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# A STUDY ON CERAIN SOLUBILIZED SYSTEMS CONTAINING CARBAMAZEPINE

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*Solubility and ultrafiltration techniques were used for studying solubilized systems containing carbamazepine. The effect of variations in the alkyl, as well as ethylene oxide chain lengths of the surfactant molecules on the degree of solubilization of this solute was investigated. The results obtained from the solubility measurements agreed well with those obtained from ultrafiltration experiments which gave further support to the partition model of solubilization.*

The formation of homogeneous liquids in acceptable dosage forms of pharmaceutical substance which have only limited solubility in water presents a technical problem to the industrial pharmacist.

To solve this problem, surfactants were used to increase the water-solubility of these pharmaceutical substances. Non-ionic surfactants were preferred over cationic and anionic surfactants as they are less toxic to biological system[1], effective as solubilizer at small concentration due to their low CMC value and compatible with most of the insoluble drugs[2].

Carbamazepine[3,4], an antiepileptic drug, was reported to have a very slight water-solubility which is inadequate for formulating it in aqueous solution suitable for giving the therapeutic dose. The purpose of this work was to study the solubilization of carbamazepine using series of non-ionic surfactant solutions which form micelles with different structures in the core and capsule regoins. Krasowska et al[5], studied the influence of surfactant structure on solubilization of indomethacin and cinmetacin. In the present work, solubility, as well as ultrafiltraction techniques were used for studying saturated and under-saturated solubilized system containing carbamazepine.

## EXPERIMENTAL

### Materials:

Carbamazepine (Ciba-Geigy Limited, Basle Switzerland). Polyoxyethylene (20) sorbitanmonolaurate, polyoxyethylene(20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate (Tween 20, 60 and 80 respectively), polyoxyethylene (40) starate, polyoxyethylene(50)stearate , polyoxyethylene (100) stearate (Myrj 52, 35 and 59, respectively), polyoxyethylene (20) cetyl ether, polyoxyethylene (23) lauryl ether (Brij 58 and 35, respectively) (Atlas Chemical Industrial, Inc. Will. Del. U.S.A.). Cetyl stearyl alcohol with 20 ethylene oxide units and cetyl stearyl alcohol with 30 ethylene oxide units (Eumulgin C 1000 and Eumulgin C 1500, respectively) (Henkel International, Dusseldrof, Western Germany).

### Apparatus:

Spectrophotometer (Pye-Unicam SP 400 - England). Amicon Ultrofiltration cell[1] model C 12 of capacity 10 ml.

Diaflo membrane UM05 (Amicon Corporation, Massachusetts, U.S.A.).

Methods :

1- Solubility determinations:

The solubility of carbamazepine was determined by equilibrating exess of carbamazepine with various concentrations of the surfactant solutions for 10days at 25° and 35° ± 0.1°C. Samples for assay were taken after centrifugation of the whole solution and their contents of carbamazepine were determined by reading the absorbance at 285 nm after appropriate dilutions with distilled water. The presence of surfactants did not interfere with the assay.

2- Ultrafiltration technique:

The semi-continuous method was used[6] for investigating the systems containing carbamazepine in 2% and 5% w/w surfactant solutions at a temperature of (32 ± 2°C). Carbamazepine solutions(10 ml + the dead volume 0.1 ml) were ultrafiltered through UM-05 membrane. A pressure of 50 lb/in$^2$ was applied to the ultrafiltration cell model C 12 (Amicon corporation) and stirring was started. Five fractions of effluent, each of 5 ml were collected in two portions, each fraction was replaced by 5 ml of distilled water. Carbamazepine was analysed in the second portion of each fraction by reading the absorption at 285 nm after appropriate dilutions with distilled water. Results obtained were plotted as $-\log \frac{Cn}{Co}$ against (n-1), where Cn and Co are the concentrations in the effluents and the initial concentrations respectively, and n is the number of effluents collected.

## RESULTS AND DISCUSSION

### 1- Solubility measurements:

The systems investigated were one liquid, plus solid which is carbamazepine. It was found that the solubility of carbamazepine increases linearly by increasing the surfactant concentrations. As shown in Fig 1,2 which indicates that micellar solubilization is the main process involved in this case[7]. Kanig et al[8] reported that on increasing the temperature from 27 to 45°, an increase in solubility of glutethimide, griseofulvin and hexesterol in bile salt was obtained.

From Fig. 3,4 it was evident that temperature rise from 25° to 35° results in an increase in the amount of Carbamazepine solubilized. This may be due to increase in aggregation number, consequently the micelle becomes more larger in size which can accomodate more of this lipophilic solute. The distribution coefficient defined as Km= Cm/Cw, where Cm is the concentration of the solute in the micelle (w/w) and Cw is the concentration of the solute in the aqueous phase (w/w), were found to differ by veriations in the surfactant molecular structure as shown in Table 1.

The higher the value of the distribution coefficient, the greater the amount of solute that can be incorporated within the micelles, assuming that the solute was solubilized by partition between the micellar and aqueous phases. On using Tween or Brij series which possess different hydrocarbon chain lengths, but the same ehtylene oxide part for solubilization of carbamazepine, it was found that the solubility increased generally by extending the hydrocarbon chain length from Tween 20 to 60 to 80 and Brij 35 to 58

respectively. This may be due to the increase in the core volume of the micelle.

