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EFFECT OF pH AND ORGANIC HYDROXYLATED ADDITIVES ON N-DES-METHYLDIAZEPAM SOLUBILIZATION BY NON-IONIC SURFACTANTS

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ABSTRACT

N-desmethyldiazepam, was solubilized in different non-ionic surfactant solutions including members of polysorbates, Myrjs, Eumulgins and Brijs at 25 and 35 C.

Polysorbate 80 was more efficient in solubilizing the drug 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 found to be more efficient than Myrj 53 and Myrj 59 respectively.

Always raising the temperature of the investigated solutions caused a positive temperature effect and a decrease in Km values.

Adjusting the pH of Eumulgin and Brij solutions caused a gradual decrease in the quantity of the drug solubilized by raising the pH from pH 4.0 to 7.4.

Theoretical treatment to quantify the role of of both the core and the capsular regions of the micelle in N-desmethyldiazepam solubilization showed that the core of the micelle plays the most important role in solubilizing the drug.

The drug was solubilized in Eumulgin and Brij series containing 5 and 10% w/v of propylene glycol, glycerol, polyethylene glycol 400 (PEG 400)

and polyethylene glycol 4000 (PEG 4000). The incorporation of propylene glycol, glycerol and PEG 400 or 4000 increased the solubilizing efficiencies of the surfactants toward the drug at 25 C.

Incorporation of 5% w/v of these additives in the tested Eumulgin and Brij solutions caused an increase in the Km values of the drug and the revrese is true for 10% w/v of these additives.

INTRODUCTION

The interaction between drugs and non-ionic surfactants is both of profound theoretical interest and considerable practical importance in pharmaceutical formulations. The prime aim in pharmaceutical formulations is to solubilize practically water-insoluble drugs to bring them in solution[1-3] for their further formulations in liquid dosage forms. Another aim is the investigation of the solubilized systems[4] concerning factors affecting solubilization, mode of incorporation[5] of the drugs in the solubilized systems, stability of drugs in solubilized systems[6,7] and pharmacological availability[8] of drugs from solubilized systems.

Adjusting the pH of the non-ionic surfactant solutions[9,10] was found to have a role in drug solubilization.

The effect of certain hydroxylated additives on the solubilization process is well demonstrated. When these additives were incorporated in certain non-ionic surfactant solutions they increased the solubilizing efficiencies toward certain drugs and reduced the concentration of such solubilizers needed to attain the therapeutic doses of such water-insoluble drugs[11]. This process is termed co-solubilization. The solubilizing efficiencies of certain non-ionic surfactant solutions

towart chloramphenicol were found to increase depending upon the nature of the additives used[12,13].

The effect of different additives on the micellar solubilization of methotrimeprazine [14] and carbamazepine[15] was also reported.

Since N-desmethyldiazepam is practically water-insoluble and is presented only in solid dosage forms of 2-5 mg, the aim of the present work is to study:

1- Solubilization of the drug in series of different non-ionic surfactant solutions.
2- effect of adjusting the PH of the tested Eumulgin and Brij solutions to pH 4.0, 6.0 and 7.4 on the drug solubilization.
3- Role of the core and the capsule of Myrj micelles on the drug solubilization.
4- Effect of certain organic hydroxylated additives including propylene glycol, glycerol, PEG 400 and PEG 4000 on the process of N-desmethyldiazepam solubilization.

EXPERIMENTAL

Materials:

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

Polysorbates:

(Atls Chemical Industries, Inc. Willimington Delaware, (USA) were polysorbate 20 and polysorbate 80.

Eumulgins:

(Henkel International, Dusseldrof, Fedral Rebuplic of Germany) were Eumulgin C1000 and Eumulgin C1500.

Myrjs:

(Atlas Chemical Industries, Inc. Willimington Delaware, USA) were: Myrj 52, Myrj 53 and Myrj 59.

Brijs:

(Atlas Chemical Industries) were Brij 35 and Brij 58.

Buffer Components:

(BDH. Poole, England) were: sodium dibasic phosphate and citric acid (McIlvian buffer).

The additives: were propylene glycol (Prolabo, Pelee Paris, France), glycerol (BDH, Poole, England), PEG 400 and PEG 4000 (Sigma Chemical Company).

Apparatus:

Thermostatically controlled shaker (Seity Company, Cairo, Egypt). UV-self-recording spectrophotometer (Pye-Unicam, SP-1025, England).

Single beam UV- spectrophotometer (Pye Unicam, SP-400, England). pH meter (Problabo, Pelee Paris, France).

Centrifuge (Prolabo, Pelee, Paris, France).

Methods:

1-Solubilization of N-desmethyldiazepam in non-ionic surfactant solutions:

Excess of the drug was equilibrated with 10 ml of different concentrations (2.5, 5,7.5 and 10% w/v) of the non-ionic surfactant solution in 15 ml screw-capped tubes. The tubes were shaken top to bottom in a constant temperature waterbath of 25 and 35 C. After equilibration for four days, the tubes were centrifuged to sediment excess solid drug. The tubes were then re-equilibrated without shaking for further 24 hours period at the same investigated temperatures. Samples were withdrawn from the supernatant liquid in the tubes and their drug content was determined spectrophotometrically

at 231 nm after appropriate dilution with distilled water. The drug concentrations were determined from Beer's plot which is linear over the determined concentrations. It was found that the presence of the non-ionic surfactant solutions in the dilution range used, neither interferred in the spectrophotometric assay of the drug nor produced any shift of its maximum absorbance[14,15].

2-Solubilization of N-desmethyldiazepam in certain non-ionic surfactant solutions of controlled pH values:

The pH of the Eumulgin and Brij solutions was adjusted to pH 4.0,6.0 and 7.4 using McIlvian buffer. The solubilizing efficiencies of those solutions of the previously mentioned pH values toward the drug were carried out as mentioned before.

