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EFFECT OF SOME HYDROXYLATED ADDITIVES ON THE MICELLAR SOLUBILIZATION OF METHOTRIMEPRAZINE

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ABSTRACT

The effect of different hydroxylated compounds on the solubility of Methotrimeprazine in non-ionic surfactant solutions was investigated at two different temperatures. Ethanol, glycerol, polyethylene glycol (PEG) 600 and PEG 4000, mannitol and sorbitol were studied as additives in systems containing Eumulgin C 1000, Eumulgin C 1500, Brij 35 and Brij 58 as the solubilizing surfactants.

Micellar solubilization of Methotrimeprazine was found to be increased in Brij 35 systems with all additives except at low concentration (5% w/v) of PEG 600. It also increased in systems of Brij 58 containing PEG 600, PEG 4000, mannitol and sorbitol.

A marked decrease in micellar solubilization of the drug was effected in systems of Eumulgins and Brij-58 containing ethanol or glycerol due to decreased micellization. Also, PEG 4000, mannitol and sorbitol decreased solubilizing effect of Eumulgins except for PEG 4000 with Eumulgin C 1000 at 35°.

INTRODUCTION

Mono-and Poly-hydroxylated organic compounds of different molecular weights were used to increase the solubility of drugs[1-4].

The solubilities of some sulfonamides in several normal alcohols were determined over a limited temperature ranges[1].

Polyoxyethylene glycol 300 was added to increase the solubility of sulfamethoxypyridazine[2]. Increase in equeous solubility of various drugs was effected by the use of PEG 400[3].

The effect of combination of polyethylene glycols and polysorbates on the solubility of salicylic acid was studied[4].

In this investigation, the effect of different hydroxylated compounds on the solubility of Methotrimeprazine was investigated at two different temperatures. Ethanol, glycerol , polyethylene glycol (PEG) 600 and PEG 4000, mannitol and sorbitol were studied as additives in systems containing Eumulgin C 1000, Eumulgin C 1500, Brij 35 and Brij 58 as the solubilizing surfactants.

EXPERIMENTAL

Materials:

Methotrimeprazine (American Cyanamide Co., USA), Cetyl stearyl alcohol with 20 ethylene oxide units (Eumulgin C1000), cetyl stearyl alcohol with 30 ethylene oxide units(Eumulgin C 1500), Henkel International, W. Germany), Polyoxyethylene-23-lauryl ether (Brij 35) and Polyoxyethylene-20-cetyl ether (Brij 58) (Atlas Chemical Co., USA), Ethanol, glycerol,

polyethylene glycol)(PEG) 600 and PEG 4000, Mannitol and sorbitol (B.D.H Chemicals, England). All chemicals of the commercial pure grades, were used without further purification.

Solubility determination:

Excess of Methotrimeprazine was equilibrated with 8 ml volume of the additive solution (5%, 10% or 20% w/v) containing surfactant (0, 2.5, 5, 7.5 and 10% w/v) in a 15-ml screw capped brown tubes. The tubes were shaken in shaking water bath (GFL, Germany) kept at a temperature of 25° and 35° + 0.2°C. The time required for equilibration was established by repetitive sampling and analysis. After equilibration, the tubes were centrifuged, reequilibrated, appropriately diluted and assayed spectrophotometrically (Pye-Uncam SP6-400) at 251.5 nm. In all cases, the presence of the solubilizers or additives did not interfere with the assay. A proprely prepared blank was used during the measurements. The drug was protected from light allover the experimental work.

RESULTS AND DISCUSSION

The micellar solubilization of Methotrimeprazine in different concentrations of non-ionic surfactants was the subject of previous report[5]. The studied additives affect the solubility of Methotrimeprazine in surfactant solutions (Table 1 and Fig. 1-4). Ethanol decreased the solubility of Methotrimeprazine to a great extent in all the studied

solutions except Brij 35 solution. Ethanol has been known to affect the CMC of surfactants and in concentrations above 5% it even inhibits micellization[6].

