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Improving the Oral Bioavailability of Albendazole in Rabbits by the Solid Dispersion Technique

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Abstract

We have investigated the oral bioavailability of granules of albendazole, a drug used for treating echinococcosis in man, prepared by the solid dispersion technique.

Rapid dissolution and supersaturation were observed when hydroxypropylmethylcellulose and hydroxypropylmethylcellulose phthalate were used as carriers in the solid dispersion. They inhibited the crystallization of albendazole from the supersaturated solution and maintained an amorphous state for 8 h. Gastric acidity-controlled rabbits were used to evaluate the variation in absorption after oral administration of the albendazole solid dispersion. For rabbits with low gastric acidity the bioavailability of orally administered albendazole in the granular form prepared by solid dispersion was more than three times that of albendazole in physical mixtures.

These results suggest that the bioavailability of albendazole in solid dispersions might be high even if there is a great variation in the gastric pH of patients.

Alveolar echinococcosis is considered to be the most lethal type of helminthiasis in man, and the number of such cases is increasing, especially in northern hemisphere countries (Kumar & Chattopadhyay 1992). Albendazole has a wide-spectrum anthelminthic effect and has been used clinically in inoperable or disseminated hydatidosis (Uchino et al 1993; Ishizu et al 1997; Luchi et al 1997). Clinical studies, including our previous study (Sato et al 1994), have shown a great inter-subject variability in the bioavailability of albendazole (Marriner et al 1986; Jung et al 1992), possibly because of the poor water-solubility of the drug. When taken with a fatty meal, absorption of albendazole was improved fivefold (approx.) (Lange et al 1998). In a pharmaceutical investigation, the addition of surfactants, co-solvents or a solid dispersion mixed with polyvinylpyrrolidone improved the rate of dissolution of albendazole (del Estal et al 1994; Torrado et al 1996a, b). However, few such preparations have been used clinically.

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Our previous study showed that intestinal absorption of albendazole was significantly lower for rabbits with low gastric acidity than for those with high gastric acidity, because of the poor solubility of albendazole in weakly acidic and neutral solutions (Kohri et al 1998). In the current study we have attempted to improve the rate of dissolution of albendazole, by using a solid dispersion technique, and to evaluate oral bioavailability after administration of the solid dispersion to gastric acidity-controlled rabbits.

Materials and Methods

Chemicals

Albendazole sulphoxide was provided by Smith-Kline Beecham (Madrid, Spain). Albendazole and phenacetin were purchased from Sigma (St Louis, MO). Mebendazole was provided by Janssen Kyowa (Tokyo, Japan). Lansoprazole (Takepron) was obtained from Takeda (Tokyo, Japan). Hydroxypropylmethylcellulose (TC-5) and hydroxypropylmethylcellulose phthalate (HP-55) were obtained from Shin-Etsu (Tokyo, Japan). All other

Table 1. Composition (g) of albendazole preparations.

Preparation	Albendazole	TC-5	HP-55	Lactose
Physical mixture	0·1	–	–	1·5
Solid dispersion with TC-5	0·1	1·0	–	0·5
Solid dispersion with HP-55	0·1	–	1·0	–
Solid dispersion with TC-5 and HP-55	0·1	0·5	0·5	0·5

TC-5 = hydroxypropylmethylcellulose, HP-55 = hydroxypropylmethylcellulose phthalate.

chemicals were of the highest grade available and used without further purification.

Preparation of dosage forms

A physical mixture was prepared by mixing albendazole and lactose with a pestle and mortar; the mixture obtained was passed through a 100-mesh sieve.

Solid dispersions were prepared by use of a solvent method. Albendazole and the polymers were dissolved in ethanol–dichloromethane (1 : 1, 75 mL) at room temperature and mixed with lactose. For hydroxypropylmethylcellulose phthalate preparations, albendazole and the polymer were dissolved in 75 mL acetone (50–60°C), and lactose was not included. The solution was then evaporated immediately at 45°C on a water bath. The residue was dried for 12 h under vacuum and passed through a 100-mesh sieve. Powder X-ray diffractometry was performed with an RU-300 (Rigaku Denki, Japan; CuKa; 50 kV; 100 mA; $3^\circ\,min^{-1}$). The chemical compositions of preparations are shown in Table 1.

