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Improving the solubility of ampelopsin by solid dispersions and inclusion complexes

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Abstract

The aim of this study was to increase the solubility of ampelopsin (AMP) in water by two systems: solid dispersions with polyethylene glycol 6000 (PEG 6000) or polyvinylpyrrolidone K-30 (PVP K30) and inclusion complexes with β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD). The interaction of AMP with the hydrophilic polymers was evaluated by differential scanning calorimetry (DSC), Fourier transformation-infrared spectroscopy (FTIR), scanning electron microscopy (SEM). The results from DSC, FTIR and SEC analyses of solid dispersions and inclusion complexes showed that AMP might exist as an amorphous state or as a solid solution. On the other hand, the SEM images of the physical mixtures revealed that to some extent the drug was present in a crystalline form. The influence of various factors (pH, temperature, type of polymer, ration of the drug to polymer) on the solubility and dissolution rate of the drug were also evaluated. The solubility and dissolution rates of AMP were significantly increased by solid dispersions and cyclodextrin complexes as well as their physical mixtures. The improvement of solubility using polymers was in the following order: HPBCD ≈ BCD > PVP K30 > PEG 6000.

Keywords: Ampelopsin; Polyethylene glycol 6000; Polyvinylpyrrolidone K-30; β-Cyclodextrin; Hydroxypropyl-β-cyclodextrin; Inclusion complex; Solid dispersion

1. Introduction

Ampelopsin (3,5,7,3′4′5′-hexahydroxyl 2,3 dihydrogen flavonol, AMP, Fig. 1), isolated from the tender stem and leaves of the plant species *Ampelopsis Grossedentata (Hand-Mazz) W.T. Wang*, was one of the most common flavonoids. AMP was reported to possess numerous pharmacological activities, such as anti-inflammatory and antimicrobial activity, relieving cough, antioxidation, antihypertension, hepatoprotective effect, and anticarcinogenic effect [1–6]. There was more than 27% of AMP in the tender stem and leaves of the species, especially, more than 40% in the cataphyll. Systematic research on AMP has been conducted to characterize its pharmacological potential and possibility for drug product development. However, AMP was poorly soluble in water (0.2 mg/ml at 25 °C). In aqueous or organic solution, AMP decomposed under exposure to light, and colored photolysis product was formed. The permeability through rat intestine mucosa determined in our laboratory was 9.3×10^{-6} cm/s, and oral drug absorption in humans based on the intestinal permeability in rats could be less than 10% [7]. Use of AMP in most pharmaceutical preparations and some research experiments was thereby limited due to its low water solubility, low intestine permeability and degradation in solution. To our knowledge, no information is available on the improvement of these drug-like properties of AMP. In this paper, increasing the solubility of AMP has been addressed.

Various techniques have been used to improve the solubility/dissolution rate of poorly water soluble drugs. Among them, the solid dispersion technique [8–10] and the complexation with cyclodextrins [11–13] are most frequently used. In solid dispersion, hydrophilic polymers have been commonly used as carriers. Polyvinylpyrrolidon (PVP) and polyethylene

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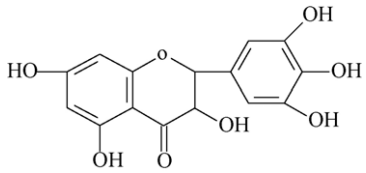

Fig. 1. Chemical structure of AMP.

glycol (PEG) have been widely employed for their low cost and high aqueous solubility. Both polymers are freely soluble in water and are available in various molecular weights, ranging from 10,000 to 700,000 for PVP and from 200, to in excess of 300,000 for PEG. The molecular size of both polymers favors the formation of interstitial solid solutions [14–16]. Cyclodextrins as pharmaceutical excipients are mainly used as solubilizing and stabilizing agents for lipophilic substances in aqueous preparations. A number of molecules are solubilized in cyclodextrin solutions through formation of an inclusion complex [17,18]. HPBCD is one of the most accepted representatives of hydroxylalkylated derivatives as hydrophilic drug carrier, because of its amorphousness, high water solubility and solubilizing ability, low cost and low toxicity.

The main objective of this work was to investigate the possibility of improving the solubility and dissolution rate of AMP including by (a) solid dispersion with PEG 6000 or PVP K30; and (b) complexation with BCD or HPBCD. In order to characterize the prepared dispersions and inclusion complexes, analyses using DSC, FTIR, SEM as well as dissolution and solubility studies were carried out.

2. Materials and methods

2.1. Materials

AMP was extracted and purified in our laboratory. PVP K30 was purchased from BASF (Germany) and PEG 6000 was supplied from Shanghai Guangming Chemical Plant (China). BCD was kindly donated by Guangdong Yunan Cyclodextren Plant (China) and HPBCD with a degree of substitution 0.66 was purchased from Yiming Fine Chemical Co., Ltd. (China). All other materials were of analytical or HPLC grade commercially available.

