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COMMUNICATION

Solubilization of Biphenyl Dimethyl Dicarboxylate by Cosolvency

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ABSTRACT

Biphenyl dimethyl dicarboxylate (BDD) is a synthetic analogue of schizandrin C, one of the components isolated from Fructus schizandrae, *and has been widely prescribed for improvement of liver functions and symptoms of patients with liver disease. However, its oral preparations have been known to have limited bioavailability due to its extremely low solubility in water, and its solubility problem also limits preparation of its parenteral dosage forms. In this research, we searched for solvent systems to solubilize BDD to overcome these problems. The ternary solvent systems of* N,N′- *dimethylacetamide (DMA)/alcohol/water and Cremophor EL/DMA/alcohol were studied intensively for this purpose. BDD was solubilized effectively in these cosolvents, and the results showed that the cosolvent systems were effective for solubilizing BDD up to the concentration that might be employed for preparation of parenteral dosage forms. Formulation of a BDD concentrate for intravenous infusion was proposed employing the cosolvent system of Cremophor EL/DMA/alcohol.*

INTRODUCTION

Biphenyl dimethyl dicarboxylate (BDD) is a synthetic analogue of schizandrin C, one of the active components isolated from *Fructus schizandrae*, a traditional oriental medicinal plant, chemically termed dimethyl-4,4′-dimethoxy-5, 6, 5′, 6′- dimethylene-dioxybiphenyl - 2, 2′-dicarboxylate (Fig. 1) (1,2). This compound was shown to protect against liver injury induced by carbon tetrachloride, thioacetamide, or D-galactosamine in animals (3,4). Currently, it is clinically prescribed in oriental countries for treatment of liver functions and symptoms

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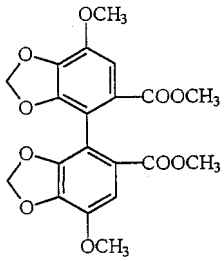

Figure 1. Structure of biphenyl dimethyl dicarboxylate.

of patients with liver diseases. This drug is nearly insoluble in water, and owing to this solubility problem, its oral preparations show limited bioavailability; there has been limitation to preparation of its parenteral dosage forms (5). There have been some research to improve bioavailability of BDD through enhancement of its dissolution rate and employing solid dispersions or pilules (5,6). However, attempts to improve the solubility of BDD in an aqueous system with cosolvents or surfactants have not been so successful (7).

In this research, we searched for aqueous cosolvent systems to enhance the solubility of BDD to overcome these problems. The ternary solvent systems of *N,N′*-dimethylacetamide (DMA)/alcohol/water and Cremophor EL/DMA/ethanol were studied intensively for this purpose. We employed these systems because DMA itself dissolves nonpolar compounds well and mixes with other polar and nonpolar solvents, and its toxicology and pharmacology are relatively well established (8). Cremophor EL (polyoxyethylated castor oil) was also included; it has been used frequently to dissolve several water-insoluble drugs (9,10).

EXPERIMENTAL

Materials

BDD was supplied from Daewoo Pharmaceutical Company (Korea). DMA, Cremophor EL, and other pharmaceuticals were obtained from Sigma Chemical Company (St. Louis, MO) or Wako Pure Chemicals (Japan). Other solvents were reagent grade and were used without further purification.

Measurements of Solubility

The solubilities of BDD were determined by placing an excess of BDD in a 10-ml screw-capped test tube with 5 ml solvent and agitating for 72 hr in a shaker bath maintained at 25°C. Preliminary studies showed that this period of time was sufficient to ensure saturation at 25°C. After equilibrium was attained, the solutions were filtered with a 0.45-μm Millipore filter. Then, the filtrates were diluted with methanol, and the absorbances at 275 nm were measured. All measurements were made three times, and the deviations were within ±5%.

RESULTS AND DISCUSSION

Solubilities of Biphenyl Dimethyl Dicarboxylate in Neat Solvents and Some Pharmaceutical Liquid Vehicles

The solubilities of BDD in neat solvents of various solubility parameters and some pharmaceutical liquid vehicles were measured; they are given in Table 1. According to the Scatchard-Hildebrand equation, the solubility of a solid nonelectrolyte in real solution is maximized in the solvent for which the solubility parame-

Table 1

Solubility of BDD in Pure Solvents at 25°C

Solvent	δ[a]	Solubility (mg/ml)
Ether	7.7	1.11
Ethyl acetate	8.9	11.54
Chloroform	9.3	>300
Acetone	9.8	35.92
Dioxane	10.0	32.58
n-Octanol	10.3	3.06
n-Butyl alcohol	11.3	0.64
n-Propyl alcohol	12.0	0.62
i-Propyl alcohol	11.5	0.53
Dimethylformamide	12.1	36.05
DMSO	13.0	56.21
Ethanol	13.0	0.81
Propylene glycol	14.8	0.58
Tetramethyl urea		40.20
N,N′-Dimethylacetamide (DMA)		90.06
Glycerol formal		16.47
Glycofurol (Tetraglycol)		17.16
1,2-*o*-Isopropylidene-rac-glycerol		10.11
Myrisitic acid isopropyl ester		0.57
Polyethylene glycol 200		7.07
300		9.52
400		13.26
600		10.63