3-Solubilization of N-desmethyldiazepam in different non-ionic surfactant solutions containing 5 and 10% w/v of the investigated additives:

The non-ionic surfactant solutions investigated containing 5 and 10% w/v of the used additives were evaluated regarding their solubilizing efficiencies. The additives used were propylene glycol, glycerol, PEG 400 and PEG 4000 .The solubilizing efficiencies of those solutions containing the additives toward the drug were carried out as mentioned before. It was found that the presence of the surfactant solutions and the additives investigated , in the dilution range used, neither interfered in the spectrophotometric assay of the drug nor made any shift of its maximum absorbance[14,15].

RESULTS AND DISCUSSION

The solubility of N-desmethyldiazepam in the investigated non-ionic surfactant solutions increases linearly by increasing the surfactant concentrations, Fig.1. The systems investigated

were always one liquid plus solid which represents true micellar solubilization of this drug.

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

The solubilities of N-desmethyldiazepam in the investigated non-ionic surfactant solutions (mg/g) at different temperatures investigated is shown in Table 1. It is evident from Table 1 and Fig. 1 that polysorbate 80 with longer hydrocarbon chain is more efficient as a solubilizer for the drug than polysorbate 20. Thus, surfactants with longer hydrocarbon chain in a homologous series are more efficient as solubilizers indicating that the drug is solubilized mainly in the micellar core.

Extending the polyoxyethylene chain length in a homologous series of surfactants leads to a decrease in the amount of the drug solubilized, as shown in Table 1 and Figs. 1 and 2. That is why Eumulgin C1500 is less efficient as a solubilizer for the drug than Eumulgin C1000. Also, Myrj 59 is less efficient for solubilizing the drug than Myrj 53 which is in turn less efficient than Myrj 52. The last finding proved that the polyoxyethylene chain; the capsular region; the mantle of the micelle, plays a little part in N-desmethydiazepam solubilization, while the hydrocarbon chain; the core of the micelle; plays the major part in this aspect. Thus, by extending the polyoxyethylene chain of the micelle, the relative volume of the core will be decreased compared to the total micellar volume. These results agree with the results obtained on the solubilization of benzoic acid and salicylamide[16] by pure series of non-ionic surfactant solutions, and other solutes by Myrj series[17].

Brij 35, although shorter in the hydrocarbon chain and longer in ethylene oxide moiety than Brij 58, was found to be more efficient as a solubilizer for N-desmethyldiazepam, Table 1 and Fig.2. This could be interpreted on the basis of the unlinked ethylene oxide chains which form mixed micelles and also some impurities present in these solutions[16].

The solubilizing capacities of the investigated non-ionic surfactant solutions in distilled water expressed as mg medicament per gm surfactant are shown in Table 1. These solubilizing capacities are the slopes of the solubility isotherms of N-desmethyldiazepam in the investigated solutions, Figs. 1 and 2. The non-ionic surfactant solutions used for solubilizing N-desmethyldiazepam at 25 C could be arranged according to their solubilizing efficiencies as follows: Brij 35 > Eumulgin C1000 > Brij 58 > polysorbate 80 > Eumulgin C1500 > Myrj 52 > Myrj 53 > polysorbate 20 > myrj 59.

The solubility of N-desmethyldiazepam in different non-ionic surfactant solutions of 35 C is illustrated in Table 1. On comparing the solubility of the drug at 25 C with that of 35 C, a positive temperature effect was observed. The solubilizing efficiencies of the non-ionic solutions investigated toward the drug drug at 35 C could be arranged as follows Brij 35 > Eumulgin C 1000 > polysorbate 80 > Eumulgin C1500 > polysorbate 20 > Brij 58 > Myrj 53 > Myrj 59.

The distribution coefficient[16] is defined as Km which equals Cm/Cw, where Cm is the concentration of the drug in the micellar phase (weight and Cw is the concentration of the drug in the aqueous phase (w/w). It was found that the Km values vary according to the variation in the surfactant molecular structure, as seen from Table 2. The higher the value of the Km, the higher the amount of the drug incorporated within the micelle, assuming

that the drug is solubilized by partition between the micellar and aqueous phases. On raising the temperature from 25 to 35C, the calculated Km values between the micellar phases fall. This may be attributed to the consideration that both the micellar and aqueous phases solubilities are changed by raising the temperature but not by the same ratio. If the effect of temperature is even on both phases, no change in the Km value would be expected, but in fact this is not the case.

For investigating the effect of pH on N-desmethyldiazepam solubilization, Eumulgins and Brijs were chosen for conducting such a study; as they possess etherial linkage, and are stable than polysorbates and Myrjs which possess ester linkage. Furthermore , Brijs and Eumulgins are more efficient as solubilizers for the drug. Thus non-ionic surfactant solution of pH 4.0,6.0 and 7.4 were used and the process of solubilization was conducted at 25 and 35 C. As seen from Table 1 and Fig. 3 and by comparing the solubilizing efficiencies of the non-ionic surfactant solutions of pH 4.0,6.0 and 7.4 and those prepared in distilled water, it is obvious that the solubility of the drug decreases as the pH of the non-ionic surfactant was increased. As the pH increases, the amount of citric acid in the buffor solution decreases and the amount of sodium dibasic phosphate increases. Citric acid probably acts as a co-solubilizer and assists in drug solubilization in the non-ionic surfactant solutions investigated, while sodium dibasic phosphate, as an electrolyte, has a salting effect on the non-ionic surfactant monomers[11], leading to a decrease in their sclubilizing efficiencies. That is why non-ionic surfactant solutions of pH 4.0 (having higher concentration of citric acid and lower concentration of sodium dibasic phosphate)are the most efficient solubilizers. Another explanation for the observed increase in the drug solubility by lowering the pH values of the investigated non-ionic surfactant

solutions involves that the pK_a of the drug is equal to 3.3 which suggests that the drug is in the non-ionized undissociated form which favours its micellar solubilization.

Among the non-ionic surfactant solutions of pH 6, Eumulgin C1000 was the best solubilizer for the drug at both temperatures investigated, while Brij 35 was the least. The same findings were observed for the non-ionic surfactant solutions of pH 7.4 at 35C.

