

EFFECT OF DIFFERENT ADDITIVES ON THE MICELLAR SOLUBILIZATION
OF CHLORAMPHENICOL

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The effect of different inorganic and organic additives on the solubility of chloramphenicol by non-ionic surfactant solutions was investigated at two different temperatures. The following additives were used namely polyethylene glycol 600, propylene glycol, glycerol, urea and potassium chloride. Urea produced a slight effect on the solubilizing efficiency of the non-ionic surfactant solutions, on the other hand a more pronounced effect on the solubilizing efficiency of these non-ionic micelles was obtained by increasing the concentration of potassium chloride in solutions. For organic additives it was found that the addition of polyethylene glycol 600 increased the solubilizing efficiency of all the non-ionic surfactant solutions than both glycerol and propylene glycol.

The solubilizing action of surface active agent itself may be sufficient for the preparation of solutions of many insoluble drugs, but if the activity of a preparation can be affected by the proportion of the agent used, or it was difficult to get solute into solution by the action of surfactant alone, addition of other component to a solubilized system may produced the desired effect.

Many complex solvent systems were developed in specific instances on an imperial bases. Saturated hydrocarbons, when added to the non-ionic surfactant solutions, did not de depress the cloud point very much, where as aliphatic alcohols, fatty acids or phenols depressed the cloud point remarkably.

Donbrow and Jacobs¹ used a potentiometric titration method for investigating solubilized systems containing polysorbate 80 and glycol ethers, and they found the uptake of benzoic acid by the micelles was increased. It was suggested that when organic substances were added to surfactant solutions, the solubilization process was dramatically affected. The CMC values varied by the addition of long chain polar or semipolar compounds², and also short chain alcohols³.

The presence of electrolytes may also affect the solubility, as a two or three fold increase was reported, although in some other systems the solubility decreased in the presence of salts⁴. The non-ionic surfactants were stable even in the presence of relatively high electrolyte concentration, This can be considered as one of their advantages^{5,6}. Many workers^{5,7,8} have studied the effect of ionic strength of the electrolyte on the lowering of the cloud point of the non-ionic surfactants, and found that the lowering was a linear function of the ionic strength of the electrolyte.

Becher and other workers⁹⁻¹¹ reported that on the addition of electrolyte to non-ionic surfactant systems a drop in the CMC was obtained, whereas the addition of urea produced the opposite effect^{10,11}.

Schick^{12,13} suggested that urea may affect the iceberg structure in water, as originally proposed by Frank and Evans¹⁴ and therefore exert their effect upon CMC by changing the hydration of the polyoxyethylene chain.

In the present work the effect of different concentrations of polyethylene glycol 600 and 4000, propylene glycol, glycerol, urea and potassium chloride on chloramphenicol solubility by non-ionic surfactant solutions was investigated at two temperatures. The results obtained were discussed and compared with other literature reports.

EXPERIMENTAL

Materials :

Chloramphenicol, El-Nasr chemical Co-Egypt. was analytical grade.

Tweens :

Polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan monooleate (Tween 80).

Myrjs :

Polyoxyl (40) stearate (Myrj 52) and polyoxyl (100) stearate Myrj (59), Atlas Chemical Industries, Delaware U.S.A.

Emulgins :

Cetyl stearyl alcohol with 20 ethylene oxide units (Emulgin C₁₀₀₀), cetyl stearyl alcohol with 30 ethylene oxide units (Emulgin C₁₅₀₀), Henkel international, Dusseldorf, West Germany.

The additives used include :-

Polyethylene glycol 600³, propylene glycol, glycerol, urea and potassium chloride, British Drug House, Poole, England.

Determination of Chloramphenicol Solubility by non-ionic surfactant solutions containing different Additives :-

Solutions containing different concentrations of the selected non-ionic surfactants in the presence of 5 or 10% w/v polyethylene glycol 600, propylene glycol and glycerol were prepared. 10 ml of each solution was transferred to 15 ml screw capped tubes and excess chloramphenicol was added. The tubes were equilibrated in thermostatically controlled water baths at 25 and 35° for 15 days with continuous shaking.

After the equilibrium time had elapsed, the tubes were centrifuged, then reequilibrated for further 24 hours.

Samples were withdrawn and after appropriate dilutions with distilled water they were analyzed spectrophotometrically at 278 nm for their chloramphenicol contents.

Different concentrations of non-ionic surfactant solutions containing 0.2 mole/l urea as well as 0.5 mole/l, 0.1 mole/l and 0.01 mole/l potassium chloride were also prepared. The pH of the last solutions containing potassium chloride was adjusted to pH 2 using 0.005 N hydrochloric acid, in this case the blank contains also 0.005 N hydrochloric acid. Experiments were carried out in the same way as mentioned before.

