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SOLUBILIZATION OF MEFENAMIC ACID BY NON - IONIC SURFACTANTS

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Mefenamic acid was solubilized by series of non-ionic surfactant solutions. It was found that the solubilizing capacity of the surfactant solution increased linearly by increasing the surfactant concentrations above their CMC's.

The solvent power of the different micelles was affected by change in surfactant structure.

Surface active agents are widely used as formulation adjuvants. Numerous reports indicate that they play an important role in the absorption and efficacy of certain drugs. Either enhancement[1-3] or inhibition[1-5] of the absorption and pharmacological activity of drugs may be observed when surfactants are included in a formulation. Much of the difficulties in interpreting studies involving surfactants has been related to the different effects such compounds can exert. These include interaction of

these agents with biological membranes, with the drug, with the dosage form, as well as their possible pharmacological effect and ability to modify membrane permeability.

Mefenamic acid is analgesic drug with anti-inflammatory properties, used to relief mild pain and pain resulting from dental extractions[6,7]. It has poor water-solubility and a common side effect which is gastric irritation, so,it is contraindicated in patients with ulceration of the upper or lower intestinal tract. The less time this drug is in contact with the gastrointestinal mucosa, the lower the incidence of this adverse effect, so it should be so formulated as to ensure rapid absorption. Such rapidly absorbed formula improves the drug bioavilability by producing a more consistant therapeutic response and diminishing the influence of biological variables on the absorption process.

The objective of this investigation was to solubilize mefenamic acid by different types of non-ionic surface active agents, in order to reduce the gastric irritation and improve bioavailability.

EXPERIMENTAL

Materials:

Mefenamic acid (was kindly supplied by El-Nile Company for Pharmaceuticals and Chemical Ind.; Tweens 20, 40, 60, and 80, Brijs 35, 96 and 98, Myrjs 52, 53 and 59.(Atlas Chemical Ind., Wilmington. Dela, U.S.A.)

Methods:

1- Detemination of Mefenamic acid: The ultra-violet spectrum of mefenamic acid in water and 0.1 N sodium

hydroxide was measured and it was found to be characterized by 2 peaks at 283 nm. and 333 nm. The ultra-violet spectrum of the surfactants used showed absorbance at 283 nm. and not at 333 nm. So, a standard curve for absorption of mefenamic acid in 0.1 N sodium hydroxide was determined at 333 nm. and found to obey Beer's law. This emphasizes that the suggested method was valid for the estimation and, thus, was of choice for this study.

2- Solubility measurements: The solubility measurements were performed by shaking excess mefenamic acid with various concentrations of the surfactant solutions for 14 days at $30^{\circ} \pm 1$. Samples for assay were filtered through No 3 seitz filter and their mefenamic acid contents were determined by reading the absorbance at 333 nm. after appropriate dilutions.

RESULTS AND DISCUSSION

The solubility of mefenamic acid was found to increase linearly by increasing the surfactant concentrations above CMC. This linearity indicates that micellar solubilization could be the possible mechanism[8].

On using Tween series which possess different hydrocarbon chain lengths, but the same ethylene oxide part, for the solubilization of this drug, it was found that the solubility increased by extending the hydrocarbon chain lengths from Tweens 20, 40, 60 to 80 as shown in Fig. 1. This indicates that the volume of the core of these micellar forming materials was mainly responsible for their solvent power, assuming that there is a balanced volume of

the capsule to give rise to water-soluble surfactant with suitable HLB value. In this case, the greater the volume of the core, the higher the amount of such solute that can be solubilized by micelles. This can explain the higher solvent power of Tween 80 over Tweens 60, 40, and 20 solutions for mefenamic acid and indicates that this drug was solubilized mainly in the core of the micelles.

