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Effect of different carriers on *in vitro* dissolution behavior and physicochemical characterization of glycyrrhetinic acid solid dispersions

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Abstract: The effect of PEG 4000, PVP K30, poloxamer 407 and urea as carriers glycyrrhetinic acid solid dispersions (GA-SDs) on dissolution behavior and physicochemical properties were investigated. In vitro dissolution test results show that GA-SDs prepared with four different carriers have better dissolution properties compared with pure drug and corresponding physical mixtures. The enhancement effect of four carriers on dissolution rate and equilibrium solubility shows that PVP K30>PEG 4000>P 407>urea. In addition, the dissolution rate and solubility of the GA-SDs with a carrier-drug ratio of 8:1 were better than the samples of 4:1. The DSC and XRD patterns showed that crystallization of GA-SDs prepared by PVP K30 was significantly inhibited and both were transformed to amorphous. Based on FTIR detection, hydrogen-bond between carriers (PVP K30, PEG 4000 and P 407) and GA molecules were formed. SEM results showed that compared to GA-SDs prepared by the other three carriers, GA-PVP K30-SDs have a smoother surface and clearer boundary. In conclusion, the findings of this study demonstrated that the dissolution performance of the GA-SDs prepared by the solvent method is related to carrier type. The samples with PVP K30 as the carrier have the best dissolution performance.

Keywords: Glycyrrhetinic acid, solid dispersions, carrier type, dissolution rate.

INTRODUCTION

Glycyrrhetinic acid (GA) is one of the main active ingredients extracted from the root or rhizome of licorice (Green *et al.,* 2018). It is also the hydrolysis product of oral preparations of glycyrrhizic acid (salt) in the gastrointestinal tract (Meteleva *et al.,* 2019). The molecular formula of GA is $C_{30}H_{46}O_4$, and its structural formula is shown in fig1. Studies have shown that GA has anti-inflammatory, antiviral, antitumor and analgesic effects (Khudobko *et al.,* 2014, Liu *et al.,* 2019, Chen *et al*., 2019, Zhao *et al*., 2013). However, glycyrrhetinic acid has extremely poor solubility in water and low bioavailability, which limits its oral bioavailability (Dai *et al*., 2019).

Generally, the solubility of hydrophobic drugs can be improved through micronization and amorphization. In recent years, some preparation technologies including the combination of emulsification-solvent evaporation and sonication to improve the oral absorption of GA have been studied (Fan *et al*., 2011, Rizza *et al*., 2010, Mai *et al*., 2020, Onishi *et al*., 2005). Using solid dispersion technology, the drug can be dispersed in the carrier in an amorphous or microcrystalline state. Since the amorphous state of the drug has higher free energy than its stable crystalline state, it is significantly better in solubility than the stable crystalline compound, and can form a supersaturated drug solution after dissolution (Fine-Shamir *et al.*, 2017). Therefore, the solid dispersions technique is an effective method for improving the dissolution and oral bioavailability of poorly soluble drugs.

The choice of carrier is the most important part of the study of solid dispersions. Different carriers have obvious effects on the dissolution properties and recrystallization ability of solid dispersions (Tekade and Yadav, 2020). This is because the carrier can not only increase the wettability of the drug and ensure a high degree of dispersion of the drug, but also play a major role in inhibiting the transformation of the drug crystal form and improving the stability of the formulation. The drug dissolution behavior of the solid dispersion and the time to maintain the supersaturated dissolution depends on the type of carrier and the ratio of the carrier to the drug (Essa and Mai, 2015). Whether the carrier can effectively inhibit the recrystallization of the drug depends mainly on the interaction between the carrier and the drug and whether the carrier can increase the glass transition temperature of the system (Xiang *et al.,* 2015). Commonly used water-soluble carrier materials for solid dispersions include polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), poloxamer and urea. PEG has a low melting point, a fast-curing speed, a strong ability to form a solid drug solution, and is easily soluble in a variety of organic solvents (Akbari *et al.,* 2015). Polyvinylpyrrolidone (PVP) is an amorphous polymer that is easily soluble in water and a variety of organic solvents. Therefore, the solvent method is usually used to prepare solid dispersions with PVP as a carrier (Kawtikwar *et al.,* 2012). Poloxamer is a block polymer of ethylene oxide and propylene oxide, with strong solubilization ability

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(Andrew *et al.,* 2018). It has the advantages of low melting point, surface activity and safety. Urea is a commonly used crystalline carrier for solid dispersions and crystalline drugs are dispersed in urea to form a eutectic mixture or a monotectic mixture, thereby increasing the dissolution rate (Soares *et al.,* 2021). However, it is very difficult to obtain a solid dispersion with a precise eutectic level in practical applications. The structures of the four carriers are shown in fig. 1.

The molecular structure of different carriers is different, which leads to the difference in the degree of dispersion of the drug in the solid dispersion and the ability to form hydrogen bonds and the dissolution properties are also different. For this reason, this study selects four commonly used solid dispersion carriers to prepare glycyrrhetinic acid solid dispersions and investigates the influence of different carriers on the dissolution properties of glycyrrhetinic acid solid dispersions. In addition, through microscopic morphology, chemical structure, phase properties, etc., the physical and chemical properties of solid dispersions prepared by different carriers were further investigated. This confirms the relationship between the physical and chemical properties of solid dispersions prepared by different carriers and their dissolution properties.

