Bull. Pharm. Sci., Assiut University
Vol. 6, part 2, PP. 310-320

SOLUBILIZATION OF CARBAMAZEPINE USING COSOLVENTS

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Solubilization of Carbamazepine was achieved through cosolvency using binary or ternary solvent systems at 25°. It was found that the aqueous solubility of the medicament was increased. However, the extent of the solubility promoting effect was dependent on the type and the concnetration of the cosolvent used.

In the practicalof pharmaceutical formulation, the challenge of improving the solubility of many poorly soluble drugs in solution dosage forms is common. To solve such problem, it is desirable to incorporate one or more cosolvents with water to overcome the poor aqueous solubility of the drug.

It is now well known that a mixture of the indifferently effective solvents may have solvent properties far exceeding those of individual components. The solubility of chloramphenicol palmitate in propylene glycol-water has been determined[1]. The aqueous solubility of steroids was exponentially increased following the addition of a co-solvent like, propylene glycol, polyethylene glycol 400, N,N-dimethylacetamide and 95% ethanol[2]. It was found that methyl

alcohol increases the solubility and affects in-vitro binding characteristics of phenytoin[3]. Urethane and ethanol were found to increase the solubility of Khellin when used for the preparation of injections[4]. Polyethylene glycols 400 and 600 are excellent solvents for many steroids and are used in-vitro since they have very low toxicities[5]. solubilization of chlorothiazide and hydrochlorothiazide was achieved through cosolvency using binary and ternary solvent systems may prevent the occurrence of undesirable toxicity which may result from the use of high volume fraction of a single co-solvent.[6] The aim of this work is to investigate the effect of different mixed solvents, either in binary or ternary solvent system, on the solubility of the practically insoluble antiepileptic drug Carbamazepine.

EXPERIMENTAL

Materials:

Carbamazepine (Ciba-Geigy limited, Basle, Switzerland).

Solvents used were ethyl alcohol, glycerol, propylene glycol, polyethylene glycol 600, methyl alcohol, dioxan, formamide, dimethylformamide, dimethylacetamide and dimethylsulfoxide, all are of analytical or pharmaceutical grade.

Procedure:

Measurement of solubility of Carbamazepine in mixed solvent systems:

The different solvent systems were prepared in weight percent as follows:

A- Binary solvent systems:

Prepared by mixing one of the solvents, mentioned before with water in a concentration or 2.5, 5, 7.5 and 10% w/v respectively.

B- Ternary solvent systems:

These systems were prepared through modification of the original binary systems containing 90% of water and 10% of organic solvents, namely, 1,2-propylene glycol, formamide , dimethylformamide, dimethylacetamide and dimethyl sulfoxide. The modification involved substitution of increasing proportions of the organic cosolvents in the system by equal quantities (by weight) of ethyl alcohol .

Excess of Carbamazepine was equilibrated with 10 ml of each of the different concentrations mentioned before in a 15 ml screw capped tubes. The tubes were shaken in a constant temperature water bath at 25° ($\pm$ 0.1°). After equilibration for 10 days, they were centrifuged, then reequilibrated for further 24 hours. Samples were withdrawn and after appropriate dilutions with distilled water, they were analysed spectrophotometrically at 285 nm for their Carbamazepine contents. The presence of these cosolvents did not interfere with the spectrophotometric assay of the drug.

RESULTS AND DISCUSSION

a) Effect of binary solvent system on the solubility of Carbamazepine:

From Fig. 1,2 and Table 1, it is clearly obvious that there is an increase in aqueous solubility of Carbamazepine on the addition of cosolvents.

The solubility of this drug was affected by the type and volume fraction of the cosolvent used. Dimethylacetamide shows the highest effect and glycerol shows the lowest effect on

the solubility of the drug.

A comparison of the solubilizing capacity of the tested cosolvents towards the medicament is shown in Table 2.

Ethyl alcohol, an aliphatic alcohol, exhibited better solubilizing power than methyl alcohol as it has a longer hydrocarbon chain. Also, polyhydric alcohols which have a longer hydrocarbon chain length show higher solubilizing powers, so PEG 600 shows the highest solubilizing power followed by propylene glycol then glycerol.

b) Solubility studies of Carbamazepine in ternary solvent systems:

From Tables 3,4,5,6, and 7, it can be concluded that ternary solvent systems can be considered better solubilizer in certain cases, and might suppress the solubility in other cases, according to the specific solvent substituted.

