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EFFECT OF PH,TEMPERATURE AND CERTAIN ADDITIVES ON THE SOLUBILIZATION OF CARBAMAZEPINE BY SELECTED NON-IONIC SURFACTANT SOLUTIONS

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The effect of incorporation of various organic additives on the solvent power of the different micelles for Carbamazepine was investigated. The variation in the pH value as well as the temperature of these solution on the degree of solubilization of Carbamazepine was also studied .

It was found that propylene glycol increased the solvent power of the different micelles, while glycerol and PEG 1000, 4000 and 6000 decrease their solubilizing capacity. Raising the temperature and lowering of pH value also increased the solvent power of the micelles.

Formulation of drugs in aqueous solutions is essentially important when uniformity of dosage, rapid and constant absorption should be insured. However, the limited solubility of certain drugs in water makes this requirement not easily accessible. In most cases drug administered in solution form is immediately available for absorption and giving more rapid action than if the same dose is administered in a Tablet form[1].

The objective of this investigation is to solubilize Carbamazepine[2,3] so as to obtain a solution of Carbamazepine suitable for formulating aqueous preparations from this drug. In case of Carbamazepine, it is important to achieve rapid absorption and immediate action especially in the case of attack and to give easily administered liquid preparations even to children.

EXPERIMENTAL

Materials:

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

Non-ionic surfactants used which include:

Cetyl stearyl alcohol with(20) ethylene oxide unites, Cetyl-stearyl alcohol with (30) ethylene oxide units(Eumulgin C_{1000} and Eumulgin C_{1500}, respectively, (Henkel International Dusseldrof, Western Germany). Polyoxyethylene (20) cetyl ether and polyoxyethtlene (23) lauryl ether (Brij 58 and 35 respectively, (Atlas Chemical Industries, Inc. Will. Del. U.S.A.).

The additives used include:

Glycerol, propylene glycol(British Drug houses. Pool England), polyethylene glycol 1000, polyethylene glycol 4000 polyehtylene glycol 6000 (Adwic Prolabo Company L.T.D).

Buffers (British Drug houses. Poole England):

- Sodium dibasic phosphate.
- Citric acid.

Apparatus:

Spectrophotometer(Pye-Unicam SP400. England).

pH-meter (Seibold, Austria).

Methods:

Determination of Carbamazepine solubility in non-ionic surfactant solution containing different additives:

A- Glycerol:

Solution containing different concentrations of the non-ionic surfactants and 5 or 10% w/v glycerol were prepared. 10 ml of each solution was transferred to 15 ml screw capped tubes and excess Carbamazepine was added. The tubes were equilibrated in thermostatically controlled water baths at 25° and 35° ± 0.1°C, for 12 days with continuous Shaking. After the equilibrium time had elapsed, the tubes were centrifuged , then re-equilibrated for further 24 hours. Samples were withdrawn and after appropriats dilutions with distilled water, they were analysed spectrophotometrically at 285 nm for their Carbamazepine contents.

B- Propylene Glycol:

Different non-ionic surfactant solutions containing 5% or 10% w/v propylene glycol were prepared. The experiments were performed as mentioned before for glycerol.

C- Polyethylene Glycols 1000, 4000 and 6000:

Different non-ionic surfactant solutions containing 5% or 10% of each of the different polyethlene glycol were prepared. The experiments were performed in the same manner as in the case of glycerol.

Determination of Carbamazepine solubility by non-ionic surfactant solutions of different pH values:

Solution containing different concentrations of the selected

non-ionic surfactants of pH 2.2, 6 and 7.4 were prepared by using Mc-Ilvaine citric acid-disodium phosphate buffer[4].

Solutions of pH 2.2, 6 and 7.4 respectively. The experiments were performed as mentioned before.

The presence of either additives or buffer components did not interfere with the assay of Carbamazepine in the dilution range used.

RESULTS AND DISCUSSIONS

1) Effect of different additives on the degree of solubilization of Carbamazepine:

Fig. 1 shows the effect of 5% w/v propylene glycol in the different non-ionic surfactant solutions on the solubility of Carbamazepine at 25°. On comparing the solubilizing efficiency of the non-ionic surfactant solutions in the absence and in the presence of 5% w/v propylene glycol, towards Carbamazepine it was found that the presence of this low concentration caused a slight increase in the solubilizing efficiency of the respective surfactants. This increase can be attributed to the enhanced solubility of Carbamazepine in micelles which have been enlarged in size and the suppression of liquid crystal formation which can oppose micellar solubilization[4]. Raising the concentration of propylene glycol to 10% in the non-ionic surfactant solutions caused a slight increase in the solubilizing efficiency of the latter

Fig. 2 demonstrates the effect of 5% w/v glycerol on the solubilization of Carbamazepine by different non-ionic surfactant solution at 25°. Being hydrophilic, glycerol is incorporated in the polyoxyethylene chain of the micelle causing

enlargement of this layer. Consequently, a relative decrease in the core volume to the micellar volume occurred. In this case, a decrease in the solubilizing efficiency of the non-ionic surfactant solutions was obtained. Raising the concentration of glycerol to 10% caused a slight decrease in the solubilizing efficiency.

Fig. 3, 4 and 5, illustrate the effect of 5% w/v PEG 1000, PEG 4000 and PEG 6000 respectively, on the solubilizing efficiency of the investigated non-ionic surfactants towards Carbamazepine at 25°. It was found that the presence of PEG'S caused a decrease in the solubilizing efficiency of the selected non-ionic surfactants. This decrease may be due either to the increase in the hydrophilicity of the non-ionic surfactant micelles, or to the decrease in the relative volume of the micellar core to the total micellar volume.