On examining the quantity of mefenamic acid in a homologous series having the same polyoxyethylene chain, the same capsule, but differing in the length of the hydrocarbon chain, the core, as Brijs, it is obvious that the longer the hydrocarbon chain, the greater the amount of mefenamic acid solubilized. That is why Brij 98 is more efficient as a solubilizer than Brij 35. This finding agrees with other workers[9,10].

In a homologous series of nonionic surfactants having the same hydrocarbon chain, but differing in the polyoxyethylene chain of the micelle, i.e., Myrj, it was found that increasing the length of the polyoxyethylene chain caused a marked decrease in the amount of mefenamic acid solubilized. That is why Myrj 59 is less efficient as a solubilizer than Myrj 52. This finding agrees with other workers[8,11-14].

The distribution coefficient (km) was found to be higher for those micelles with bigger core volume as shown in Table 1. The higher the value of the distribution coefficient, the greater the amount of mefenamic acid that can be solubilized by micelles, these values were affected mainly by the difference in the surfactant molecular structure.

For example, on using the Tween series, the solubility increased by extending the hydrocarbon chain lengths. On the other hand, when using non-ionic surfactants with different ethylene oxide chain lengths for the same hydrocarbon part, as in the case of Myrj series, the reverse action occurs. This may be due to decrease in the relative volume of the core to the total micellar volume by extending the volume of the capsule, and consequently a decrease in the amount of such solutes solubilized by micelles. This also indicates that the solvent power of the different non-ionic surfactants for the drug depends mainly on the length of their hydrocarbon chains, and consequently the volume of their cores as shown in Table 1.

Comparing the effect of different surfactants on the solubility of mefenamic acid, it is obvious that at 10% concentration, solubility of mefenamic acid increased 8, 6, 5 and 6 folds by Brij 98, 96 and 35 respectivly, while Tweens 80, 60, 40 and 20 increased the solubility 6.5, 6, 4 and 3 folds. On the other hand, Myrjs 59, 53 and 52 increased the solubility 2,3 and 3.5 folds only. Thus, the efficiency of surfactants toward solubilization of mefenamic acid can be arranged in the following order:

Brij 98 > Brij 96 > Tween 80 > Tween 60 = Brij 35 > Tween 40 > Myrj 52 > Myrj 53 > Tween 20 > Myrj 59.

The results obtained from the solubility measurements were analyzed as described by Mukerjee[15]. The distribution of mefenamic acid between the cores and the capsules of these non-ionic micelles was studied. Plotting the equivalents of drug solubilized per equivalent of ethylene oxide (S/C_{EO}) against stearate: ethylene oxide molar ratio (C_R/C_{EO}) for Myrj series, a linear relationship was obtained, from which the values of intercept and slope were calculated by the least square method. The ratios of the amount of drug in the capsule to the amount in the core were then calculated. From these data(Table 2 and Fig. 4) it would appear that solubilized mefenamic acid is localized mainly in the hydrocarbon cores and less associated with polyoxyethylene chains of the micelles. This finding agrees with other workers[16,17].