MATERIALS AND METHODS

Materials

GA (>98% pure) and reference compound of GA (analytically pure) were obtained from Dalian Meilun Biology Technology Co., Ltd (Dalian, China). Poloxamer 407 (P 407) and PVP K30 (analytically pure) were obtained from BASF Corporation (Shanghai, China). PEG 4000, urea and ethanol were purchased from Sinopharm Chemical Reagent Co., Ltd (Beijing, China). Pure water was prepared by a Milli-Q water-purification system (Millipore, Bedford, MA, USA).

Methods

Preparation of solid dispersions

GA-PEG 4000- SDs, GA-P 407-SDs, GA-PVP K30-SDs and GA-Urea-SDs were prepared by the solvent method. Briefly, the GA and carrier were weighed based on the formulated amount and placed in an evaporating dish. They were then co-dissolved in 95% (V/V) ethanol-water solution and heated in a water bath (80±1°C) with stirring. After the removal of ethanol, the mixture was taken out and placed in a vacuum dryer for several days, and then it was milled and sieved with an 80mesh sieve for subsequent experiments.

Preparation of physical mixtures

Physical mixtures (PMs) were prepared by manually mixing GA and different carriers which were previously sieved through an 80mesh sieve in a mortar for 5 min until a homogenous mixture was obtained.

Determination of particle diameter

The sample particle diameter was measured using a Sympatec laser diffraction particle diameter analyzer (SUCELL/M, Clausthal-Zellerfeld, Germany) with the RODOS dry dispersion unit. 30mg of powder was loaded into a measuring vial, which was dispensed using the ASPIRES (Sympatec GmbH, Clausthal-Zellerfeld, Germany) micro-dosing unit. The powder was then dispersed into the HELOS system using the RODOS dry disperser with a primary air dispersion pressure of 4.5bar. The Vibri feeder was operated at 60% feed rate. Each measurement was performed in triplicate.

Determination of equilibrium solubility

Excess samples were added to 10mL of pure water, PBS (pH=6.8) and 0.1 N HCl solution under magnetic stirring (300 rpm) at 25°C in a temperature-controlled water bath until equilibrium was achieved (48h). The samples were filtered through a 0.45μm Teflon membrane filter，suitably diluted with methanol and analyzed via high-performance liquid chromatography (HPLC) as described below. The drug solubility was assayed using a LabAlliance (model Series III) HPLC system (Lab Alliance, Tianjin, China) equipped with a quaternary pump, an autosampler and a column compartment, coupled to a UV detector. Separation was performed on a C18column (4.6mm × 250mm; 5μm; Dikma Technologies, Beijing, China). The mobile phase comprises methanol, water and acetic acid (89:10:1, v/v/v) at a flow rate of 1.0mL·min^{-1}. The analytes were detected by a UV detector at 250nm (21). Good linearity was found for GA in the range of 0.5-50μg·mL^{-1}.

In vitro dissolution testing

The dissolution rate was determined using a USP type II Apparatus (RCZ-8A, Tiandatianfa Tech., Ltd., Tianjin, China). 900mL of phosphate buffer solution (pH=6.8) was used as the dissolution medium (37^{o}C±0.2^{o}C) for the solid sample (equivalent to 10.0mg drug) with the paddle rotation speed of 100 rpm. At pre-determined time intervals, 5mL aliquots were withdrawn, filtered through a 0.45μm Teflon membrane filter and analyzed by HPLC. The removed volume was replaced with fresh media to maintain a sink condition.

Differential scanning calorimetry (DSC)

DSC measurements were performed on an HSC-1 DSC scanning calorimeter (Hengjiu Instrument, Ltd., Beijing, China). Samples were precisely weighted (10mg) and were sealed in the aluminum crucible. The samples were heated from 25 to 350°C at a rate of 10°C·min^{-1} under a nitrogen atmosphere.

X-ray diffraction (XRD)

The structural properties of samples were obtained using the D8 Focus X-ray diffractometer (Bruker, Germany) with Cu-Kα radiation. Measurements were performed at a voltage of 40kV and 40mA. Samples were scanned from 5° to 60°, and the scanned rate was 5°·min^{-1}.

Fourier transform infrared spectroscopy (FTIR)
The FTIR spectra of samples were obtained on a Nicolet 6700 FT-IR spectrophotometer (Thermo Scientific, Waltham, MA, USA). Every sample and potassium bromide was mixed with an agate mortar and compressed into a thin disc. The scanning range was 4000-400cm^{-1} and the resolution was 4cm^{-1}.

Scanning electron microscopy (SEM)
The samples were fixed to an SEM stub with carbon conductive and sputter-coated with gold using an SBC-12 sputter-coater (KYKY Tech., Ltd., Beijing, China). The surface morphology of the sample was then observed by an S-4300 scanning electron microscope (Hitachi, Tokyo, Japan).

STATISTICAL ANALYSIS

All data were reported as mean ± standard deviation (SD). One-way analysis of variance was performed to reveal statistical differences between sample groups. All statistical analyses were executed using SPSS Software version 17.0.