2.2. AMP assay

The concentration of AMP was measured by a reverse-phase HPLC method described below. A Shimadzu HPLC system was equipped with a SPD-10A SHIMADZU UV–vis detector, a 20 μl loop injection valve, a reversed phase Versapack C18 (25 cm × 4.6 mm; 10 μm particle) column in conjunction with a precolumn insert. The mobile phase was composed of CH_3OH and H_2O (60:40), and pH was adjusted to 3 with phosphoric acid. The mobile phase was filtered through a nylon membrane filter (0.45 μm) and degassed by ultrasonication before use. The flow rate was 1.0 ml/min, and the detection wavelength was 292 nm. The retention time of AMP was approximately 4 min. Quantification of the compound was carried out by measuring the peak area in relation to the concentration of standards chromatographed under the same conditions. The standard curve was linear ($r^2 > 0.9998$) over the range of concentrations of interest (50–400 μg/ml). The relative standard deviation of the inter- and intra-day assay was less then 5% ($n = 3$).

2.3. Determination of solubility

Drug solubility was determined by adding excess amounts of AMP to water or buffer solutions with different pHs (pH 1.2, 2.8, 4.6, 6.0, 7.4) at 25 ± 0.5 °C. The suspensions formed were equilibrated under continuous agitation for 1 week and then filtered through a 0.45 μm membrane filter to obtain a clear solution for HPLC assay. Phase-solubility studies were carried out in the same way as solubility studies. Excess amount of AMP was added to aqueous solutions containing various concentrations of PVP K30, PEG 6000, HPBCD (5, 10, 15 and 20% w/v, respectively) and BCD saturation solution. The suspensions were shaken at 25 ± 0.5 °C for 7 days, and then the samples were filtered through a 0.45 μm membrane filter. The AMP concentrations were determined using the HPLC method. Each sample was determined in duplicate.

2.4. Preparations of physical mixtures, solid dispersions and inclusion complexes

2.4.1. Physical mixtures

AMP and excipients (PVP K30, PEG 6000, BCD or HP-BCD) were accurately weighed at a ratio of 1:10, pulverized and then mixed thoroughly in a mortar with a pestle until a homogeneous mixture was obtained. The mixture was passed through a 200 μm sieve for further experiments.

2.4.2. Solid dispersions

Solid dispersions of AMP in PVP K30 or PEG 6000 containing three different ratios (1:5, 1:10, 1:15 w/w for PVP and 1:10, 1:15, 1:20 w/w for PEG) were prepared by the solvent method. Briefly, AMP and the polymer were dissolved in a minimum amount of purified ethanol. The solvent was then removed by evaporation under reduced pressure at 40 °C. The resulting residue was dried under vacuum for 3 h and stored overnight in a desiccator. After drying, the residue was ground in a mortar, and then passed through a 200 μm sieve. The resultant powders were stored in a desiccator until further investigation.

2.4.3. Inclusion complexes

AMP and β-CD or HP-β-CD at 1:1 molar ratio were dissolved in distilled water. The resulting mixtures were stirred at 25 °C for 7 days. After dissolution was completed, the solutions were filtered through a 0.45 μm membrane filter. The

clear solutions were subjected to evaporation at 40 °C and under vacuum. Then, the drying powders were treated as the preparation of solid dispersions.

2.5. Differential scanning calorimetry analysis

Thermal characteristics of the pure materials, the physical mixtures, the solid dispersions and inclusion complexes of AMP with excipients were determined by a differential scanning calorimeter (DSC 204, Netzsch, Germany). The scanning rate was 10 °C/min, and the scanning temperature range was between 30 and 350 °C.

2.6. FTIR spectroscopy

FTIR spectra of the samples were obtained on a SHIMADZU FTIR −8400 s spectrometer (Japan). Samples were prepared into KBr disks (2 mg sample in 200 mg KBr). The scans were obtained from 4000 to 400 cm^{-1} at resolution of 1 cm.

2.7. Scanning electron microscopy (SEM)

The images of the samples were analyzed by SEM (AKASHI SX-40, Japan). Samples were mounted on a double-faced adhesive tape, sputtered with platinum prior to analysis. The pictures were taken at a magnification of 600-fold or 2000-fold.

2.8. In vitro dissolution

The dissolution studies of AMP and different drug–polymer combinations were performed in water at 37 ± 0.5 °C according to the dispersed amount method [19]. Samples equivalent to 100 mg of AMP were added to 100 ml of water in a 200 ml beaker, which was stirred with a rotating paddle at 100 rpm. At predetermined intervals, 1 ml samples were withdrawn, filtered (pore size 0.45 μm), and analyzed with HPLC for AMP. The same volume of fresh medium was replaced and the correction for the cumulative dilution was calculated. Dissolution experiments were carried out in triplicate.