Table 1: Effect of Various Binary Solvent Systems on the Solubility of Carbamazepine at 25°

Concentration % w/v	*Amount of Carbamazepine % w/v solubilized using the following binary systems*									
	Propylene glycol/ water	*Glycerol/ water*	*Dioxan/ water*	*PEG 600/ water*	*Ethyl alcohol/ water*	*Methyl alcohol/ water*	*Formamide/ water*	*Dimethyl-formamide/ watetr*	*Dimethyl-acetamide/ water*	*Dimethyl-sulfoxide/ water*
2.5	0.020	0.019	0.024	0.025	0.024	0.021	0.018	0.025	0.035	0.026
5	0.022	0.020	0.024	0.035	0.029	0.024	0.024	0.040	0.052	0.032
7.5	0.025	0.022	0.037	0.045	0.035	0.035	0.030	0.058	0.069	0.036
10	0.027	0.023	0.057	0.054	0.044	0.032	0.037	0.081	0.089	0.047

Table 2: Solubility Augumenting Capacities of Different Binary Solvent Systems Towards Carbamazepine.

Concentration % w/v	*Solubility augumenting capacity* $\frac{S-So}{So}$ *of:*									
	Propylene glycol/ water	*Glycerol/ water*	*Dioxan/ water*	*PEG 600/ water*	*Ethyl alcohol/ water*	*Methyl alcohol/ water*	*Formamide/ water*	*Dimethyl-formamide/ watetr*	*Dimethyl-acetamide/ water*	*Dimethyl-sulfoxide water*
2.5	0.156	0.075	0.387	0.445	0.364	0.214	0.075	0.445	1.000	0.502
5	0.272	0.156	0.387	1.023	0.659	0.387	0.105	1.312	2.000	0.850
7.5	0.422	0.248	1.138	1.584	1.006	1.023	0.134	2.375	2.988	1.080
10	0.578	0.306	2.312	2.104	1.543	0.850	1.156	3.658	4.144	1.699

S : Solubility g% in mixed solvents system.
So: Solubility g% in pure water.

Table 3: Solubility of Carbamazepine in Ethyl Alcohol-1,2-propylene glycol-water System.

System Composition (% by weight)			*Solubility (g%) of Carbamazepine*
Ethyl alcohol	*1,2-Propylene glycol*	*Water*	
0	10	90	0.0270
2	8	90	0.0273
4	6	90	0.0266
6	4	90	0.0273
8	2	90	0.0360

Table 4: Solubility of Carbamazepine in Ethyl alcohol formamide-water System.

System Composition (% by weight)			*Solubility (g%) of Carbamazepine*
Ethyl alcohol	*Formamide*	*water*	
0	10	90	0.0373
2	8	90	0.0370
4	6	90	0.0363
6	4	90	0.0413
8	2	90	0.0380

Table 5: Solubility of Carbamazepine in Ethyl alcohol-dimethylformamide-water System.

System Composition (% by weight)			*Solubility (g%) of Carbamazepine*
Ethyl alcohol	*Dimethyleformamide*	*Water*	
0	10	90	0.081
2	8	90	0.069
4	6	90	0.067
6	4	90	0.053
8	2	90	0.047

Table 6: Solubility of Carbamazepine in Ethyl alcohol dimethyl acetamide-water System.

System composition (% by weight)			Solubility (g%)
Ethyl alcohol	*Dimethyl-acetamide*	*Water*	*of Carbamazepine*
0	10	90	0.089
2	8	90	0.072
4	6	90	0.059
6	4	90	0.046
8	2	90	0.047

Table 7: Solubility of Carbamazepine in Ethyl Alcohol-dimethyl sulfoxide-water System.

System Composition (% by weight)			Solubility (g%)
Ethyl alcohol	*Dimethyl-sulfoxide*	*Water*	*of Carbamazepine*
0	10	90	0.047
2	8	90	0.042
4	6	90	0.044
6	4	90	0.040
8	2	90	0.056