RESULTS

Particle diameter determination
The results of particle diameter for SDs and PMs with different carriers are given in table 1. The particle diameter determination showed that the mean particle diameter of physical mixtures prepared by the four carriers is less than 64μm. The mean particle diameter of PVP-GA-SDs with an 8:1 carrier drug ratio is relatively larger ($p<0.05$) than that of other samples, the diameter of GA-Urea-SDs is the smallest. On the other hand, the mean particle diameter of GA raw material is 11.85±1.83 μm which is smaller ($p<0.05$) than the physical mixture and solid dispersion samples.

The equilibrium solubility
Oral preparations need to be examined for their dissolution under gastrointestinal pH conditions. In this research, the equilibrium solubility of solid SDs in pure water, PBS, and hydrochloric acid solution was determined by HPLC, respectively. The results are shown in table 2.

The data showed that the solubility of GA-SDs prepared with four different carriers were improved compared with the GA raw material in pure water and PBS. In PBS media, the equilibrium solubility of GA-PVP K30-SDs with an 8:1 carrier drug ratio is significantly greater ($p<0.05$) than that of GA-SDs prepared by the other three carriers. In water media, the equilibrium solubility of GA-Urea-SDs is smaller ($p<0.05$) than in the other three solid dispersions. In a hydrochloric acid solution, GA-PVP K30-SDs maintained certain solubilization, but the solubility of other SDs and GA raw material could not be detected. Furthermore, the result proved that the carrier-drug ratio had an impact on the solubilization of GA, which showed that the solubilization of SDs with the carrier-drug ratio in 8:1was better than in 4:1.

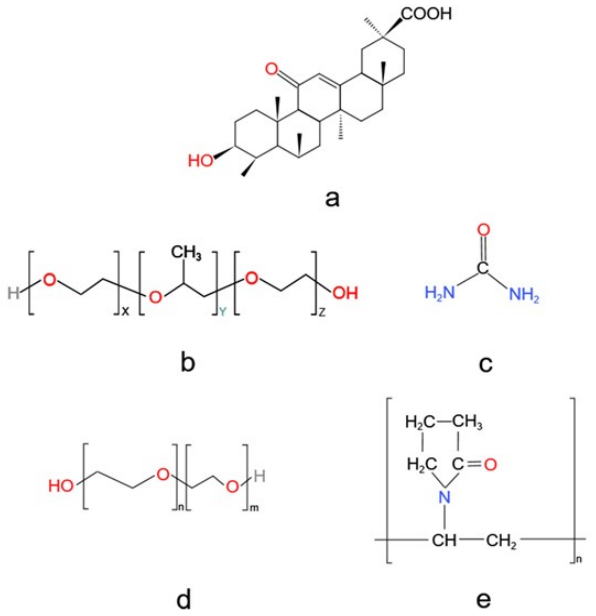

Fig. 1: Chemical structure of glycyrrhetinic acid (a), poloxamer 188 (b), Urea (c), PEG 4000(d), PVP K30 (e)

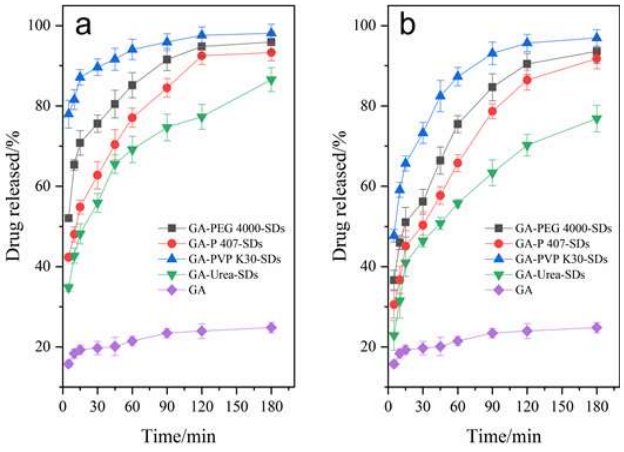

Fig. 2: Dissolution profiles of pure GA, GA-PEG 4000-SD, GA-P 407-SD, GA-PVP K30-SD and GA-Urea-SD in phosphate buffer solution. (a) carriers/GA weight of 4:1. (b) carriers/GA weight ratio of 8:1. One way ANOVA was performed where differences considered significant at $p < 0.05$.

Determination of in vitro dissolution rate
PBS and the hydrochloric acid solution were used as simulated intestinal and gastric fluid, respectively. Except for GA-PVP-SDs, the GA-SDs prepared by the other three carriers are insoluble in hydrochloric acid. In order to maintain a sink condition, hydrochloric acid is not used as a dissolution medium.