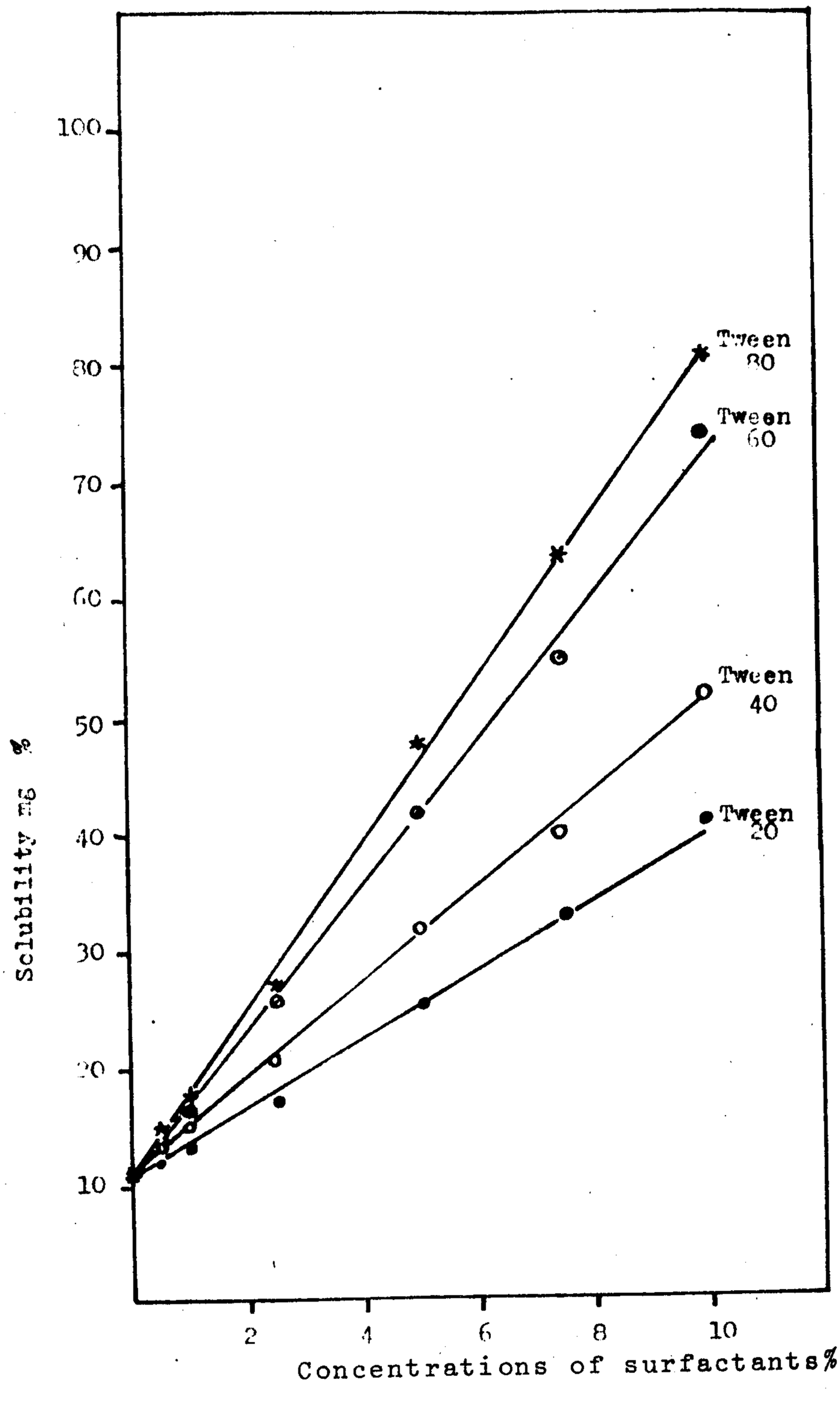
Table 1: Distribution Coefficients (km) of Mefenamic Acid Between the Micellar and Aqueous Phases at 30°

Surfactant		*Distribution coefficient (km)*
Tween	20	26
Tween	40	39
Tween	60	57
Tween	80	64
Brij	35	58
Brij	96	64
Brij	98	74
Myrj	52	31
Myrj	53	28
Myrj	59	16

Table 2: Distribution of Mefenamic Acid Between the Cores and Capsules of the Myrj-Micelles Calculated by Mukerjee's Method.

Surfactant	*Surfactant molecular mass*	*Weight of ethylene oxide part*	S/C_{EO}	C_R/C_{EO}	*Ratio of mefenamic acid in capsule and core*
Myrj 52 C_{17} E_{40}	2046	1777	0.0063	0.025	0.1028
Myrj 53 C_{17} E_{50}	2486	2217	0.0053	0.020	0.1088
Myrj 59 C_{17} E_{100}	4686	4417	0.0029	0.010	0.1150

N.B. The amount of mefenamic acid solubilized in the capsule equ/equ = 0.0006 and the amount solubilized in the core equ/equ = 0.2286.