[a] Values from Ref. 11.

ter δ is close to that of the solute (11). The results of the experiments showed that BDD was solubilized exceptionally well in chloroform (δ = 9.3) and moderately in solvents for which solubility parameters lie around 9. 3. Consequently, the solubility parameter of BDD is estimated to be about 9. 3. However, other solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide, for which the solubility parameters are quite different from that of chloroform, were also effective in solubilizing BDD. DMA and tetramethylurea, for which the solubility parameters are not reported yet, were also good solvents for BDD. This suggests that the solutions of BDD in these solvent systems are irregular, and an interaction between BDD and a carbonyl or sulfonyl group might be operating. This kind of interaction might enhance the solubility of BDD in these solvents.

Of the pharmaceutical liquid vehicles tested, DMA solubilized BDD up to the concentration of 90 mg/ml. These results suggest that DMA itself or its cosolvents might be employed as vehicles for preparation of parenteral or other liquid dosage forms of BDD.

Solubilization of Biphenyl Dimethyl Dicarboxylate in Cosolvent Systems of Dimethylacetamide/Ethanol/Water

Although DMA is intravenously injectable, it is desirable to reduce its content in the dosage forms as much as possible. For this purpose, ethanol and water were selected as cosolvents of DMA. The solubilities of BDD were measured in the binary cosolvents of DMA/water and DMA/ethanol (Tables 2 and 3, respectively) and in the ternary cosolvents of DMA/ethanol/water (Tables 4 and 5). The results are represented in the ternary phase diagram in Fig. 2. The border lines of estimated solubilities of BDD in the ternary solvents representing 30 mg/ml, 20 mg/ml, 10 mg/ml, and 1 mg/ml were drawn.

The results show that the solubility of BDD in the binary cosolvent of DMA/water was reduced drastically by the presence of water. The addition of ethanol to DMA also reduced the solubility of BDD. However, the effect of ethanol was less pronounced than that of water. These results confirm the extreme hydrophobicity of BDD. The solubility of BDD in the ternary cosolvent systems also decreased as the concentrations of ethanol and water increased. However, the results show that proper choice of the composition of the cosolvent could solubilize BDD up to more than 10 mg/ml, which might be employed for intravenous injection of the drug. However, the solutions of BDD in these cosolvents became turbid on dilution with water, and it is suspected that BDD will precipitate when the formulation is diluted in the bloodstream, possibly causing thrombophlebitis.

Table 2

Solubility of BDD in Binary Solvent System of DMA and Water at 25°C

DMA (ml)	Water (ml)	Solubility (mg/ml)
10.0	0.0	90.60
9.0	1.0	52.12
8.5	1.5	27.70
8.0	2.0	13.76
7.5	2.5	6.54
7.0	3.0	5.18
6.0	4.0	1.22
5.0	5.0	0.83
4.0	6.0	0.33
3.0	7.0	0.35
2.0	8.0	0.34
1.0	9.0	0.10
0.0	10.0	2.4×10^{-3}

Solubilization of Biphenyl Dimethyl Dicarboxylate in the Cosolvent Systems of Cremophor EL/Dimethylacetamide/Ethanol

The solubilities of BDD in the cosolvents Cremophor EL/DMA/ethanol were measured and are listed in

Table 3

Solubility of BDD in Binary Solvent System of DMA and Ethanol at 25°C

DMA (ml)	Ethanol (ml)	Solubility (mg/ml)
10.0	0.0	90.60
9.5	0.5	75.83
9.0	1.0	54.90
8.5	1.5	38.05
8.0	2.0	36.58
7.5	2.5	22.01
7.0	3.0	19.53
6.5	3.5	14.42
6.0	4.0	17.57
5.0	5.0	11.26
4.0	6.0	5.86
3.0	7.0	3.34
1.0	9.0	1.59
0.0	10.0	0.81

Table 4

Solubility of BDD in Ternary Cosolvent System of DMA, Ethanol, and Water at 25°C

DMA (ml)	Ethanol (ml)	Water (ml)	Solubility (mg/ml)
8.5	1.0	0.5	37.28
8.0	1.5	0.5	36.24
8.0	1.0	1.0	30.21
7.5	2.0	0.5	23.75
7.5	1.5	1.0	22.51
7.0	1.5	1.5	14.64
7.0	2.0	1.0	19.27
7.0	1.0	2.0	11.76
7.0	2.5	0.5	20.66
7.0	3.0	2.0	7.83
7.0	3.0	1.0	10.83
7.0	2.0	2.0	6.21
6.5	3.0	0.5	17.12
6.5	2.5	1.0	17.05
6.5	2.0	1.5	12.91
6.5	1.5	2.0	11.08
6.0	3.0	1.0	12.85
6.0	2.5	1.5	11.91
6.0	2.0	2.0	10.54
6.0	1.5	2.5	4.20
6.0	1.0	3.0	3.81
6.0	4.0	1.0	7.40
6.0	4.0	2.0	5.36
5.5	3.5	1.0	9.06
5.5	3.0	1.5	7.58
5.0	3.0	2.0	4.42
5.0	4.0	1.0	9.02
5.0	4.5	0.5	11.78
5.0	3.0	2.0	4.43
5.0	1.0	4.0	0.93