The order of efficiency of the different non-ionic surfactant solutions containing the above mentioned additives for solubilization of Carbamazepine can be arranged as follow:

Eumulgin C_{1000} > Brij 58 > Eumulgin C_{1500} > Brij 35.

2- <u>Effect of variation in temperature on the degree of solubilization of Carbamazepine</u>:

Temperature is an important factor which has a varying effect on the extent of micellar solubilization. Many studies made by Mc-Bain and co-workers[5] on the effect of temperature variation on micellar solubilization. Upon icreasing the temperature of the non-ionic surfactant solutions containing 5% w/v or 10% w/v propylene glycol, glycerol or P.E.Gs. from 25° to 35°, a positive temperature effect was observed as shown in Figs (6-10), i.e., there was an increase in solubility of Carbamazepine with increase in

temperature. This may be due to increase in aggregation number, consequently the micellar size would be enlarged which can accomodate more amount of the solubilizate.

Table 1 shows the solubility g/g by non-ionic surfactant solutions in the absence and in presence of 5% w/v or 10% w/v of the various additives at 25° and 35°. From this table, it can be noticed that the solubilizing efficiency of the selected non-ionic surfactants may increase by the presence of organic additives as in case of propylene glycol or decrease as in case of the other additives, namely, glycerol, PEG 1000, PEG 4000 and PEG 6000.

Table 2 gives an idea about the distribution of Carbamazepine between the micellar pseudo-phase and the aqueous phase, i.e., K_m value at the two temperature used in this study, and also effect of the various additives on this value. As shown from the table, the effect of the additives on the solubility of the drug in the aqueous phase and the micellar pseudo-phase may cause the K_m value to decrease or increase. This indicates that when K_m increases, this means that the additives induces more solubilization of Carbamazepine in the micellar phase than in the continuous phase, and the reverse occurs when K_m value decreases.

It is noticed that the K_m value decreases by raising the temperature from 25° to 35°. This can be attributed to the fact that both the aqueous and micellar solubilities of the medicament are changed by increasing the temperature, but not by the same rate.

From the previous results, it can be concluded that among the organic additives studied, propylene glycol can be considered the best to be used in conjunction with non-ionic surfactants in solubilized system of Carbamazepine . The solubilization of Carbamazepine increases as the amount of propylene glycol increases and also with rise in temperature. But, glycerol, PEG 1000, PEG 4000 and PEG 6000 are not recommended to be incorporated in solubilized systems containing Carbamazepine.

3- Effect of different pH values on the degree of solubilization of Carbamazepine:

The different solubilized systems containing Carbamazepine were prepared at various pH values[6,7]. It is of interest to investigate the effect of pH change on the solubility of Carbamazepine: The pH values of the selected surfactant solutions, e.g., Eumulgin C_{1000}, Eumulgin C_{1500} , Brij 35 and Brij 58, were adjusted to pH 2.2, 6 and 7.4 by using MC—Ilvain[8] citric acid disodium phosphate buffer. This study on the effect of pH on the solubilization was performed only at 25^{o}. From Fig. 11&12, it is obvious that on increasing the pH of non-ionic surfactnat solutions, a slight decrease in the amount of Carbamazepine solubilized was obtained.

This may be due to the fact that Carbamazepine being an amide ~~could~~ be ionized at higher pH values. It is well known that the unionized form of amides could be solubilized only within the micellar interior, while the ionized form of this solute, mostly, favours the aqueous phase.

From the previous results, one may conclude that the solubilizing efficiency of the used non-ionic surfactants towards Carbamazepine increased as the pH value of the system decreased from 7.4 to 2.2

Table 1: Solubility of Carbamazepine g/g x 10^3 by Non-ionic Surfactant solutions in the Presence of Various Additives.

Non-ionic Surfactants	Solubility g/g of Carbamazepine calculated from solubility measurements																				
	Surfactant Alone		+5%w/v Propylene Glycol		+10%w/v Propylene Glycol		+5%w/v Glycerol		10%w/v Glecrol		+5%w/v PEG 1000		10%w/v PEG 1000		+5%w/v PEG 4000		1+10%w/v PEG 4000		PEG 6000		PEG6000
	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	35°
Eumulgin C 1000	29.7	36.2	29.9	35.7	30.7	40.2	25.5	32.0	26.7	39.7	25.1	34.4	23.6	32.9	26.2	35.5	25.4	32.6	26.8	33.3	32.4
Eumulgin C 1500	23.7	32.8	24.7	32.5	24.4	33.6	19.2	26.1	23.8	32.9	17.8	25.6	19.2	26.0	23.0	31.2	22.4	25.0	19.5	26.6	23.7
Brij 35	20.4	27.8	20.9	26.6	21.3	25.5	17.1	21.8	19.3	28.6	15.4	21.7	16.9	24.6	19.0	25.4	19.2	21.9	16.8	25.9	19.3
Brij 58	27.7	36.4	27.8	33.2	28.4	37.2	20.6	28.7	25.2	38.7	21.5	26.1	20.0	30.2	25.2	34.8	25.3	28.4	21.5	28.4	30.9

Table 2: Distribution coefficient (K_m) calculated from solubility measurement

non-ionic Surfactant	Surfactant alone		Surfactant containing 5% w/w of the following additives									
			Propylene glycol		Glycerol		PEG 1000		PEG 4000		PEG 6000	
	25°	35°	25°	25°	25°	35°	25°	35°	25°	35°	25°	35°
Eumulgin C 1000	165	125	175	125	150	112	168	132	137	139	138	138
Eumulgin C 1500	139	108	148	113	120	96	137	101	174	123	150	118
Brij 35	112	90	124	93	108	79	109	98	139	108	134	112
Brij 58	154	119	162	117	126	103	154	110	177	134	162	124