The presence of glycerol likewise decreased the solubility of the drug in the surfactant solutions, but to a lesser extent (Fig. 2). The decrease in solubilizing power of surfactants was greater when the concentrations of glycerol was increased from 10 to 20%. Glycerol increased the amount of Methotrimeprazine solubilized in Brij 35 solution. Glycerol decreased the solubilization in Eumulgin and in Brij 58 probably because the drug is incorporated mainly in, or near the lipophilic core, while glycerol is oriented to the polyoxyethylene capsule resulting in an increase in the capsular volume on the expense of the core volume with subsequent decrease in drug solubilized.

The presence of polyethylene glycols increased the solubility of Methotrimeprazine in water, i.e, it acted as a co-solubilizer for Methotrimeprazine in the continuous phase. This is evident by comparing the intercept in Fig 1 and that of Fig. 3 and by the decrease in distribution coefficient (K_m) for Methotrimeprazine (Table 1) calculated as C_m/C_w, where C_m is the concentration of the drug in the micellar phase and C_w is the concentration of the drug in the aqueous phase.

The effect of PEG 4000 compared with the effect of a similar concentration of PEG 600 is as follows: for Eumulgin C 1000, and because of its shorter polyoxyethylene chain, PEG 4000 has a less effect on solubilization of Methotrimeprazine than PEG 600 at 25°. For Brij 35 of longer polyoxyethylene

chain an increase in the amount solubilized took place in the the presence of PEG 4000 than PEG 600.

The sugar alcohols mannitol and sorbitol increased the solubilizing power of Brij 35 >> Brij 58, while they decreased the solubility of Methotrimeprazine in Eumulgin C 1000 and C 1500 solutions.

By raising the temperature from 25° to 35°, the systems containing glycerol, mannitol and srobitol showed a negative temperature effect on the solubilizing capacity of the non-ionic surfactants studied toward Methotrimeprazine (Table 1). The penetration of these hydroxylated molecules increases by thermal agitation into the solubilizing core or polyoxyethylene region close to the micellar core, thus decreases the solubility of the drug.

According to Elworthy and Patel[7] the main locus of solubilization appears to be the polyoxyethylene mantle close to the micelle core/mantle interface and not the hydrocarbon core itself. Most of the results obtained can be explained in view of this assumption. The change of solubilizing power of the studied non-ionic surfactants in the presences of such hydrophilic additives can be explained by their effect either on the density of the polyoxyethylene mantle in the solubilizing region near the core, or on the geometry of the region and the way by which the solubilizate molecule fits into the concentrated polyoxyethylene region.

Table 1: The effect of different additives on the solubility (S) and the distribution coefficient (K_m) of Methotrimeprazine in different non-ionic surfactant solutions at 25°and 35°C

Additive	*Conc w/v*	*Eumulgin C 1000*				*Eumulgin C 1500*				*Brij 35*				*Brij 58*			
		25°		*35°*		*25°*		*35°*		*25°*		*35°*		*25°*		*35°*	
		S	K_m	*S*	K_m	*S*	K_m	*S*	k_m	*S*	K_m	*S*	K_m	*S*	K_m	*S*	K_m
None		19.3	414.3	19.9	282.3	14.8	284.3	15.2	219.6	27.8	533.1	29.7	420.7	14.6	275.8	23.6	316.7
Ethanol	10%	5.6	75.8	8.5	93.4	4.6	63.0	6.2	62.9	171.3	2630.9	150.2	1820.9	6.8	92.5	11.5	120.8
Glycerol	10%	17.6	104.7	16.7	96.5	11.2	74.0	10.7	52.3	273.4	1401.5	242.3	1324.8	13.4	82.8	12.1	82.2
Glycerol	20%	7.6	33.6	6.9	30.2	5.9	22.7	5.5	13.4	267.2	1221.9	297.8	1134.5	11.7	61.3	11.3	52.6
PEG 600	5%	19.7	61.4	27.1	84.2	12.5	34.7	17.3	53.5	25.8	76.6	28.7	91.7	14.1	42.3	30.8	102.5
PEG 600	10%	19.4	54.3	21.0	56.9	11.7	33.3	12.4	33.4	158.2	334.1	198.0	429.8	47.3	124.5	48.0	129.1
PEG 4000	10%	11.1	135.6	28.1	245.3	7.2	163.0	16.3	137.3	191.2	1711.7	200.5	1528.7	18.6	202.7	[illegible]	450.9
Mannitol	10%	14.8	116.4	13.8	150.7	12.0	85.0	11.4	99.0	280.7	2012.3	254.5	2692.4	18.7	152.0	16.3	176.8
Sorbitol	10%	17.7	137.4	16.1	126.7	13.5	98.5	12.7	97.6	350.9	2595.2	313.4	2661.0	20.2	155.8	17.8	192.3