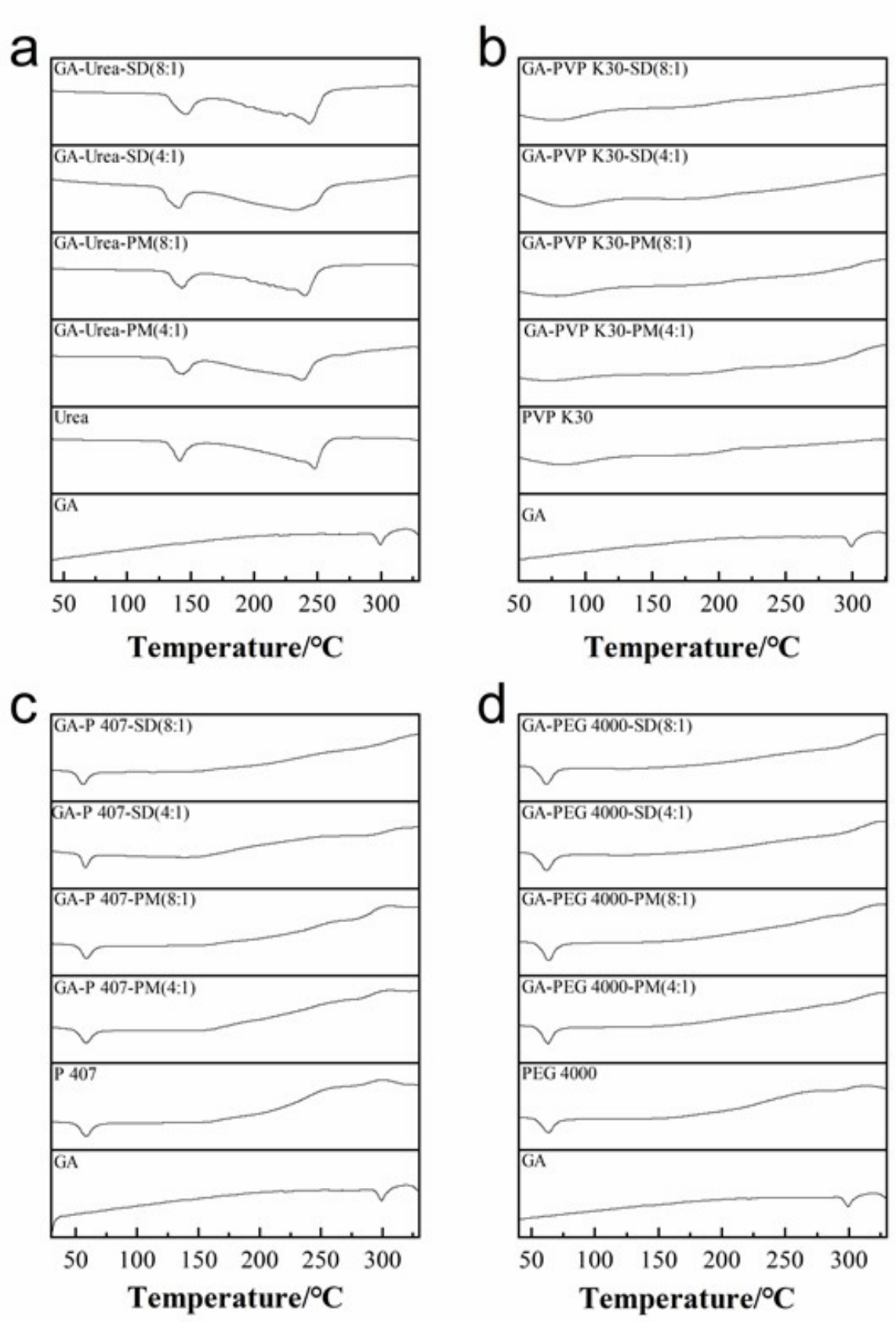

Fig. 3: DSC curves of SDs and PMs of GA prepared using (a) PEG 4000, (b) PVP K30, (c) Urea and (d) P 407.

