Effect of carrier materials on the properties of the andrographolide solid dispersion

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In the work the andrographolide (AG)-solid dispersions (SDs) were prepared by the spray-drying method, using polyethylene glycol 8000 (PEG8000), Poloxamer188, polyvinylpyrrolidone K30 (PVPK30), Soluplus® as carrier materials. The effect of different polymers as carrier materials on the properties of the AG-SDs were studied. The results showed obvious differences in intermolecular interaction, thermal stability, drug state, powder properties, dissolution behavior, and so on of AG-SDs prepared using different polymers as carrier materials. AG-PEG8000-SD was a partial-crystalline and partial-amorphous powder with smaller surface area and pore volume, but it was easy to wetting and did not swell in contact with dissolved medium. AG-Soluplus®-SD was completely amorphous powder with larger specific surface area and pore volume, but it swelled in contact with water. Therefore, the dissolution profile of AG in AG-PEG8000-SD was similar to that in AG-Soluplus®-SD. Soluplus® and PEG8000 were suitable polymers to design AG-SDs, considering both physicochemical properties and dissolution behaviors. The results of this research showed that when selecting carrier materials for SD, we should not only consider the state of drugs in SD and the powder properties of SD, but also consider whether there is swelling when the carrier materials are in contact with the dissolution medium.

Keywords: Andrographolide. Solid dispersion. Physicochemical properties. Dissolution.

INTRODUCTION

Over 40% of active pharmaceutical ingredients in development pipelines are poorly water-soluble drugs which limits formulation approaches, clinical application and marketability because of their low dissolution and bioavailability (Zhang et al.; 2015; FDA, 2000). Solid dispersion (SD) is used as a useful approach to improve the solubility, dissolution rate and bioavailability of poorly water-soluble active pharmaceutical ingredients (Chiou, Riegelman, 1971; Bikiaris et al., 2005; Chokshi et al., 2007; Kawabata et al., 2011; Vo, Park, Lee, 2013; Singh et al., 2017; Hu, Lou, Hageman, 2018; Zhao et al., 2019). The poorly water-soluble drugs in solid dispersion can be dispersed as separate molecules, amorphous particles, or crystalline particles. Solid dispersion has many advantageous properties in improving the solubility and dissolution rate of poorly water-soluble drugs. These advantageous properties include changing of the drug crystal structure into an amorphous structure, reducing particle size and aggregation, enhancing wettability and porosity, and so on.

Most of the carrier materials used in solid dispersions are polymers, such as polyethylene glycol (PEG), poloxamer, polyvinylpyrrolidone (PVP), Soluplus®, and so on (Reginald-Opara et al., 2015; Barmpalexis et al., 2013; Mahmah et al., 2014; Thenmozhi, Yoo, 2017; Eloy, Marchetti, 2014; Chutimawarapan et al., 2000; Ramadhani et al., 2014; Thiry et al., 2016). The carrier material has an important influence on the
existing state and dissolution behavior of the drug in SD, thermal properties and powder properties of SD, and so on. PEG is widely used in solid dispersion owing to its low melting point, excellent solubility in water or organic solvents, low toxicity and low cost. PEG is very suitable for the preparation of SDs by the melting method and the solvent method. PVPK-30 is a high-molecular-weight water-soluble polymer, its high viscosity can prevent the recrystallization of drugs in the preparation, storage and dissolution process. Poloxamer is nonionic surfactants and polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®) is slightly surface-active, this property can be useful to maintain supersaturation of poorly soluble drugs in the gastrointestinal tract. It is generally believed that the drug in SD exists in amorphous state, and the SD powder has a large specific surface area and pore volume, which is beneficial to the dissolution of the drug in SD. Therefore, in this work, SDS were prepared using different polymers as carrier materials, and the effects of different polymers on the physicochemical properties and solubility behavior of the SDs were studied to find a suitable polymer for the application of SDs.

