RESEARCH PAPER

Accepted 23 September 2003
Revised 31 July 2003
Received 6 Junuary 2003
Indian J. Pharm. Sci., 2003, 65(6): 605-612

Enhancement of Dissolution and Bioavailability of Mebendazole for the Effective and Safe Management of Human Echinococcosis

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Mebendazole and β-cyclodextrin molecular inclusion complexes and mebendazole solid dispersions with polyethylene glycol 6000 were prepared by solvent method in different mixing ratios to increase the rate and extent of dissolution and absorption of mebendazole for an effective chemotherapy of human echinococcosis. The enhancement of dissolution of mebendazole was dependent on the carriers used and the nature of presentation of mebendazole in the carriers (physical mixture/solid dispersion/molecular inclusion). The differential scanning calorimetry indicated the solid inclusion complex formation of mebendazole and β-cyclodextrin at 1:2 molar ratio and mebendazole-polyethylene glycol solid dispersion at 1:4 weight ratio. Stability study reported a significant decline in the potency of mebendazole in all mebendazole-polyethylene glycol solid dispersions. Dissolution rate and dissolution efficiency of mebendazole were improved by both molecular inclusion complexes and solid dispersions of all mixing ratios than the corresponding physical mixtures and pure drug, 1:2 mebendazole-βcyclodextrin showing the highest dissolution among all the preparations. As mebendazole has been reported to undergo extensive first pass metabolism, also a single dose plasma level bioavailability study in rabbits was conducted to confirm the bioavailability performance of mebendazole from the 1:2 mebendazole-βcyclodextrin complex. In the study, not only a statistically significant ($p<0.05$), but also a great improvement in bioavailability of mebendazole was achieved with 1:2 mebendazole-βcyclodextrin complex as compared to its physical mixture. Bioequivalency study was also performed for 1:0.5 mebendazole-βcyclodextrin complex and 1:4 mebendazole-polyethylene glycol solid dispersion (which were equivalent to each other in dissolution behavior) and this study showed a result opposite to what was expected on the basis of their *in vitro* drug release profiles. The reported risks in the use of cyclodextrins and the observed stability problem associated with mebendazole-polyethylene glycol solid dispersions were considered in deciding a choice for the treatment of human echinococcosis.

Mebendazole (MBZ) is a well known drug for the treatment of intestinal worm infestations, but it is also recommended for the treatment of human echinococcosis (Hydatid disease)[1]. The causative organism of this disease is the larval form of *Echinococcus granulosus*, an important zoorotic parasite widely found in Hokkaido, Japan[2]. For the patient suffering from echinococcosis, the only available treatment is surgery, which is often ineffective in extreme secondary alveolar echinococcosis[3-4]. Mortality is also reported with repeated surgery[3]. Hence, post-operative or pre-operative chemotherapy with benzimidazole derivatives has been suggested for few months to years according to WHO informal working group on Echinococcosis[4]. Thus systemic absorption of MBZ is mandatory for the treatment of lung and liver echinococcosis[4].

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Due to its practically insoluble nature[5], only 10% of orally administered dose of MBZ has been reported to be absorbed[6]. If it is taken during a fatty meal, its absorption is likely to be more and so individual variations in absorption have also been reported[3]. To avoid poor and erratic bioavailability, development of industrially adaptable and safe means of dissolution improvement is required. As MBZ undergoes extensive first pass metabolism[3], a confirmative test for the improved bioavailability due to enhanced dissolution is also mandatory.

The most promising and widely used methods for promoting dissolution at present are the solid dispersion and molecular inclusion techniques. In the later technique, cyclodextrins are employed. However, in pharmaceutical formulations cyclodextrins should be avoided as far as possible or their quantity must be kept at a minimum level. This is because of the reason that they have been reported to increase the dissolution and o/w partition coefficient (absorption) of lipophilic toxicants that are naturally present in the common human diet and responsible for 25% of human cancers[7]. In addition, the absorption of certain carcinogenic substances trapped in saliva from the polluted air is improved by cyclodextrins[7]. Hence the study was started from the lowest ratio of β-cyclodextrin (βCD), though the minimum molar ratio for the formation of molecular inclusion complex is logically 1:1 (MBZ and βCD in Molar ratio).