Table 6. BDD was also effectively solubilized in these cosolvents. Water was excluded in this cosolvent system because the presence of even a small amount of water reduced the solubility of BDD down to a concentration not practical for preparation of any dosage forms of BDD. The solubility of BDD in Cremophor EL increased markedly on addition of DMA. However, this trend was hampered by the presence of ethanol in this cosolvent system. It is worthwhile to note that, on dilution of the solutions of BDD in these cosolvents with water, the appearance of turbidity was far less immediate compared with the solution of BDD in the cosolvents of DMA/ethanol/water.

Table 5

Solubility of BDD in Ternary Cosolvent System of DMA, Ethanol, and Water

DMA (ml)	Ethanol (ml)	Water (ml)	Solubility (mg/ml)
4.0	5.0	1.0	5.54
4.0	4.0	2.0	2.56
4.0	3.0	3.0	1.81
4.0	2.0	4.0	0.85
4.0	1.0	5.0	0.38
3.3	3.3	3.3	1.82
3.0	5.0	2.0	2.10
3.0	4.0	3.0	1.53
3.0	3.0	4.0	0.86
3.0	2.0	5.0	0.48
2.0	6.0	2.0	1.64
2.0	5.0	3.0	1.19
2.0	4.0	4.0	0.80
2.0	3.0	5.0	0.36
2.0	2.0	6.0	0.31
1.0	8.0	1.0	1.28
1.0	7.0	2.0	0.91
1.0	6.0	3.0	0.85
1.0	5.0	4.0	0.60

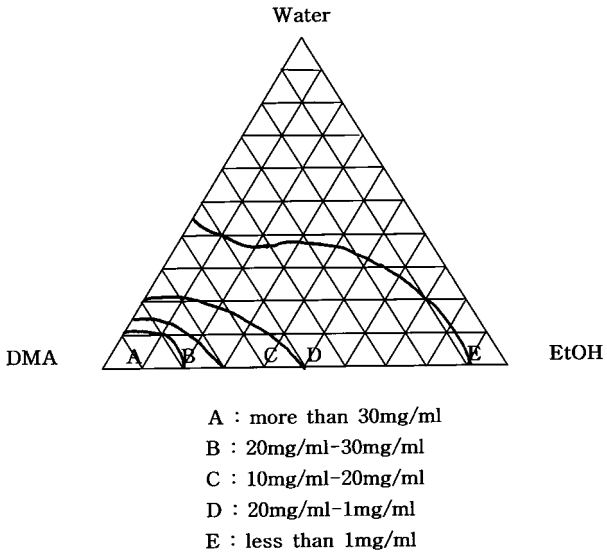

Figure 2. Estimated solubility profiles in ternary solvent system of DMA, ethanol, and water at 25°C.

Table 6

Solubility of BDD in Cosolvent System of Cremophor EL, DMA, amd Ethanol at 25°C

Cremophor EL (ml)	DMA (ml)	Ethanol (ml)	Solubility (mg/ml)
10	0	0	13.26
9	1	0	14.60
8	2	0	18.21
7	3	0	26.40
5	5	0	45.50
9	0	1	11.37
8	0	2	10.58
7	0	3	10.49
6	0	4	10.16
5	0	5	8.40
5	4	1	19.79
5	3	2	15.60
5	2	3	14.86
4.5	3.0	2.5	14.37
4.5	1	4.5	6.20
4	4	2	20.33
4	3	3	12.16
3.3	3.3	3.3	14.80
3	4	3	15.13
3	3	4	9.95

Formulation of a Concentrate of Biphenyl Dimethyl Dicarboxylate for Intravenous Infusion

BDD (100 mg) was solubilized in 10 ml of the cosolvent of Cremophor EL/DMA/ethanol (5:2:3 ml). This solution was kept at 5°C for 1 week, and BDD was not crystallized under this condition. On addition of 1.5 ml of this concentrate to 500 ml of 5% dextrose injection, it remained clear to the naked eye within 5 hr at 25°C. On standing longer, it became slightly turbid very slowly. This reveals that the diluted solution of BDD in dextrose injection is in a metastable state. A single oral dose of BDD is usually 25 mg, and 15 mg of BDD are considered to be applicable in parenteral dosage forms. These results suggest that this solution could be employed as a concentrate for BDD for intravenous infusion.

CONCLUSIONS

The solubilities of BDD in solvents of various solubility parameters at 25°C were measured, and the results show that the solubility parameter of BDD is estimated to be about 9. 3. Of the solvents tested, DMA was exceptionally effective in solubilizing BDD. The cosolvent systems of DMA/ethanol/water and Cremophor EL/DMA/ethanol were also moderately effective in solubilizing BDD. This suggests that these systems could be employed for preparations of parenteral or other liquid dosage forms of BDD. A formulation of the cosolvent system of Cremophor EL/DMA/ethanol for preparation of a concentrate of BDD for intravenous infusion was proposed.

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