**Andrographis paniculata** (Burm. F.) Nees. is a herbaceous medicinal plant in the family of Acanthaceae and is native to China, India and other southeast Asian countries. The aerial parts (stems and leaves) of *Andrographis paniculata* have been widely used to treat internal body heat, common cold, non-infectious diarrhea, inflammation, herpes, sore throat and a variety of other chronic infectious diseases. Andrographolide (AG), a diterpenoid lactone, is the primary bioactive constituent of *Andrographis paniculata*, and has proven to be mainly responsible for the therapeutic properties of this herbal medicine. AG has many pharmacological actions, such as analgesic, antipyretic, anti-inflammatory, anti-infection, antiviral, anticancer, anti-hyperglycemia, anti-angiogenesis, immunostimulation, hepatoprotection, antifertility and anti-HIV effects. The potential use of AG has attracted wide attention in recent years. However, AG is a colorless and crystalline bicyclic compound, sparingly soluble in water. It has high lipophilicity (log P = 2.63) and low aqueous solubility (74 μg/mL). The therapeutic use of AG is restricted by its poor solubility in water which results in low bioavailability after oral administration (Zhang et al., 2015; Matsuda et al., 1994; Calabrese et al., 2000; Zhang, Tan, 2000; Shen et al., 2002; Singha, Roy, Dey, 2007; Sermkaew et al., 2013; Wen et al., 2014; Jiang et al., 2014). Therefore, AG was chosen as the model drug in this work.

In this paper, the AG-SDs were prepared by the spray-drying method (Bhardwaj et al., 2018; Marasini et al., 2013; Thybo et al., 2008), using PEG8000, Poloxamer188, PVPK30 and Soluplus® as carrier materials. The SDs and physical mixtures were characterized by Fourier transform infrared spectroscopy, thermogravimetric analysis, differential scanning calorimetry, X-ray diffractometry, scanning electron microscopy, particle size, specific surface area, pore volume and dissolution profile. The effects of different polymers on the physicochemical properties and dissolution behavior of AG-SDs were studied.

**MATERIAL AND METHODS**

**Material**

Andrographolide (AG), polyethylene glycol 8000 (PEG8000), poloxamer 188 and polyvinylpyrrolidone K30 (PVPK30) were purchased from Hao-Xuan Biotechnology Co., Ltd (Xi’an, China), MP Biomedical Co., Ltd. (Santa Ana, Cali., USA), Chineway Pharmaceutical Technology Co., Ltd. (Shanghai, China) and Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China), respectively. Soluplus® was kindly gifted from BASF SE (Germany).

**Methods**

**Preparation of AG-SD by spray drying method**

The spray-drying process was performed using a B-290 mini spray dryer (Büchi, Flawil, Switzerland). All spray-dried powders were obtained from solutions of AG and carrier material in 80% ethanol. The mass ratio of AG and carrier material was 1:3 (Zhao et al., 2019). The spray-drier inlet temperature was set at 40 °C, the pump rate was 2 mL/min, and the aspirator was set at 100% and the N2 flow at 40 m³/h. The powder was collected,
and then stored in a desiccator at room temperature for characterization and dissolution. The prepared SDs were denoted as AG-PEG8000-SD, AG-Poloxamer188-SD, AG-PVPK30-SD and AG-Soluplus®-SD, respectively.

**Preparation of physical mixture (PM)**

Appropriate quantities of AG and carrier material with mass ratio of 1:3 were ground together using a pestle and mortar, and then sieved by a standard sieve (60 mesh) to produce a physical mixture. The prepared physical mixtures were denoted as AG-PEG8000-PM, AG-P188-PM, AG-PVPK30-PM, and AG-Soluplus®-PM, respectively.

**Fourier transform infrared spectroscopy (FT-IR)**

FT-IR spectra were obtained using a Spectrum Two FT-IR spectrometer (PerkinElmer Corp., USA). About 2–3 mg of the sample was mixed with dry KBr. The powder was compressed in a hydraulic press to form a disc by a powder compressing instrument (FW-4A, Uncommon, Tianjin, China) for FT-IR analysis. The spectra of samples were scanned over a frequency range of 4000–400 cm⁻¹ with a resolution of 4 cm⁻¹.

**Thermogravimetric (TG) analysis**

TG analysis was carried out using a TG/DTA6300 thermal analysis instrument (SII Nano Technology Inc., Tokyo, Japan). Approximately 5 mg sample were placed in aluminum pans and heated from 30 to 500 °C with a heating rate of 10 °C/min.