S = Solubility mg/g of Methotrimeprazine in the surfactant calculated from the slopes of the least square plots.

K_m = C_m/C_w where C_m is the concentration of the drug in the micellar phase and C_w is the concentration of the drug in the aqueous phase.

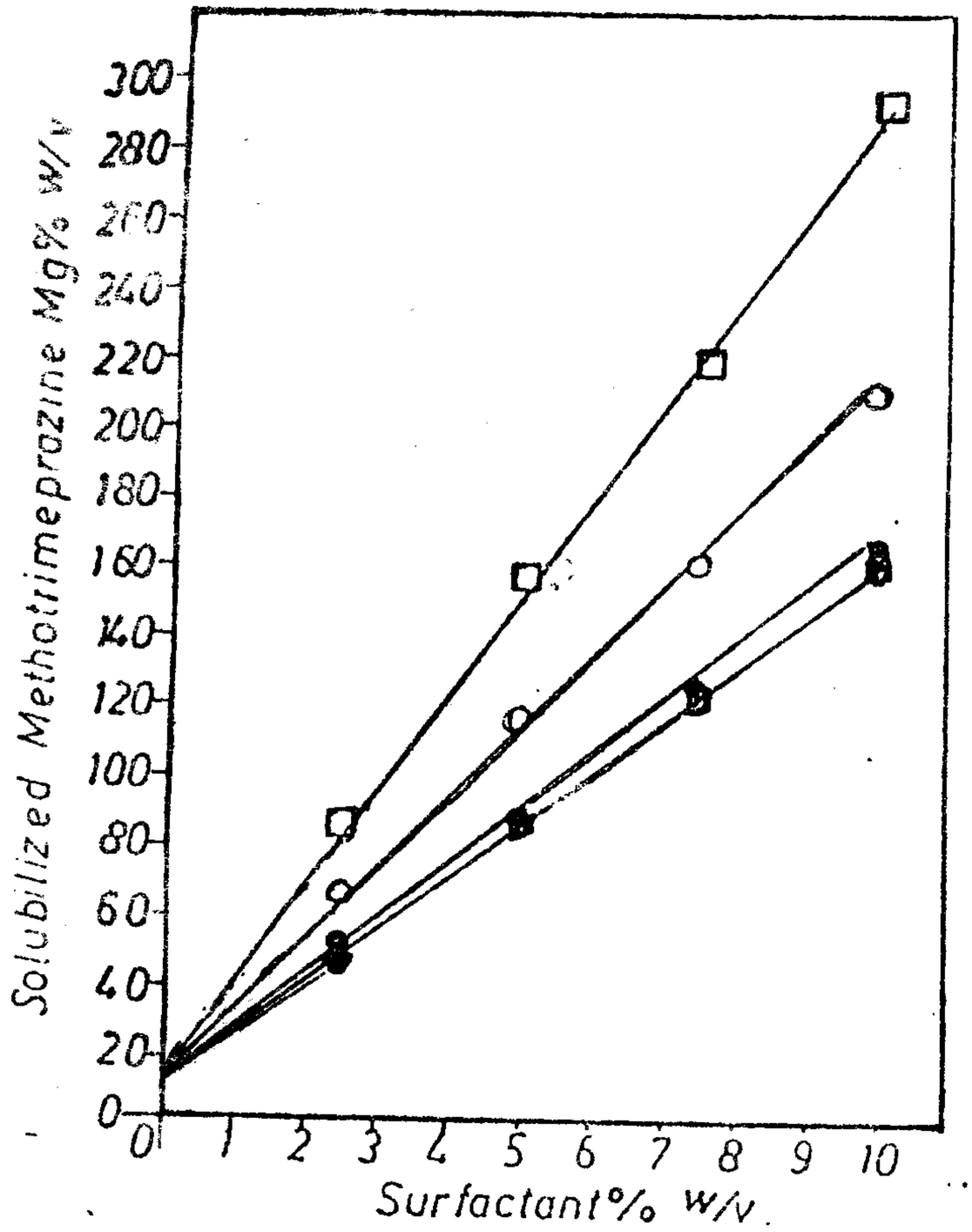

Fig. 1: Effect of different concentrations of non-ionic surfactants on the solubilization of methotrimeprazine at 25°.
○ Eumulgin C 1000 ● Eumulgin C 1500
□ Brij 35 , ■ Brij 58