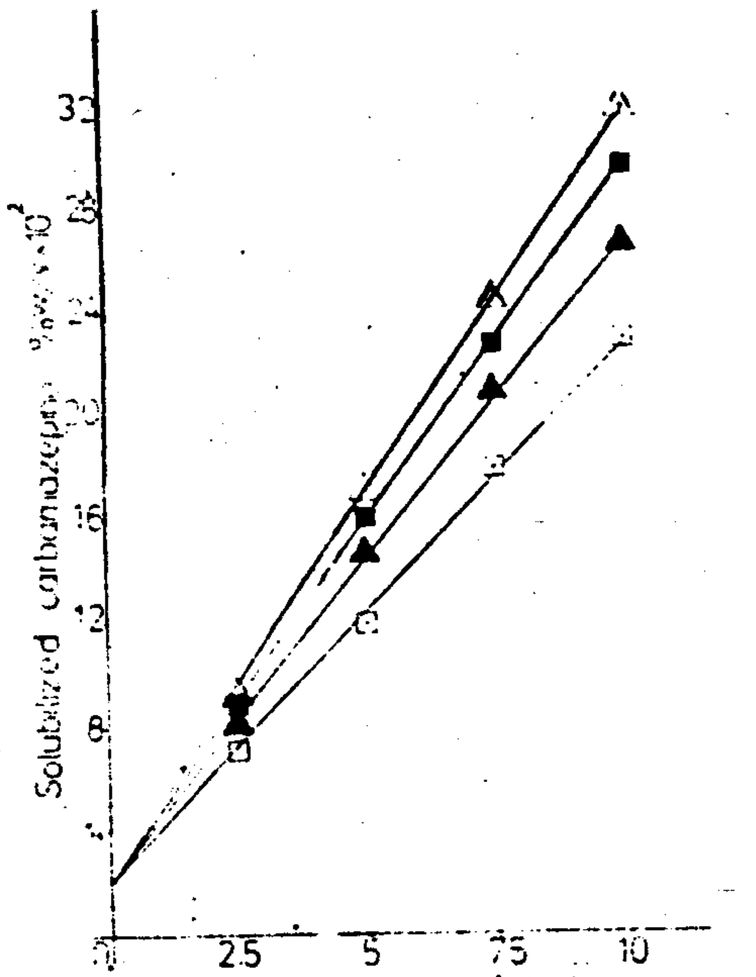


Fig (1) Solubility of carbamazepine in different nonionic surfactant solutions containing 5% w/v propylene glycol at 25°

Key △ Eumulgin C1000. ▲ Eumulgin C1500
□ Brij 35. ■ Brij 58.

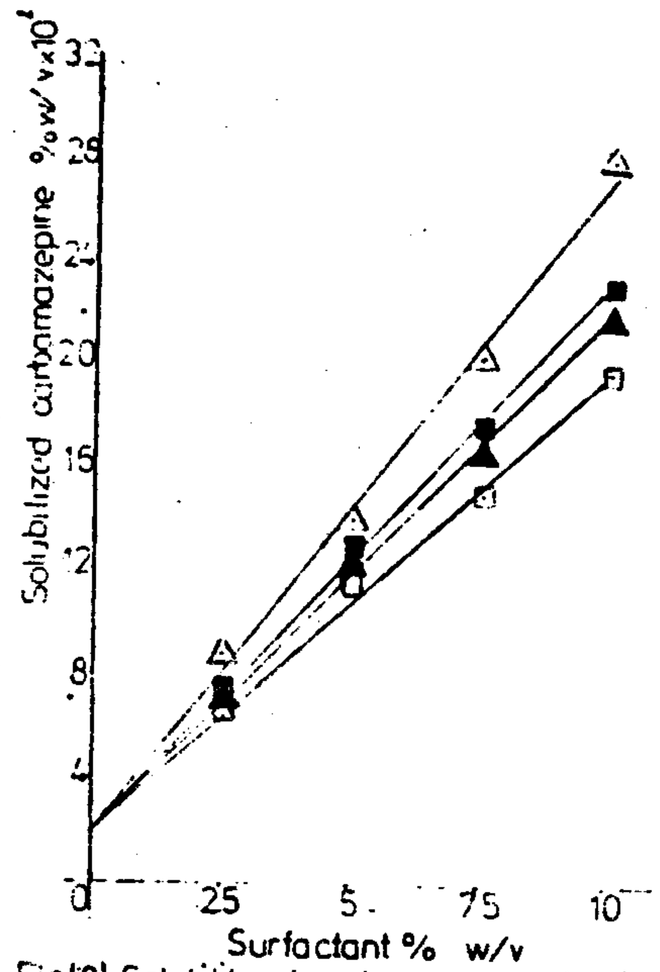


Fig (2) Solubility of carbamazepine in different nonionic surfactant solutions containing 5% w/v glycerol at 25°

Key The same as in Fig (1)