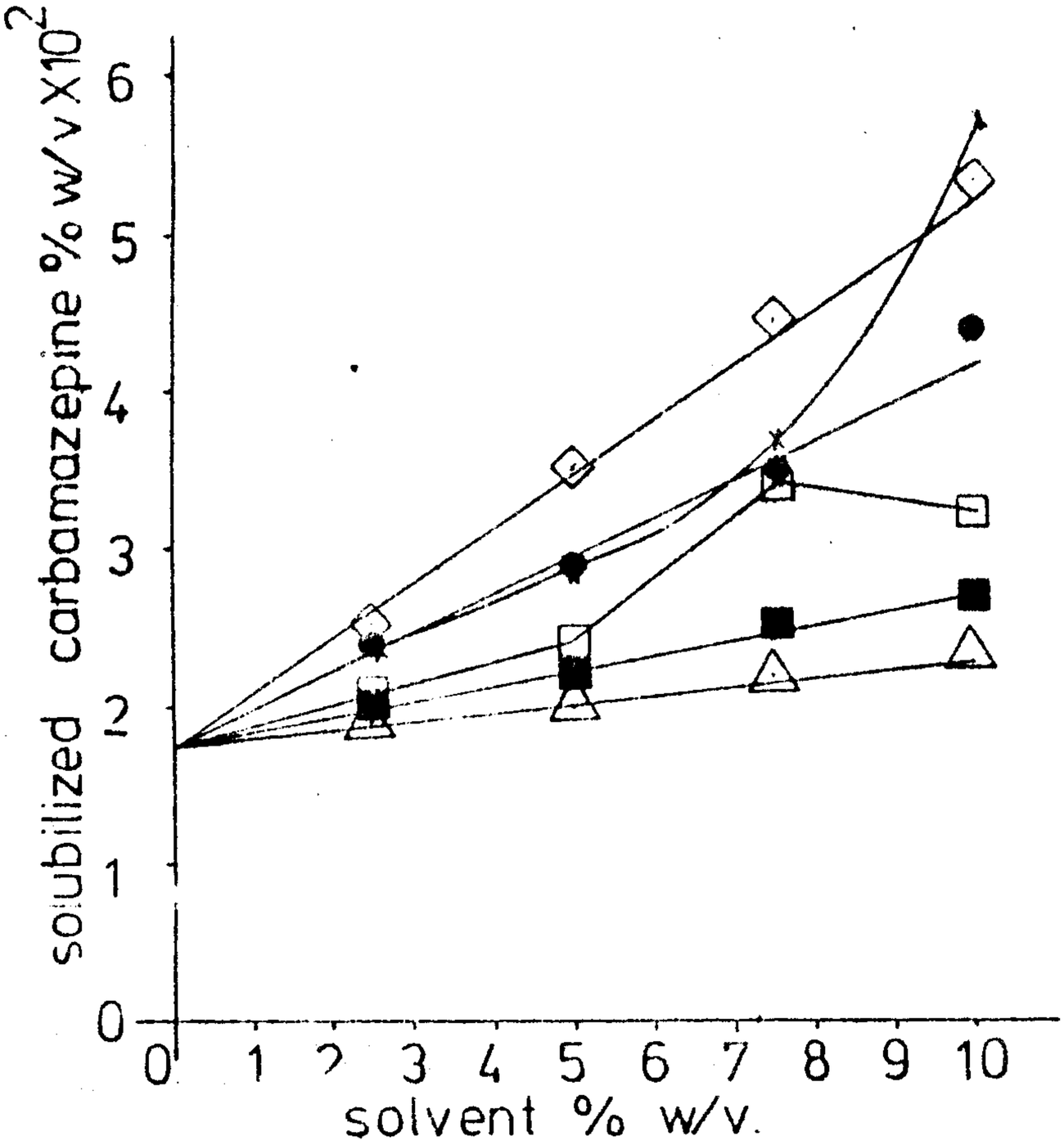

fig.(1): Solubility of carbamazepine in binary solvent systems.

key: ■ Propylene glycol,
△ Glycerol, x Dioxan,
◇ P.E.G. 600,
● Ethyl alcohol, □ Methyl alcohol.