MATERIALS AND METHODS

Mebendazole USP, albendazole IP, polyethylene glycol 6000 IP and β-cyclodextrin were gift samples from M/s Cadila Pharmaceuticals, Ahmedabad. Methanol (Qualigens, Mumbai), chloroform (Merck, Mumbai), acetonitrile (Qualigens, Mumbai) and phosphoric acid (S. D. Fine Chemicals, Mumbai) all of analytical reagent grade were purchased from commercial sources. All the particles used (raw materials and the preparations) were passed through 100 mesh. Rabbits obtained from the Central Animal House of Annamalai University, Annamalai Nagar were housed at standard temperature (23±1°) and fed with standard pellet diet (Kamethenu Agencies, Bangalore).

Preparation of solid dispersions:

MBZ and polyethylene glycol 6000 (PEG) were dissolved in methanol and the solvent was evaporated at 45° under reduced pressure, followed by drying at room temperature under reduced pressure for 24 h.

Preparation of molecular inclusion complexes:

The aqueous solution of βCD was mixed with the methanolic solution of MBZ and after stirring for 1 h, the solvent mixture was evaporated under reduced pressure. The residue was dried for 24 h under reduced pressure at room temperature.

Preparation of physical mixtures:

The physical mixtures were prepared by mixing MBZ and the carriers of different ratios by trituration using mortar and pestle following 5 min duration of mixing for all cases. Solubility studies were performed as described by Higuchi and Connors[8] in presence of different concentrations of these two carriers. All preparations including physical mixtures were subjected to thermal analysis by using DSC (model 220 C, Sieko, Japan) at a scanning speed of 10°/minute in the temperature range of 35° to 350°.

Dissolution study:

In vitro dissolution studies for pure drug and all the preparations including physical mixtures equivalent to 3 mg of MBZ were carried out in 900 ml of distilled water at 37°, using USP XXIII type 2 dissolution apparatus (model TDT-06P, Electrolab) with an agitation of 100 rpm. The filtered (membrane pore size 0.45 μm) samples withdrawn at different time intervals were assayed for MBZ by HPLC.

Pharmacokinetic study:

Experimental protocols for the animal study were approved by the Institutional Animal Ethics Committee (CPCSEA/160/1999). Six male white New Zealand rabbits (weight 3.0±0.5 kg) fasted for 18 h, providing only water, were taken and divided into two balanced groups. One group was orally administrated the physical mixture of 1:2 MBZ and β-CD where as the other group was given 1:2 MBZ-βCD complex, each receiving 25 mg of MBZ per kg of body weight with 25 ml of water. Also a cross over study was conducted after 15 d washout period.

After 20 d from the above study, bioequivalency study was performed for the products of nearly similar *in vitro* drug release performance (1:0.5 MBZ-βCD complex and 1:4 MBZ-PEG solid dispersion), which also included a cross over study after 15 d washout period. From the marginal ear vein about 1.75 ml of blood was withdrawn at 0, 20, 40 min and 1, 2, 3, 4, 5, 6 and 8 h by using 0.6x25mm disposable sterile needle and collecting the blood in an Eppendorf tube containing 0.15 ml of sodium citrate anticoagulant solution. Blood samples were centrifuged (Remi Centrifuge model R-23) at 3000 rpm for 10 min running time. The supernatant clear liquid (plasma) was separated and stored at –20° until as-

sayed for the drug content.

Estimation of mebendazole by HPLC:

To 0.75 ml of dissolution sample solution/plasma in 20 ml test tube, 4.5 ml of borate buffer and 6 ml of chloroform were added. The test tube was shaken for 10 min and then centrifuged (Remi Centrifuge model R-23) at 1000xg for 10 min. The chloroform layer (2 ml) was transferred to another test tube and was evaporated to dryness under reduced pressure at 45°. The residue in the test tube was reconstituted with 100 μl of acetonitrile containing 50 ng of albendazole as an internal standard. Sample solution (20-40 μl) was injected into the HPLC system (Hitachi 635 A).

For this study a liquid chromatograph equipped with a high pressure sampling valve (Hitachi 638-0801, 1-150 μl) was used. A reverse phase column (Hitachi 3053, 4.6 mm i.d. x 25 cm) was used for the stationary phase. The column was warmed at 55° using a constant temperature water bath circulator. The mobile phase consisted of a 0.05 M phosphate buffer (pH 7.0)-acetonitrile (55:45). pH of the 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/cm^2. Detection was at 310 nm using a variable wavelength ultra violet monitor (Hitachi 638-41) at 0.005 absorbance unit full scale. The retention times for MBZ and internal standard were 8 and 10 min, respectively.

