Bull. Pharm. Sci., Assiut University,
Vol. 14, Parts 1&2, PP 35-45

FACTORS AFFECTING CHLORDIAZEPOXIDE SOLUBILIZATION BY NON-IONIC SURFACTANTS

A. A. Abdel Rahman, A.E. Aboutaleb and E.M. Samy .

Dept. of Industrial Pharmacy, Faculty of Pharmacy,
Assiut University, Assiut, Egypt

ABSTRACT

Ceratain factors affecting chlordiazepoxide solubilization in series of non-ionic surfactant solutions were investigated viz., surfactant structure, the pH, the temperature and the incorporation of certain hydroxylated organic additives.

Polysorbate 80 was more efficient for the drug solubilization than polysorbate 20 and Brij 35 was more efficient than Brij 58. On the other hand Eumulgin C1000 was found to be more efficient than Eumulgin C1500 and Myrj 52 was more than Myrj 53 than Myrj 59.

Increasing the pH of Eumulgin and Brij solutions caused a gradual decrease in the quantity of the drug solubilized.

Mukerjee treatment was adopted to quantify the role of both the core and capsular regions of Myrj micelles in solubilizing the drug.

The drug was solubilized in Eumulgin and Brij series containing 5 or 10% w/v propylene glycol, glycerol, PEG 400 and PEG 4000. Brij 35 containing 5% w/v propylene glycol was the most efficient solubilizer for chlordiazepoxide.

The distribution coefficient, Km, of the drug between the micellar and aqueous phases was calculated.

INTRODUCTION

Bringing water - insoluble drugs into solution is one of the main problems encountered in foumulating such drugs in liquid dosage forms.

Many literatures [1-3] dealt with the solubilization of such drugs, yet, the problem of each drug in this aspect must be considered separately, irrespective of the behaviour of other drugs. The investigation of the solubilized system [4] of such drugs concerning the mode of incorporation [5] stability [6,7], pharmacological availability [8], effect of pH [9,10], effect of hydroxylated additives [11-15] are other goals of investigating solubilization.

Chlordiazepoxide, a 1.4-benzodiazepine derivative, used as a tranquillizer and a hypnotic agent, is practically water - insoluble. The aim of the present work was solubilizing it in different non-ionic surfactants in solutions of distilled water, of different pH values and containing different organic hydroxylated additives as propylene glycol, glycerol, PEG 400 and PEG 4000. The role of both the core and capsular regions of Myrj micelles on chlordiazepoxide solubilization was followed up adopting Mukerjee treatment [5].

EXPERIMENTAL

Materials:

Chlordiazepoxide (Hoffman - La Roche Co. Ltd, Basle, Switzerland).

The non-ionic surfactants:

Polysorbates: Polyoxyethylene (20)sorbitan monolaurate(Polysorbate 20) and polyoxyethylene(20)sorbitan monooleate(Polysorbate 80), (Atlas Chemical Industries, Inc. Willimington Delaware, U.S.A.).

Eumulgins: Cetyl stearyl alcohol with (20) ethylene oxide units

(Eumulgin C1000) and cetyl stearyl alcohol with (50) ethylene oxide units (Eumulgin C1500), (Henkel International, Dusseldorf, Germany).

Myrjs: Polyoxyethylene (40) stearate (Myrj 52), polyoxyethylene (50) stearate (Myrj 53) and polyoxyethylene (100) stearate (Myrj 59), (Atlas Chemical Industries, Inc., Willimington, Delaware, U.S.A.).

Brijs: Polyoxyethylene (23) lauryl ether (Brij 35) and polyoxyethylene (20) cetyl ether (Brij 58), (Atlas Chemical Industries, Inc., Willimington Delaware, U.S.A.).

The number between brackets denotes the ethylene oxide groups in the surfactant molecule.

Buffer components: Sodium dibasic phosphate and citric acid (McIlvian buffer), (BDH Poole, England).

The additives: Propylene glycol (Prolabo, Pelee, Paris, France), Glycerol (BDH, Poole, England) and PEG 400 and PEG 4000 (Sigma Chemical Company, U.S.A.).

Equipment:

Thermostatically controlled water bath with a shaker (Siety company, Cairo, Egypt). Self-recording UV spectrophotometer SP 400 (Pye Unicam, England).

A pH meter and a centrifuge (Prolabo, Pelee, Paris, France).

Methods:

Solubilization of chlordiazepoxide in the investigated surfactant solutions:

Excess of the drug was equilibrated with 10 ml of the investigated solutions in screw capped tubes at 25 & 35°C. The investigated solutions were: non-ionic surfactant solutions in distilled water, non-ionic surfactant solutions of pH 4.0, 6.0 and 7.4 adjusted by McIlvian and non-ionic surfactant solutions containing 5 & 10% w/v of propylene glycol, glycerol, PEG 400 and PEG 4000.

