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Preparation and characterization of baicalin-poly -vinylpyrrolidone coprecipitate

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ABSTRACT

Baicalin-polyvinylpyrrolidone (PVP) coprecipitate was prepared by the solvent method of solid dispersion technology to improve the dissolution rate of baicalin. The coprecipitate was characterized using differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared spectrometry (IR) and dissolution testing. Furthermore, AFM·IPC-208B high-resolution atomic force microscopy (AFM) was utilized to characterize the molecular morphology of baicalin within its carrier and the interaction between baicalin and its carrier. The results of DSC and XRD indicated that baicalin resided in PVP polymers in an amorphous or molecular phase, dissolution test results demonstrated that the dissolution rate of the coprecipitate was 21.4 times that of the active pharmaceutical ingredient (API). The results of IR indicated the possibility of the formation of intermolecular hydrogen bonds. The AFM·IPC-208B findings revealed that baicalin was dispersed in PVP polymers with a molecular size of 2 nm and either wrapped or surrounded by approximately 0.4 nm of a five-membered ring of PVP arranged along the carbon chain sequentially. An intermolecular hydrogen bond was formed between the 4-OH of the glucuronide of baicalin and the O of the carbonyl group from PVP in addition to the formation of intramolecular hydrogen bonds within baicalin.

1. Introduction

Baicalin, a single active ingredient extracted from the dried roots of *Scutellaria baicalensis* of the Labiate family, is a flavonoid used to treat acute icteric, acute non-icteric and chronic hepatitis. Current studies have shown that baicalin is able to inhibit multiple cancer cells from growing or multiplying (Ikemoto et al., 2000; Shieh et al., 2000; Chan et al., 2000) and protect the liver from drug-induced injuries (Jang et al., 2003; Wan et al., 2008; Park et al., 2008). Poor solubility of the currently marketed oral preparations including tablets and capsules has resulted in poor dissolution and bioavailability. The absolute bioavailability of baicalin has been found to be only $2.2 \pm 0.2\%$ in rats after oral administration (Xing et al., 2005). Although a baicalin–phospholipid complex (Wu et al., 1999) and a dispersible tablet of baicalin (Liu et al., 2009) have been prepared with almost a twofold increase in bioavailability and an over twofold improvement in dissolution, other formulations using different technologies should be prepared for further improvement.

Solid dispersion technology is a new technology used to improve dissolution rates of insoluble drugs within solid dispersions into carriers in microcrystallite, amorphous and molecular phases that are called simple eutectic mixtures, coprecipitates (also called vitreous state solid solutions) and solid solutions, respectively. Drug dispersity in a given carrier directly affects its dissolution rate and places molecular, amorphous and microcrystalline phases in a descending order of sequence in terms of dissolution rate (Chiou and Riegelman, 1971). In addition, different carriers also have a direct impact on drug dispersion morphology. The high molecular weight compound polyvinylpyrrolidone (PVP) has a strong hydrophilicity and is able to form hydrogen bonds or complex compounds with drugs due to the large number of repetitive lactam groups embedded in its chemical structure, shown in Fig. 1 (Leuner and Dressman, 2000; Sharma and Joshi, 2007). It is extensively used as a drug carrying substance because of the remarkable increase in dissolution rate (Kanaze et al., 2006; Karavas et al., 2006; Patel and Patel, 2007; Choudhary et al., 2009) and stability (Mooter et al., 2001; Gupta and Bansal, 2005; Thybo et al., 2007) of drugs when they are dispersed in an amorphous or molecular phase after the formation of the coprecipitate. Polyvinylpyrrolidone is widely used to prepare coprecipitates with drugs using the solvent method and is especially suitable for drugs with high melting points or for drugs that can be easy oxidization because of their high melting point and

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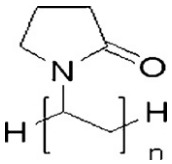

Fig. 1. Molecular structure of PVP.

favorable solubility. It can be noted in the baicalin structure shown in Fig. 2 that both flavones and glucuronide can form intramolecular hydrogen bonds that may be responsible for the poor solubility and high melting points (223–225 °C of baicalin molecules. In addition, the 2-OH, 3-OH or 4-OH of glucuronide in baicalin molecules may serve as proton donors to form hydrogen bonds with the O of the carbonyl group from PVP. In light of the above structural analysis of baicalin and PVP, the solvent method of solid dispersion technology was employed in this study to disperse baicalin extensively into PVP and to obtain a baicalin-PVP coprecipitate; this method was employed to increase the dissolution rate and stability of baicalin in its carrier. Because the interaction of hydrogen bonds can help drugs maintain stability within the carrier during storage (Karavas et al., 2005; Papageorgiou et al., 2009), understanding the molecular morphology and interaction of baicalin with the carrier is important. However, no study has been reported on the molecular morphology of baicalin. Therefore, the method used for phase identification and characterization of drugs in a baicalin-PVP coprecipitate becomes critical in determining whether the coprecipitate has been formed.