RESULTS AND DISCUSSIONS

It is obvious that the presence of polyethylene glycol 600 increases the solubilizing capacity of all non-ionic surfactants solutions, namely Tween 20, Tween 80, Emulgin C₁₀₀₀, Emulgin C₁₅₀₀, Myrj 52 and Myrj 59. This increase in solubility caused by the presence of polyethylene glycol 600 may be due to its effect on the process of micellization. The presence of this long-chained alcohol in solution may induce the aggregation of monomers into micelles, consequently the CMC value decreased and the solubilizing capacity of the surfactant solution could be increased. Low molecular weight alcohols as P.E.G 600 may also act as Co-solubilizer for this solute. Emulgin C₁₀₀₀ solution containing 5% w/v P. E. G 600 has a more solubilizing efficiency than Emulgin C₁₀₀₀ solution alone at 35° but this was not the case with Emulgin C₁₅₀₀. This may be due to depression of the cloud point of Emulgin C₁₀₀₀ by the presence of P. E. G 600, consequently, its solubilizing efficiency would be expected to increase due to the increase in aggregation number and micellar molecular weight.

It is well known that the solubility of many solutes reaches to maximum near the cloud point of surfactants which may be due to formation of giant micelles¹⁵⁻¹⁸ but, this was not expected for Emulgin C₁₅₀₀ as its cloud point was much higher than Emulgin C₁₀₀₀ due to its longer ethylene oxide chain length. Myrjs solutions showed very slight change in their solubilizing capacity in the absence and in the presence of 5% w/v P. E. G. 600 at 35°. The solvent power of non-ionic surfactant solutions in presence of 5% w/v P.E.G. 600 at 25° can be arranged as follows as shown in Figure 1. Emulgin C₁₀₀₀ > Emulgin C₁₅₀₀ > Tween 80 > Tween 20 > myrj 52 > Myrj 59. Non-ionic surfactant solutions containing 10% w/v P. E. G. 600 can be arranged in the following sequence according to their solubilizing efficiency toward chloramphenicol at 25° : Emulgin C₁₀₀₀ Tween 80 Emulgin C₁₅₀₀ Tween 20 Myrj 59. This change in the sequence at higher concentration may be due to the effect of the addi-

tives on the cloud point of these surfactants consequently their solubilizing efficiency can be affected. On comparing the solubilizing capacity of the non-ionic surfactant solutions alone and those containing 10% glycerol at 35° as shown in Figure 2 and Table 1, it was noticed that the latter solutions have greater solubilizing capacity for chloramphenicol, but to different extent which depend upon the surfactant molecular structure. The larger the capsule the more the volume available for the incorporation of such hydrophilic branched chain alcohol, together with more hydration of the capsule, in this case the relative volume of the core to the total micellar volume would be decreased and therefore the solubilizing capacity of the micelle was expected to decrease for non-polar solutes such as chloramphenicol.

On comparing the effect of 5% w/v polyethylene glycol 600 and 5% w/v propylene glycol on the solubilizing capacity of the different non-ionic surfactants at 25°, it was noticed the solutions of the former showed more pronounced effect for making the different non-ionic surfactant solutions more efficient solubilizer for chloramphenicol than the latter. This is because P.E.G 600 has a longer hydrocarbon chain than propylene glycol, which makes the former more efficient as a Co-solubilizer than the latter.

The order of efficiency of the different non-ionic solutions containing 5% w/v propylene glycol for chloramphenicol solubilization can be arranged at 25° as follows as shown in Figure 3 : Emulgin C₁₀₀₀ > Emulgin C₁₅₀₀ > Tween 80 > Myrj 52 > Tween 20 > Myrj 59. Of course, on raising the temperature from 25° to 35° a positive temperature effect occurred, i.e. an increase in the solubilizing capacity of all the non-ionic surfactant solutions containing the glycol by raising the temperature. Furthermore on comparing the solubilizing efficiency of non-ionic surfactant solutions in absence and in presence of propylene glycol at the higher temperature of 35°, a slight change in solubility was obtained. Propylene glycol in this case may not affect the solubilizing capacity of the surfactant as it opposed the formation of

liquid crystal at lower temperature. On the other hand the formation of liquid crystal was usually hindered at high temperature. It was found that P.E.G. 600 caused a more increase in solubilizing efficiency of the different non-ionic surfactant solutions than glycerol. This is can be because P.E.G. 600 has a longer hydrocarbon chain than the latter.

On comparing the solubilizing efficiency expressed by g. chloramphenicol solubilized per g. micelles for the non-ionic surfactant solutions containing 0.2 mole/l urea and the non-ionic surfactant solutions alone at 25° and 35° as shown in Figure 4 and Table 1. It was obvious that the former has more solubilizing efficiency than the latter. This agreed with the finding of Daabis et al¹⁹, who stated that urea induced the solubility of other insoluble drugs specially at higher temperature. It was possible that urea may exert its effect by changing the iceberg structure of water. Also it was considered that urea acts as indirect structure breaker when added to water.. For non-ionic surfactant solutions urea may induce micelle formation by breaking down the structure of water thus promoting micelle formation and increases solubility. Increasing temperature from 25° to 35° causes a positive temperature effect. The order of efficiency of non-ionic surfactant solutions containing 0.2 mole/l urea toward chloramphenicol at 25° and 35° can be arranged as followed: Emulgin C₁₀₀₀ > Tween 80 > Emulgin C₁₅₀₀ > Tween 20 > Myrj 52 > Myrj 59.

