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IN-VITRO AND IN-VIVO STUDIES ON OPHTHALMIC PREPARATIONS OF XYLOCAINE HYDROCHLORIDE

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ABSTRACT

A number of both hydrophilic and lipophilic surface active agents was employed for preparing simple O/W and mutiple W/O/W emulsion systems. The dynamic dialyses of xylocaine HC1 from its aqueous, micellar solutions and O/W as well as W/O/W emulsion systems were studied. The transfer of xylocaine HC1 across standard cellophane membrane was found to follow the diffusion controlled mechanism. The data revealed that, the nature of surfactant and the emulsion type had a significant role in diffusion of the drug molecules. Generally, the release pattern of the drug from micellar solution or emulsion systems was less than that of the control.

In a blind-controlled clinical study, four coded W/O/W and two coded O/W emulsions of 2.5 % xylocaine HC1 were compared with an aqueous solution of the drug at the same concentration. The longest mean of surface anaesthetic duration, 9.8, minutes was attained with W/O/W emulsion formed of span 60 as a lipophilic emulsifier and Myrj 52 as a hydrophilic one. The clinical application of emulsion formulations in human eyes was found to prolong the mean anaesthetic duration, decrease the eye irritation and improve the performance of the needed clinical manoeuvres.

INTRODUCTION

In last decades many attempts have been made so as to anaesthetize the cornea and the conjunctiva without the use of the invasive methods. This effect has been achieved by using high concentrations of the active substance[1], Penetration enhancers[2] or iontophoresis[3].

Xylocaine and its hydrochloride are mostly used as local anaesthetics which produce a more prompt, intensive and extensive anaesthesia than procaine hydrochloride when they are used at the same concentration level[4]. Nygvist-Mayer et al[5] studied the release of xylocaine using emulsion formulation based on an eutectic mixture of xylocaine and prilocaine as the dispersed phase. They, also, investigated the influence of the active substances on the diffusivities of each other, and the effect of the surfactant and thickening agent on the drug release.

The fact that emulsions are used as vehicles for medicinal agents is well established, and many investigators have studied the release of drugs from different emulsion systems (6-10). During most of these studies, the composition of the emulsion was considered as one of the most important factors affecting drug release. It is worthy to note that the formulation of a drug in a simple aqueous solution, as eye drops, does not provide a convenient means of drug delivery to the ocular tissue. The main disadvantages of eye drops are : the short duration of action, ocular irritation, systemic side effects and the susceptibility for bacterial and/ or fungal contamination.

In recent years, interest is growing progressively to develop new drug-delivery systems for the ophthalmic preparations (4,5&9). Recently, there is an interest to use emulsions as drug delivery systems. A W/O or an O/W emulsion can be further emulsified to produce multiple emulsion systems(W/O/W or O/W/O). These emulsions that contain one dispersed phase inside another one, have been used as convenient sustained-release dosage froms.

In-Vitro and in-Vivo Studies on Ophthalmic Preparations of Xylocaine Hydrochloride.

The ability of multiple emulsions to entrap the drug molecules is one of their most useful application, and so the passage of molecules from the internal to the external phase across the middle phase is important. This is of interest in the pharmaceutical systems where multiple emulsions are considered as possible controlled-release drug delivery systems.

The goals of the present work are: a) to investigate the in vitro release profile of xylocaine HCl from different simple and multiple emulsion systems; b) to evaluate the anaesthetic effect of the drug on the cornea as regards the anaesthetic duration, tolerance and efficacy in doing such diagnostic procedures as tonometry, gonioscopy, and minor surgical procedures like, debridement, cauterization, tattooing; and c) to find-out a relationship between the in vitro release pattern and the in vivo application of xylocaine HCl.

EXPERIMENTAL

Materials:

Xylocaine HCl (Astra Pharm. Prod., Sweden); Tweens 20, 60 and 80; Myrjs 52. 53 and 59; Spans 40, 60 and 65 (Atlas Chem. Ind., Wilmington, USA), liquid paraffin (USP), standard cellophane membrane 30/32 (Fischer Sci. Co., London). All other chemical used were of reagent grade.

