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EFFECT OF CERTAIN MACROMOLECULES ON THE EXTRACTION OF SOPHORA ALKALOIDS

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ABSTRACT

Sophora matrine alkaloids have recently been useful in the treatment of some types of cancer.

Certain classes of macromolecules including non-ionic surfactants, polyethylene glycols and cyclodextrins have been investigated for their effects on the extraction of Sophora alkaloids from the leaf, the bark and the seed.

Increasing the non-ionic surfactant solutions above CMC improved the yield of the extracted alkaloids calculated and quantified after TLC separation as cytisine. Extending the hydrocarbon chain in a homologous series of non-ionic surfactants containing the same polyoxyethylene chain improved the extraction from the leaf, the bark and the seed and vice versa. That is why polysorbate 80 is more efficient than ploysorbate 20 and Brij 58 is more efficient than Brij 35. On the other hand Eumulgin C 1500 is less efficient than Eumulgin C 1000 and Myrj 59 is less efficient than Myrj 53.

PEGs improved the extraction of Sophora leaf alkaloids irrespective of the concentration. Increasing the molecular weight of PEGs leads to decrease in the yield of cytisine extracted from the leaf.

Cyclodextrins improved the yield of cytisine extracted from Sophora leaf. It was found that ß-cyclodextrin is more effective than α-cyclodextrin in this concern. In both cases the inclusion isotherm was found to be A_N type with no precipitation of the inclusion compound.

INTRODUCTION

The use of certain macromolecules including non-ionic surfactants and PEGs for increasing the yield of the aqueous extract of certain medicinal plant powders has been demonstrated[1]. Thus the yield of sennosides in aqueous extract has been increased by incorporating different concentrations of such macromolecules in the extraction medium.

The aim of the present work is to investigate the effect of different classes of non-ionic surfactants including polysorbates, Eumulgins, Brijs, Myrjs as well as PEGs and cyclodextrins on the extraction of *Sophora* alkaloids calculated as cytisine.

The effect of concentration of non-ionic surfactants below and above their respective critical micellar concentration (CMC) on the extraction process has been also demonstrated.

Sophora whole extract is extremely poisonous and hallucinogenic[2-4]. The toxicity of the plant is believed to be due to the alkaloid cytisine[5] and cytisine type alkaloids[6]. The matrine alkaloids, extracted from some genera of *Sophora*, have recently been useful in the treatment of some types of cancer[7].

EXPERIMENTAL

Materials

Cytisine pure authentic powder (obtained from Prof. K.F. Blinova, Chemical and Pharmaceutical Institute, Leningrad USSR).

Sophora leaf, bark and seed comminuted to 400-500 μm particle size, (Aswan plant garden, Egypt).

Non-ionic surfactants

Polysorbates, polyoxyethylene (20) sorbitan monolaurate (polysorbate 20) and polyoxyethylene (20) sorbitan monooleate (polysorbate 80), (Atlas Chemical Industries Inc., Willimington Delaware, USA).

Eumulgins, cetyl stearyl alcohol with (20) ethylene oxide units (Eumulgin C1000), and stearyl alcohol with (50) ethylene oxide units (Eumulgin C1500), (Henkel International, Dusseldorf, Germany).

Brijs, Polyoxyethylene (23) laurylether (Brij 35) and polyoxyethylene (20) cetylether (Brij 58), (Atlas Chemical Industries Inc., Willimington Delaware USA).

Myrjs, Polyoxyethylene (50) stearate (Myrj 53) and polyoxyethylene (100) stearate (Myrj 59), (Atlas chemical Industries Inc., Willimington Delaware USA).

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

Polyethylene glycols, (PEGs), PEG 1000, PEG 4000, and PEG 6000, (Sigma Chemical Company St. Louis, Mo, USA).

TLC silica gel G plates (E. Merck, Germany).

Equipment:

Thermostatically controlled water bath with a flask shaker (karl kolb Scientific technical Supplies D-6072 Dreieich, Germany).

Ultraviolet self-recording spectrophotometer SP 1750 (Pye Unicam, England) and Ultraviolet double beam spectrophotometer (UV-IDEC 320 Jasco, Japan).

Methods

1- Determination of the maximum absorbance of pure authentic cytisine:

Known concentration of pure authentic cytisine was dissolved in small amount of methanol and completed with distilled water. The solution was screened for its maximum absorbance wave length using UV self-recording spectrophotometer. It was found that cytisine has three maximal absorbance wave lengths 204, 232 and 304 nm. The latter max is more intense and more sensitive in absorption Fig. 1, and thus adopted for constructing the calibration curve which follows Beer's lambert law. This maximum wave length, 304 nm, was used also for the assay of cytisine in the extract after TLC separation.

2- TLC separation of cytisine from the plant extract and determination of its maximal absorbance:

Known volumes of the aqueous extract af the leaf as well as the bark or the seed were spotted on silica gel G plates. Pure authentic cytisine was dissolved in methanol and spotted on the same plate. Chloroform-methanol-28% ammonia (100:10:1) was used as a developing system. After development the front line was marked and the plates were visualized under UV light. The spots of the extracts with the same R_f value of the spotted pure authentic cytisine were located (R_f value of 0.56), circled and scratched in test tubes containing 10 ml methanol and shaken for 30 minutes. The methanolic extract was completed to 100 ml distilled water and

screened for UV maximal absorbance using self recording ultraviolet spectrophotometer. It was found that cytisine separated from the plant extract by TLC is identical to pure authentic cytisine with three maximal absorbances at 204, 232 and 304 nm, Fig.2.

The last procedure was repeated exactly but in presence of the highest concentration used of the investigated macromolecules in order to check their effects on the separation and assay of cytisine. It was found that the presence of the macromolecules neither interferred with the separation of cytisine nor they made any shift for its maximal absorbance in the dilution range used.

3- Percentage recovery determination:

Specific concentration of pure authentic cytisine was dissolved in methanol and spotted on silica gel G plates and developed using the previously mentioned system. The spots were located under UV light and scratched in a test tube containing 10 ml methanol and shaken for 30 minutes. The methanolic extract was completed to 100 ml with distilled water and assayed for cytisine content spectrophotometrically at 304 nm. The percentage recovery was determined and considered in the comming calculations.

