Bull. Pharm. Sci., Assiut University
Vol. 6, Part 2, PP. 373-386

SOLUBILIZATION OF CARBAMAZEPINE USING HYDROTROPIC AGENTS

A.E. Aboutaleb & S.M. Ahmed
Department of Industrial Pharmacy, Faculty of Pharmacy,
Assiut University, Assiut, Egypt.

The effect of number of hydrotropic agents belonging to diverse chemical groups, e.g. sugars, sugar alcohols, amides, imides, acids and salts, on the water-solubility of the practically insoluble antiepileptic drug Carbamazepine at 25° was studied. Also, comparison of the solubilizing efficiency of the different hydrotropic agents was performed. It is clearly evident that the solubilizing efficiency of these hydrotropic agents depends upon both type and concentration of the tested additives used in this study.

One of the effective and widely used method for increasing drug solubility of insoluble drugs is to use hydrotropes The term hydrotropy has been used to designate the increase in aqueous solubility of organic substances normally insoluble or slightly soluble in water by the addition of large amounts of additives[1]. Some workers have postulated that hydrotropy is simply another type of solubilization, where the solute is dissolved in oriented clusters of the hydrotropic agent[2]. The salting in mechenism have been suggested for this phenomenon by McKee[3]. Others felt that this phenomenon is more closely related to complexation with a weak interaction existing between the hydrotropic agent and the solute[2]. Ueda[4] decided that both factors, i.e., complex formation and salting in, play a part in the hydrotropic properties.

The hydrotropic action may extend to be more beneficial, and influences the activity, absorption and stability of drugs. A large number of hyrotropic agents were subject of many investigations dealing with the enhancement of water-solubility of sparingly soluble drugs, yet no attention has been awarded to investigate their effect on the solubility of Carbamazepine. In this work, the effect of some hydrotropic agents on the solubility of Carbamazepine was investigated.

EXPERIMENTAL

Materials:

- Carbamazepine[a]
- Hydrotropic agents used:
  - Sorbitol, mannitol, glucose, sucrose, lactose, urea, thiourea, nicotinamide, saccharin-sodium, succinimide-sodium, citric acid, tartaric acid, potassium chloride, potassium citrate, sodium benzoate and sodium tartrate[b].

  All the above mentioned materials are either of pharmaceutical or analytical grade.

Apparatus:

Spectrophotometer (Pye-Unicam SP400-England).

Procedure:

Determination of the solubility of Carbamazepine:

Excess of Carbamazepine was equilibrated with 8 ml of the solutions of different concentrations of the

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a- Ciba-Geigy Limited, Basle, Switzerland.

b- British drug houses, Poole, England.

hydrotropic agents in a 15 ml screw capped tubes. The tubes were shaken in a constant temperature water bath at 25° (± 0.1°). After equilibration for 10 days, they were centrifuged and reequilibrated for further 24 hours. Samples were withdrawn and after appropriate dilution with distilled water, they were analysed spectrophotometrically at 285 nm for their Carbamazepine contents using a blank solution containing the same concentration of the hydrotropic agent.

The presence of the hydrotropic agents in the dilution range used was examined and it was found that they were neither interfered with the spectrophotometric assay nor they made any shift in the wave length of maiximum absorbance of the medicament.

RESULTS AND DISCUSSIONS

Fig. 1 and Table 1 show the effect of sugars, namely, lactose, sucrose and glucose, as well as sugar alcohols, namely mannitol and sorbitol on the aqueous solubility of Carbamazepine at 25°. It can be seen that sugar alcohol show higher solubilizing action than the other sugars. Sorbitol shows higher solubilizing action than mannitol towards Carbamazepine. Glucose is the best solubilizer at concentrations up to 25.8% w/v, but above which sucrose was found to be better. This effect can be explained on the basis that sugars and sugar alcohols may break up water clusters surrounding the drug molecules. This effect increases the entropy of the system, and produces a driving force for solubilization of the drugs.