In the present study, baicalin-PVP coprecipitate was prepared using the solvent method of solid dispersion technology. The AFM·IPC-208B technique was used to characterize the molecular morphology of baicalin in the coprecipitate and the interaction between the drug and the carrier at the molecular level.

2. Materials and methods

2.1. Materials

Baicalin was obtained from Dongfangyuan Biological Technology Co Ltd. (Mianyang, China). Polyvinylpyrrolidone K30 was purchased from BASF (Germany). Unless otherwise stated, all other materials were of analytical grade.

2.2. Methods

2.2.1. Preparation of baicalin-PVP coprecipitate

Baicalin-PVP coprecipitate was prepared by the solvent method as follows. Baicalin, 700 mg, was dissolved in 100 mL absolute ethanol by ultrasonication at 72 ± 2 °C water and the appropriate amount of PVP was added according to a 1:3 weight ratio of baicalin to PVP. The resulting solution was mixed with gentle shaking for 30 min at room temperature and the solvent was evaporated under reduced pressure at 65 °C. The resulting residue was dried under vacuum in a desiccator for at least 24 h, then ground in a mortar and sieved through a # 80 sieve.

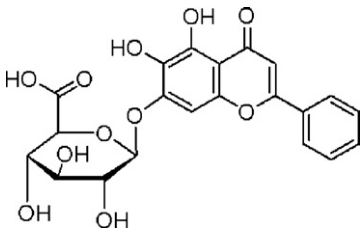

Fig. 2. Molecular structure of baicalin.

2.2.2. Preparation of the baicalin-PVP physical mixture

The baicalin-PVP physical mixture was prepared in a 1:3 weight ratio of baicalin: PVP by thoroughly blending baicalin and PVP in a mortar until a homogeneous mixture was obtained. The resulting mixture was sieved through a # 80 sieve.

2.2.3. Preparation of capsules containing the coprecipitate and physical mixture

A baicalin-PVP coprecipitate capsule and a physical mixture capsule containing 0.125 g baicalin, half the weight of a baicalin in a capsule sold on the market, were prepared. Baicalin-PVP coprecipitate, 0.500 g, and physical mixture were transferred into number 0 gastric capsules. A baicalin active pharmaceutical ingredient (API) capsule with 0.250 g API was prepared as mentioned above as a control.

2.2.4. Differential scanning calorimetry (DSC) analysis

Thermal characteristics of the baicalin, PVP, physical mixture and coprecipitate were determined using a STA449-C instrument (NETZSCH, Germany) under a 10 mL/min stream of nitrogen purge. Three to eight milligrams of the samples were heated from room temperature to 300 °C at rate of 10 °C/min in an open aluminum pan, and TA4 Analysis software was used for analysis.

2.2.5. X-ray powder diffraction (XRD) analysis

The physical state of the baicalin, PVP, physical mixture and coprecipitate was evaluated by XRD with a D/MAX 2500-PC X-ray powder diffractometer (Rigaku, Japan). A Cu-Kα source operation (40 kV, 150 m A) was employed. The diffraction patterns were recorded over a 2θ angular range of 3–60° with a step size of 0.4° in 2θ and a 6 s count per step at room temperature.

2.2.6. Dissolution test

Dissolution testing of the coprecipitate, physical mixture and baicalin API capsules was performed according to the Chinese Pharmacopoeia (rotating basket). The samples were sequentially added into two 500 mL solutions and one 1000 mL solution of 0.1 mol L^{-1} HCl and stirred at 100 rpm at 37 ± 0.5 °C. A 5 mL aliquot was withdrawn from the dissolution medium at 10, 20, 30, 40, 50 and 60 min, while equal amounts of fresh dissolution media was added. The aliquots were filtered with a 0.45 μm hydrophilic filter disk, and the filtrate was mixed with the same volume of methanol as the final testing sample. The concentration of baicalin was determined by measuring its absorbance at 278 nm with a UV-3105 spectrophotometer (SHIMADZU, Japan). The PVP and capsule shell used did not interfere with the sample absorption at the wavelength used. Each data was obtained in three independent experiments performed in duplicate.

2.2.7. Infrared spectrometry (IR) analysis

The IR spectra of the baicalin, PVP, physical mixture and coprecipitate were determined using a Spectrum One spectrophotometer (Perkin-Elmer, USA). Approximately 2 mg of the samples were mixed with an equal weight of dried KBr, and the mixture was compressed into a disc. The resulting disc was scanned 32× from 4000–400 cm^{-1}.