Procedure:

Preparation of Drug-Surfactant Solution.

A 5% of hydrophilic surfactant solution in Srensen phosphate buffer, pH 6.8, was prepared by weighing 5 g surfactant followed by the addition of a proper volume of buffer solution. The blend was warmed to, approximately, 60°C with the aid of gentle stirring and allowed to cool to 37°C. The calculated amount of the drug, 2.5 g, was dissolved in the surfactant solution and the volume was completed to 100 ml with buffer. This procedure was adopted for both Tweens and Myrjs.

Preparation of O/W Emulsions Containing 2.5% Drug.

A 5% surfactant solution, Table 1, was prepared in an isotonic phosphate buffer, at pH 6.8. The calculated amount of the drug, 1.25 g, was dissolved in 28.75 ml of the tested surfactant solution. The drug solution was poured into the glass container of the blender (Braun) into which 20 g of liquid paraffin was previously introduced. The blender was adjusted to the lowest speed. An amulsion was immediately formed, and the blender was run exactly for 10 minutes. The contents were transferred into a glass stoppered bottle and allowed to equilibrate for one hour before use.

Preparation of W/O/W Multiple Emulsions Containing 2.5% Drug.

The two-step emulsification procedure was adopted for preparing W/O/W multiple emulsion. In the first stage, preparation of W/O, 20 ml of the aqueous solution of the drug, the internal aqueous phase, was poured into 52 g of liquid paraffin containing 8 g of the tested lipophilic emulsifier. The two phases were allowed to be emulsified for 10 minutes so as to prepare a W/O emulsion, the first emulsification process. In the second step, an equal volume of 5% hydrophilic surfactant solution, 80 ml, outer aqueous phase, was poured into the first prepared W/O emulsion. The blender was run exactly for further ten minutes at the lowest speed to produce a W/O/W emulsion. Both lipophilic and hydrophilic emulsifiers used for preparing emulsions are presented in Table 1.

Physical Stability of both O/W and W/O/W Emulsions:

Freshly prepared O/W or W/O/W emulsions were introduced into glass-stoppered measuring cylinders and stored in an incubator at 37°C for four months without any disturbance. At suitable time intervals the emulsions were checked for any sign of emulsion separation.

Apparatus Used for the Release Study :

The apparatus is fully described in Figure 1. It consists of two compartments, the donor and the acceptor. The donor is a glass test tube opened at both ends with an internal diameter of 2.2 cm

The upper opening is covered with a nylon membrane and at the lower end a semipermeable membrane is placed. The outer compartment is a 100 ml beaker containing an isotonic phosphate buffer at pH 6.8 as a sink solution.

In-Vitro Release Study :

A standard cellophane membrane was soaked in distilled water for 24 hours, for the purpose of hydration prior to its use for the release study. The membrane was stretched firmly on the lower end of the donor with the aid of a cotton thread. At the end of equilibration of the prepared emulsion, one hour, the contents of each glass stoppered bottle were gently swirled by hand. The dialysis cell was weighed exactly and 2 g of the tested solution was introduced into the donor. A 20 ml sample of the isotonic phosphate buffer, pH 6.8, (sink solution) was pipetted into the outer compartment (acceptor). For each experiment three dialysis cells were used. The cells were placed into a constant temperature water-bath shaker, previously adjusted at 37°C and 50 shake/minute. At suitable time intervals, 1 ml sample was withdrawn from each acceptor and the UV absorbance was measured at 262 nm after appropriate dilution with distilled water.It is worth to note that the absorbance was measured against a blank similarly treated. The amount of the drug diffused into the sink solution was calculated.

Mechanism of Drug Release :

The percentage of drug released into the sink solution was calculated and the data were analyzed according to zero order, first order and the simplified Higuchi model[13].

Surfactant Dialysis from the Donor to Acceptor :

It is essential to determine whether the surfactants would permeate the membrane during the experimental study or not. To ascertain that, a separate surfactant solution was prepared and allowed to dialyze through the standard cellophane membrane, in the same manner. The surface tension of the sink was checked at the begining of the run and at intervals

throughout the total dialysis time. Since surface tension of the sink did not change markedly during the extended dialysis, it was concluded that Tweens and Myrjs did not dialyze.