The screw capped tubes were shaken top to bottom for 4 days. After equilibrium has attained samples were withdrawn from the supernatant and assayed spectrophotometrically for drug content at 245 nm against a similar blank. It was found that the presence of surfactant and or the additive solution, in the dilution range used, neither interferred with the spectrophotometric assay of the drug nor they made any shift of its maximum absorbance [11,15]. The drug was certainly stable over the equilibrium time solubility period [11].

RESULTS AND DISCUSSION

The solubility of chlordiazepoxide in the investigated non-ionic surfactant solutions increased linearly, by increasing surfactant concentration, Figures 1-4, confirming the partition model [16] of chlordiazepoxide solubilization. The systems investigated were always one liquid plus solid representing true micellar solubilization of this drug [1-4].

Cloudness was not observed in the solubilized systems because of the relatively high content of ethylene oxide moities in the surfactant molecules investigated, which gives rise to surfactants with relatively high cloud points. Furthermore, chlordiazepoxide did not depress the cloud points of the investigated surfactants even at the highest temperature investigated.

The solubility of chlordiazepoxide in the investigated non-ionic surfactant solutions (mg/g) which are the slopes of the solubility isotherms is shown in Table 1. It

is evident from Table 1 and Figures 3&4 that polysorbate 80 with longer hydrocarbon chain is more efficient as a solubilizer than polysorbate 20. Extending the polyoxyethylene chain length in a homologous series of surfactants leads to a decrease in the amount of the drug solubilized. That is why Eumulgin C1500 is less efficient than Eumulgin C1000 and Myrj 59 is less efficient than Myrj 53 than Myrj 52, Table 1 and Figures 1-4. These results agreed with previous findings on benzoic acid and salicylamide [16] and other solutes [17] solubilization by Myrj series.

Brij 35, although shorter in the hydrocarbon chain and longer in the ethylene oxide moiety than Brij 58, was found to be more efficient for the drug solubilization, Table 1 and Figure 1. This could be interpreted on the basis of unlinked ethylene oxide chains which form mixed micelles and also some impurities present in certain surfactants [16].

Brij 35 was found to be the most efficient solubilizer for chlordiazepoxide at 25°C followed by Brij 58 then Eumulgin C1000 > Eumulgin C1500 > polysorbate 80 > polysorbate 20 > Myrj 52 > Myrj 53 > Myrj 59.

Raising the temperature of the investigated solutions from 25 to 35°C caused a positive temperature effect, i.e., increase in the amount of chlordiazepoxide solubilized. An exceptional Myrj series, Figures 1-4 and Table 1. This positive temperature effect could be attributed to the increase in the aggregation number of surfactant monomers within the micelles, forming larger ones[16].

In Myrj series however, raising temperature may increase the translational freedom of the monomers within the micelles, a factor opposing the micellar formation[16].

The effect of solutions pH on the solubility of drugs was documented [8]. For investigating the effect of adjusting the pH of the investigated non-ionic surfactant solutions toward chlordiazepoxide solubilization, Eumulgin and Brij solutions were adjusted to pH 4.0, 6.0 and 7.4. Eumulgin and Brij were chosen for conducting such a study as they are etherial linkage surfactants which rendering them more stable than polysorbates and Myrjs which are ester linkage. Furthermore, Eumulgins and Brijs are more efficient as solubilizers than polysorbates and Myrjs.

The investigated non-ionic surfactant solutions of controlled pH gave linear isotherms at 25&35°C For chlordiazepoxide solubilization, Figures 5&6, the slopes of which represent the solubility of the drug mg/g surfactant, Table 1. the solubility of the drug generally increased at the investigated solutions of lower pH values compared to the higher pH ones except for Eumulgin C1000. This may be attributed to the solubility of the non-dissociated form of the drug, as the drug moleocule contains Cl, O and tertiary N and of pka of nearly 3. As the pH of the investigated solutions increased from 4.0 to 6.0 to 7.4 their solubilizing efficiencies were generally decreased, as the dissociated form of the drug become hardly incorporated within the micellar core. Also, as the pH increases, the amount of citric acid engaged in McIlvian buffer decreased and sodium dibasic phosphate increased. The former probably acts as a co-solubilizer and assists in drug solubilization while the later, as an electrolyte has a salting out effect on the surfactant molecules[11], leading to a decrease in their solubilizing efficiencies.

Adjusting the surfactant solutions to pH 4 did not lead to sig-

nificant change in their solubilizing efficiencies toward chlordiazepoxide compared to the non-adjustable ones except for Brij 35 and Brij 58. A positive temperature effect was observed by raising the temperature of the pH adjusted surfactant solutions, Table 1, except for Brij 35 at pH 4 and 6 as the factors opposing micellization may increased on raising the temperature in this exception.