Fig. 2 and Table 2 show the effect of amides namely, urea, thiourea and nicotinamide on the water solubility of Carbamazepine. The solubility of the drug in presence of nicotinamide was much more than its solubility in the presence of thiourea and urea. Also, the solubilizing power of thiourea was higher than that of urea. This reveals that substitution of the oxygen atom in the carbonyl group of urea with sulfur atom is in the favour of the hydrotropic efficiency of the molecule. Furthermore, the solubilizing power of urea is independent on its concentration.

Fig. 3 and Table 3 illustrate the effect of two imides, saccharin sodium and succinimide sodium, on the water-solubility of Carbamazepine. More than 0.02 mole/L concentration, saccharin sodium was much better than succinimide sodium, while the reverse was true below this concentration. It is possible to consider the changes in the solubility of the medicament by the tested amides and imides to occur party through the same postulated mechanism given by Long and McDevit[5] . On the other hand, Frank and Franks[6] considered that urea acts as indirect structure breaker when added to water. Those which are used as their salts may participate in the solubilizing action through the dissociation of their molecules in solution and their ability to be engaged in ion-dipole attraction forces together with the drug molecule.

The effect of citric and tartaric acids on the solubility of Carbamazepine in water at 25° was investigated as shown in Fig. 4 and Table 4 Tartaric acid caused a more pronounced increase in the solubility of the drug. The solubility promoting effect of these two aliphatic acids may be due to the

the following mechanism: ion-dipole interaction between the anionic moiety of the acid and water molecules which could lead to " breaking up" of ice-bergs[7] in liquid water and result in the formation of more open"lattice" structure.

Fig. 5 and Table 5 show the effect of some salts on the water-solubility of Carbamazepine. Sodium benzoate showed the highest solubilizing power among the salts used. The solubilizing action of these salts could occur, at least partly, through break-up of water molecule clusturs or " iceberges", thus increasing the water activity which could result in breaking up of the hydrotropic bonding and self-association of the drug molecules.

Table 1: Solubilizing Powers of Sugars and Sugar alcohols Towards Carbamazepine.

Sugar concentration % w/v	Solubilizing Powersg/g x 10^6				
	Glucose	Sucrose	Lactose	Sorbitol	Mannitol
5	1.20	-4.60	-4.60	9.40	7.40
7.5	1.47	-4.40	-----	----	----
10	1.40	-4.60	1.30	5.70	2.70
15	1.53	0.00	-0.33	4.27	3.33
20	1.35	0.65	-0.80	3.50	3.35
30	1.23	1.57	-1.33	2.80	2.43
60	1.45	2.62	-0.43	2.12	1.62

Table 2: Solubilizing powers of Amides Towards Carbamazepine.

Hydrotropic concentration Mole/1	Solubilizing Powers(Mole/mole)		
	Urea	Thiourea	Nicotinamide
0.1	0.00057	0.00167	0.00667
0.2	0.00057	0.00198	0.00609
0.3	0.00057	0.00189	0.00522
0.4	0.00057	0.00192	0.00442

Table 3: Solubilizing Powers of Imides Towards Carbamazepine.

Hydrotrope Concentration Mole /1	Solubilizing Powers (Mole/mole)	
	Succininide-sodium	Saccharin-sodium
0.01	0.0127	0.0114
0.02	0.0092	0.0085
0.04		0.0099
0.05	0.0040	0.0083
0.1	0.0021	0.0051
0.2	0.0013	

Table 4: Solubilizing Powers of Aliphatic Acids Towards Carbamazepine.

Hydrotrope Concentration Mole/1	*Solubilizing Powers (Mole/mole)*	
	Citric acid	*Tartaric acid*
0.01	0.000	0.0170
0.02	0.000	0.0106
0.05	0.0003	0.0055
0.1	0.0009	0.0030

Table 5: Solubilizing Powers of Salts Towards Carbamazepine.