On comparing the amount of chloramphenicol solubilized by each surfactant micelle as g per g in the presence and absence of different concentration of potassium chloride, it was obvious that the presence of electrolyte produced an increase in the amount of chloramphenicol solubilized per gram micelles at the two temperatures investigated .

Kuriyama^{7,8} explained that the addition of electrolyte at a specific temperature did not necessarily increase the micellar weight but it can affect the degree of hydration of micelles.

The salting effect of potassium chloride would be more pronounced with the more hydrophilic longer polyoxyethylene chain compounds, therefore it may decrease their solubilizing efficiency toward chloramphenicol, than short chained non-ionic surfactants .

The salting out of non-ionic surfactants from solutions was increased by increasing electrolyte concentration and with decreasing radii of hydrated ions. For this reason the increase in potassium chloride concentration from 0.01 mol/l to 0.1 mole/l at 25° may produce a decrease in the solubilizing efficiency of these surfactant solutions toward chloramphenicol. Thus by increasing electrolyte concentration it was claimed²⁰ that there was firstly a removal of hydrogen bonded water molecules from the ether oxygens of the ethylene oxide chain, and secondly that the extent of hydration of the ethylene oxide chain was determined by the closeness of approach of the potassium ion to the ether oxygens, Temperature rise from 25° to 35° in all non-ionic surfactant solutions, containing different concentrations of potassium chloride , causes a positive temperature effect. At 35° an increase in electrolyte concentration from 0.1 to 0.5 mole/l causes an increase in the solubilizing efficiency of the non-ionic surfactant solutions containing these concentrations despite the theory of salting out of surfactants upon increasing electrolyte concentration, where at 25° an increase in potassium chloride concentration from 0.01 to 0.1 mole/l causes a decrease in the solubilizing efficiency of the non-ionic surfactant solutions perhaps due to salting out of the surfactant by increasing electrolyte concentration, but further increase of the electrolyte concentration from 0.1 to 0.5 mole/l , causes an increase in the solubilizing efficiency of the non-ionic surfactants., as shown in Figure 5 and Table 2.

The effect of different additives on the distribution of chloramphenicol between the micellar and aqueous phases if compared with the distribution coefficient obtained in the presence of the different additives was shown in Table 3.

It can be observed that the presence of 5% w/v P/E.G 600 caused an increase in K_m value, i.e. increased the concentration of chloramphenicol in the micellar phase. Further increase in P.E.G 600 up to 10% w/v caused more increase in the K_m value. On the other hand non-ionic surfactant solutions containing 5% w/v propylene glycol caused slight increase in K_m value. This was also the case on the addition of 10% w/v glycerol as it produced an increase in the K_m value. The addition of urea in 0.2 molar concentration to the surfactant solutions tend to increase chloramphenicol in the micellar phase more than in the aqueous phase, hence its presence caused an increase in K_m value of the different non-ionic surfactants.

Generally, the increase in temperature from 25° to 35° caused a decrease in the K_m value obtained. This may be due to the relative increase in the solubility of chloramphenicol in both aqueous and micellar phases by different extent and each temperature. The increase in potassium chloride concentration in the non-ionic surfactant solutions at 35° from 0.01 to 0.1 or 0.5 mole/l, produced an increase in K_m value. On the other hand increase in potassium chloride concentration at 25° from 0.01 mole/l, caused a decrease in K_m value. Further increase in potassium chloride, e.g 0.5 mole/l, caused a significant increase in K_m value. This may be due to the salting out effect which was more pronounced at lower temperature by relatively smaller concentration of electrolyte concentration. The presence of higher concentration of electrolyte especially at higher temperature may induce micellization and the incorporation of more amount of solubilizate within the micelles which were expected to be larger in volume at this relatively elevated temperature.

Table 1 : Solubility of Chloramphenicol by Non-ionic Surfactant Solutions Containing Different Organic Additives .