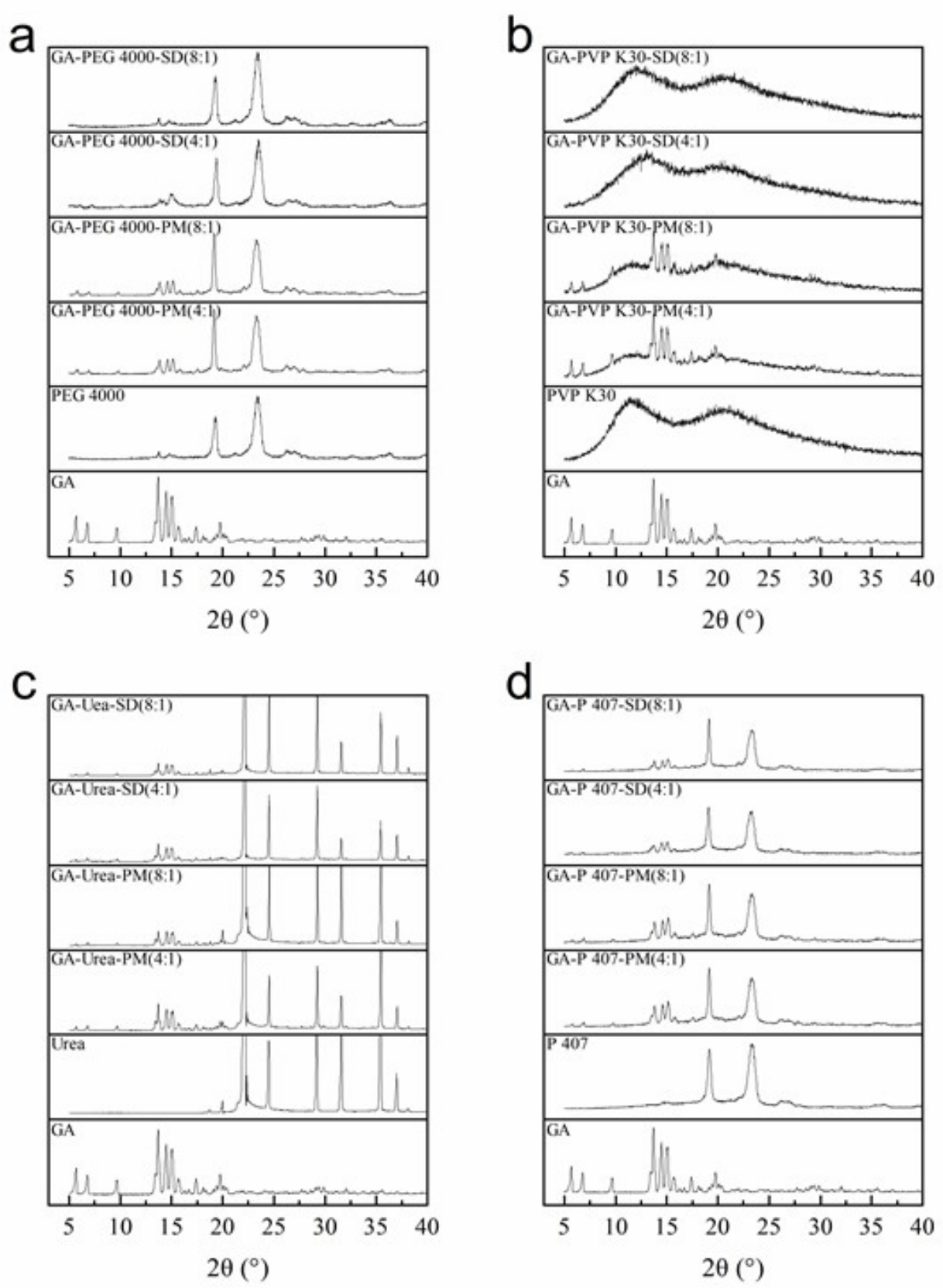

Fig. 4: X-ray diffractogram of SDs and PMs of GA prepared using (a) PEG 4000, (b) PVP K30, (c) Urea and (d) P 407.

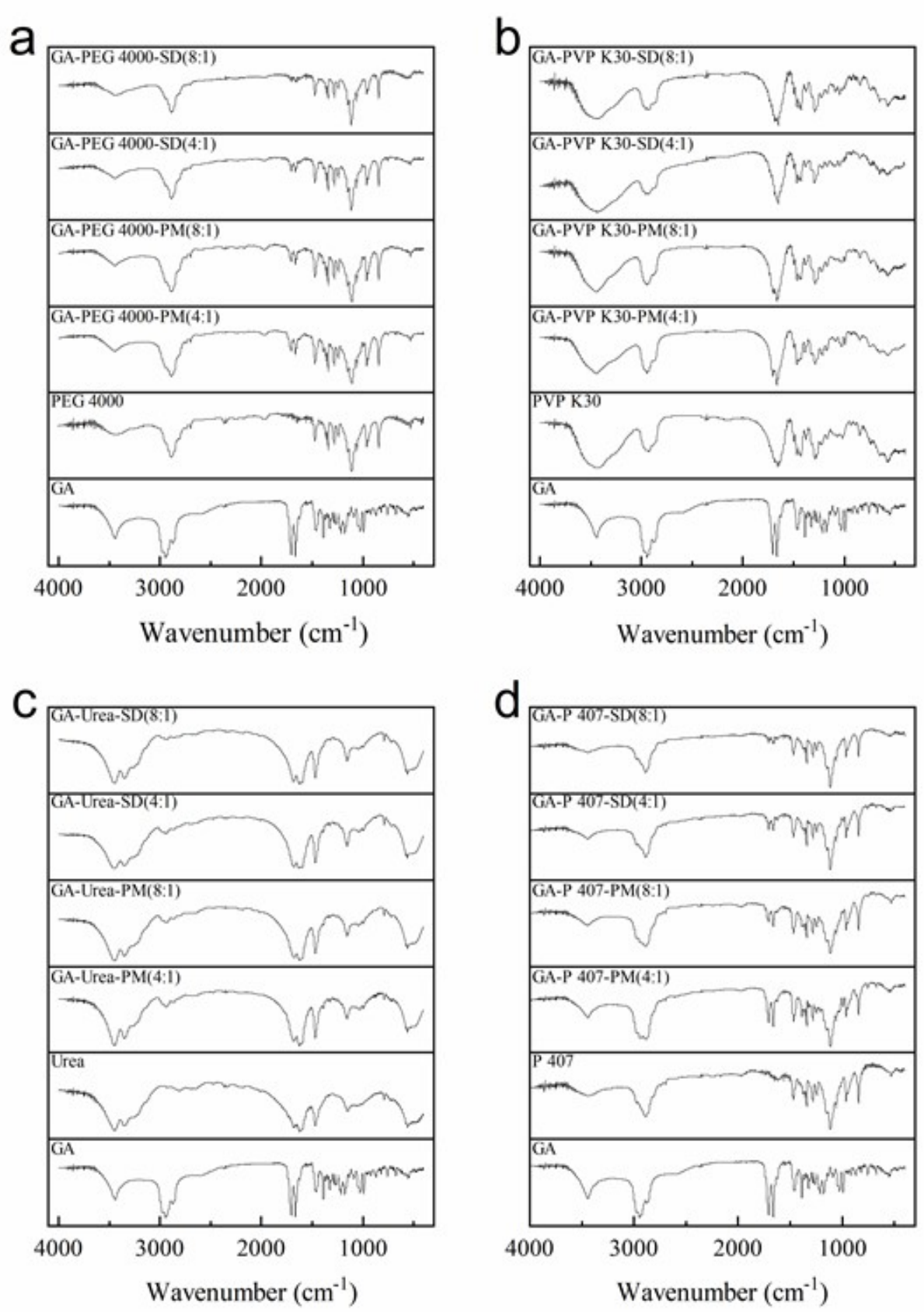

Fig. 5: FTIR spectra of SDs and PMs of GA prepared using (a) PEG 4000, (b) PVP K30, (c) Urea and (d) P 407.