The theoretical treatment proposed by Mukerjee[5,18,19] and by Goodhart and Martin[20] has been adopted to quantify the role of both the core and the capsular region of the micelle in solubilizing the drug.

Assuming that the solubilizate will be distributed between the micellar core composed of the stearyl groups (R) and the micellar capsule, consisting of the ethylene oxide groups (Eo), Goodhart and Martin[20] expressed the micellar solubility as equivalents of solubilizate per equivalent of (Eo) groups. The amount solubilized in equivalent per liter of solution S, will be given by the equation:

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

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

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

So that if S/C_{Eo} in equivalent per equivalent is plotted against C_R/C_{Eo}, Table 3, a linear relationship should be obtained with the intercept (a) representing the solubilization in the capsule (equivalent of solubilizate per equivalent of Eo groups). The slope (b) represents the solubilization in the core (equivalent of solubilizate per equivalent of R groups).

Fig. 4 shows the plot of the data obtained on solubilizing the drug using Myrj series (Myrj 52, 53 and 59), according to Mukerjee treatment at 25 and 35 C. These data are also represented in Table 3. The values of (a) and (b) are shown in Table 4.

It could be noticed that N-desmethyldiazepam was solubilized mainly in the core of the micelles. Furthermore, the amount of the drug solubilized in the capsule decreased by extending the polyoxyethylene chain from 40 (Myrj 53) to 50 (Myrj 53) to 100 (Myrj 59) at the two temperatures investigated.

Table 3 also shows that the ratio between the amount of the drug solubilized in the core and the capsule was constant at the two temperatures investigated for each Myrj member.

The solubilizing efficiencies of Eumulgin and Brij aqueous solutions containing 5% w/v propylene glycol at 25° are shown in Table 5 and Fig. 5. It is clear that propylene glycol produced an increase in the solubilizing efficiencies of the respective surfactants. This increase could be attributed to the suppressive effect of propylene glycol on the liquid crystal formation in the non-ionic surfactant solutions[16].

Table 5 and Fig. 6 illustrate the solubilizing efficiencies of Eumulgin and Brij solutions containing 10% w/v propylene glycol at 25 C. It is obvious that this high concentration of propylene glycol caused a decrease in the solubilizing efficiencies of the investigated solutions. The observed decrease may be attributed to the increased hydrophilicity of the non-ionic surfactant micelles, by incorporating this higher concentration of propylene glycol in the capsular region of the micelles[11]. Furthermore, the expanded capsular region caused relative decrease in the core volume, which is mainly responsible for the drug solubilization, to the whole micellar volume.

On raising the temperature of the investigated solutions containing propylene glycol from 25 to 35 C, solutions containing 5% w/v showed a negative temperature effect, except for Brij 35, while the non-ionic surfactant solutions containing 10% w/v of this additive showed a positive temperature effect, Table 5.

Table 5 and Fig. 7 demonstrate the effect of 5% w/v glycerol on the solubilizing efficiencies of Eumulgin and Brij solutions toward N-desmethyldiazepam at 25 C. On comparing the efficiencies of the investigated non-ionic surfactant solutions alone to those containing this concentration of glycerol, it is clear that the incorporation of a such concentration caused a marked increase in the efficiencies of the latter. This increase could be attributed to the effect of glycerol as a co-solubilizer for this drug, consequently the solubility could be increased[21].

The effect of 10% w/v of glycerol is also shown in Table 5. The investigated solutions containing this concentration of glycerol showed a pronounced increase in case of Brij 58 than Brij 35 and Eumulgin C1000 than Eumulgin C1500, especially if compared with the non-ionic surfactant solutions alone at 25 C. Glycerol, incorporated in the capsular region of the micelle made a relative decrease in the core volume to the totally expanded micelle containing glycerol, resulting in a decrease in the micellar solubilizing capacities. Raising the temperature caused a negative temperature effect to those solutions containing 5% w/v glycerol and the reverse was found for those solutions containing 10% w/v of this additive.

Fig. 8 and Table 5 illustrate the effect of 5% w/v PEG 400 on the solubilizing efficiencies of Eumulgin and Brijs at 25 C.

Comparing the effiencies in absence and in presence of this concentration of PEG 400 at 25 C it is clear that its presence caused a slight increase in the efficiencies of Eumulgin C1500 and Brij 58. Table 5 illustrate also the effect of 10% w/v PEG 400 on the solubilizing efficiencies of the investigated Eumulgin and Brij solutions at 25 C. Higher concentrations of PEG 400 caused an increase in the solubilizing efficiencies of the investigated solutions compared to 5% w/v of the same additive except for Eumulgin C1500 solution. The decrease observed in the solubilizing efficiency of Eumulgin C1500 containing 10% w/v PEG 400 may be attributed to the incoporation of this higher concentration of PEG 400 in the relatively longer polyoxyethylene chain of Eumulgin C1500 (50 ethylene oxide units) leading to a relative decrease in the micellar core volume. The observed increase in the rest of the non-ionic surfactant solutions contaning 10% w/v may be due to the effect of this additive at this concentration on the process of solubilization. The presence of this long chained alcohol in this concentration may induce the aggregation of monomers into micelles, consequently the cmc values decreased and the solubilizing efficiencies was increased. Low molecular weight alcohols may act also as a co-solubilizer for this drug[22].

Raising the temperature for the investigated solutions containing PEG 400, from 25 to 35 C, caused a negative effect in case of 5% w/v except for Brij 35 and a positive effect was observed in case of 10% w/v.

The effect of 5% w/v PEG 4000 on the solubilizing efficiencies of the investigated non-ionic surfactant solutions at 25C is shown in Table 5,Comparing these efficencies in absence and in presence of this concentration of PEG 4000,implies that its presence caused an increase in the solubilizing efficiencies of the investigated solutions, even more than the same concen-

tration of PEG 400 at the same temperature. This may support the assumption that these additives affect the micellar volume to different extents, depending upon the hydrophilic and the hydrophobic characteristics of both the surfactant and the additive molecules.

