

Preparation and dissolution property of ipriflavone solid dispersion

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KEY WORDS ipriflavones; isoflavones; pharmaceutical preparations; povidone; polyethylene glycols

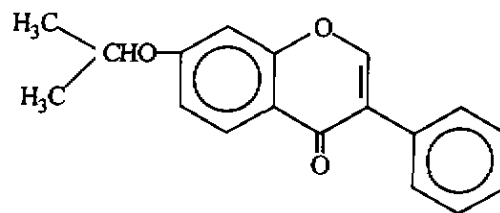
ABSTRACT

AIM: To prepare and identify ipriflavone (IP) solid dispersion, and determine its dissolution property. **METHODS:** The solvent method was used for preparation and differential scanning calorimetry (DSC), X-ray diffraction and infrared spectrophotometry for identification of IP solid dispersion. The dissolution of the dispersion was determined with paddle method. **RESULTS:** The dissolution of IP solid dispersion consisting of IP and povidone-k30 (PVP) (1:8) in artificial gastric juice is 6.15 times as high as that of IP alone. The DSC curves, X-ray diffraction patterns and infrared spectrophotometries of IP have been changed obviously by the dispersion. **CONCLUSION:** The dissolution of IP is increased by solid dispersion method.

INTRODUCTION

IP (7-isopropoxyisoflavone), a nonhormonal isoflavone derivative, is currently used in several countries for prevention and treatment of postmenopausal osteoporosis^[1]. IP has been shown to be effective in reducing bone turnover rate mainly through an inhibition of bone resorption, and in stimulating bone formation^[2-4]. But IP had a poor bioavailability because of its poor water solubility and strong first-pass metabolism^[5-7]. It has been reported that the solubility of IP was increased dramatically with being

encapsulated in β -cyclodextrin, for example, from 0.4 mg·L⁻¹ to 13.2 mg·L⁻¹ in one minute, and plasma levels were increased 10 - 15 times^[8]. The solid dispersion technology has been used widely to enhance the dissolution rate of poorly water-soluble medicines by dispersing them into water-soluble carriers, and to improve their bioavailability^[9-11]. In this paper, IP solid dispersion was studied, and its dissolution was determined and compared with IP alone.



7-Isopropoxyisoflavone

MATERIALS AND METHODS

Instrument and chemicals DSC (Perkin-Elmer, 7 Series Thermal Analysis System), X-ray diffraction (Geigerflex RAD-IB, Rigaku), Infrared spectrophotometry (Magna FTIR-750, Nicolet Co), Dissolution teste (ZRS-4, Tianjin University Electronic Factory), Ultraviolet Spectrophotometer-260 (UV-260, Shimadzu Co Japan). IP was kindly donated by Department of Synthetic Drugs, Shanghai Institute of Materia Medica, Chinese Academy of Sciences. PVP was purchased from Henan Yuyuan Chemical Industrial Co. Polyethylene glycol-6000 (PEG) was purchased from Shanghai Gaonan Chemical Industrial Co. All other chemicals were of AR grade.

Preparation of samples Six types of solid dispersion powders consisting of IP and PVP or PEG (1:4, 1:6, and 1:8) were prepared as follows: The

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mixed powder (20 g) of the IP and the polymers at aforementioned proportions was dissolved in ethanol (100 mL), and the solvent was then evaporated. The residue was dried at 25 °C, and then ground and sieved (180 μm). The physical mixtures were the mixed powder (180 μm) of the IP and the polymers (1:8). Finally, solid dispersions and physical mixtures were filled into capsules with 50 mg of IP in a capsule, respectively.

Standard solution Stock solution of IP was prepared in ethanol at the concentration of 1.0 g·L⁻¹, and stored below 4 °C. Standard solutions were obtained from stock solution diluted with artificial gastric juice to concentrations of 0.4, 1.0, 2.0, 4.0, 6.0, and 8.0 mg·L⁻¹.

Dissolution study The dissolution of IP from solid dispersion were observed with the paddle method (CP 1995 XC), at 50 rpm, using artificial gastric juice 900 mL as dissolution medium at (37.0 ± 0.5) °C. The quantity of ipriflavone was determined with UV spectrophotometry by the absorbance at 242 nm.

Thermal analysis The DSC curves were measured at the heating rate of 5 °C per min, sample size, 10 mg.

Powder X-ray diffractometry The powder X-ray diffraction patterns were measured with operating conditions as follows; target, CuKα; filter, Ni; voltage, 30 kV; current, 50 mA and scanning speed, 2°·min⁻¹.

Infrared spectrophotometry The infrared spectrophotometries of IP solid dispersion were measured with operating conditions as follows; resolution, 4.0; sample gain, 2.0; mirror velocity, 0.6; aperture, 100; detector, DTGS KBr; beamsplitter, KBr; source, IR.

RESULTS

Linearity and recovery The standard curves showed a good linearity over a range of 0.4–8.0 mg·L⁻¹ for IP. Linear equation: $C = 9.551A - 0.0465$, correlation coefficient (r) was 0.9998. The excipients had 0 absorption at 242 nm. The average recoveries of IP were >98.9%. Coefficients of variation (CV) were <1.0% ($n=6$).