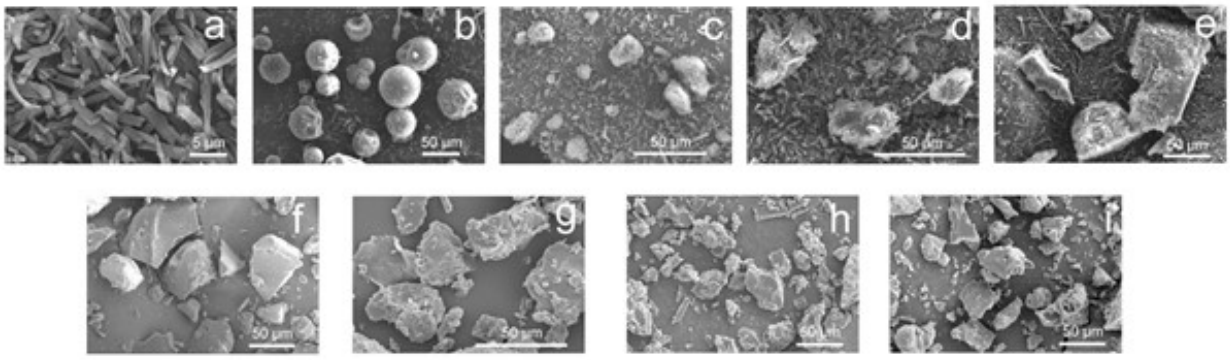

Fig. 6: SEM images of (a) pure GA, PMs of GA prepared using (b) PVP K30, (c) PEG 4000, (d) P 407, (e) Urea and SDs of GA prepared using (f) PVP K30, (g) PEG 4000, (h) P407, (i) Urea.

Table 1: Particle diameter of PMs and SDs (mean ± SD, n=3). One way ANOVA was performed where differences considered significant at $p < 0.05$.

Product	Mean particle diameter (μm)	Product	Mean particle diameter (μm)
GA-PEG 4000-PM(4:1)	53.54 ± 10.15	GA-PEG 4000-SD(4:1)	63.32 ± 13.56
GA-PEG 4000-PM(8:1)	62.87 ± 10.98	GA-PEG 4000-SD(8:1)	58.69 ± 19.03
GA-PVP K30-PM(4:1)	34.86 ± 6.25	GA-PVP K30-SD(4:1)	80.49 ± 8.65
GA-PVP K30-PM(8:1)	48.06 ± 11.02	GA-PVP K30-SD(8:1)	86.57 ± 18.65
GA- P 407-PM(4:1)	28.53 ± 9.96	GA-P 407-SD(4:1)	56.51 ± 6.19
GA- P 407-PM(8:1)	33.96 ± 11.25	GA- P 407-SD(8:1)	62.69 ± 18.03
GA-Urea-PM(4:1)	26.03 ± 6.58	GA-Urea-SD(4:1)	43.62 ± 11.16
GA-Urea-PM(8:1)	63.34 ± 18.35	GA-Urea-SD(8:1)	47.25 ± 8.65
GA	11.85 ± 1.83		

Table 2: Equilibrium solubility (μg/mL) of samples in different dissolving medium (mean±SD, n=3). One way ANOVA was performed where differences considered significant at $p < 0.05$.

Carrier-drug weight ratio	4:1			8:1		
Dissolving medium	Pure water	PBS (pH 6.8)	0.1 N HCl	Pure water	PBS (pH 6.8)	0.1 N HCl
GA-PEG 4000-PM	4.98±0.51	7.59±0.69	-	5.49±0.64	8.82±0.91	-
GA-PEG 4000-SD	20.56±0.16	28.38±1.17	-	27.29±1.63	76.91±4.35	-
GA-PVP K30-PM	5.63±0.41	9.53±0.71	-	9.35±0.71	15.78±1.23	-
GA-PVP K30-SD	19.78±1.81	417.12±35.15	9.03±0.97	34.06±3.41	563. 28±35.61	18.69±1.27
GA-P 407-PM	5.58±0.67	7.28±0.89	-	7.57±0.91	8.39±0.71	-
GA-P 407-SD	16.99±1.95	33.92±2.97	-	31.43±4.03	63.55±6.59	-
GA-Urea-PM	4.83±0.47	5.37±0.61	-	5.44±0.67	7.72±0.85	-
GA-Urea-SD	12.69±1.04	23.57±1.09	-	16.68±1.46	26.16±1.92	-
GA	5.86±0.45	6.72±0.47	-	5.86±0.45	6.72±0.47	-

"-"indicates that the concentration is below detection limit.

