

---

## Solubilization of Carbamazepine for Solution Dosage Forms

---

SARASIJA SURESH\* AND S.S. DHIR  
Department of Pharmaceutics,  
Al Ameen College of Pharmacy  
Bangalore, 560 027, Karnataka

Various techniques of solubilization such as surfactant solubilization, solid dispersion, cosolvent method and liquid molecular dispersions were studied to solubilize carbamazepine. Carbamazepine was successfully solubilized by cosolvent method to get a concentration of 20 mg/ml. It can also be solubilized by solid liquid dispersion method to obtain a concentration of 40 mg/ml.

**A**QUEOUS solubility has been recognized for long as a key factor in controlling the drug efficacy. Side effects of many drugs have been attributed to poor solubility. Before an orally administered drug becomes available at the receptor site, it must first dissolve in gastrointestinal fluid. Carbamazepine is a potent anticonvulsant drug<sup>1</sup> used in the treatment of patients with partial seizures with complex symptomatology psychomotor seizures and generalised tonic-clonic seizures (grand mal). It is considered as a drug of choice for children<sup>2</sup>. It does not induce drowsiness as does phenobarbital nor coarsening of facial features, hirsutism and gingival hypertrophy as in the case with phenytoin<sup>3</sup>. Carbamazepine is considered the drug of choice for trigeminal neuralgia<sup>4</sup>. It has a psychotropic effect<sup>5</sup> in that it increases alertness and elevates mood in many depressed patients with epileptic problems.

This investigation was initiated to evaluate different methods of solubilization of carbamazepine to prepare solution dosage forms for faster bioavailability and therapeutic action. Various techniques of solubilization that were employed are: surfactant solubilization, solid-dispersion, employing a co-solvent and liquid molecular dispersion.

### MATERIALS AND METHODS

Carbamazepine was obtained from Microlabs Pvt. Ltd, Bangalore, PEG-4000, PEG 6000, mannitol, citric acid, urea, PVP 44,000, ethanol, Tween 20, Tween 40 and Tween 60 all were of AR grade and were obtained from S.D. Fine Chemicals and Loba Chemie.

#### Surfactant Solubilization

Tween 20, Tween 60 and Tween 80 in 10%, 15% and 20% v/v aqueous solutions were prepared. Fifty mg of carbamazepine was added and shaken in a thermostatic shaker (Remi Shaker Water Bath) set at 30 cycles/min and agitated for 24 h at 37±1° after which the solutions were filtered and concentration determined by diluting with ethanol and measuring the optical density in a Carl Zeiss Spectrophotometer at 285 nm,  $E_{1\%}^{1\text{cm}}$  value 290<sup>6</sup>.

#### Solid Dispersion

Carrier such as PEG 4000, PEG 6000, mannitol, citric acid, urea, PVP 44,000 were used to prepare solid dispersions. Solid dispersions were prepared by fusion method using PEG 4000, PEG 6000, mannitol and citric acid. Solvent method was used for preparations of solid dispersions with urea and PVP 44,000.

---

\*For correspondence

## Fusion or Melting Point Method

Drug to carrier ratio of 1:5 was mixed thoroughly, melted on a sand bath with continuous stirring until the mixture melted. The temperature was maintained at a constant value. The molten mixture was poured on a porcelain tile previously cooled in an icebath for solidification, dried in a dessicator over anhydrous calcium chloride, pulverized and passed through the sieve no. 80.

## Solvent Method

Drug to carrier ratio of 1:5 was dissolved in a suitable solvent, evaporated on a boiling water bath at 60° with continuous stirring till all the solvent evaporated, which was confirmed by IR analysis, poured on a porcelain tile previously cooled in an ice-bath. The solidified mass formed was dried in a dessicator over fused calcium chloride, pulverized and passed through the sieve no. 80.

## Characterization of Solid Dispersion

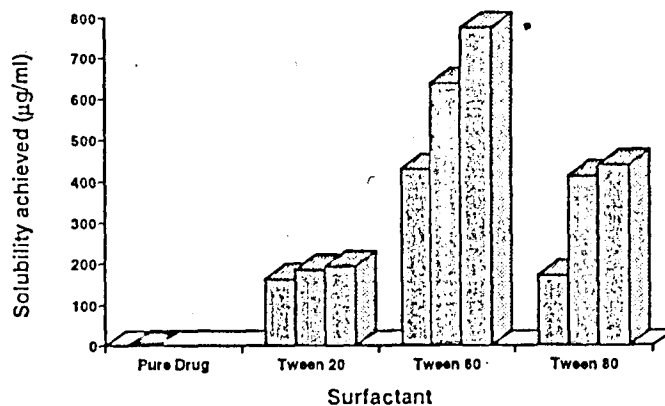
Solid dispersions were further investigated to establish the identity of the drug in the system by TLC and IR analysis. These studies help to out the possibility of either drug degradation or interaction with components of the system. Solubility studies of carbamazepine and its dispersion were conducted in a thermostatic shaker water bath by shaking a saturated solution for 24 h at 37 +/- 1° at 30 rpm.