In-Vivo Study :

Six different emulsion formulations, each containing 2.5% drug, were tested for their local anaesthetic effect on the human eye. The formulations tested were No. 9, 11, 14, 16, 17 and 18 in addition to the control., No. 1, Table 1,. Each formulation was applied on a group of 25 patients of the out patient clinic of the department of ophthalmology of Assiut Univ. Hospital.

One drop of the tested xylocaine HCl solution was instilled in the lower fornix of the cul-de-sac, and after an elapse of one minute a gross qualitation method of the cornealsensitivity was performed[12]. This was clinically achieved simply with a teased-out wisp of cotton a few millimeters longer than the ordinary cotton tipped applicator. The patient should be intstructed to look to the opposite side from the eye being tested. The examiner gently keeps the lids separated with the thumb and the forefinger of one hand so as to avoid undesirably contacting a lash, and then brings the cotton in from a lateral position, nearly parallel to the plane of iris. This, avoids the patient seeing the approach and making a visual avoidance response. When normal sensation is present, a lightly applied touch to either cornea should evoke : a) a blink reflex, b) a slight discomfort, and c) an increased lacrimation.

The manoeuvre was done every three minutes, and the needed diagnostic or therapeutic procedure such as tonometry, gonioscopy, cauterization... etc was performed during the period of anaesthesia. The behaviour of the patient was noticed, and graded as bad, good and very good. The eye reaction to the instilled formulation was graded as mild, moderate and severe. The anaesthetic duration was measured when the corneal touch evoked a blink reflex and discomfort (Table 2).

In-Vitro and in-Vivo Studies on Ophthalmic Preparations of Xylocaine Hydrochloride.

RESULTS AND DISCUSSION

In-Vitro Study :

The percentage of xylocaine HCl dialyzed into the sink from aqueous solution, micellar solutions, O/W and W/O/W emulsion systems was calculated. The data were analyzed according to zero-order, first-order kinetics and simplified Higuchi model[13]. A linear relationship was observed when the data were plotted according to the following equation :

$$\left(\frac{\%Q}{A}\right) = 2\,C_o\left(\frac{DT}{\pi}\right)^{\frac{1}{2}}$$

Where; Q is the amount of the drug diffused into the sink; A, is the cross sectional area of the membrane; C_o, is the initial amount of the medicament inside the donor; D, is the observed diffusion coefficient and t, is the sampling time.

Release of Xylocaine HCl from Aqueous Surfactant Solutions:

Figures 2 & 3 represent the release pattern of the drug from 5% Tweens or Myrjs respectively. As expected, the line representing the aqueous solution, control, goes through the origin with a slope of 1.231. A linear regression analysis shows that the micellar solution lines do not pass the origin and having a negative intercept, which is an indication for the presence of a lag time. However, as seen from Table 1, Keeping the surfactant concentration constant, 5%, yields a slope slightly higher than that of the control. Generally, the amount of the drug released after 90 minutes, in presence of surfactant, is lower than that of the control. From the same table, it is quite to observe that the slope of lines obtained in case of Tweens is generally higher than those obtained by Myrjs.

The pronounced difference in the slope values suggests some kind of interaction between the surfactant molecules and the drug. Basically, the degree of interaction is affected by both the hydrophilic and lipophilic moieties of the surfactant molecules.

In order to verify the presence of such interactions UV spectra for xylocaine solution, 200 mcg/ml, in absence and presence of 1% of either Tweens or Myrjs were constructed and presented in Figures 4 and 5 respectively. From these figures one can observe a decrease in the extent of absorbance of the drug when it was dissolved in the tested surfactant solutions. It is worth to note that the absorbance of the drug solution was measured against a blank similarly treated.

Generally, in no case did the drug release from the drug surfactant-water mixtures exceed the control value after 90 minutes, which is an indication that the drug was interacting, to a certain degree, with Tweens and Myrjs in water. This improper release, probably, was due to physical trapping of drug molecules into the micelles of those surface-active agents.