10% w/v PEG 4000 incorporated in the investigated non-ionic surfactant solutions generally caused a decrease in their solubilizing efficiencies compared to 5% w/v, which could be attributed to the increased hydrophilicity of the medium by increasing the concentration of PEG 4000 at both temperatures.

Raising the temperature for the investigated non-ionic surfactant solutions containing 5 and 10% w/v of PEG 4000 generally caused a positive temperature effect except Brij 58 containing 5% and Eumulgin C1500 containing 10%.

Table 6 gives an idea about the distribution of N-desmethyldiazepam between the micellar pseudophase and the aqueous phase, i.e. the Km values[11,21] of the drug in the different investigated solutions. The effect of temperature and different included additives on the Km values was also investigated. The effect of the additives on the solubility of the drug in the micellar and the aqueous phases caused the Km values to decrease or increase[11,21] according to the effect of the additive and whether it promotes aqueous or micellar solubilization. This indicates that when the Km value was increased (compared to its value in the surfactant alone) the additive induced more solubilization of N-desmethyldiazepam in the micellar pseudophase than in the aqueous phase, and the revrese is true when the Km value was decreased. It is noticed that the Km values was generally decreased on raising the temperature from 25 to 35 C indicating that more solubilization of the drug in the continuous aqueous phase was induced at higher temperature.

The Km values of the drug were generally increasedin presence of 5% w/v of: propylene glycol, glycerol, PEG 400 and PEG 4000 at both temperatures investigated, and the revrese was true for 10% w/v of the last mentioned additives. This could be attributed to the increased aqueous solubilities of the drug in the presence of 10% w/v of those additives.

Table 1: Effect of Different non-ionic Surfactant Solutions of Different pH Values on N-Desmethyldiazepam Solublization at 25 and 35 C.

Surfactant	Solubility of N-desmethyldiazepam mg/g surfactant:							
	in D. water*		of pH 4		of pH 6		of pH 7.4	
	25 C	35 C	25 C	35 C	25 C	35 C	25 C	35 C
Polysorbate 20	7.39	14.56						
Polysorbate 80	13.15	16.73						
Eumulgin C1000	15.18	17.74	10.97	14.79	10.93	14.44	9.11	16.56
Eumulgin C1500	11.67	15.16	9.80	12.77	9.61	12.07	10.65	15.56
Myrj 52	8.89	10.95						
Myrj 53	7.49	7.99						
Myrj 59	4.28	4.79						
Brij 35	15.84	20.89	5.79	9.54	5.22	6.75	6.02	7.74
Brij 58	13.06	14.33	10.53	13.93	9.20	13.33	5.04	8.37

* Distilled water of pH 6.

Table 2 : Distribution Coefficient (Km) of N-Desmethyldiazepam between the Micellar and Aqueous Phases at 25 and 35 C .

Surfactant	Distribution coefficient (Km)	
	25 C	35 C
Polysorbate 20	504	410
Polysorbate 80	856	487
Eumulgin C1000	1004	549
Eumulgin C1500	737	457
Myrj 52	536	356
Myrj 53	433	295
Myrj 59	295	146
Brij 35	1131	645
Brij 58	835	444

Table 3 : Distribution of N-Desmethyldiazepam between the Cores and Capsules* of Myrj Micelles at 25 and 35 C.

Surfactant	Surfactant mol. wt.	Wt. of ethylene oxide part	S/C_{Eo}		C_{R}/C_{Eo}	Ratio of the amount of N-desmethyldiazepam in capsule and core	
			25	35		25	35
Myrj 52 (C17 E40)	2046	1777	0.0166	0.0199	0.025	0.230	0.230
Myrj 53 (C17 E50)	2486	2217	0.0135	0.0145	0.020	0.223	0.223
Myrj 59 (C17 E100)	4686	4417	0.0075	0.0082	0.010	0.208	0.208

* Calculated by Mukerjee's method[5,18,19]

Table 4 : Amount of N-Desmethyldiazepam incorporated in Capsule (a) eq./eq. and core (b) eq./eq. for the Myrj series calculated by Mukerjee's method, at 25 and 35 C.

Surfactant	25 C		35 C	
	(a)	(b)	(a)	(b)
Myrj 52	1.66	7.2	1.99	8.69
Myrj -53	1.35	6.05	1.45	6.51
Myrj 59	0.75	3.59	0.82	3.96

Table 5 : Solubility of N-Desmethyldiazepam g/g X 10^4 by Non-ionic Surfactant Solutions in presence of various Additives at 25^o and 35^o

Non-ionic Surfactant	Solubility g/g of N-Desmethyldiazepam Calculated from Solubility Measurements																	
	Surfactant		Surfactant+ Propylene Glycol				Surfactant + Clycorol				Surfactant + P.E.G. 400				Surfactant + P.E.G. 4000			
	Alone		5%		10%		5%		10%		5%		10%		5%		10%	
	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o	25^o	35^o
Eumulgin C_{1000}	152	177	165	157	139	146	189	149	174	195	88	30	157	186	167	166	130	146
Eumulgin C_{1500}	117	152	157	130	101	104	189	126	111	149	122	61	82	99	124	129	158	151
Brij 35	158	209	189	213	105	179	203	198	138	201	153	169	203	233	182	215	176	188
Brij 58	136	143	177	171	90	147	164	139	160	187	140	100	142	167	162	155	137	155

Table 6 : Effect of Different Additives on the Distribution Coefficient (Km) of N-Desmethyldiazepam between Micellar and Aqueous Phases at 25° and 35°

	Distribution Coefficient, Km, Calculated from Solubility Measurements																	
	Surfactant Alone		Surfactant + Propylene Glycol				Surfactant + Clycerol				Surfactant + P.E.G. 400				Surfactant + P.E.G. 4000			
			5%		10%		5%		10%		5%		10%		5%		10%	
	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°	25°	35°
Eumulgin C_{1000}	1004	549	1120	478	89.1	70	1290	486	571	438	715	151	245	231	1118	517	272	307
Eumulgin C_{1500}	737	457	994	421	62.1	49	923	368	376	334	943	270	121	126	909	397	321	361
Brij 35	1131	645	1318	640	71.6	97	1422	615	454	456	1194	568	312	318	1301	648	360	394
Brij 58	835	444	1147	518	58.2	78	1052	444	513	410	1054	369	204	214	1088	481	289	331

Effect of pH and Orgainc Hydroxylated Additives on N-Desmethyl diazepam Solubilization by Non-ionic Surfactants.