Fir. 1: Solubilization of Mefenamic Acid by Different Brands of Tweens at 30°.

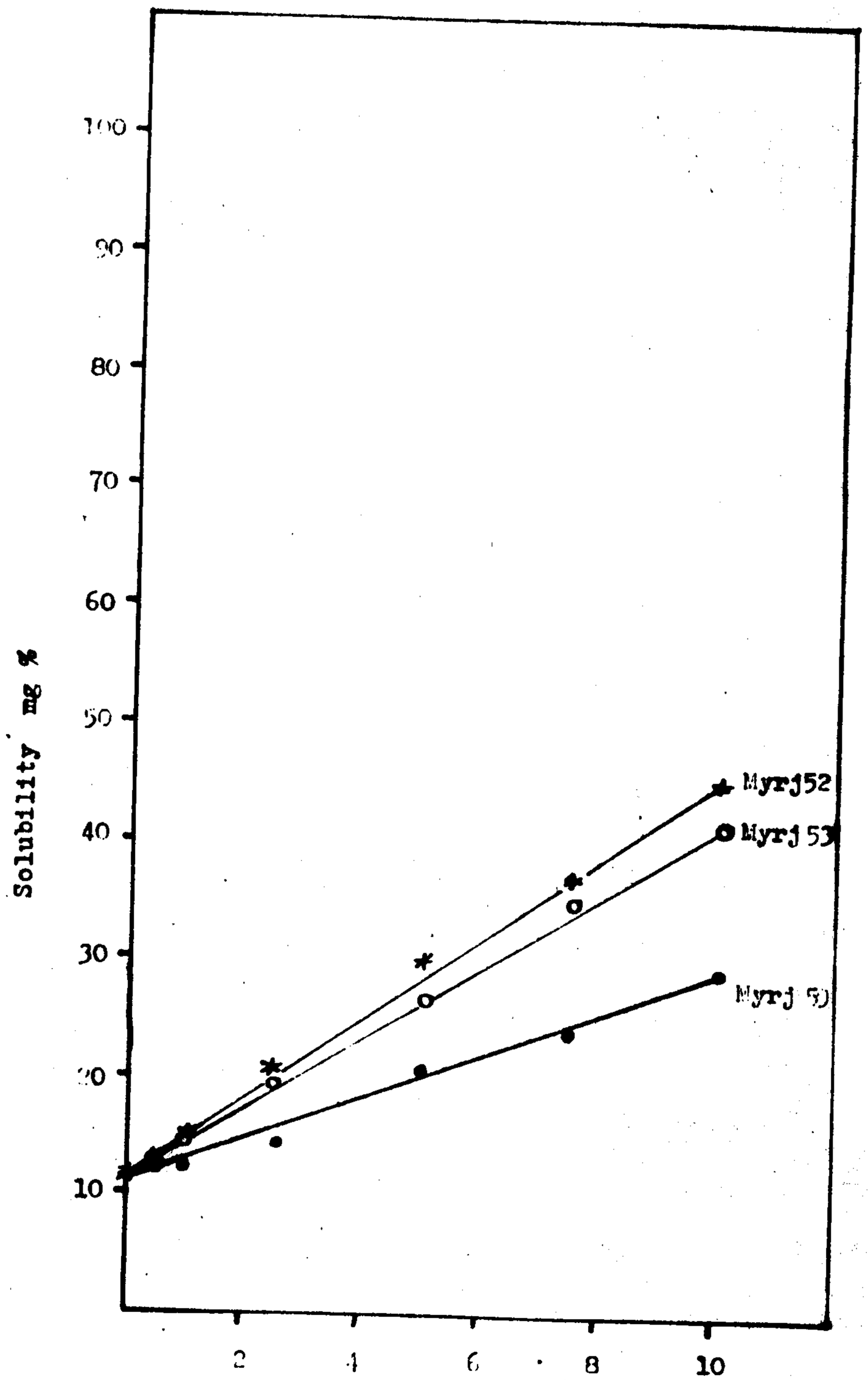


Fig. 2: Solubilization of Mefenamic