2.2.8. AFM·IPC-208B analysis

The AFM·IPC-208B image of the baicalin-PVP coprecipitate was collected by employing AFM·IPC-208B (Chongqing University, China). Baicalin-PVP coprecipitate, 0.1 g, was dissolved in 10 mL ethanol. Approximately 0.05 mL solution was dropped on the gold surface, dried, and tested. The AFM·IPC-208B measurement was

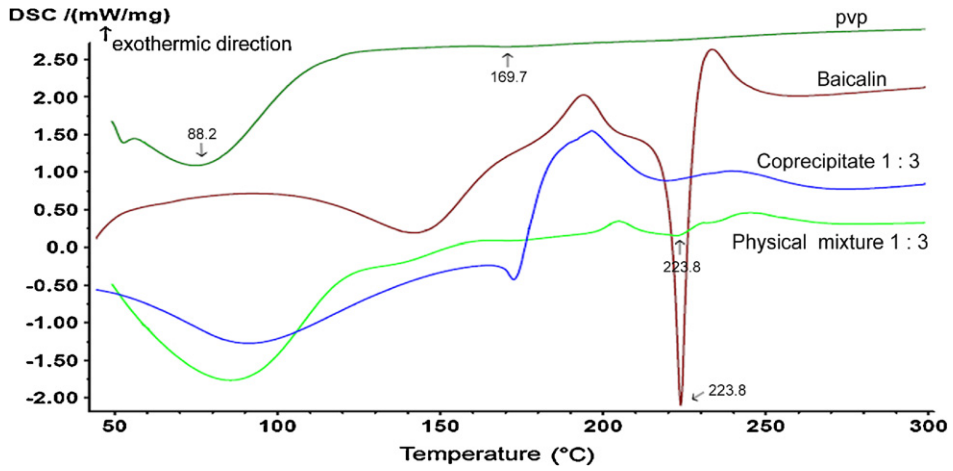

Fig. 3. DSC Thermographs of baicalin, PVP, the baicalin-PVP physical mixture 1:3, and the baicalin-PVP coprecipitate 1:3.

performed under the following conditions: tungsten probes (force constant 0.06 Nm), scan range of 10.5 nm × 10.5 nm, tapping mode imaging, and scanning point by point at room temperature. G3DR software was applied to process data.

3. Results and discussion

3.1. DSC analysis

Differential scanning calorimetry data are presented in Fig. 3. The endothermic peak with PVP at 88.2 °C may result from moisture evaporation in PVP, and 169.7 °C was the glass transition temperature of PVP, and the sharp endothermic peak with baicalin at 223.8 °C was its melting point peak. The presence of a broad endothermic peak for the baicalin-PVP physical mixture at 223.8 °C suggests that the drug be melted gradually in the polymer matrix. This is because PVP had a glass transition temperature at 169.7 °C, leading to the drug to be melted in the liquid phase of PVP with increasing the temperature. The absence of the drug's endothermic peak for the baicalin-PVP coprecipitate indicates that baicalin resided in PVP polymers in non-crystalline state. This was primarily attributable to the destruction of the crystalline phase of baicalin during the dispersion in the PVP polymer matrix.

3.2. XRD analysis

To further elucidate the non-crystalline state of baicalin in the coprecipitate obtained by DSC analysis, the phase state was analyzed by XRD. The results observed are shown in Fig. 4. Several diffraction peaks at the 2θ angle position of 8.62°, 10.34°, 12.40°, 14.64°, 16.96°, 20.62°, 23.76°, 25.40°, 27.96° and 29.38° indicated the presence of the crystal phase of baicalin; the carrier PVP appeared to be non-crystal powder because no characteristic diffraction peak was detected at 3–60° with PVP. However, the clear crystal diffraction peak of the drug in the baicalin-PVP physical mixture was readily visible. The reduction of the peak value intensity with lower drug contents suggested that the drug was still present in the crystal phase, and physical blending did not alter the crystal state of the drug; however, the disappearance of the crystal diffraction peak of the drug in the coprecipitate indicated that the baicalin was highly dispersed in the carrier substance in the amorphous or molecular phase. The result further clarified the non-crystalline state of baicalin in the coprecipitate observed by DSC. A possible explanation was that the reticular structure of the PVP molecules helped stabilize dispersion and inhibit aggregation of the drug molecules.

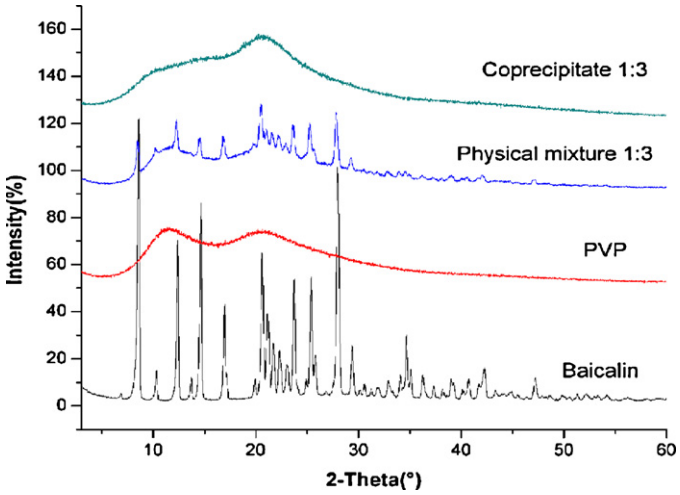

Fig. 4. XRD spectra of baicalin, PVP, the baicalin-PVP physical mixture 1:3, and the baicalin-PVP coprecipitate 1:3.