3. Results and discussion

3.1. Solubility studies

The solubility of AMP in water and the solutions with different pHs was shown in Table 1. The solubility of AMP in water at 25 °C was found to be 200.3 μg/ml. The pH of solutions had little effect on the solubility of AMP, but had significant effect on the stability of AMP. When pH was between 1.2 and 4.6, the solution was stable. When pH was 6.0, there was some degradation observed. The solubility at pH 7.4 could not be determined because it had decomposed before it reached saturation.

The effect of different carriers and temperatures on the aqueous solubility of AMP was displayed in Fig. 2. Solubility experiments showed that the saturation concentration of AMP in water is notably affected by temperature, from 0.2 mg/ml at 25 °C to 0.9 mg/ml at 37 °C. In the phase-solubility diagrams (Fig. 2), the results that the concentration of AMP in water increased as a function of PEG 6000, PVP K30 and HPBCD concentration were observed at both temperatures. The relationship appeared to be linear ($r^2 > 0.9$). The increase of the solubility with increasing temperature revealed the endothermic nature of this process. The improvement of the solubility due to presence of hydrophilic excipients might be attributed to the improved wetting of AMP by forming intermolecular hydrogen bonding between AMP and PVP K30 or PEG 6000, but forming 1:1 cyclodextrin complex between AMP

Table 1
Solubility of AMP at 25 °C in water and aqueous solutions with different pHs

Media	Water (pH 6.1)	pH 1.2	pH 2.8	pH 4.6	pH 6.0	pH 7.4
Solubility (μg/ml)	200.3	202.0	223.3	217.9	214.5	ND[a]

Data are the mean of two determinations.
[a] Not determined.

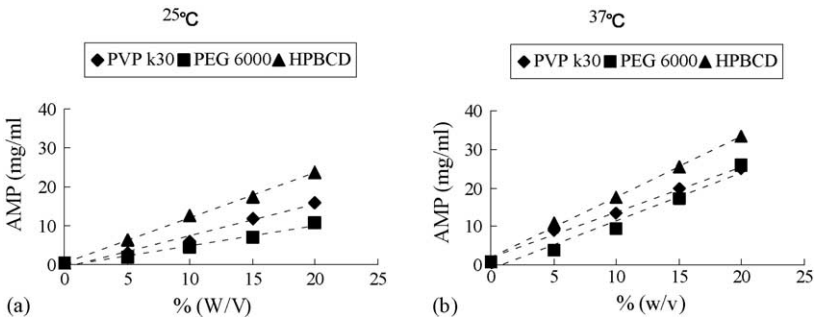

Fig. 2. Phase-solubility diagrams for AMP in the presence of PVP K 30, PEG 6000, HPBCD in water at 25 ± 0.5 °C ($n = 2$) (a) and 37 ± 0.5 °C ($n = 2$) (b).