Release of Xylocaine HCl from O/W Emulsions :

Figures 6 and 7 show the release pattern of xylocaine HCl from O/W emulsions prepared by Tweens and Myrjs respectively. These in vitro results indicate that an almost linear relationship when %Q/A is plotted versus $\sqrt{t}$.

Using the linear regression analysis; the slope, intercept, and correlation coefficient were calculated and tabulated in Table 1. Also, the lag time for each system was surveyed in the same table. From such plots it could be indicated that the emulsified system suppressed the release rate of the drug over the control value.

The percent of drug released was found to be surfactant dependent. Generally, the amount of drug released from O/W emulsions prepared by Tweens is less than that prepared by Myrjs. A result which indicates that the lipophilic portion of the surfactant molecule may play partly in retarding the drug release.

Such data obtained, Table 1 and Figures 6&7, indicate that the emulsifier candidate can be considered as one of the relevant factors that may, considerably, affect the release pattern.

Release of Xylocaine HCl from W/O/W Emulsions:

Xylocaine HCl was also formulated in W/O/W double emulsions. In the primary emulsification process, a series of spans, namely; Span 40, Span 60 and Span 65 was selected as lipophilic emulsifiers for preparing simple W/O emulsions. In the second emulsification process Tween 60 and Myrj 52 were employed to prepare the W/O/W double emulsions. Tween 60 and Myrj 52 were selected in the second emulsification process, since they show the lowest slope during the release period, 0.738 and 1.16 respectively. The composition of the prepared W/O/W emulsions as well as their release parameters are summarized in Table 1.

The release pattern of xylocaine HCl from double W/O/W emulsions is graphically depicted in Figures 8 and 9. From such plots one can elucidate that the release characteristics of the drug from the tested W/O/W emulsions, F. 14 to F. 19 are similar to those from O/W emulsions, F. 8 to F. 13. It is worth to note that the drug was, also, released in a similar pattern when %Q/A was plotted versus $\sqrt{t}$.

The slope values as well as the other release parameters for the release of xylocaine HCl from different W/O/W multiple emulsions, F.14 to F. 19 were calculated and tabulated in Table 1.

From the data appeared in Table 1, it could be observed that F. 15 exhibited the lowest slope for the release pattern and the percentage of drug diffused is about half that of the control, 25.97%. When Tween 60 was selected as the second emulsifier the percent of drug diffused can be ranked as : F. 15 < F. 16 < F. 14. On the other hand, when Myrj 52 was selected to prepare W/O/W the formulations are arranged as : F. 17 < F. 18 < F. 19.

In-Vivo Study :

The clinical applications of xylocaine HCl were carried out using six formulations in addition to the control. The formulations tested were : F. 9, F. 11, F. 14, F. 16, F. 17 and and F. 18. These formulations were selected due to their higher degree of their physical stability, less creaming. Each formulation was tested for its anaesthetic duration of a action on a 25 patients group of the out-patient clinic of the ophthalmology department of Assiut University Hospital.

From the clinical point of view the longest surface anaesthetic mean duration was 9.08 minutes, average of 25 readings, was obtained with F. 17, Table 2. In contrast, the shortest mean surface anaesthetic duration was attained with the control and was found to be 5.24 minutes. The tested formulations could be ranked according to their anaesthetic duration as follows : control < F. 18 < F. 14 < F. 11 < F. 9 < F.16 < F. 17.

Table 2 shows the duration of anaesthetic action, eye irritation (eye reaction) and the behaviour of the patient. From Tablesl and 2, it seemed difficult to correlate the in-vitro results with the in-vivo ones. This may be attributed to the reflex lacrimation which was induced by the tested formulations. This is the prime factor which, basically, influences the biological activity of the drug.

Reflex lacrimation removes the drug in the lacrimal lake and promotes the drainage in the lacrimal fluid and drug reservoir. Consequently, making the drug less available to elicit its local anaesthetic effect or absorbed into the eye [14].