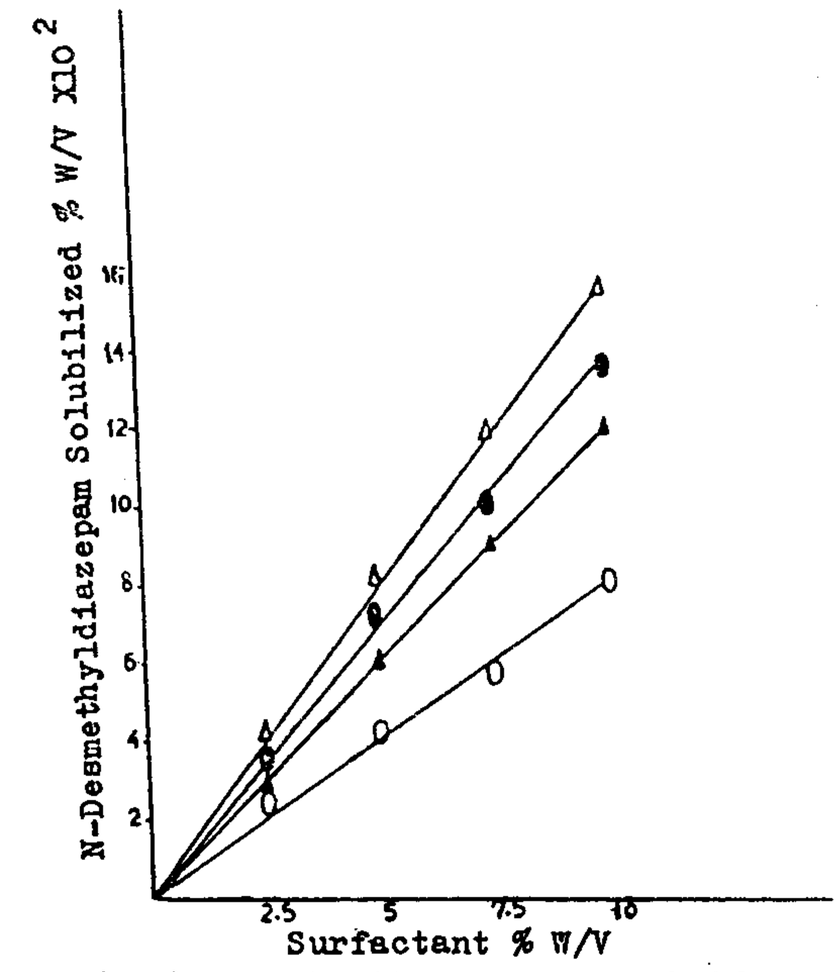

Fig.(1): Solubility of N-Desmethyldiazepam in Different Non-Ionic Surfactant Solutions at 25°.

Key :Δ EumulginC1000, ▲ EumulginC1500, OPolysorbate 20, ● Polysorbate 80.

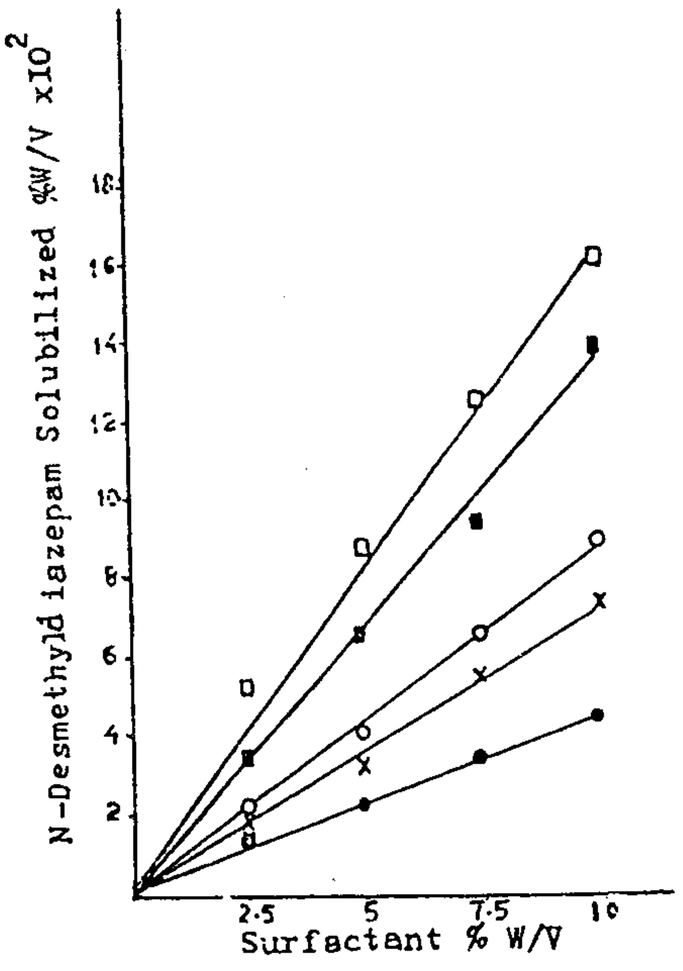

Fig.(2):Solubility of N-Desmethyl -diazepam in Different Non -Ionic Surfactant Solutions at 25°.

Key :□ Brij 35, ■ Brij 58, O Myrj 52, X Myrj 53, ● Myrj 59.