Hydrotrope Concentration Mole/1	*Solubilizing Powers (Mole/mole)*			
	Potassium Chloride	*Potassium Citrate*	*Sodium Benzoate*	*Sodium Tartrate*
0.01	-------	0.0100	--------	0.0100
0.0175	-------	-------	0.0089	------
0.02	0.0015	0.0043	------	0.0059
0.04	0.0007	0.0014	0.0044	-------
0.05	0.0006	-0.0003	0.0042	0.0011
0.075	------	------	0.0034	------
0.1	0.0003	-0.0008	0.0034	-0.0003

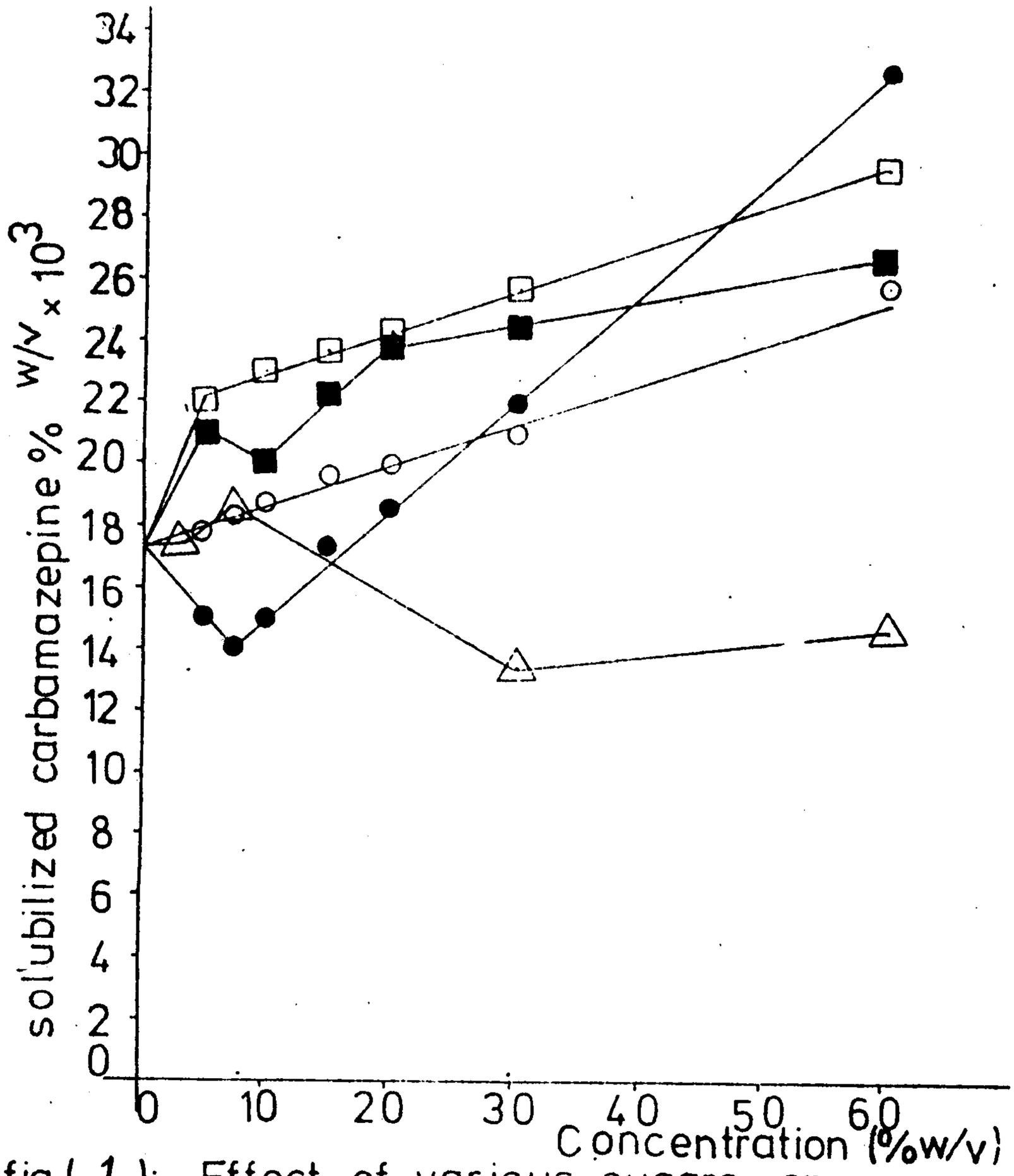


fig.(1): Effect of various sugars on the solubility of carbamazepine in water at 25°.

Key: ● Sucrose, ○ Glucose,
□ Sorbitol, ■ Mannitol,
△ Lactose.