4- Investigation of the effect of macromolecules on the extraction of *Sophora* alkaloids calculated as cytisine:

One gm of the powdered leaf, bark or seed (400-500 μm) was shaken with different concentrations of the investigated macromolecules in stoppered conical flasks in a thermostatically controlled water bath at 37 ± 0.1°C over night. The macromolecules investigated were non-ionic surfactants including polysorbate 20, polysorbate 80, Eumulgin C1000, Eumulgin C1500, Brij 35, Brij 58, Myrj 53 and Myrj 59. PEG 1000, PEG 4000, PEG 6000, α-cyclodextrin and ß-cyclodextrin were also investigated. The concentrations of the non-ionic surfactant solutions investigated were selected to be below and above their critical micellar concentration. After equilibrium was attained, the extracts were filtered and 1 ml of the extracts were spotted on silica gel G plates and developed using chloroform-methanol-28% ammonia (100:10:1). The cytisine zone was located under UV light (R_f value of 0.56) and scratched quantitatively into 10 ml methanol in a stoppered tube and shaken for 30 minutes. The methanolic extract was completed to 100 ml with distilled water assayed and spectrophotometrically for its cytisine content at 304 nm. The concentration of cytisine was found from the constructed calibration curve and the percentage recovery factor was considered.

RESULTS AND DISCUSSION

Cytisine pure authentic sample gave 3 max in the ultraviolet region 204, 232 and 304nm, Fig. 1. Since the latter wave length was more distinct and sensitive in absorption, it was used for the assay.

Cytisine separated from *Sophora* leaf, bark or seed by TLC in absence and in presence of the investigated macromolecules gave 3 maximal absorbance wave lengths identical to pure authentic cytisine, Fig.2. This indicates that the presence of the macromolecules investigated neither

interferred with the separation of cytisine nor they made any shift for its maximal absorbances in the dilution range used.

The effect of the investigated nonionic surfactant solutions including polysorbates, Eumulgins, Brijs and Myrjs on the extraction of cytisine from *Sophora* leaf is shown in Table 1 and Fig. 3. The concentrations of the investigated surfactants were selected to be below and above critical micellar concentration (CMC) in order to investigate the effect of micelle formation on the extraction of the alkaloids calculated as cytisine. Table 1 contains the reported CMC values of the investigated non-ionic surfactants[8,9]. In absence of the investigated non-ionic surfactant solutions, distilled water extracted 19.15 mg cytisine from 1 gm powdered leaf. The little increase in the extraction power of the investigated non-ionic surfactant solutions, below CMC is related to the formation of the limited association of surfactant monomers at the local association concentration[10] level which assist the extraction of cytisine by forming small monomer aggregates.

The pronounced increase in the amount of cytisine extracted by the non-ionic surfactant solutions investigated above their respective CMC values is referred to the incorporation of cytisine in the formed non-ionic surfactant micelles hence assist sharply cytisine extraction. Thus the increase in the extraction power of the non-ionic surfactant solutions toward cytisine could be related to the solubilization[1] of the non-polar cytisine[11] within the non-ionic surfactant micelles. On increasing the concentration of the investigated non-ionic surfactant solutions above their respective CMC values, distinct increase in the amount of cytisine extracted was observed, Fig. 3. This could be related to the more micelles formed which incorporate more of the non-polar cytisine within the micellar core composed of hydrocarbon chains[10]. Extending the hydrocarbon chain in a homologous series of non-ionic surfactants containing the same polyoxyethylene chain as in polysorbates and Brijs increased the extraction power towards cytisine. This result emphasizing the conclusion that cytisine is incorporated within the miceller interior, the core region of the micelle composed of the hydrocarbon chains, rather than the capsular region of the micelle formed of the polyoxyethylene chains[12-14]. Another evidence of the last finding is that, on extending the polyoxyethylene chain length in a homologous series of non-ionic surfactants having the same hydrocarbon chain, the extracting power for cytisine was decreased. That is why Eumulgin C1500 is less efficient than Eumulgin C1000 and Myrj 59 is less efficient than Myrj 53[15-16], Table 1 and Fig.3. That is because extending the polyoxyethylene chain decreases the core/capsular ratio of the micelle, thus decreases the extraction power which attributed mainly to the core of the micelle. The non-ionic surfactant solutions investigated could be arranged for their extracting power as follows; polysorbate 80> polysorbate 20> Brij 58> Eumulgin C1000> Brij 35> Eumulgin C1500> Myrj 53> Myrj 59, Fig.3.

The effect of the non-ionic surfactant solutions investigated on the extraction of *Sophora* alkaloids calculated as cytisine from *Sophora* bark is shown in Table 2 and Fig. 4. In absence of non-ionic surfactant solutions, 17.08 mg cytisine was extracted from 1 gm bark powder. The increase in the quantity of cytisine extracted below the CMC of the investigated non-ionic surfactant solutions is due to the local associa-

tion of the monomers. The pronounced increase in the quantity of cytisine extracted above the CMC may be due to the solubilization of cytisine within the micellar core[10]. The quantity of cytisine extracted was increased by increasing the non-ionic surfactant concentrations as the number of the formed micelles increased[10]. Extending the hydrocarbon chain in a homologous series containing the same polyoxyethylene chain resulted in an increase[12-14] in the amount of cytisine extracted from the bark. That is why polysorbate 80 is generally more efficient than polysorbate 20 and Brij 58 is more efficient than Brij 35. The last finding confirm the incorporation of cytisine within the hydrocarbon chain, the core of the micelle. Extending the polyoxyethylene chain, the capsular region of the micelle, in a homologous series of non-ionic surfactants containing the same hydrocarbon chain length resulted in a decrease[15-16] in amount of cytisine extracted as the core / capsular ratio of the micelle decreased. That is why Eumulgin C1000 is more efficient than Eumulgin C1500 and Myrj 53 is more efficient than Myrj 59. The presence of the non-ionic surfactants in the extraction medium actually improved the yield of cytisine extracted specially at the highest concentrations investigated (nearly 2.5 folds increase).

The effect of the investigated non-ionic surfactant concentration on the extraction of cytisine from *Sophora* seed is shown in Table 3 and Fig. 5. At zero surfactant concentration the amount of cytisine extracted was 19.05 mg per 1 g powdered seed (400-500 μm particle size). The local association of monomers below CMC is responsible for the increase observed in the amount of cytisine extracted.