RESULTS AND DISCUSSION

The reason for selecting a higher molecular weight PEG (PEG-6000 vs PEG-4000) was that higher molecular weight PEGs would be more viscous to the system and thereby presumably preventing drug recrystallisation during the preparation of solid dispersion[9] by solvent or melting method.

DSC thermograms of MBZ (pure drug), βCD and MBZ-βCD preparations are shown in fig. 1. Fig. 2 shows the DSC thermograms of PEG 6000 and MBZ-PEG products. MBZ (pure drug) showed a sharp melting peak at 291-295°. No MBZ melting peak could be distinguished only in 1:4 MBZ-PEG solid dispersion and 1:2 MBZ-βCD complex and so these two were assumed to be better dispersion and molecular inclusion systems respectively.

The solubility of MBZ in distilled water was found to be 0.93 μg/ml at 37°. The phase solubility diagram for complex formation between MBZ and βCD is shown in fig. 3. The aqueous solubility of MBZ increased linearly (r=0.988) as a

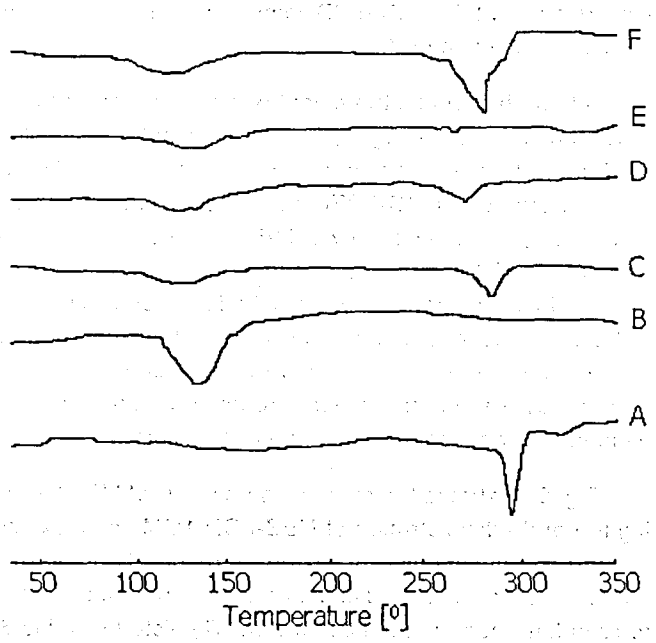

Fig. 1: DSC thermograms of MBZ, βCD and MBZ-βCD products.

DSC thermograms of MBZ (A), βCD (B), 1:0.5 MBZ-βCD (C), 1:1 MBZ-βCD (D), 1:2 MBZ-βCD (E) and 1:2 Physical mixture of MBZ and βCD (F).

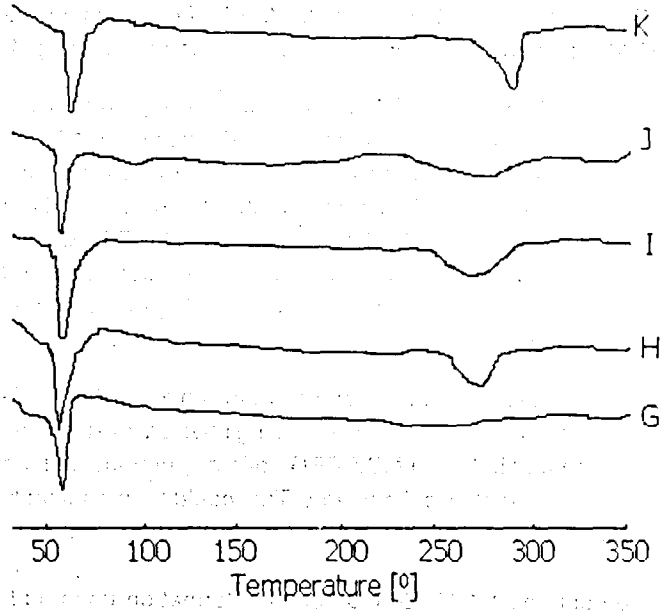

Fig. 2: DSC thermograms of PEG and MBZ-PEG products.

