Improved Dissolution of Oleanolic Acid with Ternary Solid Dispersions

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ABSTRACT

The purpose of this study was to enhance the dissolution of oleanolic acid by solid dispersions consisting of the drug, a polymeric carrier, and a surfactant. Binary solid dispersions consisting of oleanolic acid and polyvinylpyrrolidone were prepared for comparison. Polysorbate 80, a nonionic surfactant, was incorporated into binary solid dispersions as the third component to prepare ternary solid dispersions. Solid dispersions were characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy, and dissolution tests. The crystallinization of OA was prohibited in solid dispersions. Both the binary and ternary solid dispersions enhanced the dissolution of OA. Moreover, the dissolution of ternary solid dispersion was faster compared with that of binary solid dispersion. Polysorbate 80 played an important positive role in dissolution of the solid dispersion.

KEYWORDS: Oleanolic acid, ternary solid dispersions, PVPk30, Polysorbate 80.

INTRODUCTION

Oleanolic acid (OA; 3β-3-hydroxyolean-12-en-28-oic acid, Figure 1) is a triterpenoid compound that exists widely in natural plants in the form of free acid or aglycones for triterpenoid saponins.[1,2] OA has multiple pharmaceutical functions such as anti-inflammatory,[3,4] hepato-protection,[1] and enhancement of human body defense systems.[5] Because OA is poorly water soluble, it is important to introduce effective methods to enhance its dissolution.

Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods.[6-8] In solid dispersions, the particle size of the drugs was reduced, and the wettability and the dispersibility of the drugs were enhanced; therefore, drug dissolution was improved markedly.[9,10] Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs.[10,11]

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Hydrophilic polymers have been commonly used as carriers for preparing solid dispersions. Among them, Polyvinylpyrrolidone (PVP) was widely employed for its high aqueous solubility, high physiological tolerance, and low toxicity. In recent years, the interest in incorporating a surface-active carrier into solid dispersion increased greatly and a high improvement in drug dissolution was reported.[12-15] Mura et al[16] reported that the dissolution of naproxen from solid dispersions in polyethylene glycol (PEG) 4000, 6000, and 20000 could be further enhanced when Polysorbate 80 was incorporated into the system. Dannenfelser et al[17] found that a combined carrier consisting of PEG and Polysorbate 80 could improve the dissolution and enhance the bioavailability of LAB687, a poorly water-soluble drug with an aqueous solubility of 0.17 μg/mL at room temperature.

In this study, OA was used as a model drug and PVPk30 was used as a polymeric carrier to prepare binary solid dispersions. Polysorbate 80, a nonionic surfactant with HLB of 15, was used as the third component to prepare ternary solid dispersions. Differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), and dissolution tests were employed to characterize the solid dispersions.

MATERIALS AND METHODS

Materials

OA powder was obtained from Chengdu Jianjiang Pharmaceutical Factory (Sichuan, China), PVPk30 was purchased from Huzhou Zhanwang Pharmaceutical Co., Ltd (Zhejiang, China), and Polysorbate 80 from Wenzhou Qingming Chemical Co., Ltd (Zhejiang, China). Methanol (high-performance liquid chromatography [HPLC] grade) was supplied by Tianjin Shield Co (Tianjin, China). HPLC-grade water was used for the HPLC analysis. All other reagents used were of analytical grade.

Preparation of Solid Dispersions

Binary and ternary solid dispersions were prepared by the solvent method. Briefly, in binary solid dispersions, different weight ratios of OA and PVPk30 (1:1, 1:3, 1:5, 1:7, 1:9) were dissolved in 20 mL absolute ethanol responding to 0.1 g OA, then the solvent was removed in a water bath at 60ºC.[18,19] The residues were dried in an oven at 50°C for 24 hours, then ground in a mortar and passed through a 154-μm sieve. The resultant granules were kept in a

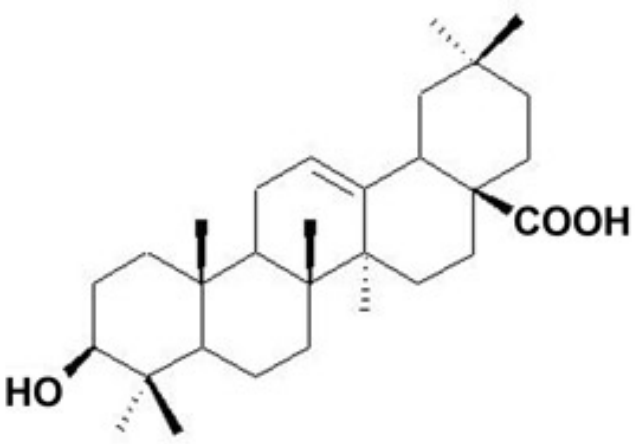

Figure 1. The chemical structure of OA.