At 5 and 1% polysorbate 20 and polysorbate 80 respectively and above, precipitation in the extraction medium took place as the high fat content of the seed interacted with the higher concentration of polysorbates. Thus measuring cytisine extracted in those solutions was impossible since the precipitate could not be filtered. Polysorbate 80 is more efficient in assisting the extraction of cytisine than polysorbate 20 and Brij 58 is more efficient than Brij 35. On the other hand Eumulgin C1000 is more efficient than Eumulgin C1500 and Myrj 53 is more efficient than Myrj 59 for the last mentioned reasons. The non-ionic surfactants investigated could be arranged according to their efficiencies in cytisine extraction as follows: Brij 58 > Eumulgin C1000 > Myrj 53 > Brij 35 > Eumulgin C1500 > Myrj 59.

The effect of polyethylene glycols 1000, 4000 and 6000 on the extraction of *Sophora* alkaloids calculated as cytisine from *Sophora* leaf is shown in Table 4 and Fig. 6. The amount of cytisine extracted in zero PEGs concentration was 19.15 mg cytisine per 1 gm leaf powder. PEGs caused marked increase in the amount of cytisine extracted even at the lowest concentration used. Further increase in PEGs concentration caused little increase in the amount extracted as PEGs are non-micellar forming materials[8,10]. Hydrogen bonding, Van der Wall forces and electrostatic attraction may be responsible for the increase in extraction of cytisine in solutions containing PEGs. As the molecular weight of the investigated PEGs increased, the extractive power decreased. That is why PEG 1000 was more efficient than PEG 4000 and the latter was more efficient than PEG 6000. This may be attributed to the increased hydrophilicity of the extraction medium by increasing the number of glycol groups[8,10] as the molecular

weight of PEG increased rendering the extraction medium more hydrophilic thus decreased the extraction of lipophilic cytisine.

Comparing the effect of the non-ionic surfactant and PEG solutions investigated on the extraction of cytisine from the leaf Table 1, Fig. 3 with Table 4, Fig. 6, it is clear that the former class is more efficient in assisting cytisine extraction specially above their respective CMC values.

The effect of α- and ß-cyclodextrin on the extraction of cytisine from *Sophora* leaf is shown in Table 5 and Fig. 7. It is evident that the presence of both α- and ß-cyclodextrin caused marked increase in the amount of cytisine extracted specially with ß-cyclodextrin as its inclusion cavity is wider than α-cyclodextrin (Inclusion cavities are 5.2 and 6.4 A° for α- and ß-cyclodextrin respectively[17]), although ß-cyclodextrin has limited water solubility 0.1 moles/l is insoluble, Table 5). It is supposed that the increase in extraction caused by the cyclodextrins is related to the inclusion of the hydrophobic cytisine in the hydrophobic cyclodextrin cavities composed of hydrocarbon groups. The shape of cytisine inclusion isotherm in α- and ß-cyclodextrin, Fig. 7, supposed to be A_N type[17] with no precipitation of the inclusion compound.

The solubility of α-cyclodextrin was up to 0.4 moles / L and it assist the extraction of nearly 34 mg cytisine from 1 gm leaf powder. The use of cyclodextrins in such purposes is preferable as they are naturally occuring, non-toxic and non-hemolytic.

Table 1: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloids calculated as cytisine from Sophora leaf at 37±0.1°C.

Surfactant	Reported CMC values[8,9] gm %	mg cytisine per 1gm powder, Surfactant Conc. % 0.005	0.024	1	5	10	20
Polysorbate 20	0.006	19.80	26.71	30.81	36.14	38.67	42.19
Polysorbate 80	0.0013	25.04	28.30	26.95	38.65	46.44	47.90
Eumulgin C 1000	0.0011	22.15	26.31	30.25	33.12	35.20	36.29
Eumulgin C 1500	0.0012	20.50	20.92	27.75	30.05	32.72	33.01
Brij 35	0.001	24.95	24.98	26.01	30.57	31.65	34.56
Brij 58	0.0011	29.31	28.82	32.42	36.69	38.02	40.27
Myrj 53	0.014	25.99	25.90	27.30	30.06	32.08	33.72
Myrj 59	0.020	24.01	24.20	26.50	27.00	28.23	29.47

* mg cytisine extracted from 1 gm leaf powder at zero surfactant concentration was 19.15.

Table 2: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloids calculated as cytisine from Sophora bark at 37±0.1°C.

Surfactant	mg cytisine per 1gm powder, Surfactant Conc. % 0.005	0.024	1	5	10	20
Polysorbate 20	19.20	19.51	20.59	26.35	32.25	43.99
Polysorbate 80	21.51	21.01	23.04	27.65	37.23	40.27
Eumulgin C 1000	21.08	23.81	30.89	34.35	35.21	37.35
Eumulgin C 1500	19.53	19.59	27.27	29.90	33.97	36.28
Brij 35	24.12	23.26	24.30	25.89	28.82	29.02
Brij 58	25.74	25.10	29.13	30.24	32.40	33.80
Myrj 53	22.30	22.70	25.20	27.72	29.40	30.55
Myrj 59	20.50	20.69	23.15	26.97	35.12	41.91

* mg cytisine extracted from 1 gm bark powder at zero surfactant concentration was 17.08.

Table 3: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloids calculated as cytisine from Sophora seed at 37±0.1°C.

Surfactant	mg cytisine per 1gm powder					
	Surfactant Conc. %					
	0.005	0.024	1	5	10	20
Polysorbate 20	26.92	28.36	29.90	pp	pp	pp
Polysorbate 80	27.71	30.29	pp	pp	pp	pp
Eumulgin C 1000	19.91	20.12	26.50	28.80	30.80	31.27
Eumulgin C 1500	19.00	19.11	24.12	25.21	27.21	29.11
Brij 35	24.68	24.86	25.08	27.06	27.80	28.98
Brij 58	24.21	25.87	26.55	29.85	32.62	34.80
Myrj 53	24.25	24.39	25.20	28.30	30.38	33.63
Myrj 59	23.04	23.96	24.18	25.06	26.05	27.50

* mg cytisine extracted from 1 gm seed powder at zero surfactant concentration was 19.05.
* pp, precipitation in the extraction media.