On using non-ionic surfactants with different ethylene oxide chain lengths for the same hydrocarbon part, as in case of Eumulgin and Myrj series, it was found that the solubility decreased by extending the ethylene oxide chain length from Eumulgin C 1000 to Eumulgin C 1500 and Myrj 52 to 53 to 59 respectively. This may be due to dcrease in the relative volume of the core to the total micellar volume by extending the ethylene oxide chain length, and consequently a decrease in the amount of carbamazepine that can be solubilized by micelles. This also indicates that carbamazepine was solubilized mainly within the core of micelles rather than the capsule.

II- Ultrafiltration technique:

The results obtained from the ultrafiltration experiments were plotted in the appropriate manner as shown in Figs. (5-8), and were found to give straight lines which agrees with the proposed theoretical treatment as a partition process ( 9,10). The distribution coefficient obtained using the fraction free F agrees with those obtained from the solubility measurements as shown in table 2.

This method is of particular interest as it can be used for estimating the degree of interaction between the solute and non-ionic surfactants within a short time (11). Shimamoto et al[12], used ultrafiltration technique for studying the effect of polyols on the interaction of p-hydroxybenzoic acid esters with polyoxyethylene dodecyl ether. In these experiments, the availability of carbamazepine from solution (amount free)containing these non-ionic surfactants can be determined precisely even on using very low concentration of this solute in the surfactant solution and within a considerably shorter time.

Table 1: Distribution Coefficient (Km) of Carbamazepine between the Micellar and Aqueous Phases at Different Temperatures.

| *Non-ionic Surfactant* | | *Distribution Coefficient (Km)* | |
|---|---|---|---|
| | | *25°* | *35°* |
| Polysorbate | 20 | 96 | 55 |
| Polysorbate | 60 | 112 | 69 |
| Polysorbate | 80 | 122 | 83 |
| Eumulgin C | 1000 | 165 | 125 |
| Eumulgin C | 1500 | 139 | 108 |
| Brij 35 | | 112 | 90 |
| Brij 58 | | 154 | 119 |
| Myrj 52 | | 103 | 84 |
| Myrj 53 | | 93 | 81 |
| Myrj 59 | | 73 | 60 |
| Sod. lauryl sulphate | | 771 | 631 |
| Cetrimide | | 296 | 500 |

Table 2: Comparison between the Distribution Coefficients Calculated from the Saturated Solubility Measurements and Ultrafiltration Experiments for Solubilized Carbamazepine in Surfactant Solutions.

| *Surfactant* | | *Km Calculated from solubility measurements* | | *Km Calculated from ultrafiltration experiments* |
|---|---|---|---|---|
| | | *25°* | *35°* | *32 ± 2°* |
| Polysorbate | 20 | 96 | 55 | 81 |
| Polysorbate | 80 | 122 | 69 | 89 |
| Eumulgin C | 1000 | 165 | 125 | 125 |
| Eumulgin C | 1500 | 139 | 108 | 118 |
| Myrj 52 | | 103 | 84 | 85 |
| Myrj 59 | | 73 | 60 | 67 |