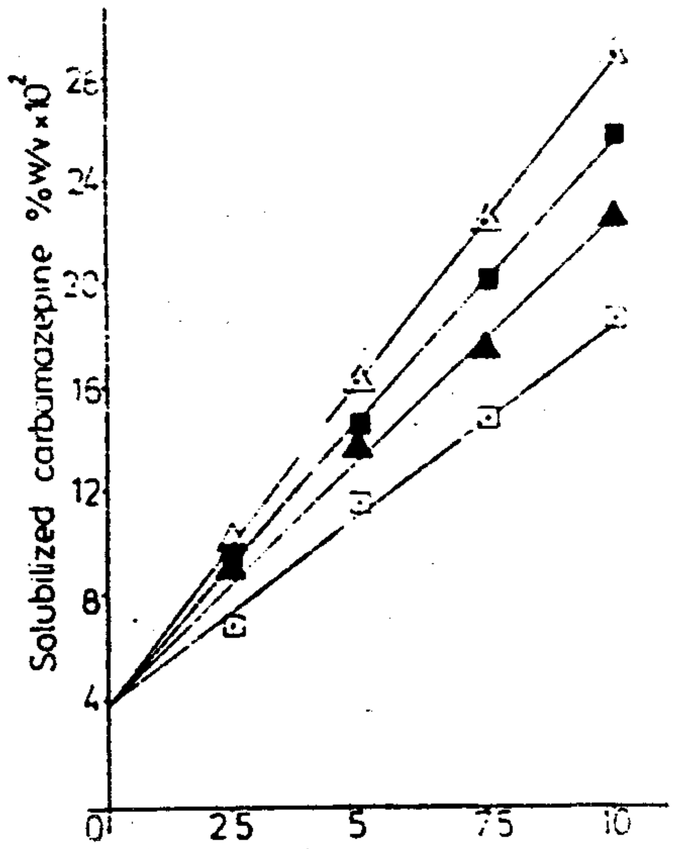
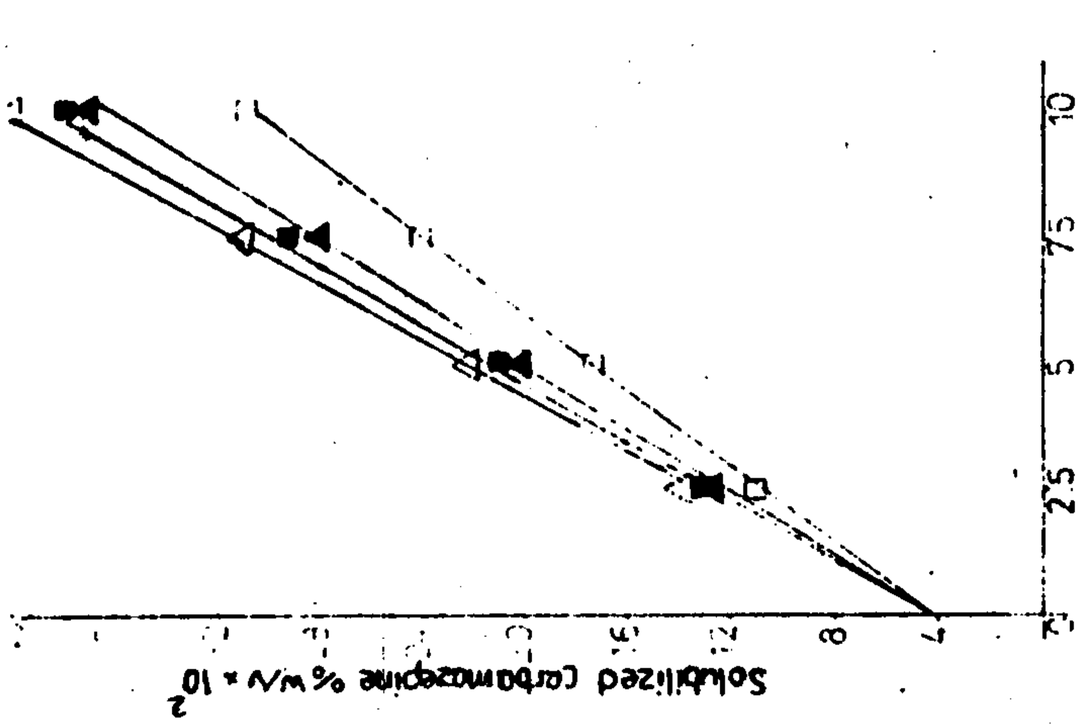
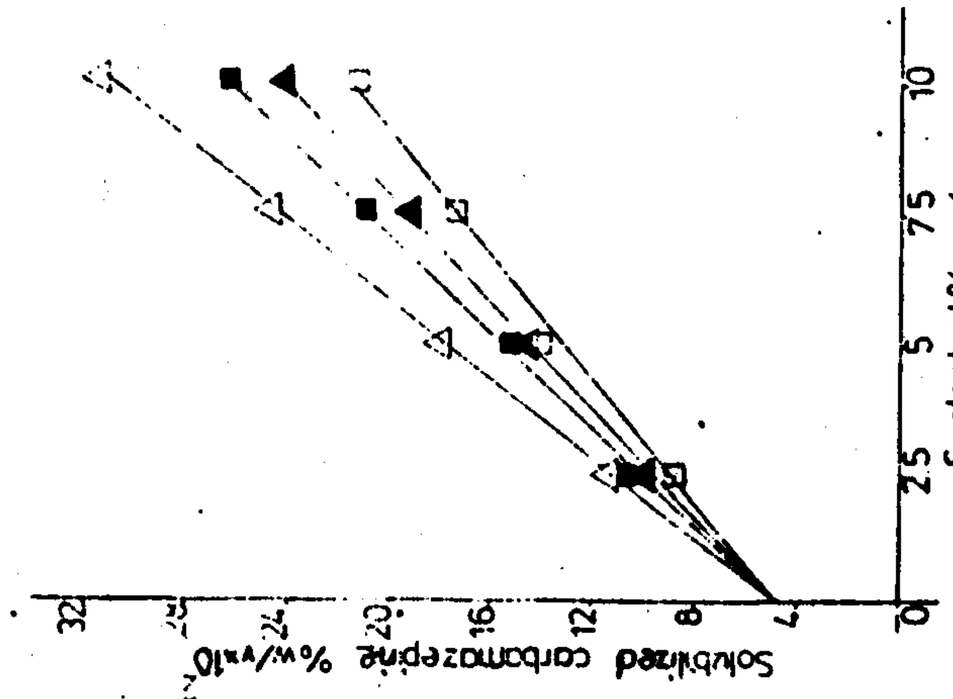


Fig (3) Solubility of carbamazepine in different nonionic surfactant solutions containing 5% w/v P.E G.1000 at 25°.