Table 4: Effect of PEGs concentration on the extraction of Sophora alkaloids calculated as cytisine from Sophora leaf at 37 ± 0.1°C.

PEG	mg cytisine per 1gm powder					
	PEG Conc. %					
	0.005	0.024	1	5	10	20
PEG 1000	26.34	26.34	26.39	26.34	26.92	27.13
PEG 4000	25.98	25.75	26.02	26.07	26.22	26.25
PEG 6000	25.98	25.77	25.80	25.79	25.94	25.90

* mg cytisine extracted from 1 gm leaf powder at zero PEG concentration was 19.15.

Table 5: Effect of cyclodextrin concentration on the extraction of Sophora alkaloids calculated as cytisine from Sophora leaf at 37 ± 0.1°C.

Cyclodextrin	mg cytisine per 1gm powder							
	Cyclodextrin Conc. moles							
	0.005	0.025	0.05	0.07	0.1	0.2	0.3	0.4
α-Cyclodextrin	28.75	28.98	30.00	31.00	31.25	31.27	32.15	33.86
β-Cyclodextrin	28.84	30.10	32.15	32.26	β-CyD insoluble	β-CyD insoluble	β-CyD insoluble	β-CyD insoluble

* mg cytisine extracted from 1 gm leaf powder at zero Cyclodextrin concentration was 19.15.

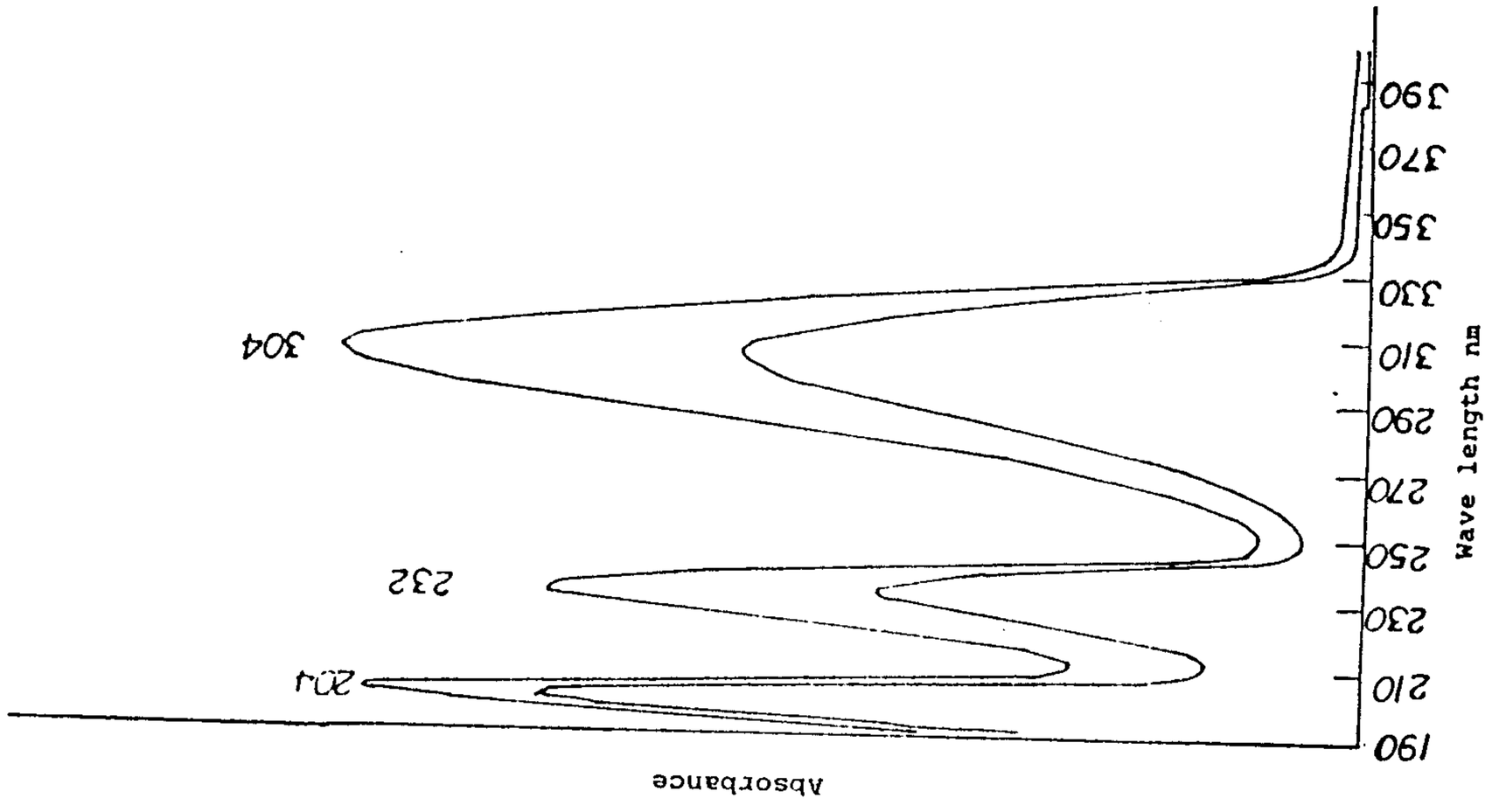

Fig. 1: Ultraviolet absorbance of cytisine authentic sample in distilled water.