DSC thermograms of PEG 6000 (G), 1:2 MBZ-PEG (H), 1:3 MBZ-PEG (I), 1:4 MBZ-βCD (J) and 1:2 Physical mixture of MBZ-PEG (K).

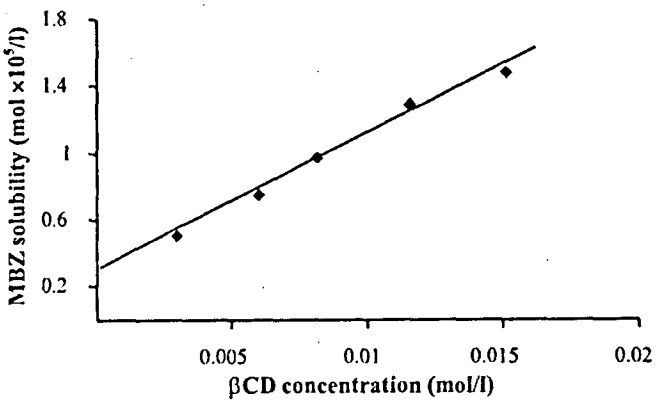

Fig.3: Phase solubility diagram of MBZ influenced by βCD.

Solubility of MBZ at different molar concentrations of βCD at 37°.

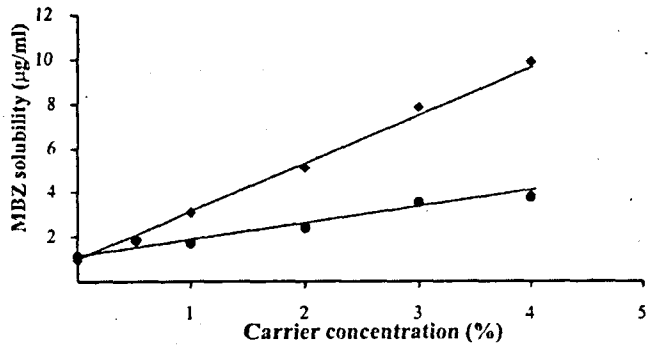

Fig.4: Phase solubility diagram of MBZ influenced by PEG and βCD.

Solubility of MBZ at different % w/v concentrations of PEG 6000(●) and βCD (♦) at 37°.

function of molar concentration of βCD. The phase solubility curve can be classified as A_L type[8]. As the straight line had a slope less than unity, it was assumed that the increase in solubility was due to the formation of a 1:1 complex. For A_L type, solid complexes can be prepared by methods such as kneading[10], freeze-drying[11], spray-drying[12] and coevaporation[13]. In the present study, coevaporation method was used to prepare solid inclusion complexes of MBZ and βCD. Phase solubility diagram for MBZ influenced by PEG 6000 (compared to the influence of βCD) is shown in fig. 4.

Dissolution rate of MBZ from pure drug and all the preparations was following first order kinetics up to 10 min. Dissolution rate constant (K_1) and dissolution efficiency (DE_{60}) were calculated as per the method of Khan[14] and are given in Table 1. All MBZ-βCD complexes and MBZ-PEG solid dispersions were exhibiting higher rate of dissolution and dissolution efficiency than the corresponding physical mixtures and pure drug.

The dissolution rate difference between any of the MBZ-βCD complexes and the corresponding physical mixture was less than that between MBZ-PEG solid dispersions and the corresponding physical mixtures. This could be presumably because of the solubilisation effect on the drug by β-CD[15] present in the physical mixture. The phase solubility study also confirms 1:1 MBZ-βCD complex formation upon adding the pure drug to the aqueous solution of β-CD. The solubility improvement in presence of PEG in water was comparatively less (in the phase solubility study), though there was improved dissolution due to enhanced wettability of MBZ from the physical mixtures (in the dissolution study).

Increases of 23.4 fold, 34.9 fold and 39.5 fold in the dissolution rate were observed respectively with MBZ-βCD complexes of 1:0.5, 1:1, 1:2 molar ratio, compared to the pure drug. The improvement in the dissolution rate of MBZ from 1:2, 1:3, 1:4 MBZ-PEG solid dispersions were 12.9, 18.9 and 24.1 folds respectively, compared to the pure drug. From the Table 1, it is understood that 1:4 MBZ-PEG solid dispersion and 1:0.5 MBZ-βCD complex have produced comparable dissolution profile.