*A Study on certain solubilized systems containing carbamazepine*

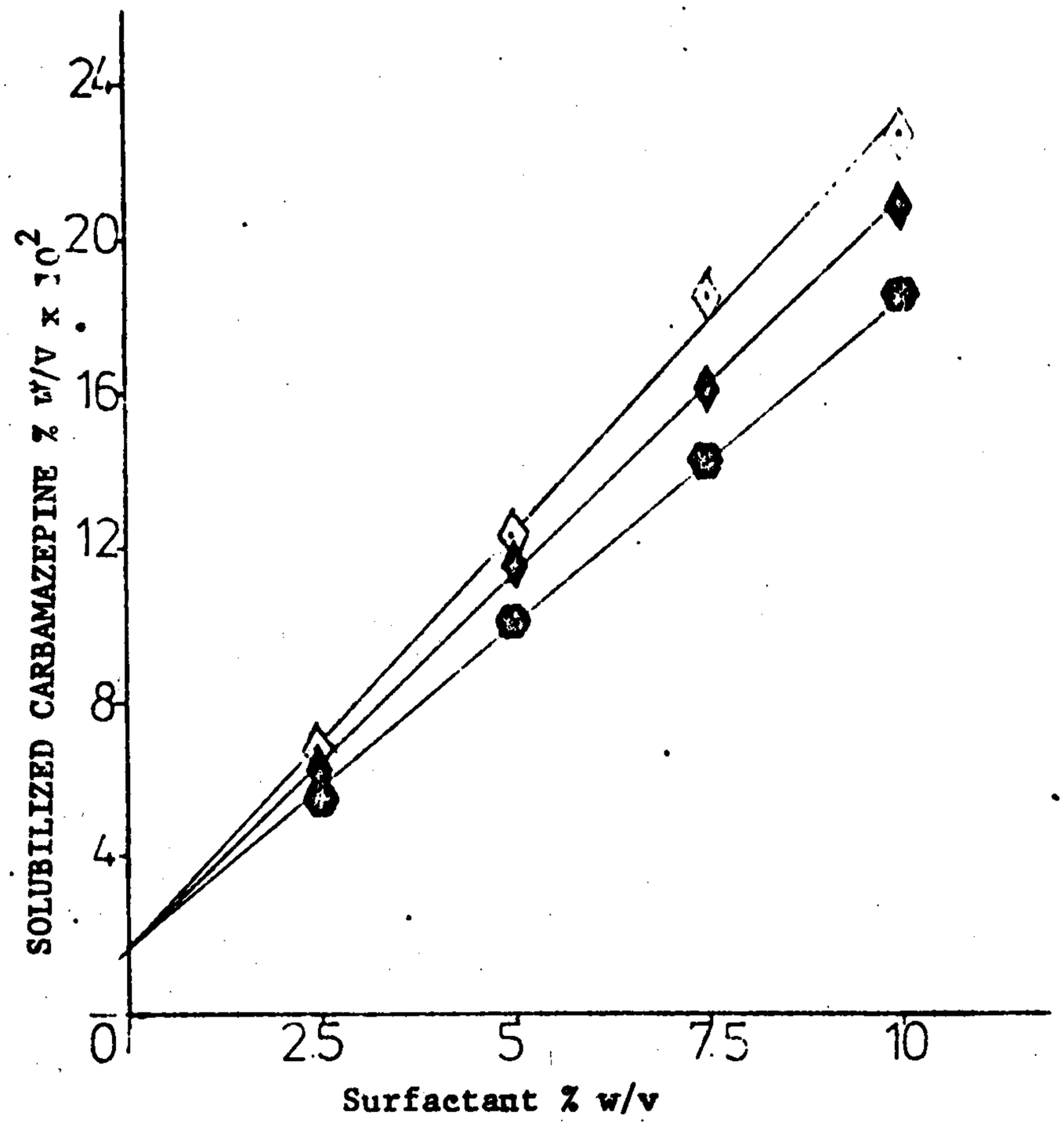


**Fig. 1: Solubility of carbamazepine in different non-ionic surfactant solutions at 25°.**

**Key:** ◇ **Polysorbate 80,** ◆ **Polusorbate 60.**
● **Polusorbate 20.**