Surfactant	Solubility of chloramphenicol g/g surfactant in the presence of different organic additives x 10 ⁻²													
	Surfactant		+ 5% P.E. G ₆₀₀		+ 10% P. E. G ₆₀₀		5% Propylene Glycol		10% glycerol		0.2 ole/l.			
	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°		
Tween 20	7.54	8.64	8.07	8.05	12.31	12.31	6.73	7.39	7.45	10.37	8.30	9.83		
Tween 80	8.75	12.24	10.00	10.12	14.02	15.34	8.68	8.97	8.73	11.11	9.37	11.04		
Emulgin C ₁₀₀₀	9.77	12.17	12.73	12.89	15.56	17.04	10.88	11.09	10.79	9.61	10.80	11.44		
Emulgin C ₁₅₀₀	8.25	9.73	10.14	10.25	13.19	13.89	9.04	10.21	10.21	7.94	8.94	10.46		
Myrij 52	6.34	8.20	7.96	6.86	6.36	10.51	6.85	8.46	7.58	7.28	7.67	8.00		
Myrij 59	3.47	3,88	5.85	4.25	6.8	9.4	9.09	4.91	4.99	5.17	4.58	7.81		

Table 2 : Solubility of chloramphenicol by non ionic surfactant solutions containing different concentrations of potassium chloride

Surfactant	Solubility of chloramphenicol g/g surfactant in the presence of potassium chloride x 10 ⁻²									
	Surfactant alone		0.5 mole/L kcal		0.1 mole/L kcal		0.01 mole/L kcal		0.01 mole/L kcal	
	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°
Tween 20	7.54	8.64	6.92	8.26	5.46	6.89	6.44	5.84		
Tween 80	8.75	12.24	9.04	9.86	6.45	8.09	8.36	7.34		
Emulgin C1000	9.77	12.17	12.09	12.07	9.19	10.55	10.46	9.71		
Emulgin C1500	8.25	9.73	9.19	10.92	7.83	8.65	8.39	8.58		
Myrj 52	6.34	8.2	5.99	7.14	4.86	6.22	5.85	5.06		
Myrj 59	3.47	3.88	3.22	4.78	3.1	4.00	4.44	2.25		

Table 3 : Effect of Different Additives on the Distribution Coefficients (K_m) of Chloramphenicol between micellar and aqueous phases at different temperatures .

Surfactant Type	Distribution coefficient (K_m) calculated from solubility measurements																	
	Surfactant containing the following																	
	(A) 25°	(B) 35°	(C) 25°	(D) 35°	(E) 25°	(F) 35°	(G) 25°	(H) 35°	(I) 25°	(I) 35°	(I) 25°	(I) 35°	(I) 25°	(I) 35°				
Tween 20	20	19	22	16	33	25	18	16	20	21	23	17	26	19	14	18	19	12
Tween 80	23	24	26	20	39	32	23	20	24	24	26	20	33	22	17	20	25	15
Emulgin C ₁₀₀₀	27	28	34	27	43	35	29	24	30	20	29	21	45	28	24	27	31	21
Emulgin C ₁₅₀₀	22	22	28	22	36	29	24	22	29	16	24	19	36	24	21	23	25	18
Myrj 52	18	19	14	23	23	22	19	18	22	15	21	22	16	16	13	16	17	11
Myrj 59	11	3	15	9	19	19	12	11	13	11	12	10	13	11	8	9	12	5