**Differential scanning calorimetry (DSC)**

DSC curves were obtained by a Diamond DSC instrument (PerkinElmer Corp., Waltham, Massachusetts, USA). Calibration of the DSC instrument was carried out using indium as standard. Samples of 5 mg were loaded in aluminum pans and placed into DSC cell. Thermal analysis of samples was carried out at a scanning rate of 10 °C/min in the purge gas of nitrogen, over a temperature range of 20 - 270 °C.

**X-ray diffraction (XRD)**

XRD patterns were collected on a D8 ADVANCE-D8X X-ray diffractometer (Bruker AXS GMBH, Karlsruhe, Germany) with a Cu Kα line as the source of radiation (λ = 1.541 Å). Standard runs were carried out using a voltage of 40 kV, a current of 40 mA, and a scanning rate of 8 °/min over a 2θ range of 5 – 55° with a step size of 0.02°. The same sample of alpha-alumina as an external standard was also scanned in order to correct for the fluctuations in detector responses.

**Scanning electron microscope (SEM)**

SEM images were recorded on a Quanta 250 scanning electron microscope (FEI Corp., Hillsboro, Oregon, USA). The samples were mounted on an aluminum stub with double-sided adhesive tape and coated under a vacuum with gold in an argon atmosphere prior to the observation.

**Specific surface area and pore volume**

The specific surface area and pore volume were determined by nitrogen gas absorption based on the Brunauer-Emmett-Teller method (Sousa, Sousa, 2002) using TriStar3000 surface area and pore volume analyzer (Micromeritics Instrument Corp., Atlanta, Georgia, USA). The amount of nitrogen adsorbed was measured at partial nitrogen vapor pressure (p/p⁰), ranging between 0.05 and 0.35. Before measurement, the samples were performed with a continuous nitrogen flow at room temperature overnight to purge out the moisture.

**Particle size**

Particle size was measured using a laser diffraction particle size analyser (Mastersizer 2000, Malvern, UK). The intake air pressure and feed rate of the operating parameters of the experiment were 2.5 bars and 55%, respectively. Each sample was tested in triplicates. The particle size quoted in this paper is D[4,3] (the volume weighted mean diameter), D[3,2] (the surface weighted mean diameter), d(0.5) (the diameter corresponding to...
50% of the cumulative size distribution) and \(d(0.9)\) (the diameter corresponding to 90% of the cumulative size distribution).

*High performance liquid chromatography (HPLC)* analysis

The content of AG was determined using an appropriate HPLC method. The analysis was performed using a 1260 HPLC system (Agilent Corp., Palo Arto, California, USA). The column was Yilite C18 (150 mm × 4.6 mm, 5 μm). The mobile phases were methanol and water (60:40, \(v:v\)), the flow rate was 1 mL/min, the column temperature was 30 °C, and the wavelength of the UV detector was 225 nm. This method for determination of AG was validated by the methodological study in the preliminary experiment.

*Dissolution testing*

The dissolution testing was tested using Pharmacopoeia of China (Chinese Pharmacopoeia Commission, 2015) type 2 dissolution testing apparatus (paddle method). A ZRS-8G dissolution tester (Tian-da-Tianfa Technology Co., Ltd., Tianjin, China) was used in this study. The samples were accurately weighed (0.10 g) and put into the vessels with 900 mL double distilled water (\(n = 6\)); paddle speed was 100 rpm, and temperature was 37 ± 0.5 °C. The dissolution process was monitored for 2 h, and the 1.5 mL samples were taken at 5, 10, 15, 30, 45, 60, 90, and 120 min and replaced with an equal volume of the same fresh medium. An aliquot of 1.5 mL was filtered through a 0.22 μm filter, and the concentration of AG was determined according to the above-mentioned HPLC condition.