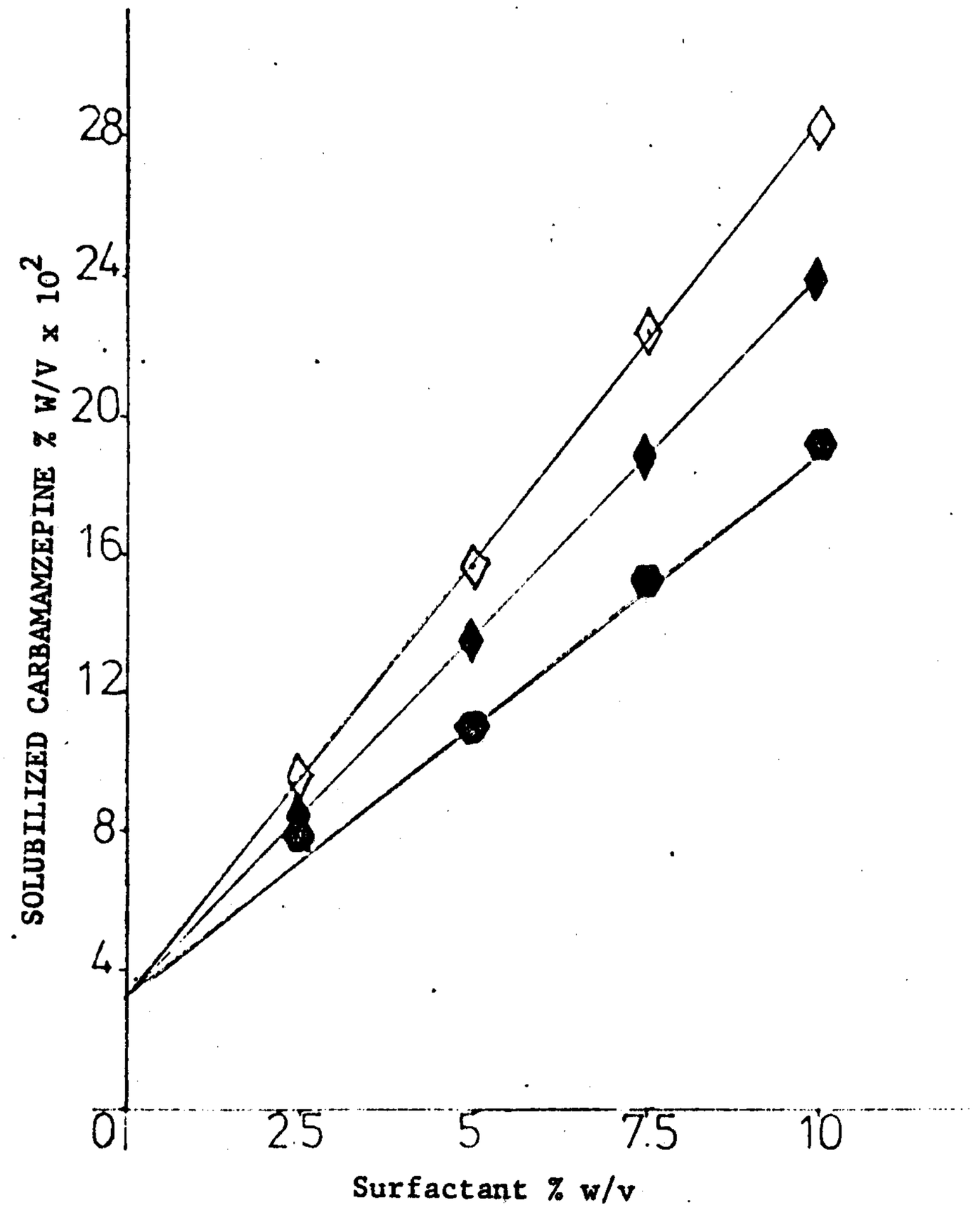


Fig. 2: Solubility of carbamazepine in different non-ionic surfactant solutions at 35°.

Key: The same as in Fig. 1

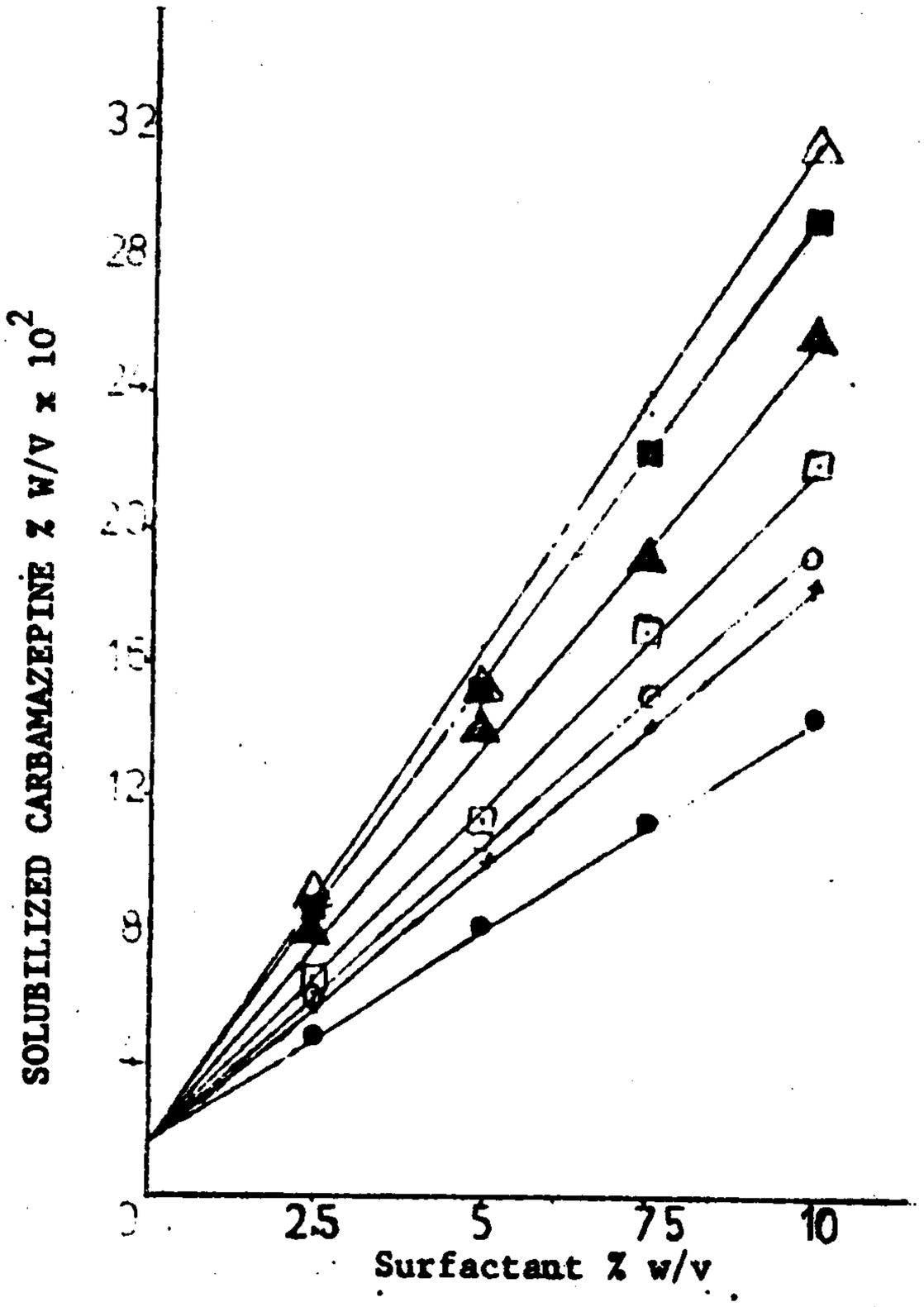


Fig. 3: Solubility of carbamazepine in different non-ionic surfactant solutions at 25°.