3.3. Dissolution test

The baicalin dissolution test results are shown in Fig. 5. The accumulative dissolution of the baicalin API capsule in 0.1 mol L^{-1} HCl solution was 1.25% at 30 min. The dissolution for the baicalin-

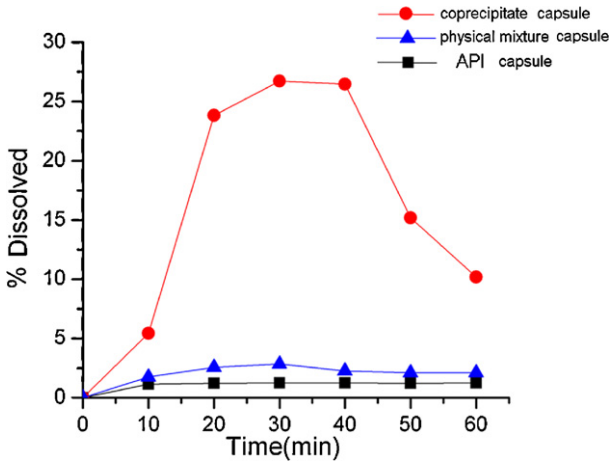

Fig. 5. Dissolution profiles of baicalin from different preparations.

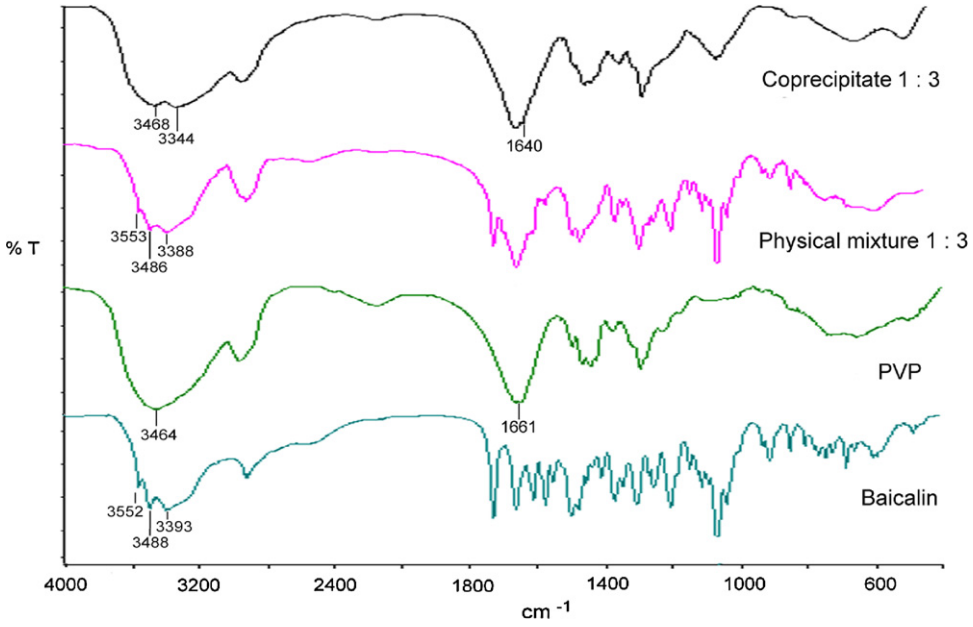

Fig. 6. IR spectra of baicalin, PVP, the baicalin-PVP physical mixture 1:3, and the baicalin-PVP coprecipitate 1:3.

PVP physical mixture capsule was 2.84%, slightly higher than the API capsule, which is possibly due to the solubilization effect of PVP. The accumulative dissolution of baicalin in the baicalin-PVP coprecipitate capsule was 26.73% or 21.4 times that of the API capsule.