The theoretical treatment proposed by Mukerjee [5,19] and by Goodhart and Martin [20] has been adopted to quantify the role of both the core and the capsular regions of Myrj micelles in solubilizing chlordiazepoxide. Assuming that it will be distributed between the micellar core composed of the stearyl groups (R) and the micellar capsule, consisting of the ethylene oxide groups (Eo). The micellar solubility was expressed as equivalents of chlordiazepoxide per equivalent of (Eo) groups. The amount of the drug solubilized (S) in equivalent per liter of solution will be:

$$S = a\ C_{Eo} + b\ C_R$$

where C_{Eo} and C_R are the concentrations of chlordiazepoxide in equivalent per liter of (Eo) and (R) groups respectively, (a) and (b) are proportionality constants. On dividing by C_{Eo} one obtain:

$$S/C_{Eo} = a + b\ C_R/C_{Eo}$$

Thus if S/C_{Eo} in equivalent per equivalent is plotted against C_R/C_{Eo}, Table 2, a linear relationship should be obtained, Figure 7, with the intercept (a) representing the solubilization in the capsule equivalent of solubilizate per equivalent of (Eo) groups and with the slope (b) representing the solubilization in the core (equivalent of solubilizate per equivalent of (R) groups). The values of (a) and (b) at 25&35°C are shown in Table 3. It could be concluded that chlordiazepoxide was solubilized mainly in the core of Myrj micelles. Furthermore, the amount of the drug solubilized in the capsule decreased by extending the polyoxyethylene chain from 40 (Myrj 52) to 100 (Myrj 59) at the two temperatures investigated.

The solubilizing efficiencies of Eumulgin and Brij solutions containing 5% w/v propylene glycol is shown in Table 4. At the two temperatures investigated, it is noticed that this concentration of propylene glycol generally caused an increase in the solubilizing efficiencies of the investigated surfactant solutions toward chlordiazepoxide. This could be attributed to the suppressive effect of propylene glycol on the liquid crystal formation in the nonionic surfactant solutions [16].

Incorporating 10% w/v propylene glycol in the investigated solubilizers decreased their solubilizing efficiencies at 25&35°C, Table 4 and Figures 8&9. The observed decrease may be attributed to the increased hydrophilicity of the micelles by incorporating such a higher concentration of propylene glycol in the capsule rendering the latter expanded, thus decrease the relative volume of the core mainly responsible for solubilization to the whole micellar volume[11]. Raising the temperature of the investigated solutions containing 5&10% w/v propylene glycol caused a positive effect, Table 4.

Incorporation of 5&10% w/v glycerol in Eumulgin and Brij solutions caused a decrease of their solubilizing efficiencies toward chlordiazepoxide at 25&35°C except for Brij 35 at 25°C, Table 4 and Figures 10&11. This decrease may be due to the hydration of the micelles due to the addition of such a hydrophilic additive, as the decrease was more pronounced in 10% w/v concentration[9].

Raising the temperature of the previous solutions caused a negative effect in those solutions containing 5% w/v glycerol and vice-versa 10% w/v.

The solubilizing efficiencies of Eumulgin and Brij solutions containing 5&10% w/v PEG 400 toward the drug at 25&35°C is shown in Table 4. It is obvious that the presence of this glycol in both concentrations caused a marked decrease in the amount of chlordiazepoxide solubilized at both temperatures than in non-ionic surfactant solutions alone except for Brij 35 which showed the reverse. Raising the temperature for the investigated solutions containing 5&10% w/v PEG 400 causes a negative effect except for Brij 35 containing 10% w/v.

The effect of 5&10% w/v PEG 4000 on the solubilizing efficiencies of Eumulgin and Brij solutions toward chlordiazepoxide at 25&35°C is shown in Table 4 and Figures 12&13. It is noted that the incorporation of PEG 4000 decreased the solubilizing efficiencies of the investigated solutions except for Brij 35 at both temperatures (nearly two folds increase). Increasing the molecular weight of PEGs from 400 to 4000 increased its co-solubilizing effect in 5% w/v at 25°C.

Brij 35 containing 5&10% w/v PEG 4000 proved to be the most efficient solubilizer for chlordiazepoxide at the two temperatures.

The linear solubility isotherms obtained for chlordiazepoxide solubilization in non-ionic surfactant solutions alone and containing the additives at 25&35°C are indicative of following the partition model of solubilization [11,20]. The distribution of the drug between the micellar pseudophase and the aqueous phase, the Km, in the different investigated non-ionic surfactant solutions alone and containing the additives at 25&35°C is shown in Table 5.

On raising the temperature, generally a decrease in the Km values are observed indicating an increase in chlordiazepoxide in the aqueous continuous phase than in the micellar phase.

The Km values of chlordiazepoxide generally increased in the presence of 5% w/v propylene glycol and decreased in the non-ionic solutions containing rest of the investigated additives except for Brij 35 showing an increase in Km values at both temperatures.

At the non-ionic surfactant of controlled pH, a marked decrease in the Km values was observed in pH 4 and pH 6 and the reverse happened in pH 7.4.

Table 1: Solubilization of chlordiazepoxide in non-ionic surfactant solutions of different pH values.