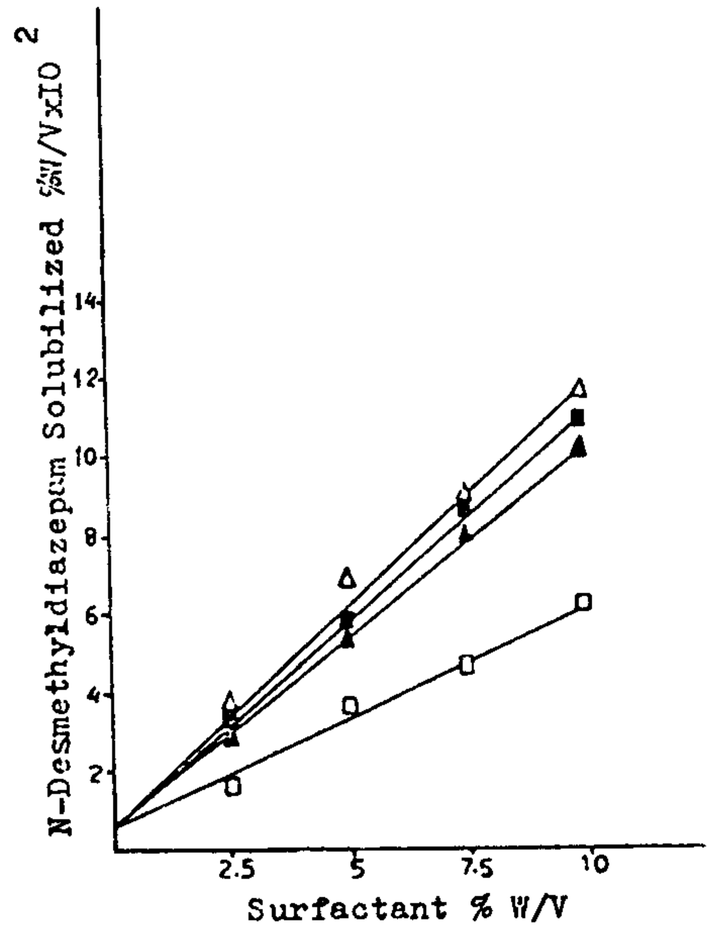

Fig.(3):Solubility of N-Desmethyl -diazepam in Different Non -Ionic Surfactant Solutions of pH 4 at 25°.

Key : The Same as Fig. 1& 2

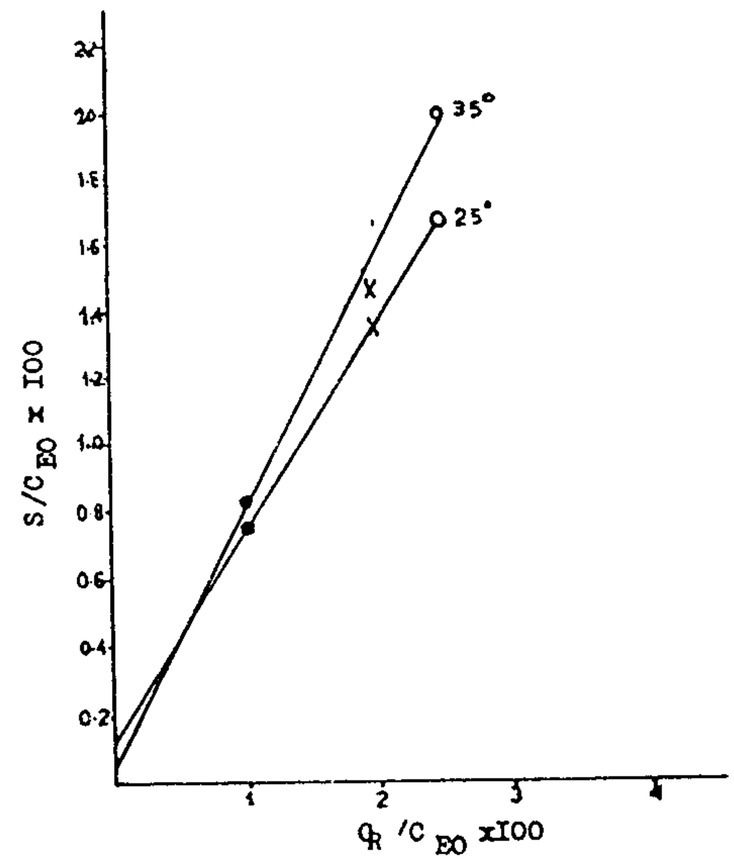

Fig.(4): Micellar Solubilization of N-Desmethyl -diazepam in Polyoxyethylene-Stearate Solutions at 25 and 35 C.

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& 2

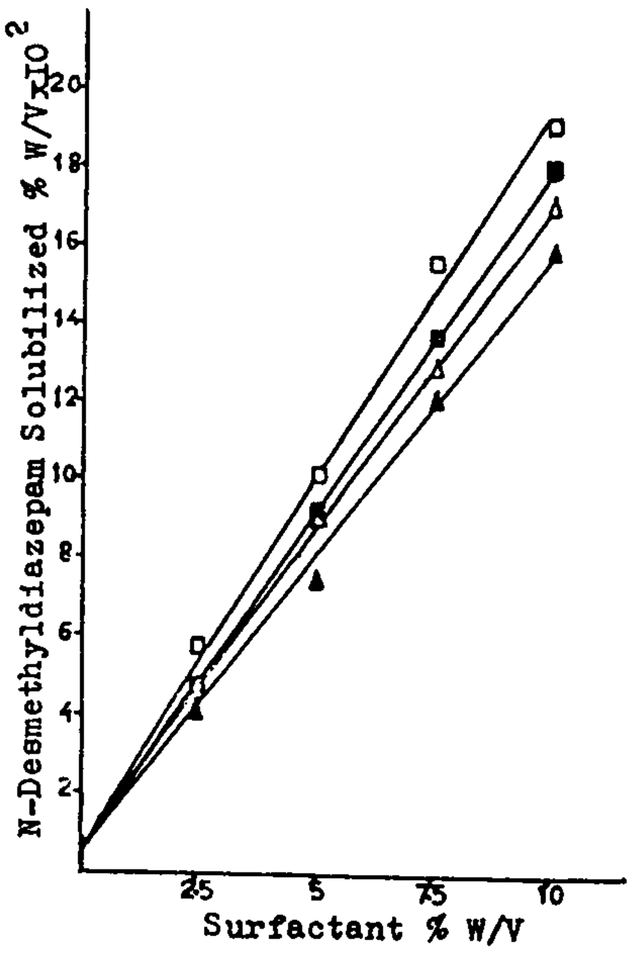

Fig.(5):Solubility of N-Desmethyldiaz -pam in Different Non-Ionic Surfactant Solutions Contain -ing Propylene Glycol 5% W/V at 25°.