Baicalin is a weak acidic drug (p*K*a = 5.047); therefore, the main absorption site is the stomach due to it remaining in a mostly molecular state through the gastrointestinal mucosa in acidic conditions (Liu and Jiang, 2006). Therefore, in this study, a 0.1 mol L^{-1} HCl solution was selected as the dissolution medium. The average postprandial gastric retention (empty) T50% is 15–20 min. If the dissolution rate is slower than the gastric emptying rate, the drug dissolution process will become a rate limiting step of absorption. Therefore, it is crucial to maximize the dissolution of drugs in the stomach within a limited time to improve absorption.The Noyes–Whitney equation: $dc/dt = KS(C_s - C)$, where dc/dt is the dissolution rate, K is the dissolution rate constant, S is the dissolving boundary area, C_s is the drug solubility, and C is the concentration of drug in solution, indicates that the dissolution rate of drugs from solid dosage forms is proportional to K, S and C_s. Therefore, drug dispersion in a carrier affects its dissolution rate directly. Higher dispersion is related to a higher dissolution rate. Baicalin in the amorphous or the molecular state dispersed to a high degree in a polymer of PVP, which is shown in DSC and XRD results. This behavior greatly increased the surface area of the drug particles, S. In addition, a hydrophilic polymer PVP can increase wetting and diffusion of the baicalin molecule. These conditions lay the groundwork for the fact that the dissolution of the baicalin-PVP coprecipitate capsules was 20.4× higher than that of the API capsule. The remarkably improved dissolution rate of baicalin created an opportunity for gastric absorption within a limited time. Compared to baicalin dispersible tablets (Liu et al., 2009), baicalin-PVP coprecipitate capsules have shown improvement in dissolution capability, which offers a greater potential for development.

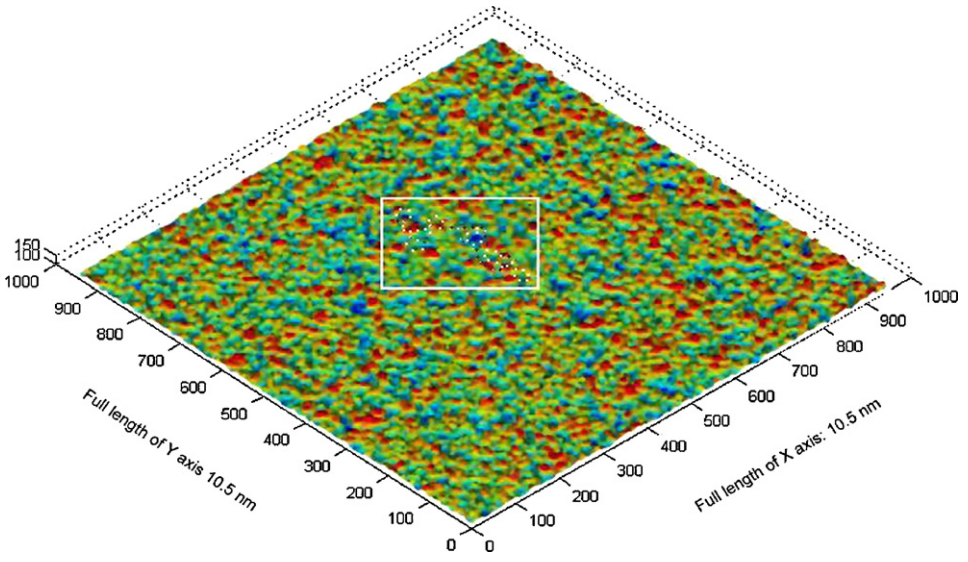

Fig. 7. Colored graphic of baicalin-PVP coprecipitate in AFM·IPC-208B.

3.4. IR analysis

To further characterize possible interactions between the drug and the polymeric carrier in the solid state, infrared spectra of all samples were recorded and are shown in Fig. 6. The presence and absence of characteristic peaks associated with specific structural characteristics of the molecule was noted. From 3600 cm^{-1} to 3200 cm^{-1}, the absorption peaks for baicalin API were observed at 3552 cm^{-1} for free hydroxyl group peak, and 3488 cm^{-1} and 3393 cm^{-1} for the binding peaks derived from intermolecular hydroxyl group. The spectrum of PVP showed, among others, important bands at 2952 cm^{-1} (C–H) and 1661 cm^{-1} (C=O). A very broad band was also visible at 3464 cm^{-1}, which was attributed to the presence of water, confirming the broad endothermic peak detected in the DSC experiments. The corresponding absorption peaks for the baicalin-PVP physical mixture at 3553 cm^{-1}, 3486 cm^{-1} and 3388 cm^{-1} were specific for its API and suggested that physical blending would not generate hydrogen bonding. There were 2 absorption peaks with baicalin-PVP coprecipitate observed at 3468 cm^{-1} and 3344 cm^{-1} with increased absorption intensity and a broadened spectral band for the bound hydroxyl group. However, the absorption peak of the bound hydroxyl group might result from intermolecular hydrogen bonds between drug and carrier, or between the drug and drug. Even the trace amount of moisture contained in API and PVP may also generate a similar absorption peak. It is difficult to judge clearly from these results. Furthermore, in the baicalin-PVP coprecipitate, the characteristic peak at 1640 cm^{-1} was observed. It may be considered that C=O stretching vibrations of PVP change in coprecipitate. So the intermolecular hydrogen bonds between the carbonyl group of PVP and hydroxyl groups of baicalin may be formed.