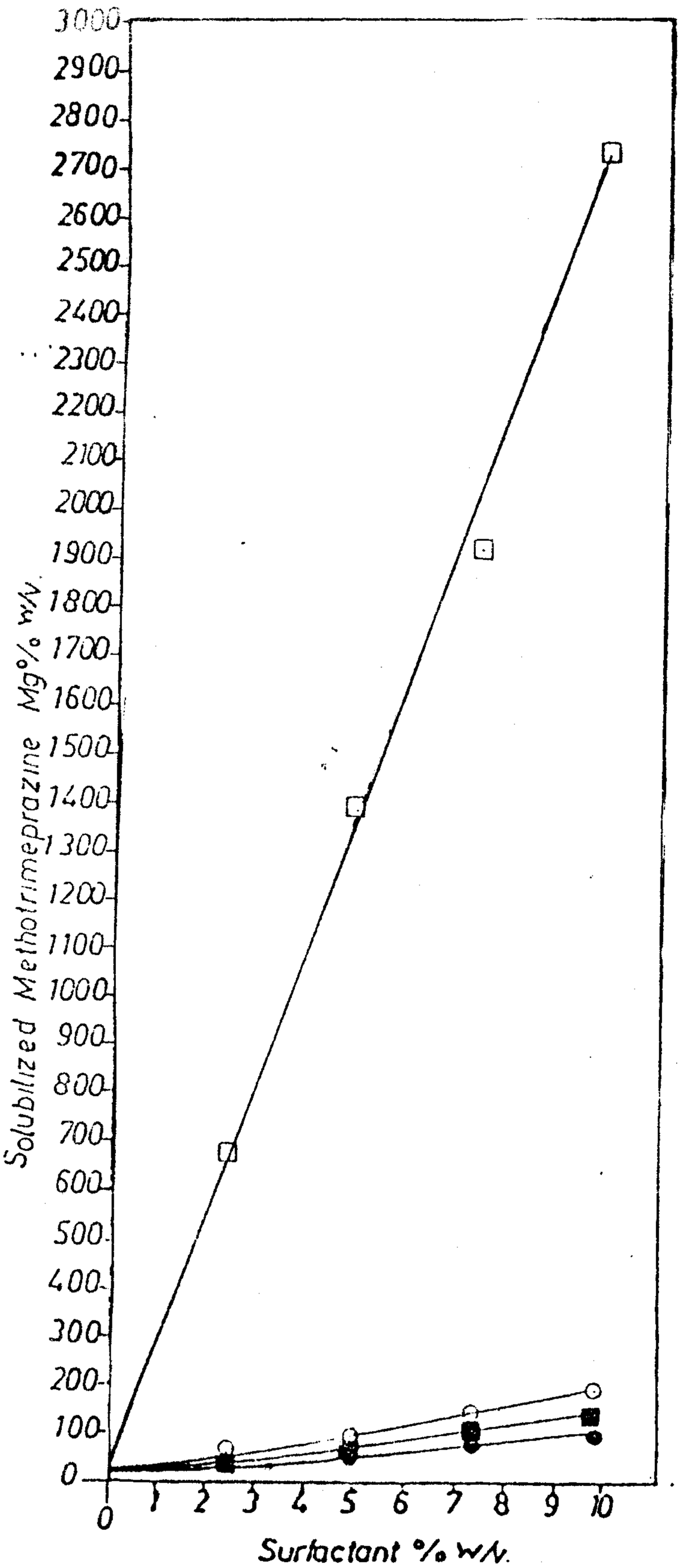

Fig. 2: Effect of different concentrations of non-ionic surfactants containing 10% glycerol on the solubilization of methotrimeprazine at 25°

o Eumulgin C 1000 • Eumulgin C 1500
□ Brij 35 , ■ Brij 58.