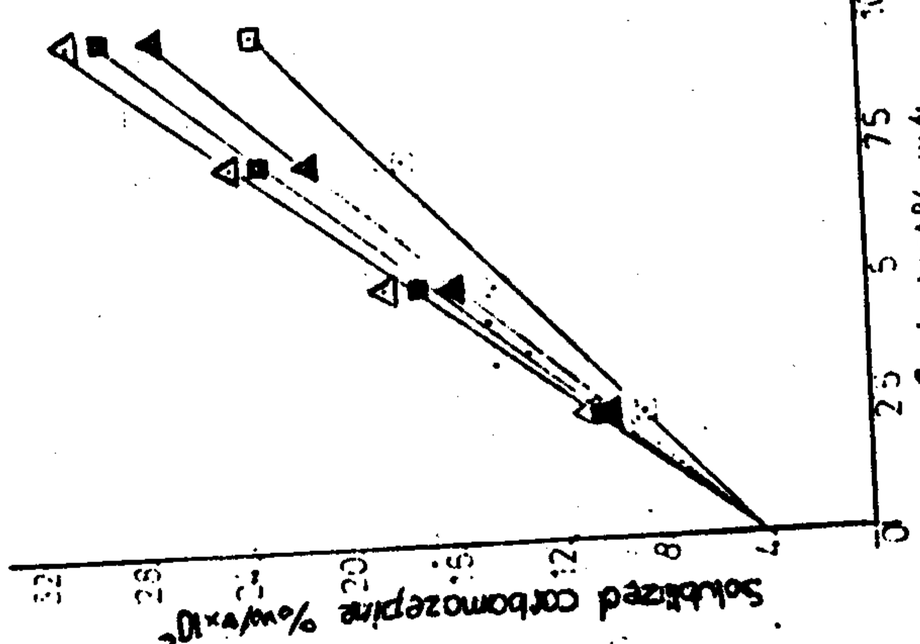
Key: The same as in Fig (1).



Fig(6) Solubility of carbamazepine in different non-ionic surfactant solutions containing 5%w/v propylene glycol at 35°.
Key The same as in Fig (1)



Fig(5) Solubility of carbamazepine in non-ionic surfactant solutions containing 5% w/v P.E.G. 6000 at 25°.
Key. The same as in Fig(1)



Fig(4) Solubility of carbamazepine in non-ionic surfactant solutions containing 5% w/v PEG 4000 at 25°.
Key The same as in Fig(1)

Effect of ph, temperature and certain additives on the solubilization of carbamazepine by selected non-ionic surfactant solutions

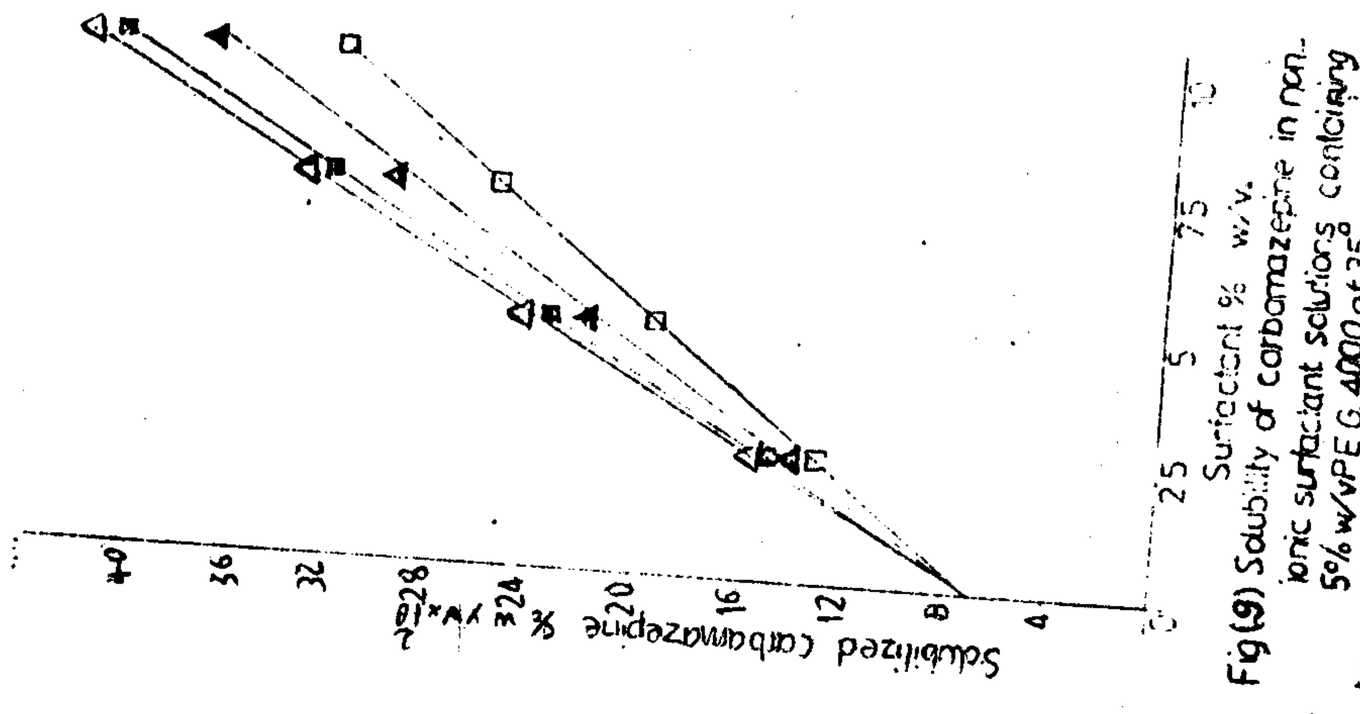


Fig (9) Solubility of carbamazepine in non-ionic surfactant solutions containing 5% w/v PEG 4000 at 35°.
key The same as in Fig(1)