Intermolecular hydrogen bonds of simple molecules could be judged directly by infrared spectra through the stretching vibration of hydroxyl groups. However, as far as molecules containing one or more hydroxyl groups, it is difficult to accurately determine which one or more hydroxyl groups participate in forming the intermolecular hydrogen bonds using infrared spectra alone (Papageorgiou et al., 2009). In this study, the 2-OH, 3-OH or 4-OH of glucuronide in the baicalin molecule maybe acting as a proton donor to form hydrogen bonds with the O from the carbonyl group of PVP. Even if the presence of hydrogen bonding interactions between baicalin and PVP was confirmed by combining FT-IR, Raman, and solid-state NMR spectroscopy (Tobyn et al., 2009), the binding-OH of the interaction might not be able to be distinguished. Therefore, other methods will be needed to further confirm the formation of hydrogen bonds between the drug and carrier in addition to the binding site of -OH.

3.5. AFM·IPC-208B of the baicalin-PVP coprecipitate

Various techniques, including SEM, TEM and AFM, have been used to observe the microstructure of solid dispersion by many researchers (Karavas et al., 2007; Dong et al., 2008; Zhu et al., 2010); however, there has been no report on molecular morphology because of the maximum resolution of these instruments, for which the maximal resolution is 10 nm, 1 nm and 1–2 nm, respectively. It is difficult to observe the benzene ring (about 0.5 nm) in the baicalin molecule using these general commercial devices. Fortunately, AFM·IPC-208B high-resolution atomic force microscopy (AFM) was independently developed by Chongqing University, which integrated the techniques of scanning tunnel microscopy (STM) and AFM, the STM is used to detect the up and down motion of the micro-cantilever and can offer maximal precision to 0.1 nm horizontally and 0.01 nm longitudinally (Yang et al., 2004). The AFM IPC-208B technique was employed to characterize antisense oligonucleotide binding with the dextran polymer from the spatial arrangement of atoms (Wen et al., 2008). The study not only gave a novel idea for the characterization of the spatial structure of baicalin-PVP coprecipitate using AFM·IPC-208B, but also provided a new method to confirm intermolecular hydrogen bonding between baicalin and PVP, including the binding site of -OH.

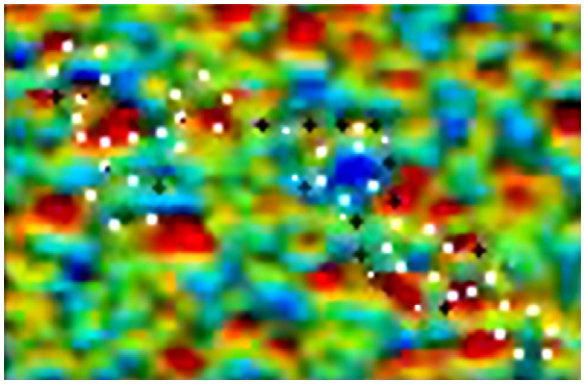

Fig. 8. Magnified image of white frame in the color graph of baicalin-PVP coprecipitate C-atom (□), N-atom (◪), O-atom (✚), H-atom (▫).

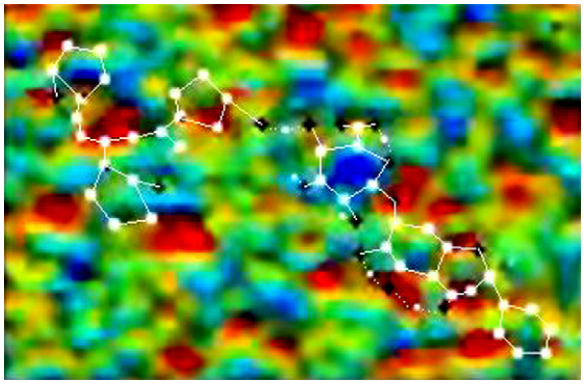

Fig. 9. Spatial structure of the baicalin-PVP coprecipitate in AFM·IPC-208B.

A colored graphic of the analytical results of baicalin-PVP coprecipitate using AFM·IPC-208B is shown in Fig. 7, in which the locations of various elements are marked by different pixels. The magnified domains of marked elements were cropped and shown in Fig. 8, where white square pixels represent C-atoms, white square pixels with black dots represent N-atoms, black crosses represent O-atoms, and relatively smaller white dots represent H-atoms. Fig. 9 shows the spatial structure of the coprecipitate that was obtained by connecting every atom in Fig. 8. Fig. 10 shows a schematic diagram of the spatial structures of PVP and the baicalin molecules that was plotted using Chemdraw software for chemical molecular structures based on data given in Fig. 9. It was observed that baicalin was dispersed in PVP polymers at a molecular size of 2 nm and wrapped or surrounded by about 0.4 nm of a five-membered ring of PVP arranged along the carbon chain sequentially. It can be seen that both the 4-OH of glucuronide in the