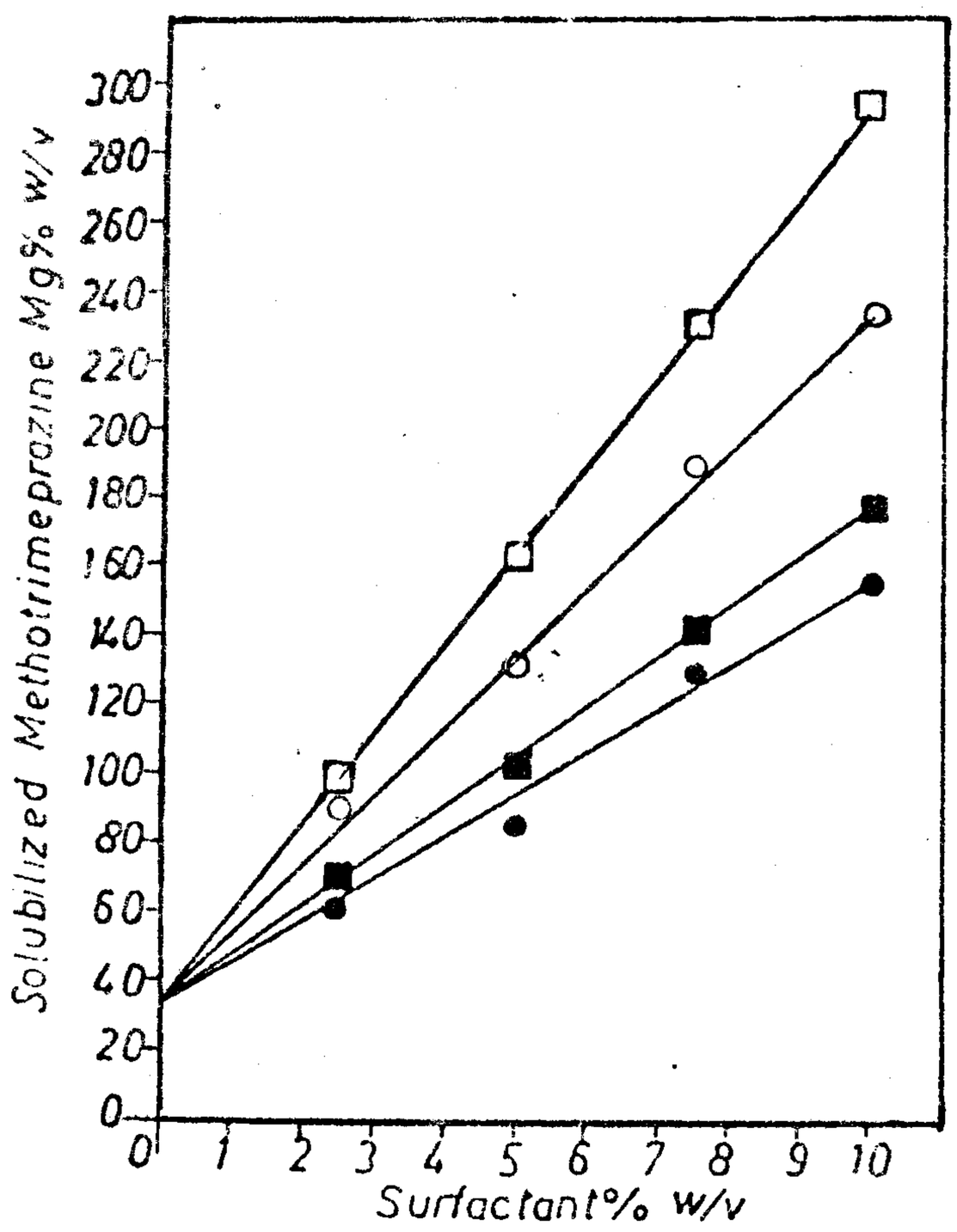

Fig. 3: Effect of different concentrations of non-ionic surfactants containing 5% w/v PEG 600 on the solubilization of methotrimeprazine at 25°.
o Eumulgin C 1000 • Eumulgin C 1500
□ Brij 35 , ■ Brij 58.