(A) Surfactant alone

(B) 5% T. E. G₆₀₀(C) 10% P. E. G₆₀₀

(D) 5% propylene glycol

(E) 10% Glycerol

(F) 0.2 Mole/L urea

(G) 0.5 Mole/L. KCl

(H) 0.1 Mole/L. KCl

(I) 0.01 Mole/L. KCl

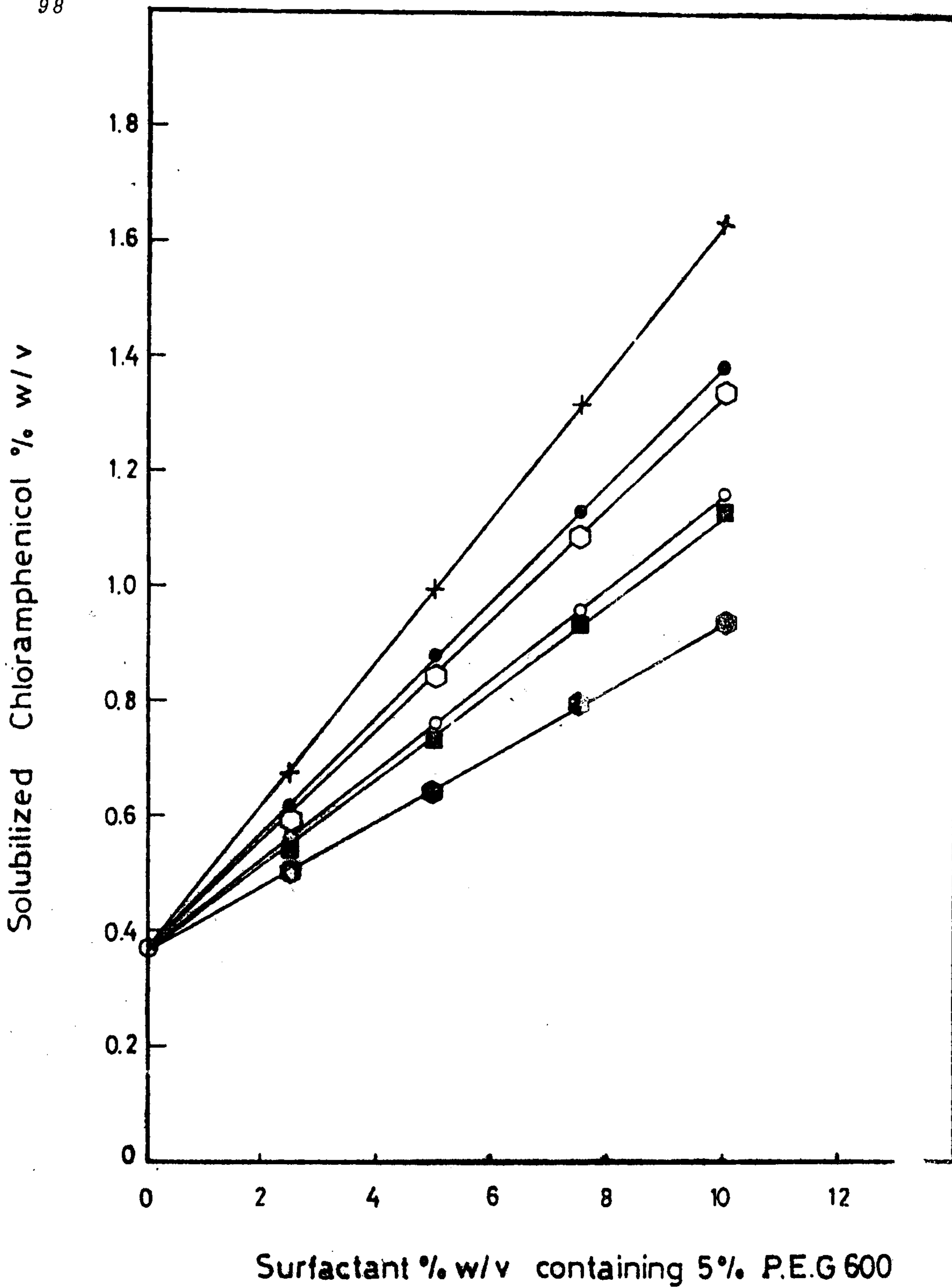


Fig.(1) Solubility of Chloramphenicol in non-ionic Surfactant solutions containing 5% P.E.G 600 at 25°.

Key: x Emulgin C1000. ● Emulgin C1500. ○ Tween 80.
o Tween 20. ■ Myrj 52. ◼ Myrj 59.