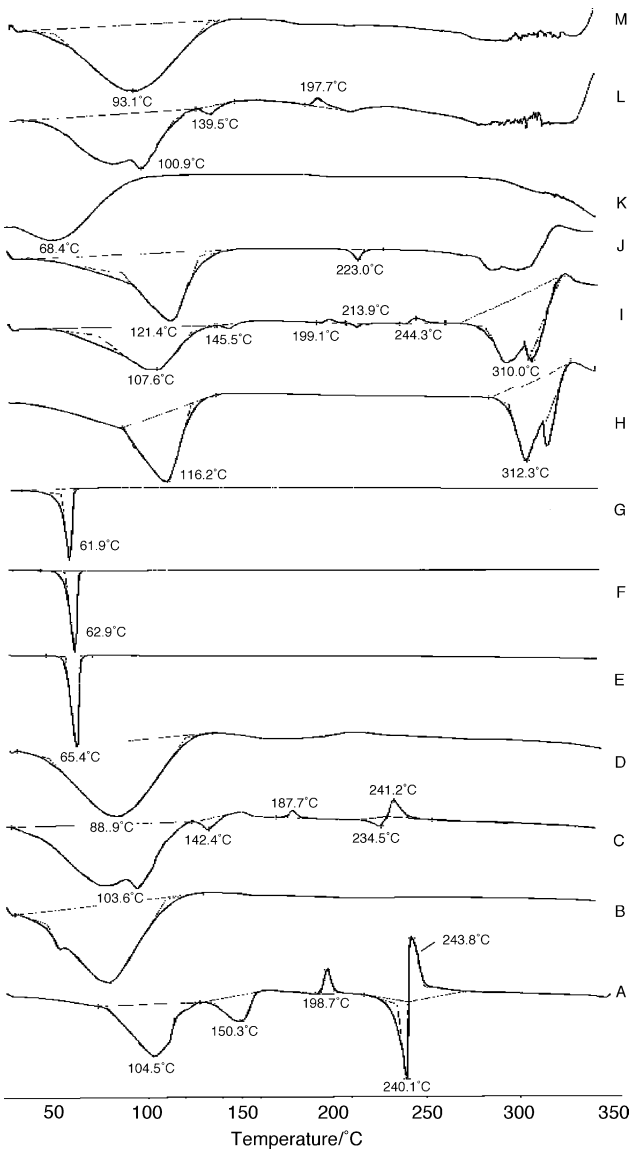

Fig. 3. DSC curves of single components and binary systems of AMP and PVP, PEG, BCD and HPBCD. (A) AMP, (B) PVP K30, (C) physical mixture of AMP/PVP, (D) solid dispersion of AMP/PVP K30, (E) PEG 6000, (F) physical mixture of AMP/PEG, (G) solid dispersion of AMP/PEG 6000, (H) BCD, (I) physical mixture of AMP/BCD, (J) inclusion complex of AMP/BCD, (K) HPBCD, (L) physical mixture of AMP/HPBCD, (M) inclusion complex of AMP/HPBCD.

and HPBCD. Similar observations have previously been reported [20,21]. In a BCD saturation solution, AMP solubility was 2.8 mg/ml at 25 °C and 9.6 mg/ml at 37 °C, respectively. Thus, enhancement of solubility for AMP was 14.1-fold at 25 °C and 10.7-fold at 37 °C by BCD.

3.2. Differential scanning calorimetry (DSC)

DSC curves obtained for pure material, solid dispersions, inclusion complexes and their corresponding physical mixtures were displayed in Fig. 3. Pure AMP powder had three endothermic peaks and two exothermic peaks corresponding to the loss of water (104.5 and 150.3 °C), recrystallizing (198.7 °C), the melting point of AMP (240.1 °C) and oxidizing (243.8 °C) respectively (Fig. 3A). In the thermogram of PEG 6000 (Fig. 3E), a sharp peak (65.4 °C) was observed, which was associated with melting endotherm of PEG. In the DSC curves of pure PVP (Fig. 3B), BCD (Fig. 3H) and HP-BCD (Fig. 3K), the peaks corresponding to the evaporation of water appeared in the temperature range of 50–150 °C. Besides the endothermic peaks corresponding to the loss of water, the thermogram of BCD displayed melting endotherm with a shoulder, which indicated the presence of more than one crystal form.

The physical mixture of AMP with PVP K30 showed spectra corresponding to superposition of their parent products (Fig. 3C). In the curve of solid dispersion with PVP (Fig. 3D), it exhibited a very broad endotherm ranging between 51.5 and 145 °C with a peak at 88.9 °C. The characteristic features of AMP peak were lost. This indicated that AMP was no longer present as a crystalline material, but was converted into the amorphous state [22]. Solid dispersions of AMP with PEG showed almost the same thermal behavior as their physical mixtures of the same composition (Fig. 3F and G), the absence of AMP peaks suggested that AMP was completely soluble in the liquid phase of PEG 6000. The same phenomenon had previously been reported [22,23]. The physical mixture with BCD (Fig. 3I) showed some characteristic feature peaks of AMP, such as peak 145.5, 199.1 and 244.3 °C, however, the melting peak of AMP was disappeared and another endothermic peak (213.9 °C) was observed. The physical mixture with HPBCD (Fig. 3L) only appeared one characteristic peak of AMP, i.e., 197.7 °C. However, all the characteristic peaks of AMP were lost in the inclusion complexes with BCD and HPBCD. The disappearance of the thermal features of the drug indicated that the drug penetrated into the cyclodextrin cavity replacing the water molecules [18,24].

3.3. Fourier transform-infrared spectroscopy

Fig. 4 shows the spectra of pure materials and respective AMP-carrier systems. The spectrum of AMP (Fig. 4A) showed three characteristic bands of the OH group which were found at 3477, 3352, and 3236 cm^{-1}. The carbonyl stretching mode appeared at 1639 cm^{-1}. Other characteristic bands were found at 1599 cm^{-1}, 1458 cm^{-1} (stretching vibration of C=C in the aromatic ring), 1155 cm^{-1} (C–O–C stretch), 1128 cm^{-1} (C–OH stretch) and 833 cm^{-1} (benzene ring with tetra-substitutions).