Acid by Different Brands of Myrjs at 30°

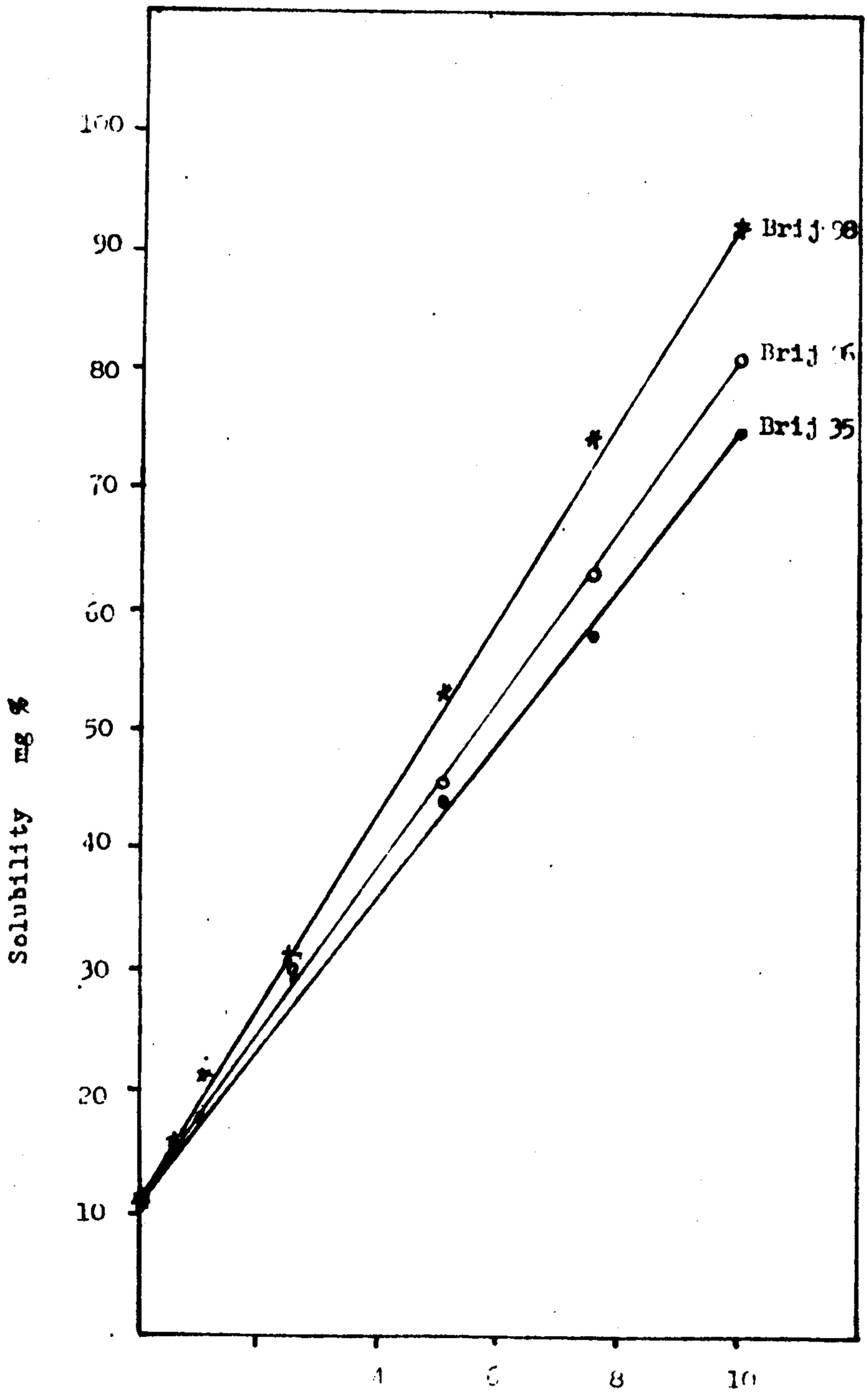


Fig. 3: Solubilization of Mefenamic Acid by Different Brands of Brijs at 30°.