Surfactant	Chlordiazepoxide mg/g surfactant In distilled water 25°C	35°C	of pH 4 25°C	35°C	of pH 6 25°C	35°C	of pH 7.4 25°C	35°C
Polysorbate 20	17.74	18.58						
Polysorbate 80	20.64	21.57						
Eumulgin C 1000	24.51	29.13	24.22	30.38	23.36	26.15	20.86	20.88
Eumulgin C 1500	23.22	24.29	17.04	26.15	17.60	23.03	17.52	19.56
Myrj 52	15.67	12.17						
Myrj 53	14.16	8.98						
Myrj 59	6.72	5.59						
Brij 35	30.70	38.00	30.62	15.98	29.33	22.07	13.86	21.59
Brij 58	24.76	29.09	27.69	36.00	20.19	24.08	23.87	25.25

Table 2: Distribution of chlordiazepoxide between the cores and capsules of Myrj micelles calculated by Mukerjee's treatment [5,19].

Surfactant	Surfactant Molecular Weight	Weight of Ethylene Oxide Part	S/C_{Eo}, at 25°C	S/C_{Eo}, at 35°C	C_R/C_{Eo}	Ratio of Amount of Chordiazepoxide in Capsule and Core at 25°C	Ratio of Amount of Chordiazepoxide in Capsule and Core at 35°C
Myrj 52 ($C_{17}E_{40}$)	2046	1777	0.0267	0.0198	0.025	0.203	0.203
Myrj 53 ($C_{17}E_{50}$)	2486	2217	0.0232	0.0140	0.02	0.197	0.197
Myrj 59 ($C_{17}E_{100}$)	4686	4417	0.01118	0.0092	0.01	0.185	0.185

Table 3: Amount of chlordiazepoxide incorporated in capsule (a) eq/eq and core (b) eq/eq for the Myrj series calculated by Mukerjee's method [5,19].

Surfactant	25°C		35°C	
	a	b	a	b
Myrj 52	2.67	13.136	1.98	9.756
Myrj 53	2.32	11.793	1.40	7.124
Myrj 59	1.12	6.059	0.92	4.969

Table 4: Solubilization of chlordiazepoxide in non-ionic surfactant solutions containing various additives.

Non-ionic Surfactant	Solubility of chlordiazepoxide mg/g surfactant																	
	Surfactant in dist. water		Surfactnat+Propylene glycol 5%			10%	Surfactant + Glycerol 5%			10%	Surfactant+P.E.G.400 5%			10%	Surfactant+P.E.G.4000 5%			10%
	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C
Eumulgin C_{1000}	24.5	29.1	26.2	26.4	19.5	25.4	23.8	18.8	17.0	21.5	11.4	7.9	15.6	16.5	25.0	18.2	10.1	10.5
Eumulgin C_{1500}	23.2	24.3	21.6	22.7	12.8	17.1	21.3	16.5	9.1	11.6	16.5	13.7	9.4	10.1	18.8	13.5	5.0	9.8
Brij 35	30.7	38.0	76.9	75.1	27.8	32.9	55.4	39.6	19.7	27.1	42.4	55.0	49.1	60.1	70.7	66.7	35.7	39.5
Brij 58	24.8	29.1	26.4	27.8	16.4	20.2	24.8	19.2	13.2	13.1	19.7	15.9	11.7	13.1	21.4	15.7	15.0	17.0

Table 5: Effect of different additives on the distribution coefficient (km) of chlordiazepoxide between Micellar and aqueous phases in non-ionic surfactant solutions.

Surfactant	Distribution Coefficient (Km)																							
	Surfactant Alone		Surfactant+Propylene glycol 5%			10%	Surfactant+Glycerol 5%			10%	Surfactant+P.E.G.400 5%			10%	Surfactant+P.E.G.4000 5%			10%	Surfactant of pH 4		6		7.4	
	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C	25°C	35°C
Eumulgin C_{1000}	124	94	149	132	92	94	70	88	105	105	23	13	61	51	90	88	59	45	36	47	100	97	143	159
Eumulgin C_{1500}	115	79	129	119	57	67	61	75	52	49	34	23	32	29	69	69	27	26	26	37	91	88	121	143
Brij 35	154	133	513	426	143	128	178	193	125	132	201	116	179	171	276	316	209	161	50	26	120	80	86	180
Brij 58	106	82	150	142	80	77	75	92	76	65	41	31	46	41	82	78	93	74	42	58	90	91	161	201

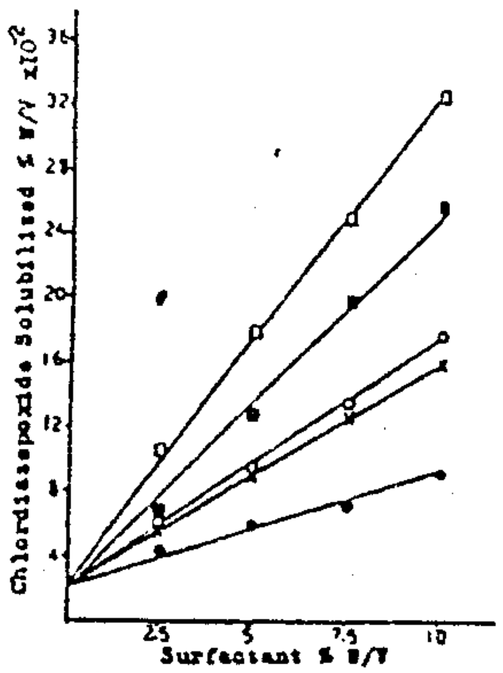

Fig.(1): Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions at 25°.