Physical mixtures of AMP/PVP (Fig. 4C) and AMP/PEG (Fig. 4F) exhibited spectra corresponding to a superposition of their parent components. In the spectra of solid dispersion (Fig. 4D and G), the absorption bands which could be assigned to the free OH and the OH involved in intramolecular hydrogen bonding changed or disappeared. The reason for this observation might be interpreted as a consequence of hydrogen bonding between OH of AMP and >N– and

C=O of PVP K30, or the lone pairs of the oxygen atom in PEG 6000. The carbonyl stretching peak of AMP was shifted from 1639 cm^{-1} towards lower frequencies, the peak of tetra-substituted benzene ring was shifted from 833 cm^{-1} towards higher frequencies in the solid dispersions. These results also suggested that hydrogen bonding interactions between AMP and PVP or PEG. IR spectra did not reveal dramatic changes in characteristic peaks of AMP frequency, suggesting the absence of chemical interactions between AMP and the excipients, as also reported by Ford [25].

The spectra of pure BCD and HPBCD (Fig. 4H and K) illustrated the vibration of free OH between 3100 and

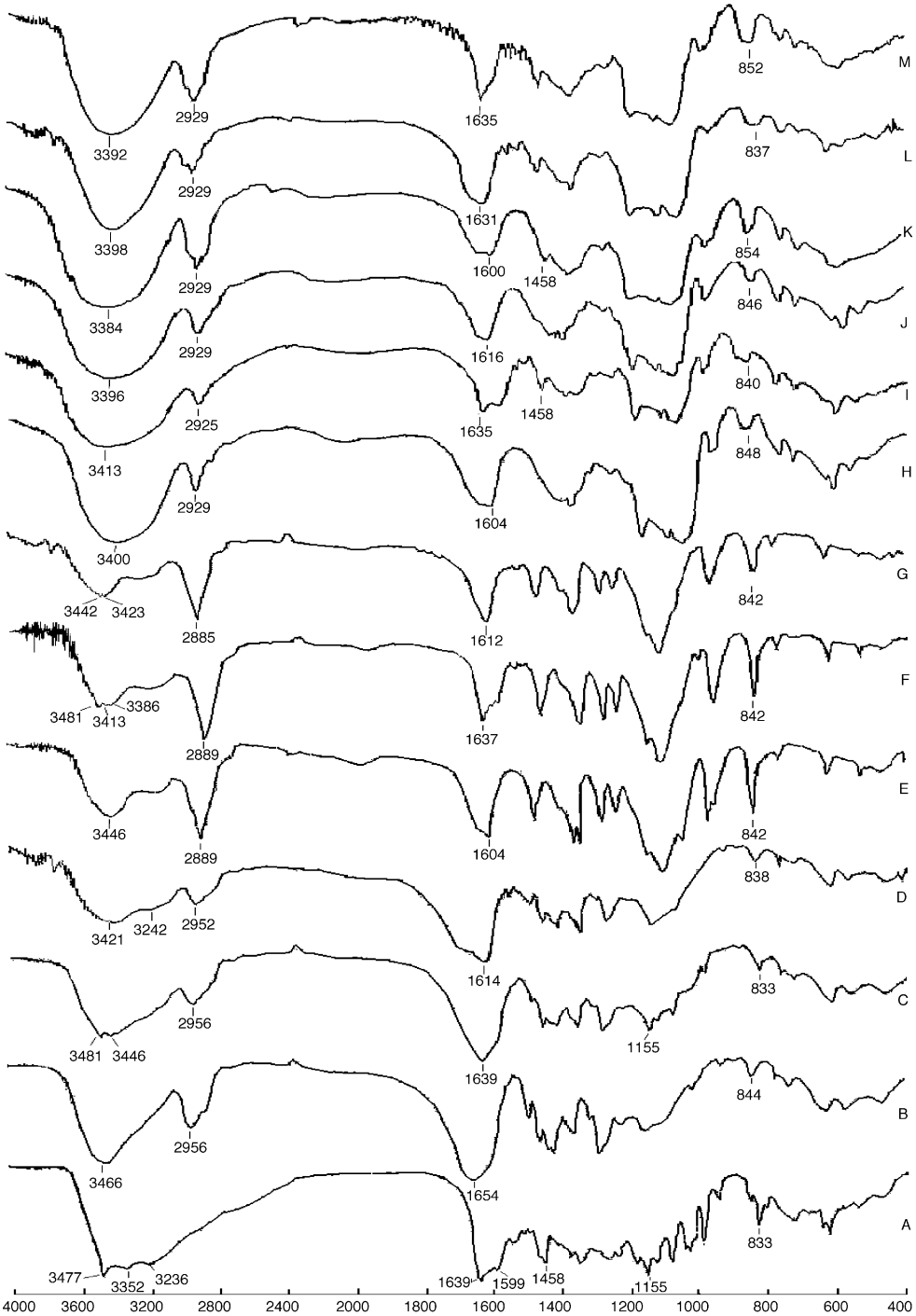

Fig. 4. FTIR spectra of pure materials, solid dispersions, inclusion complexes and corresponding physical mixtures. (A) AMP, (B) PVP K30, (C) physical mixture of AMP/PVP, (D) solid dispersion of AMP/PVP K30, (E) PEG 6000, (F) physical mixture of AMP/PEG, (G) solid dispersion of AMP/PEG 6000, (H) BCD, (I) physical mixture of AMP/BCD, (J) inclusion complex of AMP/BCD, (K) HPBCD, (L) physical mixture of AMP/HPBCD, (M) inclusion complex of AMP/HPBCD.