desiccator until further investigations. In ternary solid dispersions, Polysorbate 80 was incorporated into OA and PVPk30 to obtain the dispersions with weight ratios of 1:1:0.2, 1:3:0.4, 1:5:0.6, 1:7:0.8, and 1:9:1 (OA/PVPk30/Polysorbate 80).

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) was performed by a Perkin-Elmer DSC7 differential scanning calorimeter with a Pyris Series Workstation (Perkin-Elmer, Waltham, MA). The accurately weighed sample was placed in an aluminum pan and an empty aluminum pan was used as reference. The experiment was performed under nitrogen flow (20 mL/min) at a scanning rate of 10°C/min in the range of 50 to 330°C.

FTIR

A Nicolet Nexus FTIR 670 spectrometer (Thermo Fisher Scientific, Inc., Waltham, MA) was used for FTIR analysis. The samples were ground and mixed thoroughly with KBr, an infrared transparent matrix. Sample disks were prepared by compressing the mixtures. The scans were executed from 400 to 4000 cm^{-1}.

Dissolution Tests

Dissolution tests were performed with a dissolution apparatus (RCZ-8A, Precise Apparatus of Tianjin University Co., Ltd, China) using the paddle method according to USP XXIX.[20] Samples of original OA, physical mixtures of OA, and various solid dispersions equivalent to 30 mg OA were added to 900 mL deionized water with 1% sodium dodecyl sulfate to meet sink condition, and then stirred at 100 rpm. The temperature was maintained at 37 ± 0.5ºC. At predetermined intervals (5, 10, 15, 20, 30, 40, 50, 60 minutes), 5-mL samples were withdrawn from each vessel, filtered with a 0.45-μm membrane filter, and analyzed for OA with HPLC. The same volume of fresh medium was replaced after sampling. Each sample was performed in triplicate in dissolution tests.

HPLC Analysis

Concentration of OA was determined using a HPLC system (Dionex Corporation, Sunnyvale, CA). The system consisted of a Dionex P680A LPG-4 pump, a Dionex UVD-170U UV detector, a Dionex AST-100 automated sample injector, and a computer installed with Chromeleon version 6.60 software (Dionex Corporation).0 The wavelength of detection was set at 210 nm. Separation was achieved by using a Sepax HP-C18 column (5 μm, 120 Å, 4.6 × 150 mm). The mobile phase consisted of CH_3OH, H_2O, and H_3PO_4 at a ratio of 95:5:0.01 (vol/vol/vol). The flow rate of the mobile phase was 1 mL/min and the injection volume was 50 μL. All chromatographic separations were performed at 25°C.

Results and Discussion

FTIR

Figure 2 displays the FTIR spectra of original OA, PVPk30, physical mixture of OA/PVPk30, and OA solid dispersions. OA showed peaks of –OH stretch vibration (3437 cm^{-1}), C-H stretch vibration (2944 cm^{-1}) and –C=O stretch vibration (1697 cm^{-1}). PVPk30 exhibited peaks of C-H stretch vibration (2955 cm^{-1}) and –C=O stretch vibration (1663 cm^{-1}). The FTIR spectra of physical mixture appeared to be a summation of drug and PVPk30 spectra. In binary and ternary solid dispersions, the peaks of -OH and -C=O stretch vibration of OA shifted to 3431 cm^{-1} and 1664 cm^{-1}, respectively. This suggested that there might be H-bonding interaction between the groups of OA (-OH and –COOH groups) and the groups of PVPk30 (-C=O group and nitrogen atom). This

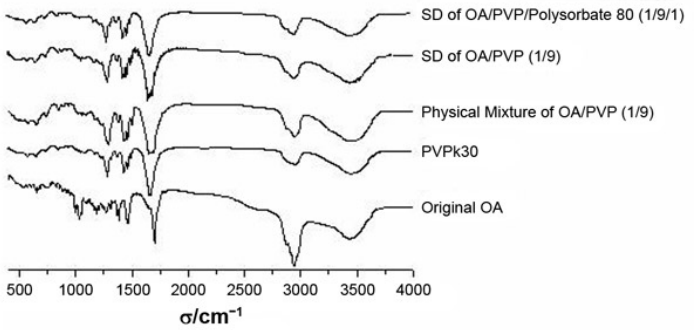

Figure 2. FTIR spectra of OA, physical mixture, and solid dispersions.