Statistical analysis of the data, Table 3 reveals that the differences between the mean anaesthetic duration for F.9, F. 11, F. 14, F. 17, F. 18 and that of the control is very highly significant. (P=0.001) except for F. 18 which was statistically insignificant (P=0.2).

Generally, all the tested emulsion systems gave longer means of anaesthetic durations in comparison with the time given by the control. These findings could be explained by the fact that a part of the drug is located within the dispersed phases of the tested emulsions which are considered as a reservoir for drug delivery. The lack of irritation for emulsions vehicles may be attributed to the oily properties of the emulsion system, which act as a protective barrier for the cul-de-sac.

Table 1. In Vitro Parameters for Xylocaine HCl Release from Aqueous, Micellar Solution, o/w Emulsions and w/o/w Multiple Emulsions.

No.	System	Parameter				
		a	b	c	t	%d
F.1	I. Aqueous Solution (Control)	1.231	0	0.997	0	44.08
	II. 5% Surfactant Solution					
F.2	Tween 20	1.660	-4.458	0.995	7.2	42.76
F.3	Tween 60	1.498	-3.807	0.994	6.5	38.04
F.4	Tween 80	1.706	-5.066	0.989	8.8	41.82
F.5	Myrj 52	1.394	-4.010	0.998	8.3	35.76
F.6	Myrj 53	1.368	-3.845	0.993	7.9	33.46
F.7	Myrj 59	1.462	-4.969	0.998	11.6	34.22
	III. o/w Emulsions prepared by:					
F.8	Tween 20	0.745	-2.563	0.998	11.8	22.81
F.9	Tween 60	0.738	-2.683	0.997	13.2	21.56
F.10	Tween 80	0.935	-4.060	0.994	18.9	24.50
F.11	Myrj 52	1.160	-4.078	0.993	12.4	34.79
F.12	Myrj 53	1.305	-4.311	0.976	10.9	39.69
F.13	Myrj 59	1.212	-3.859	0.987	10.1	38.71
	IV. w/o/w Emulsions prepared by:					
F.14	Span 40 & Tween 60	1.274	-3.330	0.994	6.8	39.20
F.15	Span 60 & Tween 60	0.665	-1.812	0.998	7.4	25.97
F.16	Span 65 & Tween 60	1.023	-2.787	0.991	7.4	36.26
F.17	Span 40 & Myrj 52	0.916	-3.418	0.996	13.9	26.46
F.18	Span 60 & Myrj 52	1.062	-4.090	0.991	14.8	30.38
F.19	Span 65 & Myrj 52	1.269	-4.707	0.999	13.8	36.26

a = slope ; b = intercept ; c = correlation coefficient

t = lag time (minutes) and d = % drug diffused after 90 minutes.

In-Vitro and In-Vivo Studies on Ophthalmic Preparations of Xylocaine Hydrochloride.

Table 2. Eye Reaction, Behaviour of the Patients and Mean Surface Anaesthetic Duration for Emulsion Formulations.

Formulation	Eye reaction			behaviour of the patients			Mean of action* (min.)
	mild	moderate	severe	bad	good	v.good	
F.1	-	10	-	-	5	20	5.24
F.9	-	1	-	-	-	25	7.52
F.11	4	3	-	-	-	25	7.16
F.14	-	7	-	-	-	25	6.84
F.16	-	3	-	-	2	23	8.24
F.17	1	4	-	-	5	20	9.08
F.18	2	1	-	-	1	24	5.64

* average of 25 readings.

Table 3. Significance Level , P Value, of the Differences Between the Mean Anaesthetic Duration for Ophthalmic Emulsions and Aqueous Solutions .

Formulation No.	Mean anaesthetic duration *	Standard Error (S.E.)	Pairs of comparison	P value
Control (F.1)	5.24	± 0.22	-	-
F.9	7.52	±0.19	F.1 Vs. F.9	0.001
F.11	7.16	±0.31	F.1 Vs. F.11	0.001
F.14	6.84	±0.20	F.1 Vs. F.14	0.001
F.16	8.24	±0.21	F.1 Vs. F.16	0.001
F.17	9.08	±0.27	F.1 Vs. F.17	0.001
F.18	5.64	±0.11	F.1 Vs. F.18	0.200

* average of 25 readings.