## 5. Solid liquid Molecular Method

Carbamazepine was dispersed at its molecular level at 60° in water-soluble liquid carries such as PEG 200, PEG 400 and propylene glycol till a clear solution was obtained. The solid dispersion so achieved was evaluated by carrying out TLC and IR analysis and the effect of the process on the drug was also determined as in the case of solvent method of preparation of solid dispersions.

## RESULTS AND DISCUSSION

Polysorbates have been very effective in solubilizing drugs, optimum being above the critical micelle concentration. They are found to be inert<sup>8-10</sup> and were chosen in the range of 10-20% solubilization (Fig. 1). Tween 60 was found to be the best surfactant and solubility was about 40



Solubility of carbamazepine was determined in the absence (□) and in the presence of surfactants, Tween 20, Tween 60 and Tween 80 at 10% (▨), 15% (□) and 20% (▤) concentrations. The concentrations of carbamazepine was determined using a method reported in the I.P.<sup>6</sup>

Fig.1 : Effect of different concentrations of polysorbates on the solubility of carbamazepine

times increased with 20% aqueous solution. A maximum solubility of 750 µg/ml was obtained. However, since a solution containing 20 mg/ml is required, therefore, this method was found to be ineffective for solubilizing carbamazepine.

Solid dispersions of carbamazepine could be prepared with carriers such as PEG 4000, PEG 6000, mannitol, citric acid, urea and PVP 44,000. Polyethylene glycols which are highly crystalline, are capable of entrapping low molecular weight compounds in their interstitial space. Carbamazepine showed good miscibility with all the carriers used in the preparation of solid dispersions.

Rapid solidification of melts were observed when porcelain tile previously cooled in ice-bath was used, solidification of solid-dispersions occurred instantaneously in case of PVP, mannitol and urea whereas in case of PEG-4000, PEG 6000, citric acid the solid dispersion required longer storage in a dessicator over fused calcium chloride.

The melting point of urea is 132.7° and at this temperature it decomposes. Fusion method could not be employed for preparing the solid dispersions of carbamazepine with urea since the fusion temperature is 134°. Hence solvent method was adopted using ethanol as the solvent.

**Table 1 - Data on the solid dispersion of carbamazepine**

S. No.	Carrier <sup>1</sup>	Method <sup>2</sup>	Hardening <sup>3</sup> (days)	m.p.	Conc <sup>4</sup> mg/ml
Drug	-	-	-	192	0.46
CI	Peg 4000	Melting	2	67	1.25
CII	Peg 6000	Melting	2	60	1.40
CIII	Mannitol	Melting	1	149	0.63
CIV	Citric acid	Melting	2	130	2.15
CV	Urea	(Solvent Alcohol)	1	134	1.03
CVI	PVP 44,000	Chloroform	1	100	3.40

1. Drug and carrier used in the ratio of 1:5 for preparation of solid dispersions.
2. Method of preparation of solid dispersions.
3. Days required at room temperature.
4. Solubility data at 37°.

**Table 2 - Solubility of Carbamazepine in water in the presence of solvents**

Propylene glycol (%)	Alcohol (%)	Carbamazepin (mg/ml)
-	-	0.46
20	-	1.43
40	-	1.86
60	-	3.21
80	-	3.93
50	10	10.58
60	10	13.46
70	10	22.95
80	10	27.55
90	10	31.63
50	20	15.43
60	20	22.70
70	20	30.10
80	20	36.22

It was observed that all the solid-dispersions prepared by either fusion method or solvent method exhibited lowering of the melting point of the drug. Lowering of melting point as a function of weight fraction for binary systems is not unexpected which appears to be a unique phenomenon.

The active drug was kept as a minor component in the dispersion systems in terms of percent weight so as to obtain a finer dispersion and to achieve faster release of the drug. TLC study ruled out the possible degradation of the drug in solid-dispersion. Comparison of the spectra of pure drug and solid dispersions showed that there has been no change in the structural assignments of pure carbamazepine and carbamazepine in solid dispersions.

In case of solid dispersions of carbamazepine with mannitol and with citric acid, a broad peak was observed in the range of 3000 to 3500 cm<sup>-1</sup>. This is possibly due to the merging of the N-H absorption band with the O-H stretching. The absence of a strong carboxylate anion stretching absorption in the range of 1650 to 1550 cm<sup>-1</sup> shows the absence of salt formation in citric acid solid dispersion.