The dissolution rates of pure GA, four PMs and four SDs in PBS are shown in fig 2. The experimental results showed that the type of carrier has a significant effect on the dissolution behavior of SDs. The dissolution rate of SDs with a carrier-drug ratios of 8:1 (W/W) and 4:1 showed that the dissolution rate of (PVP K30-SDs)> (PEG 4000-SDs)> (P 407-SDs)> (Urea-SDs), which is also consistent with the order of solubility in PBS of four solid dispersions. According to the Noyes-Whitney equation (Equation 1), when the drug saturated solubility (C_s) increases, the dissolution rate (dC/dt) also increases accordingly. On the other hand, the carrier-drug weight ratios have an obvious impact on the dissolution rate of SDs. Before 120min, the dissolution rate of SDs with a carrier-drug ratio of 8:1was faster than 4:1 under the same PVP molecular weight condition. Among all solid dispersion samples, GA-PVP K30-SD with a drug loading ratio of 8:1has the fastest dissolution rate which could reach 81% at the 10th minute, and tends to equilibrium after 60minutes. In addition, there is no negative correlation between the particle diameter of the solid dispersion and dissolution rate in combination as shown in fig. 1 and table 1. The average particle size of the PVP-SDs solid dispersion powder was the largest, but its dissolution rate was significantly higher ($p<0.05$) than that of the other three solid dispersions.

$$\frac{dC}{dt} = \frac{DS}{V\delta(C_s - C)} \quad (1)$$

Differential scanning calorimetry (DSC)

By comparing the DSC curves of drug-loaded solid dispersions, carriers and drug-carrier physical mixtures, determine whether a solid dispersion is formed by the change or disappearance of the characteristic endothermic peak of the drug in the solid dispersion (Edwards *et al*., 2010). In the DSC thermogram (fig.3), GA showed an endothermic peak at 299 ^{o}C, which is the melting peak of GA. The melting points of PEG 4000, P 407 and urea are observed at 57.6^{o}C, 58.3^{o}C and 132.7^{o}C, respectively. PVP K30 has no obvious melting point, due to its amorphous structure. No melting peak of GA was observed on the DSC curves of PMs and SDs (4:1 and 8:1 carrier-drug ratio). The reason for this phenomenon may be due to the relatively low content of the drug in the solid dispersions, which causes the thermal effect of GA to be masked. Therefore, the DSC test results cannot explain whether the crystalline structure of GA has changed. The phase properties of GA should be further identified by using X-ray diffraction and other tests.

X-ray diffraction (XRD)

Each drug has characteristic diffraction peaks of crystals in different diffraction bands and these peaks disappear after forming a solid dispersion, indicating that the drug is present in the solid dispersion in an amorphous form (Ansari *et al*., 2019). In the XRD spectrum of GA (fig.4), three obvious diffraction peaks at 13.8°, 14.5° and 15.1°can be observed, indicating that glycyrrhetinic acid is a highly crystalline compound. In the XRD spectra of the four carriers, the characteristic diffraction peaks of PEG 4000, P 407 and urea can be observed, while PVP K30 cannot be observed due to its amorphous structure.

In the spectra of GA-PEG 4000-PMs, GA-P 407-PMs, GA-PVP K30-PMs and GA-Urea-PMs, the three characteristic diffraction peaks at 13.8°, 14.5°, 15.1° of GA can still be observed. This result illustrates that GA still exists in a highly crystalline state in the three physical mixtures.

In the XRD spectra of the GA-Urea-SDs, obvious characteristic diffraction peaks of GA can still be observed. In the spectra of GA-P 407-SDs, the heights of the characteristic diffraction peaks observed for the obtained GA were significantly reduced compared to their physical mixtures. In the spectra of GA-PEG 4000-SDs, the observed characteristic diffraction peaks of GA became weak at 13.8°and 14.5°. In the spectrum of GA-PVP-SDs, the characteristic diffraction peaks of GA disappeared completely, indicating that GA was dispersed in PVP K30 in the amorphous state.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectroscopy is mainly used to determine whether there is a complex formation in a solid dispersion or whether there is an interaction between the drug and the carrier material (Ewing *et al.,* 2015). After a certain reaction between the drug and the carrier material, the drug absorption peak can be shifted or changed in intensity and the absorption peak can be generated or disappeared (Sharma and Lahiri, 2008). In the spectrum of glycyrrhetinic acid raw material (fig. 5), two characteristic bands of 1704 cm^{-1} and 1664 cm^{-1} can be observed, which is due to the carbonyl in carboxylic acid and carbonyl moieties (Dai *et al.,* 2018). The peak at 3440 cm^{-1} is attributed to the phenolic hydroxyl in C3 (Wang *et al.,* 2010).

In the infrared spectrum of PEG 4000 (fig. 5), the stretching vibration peak of the hydroxyl group can be observed at 3440 cm^{-1}. In the spectra of GA-PEG 4000-PMs and GA-PEG 4000-SDs, the absorption peak can be observed at 3440cm^{-1}, which should be the superimposed peak of glycyrrhetinic acid C3 phenolic hydroxyl group and PEG 4000 hydroxyl group. Compared with GA-PEG 4000-PMs with the same drug loading ratio, the superimposed peak of GA-PEG 4000-SDs at 3450 cm^{-1} is obviously wider and blunt. In addition, the carbonyl peaks of GA-PEG 4000-SDs at 1664 cm^{-1} and 1704 cm^{-1} are significantly weaker than those of GA-PEG 4000-PMs. From these changes, it can be inferred that the hydroxyl group of PEG 4000 may form an intermolecular hydrogen bond with the C3 hydroxyl group or carbonyl group of glycyrrhetinic acid.