In-Vitro and In-Vivo Studies on Ophthalmic Preparations of Xylocaine Hydrochloride

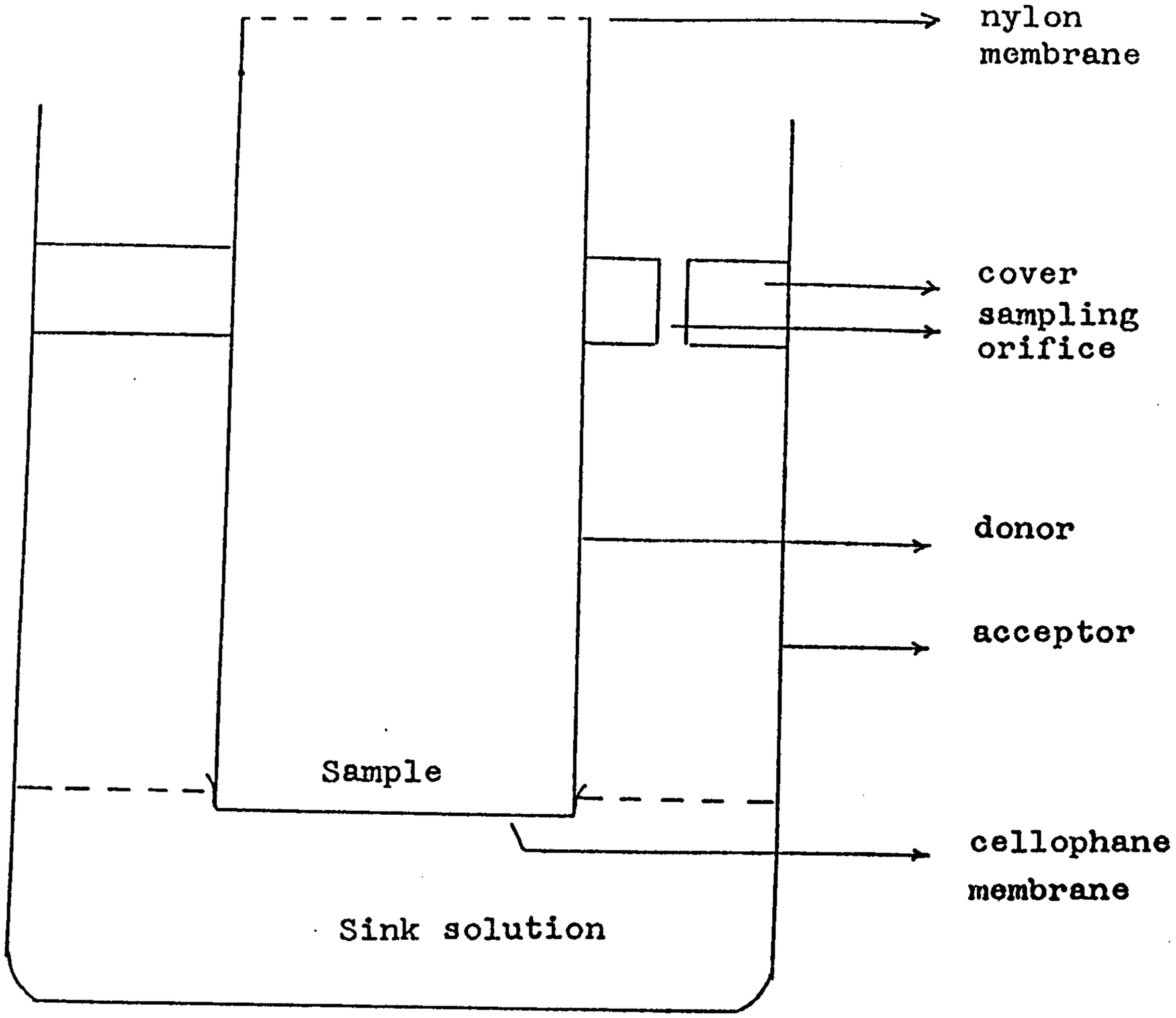


