys, G., Claudia, G., & Marcela, L. (2003). The effect of pH and triethanolamine on sulfisoxazole complexation with hydroxypropyl-β-cyclodextrin. *European Journal of Pharmaceutical Sciences*, *20*, 285–293.

Hedges, A. R. (1998). Industrial applications of cyclodextrins. *Chemical Reviews*, *98*, 2035–2044.

Higuchi, T., & Connors, K. A. (1965). Phase-solubility techniques. *Advances in Analytical Chemistry and Instrumentation*, *4*, 117–212.

Jambhekar, S., Casella, R., & Maher, T. (2004). The physicochemical characteristics and bioavailability of indomethacin from

β-cyclodextrin, hydroxyethyl-β-cyclodextrin, and hydroxypropyl-β-cyclodextrin complexes. *International Journal of Pharmaceutics*, *270*, 149–166.

Kim, J. H., Lee, S. K., Ki, M. H., Choi, W. K., Ahn, S. K., Shin, H. J., & Hong, C. (2004). Development of parenteral formulation for a novel angiogenesis inhibitor, CKD-732, through complexation with hydroxypropyl-β-cyclodextrin. *International Journal of Pharmaceutics*, *272*, 79–89.

Liu, H., Yang, X. L., Wang, Y., Tang, X. Q., Jiang, D. Y., & Xu, H. B. (2003a). Protective effects of scutellarin on superoxide-induced oxidative stress in rat cortical synaptosomes. *Acta Pharmacologica Sinica*, *24*, 1113–1117.

Liu, X., Liu, H. S., Thenmozhiyal, J. C., Chan, S. Y., & Ho, P. C. (2003b). Inclusion of acitretin into cyclodextrins: phase solubility, photostability, and physicochemical characterization. *Journal of Pharmaceutical Sciences*, *92*, 2449–2457.

Loftsson, T., & Jarvinen, T. (1999). Cyclodextrins in ophthalmic drug delivery. *Advanced Drug Delivery Reviews*, *36*, 59–79.

Loftsson, T., Fridriksdóttir, H., Sigurdardóttir, A. M., & Ueda, H. (1994). The effect of water-soluble polymers on drug-cyclodextrin complexation. *International Journal of Pharmaceutics*, *110*, 169–177.

Mura, P., Teresa Faucci, M., & Piero Bettinetti, G. (2001). The influence of polyvinylpyrrolidone on naproxen complexation with hydroxypropyl-β-cyclodextrin. *European Journal of Pharmaceutical Sciences*, *13*, 187–194.

Redenti, E., Szente, L., & Szejtli, J. (2000). Drug/cyclodextrin/hydroxy acid multicomponent systems: properties and pharmaceutical applications. *Journal of Pharmaceutical Sciences*, *89*, 1–8.

Valero, M., Pérez-Revuelta, B. I., & Rodríguez, L. J. (2003). Effect of PVP K-25 on the formation of the naproxen: β-cyclodextrin complex. *International Journal of Pharmaceutics*, *253*, 97–110.

Van Stam, J., De Feyter, S., De Schryver, F. C., & Evans, C. H. (1996). 2-Naphthol complexation by β-cyclodextrin: influence of added short linear alcohols. *Journal of Physical Chemistry*, *100*, 1995–1996.

Weerd, J., & Kazarian, S. J. (2004). Combined approach of FT-IR imaging and conventional dissolution tests applied to drug release. *Journal of Controlled Release*, *98*, 295–305.

Wolf, B. (1997). Bead cellulose products with film formers and solubilizers for controlled drug release. *International Journal of Pharmaceutics*, *156*, 97–107.

Xu, Q. Y., & Li, X. X. (1995). Influence of DZXX injection on blood viscosity in patients with high blood viscosity. *New Drugs and Clinical Remedies*, *14*, 233.

Yang, H., & Bohne, C. (1996). Effect of aminoacid coinclusion on the complexation of pyrene with β-cyclodextrin. *Journal of Physical Chemistry*, *100*, 14533–14539.

Zia, V., Rajewski, R. A., & Stella, V. J. (2001). Effect of cyclodextrin charge on complexation of neutral and charged substrates: comparison of $(SBE)_{7M}$-β-CD to HP-β-CD. *Pharmaceutical Research*, *18*, 667–673.

Copyright of Drug Development & Industrial Pharmacy is the property of Marcel Dekker Inc.. The copyright in an individual article may be maintained by the author in certain cases. Content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.