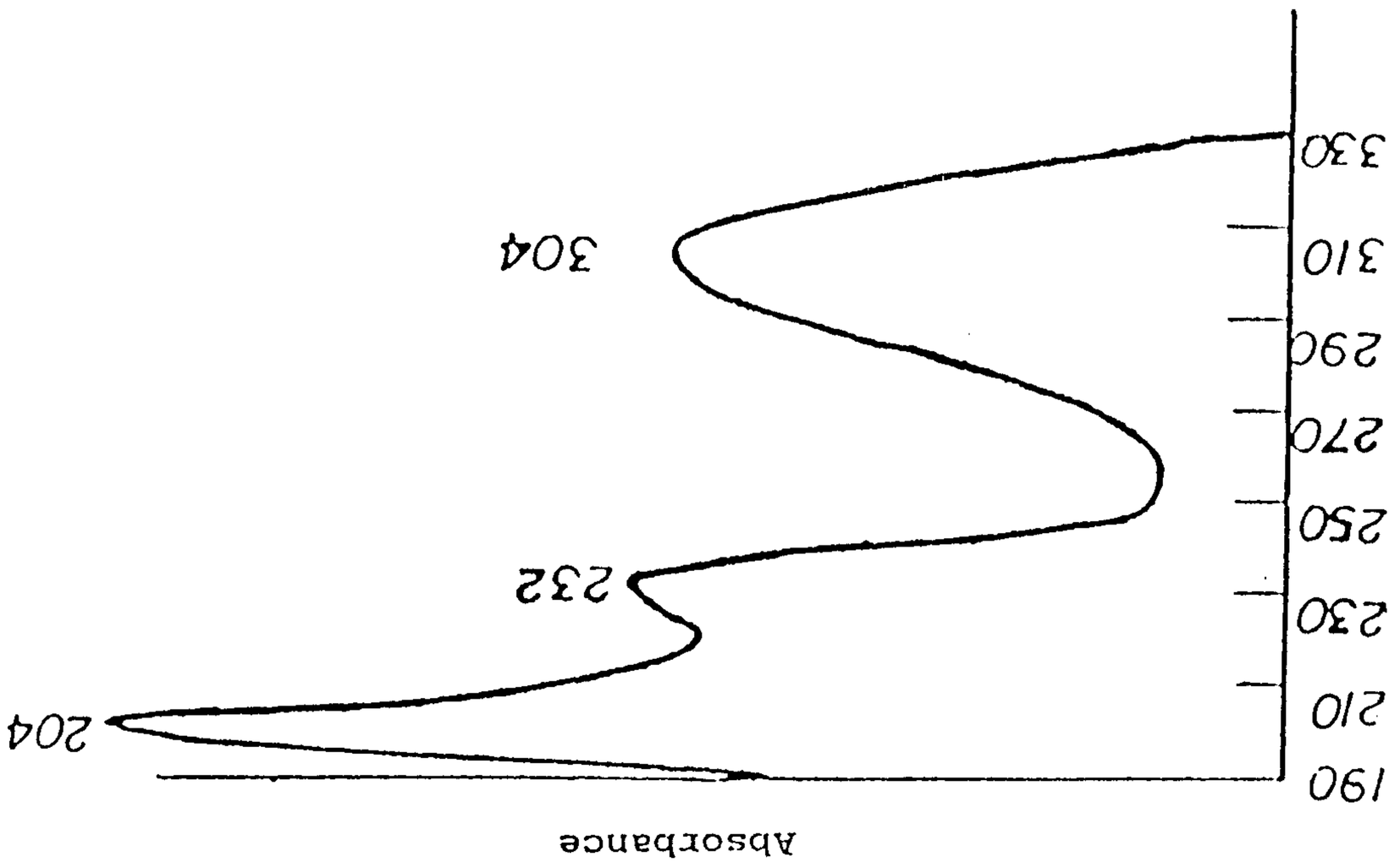

Fig. 2: Ultraviolet absorbance of cytisine separated by TLC from Sophora leaf, bark and seed.

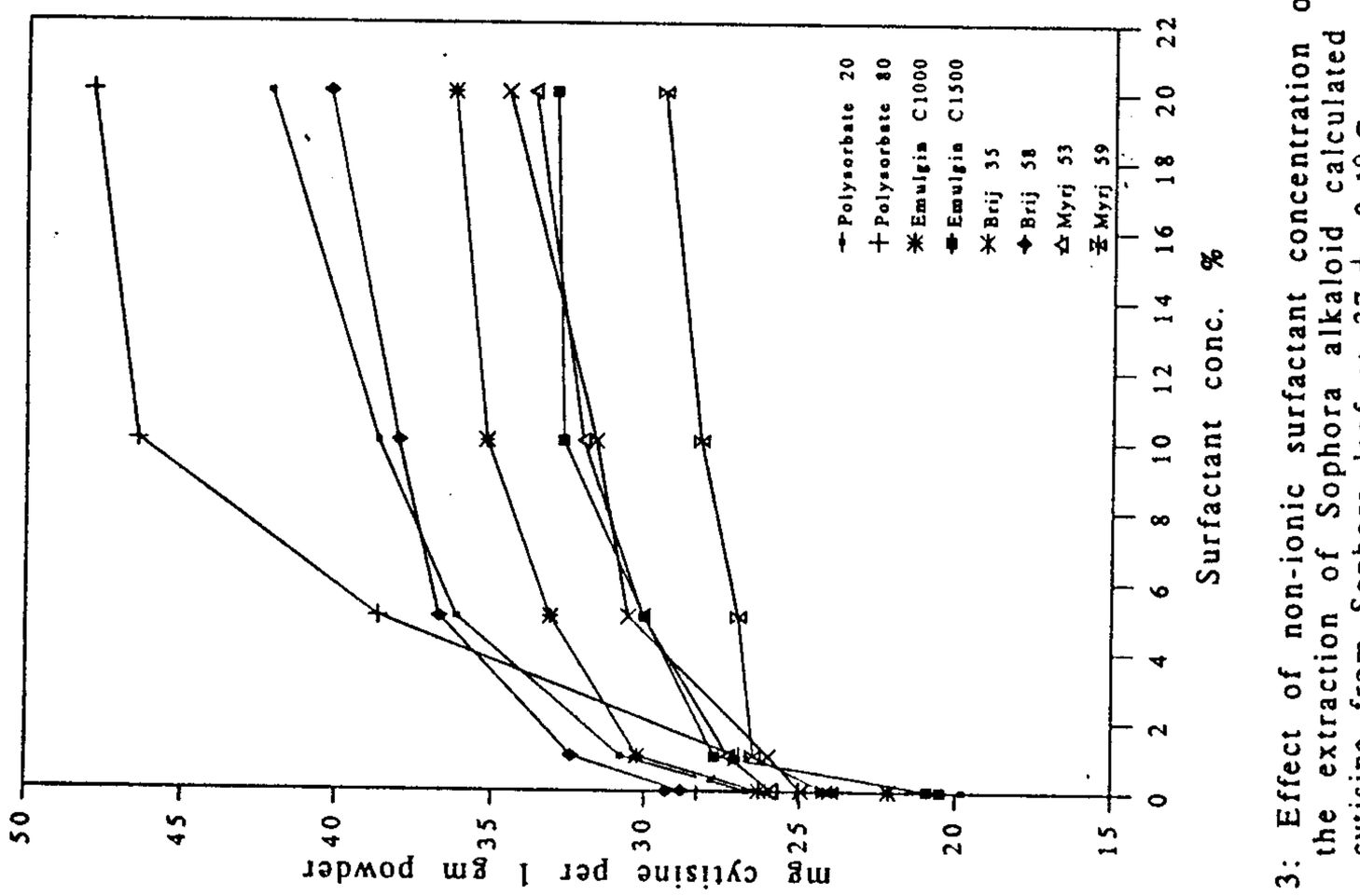

Fig. 3: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloid calculated as cytisine from Sophora leaf at 37 ± 0.1° C.