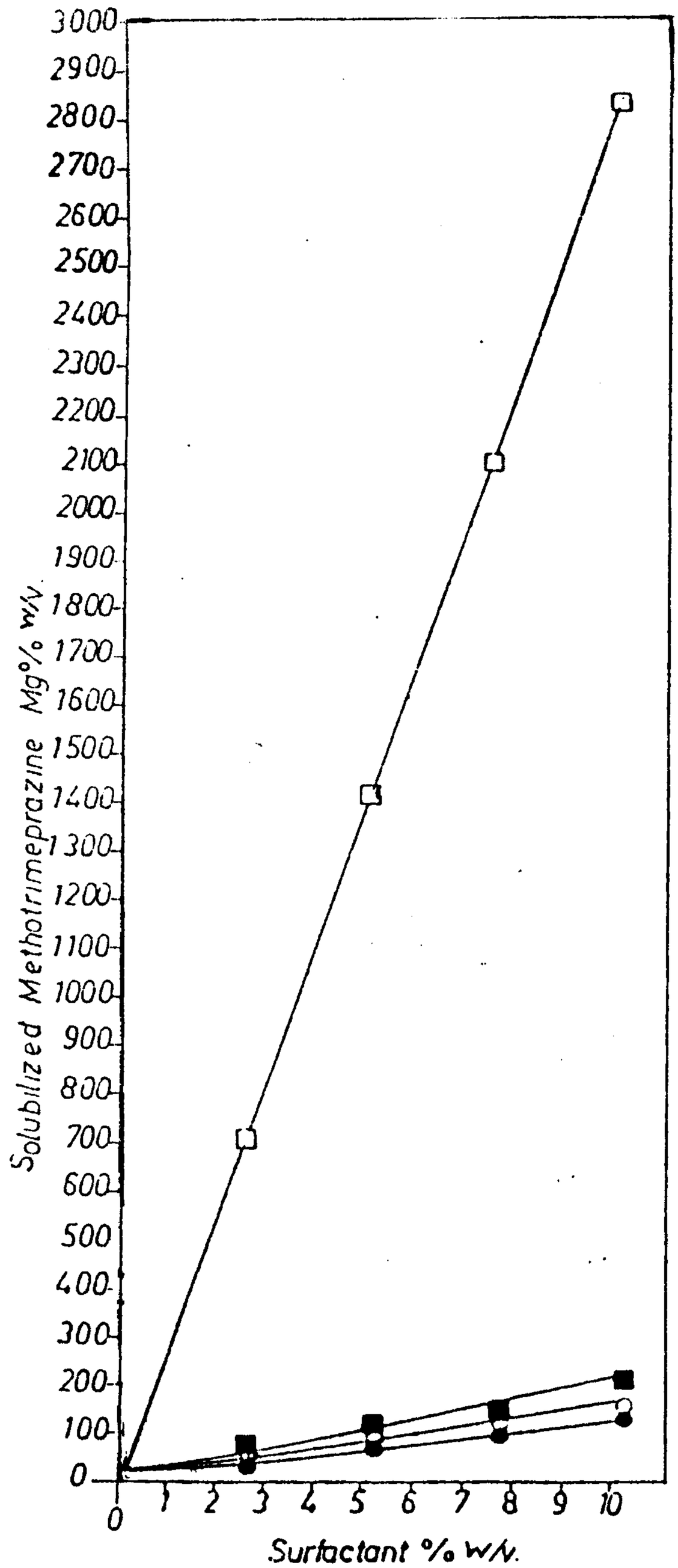

Fig. 4: Effect of different concentrations of non-ionic surfactants containing 10% mannitol on the solubilization of methotrimeprazine at 25°

o Eumulgin C 1000, ● Eumulgin C 1500
□ Brij 35, ■ Brij 58

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تأثير بعض الأضافات الهيدروكسيلية على التذويب الشبكى للميثوترای مبرازين

احمد السيد ابو طالب ـ منير صبحى مسيحة ـ على عبد الظاهر

درس تأثير بعض المركبات المحتوية على واحده أو اكثر من مجموعة الهيدروكسيل على ذائبية الميثوترای مبرازين فى محاليل منشطات السطح غير الايونية عند درجتى حرارة مختلفتين . ومن الاضافات الهيدروكسيلية استخدام كل من الايثانول والجليسرين وعديد الايثلين جلايكول ٤٠٠٠،٦٠٠ والكحولات السكرية المانيتول والسوربيتول ودرست فى انظمة الدواء المذاب فى تركيبات مختلفة من الايومالجين سى ١٠٠٠ وسى ١٥٠٠ ،بريج ٣٥ وبريج ٥٨.