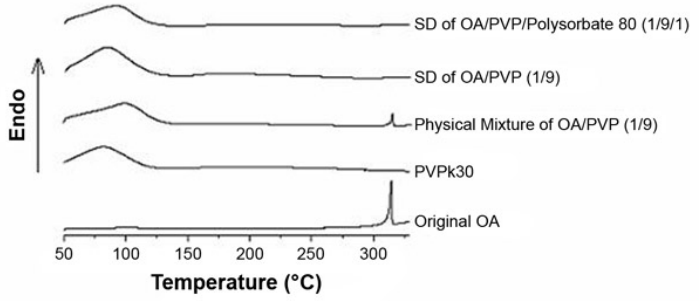

Figure 3. DSC diagrams of OA, physical mixture, and solid dispersions.

led to form a solid solution or an amorphous state of OA. The FTIR diagram of solid dispersion containing OA, PVPk30, and Polysorbate 80 was similar to that of solid dispersion containing OA and PVPk30. This might indicate that the small amount of Polysorbate 80 hardly affected the FTIR results.

DSC

The DSC thermograms of original OA, PVPk30, physical mixture of OA/PVPk30, and OA solid dispersions are shown in Figure 3. During scanning of PVPk30, a broad endothermic peak ranging from 50 to 130°C was observed, indicating the loss of water. The thermograms of physical mixture and various solid dispersions also showed similar broad endothermic peaks. The DSC diagram of OA exhibited a sharp endothermic peak at 314.5°C, indicating the melting point of OA. The physical mixture of OA/PVPk30 also showed endothermic peak of OA. However, in the case of binary or ternary solid dispersions, the endothermic peak of OA disappeared, which indicates that OA might be in an amorphous state. It might be attributed to the effect of carriers that inhibited crystallization of drugs,[9,21,22] resulting in an amorphous state or a solid solution of OA in solid dispersions. The DSC diagram of solid dispersions containing OA, PVPk30, and Polysorbate 80 was similar to that of solid dispersions containing OA and PVPk30.

Dissolution

The dissolution profiles of original OA, binary and ternary physical mixtures, binary solid dispersions, and ternary solid dispersions were plotted in Figures 4 and 5. The statistical analysis was performed between dissolution data. The paired *t* test was performed between original OA and various ratios of solid dispersions, as well as physical mixtures. The *P* values were all smaller than .05, indicating significant differences. The percentage of original OA dissolved was 35% in first 5 minutes and only 73% in 1 hour. Compared with original OA, the dissolution rate of the physical mixtures was slightly higher: the dissolution percentage was 38% in the first 5 minutes. In the case of binary and ternary solid dispersions, the dissolution rate was improved markedly. It might be that PVPk30 prohibited the crystallinization of OA[23] in the solid dispersions, which could be attributed to the H-bonding between OA and PVPk30, and Polysorbate 80 decreased drug surface tension and enhanced OA wettability in ternary solid dispersions. It could be seen that the OA dissolution rate was dependent on the ratio of drug to polymeric carrier. As the proportion of PVPk30 increased, the dissolution rate increased. These results indicated that

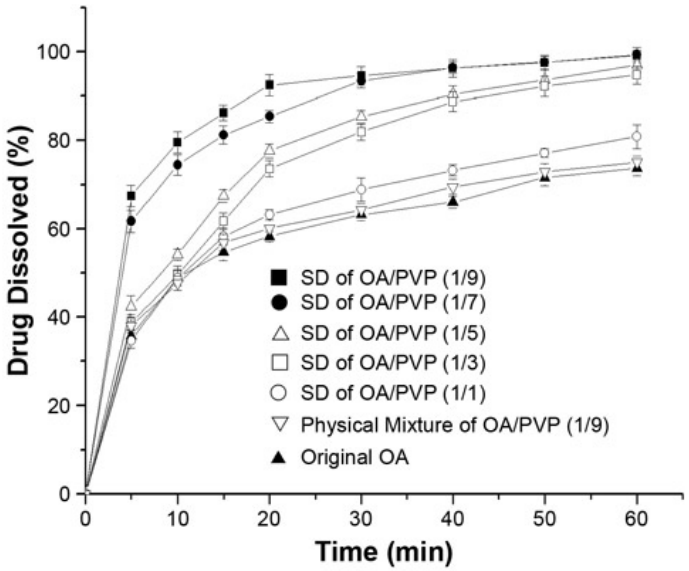

Figure 4. The dissolution profiles of OA, physical mixture, and binary solid dispersions.