Key: □ Brij35, ■ Brij58, ○ Myrj52, × Myrj 53, ● Myrj 59.

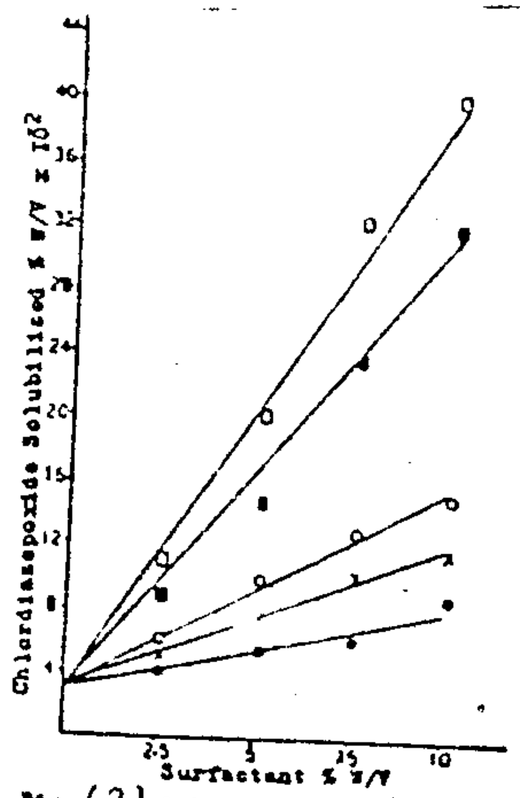

Fig.(2): Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions at 35°.

Key : The Same as Fig. 1

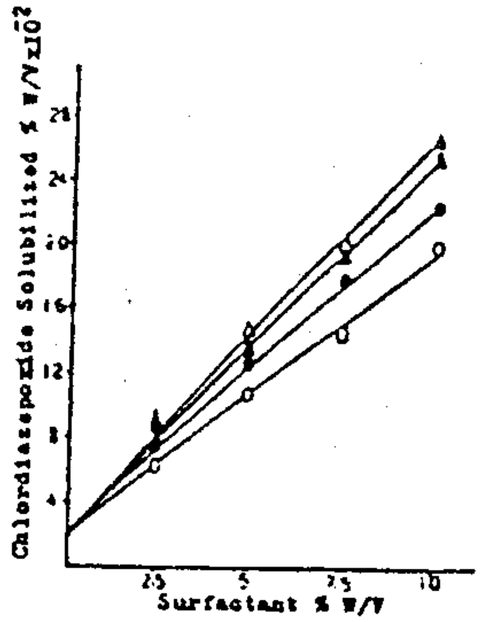

Fig.(3): Solbility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions at 25°.

Key: Δ Rumulgin C1000, ▲ Rumulgin C1500, ○ Polysorbate 20, ● Polysorbate 80.

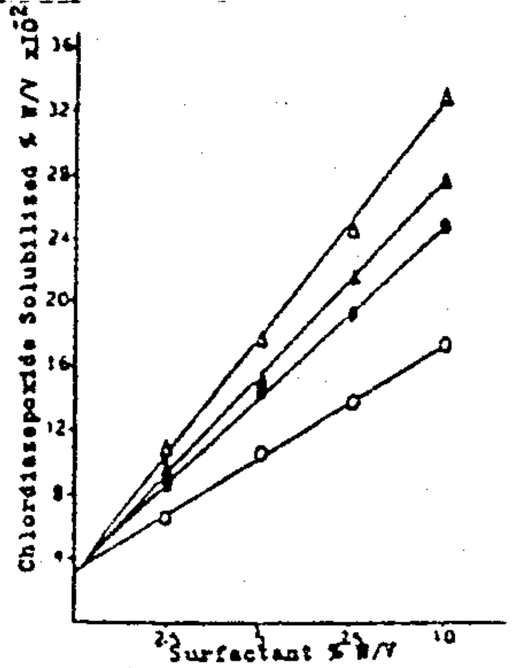

Fig.(4): Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions at 35°.

Key : The Same as Fig. 3

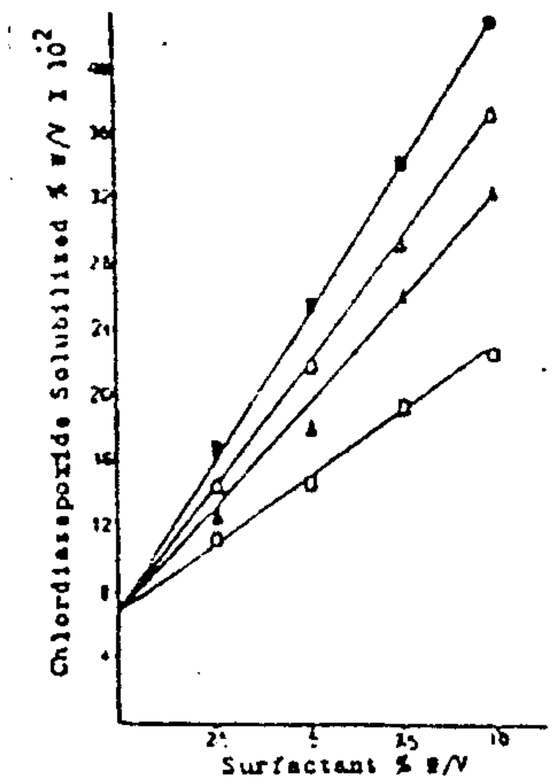

Fig.(5): Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions of pH 4 at 35°.