**RESULTS AND DISCUSSION**

**FT-IR analysis**

IR is a well-established method for characterizing intermolecular interactions such as hydrogen bonding, and has been extensively applied to probe the drug-carrier material interactions in solid dispersion (Shi *et al.*, 2013). Figure 1 showed the FT-IR spectra of pure AG, carrier material, physical mixture and SD. Table I listed the \(-\text{OH}\) and \(-\text{C}=\text{O}\) peak position of AG in different circumstances. Compared with the corresponding physical mixture, the \(-\text{C}=\text{O}\) peak position of AG was almost unchanged and the \(-\text{OH}\) peak position of AG was obviously blue-shifted in the AG-PEG8000-SD and AG-Poloxamer188-SD. It was suggested that the hydrogen bond may be formed between \(-\text{OH}\) of AG and \(-\text{OH}\) of PEG8000 or Poloxamer188. The AG-PVPK30-SD and AG-Soluplus®-SD showed the significant shift of \(-\text{C}=\text{O}\) and \(-\text{OH}\) peak position of AG, indicating that both \(-\text{C}=\text{O}\) and \(-\text{OH}\) of AG may have intermolecular interactions with PVPK30 or Soluplus®.
FIGURE 1 - FT-IR spectra of pure andrographolide (AG), carrier material, physical mixture (PM) and solid dispersion (SD) (A) PEG8000 and Poloxamer188 as carrier materials, (B) PVPK30 and Soluplus® as carrier materials.
TG analysis

TG analysis can be used to compare the thermal stability of SD and physical mixture (Albadarin et al., 2017; Veronez et al., 2015; Lim et al., 2013). The TG curves and 5% weight-loss temperature ($T_i$) of samples were shown in Figure 2 and Table II, respectively. As shown in Table II, the $T_i$ of AG-PEG8000/Poloxamer188-PM and AG-PEG8000/Poloxamer188-SD was higher than that of pure AG, in contrast to the $T_i$ of AG-PVPK30/Soluplus®-PM and AG-PVPK30/Soluplus®-SD. Moreover, the $T_i$ of all AG-SDs was obviously smaller than that of their respective AG-physical mixture, which indicated that the crystallinity of AG in AG-SDs decreased.

**TABLE I - -OH and -C=O peak position of AG in pure AG, PM and SD**

<table>
<thead>
<tr>
<th>Sample</th>
<th>-OH peak position (cm⁻¹)</th>
<th>-C=O peak position (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>3397.4, 3313.3</td>
<td>1726.8, 1675.0</td>
</tr>
<tr>
<td>AG-PEG8000-PM</td>
<td>3398.3, 3321.5</td>
<td>1727.0, 1674.9</td>
</tr>
<tr>
<td>AG-PEG8000-SD</td>
<td>3399.3, 3326.2</td>
<td>1727.1, 1675.8</td>
</tr>
<tr>
<td>AG-Poloxamer188-PM</td>
<td>3398.5, 3314.3</td>
<td>1727.2, 1674.5</td>
</tr>
<tr>
<td>AG-Poloxamer188-SD</td>
<td>3399.2, 3317.7</td>
<td>1727.2, 1675.0</td>
</tr>
<tr>
<td>AG-PVPK30-PM</td>
<td>3399.7, —</td>
<td>1726.9, 1674.6</td>
</tr>
<tr>
<td>AG-PVPK30-SD</td>
<td>3405.8, —</td>
<td>1754.4, 1662.8</td>
</tr>
<tr>
<td>AG-Soluplus®-PM</td>
<td>3399.1, 3325.4</td>
<td>1728.2, 1675.0</td>
</tr>
<tr>
<td>AG-Soluplus®-SD</td>
<td>3405.5, —</td>
<td>1737.3, 1675.0</td>
</tr>
</tbody>
</table>

AG is andrographolide, PM is physical mixture, SD is solid dispersion.
FIGURE 2 - TG curves of pure andrographolide (AG), carrier material, physical mixture (PM) and solid dispersion (SD) (A) PEG8000 and Poloxamer188 as carrier materials, (B) PVPK30 and Soluplus® as carrier materials.
TABLE II - $T_i$ and $T_m$ of pure AG, carrier material, PM and SD