Although cyclodextrin complexation is reported to improve the stability of drugs[15], there are examples of accelerated degradations in literature[15]. Hence stability study was also performed. All MBZ-PEG solid dispersions showed a faster decline in the potency of MBZ ($p<0.05$). On the contrary, MBZ-βCD complexes of all mixing ratios maintained good stability comparatively. Stability data is shown in Table 2. Hence, presence of this drug at a higher energy state (more reactive or more soluble form) in the crystalline PEG carrier may result in the adverse reaction with the environment in many aspects, requiring a costly storage.

Fig. 5 illustrates the mean plasma levels of MBZ following the oral administration of MBZ-βCD 1:2M complex and the corresponding physical mixture to rabbits. Drug plasma level profile was analyzed under noncompartmental method to calculate mean residence time (MRT), listed in Table 3. The initial increase in dissolution rate of drug from 1:2 MBZ-βCD complex was reflected in higher rate of absorption of MBZ from this preparation. Both the rate and extent of drug availability to plasma were improved. The maximum mean plasma concentration of drug (C_{max}) for 1:2 MBZ-βCD complex was 3.1 fold that of the corresponding physical mixture.

The area under the plasma level time curve (AUC) for this product showed 2.9 fold increase compared to the corresponding physical mixture.

The comparative bioavailability study (bioequivalency study) with 1:0.5 MBZ-βCD complex and 1:4 MBZ-PEG solid dispersion showed a peculiar result, which was exactly opposite to the dissolution profile of these two preparations as shown in fig. 6. Though the difference was insignificant, 1:4 MBZ-PEG Solid Dispersion was bit superior than 1:0.5 MBZ-βCD complex in the dissolution study (Table 1). On the other hand, 1:0.5 MBZ-βCD complex was superior than 1:4 MBZ-PEG solid dispersion in the plasma level study and here the difference was also statistically significant ($p<0.05$). The possible reason could be either an unexpected increase in the absorption of MBZ from MBZ-βCD system or a decrease in that from MBZ-PEG system.

TABLE 1: DISSOLUTION OF MEBENDAZOLE (MBZ) FROM FORMULATIONS.

Formulations	Mean % of MBZ dissolved (±s.d)					$DE_{60(\%)}$	K_1X10^4 (min^{-1})
	5 min	10 min	20 min	40 min	60 min		
Mebendazole (MBZ)	0.31 (0.02)	0.60 (0.04)	2.40 (0.06)	4.21 (0.21)	5.31 (0.25)	2.9	6.02
MBZ-PEG (1:2) PM	0.32 (0.04)	0.64 (0.03)	2.70 (0.11)	6.00 (0.53)	8.41 (0.29)	4.2	6.42
MBZ-PEG (1:2) SD	3.84 (0.11)	7.51 (0.09)	10.21 (0.41)	12.91 (0.91)	13.51 (0.32)	10.3	78.08
MBZ-PEG (1:3) PM	0.68 (0.14)	1.35 (0.11)	4.20 (0.09)	8.41 (1.92)	11.11 (2.21)	5.9	15.12
MBZ-PEG (1:3) SD	5.55 (0.31)	10.80 (1.30)	19.20 (2.03)	25.21 (1.72)	27.02 (2.24)	19.5	114.31
MBZ-PEG (1:4) PM	1.66 (0.21)	3.30 (1.03)	6.30 (0.51)	10.52 (0.93)	12.31 (0.78)	7.7	33.56
MBZ-PEG (1:4) SD	6.99 (0.89)	13.51 (1.21)	21.02 (1.12)	27.63 (1.22)	30.33 (2.55)	21.8	145.22
MBZ-βCD (1:0.5M) PM	3.15 (0.41)	6.20 (0.20)	7.86 (0.81)	9.62 (0.64)	12.31 (0.99)	8.2	64.09
MBZ-βCD (1:0.5M) IC	6.82 (1.02)	13.21 (1.22)	19.97 (1.40)	25.37 (2.55)	28.23 (1.71)	20.4	141.12
MBZ-βCD (1:1M) PM	3.93 (0.24)	7.70 (0.21)	9.67 (1.04)	13.11 (0.72)	15.27 (1.25)	10.6	80.14
MBZ-βCD (1:1M) IC	9.96 (0.64)	18.92 (1.26)	28.53 (3.04)	39.33 (2.23)	43.24 (3.82)	30.6	210.08
MBZ-βCD (1:2M) PM	4.31 (0.51)	8.43 (0.45)	12.38 (0.93)	16.50 (1.21)	20.45 (2.14)	13.4	88.18
MBZ-βCD (1:2M) IC	11.22 (1.68)	21.32 (3.12)	30.63 (3.10)	45.65 (2.67)	54.95 (4.13)	34.8	238.10