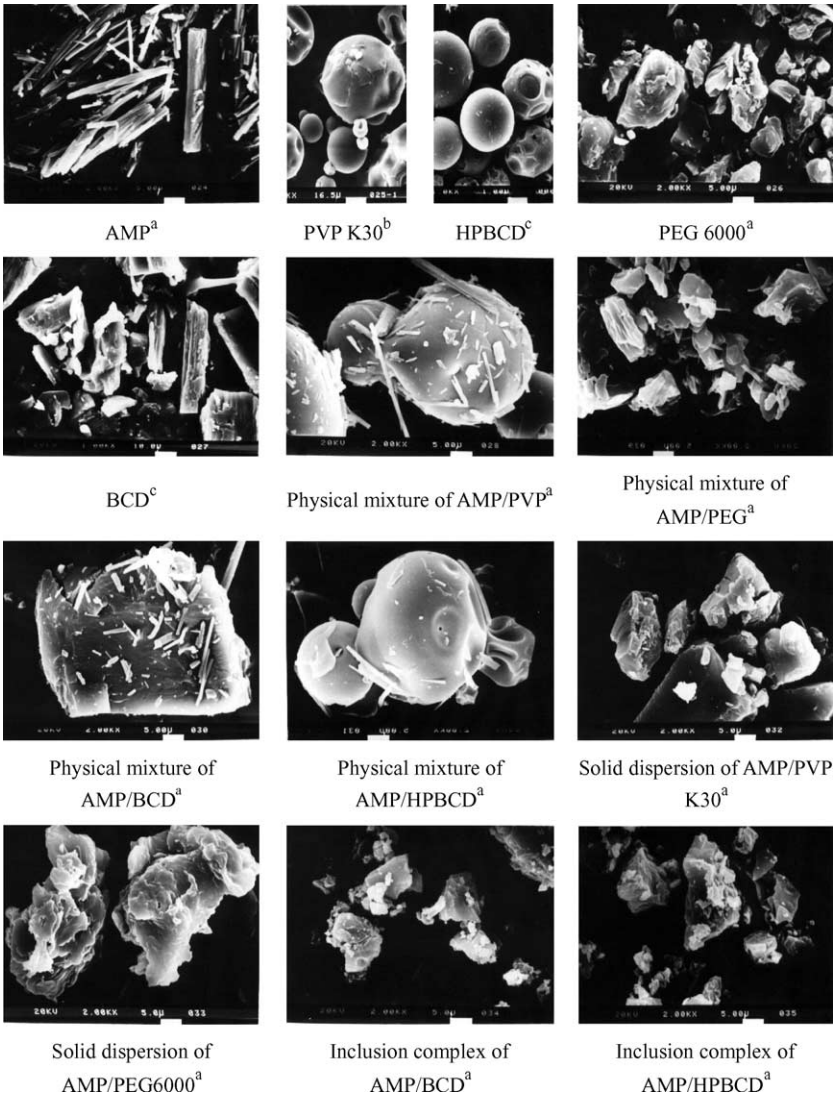

Fig. 5. SEM micrographs of single components and binary systems of AMP and PVP, PEG, BCD and HPBCD. (a) Scale bar represents 5 μm, (b) scale bar represents 16.5 μm, (c) scale bar represents 10 μm.

3800 cm^{-1} and those of the bound OH between 2800 and 3100 cm^{-1}, a shorter band between 1550 and 1700 cm^{-1}, and a large band which displayed distinct peaks in the region of 900–1200 cm^{-1}. In the IR spectra of physical mixture (Fig. 4I and L), broad bands of cyclodextrins overlap AMP main characteristic peaks. This was expected since AMP content was around 10.0% in the mixture. Nevertheless, the AMP characteristic peaks at 1639, 1458 and 833 cm^{-1} could be detected in the physical mixtures. It was clear that some of IR absorption peaks in inclusion complexes (Fig. 4J and M) were different from that of the corresponding physical mixtures, the shape and location of the bands in the region of 3100–3800, 1600–1700, 1100–1150 cm^{-1} had dramatically changed. As spectral changes always related to C–OH, C=O and C–O–C groups of AMP and CDs, it suggests that the host–guest interactions were dominated by hydrogen bonds among the groups mentioned above. These findings are in full agreement with other authors [18,26].