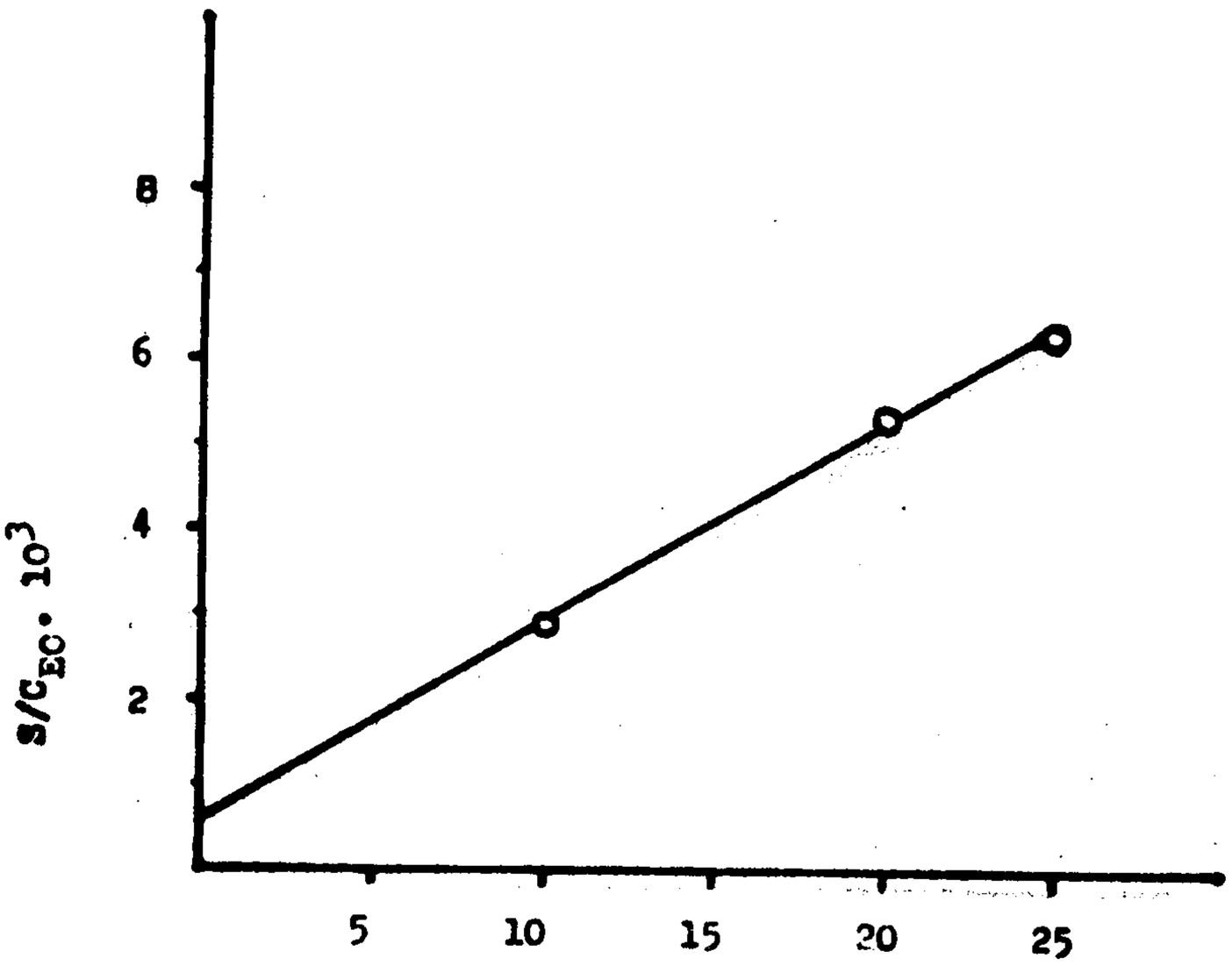


Fig. 4: Micellar solubilization of Mefenamic Acid in polyoxyethylene stearate at 30°

REFERENCES

1) *H.S. Bean; Pharm. Acta Helv., 35, 512 (1960).*

2) *P.M. Lish and J.H. Weikel; Toxicol. Appl.Pharmacol., 1, 501(1959)*

3) *K. Okuda, E. Duran, and B.F. Chow; Proc. Soc. Exp. Biol. & Med., 103, 588 (1960).*

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

5) *G. Levy, and R.H. Reuning; Pharm. Sci., 53, 1471 (1964).*

6) *Martindale " The Extra Pharmacopoeia" 25 th Ed., The Pharmaceutical Press, London (1967) p. 38.*

7) *E.A. Swingard (1980); in Remington's Pharmaceutical Sciences" Mack Publishing Company, Eston, Pannsylvania, p. 1059.*

8) *B.A. Mulley (1964) in " Advances in Pharmaceutical Sciences" Vol. 1 ed. H.S. Bean; A.H. Backett, and J.E. Carless; Academic Press London and New York, p. 90.*

9) *K. Shinoda (1963); in " Colloidal Surfactants " Academic Press Inc., New York.*

10) *P.H. Elworthy, and C.B. Macfarlane; J. Pharm. Pharmacol, 17, 65 (1965).*

11) *P.H. Elworthy, A.T. Florence and C.B. Macfarlane (1968); in"Solubilization by Surface Active Agents" Chapman and Hall LTD., London p. 13.*