Figures in parentheses are the standard deviations from the mean values. PM = Physical mixture; SD = Solid dispersion; IC = Molecular inclusion complex. 1:0.5M, 1:1M, 1:2M = Molar ratios of mebendazole and β-CD. 1:1 molar ratio (of MBZ-βCD) is equivalent to 1:3.8 weight ratio.

TABLE 2: STABILITY REPORT (ASSAY) OF MEBENDAZOLE FROM FORMULATIONS.

Weeks	At 25° storage MBZ-PEG SD Ratios in Weight			At 40° storage MBZ-PEG SD Ratios in Weight			At 25° storage MBZ-βCD IC Molar Ratios			At 40° storage MBZ-βCD IC Molar Ratios		
	1:2	1:3	1:4	1:2	1:3	1:4	1:0.5	1:1	1:2	1:0.5	1:1	1:2
0	100.6 (0.4)	101.4 (0.3)	99.5 (1.1)	100.6 (1.7)	101.4 (3.2)	99.5 (0.2)	99.4 (1.8)	98.2 (1.2)	102.2 (1.8)	99.4 (2.1)	98.2 (0.7)	102.2 (0.5)
1	100.8 (0.2)	101.0 (1.0)	98.7 (0.3)	101.0 (1.1)	100.0 (1.1)	98.4 (0.2)	99.0 (0.4)	99.2 (1.1)	102.3 (0.9)	99.9 (1.6)	100.9 (0.9)	102.0 (1.4)
2	100.2 (0.9)	100.9 (1.3)	98.2 (0.6)	99.1 (1.2)	99.3 (1.0)	98.0 (0.6)	100.4 (0.3)	97.9 (0.4)	101.9 (1.2)	100.8 (1.2)	98.4 (0.3)	101.6 (0.9)
3	100.1 (0.2)	100.9 (0.9)	98.6 (1.2)	98.4 (0.8)	99.0 (3.4)	98.2 (0.8)	98.5 (0.6)	97.4 (2.3)	102.1 (1.1)	99.2 (0.9)	99.4 (0.6)	102.6 (1.7)
4	98.1 (0.5)	100.3 (0.7)	98.6 (1.2)	97.9 (0.9)	98.3 (0.8)	97.0 (0.4)	98.9 (0.9)	98.9 (2.1)	101.7 (1.0)	98.9 (0.6)	99.0 (0.4)	101.4 (1.6)
5	99.6 (0.5)	100.4 (0.6)	96.3 (0.7)	98.3 (1.6)	97.9 (0.6)	96.9 (0.7)	99.0 (0.8)	97.9 (1.4)	100.6 (1.2)	98.8 (1.4)	98.7 (0.7)	101.3 (0.9)
6	99.8 (2.2)	99.6 (0.8)	97.6 (1.3)	98.4 (0.7)	97.1 (0.9)	96.4 (1.4)	99.4 (1.1)	98.4 (0.7)	101.0 (1.0)	98.6 (1.6)	98.7 (0.6)	100.6 (1.2)
7	99.3 (1.4)	99.6 (0.3)	97.6 (0.4)	97.1 (0.8)	96.5 (0.7)	95.8 (0.2)	99.4 (0.6)	98.2 (1.0)	101.7 (1.8)	99.8 (0.9)	98.0 (0.3)	101.4 (0.6)
8	99.0 (0.7)	99.2 (0.4)	97.0 (0.5)	97.7 (1.0)	97.0 (0.9)	95.3 (2.3)	99.1 (0.8)	97.3 (0.9)	101.1 (1.2)	98.5 (1.0)	97.6 (0.9)	101.1 (1.5)

Figures in parentheses are standard deviations for the mean values. SD = Solid dispersion; IC = Molecular inclusion complex. Significant difference ($p<0.05$) between initial (0 week) potency of MBZ and the potency after 8 weeks was noticed in MBZ-PEG Solid dispersions of all mixing ratios.