Solubilization of carbamazepine using hydrotropic agents

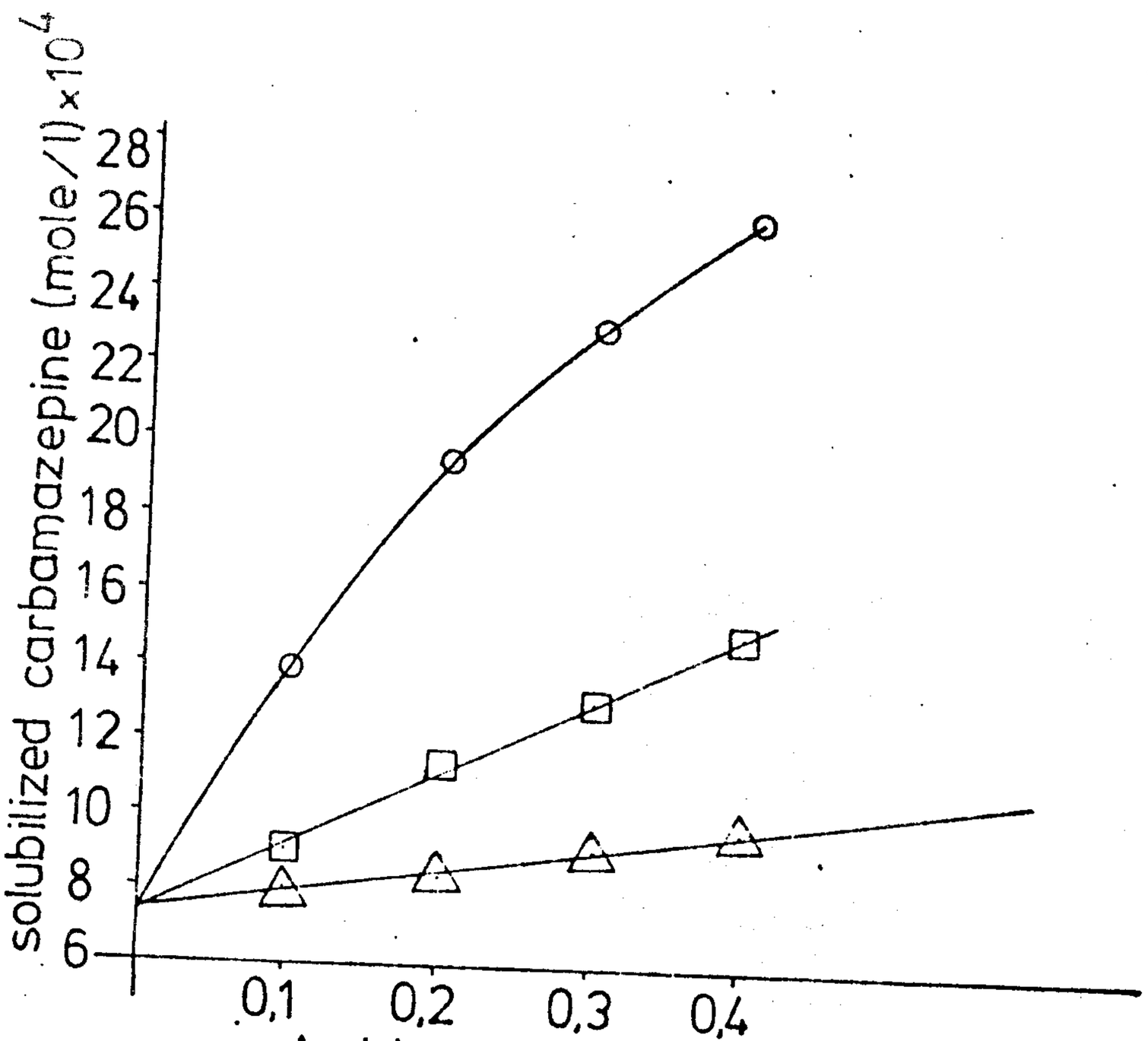


fig.(2): Effect of various amides on the solubility of carbamazepine in water at 25°.

Key: △ Urea, □ Thiourea
o Nicotinamide ..