In-vitro dissolution study

Dissolution experiments were performed by the JP XIII paddle method at an agitation speed of $100\,rev\,min^{-1}$ at 37°C. Each preparation containing 10 mg albendazole was added to 900 mL JP 2nd fluid. Test medium (400 μL) was removed at appropriate intervals and filtered through a 0·45-μm membrane filter (Toyo Roshi, Tokyo).

A dissolution test by the pH-shift method was conducted to simulate drug transition from the stomach to the small intestine (Kondo et al 1994). A sample equivalent to 10 mg albendazole was added to the test medium (pH 1·2; 500 mL). After 1 h, medium (10 mL) was removed and immediately replaced with an equal volume of 2·5 M KH_2PO_4 containing 16·72% (w/v) NaOH to adjust the pH of the medium to 6·5. The test solution was analysed by high-performance liquid chromatography (HPLC) with an Hitachi L-6000 constant flow pump and a Hitachi L-4000 UV detector operating at 310 nm. Compounds were separated on a 10 cm × 6 mm ERC-ODS 1161 reversed-phase column, particle size 3 μm (Erma Optical Works). The mobile phase was 0·05 M phosphate buffer (pH 7·0)–acetonitrile, 55 : 45 with the pH was adjusted to 6·5 with phosphoric acid; the flow rate was $1{\cdot}0\,mL\,min^{-1}$. Mebendazole was used as internal standard.

In-vivo absorption study

Experiments were performed on white male rabbits, 2·5–3·5 kg, with a 14-day wash-out period between doses. Low gastric-acidity rabbits were obtained by a method reported elsewhere (Kohri et al 1998). Briefly, rabbits were fasted for one day before the absorption study, but water was freely available. On the day of the experiment, hard gelatin capsules (JP XIII, No.3) containing lansoprazole (6 mg), an H^+-pump inhibitor, were administered orally at 0900 and 2100 h. At 0900 h on the day of the study water (10 mL) was given orally through a plastic catheter, and gastric juice was withdrawn by suction. The pH of the gastric juice was determined with pH paper (Toyo Roshi, Tokyo) for each rabbit. For intravenous administration a solution ($5\,mg\,mL^{-1}$) of albendazole sulphoxide, an active metabolite of albendazole, in dimethylsulphoxide was injected through the ear marginal vein ($1\,mg\,kg^{-1}$). Plasma samples were collected from the marginal ear vein at predetermined intervals by means of a heparinized syringe. The assay for albendazole sulphoxide in plasma was performed according to a method reported elsewhere (Kohri et al 1998). Plasma (600 μL) was mixed with $Na_2B_4O_7$ solution (0·1 M, 3 mL) containing phenacetin as internal standard for HPLC and extracted with chloroform (6 mL). The organic layer (500 μL) was evaporated, the residue was reconstituted with mobile phase (0·1 mL), and the resulting solution was analysed by the HPLC method used for in-vitro solubility studies. The mobile phase was 0·05 M phosphate buffer–acetonitrile, 75 : 25.

Analysis of plasma data

The parameters of the appropriate pharmacokinetic model were estimated using the MULTI program (Yamaoka et al 1981). The area under the plasma

concentration–time curve from 0 to 24 h ($AUC_{0-24\,h}$) was calculated by the linear trapezoidal rule. Because albendazole was completely metabolized to albendazole sulphoxide in rabbits, the bioavailability was calculated according to the equation:

$$\text{Bioavailability} = (AUC_{\text{albendazole sulphoxide oral}}/\text{dose}_{\text{oral}})/(AUC_{\text{albendazole sulphoxide intravenous}}/\text{dose}_{\text{intravenous}}) \quad (1)$$

where $AUC_{\text{albendazole sulphoxide oral}}$ and $AUC_{\text{albendazole sulphoxide intravenous}}$ represent the $AUC_{0-24\,h}$ values of albendazole sulphoxide after oral administration of albendazole and intravenous administration of albendazole sulphoxide, respectively.

Statistical differences between high and low gastric-acidity groups were assessed by use of Student's *t*-test.