Key : The Same as Figs. 1, 3

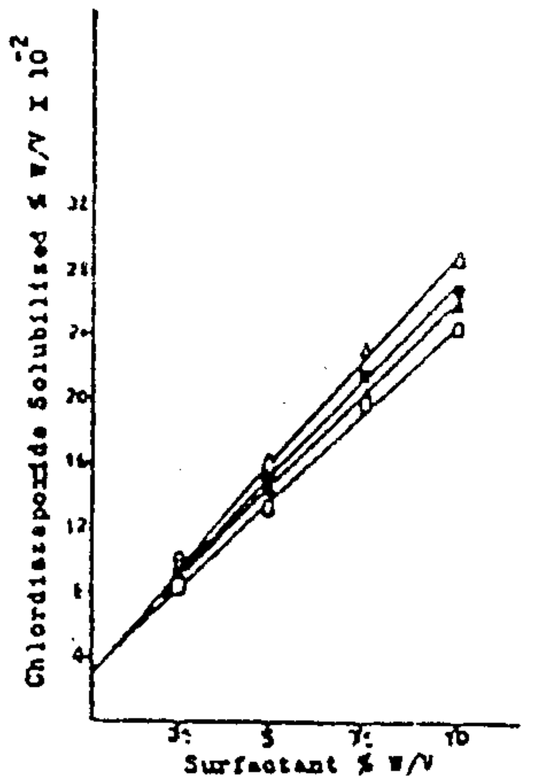

Fig.(6): Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions of pH 6 at 35°.

Key : The Same as Figs. 1, 3

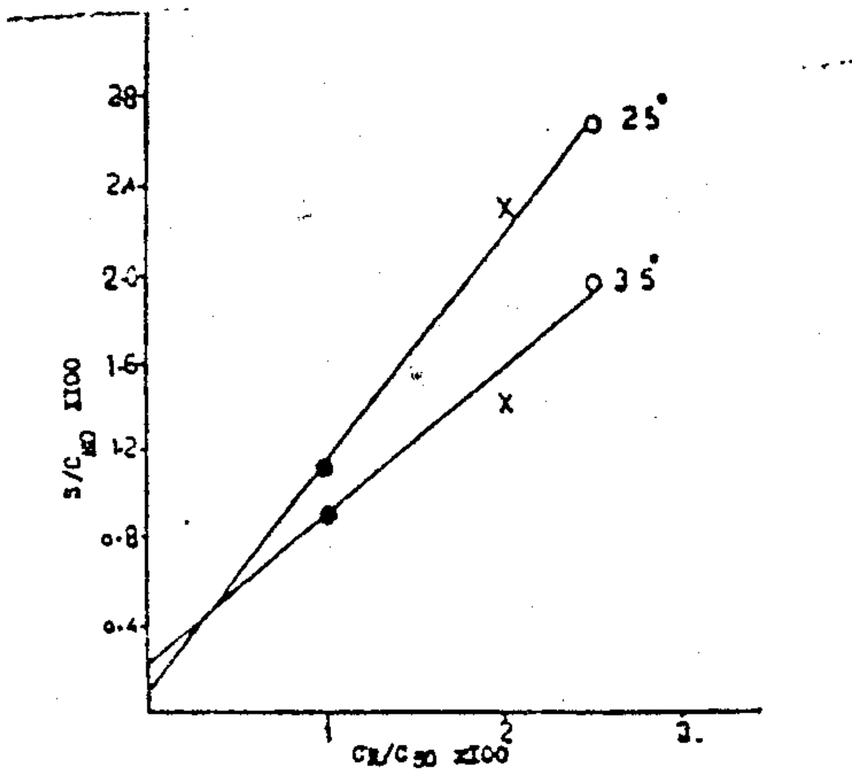

Fig.(7): Micellar Solubilization of Chlordiazepoxide in Polyoxyethylene-Stearate Solutions at Different Temperatures.
The Number of Equivalents Solubilized by Equivalent Ethylene Oxide Group (S/C_{EO}) is Plotted Against the Molar Ratio of Alkyl Ethylene Oxide (C_R/C_{EO}) for the Surfactants.

Key : The Same as Fig. 1.