Key:The same as Fig.1&2.

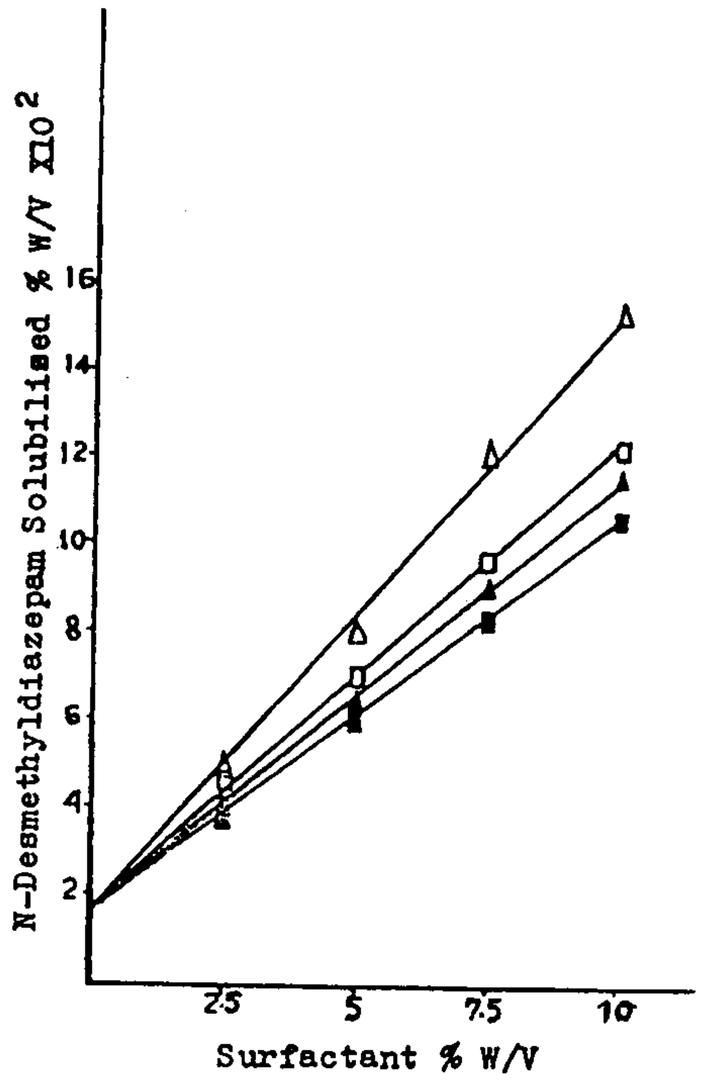

Fig.(6): Solubility of N-Desmethyldiazepam in Different Non-Ionic Surfactant Solutions Containing Propylene Glycol IO % W/V at 25°.

Key : The Same as Fig. 1&2

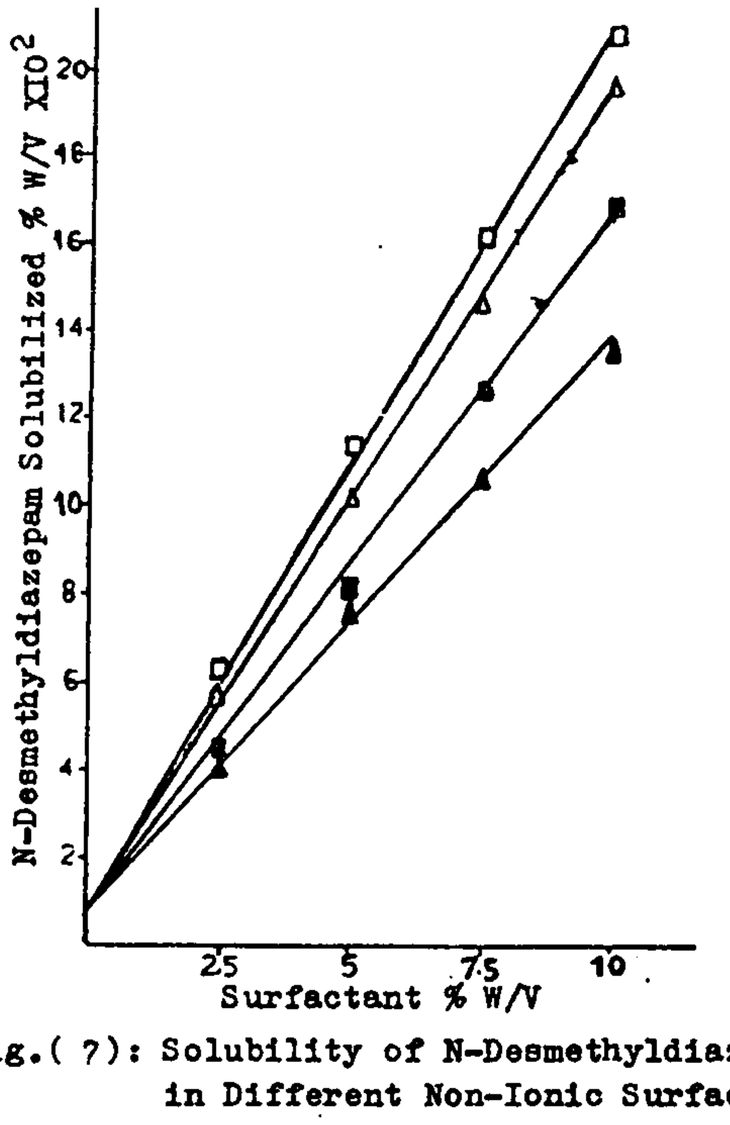

Fig.(7): Solubility of N-Desmethyldiazepam in Different Non-Ionic Surfactant Solutions Containing Glycerol 5% W/V at 25°.