وجد ان التذويب الشبكى للميثوترای مبرازين يزداد فى انظمة البريج ٣٥ المحتوية على أى من الاضافات المدروسة ماعدا التركيز المنخفض من عديد الايثلين جلايكول وازداد ايضا فى انظمة البريج ٥٨ المحتوية على الايثلين جلايكول ٤٠٠٠،٦٠٠ والمانيتول والسوربيتول .

انخفض التذويب الشبكى بوضوح فى انظمة الايومالجين وبريج ٥٨ المحتوية على الايثانول والجليسرين لتأثيرهما على تكوين الشباك . وقلل عديد الايثلين جلايكول ٤٠٠٠ وامانيتول والسوربيتول التاثير المذيب للايومالجينات باستثناء عديد الايثلين جلايكول ٤٠٠٠ مع الايومالجين سى ١٠٠٠ وعند ٣٥° .

وقد فسرت الزيادة فى ذائبية الميثوترای مبرازين فى وجود عديد الايثلين جلايكول الى تاثيرهم المباشر على ذائبية الدواء .

وقد فسرت التاثيرات المختلفة للاضافات المحبة للماء بان هذه الاضافات توثر بشكل مباشر على طبقة عديد الاوكس ايثلين فى الحويصلة الملاصقة لطبقة النواه المحب للدهون فى الشباك وربما تؤكد هذه النتائج ان مكان التذويب الفعلى للدواء يكون فى المنطقة الفاصلة بين النواة محبة الدهون والطبقة الوعائية المغلفة من مجموعات الاوكس ايثلين .

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