Dissolution test The solid dispersions consisting of IP and PVP appeared higher dissolution than that

of PEG at the same proportions. Moreover, the higher the proportion of PVP was, the faster the IP was dissolved from solid dispersion (1:8 > 1:6 > 1:4). The solid dispersion consisting of IP and PVP (1:8) showed the highest dissolution (60 min) which was 6.15 times as high as that of IP alone. Therefore, the further studies on the solid dispersion consisting of IP and PVP (1:8) were carried out as follows (Fig 1).

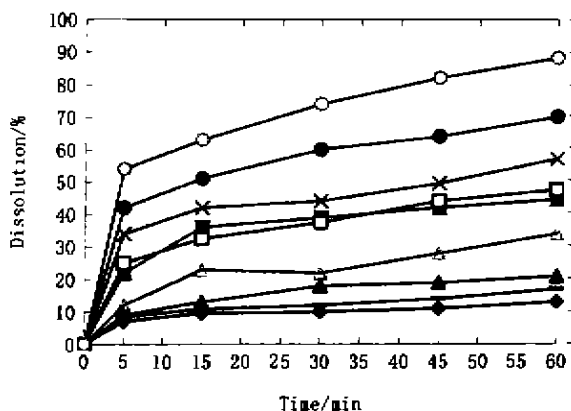


Fig 1. Dissolution of IP, physical mixtures and solid dispersions in artificial gastric juice, solid dispersion of IP and PVP, (1:8) ○; (1:6) ●; (1:4) □; solid dispersion of IP and PEG, (1:8) ×; (1:6) ■; (1:4) △; physical mixture of IP and PVP (1:8) ▲; physical mixture of IP and PEG (1:8) ◆; IP ◆.

Thermal analysis The endothermic peaks were markedly different, IP (112.5 °C), PVP (78.1 °C), physical mixture (112.1 °C) and solid dispersion (121.2 °C) (Fig 2).

X-Ray diffractometry The IP alone appeared a lot of sharp characteristic peaks, and physical mixture produced a few sharp characteristic peaks. But PVP and solid dispersion appeared no characteristic peak (Fig 3).

Infrared spectrophotometry The IP alone and physical mixture had a powerful absorption peak at 1637.3 cm⁻¹. The solid dispersion moved to 1662.4 cm⁻¹. Moreover, the solid dispersion produced lower peaks at 1265.1 cm⁻¹ and 1496.5 cm⁻¹ (Fig 4).

DISCUSSION

The systemic absorption of most drug products consists of a succession of rate processes^[12]. These processes include (1) disintegration of the drug product

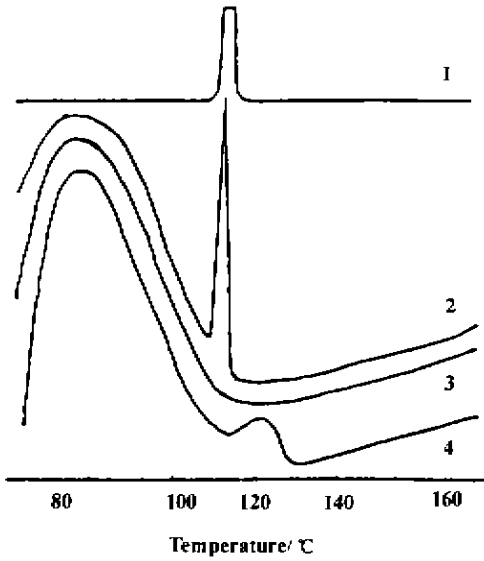


Fig 2. DSC curves of IP (1), physical mixture (2), PVP (3), and solid dispersion (4).

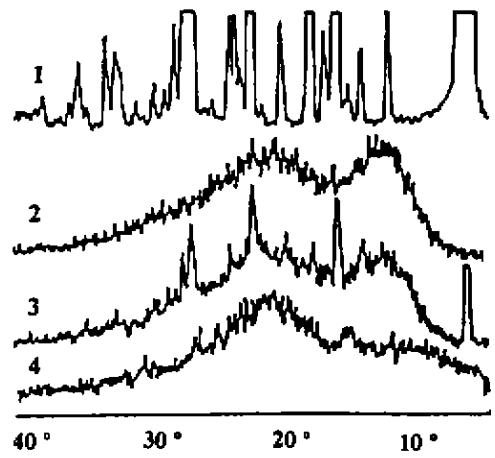


Fig 3. X-Ray diffraction patterns of powders of IP (1), PVP (2), physical mixture (3), and solid dispersion (4).

and subsequent release of the drug; (2) dissolution of the drug in an aqueous environment; and (3) absorption

across cell membrane into the systemic circulation. In the process of drug disintegration, dissolution, and absorption, the rate at which drug reaches the circulatory system is determined by the slowest step in