The results of the solubility studies show variation in the solubilities of solid dispersions of carbamazepine. Pure carbamazepine exhibited least solubility compared to its

**Table 3: Solid-liquid molecular dispersions of carbamazepine in water-miscible liquid carriers**

Carrier	Carrier : drug	Physical Appearances	H <sub>2</sub> O* (ml)
PEG 200	1:15	Clear Solution	1.1
	1:30	Clear Solution	2.6
PEG 400	1:15	Clear Solution	1.2
	1:30	Clear Solution	2.6
Propylene glycol	1:7.5	Clear Solution	4.5
	1:15	Clear Solution	9.0
Glycerol	1:15	Turbid Solution	-
	1:30	Turbid Solution	-

\* Extent of dilution without causing precipitation

solid dispersions. Solid dispersions prepared by using mannitol showed very slight increase in solubility compared to pure drug followed by solid dispersions of urea. PEG 4000, PEG 6000, citric acid, PVP 44,000 when used as carriers improved the solubility of carbamazepine (Table 1).

The solubility of carbamazepine was optimum with PVP 44,000 carrier. The solubility was 3.4 mg/ml as compared to 0.46 mg/ml of the pure drug. But to prepare a solution dosage form, a concentration of 20 mg/ml is required. Thus other techniques of solubilization were investigated.

#### Co-solvency method of solubilization

Percent propylene glycol versus concentration of carbamazepine in the presence of 0 and 20% alcohol was studied. Results are shown in Table 2. It is observed that carbamazepine is soluble in a solvent combination of propylene glycol:alcohol:water (60:20:20) up to a concentration of 22.7 mg/ml. Concentration of propylene glycol was maintained at 60% while that of alcohol was decreased to 18% to obtain 20 mg/ml concentration of carbamazepine.

Alcohol was added because it was found not only to increase the solubility but also provided stability to the solution of carbamazepine. Fifteen to 20% of alcohol

provided maximum stability of preventing recrystallization of carbamazepine from its solution in solvent mixture consisting of propylene glycol, alcohol and water.

Solubility studies of carbamazepine in a solution of 60% PEG 400, 18% alcohol and 22% water were carried out. At high temperature (60°) drug solution in PEG 200, decomposed while drug solution in 60% PEG 400, 18% alcohol and 22% water was found to crystallize at 10°. Hence both solutions were not evaluated further and were discarded.

#### Solid-liquid Molecular method of solubilization

Carbamazepine can be dispersed at its molecular level in polyethylene glycol 200, polyethylene glycol 400 and propylene glycol. These dispersions can be further diluted with distilled water. Carbamazepine dispersed in propylene glycol has advantage over the preparation of polyethylene glycol because lesser quantity of carrier to drug is required. Moreover, it can be diluted with distilled water to a greater extent so as to get a clear solution. Thus 2 g of carbamazepine could be solubilized in 50 ml of propylene glycol. This could be further diluted to 100 ml with distilled water. The temperature was maintained steady at 60° to prevent decomposition of the drug if any.

IR and TLC analysis were carried out to check for the

intactness of carbamazepine in the solid-liquid dispersion. No change in Rf value was seen during TLC study. During IR analysis molecular dispersion in propylene glycol exhibited no change. Thus indicating that no chemical change had taken place in the drug. Hence, carbamazepine could be dispersed in propylene glycol to obtain a concentration of 20 mg/ml (Table 3).

Carbamazepine was successfully solubilized by co-solvent method of solubilization. The co-solvent used was a mixture of propylene glycol:alcohol:water in the ratio of 60:18:22, and 20 mg/ml of carbamazepine could be solubilized by this method. Carbamazepine could also be solubilized by solid-liquid molecular dispersion method in propylene glycol. Two grams was dispersed in 50 ml of propylene glycol and diluted upto 100 ml.

## REFERENCES

1. Davies, E., *Med. J. Aust* 1964, 1, 150.
2. Huf, R., and Schain, R.J., *J. Pediatr.*, 1980, 97, 210.
3. **AMA Drug Evaluation**, II Edn., PSG Publishing Company, Inc., Littleton, Massachusetts, 469.
4. Blom, S., *Arch. Neuro.*, 1963, 19, 285.
5. Meinarde, H., In: Woodbury, D.M. and Dixon, M. Eds. **Antipileptic drugs**, Raven Press, New York, 1972, 487.
6. **The Indian Pharmacopoeia** by Pharmacopoeia of India, The Controller of Publication, Delhi, 1975, 1, 92.
7. Shefter, E. In Yalkowsky, S.H. Eds., **Techniques of solubilization of drugs.**, Oekker, Philadelphia, 1981, 190.
8. Jones, C.M. *Ann. Int. Med.*, 1948, 29.
9. Chow, B.F. *J. Nutrition.*, 1953, 49, 49.
10. Krehl, W.A., Cowgill, G.R. and Whedon, A.D., *J. Nutrition*, 1955, 55, 35
11. Saboc, J.C. *Drug Dev. Comm.*, 1976, 2, 359.