3.4. Scanning electron microscopy (SEM)

Fig. 5 illustrated the SEM micrographs of pure materials, the physical mixtures, solid dispersions and inclusion complexes at different magnifications. AMP existed in needle-like crystals, whereas PVP K30 and HPBCD were seen as amorphous sphericals or pieces of spherical particles. PEG 6000 and BCD consisted of large crystalline particles of rather irregular size. In the physical mixtures, the characteristic AMP crystals, which were mixed with excipient particles or adhered to their surface, were clearly detectable in all mixtures, thus, confirming the presence of crystalline drug. On the contrary, the solid dispersions and inclusion complexes appeared in the form of irregular particles in which the original morphology of both components disappeared and tiny aggregates of amorphous pieces of irregular size were present. Therefore, the reduced particle size, increased surface area, and the close contact between the hydrophilic carriers and AMP might be

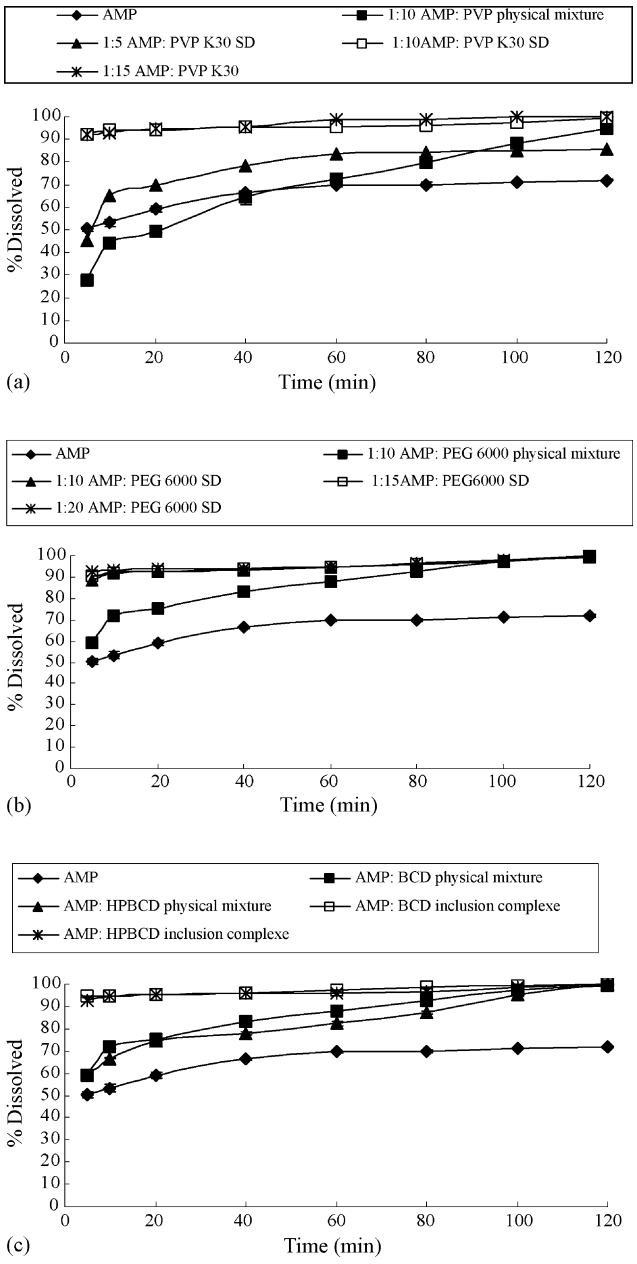

Fig. 6. (a) Dissolution curves of AMP alone and from AMP:PVP K30 solid dispersions (SD). (b) Dissolution of AMP from AMP:PEG 6000 solid dispersions (SD). (c) Dissolution of AMP from AMP:inclusion complexes.

responsible for the enhanced drug solubility found for the solid dispersion particles and inclusion complexes particles.