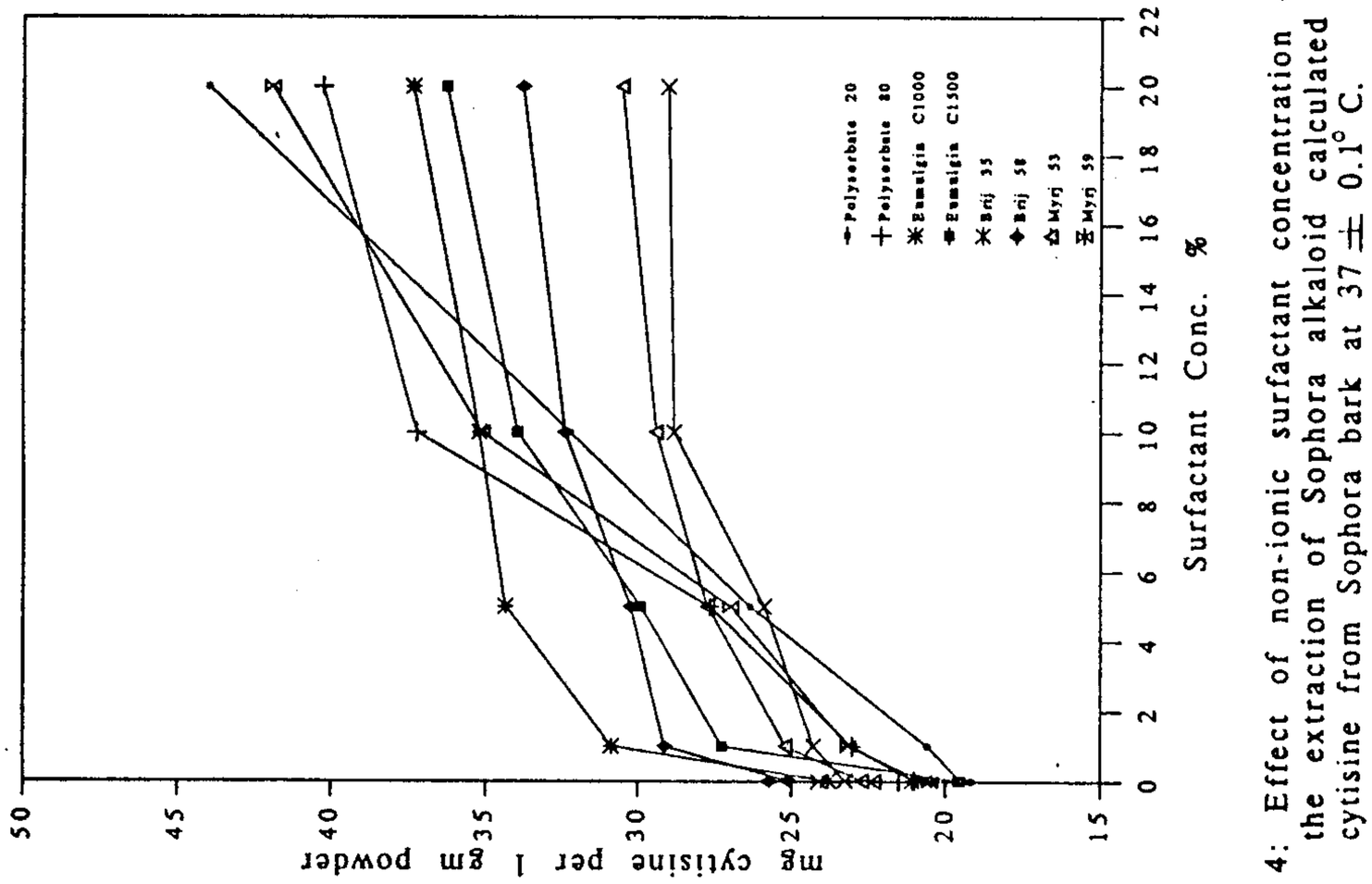

Fig. 4: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloid calculated as cytisine from Sophora bark at 37 ± 0.1° C.