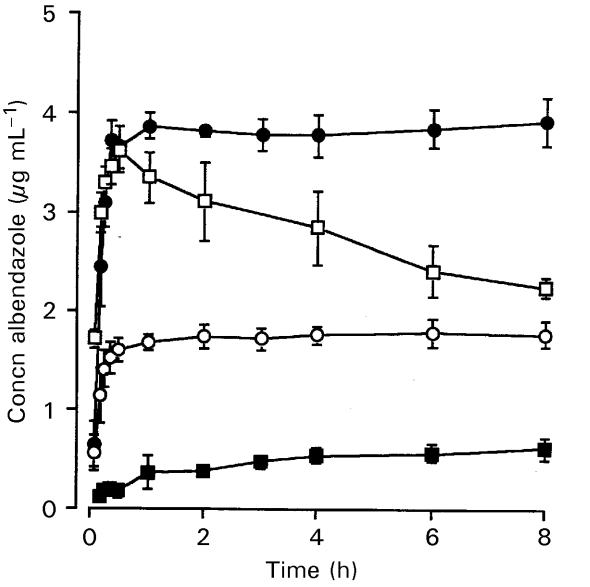

Figure 1. Dissolution behaviour of albendazole from solid dispersions in 900 mL JP XIII 2nd test fluids at 37°C: ■, physical mixture; ●, solid dispersion with hydroxypropylmethylcellulose and hydroxypropylmethylcellulose phthalate; ○, solid dispersion with hydroxypropylmethylcellulose; □, solid dispersion with hydroxypropylmethylcellulose phthalate. Each point represents the mean ± standard deviation of results from three measurements.

Results and Discussion

Dissolution study

Low molecular-weight hydroxypropylmethylcellulose (TC-5) has been used as a carrier for solid dispersion formulations to enhance the dissolution rate and saturated solubility of several water-insoluble drugs (Sugimoto et al 1982; Honbo et al 1987; Kohri et al 1992; Kagayama et al 1993). In this study, therefore, solid dispersions were prepared by use of TC-5 and by a solvent method. The chemical compositions of preparations are summarized in Table 1. The addition of lactose was necessary because a solid dispersion of TC-5 only was too hard to mill. Figure 1 shows the dissolution profiles of solid dispersions in JP III 2nd fluid (pH 6·8). The rate of dissolution was rapid for all solid dispersions, and for both formulations containing TC-5 the highest supersaturated concentration was reached after 0·5 h. Although the supersaturated concentration of the formulation prepared with HP-55 only subsequently decreased, both formulations with TC-5 maintained their maximum concentrations for 8 h. Figure 2 shows the dissolution profiles of solid dispersions in media of pH 1·2–6·5, used to simulate dissolution in the gastrointestinal tract. At pH 1·2 albendazole dissolved completely from all the preparations except that containing HP-55 only; it crystallized rapidly when the pH was changed to 6·5. However, formulations containing TC-5 maintained their supersaturated concentrations for long periods, suggesting that the crystallization of

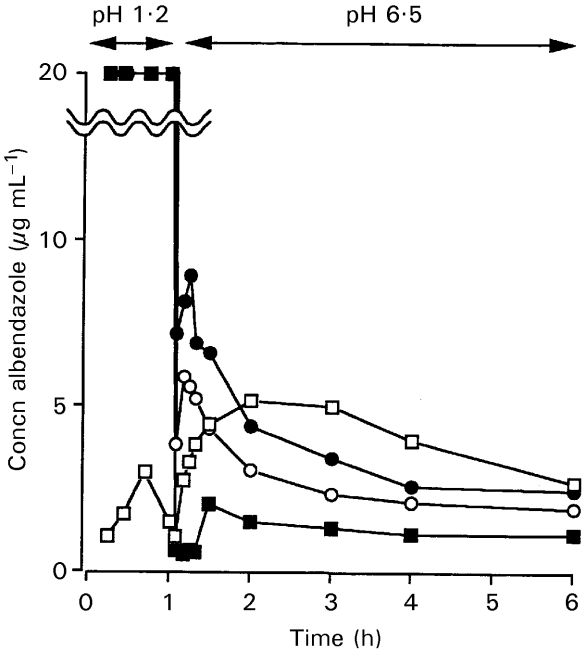

Figure 2. Dissolution behaviour of albendazole from solid dispersions in media of pH 1·2–6·5: ■, physical mixture; ●, solid dispersion with hydroxypropylmethylcellulose and hydroxypropylmethylcellulose phthalate; ○, solid dispersion with hydroxypropylmethylcellulose; □, solid dispersion with hydroxypropylmethylcellulose phthalate.