Key: △ Eumulgin C1000 ▲ Eumulgin C1500
□ Brij 35 ■ Brij 58 + Myrj 53 ● Myrj 59
○ Myrj 53

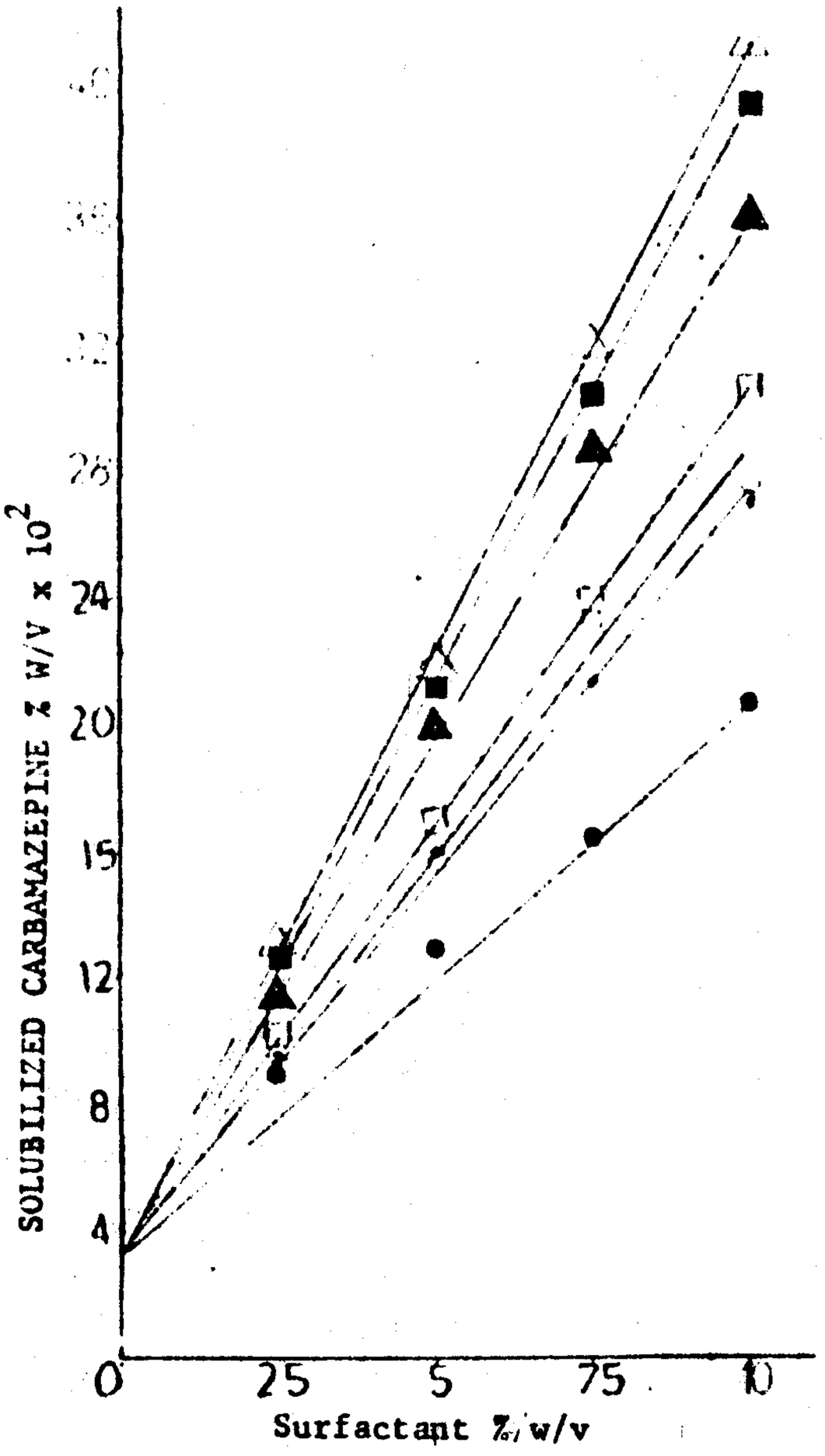


Fig. 4: Solubility of carbamazepine in different non-ionic surfactant solutions at 35°.