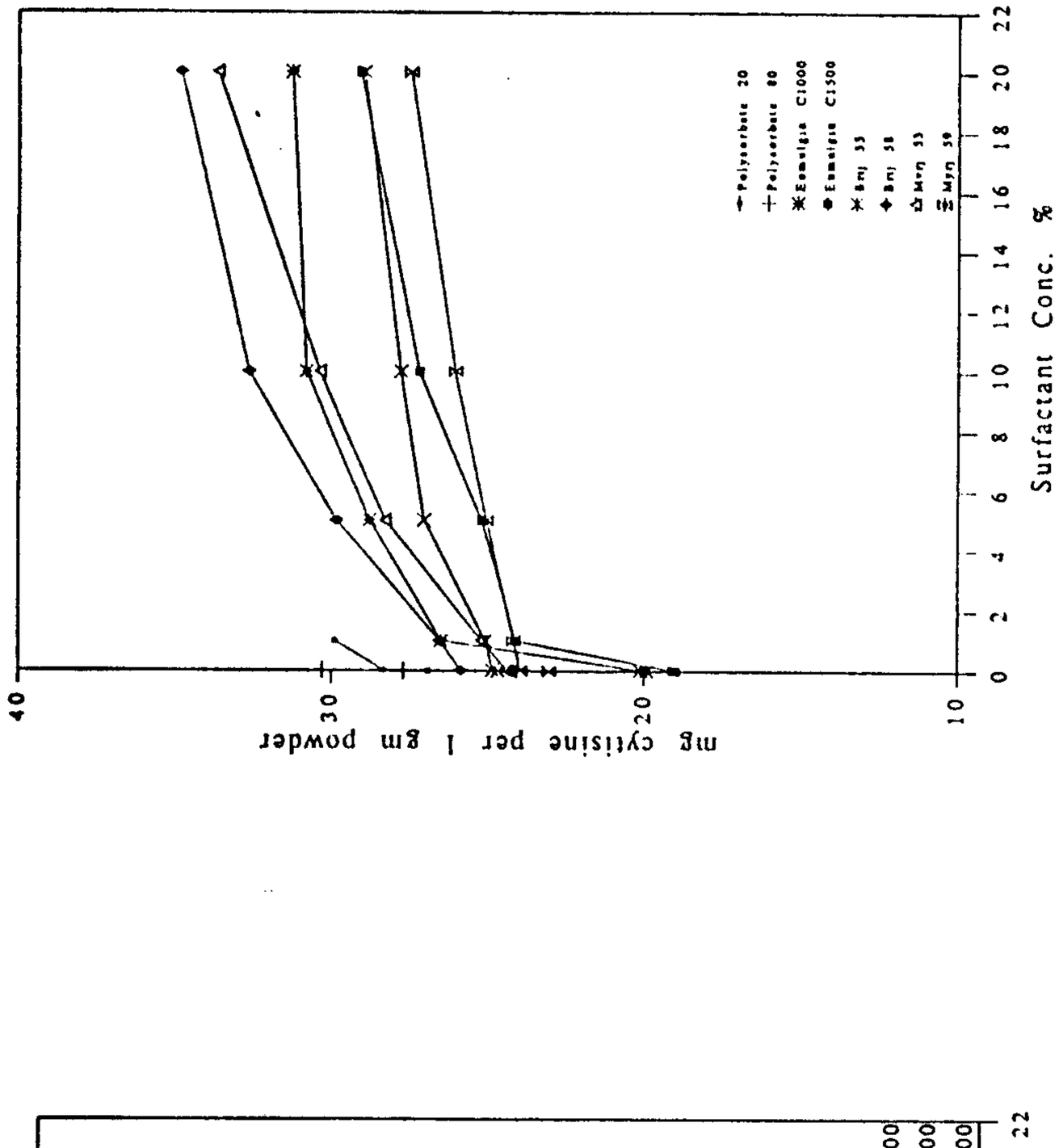

Fig. 5: Effect of non-ionic surfactant concentration on the extraction of Sophora alkaloid calculated as cytisine from Sophora seed at 37 ± 0.1° C.

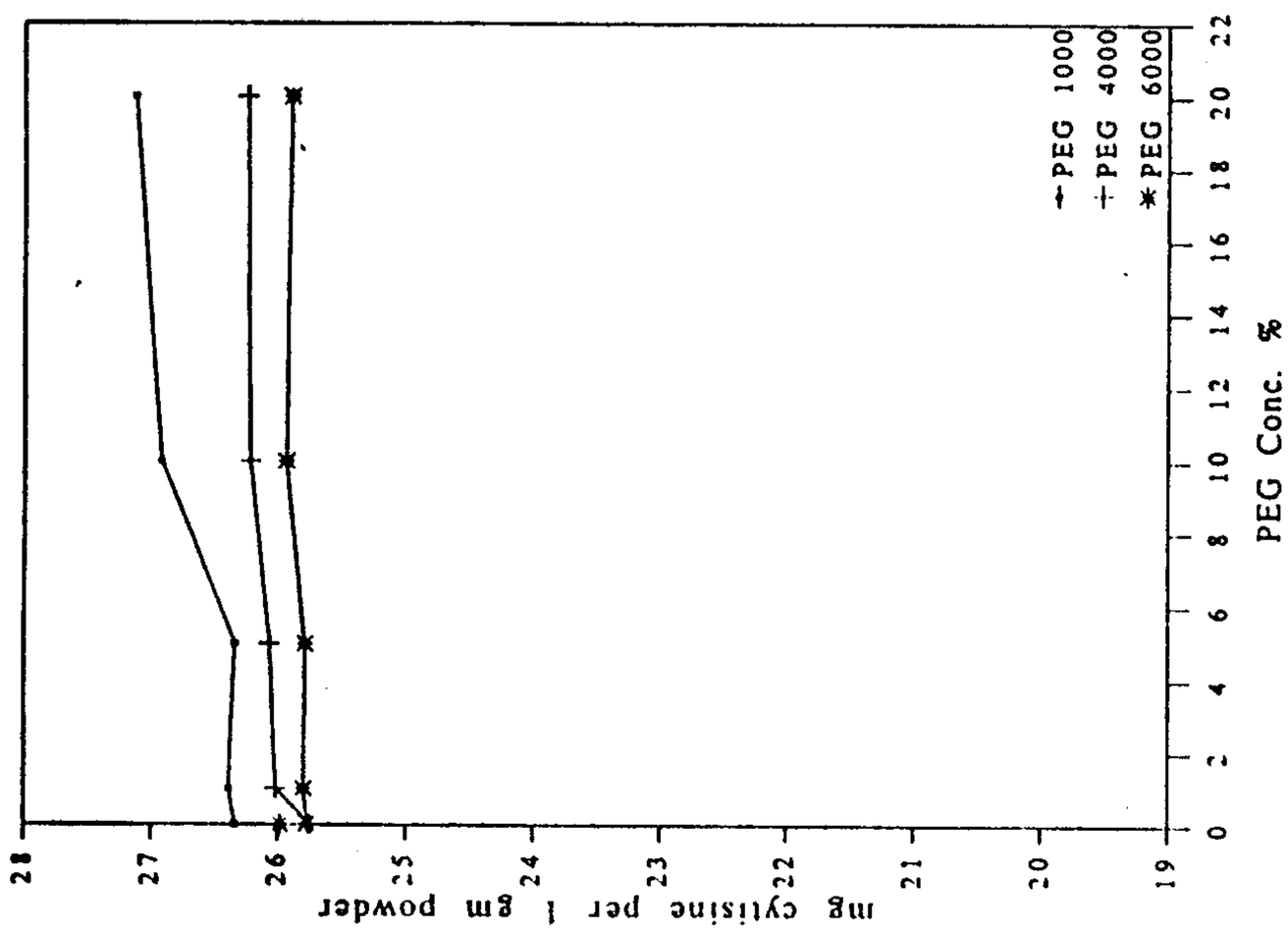

Fig. 6: Effect of PEGs concentration on the extraction of Sophora alkaloid calculated as cytisine from Sophora leaf at 37 ± 0.1° C.