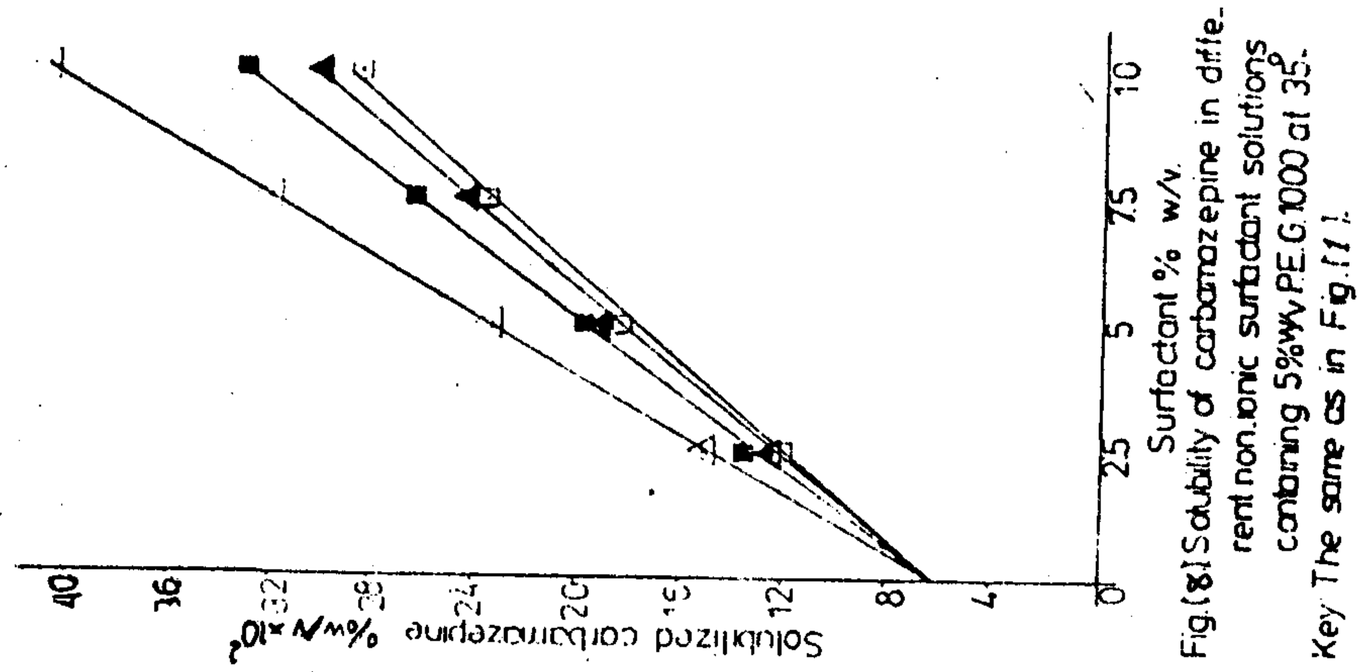


Fig (8) Solubility of carbamazepine in different non-ionic surfactant solutions containing 5%w/v PEG 1000 at 35°.
Key The same as in Fig.11.