3.5. Dissolution studies

The dissolution curves of AMP from the various examined binary systems were presented in Fig. 6. The release rate profiles were plotted as the percentage AMP dissolved from the solid dispersions, inclusion complexes, physical mixture and pure AMP versus time. Fig. 6a showed the dissolution profiles of AMP with PVP K30 at different drug-to-carrier (w/w) ratios, the corresponding physical mixture 1:10 and AMP alone. It was evident that the rate of dissolution of pure AMP was slow, less than 70% of AMP being dissolved within 1 h. Comparing with that of pure AMP, the dissolution rate of AMP from its physical mixtures was appeared faster. However, it was much lower than that of the pure AMP before 40 min while it was clearly higher since then. Indeed, during dissolution experiments, it was noticed that physical mixture powder sank immediately to the bottom of the dissolution vessel to form viscous block, whereas the pure drug floated for a long period on the surface of the dissolution medium. The viscous block prevented the release of AMP. With the dissolving of the block, the release rate was increased. The increased dissolution rate observed for physical mixtures might be mainly attributable to the hydrophilic effect of the carriers, which can reduce the interfacial tension between the AMP and the dissolution medium, thus leading to a higher dissolution rate. Comparing to the pure AMP, AMP released from SD was more rapid at a drug-SD ratio of 1:5, and it almost released completely at the ratio of 1:10 and 1:15.

The dissolution rate of AMP from the physical mixture and all the PEG 6000 solid dispersions were significantly higher than AMP alone (Fig. 6b). This demonstrated the solubilizing effects of the PEG. The higher dissolution rate of the physical mixture relative to the pure AMP might be explained by the wetting effect of PEG on AMP. In vitro dissolution of AMP from the solid dispersions with PEG 6000 at ratios of AMP:carrier as 1:10, 1:15 and 1:20 shows the profiles that were not distinctive different from each other during the 2 h dissolution period. This suggested that the dissolution of AMP from the PEG 6000 solid dispersions was unrelated to the weight fraction of PEG 6000 [27]. Comparing to the physical mixture, AMP released from solid dispersion was more rapid than from physical mixture. Several mechanisms had been proposed to account for the increase in the dissolution kinetic of drugs from solid dispersions. Decreased crystallinity, increased wettability, and reduction of drug particle size were considered to be predominant factors [8].

Fig. 6c displayed the dissolution profiles of AMP from BCD and HPBCD. It was evident that both complexes and physical mixtures exhibited faster dissolution rates than that of pure AMP. A similar trend was observed with BCD and HPBCD and no significant difference was found between these two carriers. The remarkable increase of dissolution rates was obtained for the inclusion complexes. The drug dissolved very rapid within the first 5 min and more than 90% of AMP was dissolved within 10 min in water. This behavior might be attributed to the high energetic amorphous state and inclusion complex formation [28]. Corresponding physical mixtures also demonstrated higher dissolution rate. The improvement of dissolution rate obtained with physical mixtures could be attributed to both improved drug wettability and formation of readily soluble complexes in the dissolution medium.

The Q_5, Q_{10} and Q_{60} values (i.e., percent of dissolved AMP at 5, 10 and 60 min) were showed in Table 2. Improvement of the dissolution rate of AMP was obtained by both

Table 2
The percent of dissolved AMP from various samples at 5 min (Q_5), 10 min (Q_{10}) and 60 min (Q_{60})

Sample	Q_5	Q_{10}	Q_{60}
AMP	50.4	53.2	69.5
1:10 AMP:PVP physical mixture	27.9	44.3	72.2
1:5 AMP:PVP K30 SD	45.3	64.8	83.7
1:10 AMP:PVP K30 SD	92.2	93.9	95.5
1:15 AMP:PVP K30	92.0	93.0	98.5
1:10 AMP:PEG 6000 physical mixture	59.1	71.7	88.0
1:10 AMP:PEG 6000 SD	88.6	92.0	94.7
1:15 AMP:PEG6000 SD	90.5	92.0	94.9
1:20 AMP:PEG 6000 SD	92.71	93.0	94.9
AMP:BCD physical mixture	59.1	53.2	88.0
AMP:HPBCD physical mixture	58.8	71.7	82.4
AMP:BCD inclusion complex	94.4	66.6	97.0
AMP:HPBCD inclusion complex	92.6	94.8	96.0

physical mixture and formation of solid dispersion or inclusion complex. The effect of physical mixture on the dissolution rate was less than that of solid dispersion or inclusion complex. A rapid and excellent dissolution behavior was obtained by forming solid dispersion with PVP K30 or PEG 6000 and inclusion complex with BCD or HPBCD. No significant different was observed among the dissolution rates of various solid dispersions and inclusion complexes.

4. Conclusion

In this paper, the increased solubility and dissolution rate of AMP might be achieved either by forming solid dispersion with PVP K30 and PEG 6000 or by inclusion complexation with BCD and HPBCD. Based on the results, solutions containing AMP for oral administration or for injection could be prepared to perform further pharmacological studies. Solid dosage forms of AMP with PVP K30, PEG 6000, BCD or HPBCD with high dissolution rate could be manufactured. Since AMP possessed other defects such as poor intestinal permeability and poor stability, there were still some obstacles to improve its bioavailability. Increasing its permeability and stability will be our next objects.

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