<table>
<thead>
<tr>
<th>Sample</th>
<th>$T_i$ (ºC)</th>
<th>$T_m$ (ºC)</th>
<th>Sample</th>
<th>$T_i$ (ºC)</th>
<th>$T_m$ (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>299.6</td>
<td>243.7</td>
<td>Poloxamer188</td>
<td>340.2</td>
<td></td>
</tr>
<tr>
<td>PEG8000</td>
<td>363.0</td>
<td></td>
<td>Soluplus®</td>
<td>287.1</td>
<td></td>
</tr>
<tr>
<td>PVPK30</td>
<td>64.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AG-PEG8000-PM</td>
<td>352.0</td>
<td>217.7</td>
<td>AG-Poloxamer188-PM</td>
<td>345.4</td>
<td>224.4</td>
</tr>
<tr>
<td>AG-PEG8000-SD</td>
<td>341.8</td>
<td>209.0</td>
<td>AG-Poloxamer188-SD</td>
<td>326.8</td>
<td>222.4</td>
</tr>
<tr>
<td>AG-PVPK30-PM</td>
<td>74.2</td>
<td>238.4</td>
<td>AG-Soluplus®-PM</td>
<td>267.5</td>
<td>232.0</td>
</tr>
<tr>
<td>AG-PVPK30-SD</td>
<td>54.0</td>
<td>—</td>
<td>AG-Soluplus®-SD</td>
<td>255.5</td>
<td>—</td>
</tr>
</tbody>
</table>

AG is andrographolide, PM is physical mixture, SD is solid dispersion.

DSC analysis

Figure 3 showed the DSC thermograms of pure AG, carrier materials, physical mixture and SD. Table II listed the melting temperature ($T_m$) of all the samples near 200 - 250 ºC. As shown in Figure 3, the DSC thermogram of pure AG exhibited a sharp endothermic peak at 243 ºC, indicating AG is typical crystalline substance.

There was no sharp endothermic peak of crystal AG in AG-PEG8000-PM and AG-Poloxamer188-PM, but a weakened endothermic peak at 218 ºC and 224 ºC, respectively, which was close to the endothermic peak of the corresponding SD. This was because, during the heating of measuring DSC curve the carrier material firstly melted, and then the crystal AG was partially dissolved in melted carrier material and formed SD.

Therefore, the $T_m$ of the physical mixture was similar to that of the corresponding SD. In AG-PEG8000-SD and AG-Poloxamer188-SD, a small endothermic peak was observed at 209 ºC and 222 ºC, respectively (Figure 3 and Table II). This result indicated that the completely amorphous AG-PEG8000-SD and AG-Poloxamer188-SD had not been obtained. The AG was in a partial-amorphous and partial-crystal state in the AG-PEG8000-SD and AG-Poloxamer188-SD.

The melting peak of typical crystal AG was observed at 232 ºC for AG-Soluplus®-PM, and a small endothermic peak for AG-PVPK30-PM at 238 ºC. Compared with the corresponding physical mixture, all the AG-PVPK30-SD and AG-Soluplus®-SD did not appear the melting peaks of AG.
XRD analysis

The crystallinity of pure AG, carrier materials, physical mixture and SD were examined using XRD and their diffraction patterns were displayed in Figure 4. The AG diffraction pattern demonstrated that it has a very crystalline nature with sharp intensive peaks throughout its pattern. The crystalline AG characteristic
Diffraction peaks have been observed in all the physical mixtures.

Comparing the SD and corresponding physical mixture XRD patterns, demonstrated that the AG-PEG8000-SD and AG-Poloxamer188-SD have sharp diffraction peaks associated with AG, suggesting that the AG had retained some of its crystalline nature. However, the intensity of AG diffraction peaks in the AG-PEG8000-SD and AG-Poloxamer188-SD reduced significantly more than that in the corresponding physical mixture. This indicated that AG was in a partial-amorphous and partial-crystalline state in the AG-PEG8000-SD and AG-Poloxamer188-SD. AG-PVPK30-SD had the AG very weak diffraction peaks at 2θ 12.09° and 15.75°, which imply that a small amount of crystalline AG still existed in this SD. AG-Soluplus®-SD had no diffraction peaks associated with AG and thus would suggest that the AG in this SD was completely in its amorphous state.