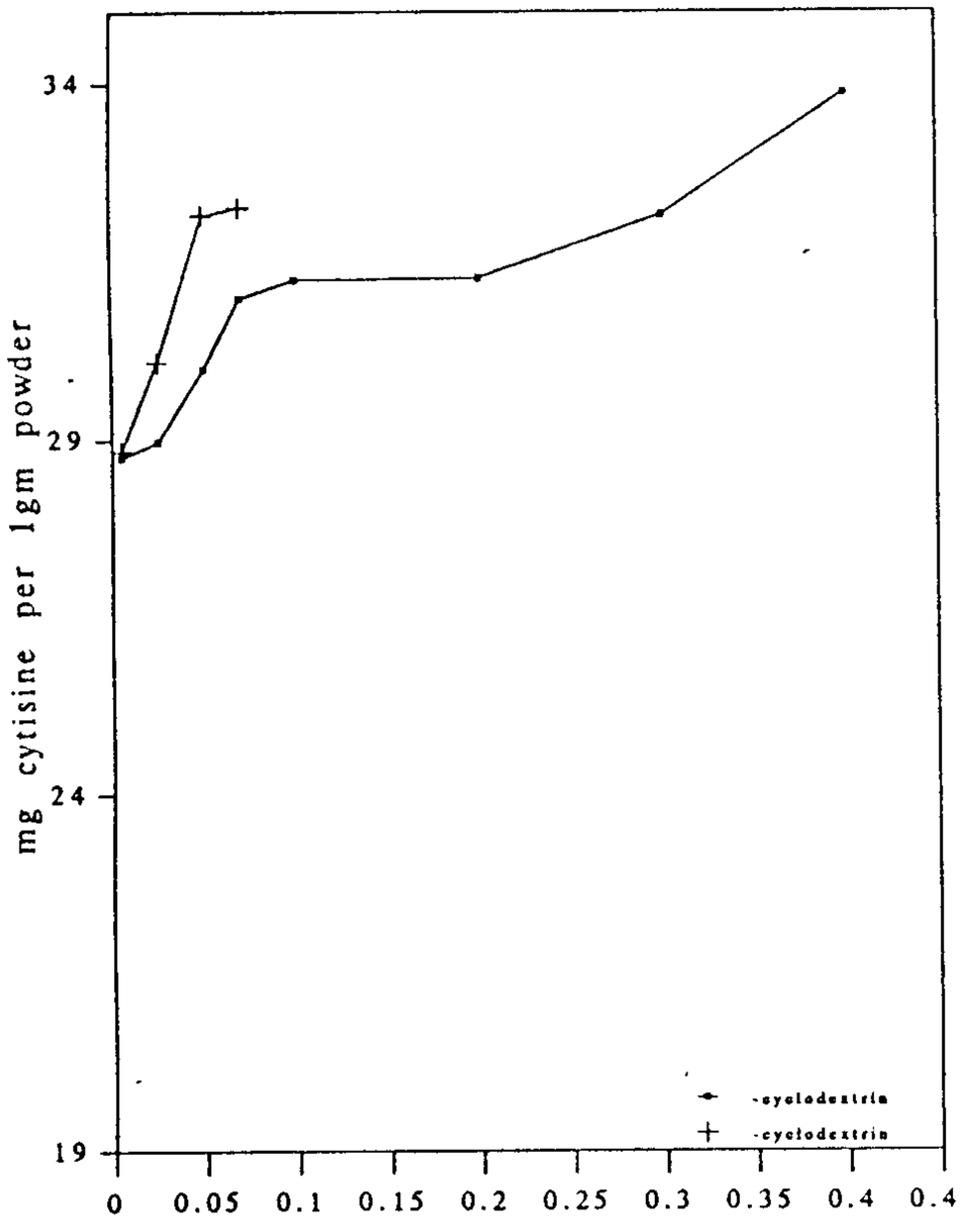

Fig. 7: Effect of cyclodextrin concentration on the extraction of Sophora alkaloid calculated as cytisine from Sophora leaf at $37 \pm 0.1^{\circ}$ C.

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تأثير جزيئات كبيرة معينة على استخلاص القلويدات من نبات السوفورا

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استخدم حديثا بعض قلويدات نبات السوفورا فى علاج انواع معينة من مرض السرطان.

ولقد استخدمت جزيئات كبيرة معينة وتشمل منشطات السطح غير المتأينة وعديدات ايثلين جليكول وكذلك السكلودكسترينات فى زيادة كمية القلويدات المستخلصة من نبات السوفورا.

ولقد وجد أن زيادة تركيز منشطات السطح غير المتأينة فوق التركيز الحرج لتكوين الشباك زاد من كمية السيتزين المستخلص بعد فصله بواسطة كروماتوجرافيا الطبقة الرقيقة من أجزاء النبات. ولقد وجد أن عديد السوربات ٨٠ أكثر فاعلية فى زيادة القلويدات المستخلصة المحسوبة على هيئة سيتزين من عديد السوربات ٢٠ وكذلك الاملجين س ١٠٠٠ أكثر فاعلية من الاملجين س ١٥٠٠ أ كذلك البرج ٨٥ أكثر فاعلية من البرج ٣٥ وأيضا ميرج ٥٣ أكبر من ميرج ٥٩ نظرا لاختلاف تلك المنشطات فى تركيبها الجزيئى.

ولقد ازادت عديدات الايثيلين جليكول من القلويدات المستخلصة من أوراق السوفورا - وعند زيادة الوزن الجزيئى لعديدات ايثيلين جليكول نقصت كمية القلويدات المستخلصة.

ولقد ازادت السيكلودكسترينات من كمية القلويدات المستخلصة من أوراق السوفورا ولقد وجد أن بيتا سيكلودكسترين أكثر فاعلية من الفاسيكلودكسترين فى هذا المجال وقد كونت السيكلودكسترينات نوع معين من المتراكبات التى لم تترسب.

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