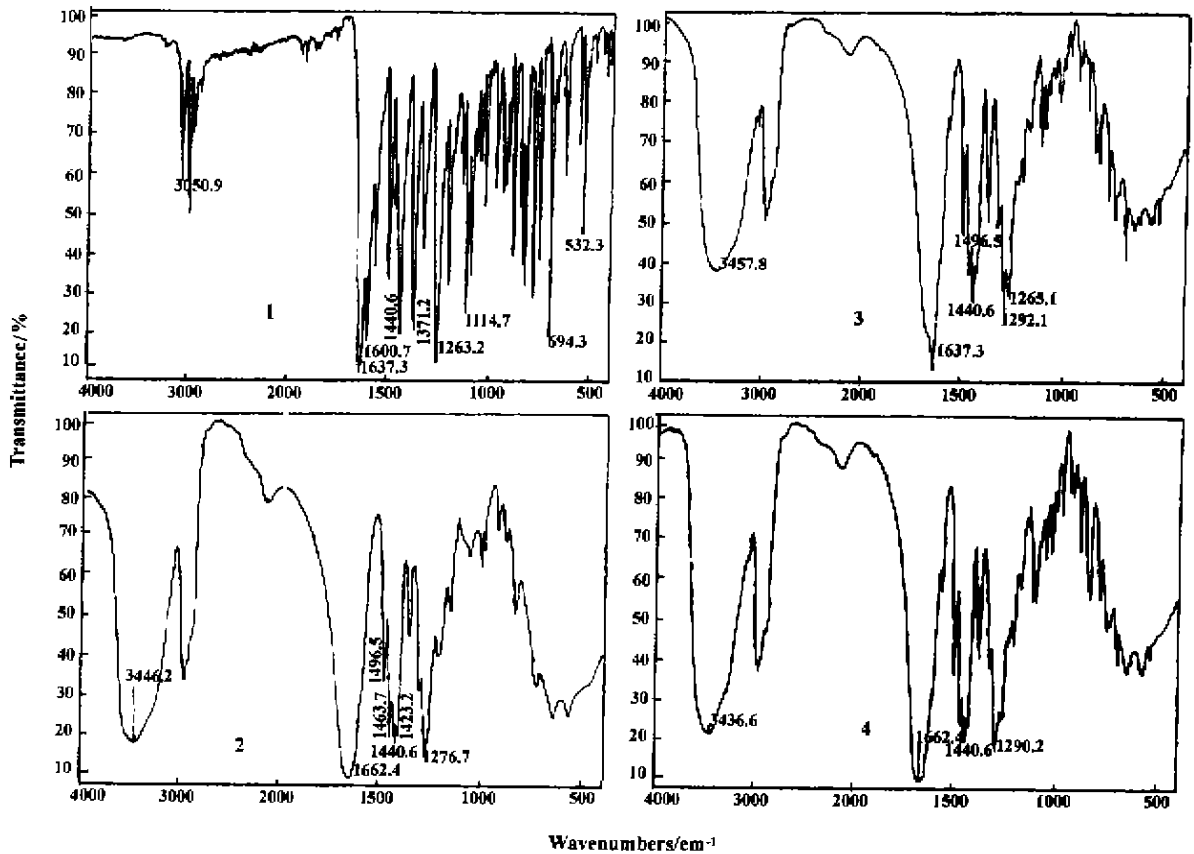


Fig 4. Infrared spectrophotometries of IP (1), PVP (2), physical mixture (3), and solid dispersion (4).

the sequence. For drugs that have very poor aqueous solubility, the rate at which the drug dissolution (dissolves) is often the slowest step, and therefore exerts a rate-limiting effect on drug bioavailability.

IP dissolves poorly in water, artificial gastric juice or artificial intestinal juice. Obviously, dissolution rate of IP is the slowest step, and a rate-limiting effect on its bioavailability. The solid dispersion method is a useful technology for increasing dissolution of drugs with a poor solubility in water, and for improving their bioavailability^[9-11]. IP dissolution increased by being prepared into the solid dispersion. This had appeared in the present study. The DSC curves, X-ray diffraction patterns and infrared spectrophotometries showed IP in solid dispersion could be dispersed in PVP with molecular or amorphous. The study on preparation and dissolution property of IP solid dispersion provided a useful reference for making further studies on its oral preparation in future.

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依普黄酮固体分散体的制备和溶出特性

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关键词 依普黄酮; 异黄酮; 制剂; 聚维酮; 聚乙二醇

目的: 制备和鉴定依普黄酮固体分散体, 测定它的体外溶出度. 方法: 用溶剂法制备依普黄酮固体分散体, 用 DSC, X 衍射和红外光谱鉴定固体分散体, 浆法测定它的溶出度. 结果: 由依普黄酮和聚维酮(1:8)组成的固体分散体, 其体外溶出度是依普黄酮的 6.15 倍, DSC 曲线, X 衍射图谱和红外光谱均产生了明显变化. 结论: 依普黄酮被制成固体分散体能明显增加依普黄酮的体外溶出度.

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