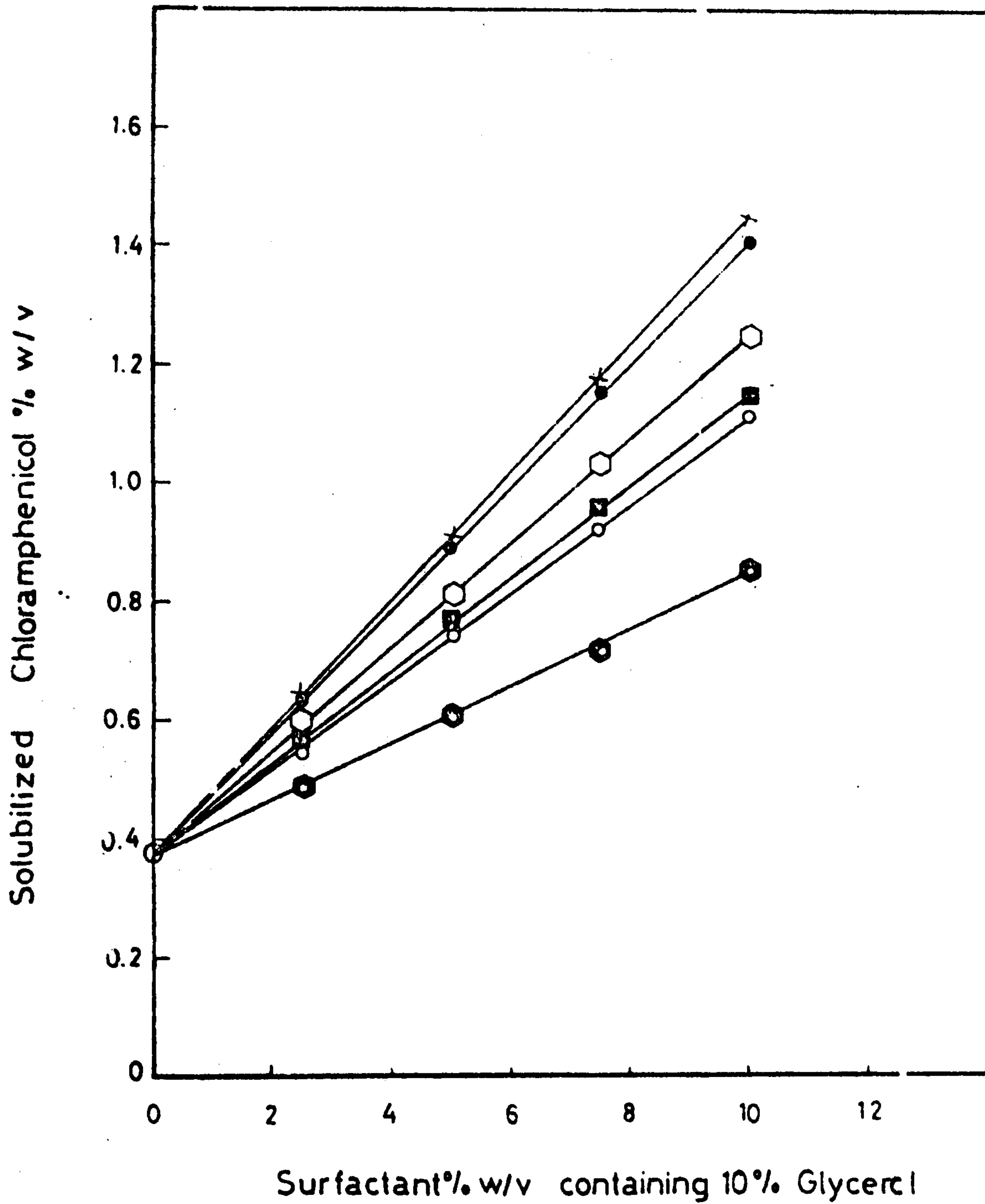


Fig.(2) Solubility of Chloramphenicol in non-ionic Surfactant solutions containing 10% Glycerol at 25°.

Key: The same as Fig.(1).

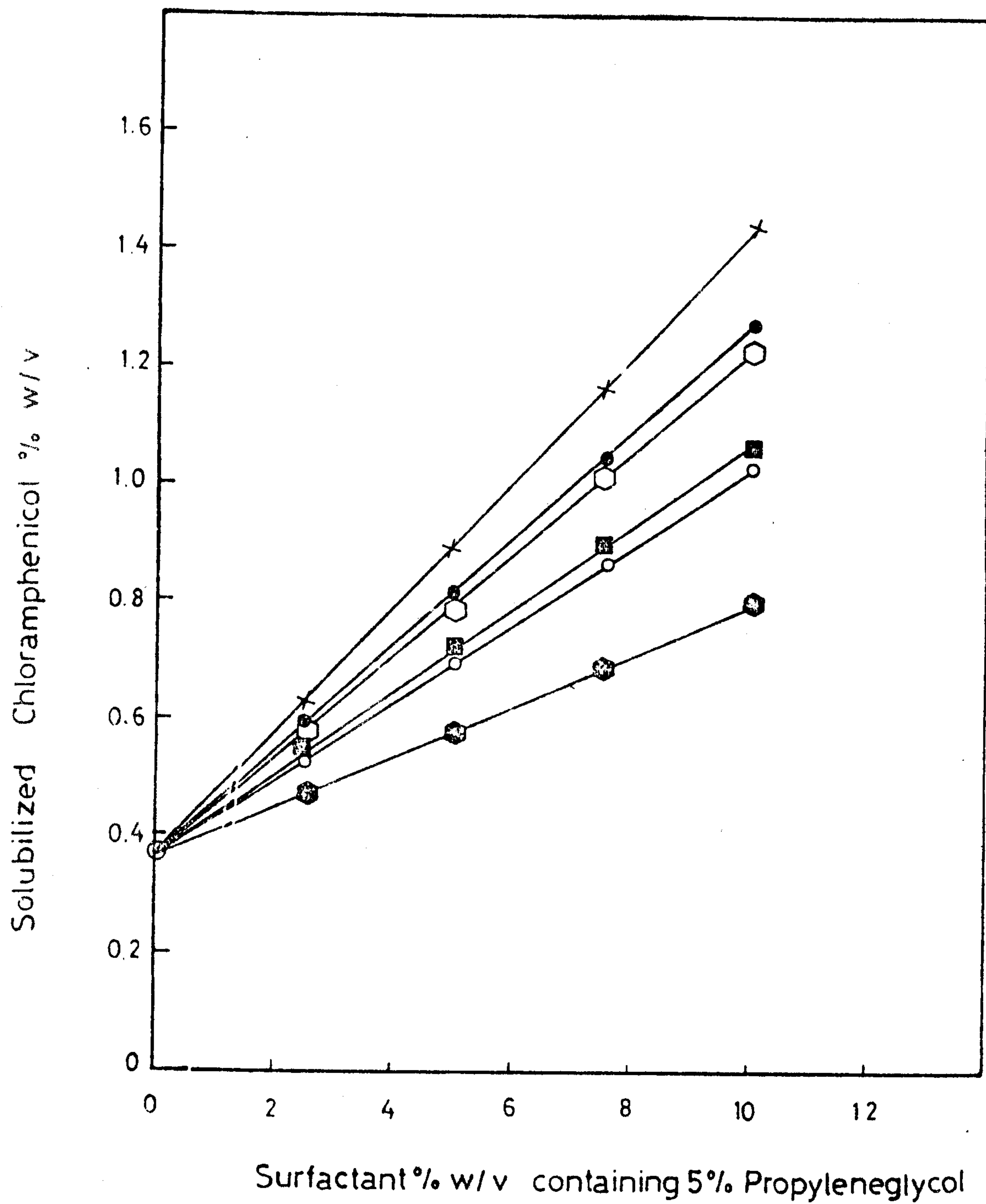


Fig.(3) Solubility of Chloramphenicol in non-ionic
Surfactant solutions containing 5% Propyleneglycol
at 25°.