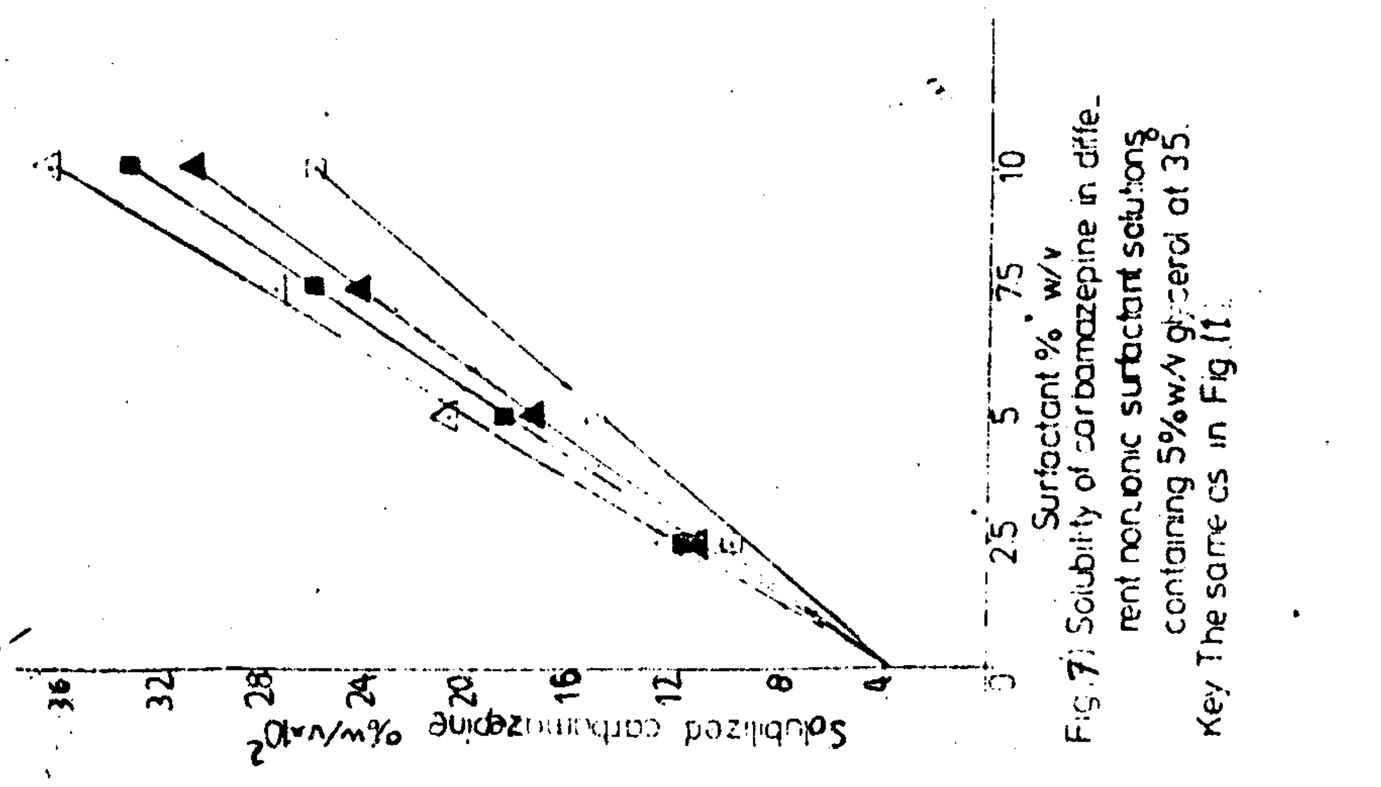
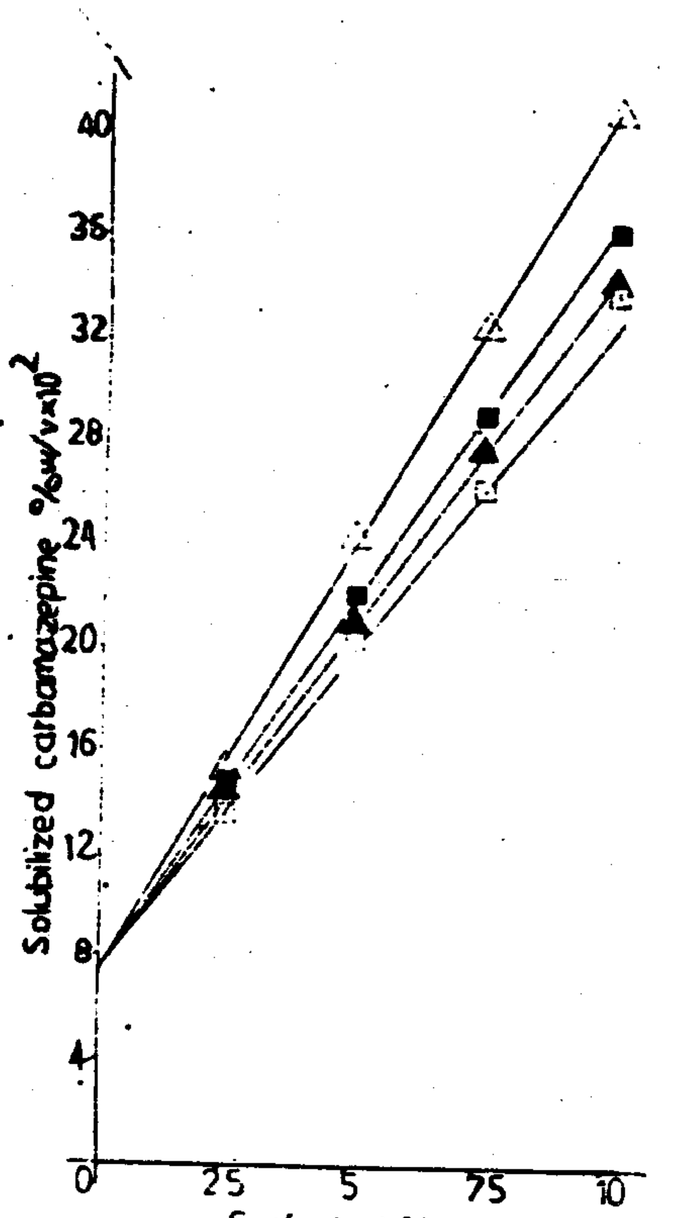
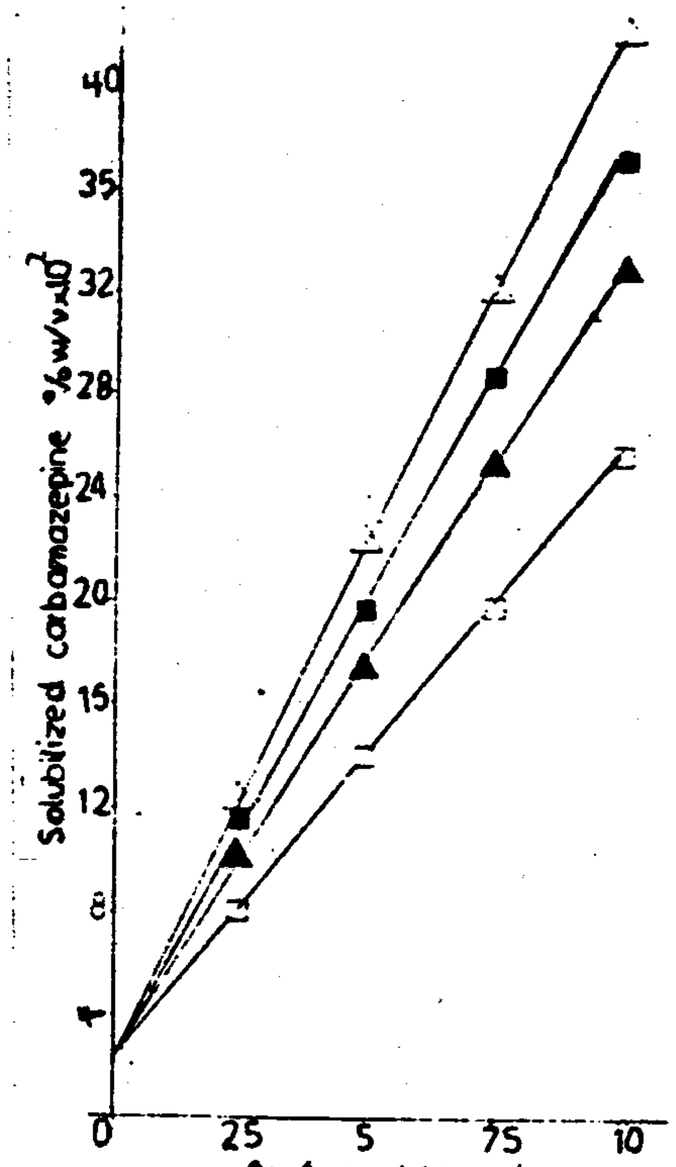