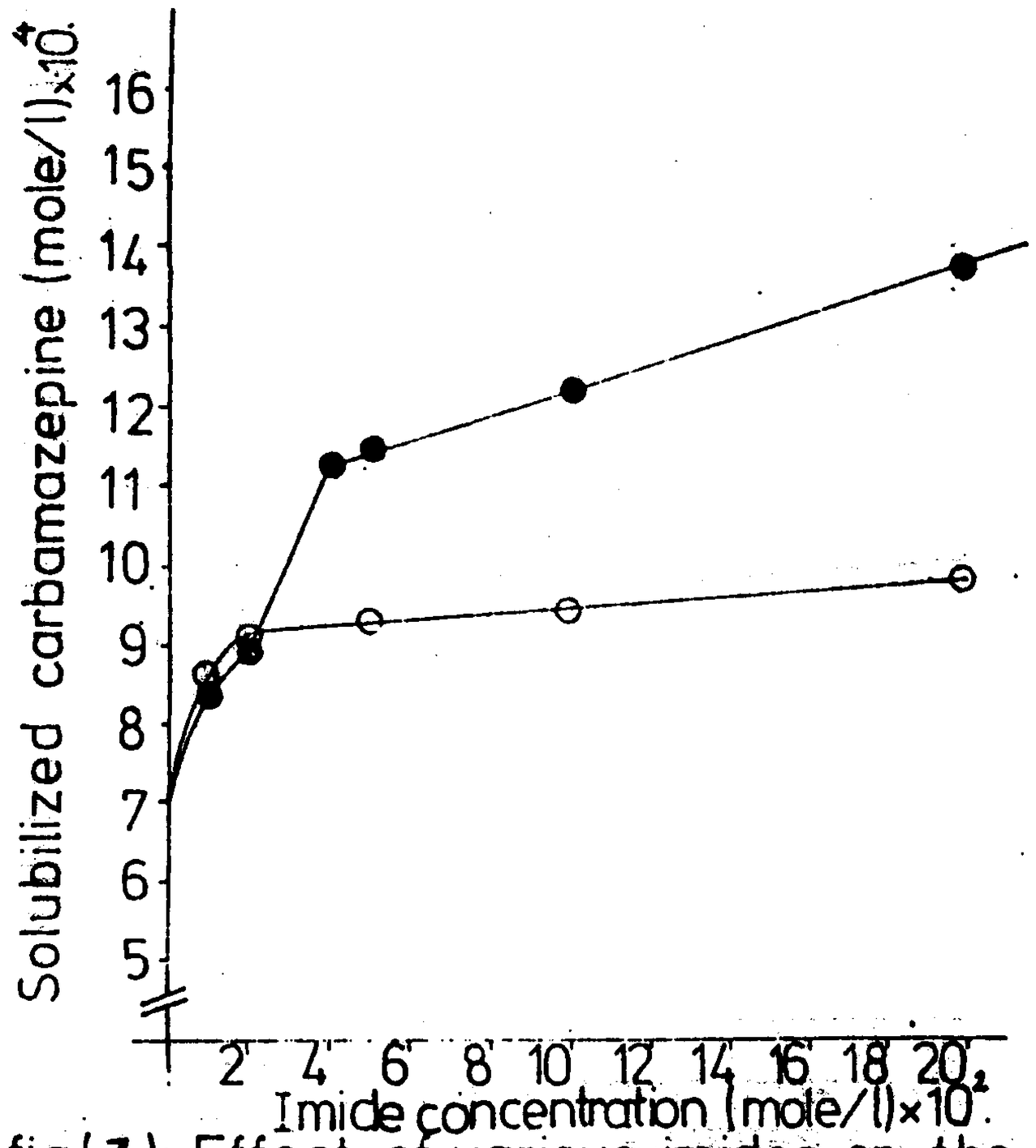


fig.(3): Effect of various imides on the solubility of carbamazepine in water at 25°.

Key: • Saccharin - sodium.

o Succinimide - sodium.