TABLE 3: PHARMACOKINETIC PARAMETERS OF MEBENDAZOLE FORMULATIONS.

Parameter	MBZ-βCD (1:2M) PM	MBZ-βCD (1:2M) IC	MBZ-βCD (1:0.5M) IC	MBZ-PEG (1:4) SD
C_{max} (μg/ml)	1.42±0.22[k]	4.41±0.31[k]	2.24±0.20	2.01±0.23
T_{max} (h)	1	1	1	1
AUC_{0-8} (μg.h/ml)	6.81±0.9[k]	19.95±2.4[k]	11.64±1.7[s]	8.45±0.8[s]
$AUC_{0-\infty}$ (μg.h/ml)	11.09±1.5[k]	28.22±3.6[k]	18.97±2.5[s]	11.39±1.3[s]
MRT (h)	6.9±0.45[k]	6.0±0.32[k]	6.6±0.44[s]	5.7±0.31[s]
$t_{1/2}$ (h)	5.2[k]±0.40[k]	4.4[k]±0.30[k]	4.7±0.27[s]	4.1±0.19[s]
K_{el} (h^{-1})	0.13±0.010[k]	0.16±0.006[k]	0.15±0.008[s]	0.17±0.006[s]
% Absorbed in 1h	18.89±2.9[k]	55.16±8.2[k]	32.31±3.9	26.12±2.9

Significant difference[k] ($p<0.05$) between PM and IC of MBZ-βCD (1:2M) and Significant difference[s] ($p<0.05$) between MBZ-βCD (1:0.5M) IC and MBZ-PEG (1:4) SD are noticeable. PM = Physical mixture; SD = Solid dispersion; IC = Molecular inclusion complex.

The increase in absorption from MBZ-βCD system may probably be due to synergistic effect of β-CD with bile surfactants[7] on the solubilisation process. It has to be confirmed by including sodium taurocholate in the dissolution medium,

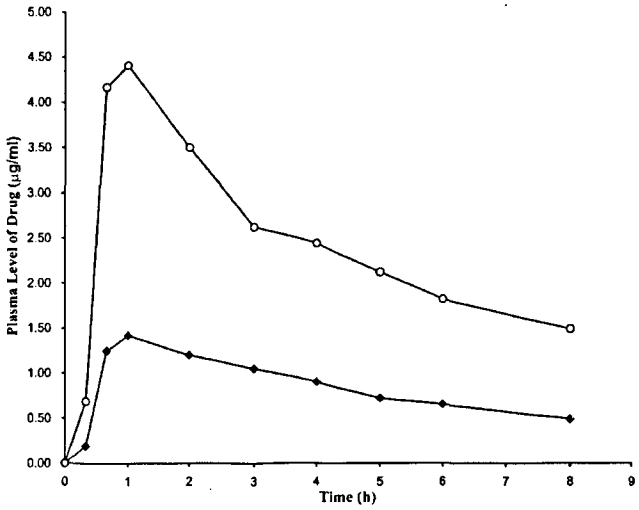

Fig. 5: Mean plasma level of mebendazole from βCD formulations.

Mean plasma level of MBZ after oral administration of 1:2MBZ-βCD molecular inclusion complex (-O-) and 1:2 MBZ-βCD physical mixture (-□-) to rabbits.

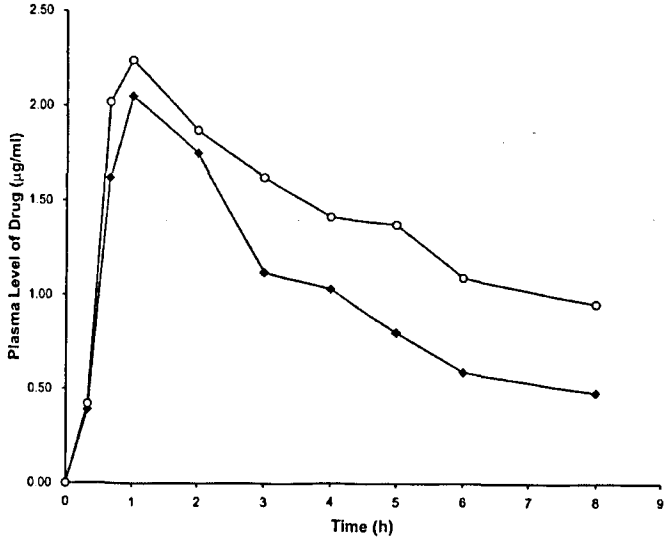

Fig. 6: Mean plasma level of mebendazole from βCD and PEG formulations.