Key: The same as in Fig. 3

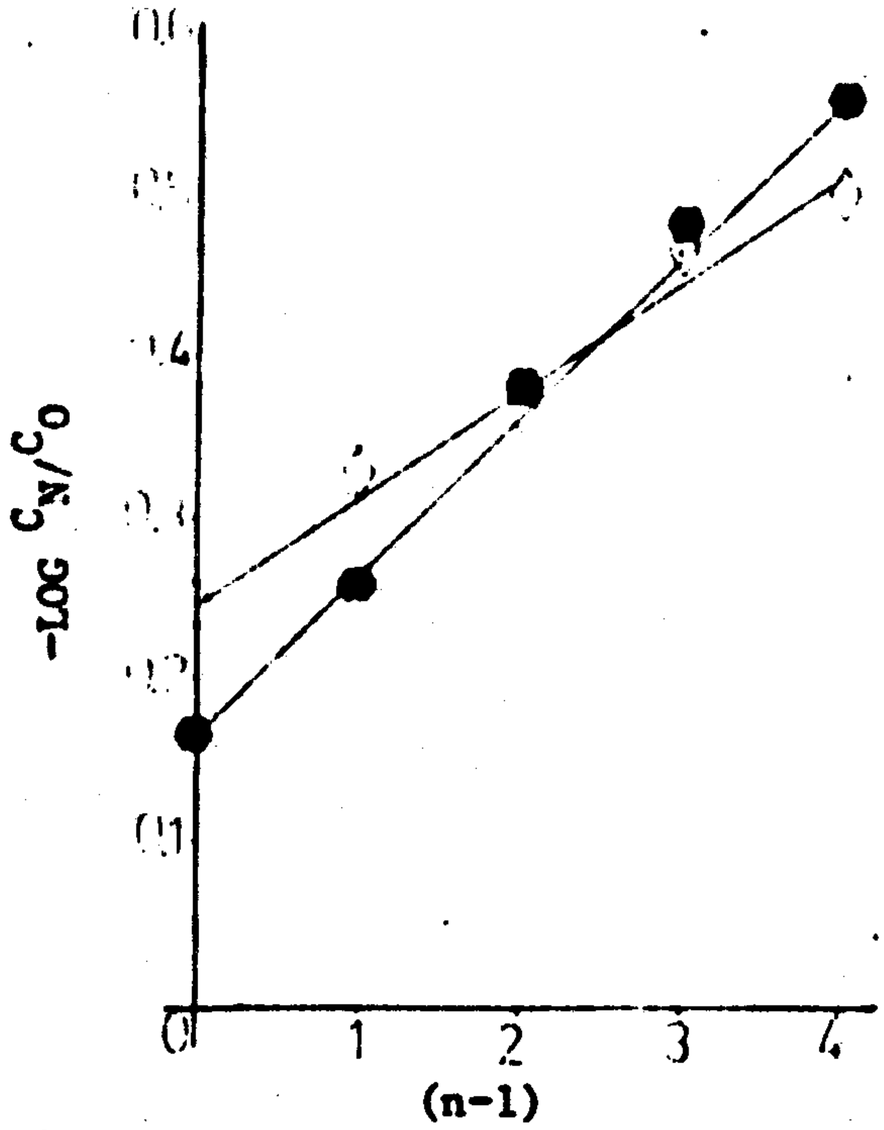


**Fig.5: Ultrafiltration experiments using different concentrations of carbamazepine in 2% w/v polysorbate solutions**

**Key: ◇ Polysorbate 80 ● Polysorbate 60**

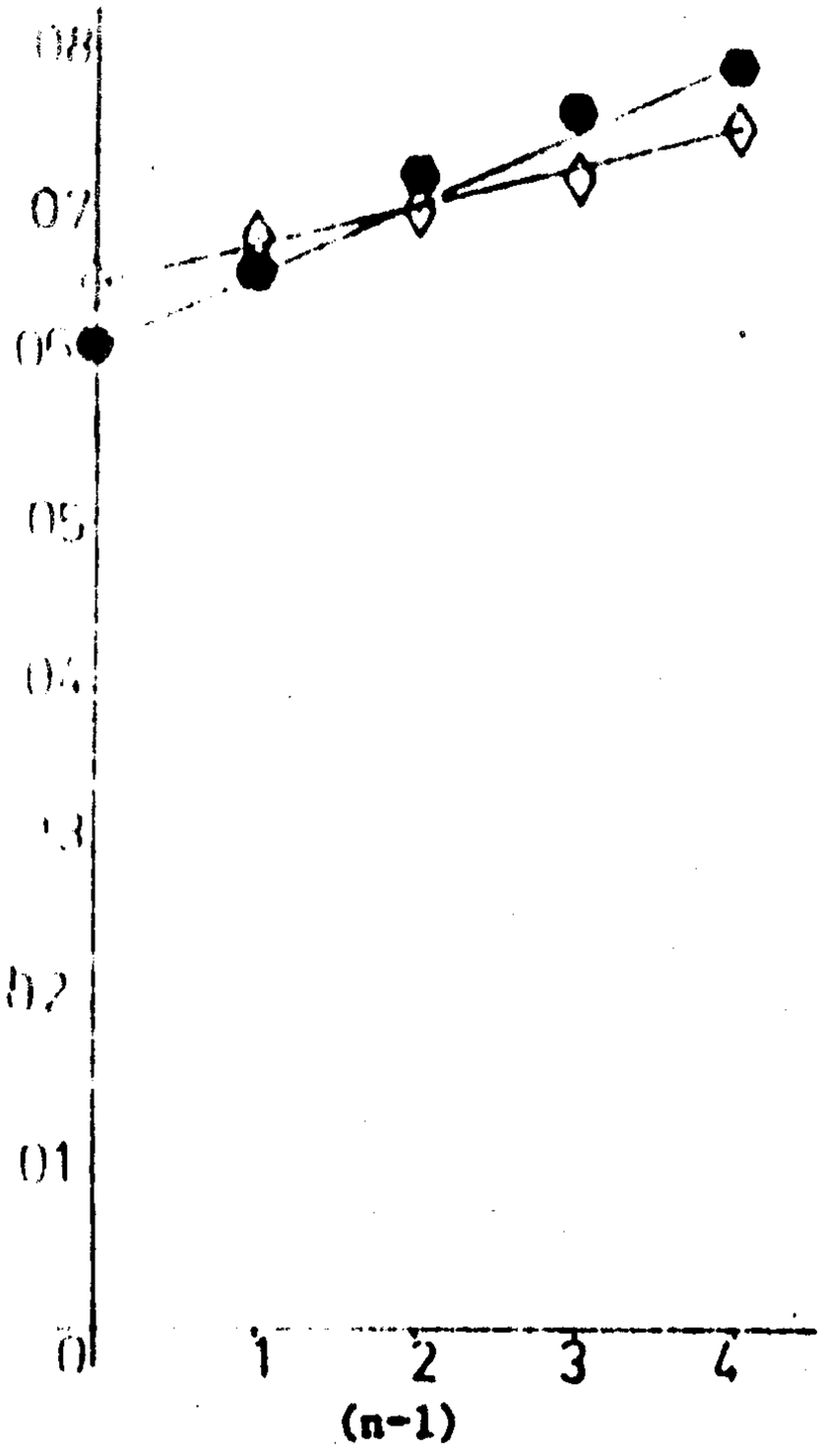