**FIGURE 4** - XRD patterns of pure andrographolide (AG), carrier material, physical mixture (PM) and solid dispersion (SD) (A) PEG8000 and Poloxamer188 as carrier materials, (B) PVPK30 and Soluplus® as carrier materials.
XRD pattern demonstrated a small amount of crystalline AG still existed in the AG-PVPK30-SD. However, the AG melting peak in AG-PVPK30-SD was not found by DSC analysis. This may be due to PVPK30 firstly melted during the heating of measuring DSC curve, and then a small amount of crystal AG was dissolved in melted carrier material. Therefore, no AG melting peak in AG-PVPK30-SD was detected in DSC analysis. The results of DSC and XRD analysis showed that the AG crystallinity in AG-PVPK30-SD and AG-Soluplus®-SD was significantly lower than that in AG-PEG8000-SD and AG-Poloxamer188-SD.

**SEM analysis**

In order to determine the morphology of SDs, SEM analysis of the samples was performed. As illustrated in Figure 5a, pure AG showed block crystalline structure with a smooth surface. In physical mixtures the AG and carrier material displayed their original surface morphology. The surface morphology of AG-SDs prepared with different polymers as carrier material had obvious differences: the powders of AG-PEG8000-SD and AG-Poloxamer188-SD were rod particles with irregular protuberances, and the particle size was large; the powders of AG-PVPK30-SD and AG-Soluplus®-SD were spherical particles with small particle size. AG-PVPK30-SD was a spherical particle with a smooth surface (Figure 5M), and AG-Soluplus®-SD was a flat spherical particle with middle depression (Figure 5Q).
FIGURE 5 - SEM photographs of samples: (A) AG, (B) PEG8000, (C) AG-PEG8000-PM, (D) AG-PEG8000-SD, (E) AG-PEG8000-SD, (F) Poloxamer188, (G) AG-Poloxamer188-PM, (H) AG-Poloxamer188-SD, (I) AG-Poloxamer188-SD, (J) PVPK30, (K) AG-PVPK30-PM, (L) AG-PVPK30-SD, (M) AG-PVPK30-SD, (N) Soluplus®, (O) AG-Soluplus®-PM, (P) AG-Soluplus®-SD, (Q) AG-Soluplus®-SD.
Effect of carrier materials on the properties of the andrographolide solid dispersion

**Particle size, specific surface area and pore volume**

Table III listed the particle size, specific surface area and pore volume of all the SDs and physical mixtures. Compared with the corresponding physical mixture, the particle size of AG-SD decreased, the specific surface area and the pore volume increased. These changes in the powder properties can significantly increase the effective contact area between the SD powder and the dissolution medium, which was beneficial to the AG dissolution in AG-SD.

In order to further study the effect of different polymers on the powder properties of AG-SDs, cluster analysis was carried out on all SDs. Based on the variable of surface weighted mean diameter (D\([3,2]\)), volume weighted mean diameter (D\([4,3]\)), d0.5, d0.9, surface area, pore volume and pore size, the samples were cluster analyzed by intergroup connection clustering method and squared Euclidean distance measured data. The cluster analysis Figure 6 was calculated by SPSS19.0 software. As can be seen from Figure 6, when the distance was less than 25, the samples can be divided into two groups: the AG-Poloxamer188-SD was the first group; the other SDs were the second group. When the distance was reduced to less than 4, AG-PEG8000-SD was isolated from the second group in a single group. Considering the results of this cluster analysis and above SEM photographs, it was shown that there were significant differences in the surface morphology, surface area and particle size between AG-PEG8000/ Poloxamer188-SDs and AG-PVPK30/Poloxamer®-SD.

