Improvement of Dissolution and Bioavailability for Mebendazole, an Agent for Human Echinococcosis, by Preparing Solid Dispersion with Polyethylene Glycol

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The solid dispersion of mebendazole was prepared with polyethylene glycol (PEG) to enhance the dissolution rate of mebendazole, an agent for the chemotherapy of human echinococcosis. The dissolution rate of the solid dispersion increased compared with the physical mixture, and also increased with the incorporation of an increasing amount of PEG-6000. An extensive improvement of the dissolution rate was observed when the ratio of the solid dispersion of mebendazole to PEG-6000 was more than 1:2. Furthermore, greater bioavailability in rabbits was obtained after oral administration of the solid dispersion compared with the physical mixture.

Keywords  echinococcosis; chemotherapy; mebendazole; solid dispersion; solvent method; polyethylene glycol; bioavailability

Introduction

Human echinococcosis is caused by the larval forms of Echinococcus granulosus or E. multilocularis. It is well known that E. multilocularis is an important zoogenic parasite in Japan, especially in eastern Hokkaido.13 Two hundred and sixty four patients with the disease caused by the larval E. multilocularis were found in Hokkaido between 1937 and 1987, and it is indicated that the number of patients will increase.23 For these patients, surgery has been the only available treatment, but it is often ineffective due to extensive secondary alveolar echinococcosis.33 Thus, it is proposed that an effective chemotherapy is needed before or after the surgery. For this purpose, benzimidazole derivatives have been used.33 However, absorption from the gastro-intestinal (GI) tract is very poor, since these drugs are slightly soluble in GI fluid.44 Therefore, it is necessary to increase the drug's GI absorption and bioavailability for effective medical treatment of hepatic or pulmonary echinococcosis. It is well known that various preparation of the solid dispersion can be used to enhance3,66 or retard5,78 the dissolution rate of the drug. Previously we prepared sustained release formulations for nifedipine59 and ketoprofen10 by using a solvent method technique for the solid dispersion.

In the present study, we used mebendazole and prepared the solid dispersion of this drug using polyethylene glycol (PEG) to enhance the dissolution rate. Furthermore, we administered this formulation to rabbits, and evaluated the GI absorption.

Experimental

Materials  Mebendazole was kindly provided by Janssen Kyowa (Tokyo, Japan, lot No. IF 401). PEG-4000 and PEG-6000 were of JP XI grade. All other reagents were of the highest grade commercially available and used without further purification.

Solubility Studies  The solubility of mebendazole in distilled water containing 0 or 0.0011% (w/v) PEG-6000 was determined by adding excess mebendazole to the medium at 37°C. After equilibrium was reached, the aliquot was filtered immediately by a membrane filter with a pore size of 0.45 µm (Toyo Roshi Co.) and diluted appropriately with the same medium. The samples were analyzed by high performance liquid chromatography (HPLC). Each solubility was determined in triplicate.

Preparation of Dosage Forms  1) Physical Mixture: Mebendazole and PEG-4000 or 6000 were mixed with a mortar and pestle, and the mixture was passed through a 100-mesh sieve.

2) Solid Dispersions: Solid dispersions of mebendazole with PEG were prepared using a solvent method.33 The drug and PEG were dissolved in methanol at room temperature, then the solution was removed in vacuo by using a rotary evaporator at 45°C on a water bath. The residue was dried in vacuo at room temperature for 24 h and passed through a 100-mesh sieve.

Dissolution Studies  The dissolution of mebendazole was tested in 900 ml of distilled water using the beaker method11 at an agitation speed of 100 rpm at 37°C. After the sample, the physical mixture or solid dispersions containing 2 mg of mebendazole, was added to the medium, 4 ml of the test medium was removed at appropriate intervals through a membrane filter (Toyo Roshi Co., pore size 0.45 µm) and immediately replaced with an equal volume of fresh test medium to maintain the original volume.

Plasma Level of Mebendazole in Rabbits  Two white male rabbits (2.5—3.5 kg), which had been fasted for 24 h but allowed free access to water, were administered the physical mixture or the solid dispersion at a dose of 20 mg/kg of mebendazole with 20 ml of water. The administration study was performed on a crossover design. About 1.5 ml of blood was drawn from marginal ear veins at 0, 20, 40 min, 1, 2, 3, 4, 6 and 8 h after administration.