Fig. 6: Ultrafiltration experiments using different concentrations of carbamazepine in 5% w/v polysorbate solutions

Key: The same as in Fig. 5

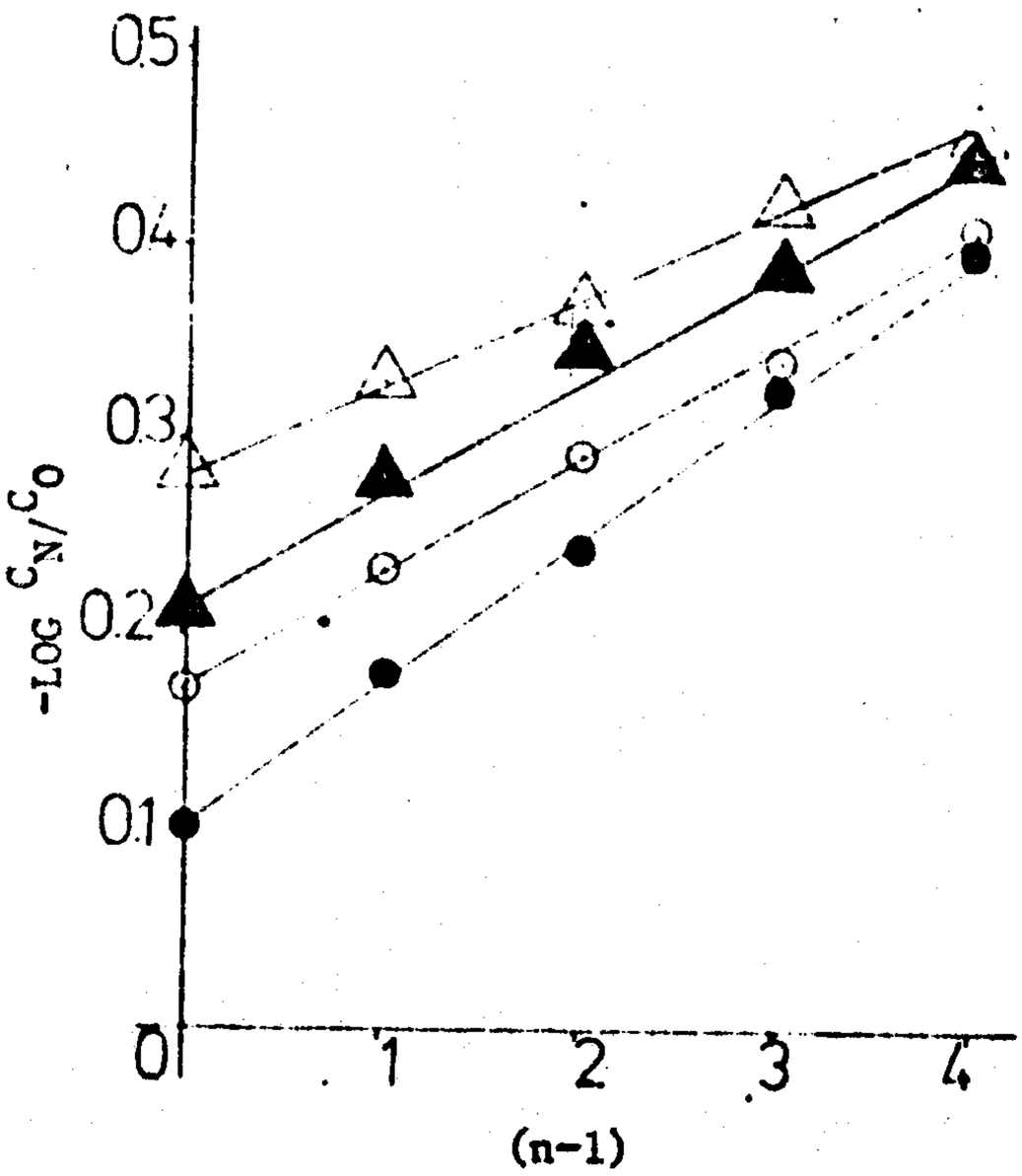


**Fig. 7: Ultrafiltration experiments using different concentration of carbamazepine in 2% w/v Eumulgin and Myrj solutions**