Fig (7) Solubility of carbamazepine in different non-ionic surfactant solutions containing 5% w/v glycerol at 35°.
Key The same as in Fig (1).



Fig(10) Solubility of carbamazepine in non-ionic surfactant solutions containing 5% w/v PEG 6000 at 35°.

Key The same as in Fig(1).



Fig(11) Solubility of carbamazepine in non-ionic surfactant solutions of pH 2 2 at 25°

Key The same as in Fig(1)

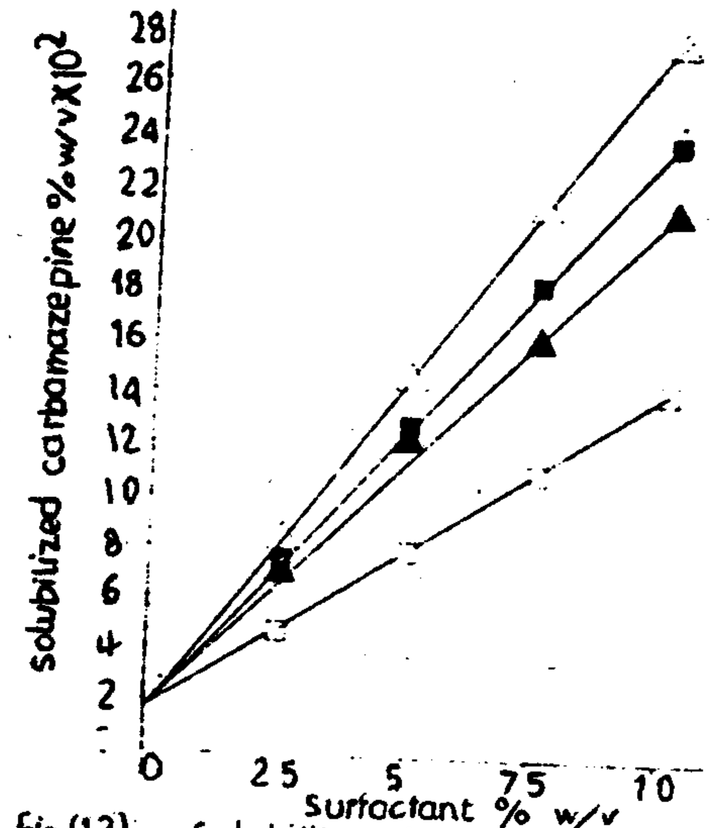


Fig.(12) Solubility of carbamazepine in non-ionic surfactant solutions of pH 6 at 25°

Key. The same as in Fig(1)

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تاثير الرقم الايدروجينى ودرجة الحرارة وبعض المواد المضافة على اذابة الكاربامازبين باستخدام بعض المواد ذات النشاط السطحى غير المتـــــائنة

احمد السيد ابوطالب - سيد ـــــ احمـــ

قسم الصيدلة الصناعيـة ـ كليـة الصيدلة ـ جامعة اسيـــــــــــوط

فـى هذا البحث تم دراسة تاثيـر بعض المواد العضوية المضافـــــة عـــلى قـــوة اذابـة بعض المـــواد ذات النشـاط السطحى غير المتاينـــــة للكـــاربـــامـــازبيـن • وتـــم ايضـــا دراسة تـاثير محـاليل ذات رقـــم أيـــدروجيـــنى متـــباين وعنـد درجـــات حرارة مختلفة عـلى درجـــــة اذابـــة المـــادة الدوائيـــة •

وقـــد تبين أن وجـــود البروبيلين جليكول يوءدى الى زيـادة فى قـــوة اذابـة المـــواد ذات النشـاط السطحى غير المتاينة للكاربامازبيـــــن بينمـــا وجـــود عـديد ايثيـلين الجليكولات والجلســرين يوءدى الـــــى نقص طفيف فـــى قوة اذابـة نفس منشـطات السطح غير المتآينة •

وقد وجد ان زيادة درجة الحرارة وأيـــضا انقاص الرقم الايدروجينـــــى يـــــوءدى الـــى زيـــادة فـــى كميـة المـــادة الدوائيـة المذابة •

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