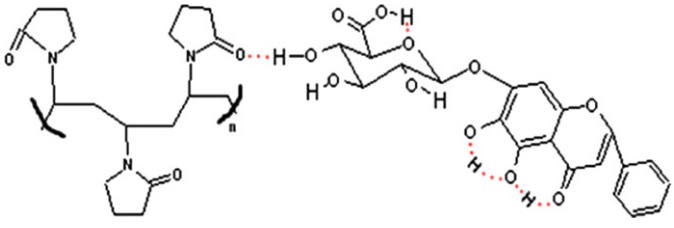

Fig. 10. Spatial structure diagrams of baicalin and PVP.

drug molecule and the O-atom of the lactam in the carrier molecule are in a straight line and able to form intermolecular hydrogen bonds. The interaction present between the baicalin drug molecule and the PVP carrier favored an extensive and stable dispersion of drug molecules in the carrier substance. Meanwhile, the C6 carboxyl group's H of glucuronide was able to form an intramolecular hydrogen bond with the intra-ring O-atom; the carbonyl O-atom in the flavone molecule was able to also form intramolecular hydrogen bonds with the 2-OH and 3-OH in the adjacent benzene ring to further constitute a relatively stable 5- or 6-membered ring whose stability will in turn increase the stability of these intramolecular hydrogen bonds. These results indicated that baicalin was highly dispersed in the carrier substance and surrounded or encapsulated by PVP. It is noted from the atomic spatial arrangement that hydrogen bonds can be formed within drug molecules and between the drug and carrier.

It has been reported that hydrogen bonds between the drug and carrier could stabilize the phase state of the drug and prevent the crystal transformation of the drug during storage (Karavas et al., 2005; Papageorgiou et al., 2009). The hydrogen bonds between the drug and carrier confirmed by AFM·IPC-208B provide the foundation for stability of baicalin-PVP coprecipitate. Studies on the stability and bioavailability of the baicalin-PVP coprecipitate will be the subject of our next study.

4. Conclusions

An improved dissolution rate for baicalin was obtained using a coprecipitate prepared with PVP by the solvent method. Baicalin was present in an amorphous or molecular state in the coprecipitate at a drug-to-polymer composition ratio of 1:3 (W/W) according to the results of DSC and XRD. The dissolution rate of baicalin from the coprecipitate was 20.4× faster than of API. Solid dispersion technology enables baicalin to highly disperse in the carrier, which greatly increases the drug surface area and leads to a significant increase in the dissolution rate of the baicalin-PVP coprecipitate. This lays a basis for the potential commercial development of baicalin-PVP coprecipitate. The AFM·IPC-208B technique was able to characterize the spatial conformation and interaction between the drug and carrier intuitively at the molecular level and confirmed the possible formation of hydrogen bonds between the drug and carrier speculated by IR; it can even distinguish the binding-OH of the interaction, overcoming many of the disadvantages of traditional methods. Therefore, AFM·IPC-208B can be used as a new characterization technique for coprecipitates in the future.