Assay Procedure  To 0.5 ml of plasma or dissolution test solution in a 15 ml test tube, 3 ml of borate buffer (0.1 M Na₂B₄O₇·8H₂O, pH 10.5) and 4 ml of chloroform was added. The tube was shaken for 10 min, then the tube was centrifuged at 1000 x g for 5 min. After aspiration of the water layer, 2 ml of chloroform was removed to another test tube and the chloroform layer was evaporated to dryness in vacuo at 40°C. The residue in the tube was reconstituted with 100 µl of acetonitrile containing 50 ng of mebendazole as an internal standard. Usually, 20—40 µl of the same solution was injected into the HPLC system.

HPLC Conditions  A liquid chromatograph (Hitachi 635A) equipped with a high-pressure sampling valve (Hitachi 638-8801, 1–150 µl) was used. For the stationary phase, a reversed-phase column (Hitachi 3053, 4.6 mm i.d. × 25 cm) was used; the column was warmed at 55°C using a constant-temperature water bath circulator. The mobile phase consisted of a 0.05 M phosphate buffer (pH 7.0)–acetonitrile (55:45). The pH of this mobile phase was adjusted to pH 6.5 with phosphoric acid. The flow rate was 0.75 ml/min and the pressure was approximately 60 kg/cm². Detection was at 310 nm using a variable wavelength ultraviolet (UV) monitor (Hitachi 638-41) at 0.005 absorbance unit full scale (a.a.f.s.). The retention times for mebendazole and an internal standard were 8.0 and 10.0 min, respectively.

Results and Discussion

Dissolution Studies  Figure 1 shows the dissolution profiles of mebendazole from the solid dispersions with PEG-4000 (mebendazole:PEG-4000 = 1:5) and with PEG-6000 (mebendazole:PEG-6000 = 1:5). The dissolution profile of the physical mixture of mebendazole–PEG-4000 is also shown for comparison. Mebendazole concentrations of two kinds of solid dispersions were significantly higher than that of the mebendazole–PEG-4000 physical mixture, indicating that the dissolution of mebendazole was improved by preparing solid dispersions with PEG.

In the following studies, we used the solid dispersion with PEG-6000, since the dissolution rate of the solid dispersion with PEG-6000 was superior to that of PEG-4000, as shown
in Fig. 1. Figure 2 shows dissolution profiles for several solid dispersions of mebendazole containing various amounts of PEG-6000 in the formulations. When the ratio of PEG to drug was greater than one, an enhanced dissolution rate was observed compared with the physical mixture of mebendazole–PEG-6000 (1:10). There was no significant difference in the dissolution rate among the solid dispersions which had the following ratios of mebendazole to PEG-6000: 1:2, 1:5, 1:10. Duclos et al. reported that the amorphous and crystalline progesterone were found in the solid dispersion with PEG-6000 by differential scanning calorimetry and X-ray diffraction.\(^\text{12,13}\) Chiu et al. reported the possibility of ultrafine or colloidal dispersions of drugs in the solid dispersion using PEG-6000.\(^\text{15}\) Therefore, it is considered that improvement of the dissolution rate of mebendazole might be due to the amorphous phase of mebendazole, the reduction of the drug particle size, or an improvement in wettability, which resulted from the interaction of mebendazole and PEG-6000.

We have also studied the dissolution rate of the solid dispersion of mebendazole–PEG-6000 (1:5) and the physical mixture which have the same ratio until 8 h (Fig. 3). Mebendazole was dissolved over its solubility (0.95 µg/ml; distilled water, 0.99 µg/ml; distilled water containing 0.0011% w/v PEG-6000). It was also found that a post-peak decline was observed when the dissolution test was continued to 32 h (data not shown). This was considered a supersaturation phenomenon caused by the amorphous mebendazole.\(^\text{14}\) Thus, we used the solid dispersion of mebendazole with PEG-6000 for the study of GI absorption.

Absorption Studies Figure 4 shows the mean plasma levels of mebendazole following the oral administration of solid dispersion (mebendazole: PEG-6000 = 1:5) and phys-
ical mixture (mebendazole:PEG-6000 = 1:5) to rabbits. An increased initial dissolution rate of the solid dispersion (Fig. 3) was reflected in the high plasma levels for the solid dispersions. It was found that the $C_{\text{max}}$ for the solid dispersion was about 3-fold that of the physical mixture. The area under the plasma concentration–time curves of the solid dispersion and physical mixture up to 8 h were 19.5 and 3.3 (µg·h/ml), respectively. Conclusively, the larger bioavailability of mebendazole resulted from improvement of the dissolution rate. From the present results, it is assumed that oral administration of the solid dispersion of mebendazole with PEG-6000 is more effective for the chemotherapy of human echinococcosis.

References