Key : The Same as Fig. 1&2 .

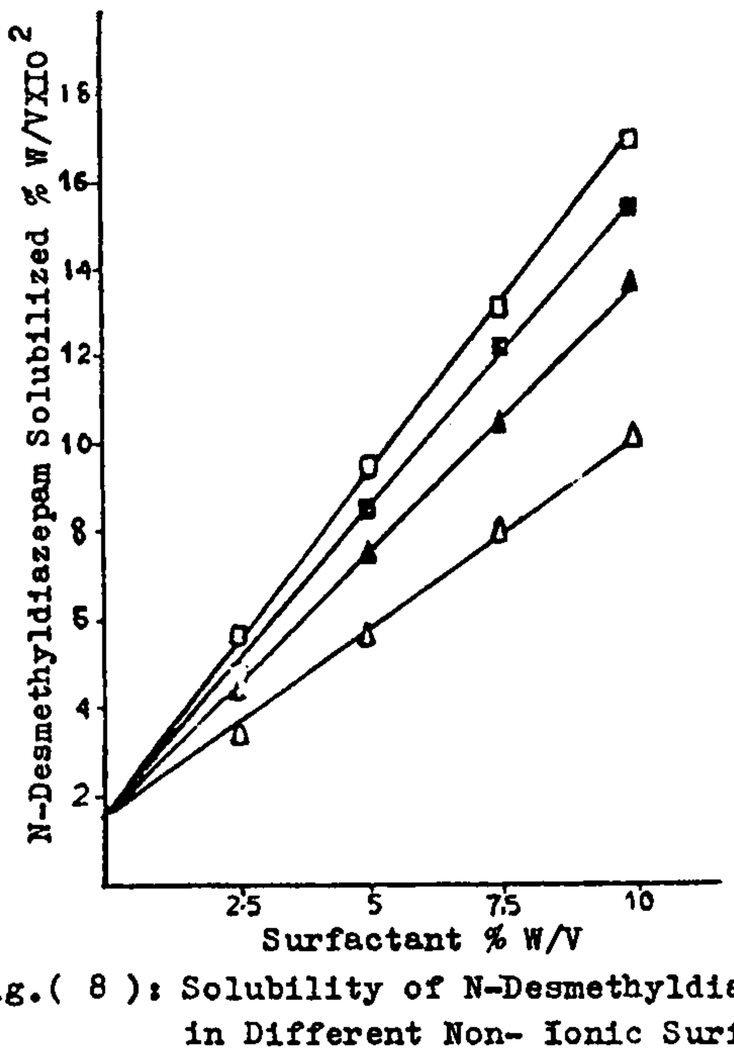

Fig.(8): Solubility of N-Desmethyldiazepam in Different Non- Ionic Surfactant Solutions Containing P.E.G.400 5% W/V at 25°.

Key : The Same as Fig. 1&2 .

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تأثير ضبط الاس الايدروجينى وكذلك بعض الاضافات العضوية الايدروكسيلية على تذويب ن ـ ديسميثيل ديازيبام بواسطة منشطات السطح غير المتأينة

احمد السيد ابو طالب ـ على عبد الظاهر عبد الرحمن ـ ايمان مصطفى سامى
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ن ـ ديسميثيل ديازيبام ـ الدواء النفس المعروف والذى لايذوب عمليا فى الماء ـ أذيب بواسطة سلاسل من منشطات السطح غير المتاينه لها نفس السلسلة الهيدروكربونية وهى عديد السوربات ٢٠ ، عديد السوربات ٨٠. ولقد وجد أن عديد السوربات ٨٠ له كفاءة ذوبانية لهذا العقار أكبر من عديد السوربات ٢٠.

ولقد وجد ان اطالة سلسة عديد أوكس ايثيلين فى مجموعة متماثلة يقلل من المقدرة الاذابية لهذه المجموعه ووجد ان ارتفاع درجة الحراره يؤدى الى زيادة الكفاءة الاذابية لمنشطات السطح غير المتأينه موضوع البحث .

ولقد ضبطت الاسس الايدروجينية لكل من محاليل الاملجينات والبرج فى أسس مقدارها ٤ ، ٦ ، ٧ر٤ وذلك لدراسة تاثير ضبط الرقم الايدروجينى على المقدرة الاذابية لمنشطات السطح آنفة الذكر .

وبصفه عامه وجد أن ارتفاع الاس الايدروجينى لهذة المنشطات قلل تدريجيا من المقدرة الاذابية الخاصة بها .

ولقد اتبعت طريقة حساب خاصة لدراسة دور كل من القلب والقشرة لشباك مجموعة الميرج فى تذويب ن ـ ديسميثيل ديازيبام كميا . ولقد وجد أن قلب الشباك هو الذى يقوم بالدور الرئيس فى تذويب العقار بينما تقوم القشره بدور ثانوى فى هذا المجال .

ولقد أذيب العقار فى مجموعتى الاملجين والبرج المحتويه على ٥ ، ١٠/وزن /حجم من بعض الاضافات الايدروكسيلية . ولقد وجد أن وجود البروبيلين جليكول والجلسرول فى تركيز ٥/ وزنا/حجم أزاد من المقدرة الاذابية لمنشطات السطح غير المتاينه موضوع الدراسة تجاه العقار فى درجة حراره ٢٥ مئوى. وأيضا وجد أن منشطات السطح غير المتأينه المحتوية على ١٠/ وزنا/حجم من كل عديد ايثليين جليكول ٤٠٠،عديد ايثليين جليكول ٤٠٠٠ أكثر كفاة فى اذابة العقار من ميثلاتها التى لاتحتوى على هذه الاضافات .

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