Solubilization of carbamazepine using hydrotropic agents

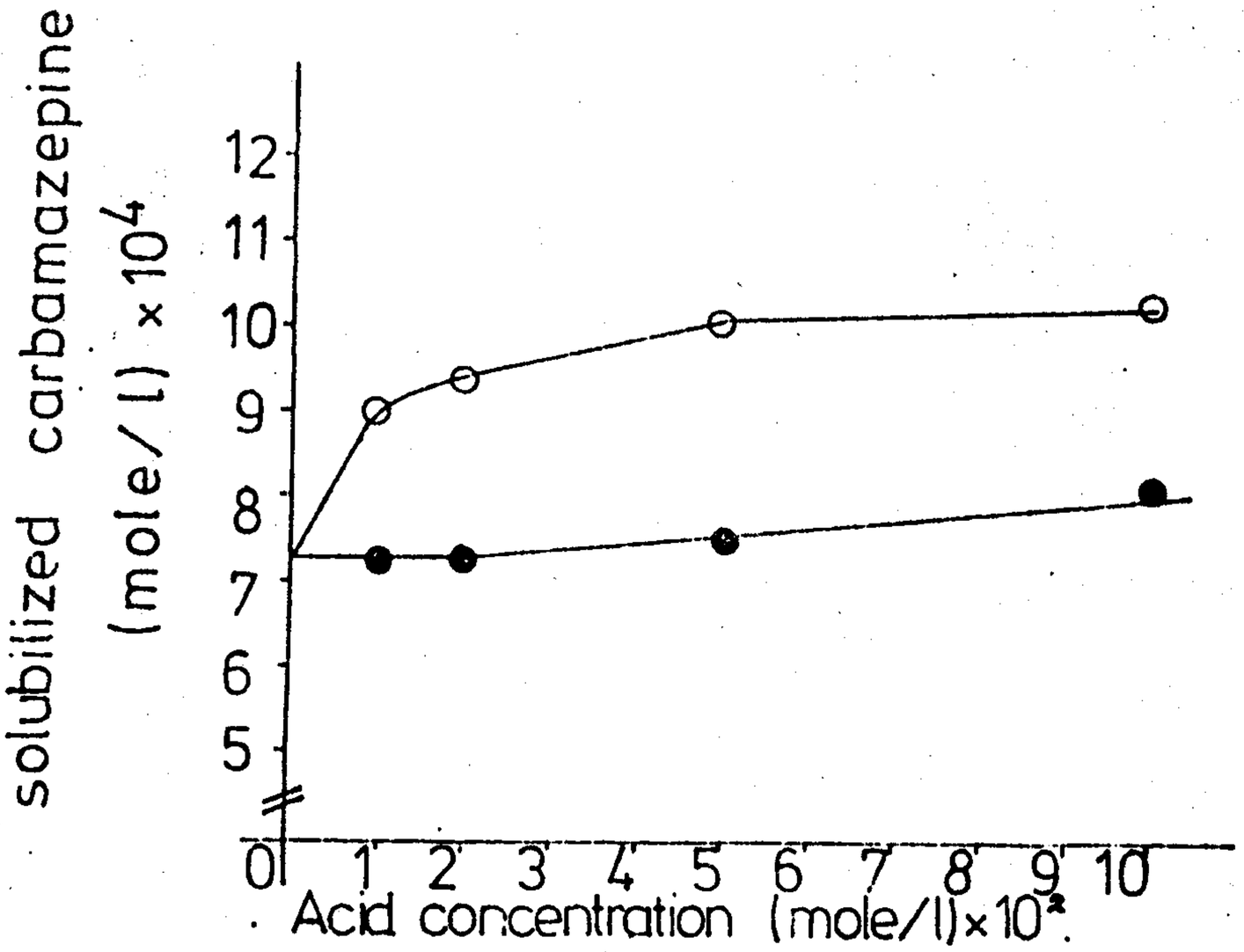
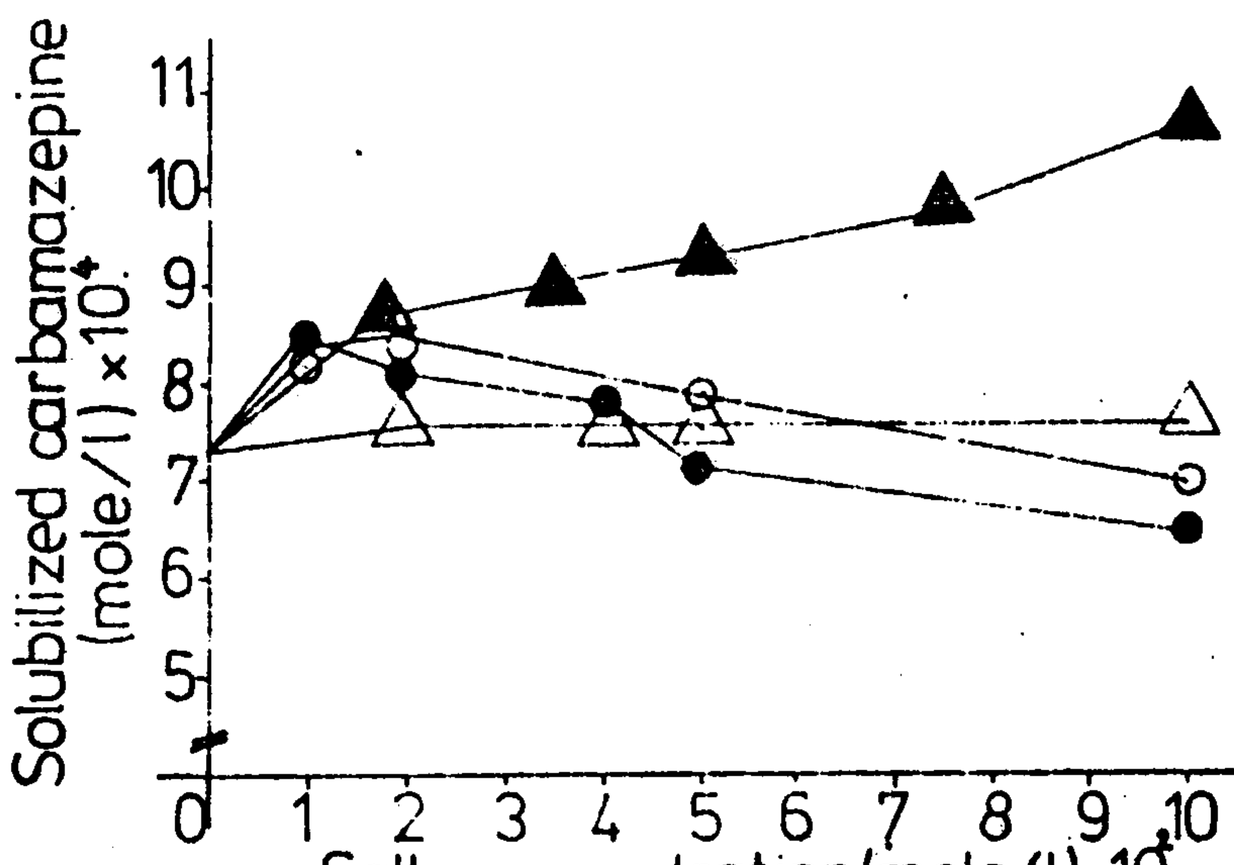


fig (4): Effect of various aliphatic acids on the solubility of carbamazepine in water at 25°.

Key: ● Citric acid, ○ Tartaric acid.



Fig(5): Effect of various salts on the solububility of carbamazepine in water at 25°.

Key: ▲Sodium benzoate, ○Sodium tartrate ●Potssium citrate, △Potassium chloride.

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تذويب الكاربامازبين باستخدام المواد الايدروثروبية

احمد السيد ابوطالب - سيد محمد احمد

قسم الصيدلة الصناعية - كلية الصيدلة - جامعة اسيوط

تم دراسة تاثير العديد من المواد الايدروثروبية التابعة لمجموعات كيميائية مختلفة مثل السكريات والكحولات عديدة الايدروكسيل والاميدات والاحماض العضوية وايضا بعض الاملاح نحو ذوبان الكاربامازبين عند درجة ٢٥°م ومقارنة كفاءة المواد المختلفة تجاهاء.

وقد تبين ان تاثير هذه المواد على اذابة الكاربامازبين يعتمد اساسا على تركيز كله منها ونوعهاء.

recieved in 18/11/1982 & accepted in 2/12/1982