Fig. 1. Apparatus for Measuring the Amount of Drug Released

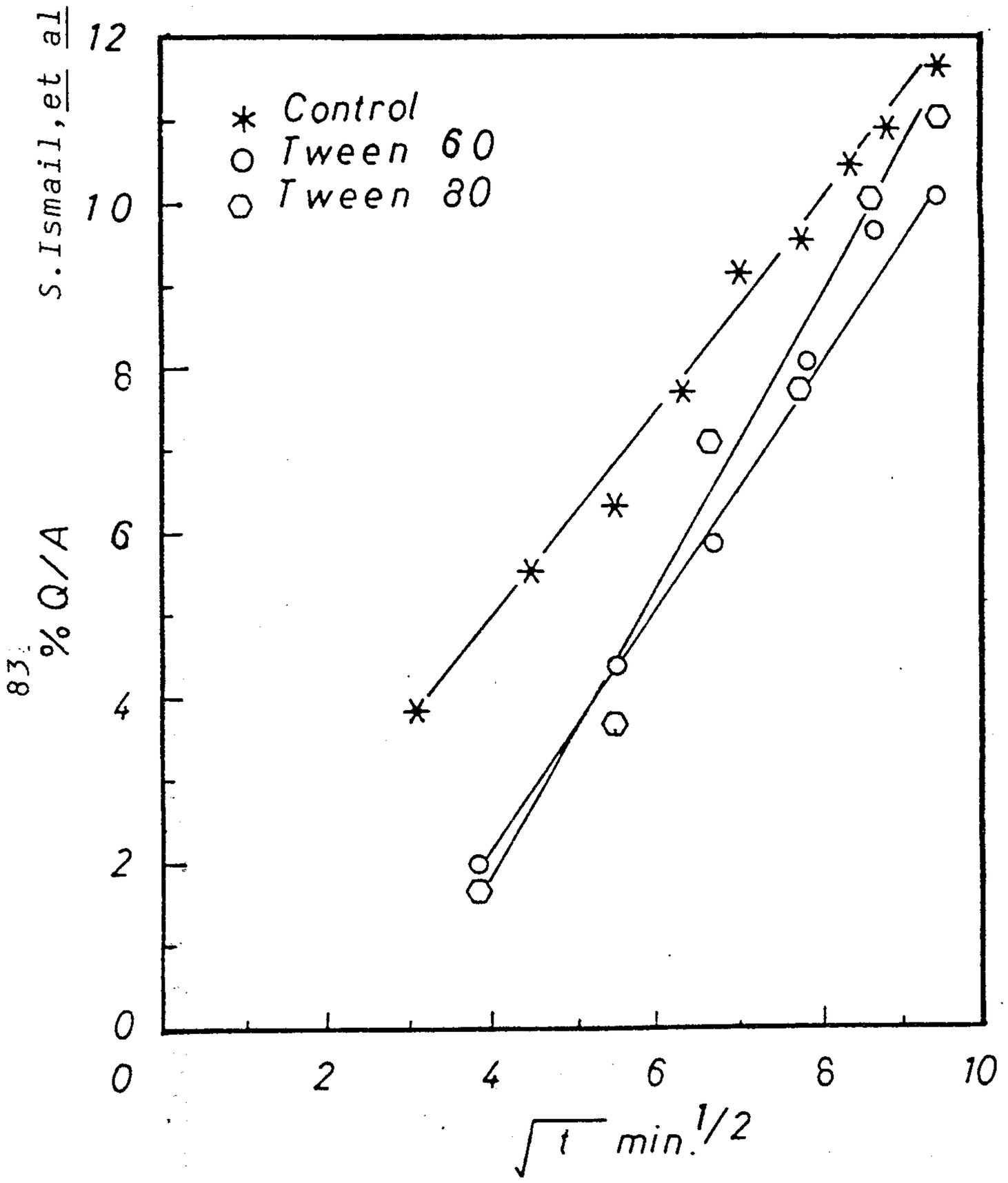


Fig. 2. Dialysis of Xylocaine