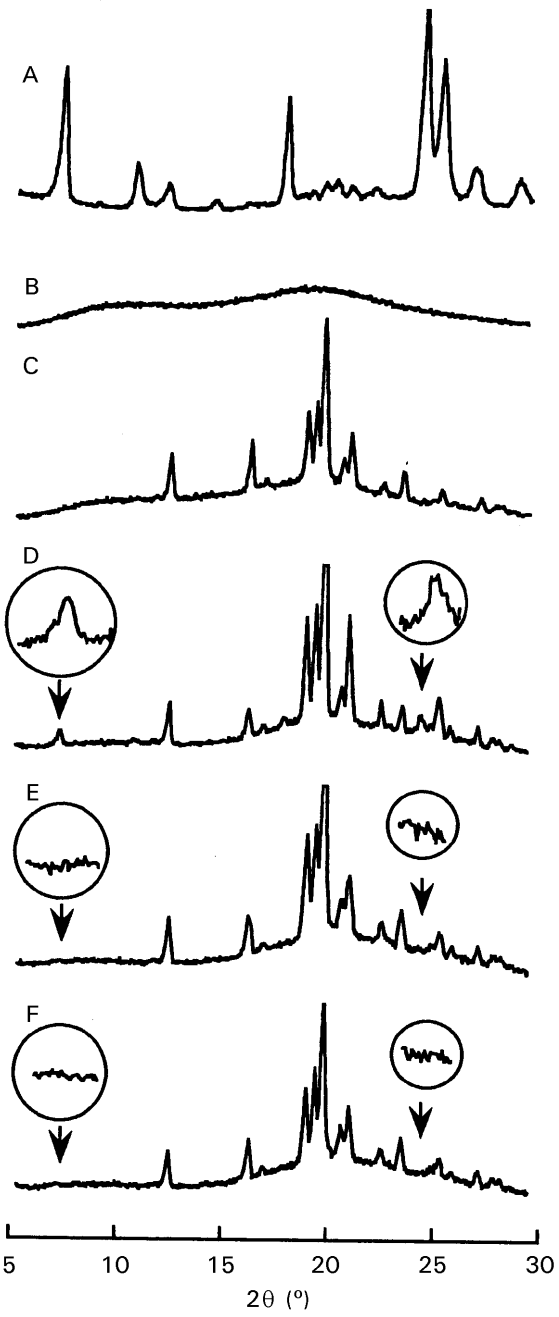

Figure 3. Powder X-ray diffraction patterns of albendazole physical mixture and solid dispersions. A. Albendazole crystals, B. 1 : 1 TC-5-HP-55, C. 1 : 1 : 1 TC-5-HP-55-lactose, D. physical mixture 1 : 5 : 5 : 5 albendazole-TC-5-HP-55-lactose, E. solid dispersion 1 : 5 : 5 : 5 albendazole-TC-5-HP-55-lactose, F. solid dispersion 1 : 5 : 5 : 5 albendazole-TC-5-HP-55-lactose after storage in a screw-cap vial at 4°C for 15 months. TC-5 = hydroxypropylmethylcellulose, HP-55 = hydroxypropylmethylcellulose phthalate.)

albendazole in these two solid dispersions is retarded by the presence of polymers. These results suggest that the formulation containing both TC-5 and HP-55 not only has excellent solubility but also prevents albendazole crystallization in a neutral medium.

Physical characterization of the solid dispersion

Figure 3 shows the powder X-ray diffraction patterns of the physical mixture and of the solid dispersion containing both TC-5 and HP-55. For the physical mixture, the peaks located at 7·3° and 24·7° (2θ) correspond to albendazole crystals; the others correspond to lactose crystals. Peaks from albendazole crystals are absent from the patterns obtained from solid dispersions with a drug-to-polymer ratio of 1 : 10, indicating that albendazole is present as the amorphous state in these formulations. Moreover, this amorphous state did not change over a period of 15 months at 4°C in a screw-cap vial.

Absorption study

The plasma concentrations of albendazole sulphoxide after oral administration of the preparations to gastric acidity-controlled rabbits are shown in Figure 4. The pharmacokinetic parameters are summarized in Table 2. For both groups the C_{max} (maximum plasma concentration) and AUC of the solid dispersion (which contained both TC-5 and HP-55) were higher than those of the physical mixture. Bioavailability from the solid dispersion was almost 100% in the normal gastric acidity group (gastric pH values were 1 (approx.)) and for the low gastric-acidity group was 3·2 times that from the physical mixture (gastric pH values were >5).