Key: The same as Fig.(1)

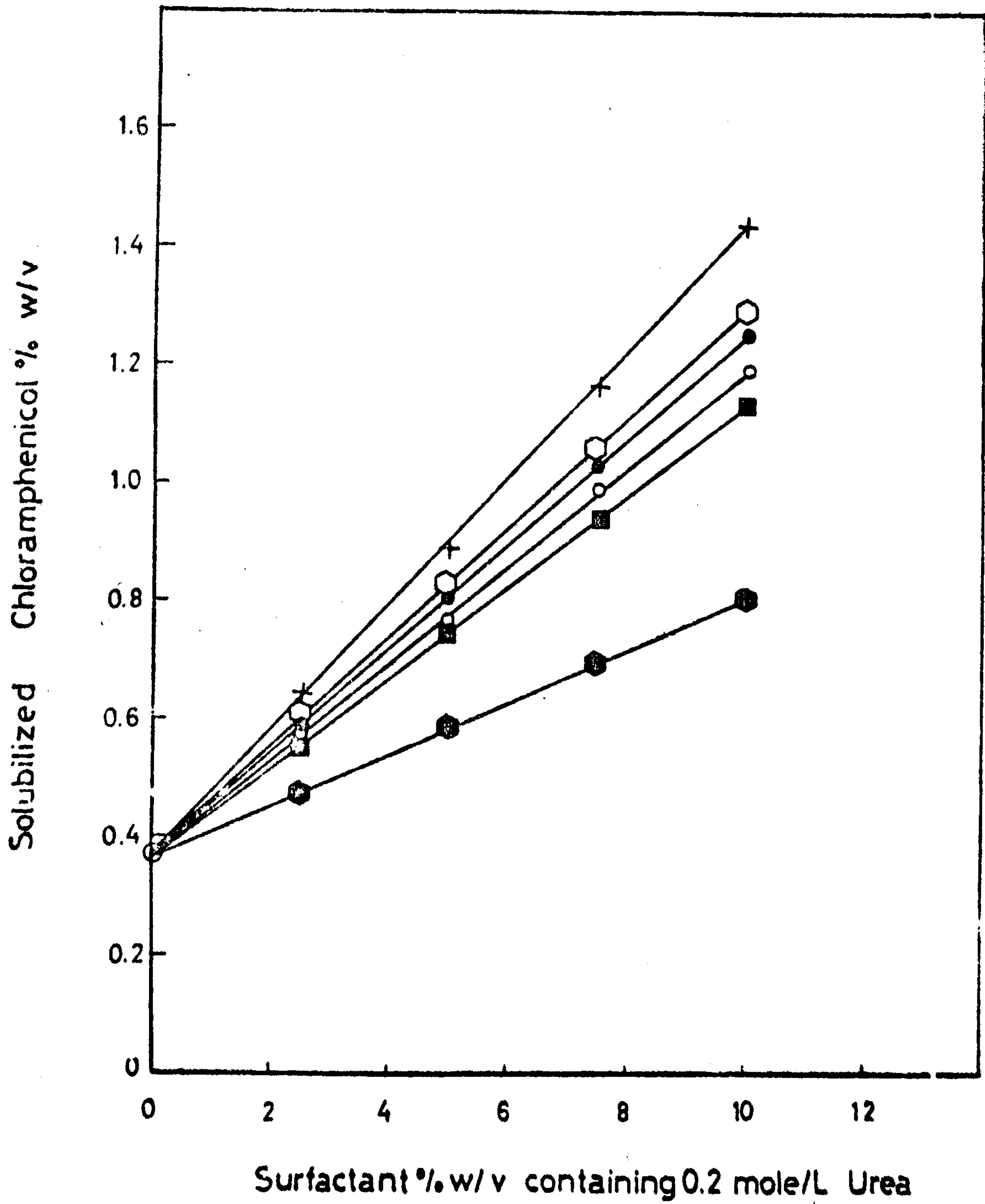


Fig.(4) Solubility of Chloramphenicol in non-ionic Surfactant solutions containing 0.2 mole/L solution Urea at 25°.

Key: The same as Fig.(1).