**Key:** △ Eumulgin C 1000 ▲ Eumulgin C 1500
○ Myrj 52 ● Myrj 59

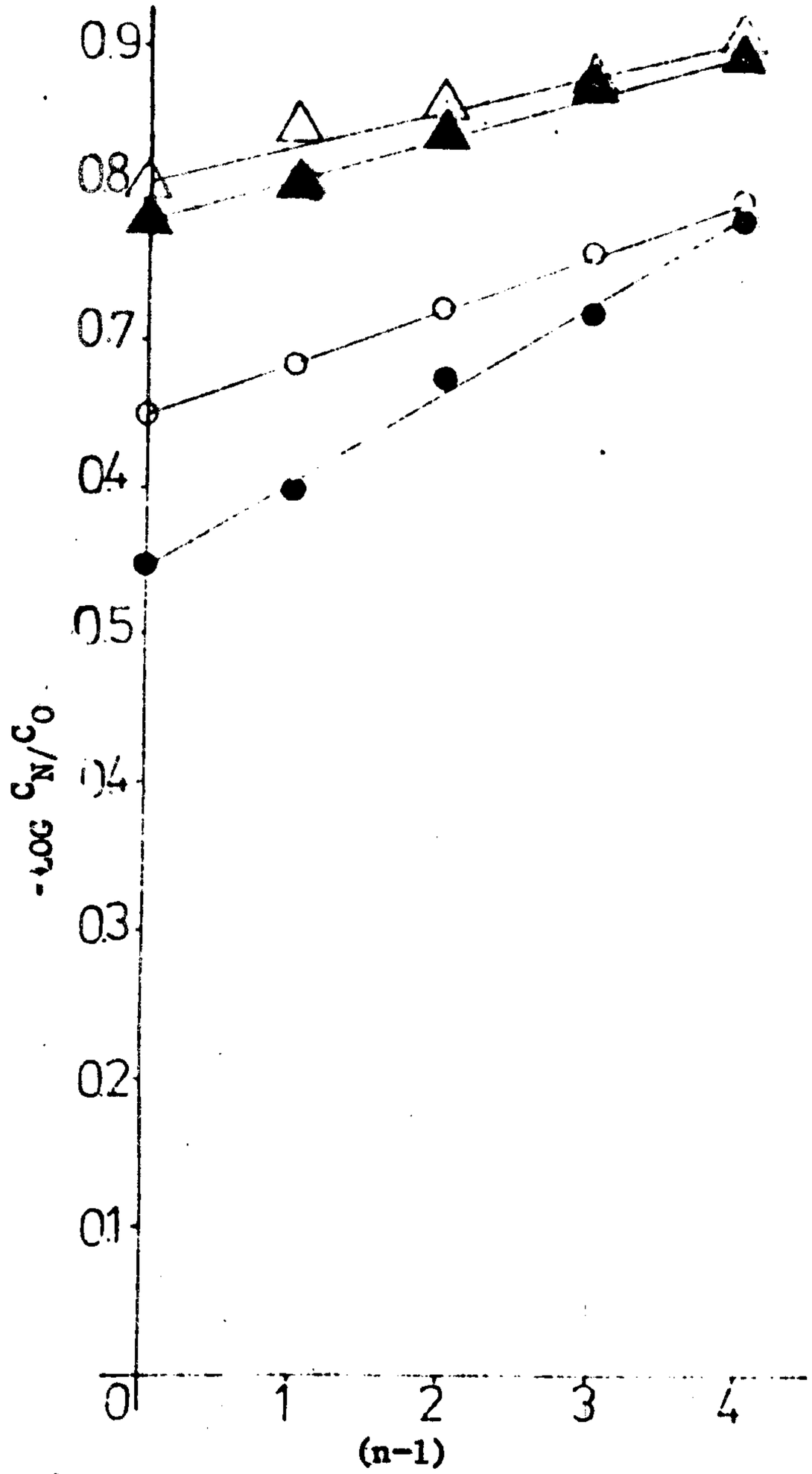


Fig. 8: Ultrafiltration experiments using different concentrations of carbamazepine in 5% w/v Eumulgin and Myrj solutions

Key: The same as in Fig. 7

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# دراسة أنظمة مذابة تحتوى على الكاربامازبين

احمد السيد ابو طالب وسيد محمد احمـــــــد
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تم استخدام طريقة الاذابة وطريقة الترشيح عند ضغط مرتفع لدراسة الانظمة المذابة التى تحتوى على مادة الكاربازبين. وتم دراسة تاثير الاختلاف فى طول كل من سلسلة الالكيل والاوكسى ايثلين فى جزئيات المواد ذات النشاط السطحى عـــلى قوة الاذابـــة لهـذه الجزئيـــات.

والنتائج التى تم الحصول عليها من طريقتى الاذابة والترشيح عند ضغـــط مرتفـع متوافقـة تمامـا وتعضد نظرية التجزىء .

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