**TABLE III** - Particle size, specific surface area and pore volume of SD and PM

<table>
<thead>
<tr>
<th>Sample</th>
<th>D([3,2]) (μm)</th>
<th>D([4,3]) (μm)</th>
<th>d0.5 (μm)</th>
<th>d0.9 (μm)</th>
<th>Specific surface area (m(^2)/g)</th>
<th>Pore volume (×10(^{-3}), m(^3)/g)</th>
<th>Pore size (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG-PEG8000-SD</td>
<td>25.9±1.8</td>
<td>168.1±11.2</td>
<td>42.8±2.9</td>
<td>557.4±35.6</td>
<td>0.4370±0.0331</td>
<td>1.241±0.0933</td>
<td>113.6±8.3</td>
</tr>
<tr>
<td>AG-PEG8000-PM</td>
<td>52.5±4.3</td>
<td>161.8±15.4</td>
<td>145.5±15.1</td>
<td>322.9±28.3</td>
<td>0.0109±0.0987</td>
<td>1.034±0.0987</td>
<td>3783.1±305.9</td>
</tr>
<tr>
<td>AG-Poloxamer188-SD</td>
<td>51.8±3.7</td>
<td>154.1±10.9</td>
<td>79.6±6.6</td>
<td>337.3±26.0</td>
<td>0.1984±0.0009</td>
<td>0.634±0.0454</td>
<td>127.7±9.5</td>
</tr>
<tr>
<td>AG-Poloxamer188-PM</td>
<td>59.1±6.0</td>
<td>198.0±18.6</td>
<td>181.8±20.1</td>
<td>389.7±39.1</td>
<td>0.9961±0.0136</td>
<td>0.627±0.0622</td>
<td>400.7±397.7</td>
</tr>
<tr>
<td>AG-PVPK30-SD</td>
<td>3.9±0.2</td>
<td>21.6±1.9</td>
<td>4.9±0.4</td>
<td>59.8±5.1</td>
<td>1.9101±0.1341</td>
<td>4.862±0.3265</td>
<td>101.8±8.4</td>
</tr>
<tr>
<td>AG-PVPK30-PM</td>
<td>29.0±2.2</td>
<td>103.1±9.5</td>
<td>52.7±5.1</td>
<td>148.0±12.3</td>
<td>0.0360±0.0040</td>
<td>0.185±0.0138</td>
<td>172.4±15.6</td>
</tr>
<tr>
<td>AG-Soluplus®-SD</td>
<td>3.2±0.2</td>
<td>4.6±0.3</td>
<td>3.9±0.2</td>
<td>8.4±0.4</td>
<td>0.7292±0.0659</td>
<td>2.673±0.1711</td>
<td>146.6±8.2</td>
</tr>
<tr>
<td>AG-Soluplus®-PM</td>
<td>62.3±4.1</td>
<td>287.3±20.1</td>
<td>283.2±18.9</td>
<td>510.3±41.5</td>
<td>0.0294±0.0027</td>
<td>0.132±0.0092</td>
<td>180.2±15.0</td>
</tr>
</tbody>
</table>

D\([3,2]\) is surface weighted mean diameter, D\([4,3]\) is volume weighted mean diameter, d(0.5) is the diameter corresponding to 50% of the cumulative size distribution, d(0.9) is the diameter corresponding to 90% of the cumulative size distribution. PM is physical mixture, SD is solid dispersion.
Dissolution testing

The dissolution of a poorly water-soluble drug is crucial where it is the rate-limiting step in the oral absorption process from a solid dosage form and is an important parameter related to bioavailability (Mohammadi et al., 2010; Bothiraja et al., 2009). The dissolution profiles of pure AG, physical mixture and SD were illustrated in Figure 7. It can be seen that the maximum dissolution percentage of pure AG in 120 min was only 22% when using water as the medium. $Q_{5\text{min}}$ (the dissolution percentage in 5 min) and $t_{75\%}$ (time required for 75% dissolution) were calculated and listed in Table IV. As shown in Table IV, all the SDs exhibited higher values of $Q_{5\text{min}}$ and lower values of $t_{75\%}$ when compared with the physical mixture and pure AG. The results indicated that the dissolution rate of AG in all the SDs was increased obviously.

FIGURE 6 - Cluster analysis tree diagram by intergroup connection on the variable of particle size, specific surface area and pore volume.