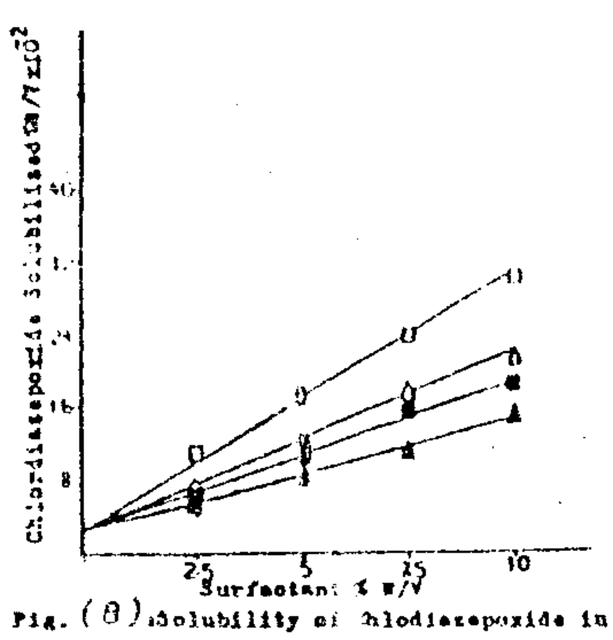

Fig. (8) :Solubility of Chlodiazepoxide in Different Non-Ionic Surfactant Solutions Containing Propylene-Glycol 10 % V/V at 25°.

Key : The Same as Fig. 1, 3

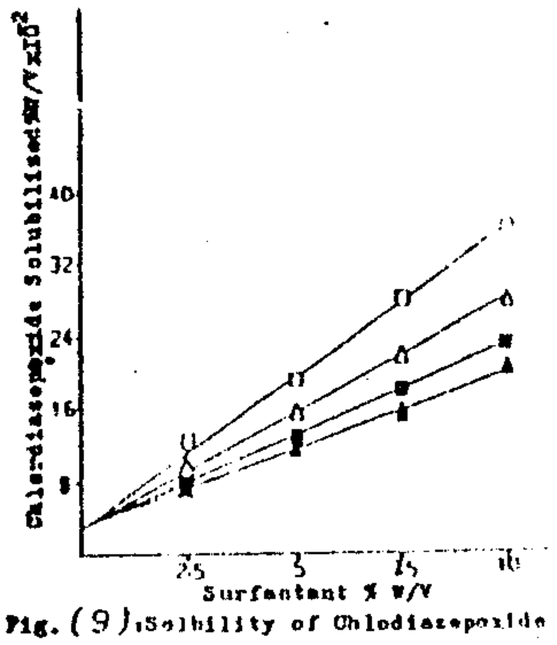

Fig. (9) :Solbility of Chlodiazepoxide in Different Non-Ionic Surfactant Solutions Containing Propylene-Glycol 10 % W/V at 35°.

Key : The Same as Fig. 1, 3

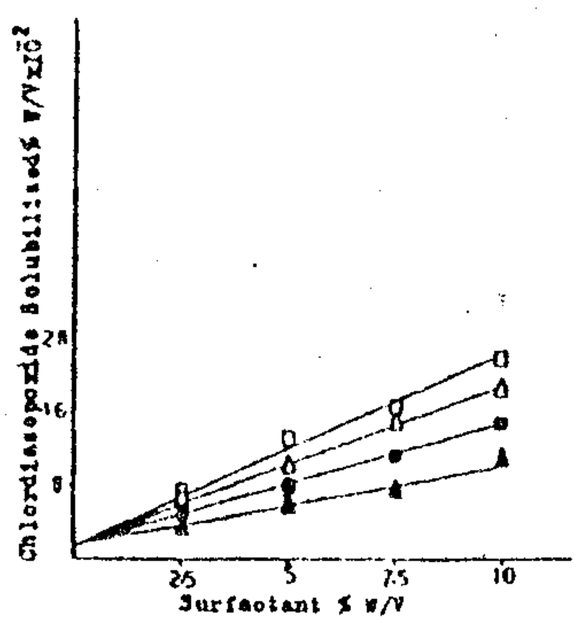

Fig. 10 :Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions Containing Glycerol 10 % W/V at 25°.

Key : The Same as Fig. 1, 3

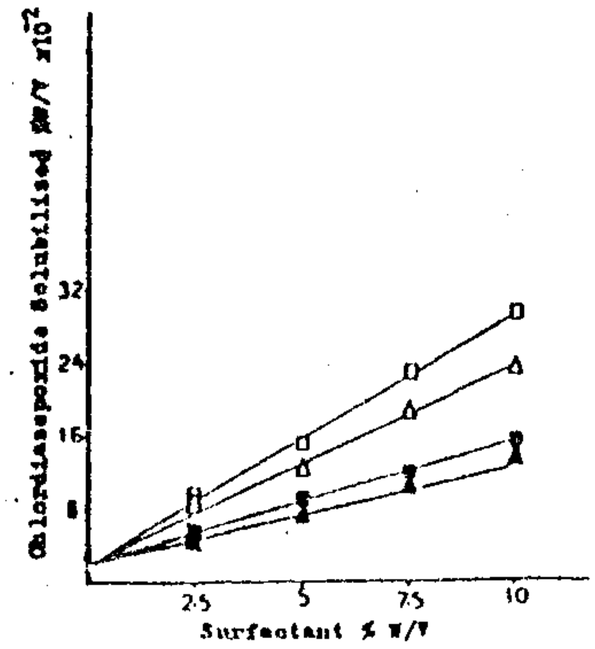

Fig. 11 :Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions Containing Glycerol 10 % W/V at 35°.