Mean plasma levels of MBZ after oral administration of 1:0.5 MBZ-βCD complex (-O-) and 1:4 MBZ-PEG solid dispersion (-□-) to rabbits.

because β-CD is also reported to form complex with sodium taurocholate precipitating the drug[16].

A decrease in absorption of MBZ from MBZ-PEG system may be possible due to a decrease in its *in vivo* dissolution rate. The existence of a viscous diffusion layer around the dissolving solid core (drug) is supposed to cause a reduction in *in vivo* dissolution[17]. The viscous diffusion layer is believed to exist because of a higher quantity of PEG in GI fluid as compared to the *in vitro* dissolution system. The quantity of PEG used for animal study was 300 mg/average animal and was very high compared to 12 mg of PEG/900ml of water in the dissolution study. Thus *in vitro* dissolution did not experience this problem. *In vitro* and *in vivo* correlation could be established for the all tested products (fig. 7). A good correlation was found for the tested βCD products.

From Table 3, it is also understood that MRT (mean residence time of drug in plasma) value is almost same (6 h) for 1:2 MBZ-βCD complex and 1:4 MBZ-PEG solid dispersion, which were assumed to be better molecular inclusion and dispersion system respectively by DSC study. But, MRT and terminal half life values were slightly higher ($p<0.05$) for MBZ-βCD (1:2) physical mixture and 1:0.5 MBZ-βCD complex, indicating a little but to statistically significant extent of prolonged drug availability. These two products might assume a "flip–flop" phenomenon[18] with slower drug release because of presence of free (uncomplexed) drug. This phenomenon could be observed in the descending phase of drug plasma level time curve of 1:0.5 MBZ-βCD (fig. 6) and 1:2 MBZ-βCD physical mixture (fig. 5). Hence MRT and terminal half life values with these two products are significantly higher than

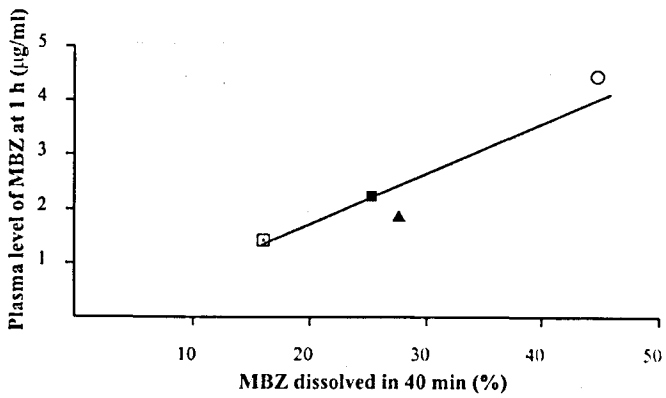

Fig. 7: *In vitro* and *in vivo* correlations for MBZ formulations.

***In vitro* and *in vivo* correlation of 1:2 MBZ-βCD physical mixture (⊡), 1:0.5 (□), 1:2 (O) MBZ-βCD molecular complex products and 1:4 MBZ-PEG solid dispersion (▲).**

these values with 1:4 MBZ-PEG solid dispersion and 1:2 M-βCD complex.

It was concluded that though 1:4 MBZ-PEG solid dispersion and 1:0.5 MBZ-βCD complex could produce comparable *in vitro* dissolution profiles, they were not bioequivalent. The 1:0.5 ratio of MBZ-βCD complex was found to be slightly superior to 1:4 ratio of MBZ-PEG solid dispersion with respect to the bioavailability of MBZ. The stability study indicated that MBZ-PEG solid dispersions of all mixing ratios were comparatively less stable. Hence, 1:0.5 MBZ-βCD complex has been decided as an industrially feasible means of bioavailability enhancement of MBZ with respect to stability and safety during storage and use. 1:2 MBZ-βCD complex exhibiting the highest bioavailability among all the preparations may be considered for a short term (3-6 mo) treatment of very severe (acute) alveolar and hepatic echinococcosis.

ACKNOWLEDGEMENTS

The authors wish to thank M/s Cadila Pharmaceuticals Ltd., Ahmedabad for their cooperation in promoting the industry-academia interaction.

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