FIGURE 7 - Dissolution profiles of pure andrographolide (AG), physical mixture (PM) and solid dispersion (SD) ($n = 6$).
TABLE IV - $Q_{5\text{ min}}$ and $t_{75\%}$ of pure AG, PM and SD

<table>
<thead>
<tr>
<th>Sample</th>
<th>$Q_{5\text{ min}}$ (%)</th>
<th>$t_{75%}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AG</td>
<td>4.32±1.84</td>
<td>&gt;120</td>
</tr>
<tr>
<td>AG-PEG8000-PM</td>
<td>21.65±0.40</td>
<td>&gt;120</td>
</tr>
<tr>
<td>AG-PEG8000-SD</td>
<td>70.73±3.23</td>
<td>11</td>
</tr>
<tr>
<td>AG-Poloxamer188-PM</td>
<td>13.47±1.99</td>
<td>&gt;120</td>
</tr>
<tr>
<td>AG-Poloxamer188-SD</td>
<td>72.07±1.45</td>
<td>11</td>
</tr>
<tr>
<td>AG-PVPK30-PM</td>
<td>6.88±0.19</td>
<td>&gt;120</td>
</tr>
<tr>
<td>AG-PVK30-SD</td>
<td>52.61±4.71</td>
<td>66</td>
</tr>
<tr>
<td>AG-Soluplus®-PM</td>
<td>3.99±0.47</td>
<td>&gt;120</td>
</tr>
<tr>
<td>AG-Soluplus®-SD</td>
<td>82.56±0.86</td>
<td>4</td>
</tr>
</tbody>
</table>

AG is andrographolide, PM is physical mixture, SD is solid dispersion.

In order to further study the effect of different polymers on the dissolution behavior of AG in the SD, all the samples were investigated by cluster analysis. Based on the variable of the dissolution percentage of AG at different time, the samples were cluster analyzed by intergroup connection clustering method and squared Euclidean distance measured data. The cluster analysis Figure 8 was calculated by SPSS19.0 software. As can be seen from Figure 8 when the distance was less than 25, the samples can be divided into two groups: the physical mixtures and pure AG were the first group; the SDs were the second group. The results suggested that SD prepared with different polymers can significantly improve the dissolution of AG.

When the distance was less than 2, the SDs were further divided into two groups: AG-Poloxamer188-SD and AG-PVK30-SD were the first group, AG-PEG8000-SD and AG-Soluplus®-SD were the second group. The dissolution percentage of AG in AG-Poloxamer188-SD and AG-PVK30-SD at 120 min was only 80.51% and 76.41%, respectively, which was due to the presence of partial-crystalline AG in both SDs. Moreover, in the process of dissolution the powder of AG-PVK30-SD was swelled and water film was formed on its surface, which prevented the diffusion of AG from SD powder to the dissolution medium. The surface area and pore volume of AG-Poloxamer188-SD were the smallest among the SDs, which reduced its effective contact area with the dissolution medium. The above factors reduced the dissolution rate of AG in AG-Poloxamer188-SD and AG-PVK30-SD.

The AG in AG-Soluplus®-SD was completely amorphous. The powder of AG-Soluplus®-SD had a larger specific surface area and pore volume, and water can easily enter into the SD. These were beneficial to the dissolution of AG. It was worth noting that the AG was in a partial-amorphous and partial-crystalline state in AG-PEG8000-SD, and the specific surface area and pore volume of AG-PEG8000-SD were much smaller than those of AG-Soluplus®-SD. However, because of the good hydrophilicity and wetting of PEG8000, the cumulative dissolution percentage of AG in AG-PEG8000-SD at 120 min was up to 91.30%.
In this paper, the AG-SDs were prepared by the spray-drying method, using PEG8000, Poloxamer188, PVPK30 and Soluplus® as carrier materials. The results showed that there were obvious differences in intermolecular interaction, thermal stability, drug crystallinity, surface morphology, specific surface area, pore volume and particle size and dissolution behavior of the AG-SDs prepared using different polymer as carrier material. Compared with AG-Soluplus®-SD, AG in AG-PEG8000-SD was a partial-crystalline and partial-amorphous state, and its specific surface area and pore volume were smaller, but AG-PEG8000-SD powder was easy to wetting and did not swell when it was in contact with dissolved medium. Therefore, the dissolution profile of AG in AG-PEG8000-SD was similar to that in AG-Soluplus®-SD. Soluplus® and PEG8000 were suitable polymers to design AG-SDs in this research considering both physicochemical properties and dissolution behaviors. The results of this work suggested that when selecting carrier materials for SD, we should not only consider the state of drugs in SD and the powder properties of SD, but also consider whether there is swelling when the carrier materials are in contact with the dissolution medium.

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