On the basis of these results we suggest that when the solid dispersion was administered to rabbits with normal gastric acidity both albendazole and TC-5 dissolved completely in the stomach. As the solid dispersion shifted to the small intestine, HP-55 began to dissolve. Thus, crystallization of albendazole was prevented by both polymers. This speculation is supported by the prolonged MRT (mean residence time) and the almost 100% bioavailability observed when the preparation was administered to rabbits with normal gastric acidity. When the solid dispersion was administered to rabbits with low gastric acidity, the dissolution of albendazole in the stomach was four times (approx.) that from the physical mixture, and the supersaturated concentration of albendazole remained in the small intestine for a long time, because of the presence of the polymers. Moreover, polymers remaining undissolved in the stomach dissolved in the small intestine. We conclude that

Table 2. Pharmacokinetic parameters after administration of albendazole (5 mg kg^{-1}) to rabbits in a cross-over study.

Parameter	Normal gastric acidity		Low gastric acidity	
	Physical mixture	Solid dispersion	Physical mixture	Solid dispersion
C_{max} (μg mL^{-1})	2·1 ± 0·2	2·4 ± 0·4	0·5 ± 0·2	1·4 ± 0·2*
T_{max} (h)	4·0 ± 0·8	3·7 ± 0·7	6·3 ± 1·6	6·7 ± 1·1
$AUC_{0-24\,h}$ (μg h mL^{-1})	22·4 ± 3·5	31·8 ± 4·7*	6·4 ± 2·6	24·8 ± 5·8*
$t_{1/2}$ (h)	2·8 ± 0·4	5·8 ± 1·7	4·8 ± 1·6	4·6 ± 0·8
MRT (h)	7·7 ± 1·1	10·6 ± 2·0*	12·0 ± 3·2	13·3 ± 2·3
Bioavailability (%)	67·6 ± 17·9	94·9 ± 12·9*	21·3 ± 9·9	68·8 ± 13·2*

Values are means ± standard error (n = 5). *$P < 0.05$ compared with corresponding values using the physical mixture. C_{max} = maximum concentration, T_{max} = time of maximum concentration, $AUC_{0-24\,h}$ = area under the plasma concentration–time curve from 0 to 24 h, $t_{1/2}$ = plasma half-life, MRT = mean residence time.

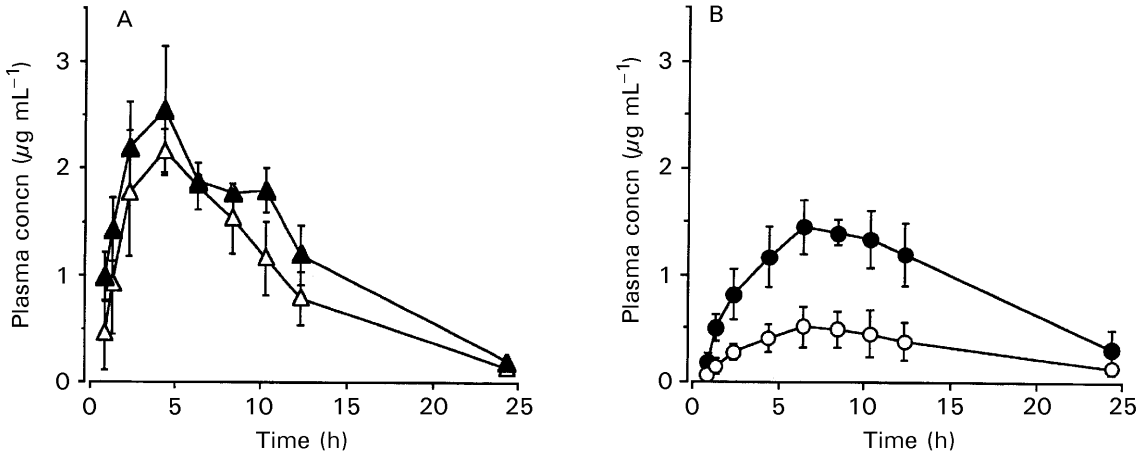

Figure 4. Mean plasma concentrations of albendazole sulphoxide after oral administration of physical mixture (△, ○) and solid dispersion (▲, ●) to normal acidity rabbits (A) and to low acidity rabbits (B) at a dose of 5 mg kg^{-1}. Each point represents the mean ± standard error of results from five rabbits.

the bioavailability of albendazole in solid dispersions might be improved even if there is a great variation in the gastric pH of patients.

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