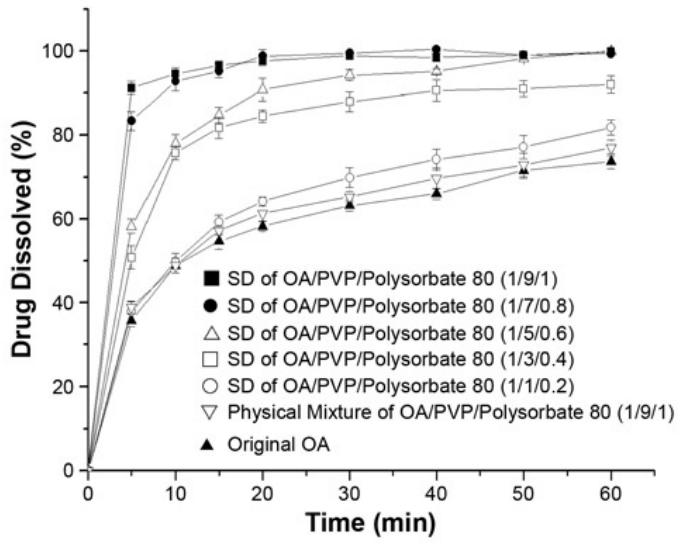

Figure 5. The dissolution profiles of OA, physical mixture, and ternary solid dispersions.

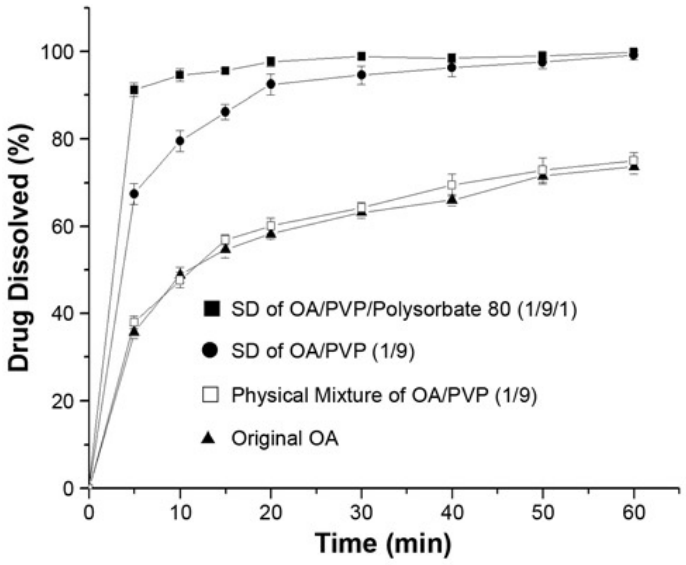

Figure 6. The comparison of dissolution profiles of binary and ternary solid dispersions.

PVPk30 enhanced the hydrophilic property of OA and a carrier-controlled dissolution in the solid dispersions.[9]

It was evident that the dissolution rate of OA from ternary solid dispersions was obviously higher than that from binary solid dispersions (Figure 6). In first 5 minutes, the dissolution percentage of binary solid dispersion was approximately 70% at the ratio of 1:9 compared with 90% of ternary solid dispersion with the ratio of 1:9:1. This could be attributed to the solubilizing effect of Polysorbate 80 existing in ternary solid dispersions. When solid dispersions came into contact with the dissolution medium, a polymeric diffusion layer was formed first. The drug must be dissolved in the polymeric diffusion layer before being dissolved into the bulk phase.[10] In ternary solid dispersions, Polysorbate 80 on the surface of OA decreased drug surface tension and increased drug wettability[24]; thus, the dissolution rate of OA was enhanced markedly.

CONCLUSION

The dissolution rate of OA could be enhanced markedly by ternary solid dispersion using PVPk30 and Polysorbate 80 as cocarriers. Polysorbate 80 played an important positive role in dissolution of OA solid dispersion.

ACKNOWLEDGMENTS

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