12) *J.W. McBain, and E. Hutchinson, (1955); in Solubilization and related Phenoman " Academic Press Inc. New York.p.11.*

13) *P.A. Winsor, (1954) in "Solvent Properties of Amphiphilic Compounds " Betteworths Scientific Publication, London (1954).*

14) *T. Nakagawa, and H. Inoue, J. Chem. Soc. Japan, 78, 636 (1957).*

15) *P. Mukerjee; J. Pharm. Sci., 60, 1528 (1971).*

16) *A.E. Aboutaleb, A.M. Sakr, and S.I. Adel-Rahman; Pharmazie, 25. 99 (1980).*

17) *A.E.Aboutaleb, A.M. Sakr, H.M. El-Sabbagh, and S.I.Abdel-Rahman, ; Pharm. Ind. 42, 940 (1980).*

تذويب حمض الميفيناميك بواسطة منشـــطات السـطوح غير المتاينـــة

محمد على على قاسم ـ جلال محمد المحروق ـ علاء الدين على قاسم

اجريـــت دراســة لتـــذويب حمض ميفينلميك بـاستخدام بعض المـــواد ذات النشـــاط السـطحى غيـــر المتاينـــة وتشمل التوينـــات والمريجـــــات وقـــد ثبـــت مـــن النتـــائج ان المـــواد ذات النشـــاط السطحى طويـــلا الايدروكربونـــات لهـــا تأثيـــر يفوق قصيـــرة الايدروكربونات.

كمـــا وجـــد ان هنـــاك علاقة بين سلسلة عديد الاوكسى اثيلين والقوة الذوبانيـــة للمواد ذات النشاط السطحى.

وقد وجد ان اذابـة المـادة الدوائية يزيد بزيادة تركيز المادة ذات النشـــاط السطحى. المستخدمـة

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