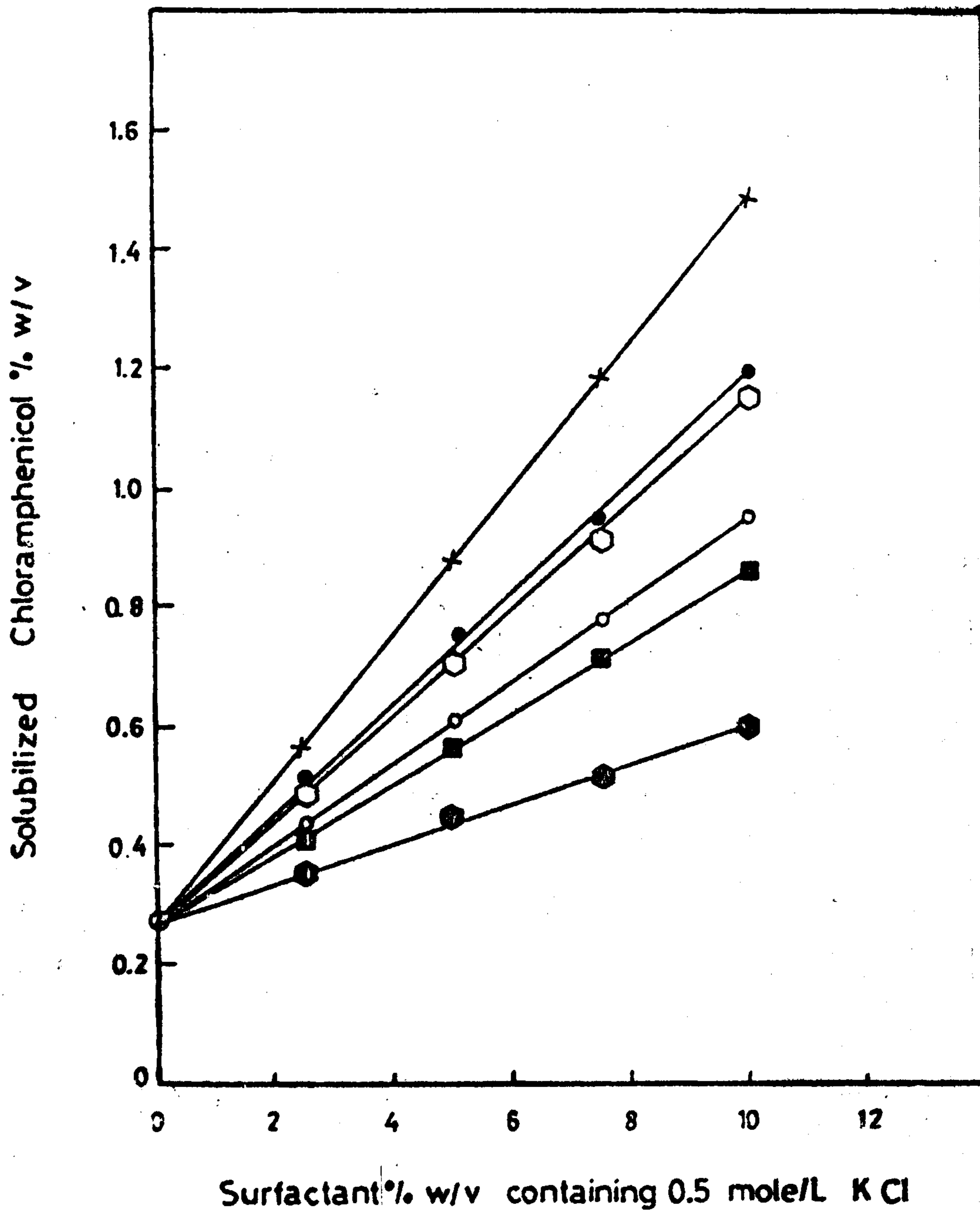


Fig.(5) Solubility of Chloramphenicol in non-ionic Surfactant solutions containing 0.5 mole/L KCl solution of pH 2 at 25°.

Key: The same as Fig.(1)

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تأثير اضافات مختلفة على الاذابة الشبكية للكلورا هينكول.

أحمد السيد أبو طالب وعلى عبد الظاهر

درس تأثير الاضافات العضوية والغير عضوية على تذويب الكلورا هينكول بواسطة منشطات السطح غير المتأينة عند درجتى حراره مختلفتين

وقد استخدمت الاضافات التالية : عديد ايثلين جليكول ٦٠٠ هـ البرولين جليكول هـ الجلسرول هـ اليوريا وكوريد البوتاسيم . وقد احدثت اليوريا تأثيرا طفيفا على مقدرة الاذابة لمنشطات السطح غير المتأينه بينما أثر كوريد البوتاسيم تأثيرا كبيرا .

ولقد وجد من بين الاضافات العضوية أن عديد ايثلين جليكول ٦٠٠ هـ زاد مقدرة الاذابة لمنشطات السطح غير المتأينه اكثر من كل من الجلسرول والبرولين جليكول .