Improvement of the Dissolution Rate of Silymarin by Means of Solid Dispersions

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Solid dispersions of silymarin were prepared by the fusion method with the intention of improving the dissolution properties of silymarin. Polyethylene glycol 6000 (PEG 6000) was used as the inert hydrophilic matrix. The dissolution studies of the solid dispersions were performed *in vitro*. And the results obtained showed that the dissolution rate of silymarin was considerably improved when formulated in solid dispersions with PEG 6000 as compared to original drug, and the increased dissolution rate might be favorable for further oral absorption.

Key words silymarin; solid dispersion; polyethylene glycol 6000; dissolution

Silymarin is extracted from the seeds of *silybum marianum* L Gaertn, and is effective for the treatment of liver diseases. It belongs to the class of flavonoid, including silybin, silydianin, silychristin and silybonol.[1,2] Major problems involved in the development of an oral solid dosage form of this drug are the extremely poor aqueous solubility and dissolution limited oral absorption. Solid dispersions are generally used to enhance the dissolution of poorly water-soluble drugs.[3,4] Aim of this work was to prepare a solid dispersion from silymarin with hydrophilic carrier and to evaluate the solubility and dissolution behaviors of silymarin incorporated solid dispersion.

Polyethylene glycol 6000 (PEG 6000) was used as hydrophilic carrier to prepare the solid dispersions due to its low melting point, low toxicity, high viscosity, wide drug compatibility and hydrophilicity. Solid dispersions were prepared by adding silymarin (with the particle size range of 50—100 μm and melting point of about 165 °C, provided by PanJin HuaCheng Pharmaceutical Factory, China) into PEG 6000 melted on a water bath at 70 °C. The resulting homogeneous mixtures were cooled under −20 °C immediately. Subsequently, the pulverized dispersions were sieved with a 200 μm mesh and then stored in a desiccator at room temperature until use.

The flavonoid compounds in silymarin act fot the main pharmacological effect. And each compound has the similar conjugated structure for ultraviolet absorption behaviors. The total flavonoids were analyzed by first derivative ultraviolet spectrophotometry at the wavelength of 338 nm.[5] The solubility of original silymarin in distilled water was found to be 58 $\mu g \cdot ml^{-1}$ at 25 °C according to the method of Higuchi and Connors.[6] Therefore, silymarin can be considered as a practically insoluble drug. As shown in Fig. 1, aqueous solution of PEG 6000 did not seem to increase the solubility of silymarin. So the physical mixtures of silymarin and PEG 6000 could not increase the dissolution of the active flavonoids. On the other hand, there were reasonably increased solubilities when silymarin were mixed into aqueous solutions of surfactants, such as polysorbate-80, sodium cholate or sodium deoxycholate (Fig. 1). Silymarin in 2.0% (w/v) polysorbate-80 has high solubility of 2406 $\mu g \cdot ml^{-1}$, which was about 40 times that in water at 25 °C. The ability of surfactant to accelerate the *in vitro* dissolution of poorly soluble drug has been attributed to wetting, micellar solubilisation or deflocculation.[7] Based on this fact, dissolution of original silymarin and the prepared solid dispersion systems were tested in aqueous solution of polysorbate-80.

The dissolution tests of the prepared solid dispersions were performed according to the basket method, which were employed with a stirring rate of 50 rpm at 37±1 °C. Sink conditions were maintained with 900 ml of 0.2% (w/v) polysorbate-80. Samples of solid dispersion loaded with about 60 mg silymarin were added into dissolution media. At predetermined time, aliquots of 2 ml were withdrawn. And the same volume of blank medium, warmed at 37 °C, was added immediately. Dissolution patterns of flavonoids were obtained by analyzing the dissolution medium samples for flavonoids content.[5]

Figure 2 shows the dissolution profiles of silymarin as a

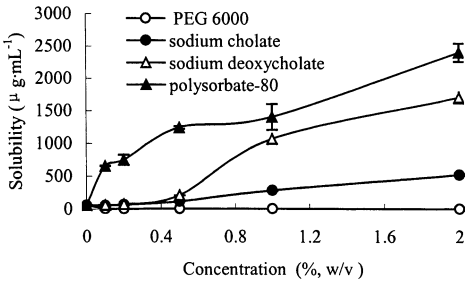

Fig. 1. Solubilities of Silymarin in Aqueous Medium with Different Concentrations of PEG 6000, Polysorbate-80, Sodium Deoxycholate or Sodium Cholate at 25 °C

$n=5$.

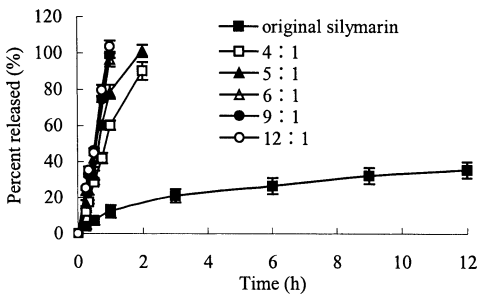

Fig. 2. Dissolution Profiles for Original Silymarin and Solid Dispersions of Silymarin in 0.2% (w/v) Polysorbate-80 at 37 °C

The ratios represent PEG 6000 to silymarin by weight. $n=3$.

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function of time. It is evident that the dissolution rate of original silymarin is very low, only 8% of flavonoids being released within 30 min, and less than 40% of silymarin released even after 12 h. This low dissolution rate might be resulted from the hydrophobicity and low solubility of the intact silymarin powder in aqueous solution. Whereas, the dissolution rate of the prepared silymarin solid dispersions was considerably enhanced. About 50% of flavonoids in silymarin were released from all formulation of solid dispersions within the first 1 h, and the flavonoids released nearly completely after 2 h. The release of silymarin became fast as the ratio of PEG 6000 in solid dispersions increased.

The present study demonstrated that solid dispersions with PEG 6000 markedly improved the dissolution properties of silymarin. The solubilization effect of PEG 6000 might be resulted from the reduction of drug particle aggregation and alteration of the surface properties of the particles during solid dispersion process.[8] These suggested the possiblity to obtain improved bioavailability for orally administered silymarin.

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