In the spectrum of GA-P 407-SDs with a carrier drug ratio of 8:1, the characteristic absorption peaks of GA at 1664 cm^{-1}and 1701 cm^{-1}were significantly weakened, and the superimposed peak at 3440 cm^{-1}became obviously broad and blunt. This is different from the spectrum of a physical mixture with an 8:1 carrier drug ratio. We speculate that the terminal hydroxyl group of P 407 and the carbonyl group of glycyrrhetinic acid may form a hydrogen bond. In addition, the infrared spectrum of the solid dispersion with a carrier-drug ratio of 4:1 has a similar situation, but the structure change is not as obvious as that of the solid dispersion with a 8:1 carrier-drug ratio.

Compared with GA-PVP K30-PMs, in the infrared spectrum of GA-PVP K30-SDs, the superimposed peak at 3440 cm^{-1} becomes broad and blunt and the peak tip disappears. This is due to the formation of an intermolecular hydrogen bond between the phenolic hydroxyl group (3440 cm^{-1}) at the C3 position of GA and the carbonyl group of PVP at 1662 cm^{-1} in GA-PVP K30-SDs. As a result, the phenolic hydroxyl peak at 3440 cm^{-1} of the GA molecule becomes broad and blunt.

In the case of the same drug loading ratio, the shape of the spectrum of the GA-urea-solid dispersion is not different from that of the physical mixture. It is because there is no hydrogen bond formation between glycyrrhetinic acid and urea molecules.

Scanning electron microscopy (SEM)

The scanning electron microscopy images of the solid dispersions prepared with different carriers are shown in fig. 6. The GA raw material presents a distinct strip shape, which is due to its high degree of crystallization. Figure 6f is an electron micrograph of GA-PVP-SDs. It can be seen that it has an irregular shape with a relatively smooth surface and sharp borders. The solid dispersions prepared by the other three carriers are also irregular in shape, but the surface is uneven and the layered shape is very obvious. In the images of the four solid dispersions, no strips of GA were observed, indicating that it had been dispersed in the carrier. In the scanning electron micrographs of the four physical mixtures, since the GA carrier is in the shape of a strip, and the shape of the carrier has its own characteristics, the carrier and the GA raw material can be clearly distinguished.

DISCUSSION

PEG has a low melting point, a fast curing speed, a strong ability to form a solid drug solution, and is easily soluble in a variety of organic solvents (Akbari *et al.,* 2015). Polyvinylpyrrolidone (PVP) is an amorphous polymer that is easily soluble in water and a variety of organic solvents. Therefore, the solvent method is usually used to prepare solid dispersions with PVP as a carrier (Kawtikwar *et al.,* 2012). PVP can effectively prevent the recrystallization of amorphous drugs, so that the solid dispersion is very stable. Poloxamer is a block polymer of ethylene oxide and propylene oxide, with a strong solubilization ability (Chutimaworapan *et al.,* 2000). Poloxamer is often used to prepare solid dispersions because of its low melting point, surface activity and safety. Urea is a commonly used crystalline carrier for solid dispersions, and crystalline drugs are dispersed in urea to form a eutectic mixture or a monotectic mixture. When the eutectic mixture is formed, the drug is well dispersed in the carrier, thereby improving solubility (Soares *et al.,* 2021). Based on the above description, these four carrier materials are suitable for use as solid dispersions of GA prepared by the solvent method.

In the equilibrium solubility comparison experiment, the solubility of the solid dispersions prepared by the four different carriers in PBS was significantly greater than the solubility in water and hydrochloric acid, which should because glycyrrhetinic acid is an acidic compound. Therefore, glycyrrhetic acid solid dispersions may have better dissolution in the small intestinal environment.

According to particle size determination and SEM image results, PVP-SDs have a larger diameter and a smaller specific surface area. According to the Noyes Whitney equation, the dissolution rate of a solid drug is proportional to its specific surface area. However, according to the dissolution curves of the four solid dispersions, the dissolution rate of PVP-SDs is faster, indicating that the particle size of the solid dispersion prepared by the water-soluble carrier has little effect on the dissolution of the drug. In terms of particle size, it may be the particle size of the drug that is highly dispersed in the carrier that has more influence on the dissolution rate. In addition, the amorphous and the degree of dispersion of the drug in the carrier showed a more important effect than the particle size. According to the analysis of XRD results, compared with the other three carriers, PVP has a better ability to inhibit drug crystallization, so its dissolution rate and solubility are better. Moreover, the dissolution rate of the solid dispersion prepared by the four carriers was negatively correlated with the degree of drug crystallinity.

CONCLUSION

This study confirmed that the carrier type has a significant influence on the drug dissolution rate from glycyrrhetinic acid solid dispersion. According to our research, compared with PEG 4000, P 407 and urea, when PVP K30 was used as the carrier, the equilibrium solubility and dissolution rate of GA solid dispersion were better. Moreover, GA-PVP K30-SDs are a completely amorphous structure. On the other hand, the carrier drug ratio also has a clear effect on the dissolution properties of glycyrrhetic acid solid dispersions. These are useful for applications that use solid dispersion technology to improve the oral absorption of glycyrrhetinic acid. It is expected that the GA-PVP K30-SDs can be used as an ideal material for the development of GA oral products.

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