: The Same as Fig. 1, 3

Fig. 12 :Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions Containing P.E.G.4000 10 % W/V at 25°.

Key : The Same as Fig. 1, 3

Fig. 13 :Solubility of Chlordiazepoxide in Different Non-Ionic Surfactant Solutions Containing P.E.G.4000 10 % W/V at 35°.

Key : The Same as Fig. 1, 3

REFERENCES

1-A.E.Aboutaleb, A.M.Sakr and Aly A.Abdel Rahman, Pharmazie 35, 99 (1980).

2-A.A.Kassem, A.E.Aboutaleb, A.M.Sakr and Aly A.Abdel Rahman, Pharmazie 36, 102 (1981).

3-A.E.Aboutaleb, A.A.Ali and R.B.Salama, ibid, 36, 35 (1981).

4-M.Donbrow, E.Azaz and R.Hamburger, J. Pharm. Sci., 59, 1427 (19).

5-P.Mukerjee, J. Pharm. Sci., 60, 1538 (1971).

6-A.P.Simonelli, A.E.Aboutaleb and Aly A.Abdel Rahman, Bull. Pharm. Sci., Assiut University 7, 322 (1984).

7-A.P.Simonelli, A.E.Aboutaleb and Aly A.Abdel Rahman, ibid, 7, 363 (1984).

8-R.K.Reddy, S.A.Khalil and M.W.Gouda, J. Pharm. Sci., 65, 115 (1976).

9-A.E.Aboutaleb, M.S.Mesiha and Aly A.Abdel Rahman, Pharmazie 6 (1982).

10-A.E.Aboutaleb and S.M.Ahmed, Bull. Pharm. Sci., Assiut University 6, 310 (1983).

11-Aly A.Abdel Rahman, Ph. D. Thesis, Assiut University (1981).

12-A.E.Aboutaleb and Aly A.Abdel Rahman, Bull. Pharm. Sci., Assiut University 3, 87 (1980).

13-S.J.A.Rogers and J.G.Narin, Canad. J. Pharm. Sci., 5, 96 (1970).

14-C.W.Peter, N.C.Ronald and H.Ulrich, J. Pharm. Sci., 474 (1980).

15-S.M.Ahmed, M. Sci. Thesis, Assiut University (1981).

16-A.E.Aboutaleb, Ph. D. Thesis, Bradford University, U. K. (1974).

17-J.J.Jacobs, R.A.Anderson and I.R.Watson, J. Colloidal Sci., 23, 766 (1971).

18-S.D.Roy and G.L.Flynn, Pharmaceutical Research 6, 147 (1989).

19-P.Mukerjee, J. Pharm. Sci., 63, 6 (1964).

20-F.W.Goodhart and A.N.Martin, ibid., 51, 50 (1962).

21-E.M.Samy, M. Pharm. Sc. Thesis, Assiut University (1986).

العوامل المؤثرة على تذويب الكلورديازيبوكسيد بمنشـــطات السـطح غـير المتـأينـة

على عبد الظاهر عبد الرحمن ـ احمد السيد ابو طالب ـ ايمان معطفى سامى

قسم الصيدلة الصناعية ـ كلية الصيدلة ـ جامعة اسيوط

درست بعض العوامل المؤثرة على تذويب الكلورديازيبوكسيد فى مجموعات من منشطات السطح غير المتأينة مثل تركيب المنشط السطحى ورقمه الايدروجينى ودرجة الحرارة وكذلك احتوائه على بعض الاضافات العضوية فى تركيز ١٠،٥٪ وزنا علـى حجـــم .

ولقد وجد ان عديد الوريات ٨٠ اعلـى كفاءة فى مقدرته الذوبانيـــة للعقار من عديد الوريات ٢٠ ، وكذلك البرج ٣٥ اعلى من البرج ٥٨ علـــى الجانب الاخر وجد ان الاملجين س ١٠٠٠ اعلى كفاءة من الاملجين س ١٥٠٠ والمرج ٥٢ اعلى كفاءة من المرج ٥٣ والاخير بدوره اعلى كفاءة من المـرج ٥٩.

ولقد اتبعت طريقة قام بها العالم ماكرجى لدراسة دور كل من القشـرة والقلب للشباك فى تذويب العقار ولقد وجد ان قلب الشباك هو الذى يقـــوم بالدور الرئيسى فى عملية التذويب .

اما عن منشطات السطح غير المتأينة الـى تحتوى على اضافات عضويـــة فلقد وجد ان البرج ٣٥ المحتوى على ٥ ٪ بروبلين جليكول هو اعلى مذيـــب لهذا العقـــار .

received in 24/3/1991 - accepted in 6/6/1991