Acknowledgments

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References

Chan, F.L., Choi, H.L., Chen, Z.Y., Chan, P.S., Huang, Y., 2000. Induction of apoptosis in prostate cancer cell lines by a flavonoid, baicalin. Cancer Lett. 160, 219–228.
Chiou, W.L., Riegelman, S., 1971. Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci. 60, 1281–1302.
Choudhary, D., Kumar, S., Gupta, G.D., 2009. Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique. Asian J. Pharm. 3, 245–251.
Dong, Z.D., Chatterji, A., Sandhu, H., Choi, D.S., Chokshi, H., Shah, N., 2008. Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation. Int. J. Pharm. 355, 141–149.
Gupta, P., Bansal, A.K., 2005. Spray drying for generation of a ternary amorphous system of celecoxib, PVP, and meglumine. Pharm. Dev. Technol. 10, 273–281.
Ikemoto, S., Sugimura, K., Yoshida, N., Yasumoto, R., Wada, S., Yamamoto, K., Kishimoto, T., 2000. Antitumor effects of Scutellariae radix and its components baicalein, baicalin, and wogonin on bladder cancer cell lines. Urology 55, 951–955.
Jang, S.I., Kim, H.J., Hwang, K.M., Jekal, S.J., Pae, H.O., Choi, B.M., Yun, Y.G., Kwon, T.O., Chung, H.T., Kim, Y.C., 2003. Hepatoprotective effect of baicalin, a major flavone from scutellaria radix, on acetaminophen-induced liver injury in mice. Immunopharm. Immunot. 25, 585–594.
Kanaze, F.I., Kokkalou, E., Niopas, I., Georgarakis, M., Stergiou, A., Bikiaris, D., 2006. Dissolution enhancement of flavonoids by solid dispersion in PVP and PEG matrixes: a comparative study. J. Appl. Polym. Sci. 102, 460–471.
Karavas, E., Ktistis, G., Xenakis, A., Georgarakis, E., 2005. Miscibility behavior and formation mechanism of stabilized felodipine-polyvinylpyrrolidone amorphous solid dispersions. Drug Dev. Ind. Pharm. 31, 473–489.
Karavas, E., Ktistis, G., Xenakis, A., Georgarakis, E., 2006. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. Eur. J. Pharm. Biopharm. 63, 103–114.
Karavas, E., Georgarakis, M., Docoslis, A., Bikiaris, D., 2007. Combining SEM TEM, and micro-Raman techniques to differentiate between the amorphous molecular level dispersions and nanodispersions of a poorly water-soluble drug within a polymer matrix. Int. J. Pharm. 340, 76–83.
Leuner, C., Dressman, J., 2000. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 50, 47–60.
Liu, C., Liu, X., Tong, J., Chen, D., Bi, K., 2009. Design and evaluation of San-Huang dispersible tablet—an efficient delivery system for traditional Chinese medicine. Pharm. Dev. Technol. 14, 506–515.
Liu, T.M., Jiang, X.H., 2006. Investigation of the absorption mechanisms of baicalin and baicalein in rats. J. Pharm. Sci. 95, 1326–1333.
Mooter, G., Van, den., Wuyts, M., Blaton, N., Busson, R., Grobet, P., Augustijns, P., Kinget, R., 2001. Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur. J. Pharm. Sci. 12, 261–269.
Papageorgiou, G.Z., Papadimitriou, S., Karavas, E., Georgarakis, E., Docoslis, A., Bikiaris, D., 2009. Improvement in chemical and physical stability of fluvastatin drug through hydrogen bonding interactions with different polymer matrices. Curr. Drug Deliv. 6, 101–112.
Park, S.W., Lee, C.H., Kim, Y.S., Kang, S.S., Jeon, S.J., Son, K.H., Lee, S.M., 2008. Protective effect of baicalin against carbon tetrachloride–induced acute hepatic injury in mice. J. Pharm. Sci. 106, 136–143.
Patel, R.P., Patel, M.M., 2007. Physicochemical characterization and dissolution study of solid dispersions of lovastatin with polyethylene glycol 4000 and polyvinylpyrrolidone K30. Pharm. Dev. Technol. 12, 21–33.
Sharma, D.K., Joshi, S.B., 2007. Solubility enhancement strategies for poorly water soluble drugs in solid dispersion: a review. Asian J. Pharm. 1, 9–19.
Shieh, D.E., Liu, L.T., Lin, C.C., 2000. Antioxidant and free radical scavenging effects of baicalein, baicalin and wogonin. Anticancer Res. 20, 2861–2865.
Thybo, P., Kristensen, J., Hovgaard, L., 2007. Characterization and physical stability of tolfenamic acid-PVP K30 solid dispersions. Pharm. Dev. Technol. 12, 43–53.
Tobyn, M., Brown, J., Dennis, A.B., Fakes, M., Gao, Q., Gamble, J., Khimyak, Y.Z., McGeorge, G., Patel, C., Sinclair, W., Timmins, P., Yin, S., 2009. Amorphous drug-PVP dispersions: application of theoretical, thermal and spectroscopic analytical techniques to the study of a molecule with intermolecular bonds in both the crystalline and pure amorphous state. J Pharm. Sci. 98, 3456–3468.
Wan, J.Y., Gong, X., Zhang, L., Li, H.Z., Zhou, Y.F., Zhou, Q.X., 2008. Protective effect of baicalin against lipopolysaccharide/d-galactosamine-induced liver injury in mice by up-regulation of heme oxygenase-1. Eur. J. Pharm. 587, 302–308.
Wen, M., Li, B.B., Bai, W., Li, S.L., Yang, X.H., 2008. Application of atomic force microscopy in morphological observation of antisense probe labeled with magnetism. Mol. Vis. 14, 114–117.
Wu, J., Chen, D., Zhang, R., 1999. Study on the bioavailability of baicalin–phospholipid complex by using HPLC. Biomed. Chromatogr. 13, 493–495.
Xing, J., Chen, X.Y., Zhong, D.F., 2005. Absorption and enterohepatic circulation of baicalin in rats. Life Sci. 78, 140–146.
Yang, X.H., Chen, H.B., Fei, D.G., Xie, C., Jin, P., Yang, H., 2004. Design and application of a high-resolution AFM. China Mech. Eng. 15, 1909–1911.
Zhu, Q., Taylor, L.S., Harris, M.T., 2010. Evaluation of the microstructure of semicrystalline solid dispersions. Mol. Pharm. 7, 1291–1300.