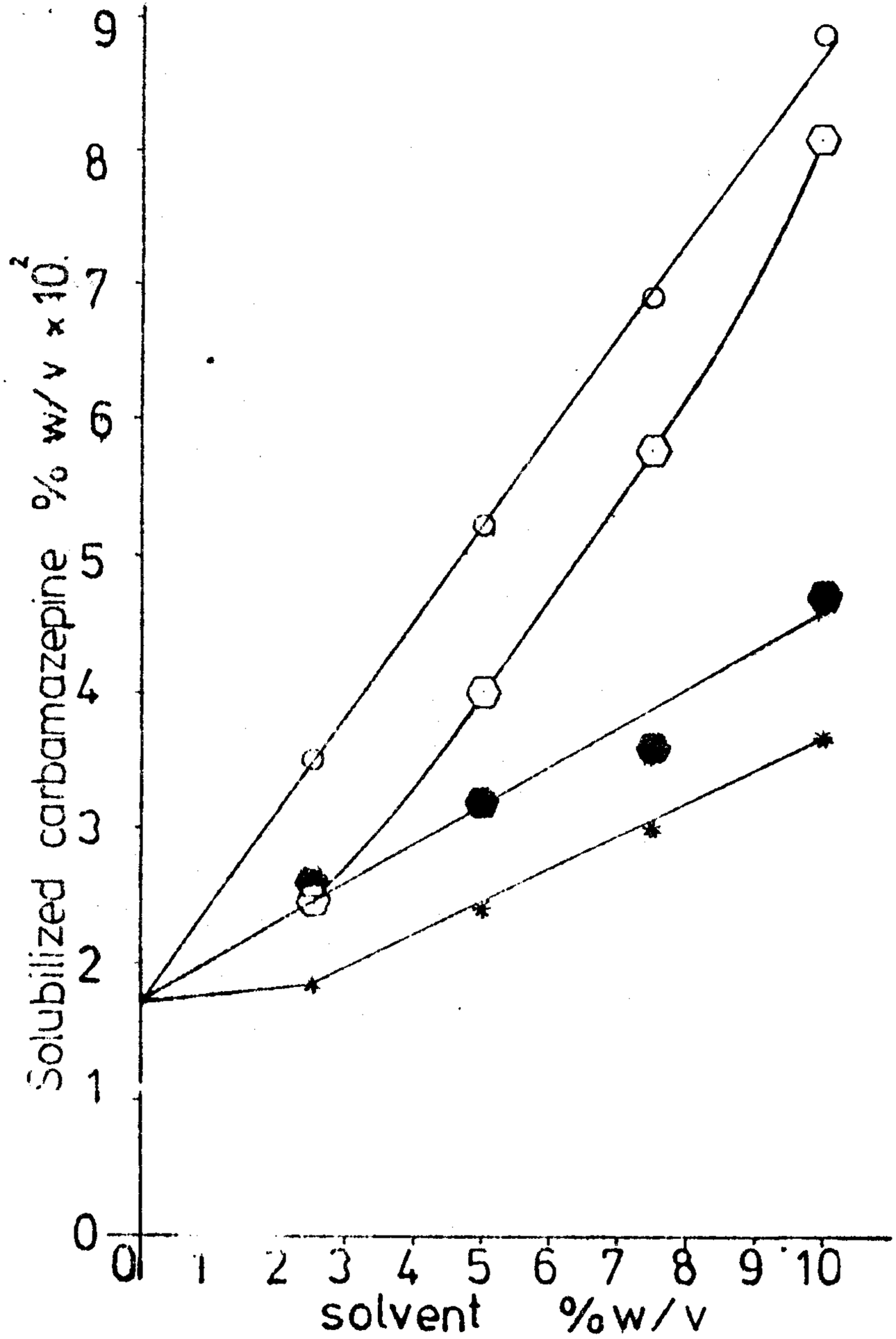

fig.(2): Solubility of carbamazepine in binary solvent systems.

Key: ✱ Formamide ○ Dimethylformamide
⊙ Dimethylacetamide, ● Dimethyl sulfoxide.

REFERENCES

1) *J.A. Rogers and J.G. Nairn, Canad. J. Pharm. Sci., 8, 75 (1973).*

2) *Y.W. Chien and H.J. Lambert , Chem. Pharm. Bull., 23, 1085 (1975).*

3) *C.T. Rhodes and P.A. Schwatz, J. Pharm. Sci., 66, 994 (1977).*

4) *R. Jachawicz, L. Krowczynski and Z. Kubiak, Farm. Pol., 33, 413 (1977). Through, International Pharm. Abstr., 15, 150401 (1978).*

5) *C.W. Peter Ronald and H. Ulrich, J. Pharm. Sci., 69, 747 (1980).*

6) *T.H. El-Faham, Master thesis, Assiut Univ., (1979).*

" تذويب الكاربامازبين باستخدام المذيبات المساعدة

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تم اذابة الكاربامازبين عن طريق خاصية التعاون الاذابى باستخدام انظمة مذيبات ثنائية او ثلاثية التكوين عند ٢٥° م . وقد وجد ان وجود هذه المذيبات المساعدة تؤدى الى زيادة ذوبان الكاربامازبين فى الماء . كما وجد ان درجة ذوبان المادة الدوائية تعتمد على نوع المذيب المساعد المستخدم وتركيزه .

recieved in 20/10/1982 & accepted in 4/11/1982