HCl from 5% Tween Solutions

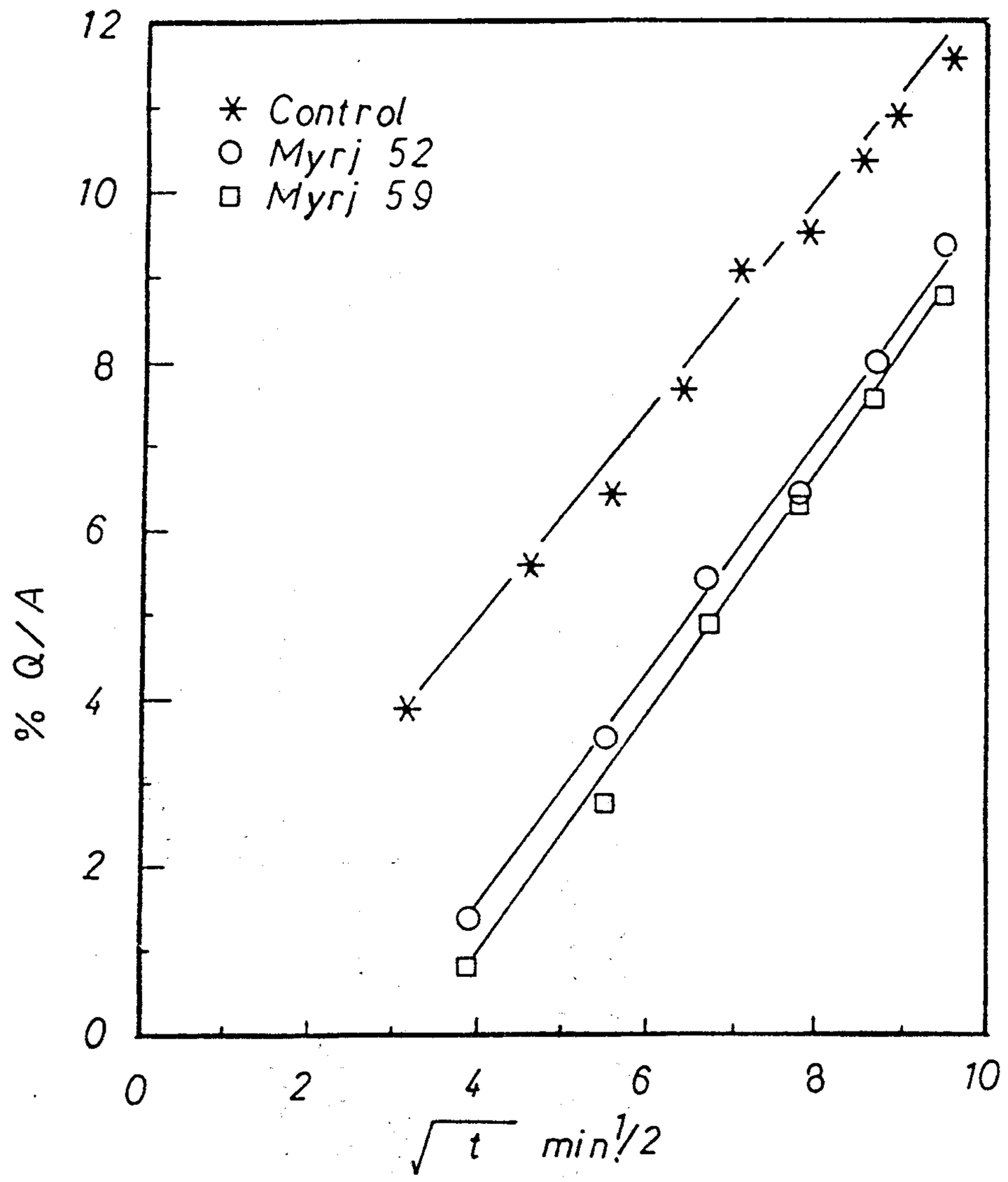


Fig. 3. Dialysis of Xylocaine HCl from 5% Myrj Solutions.

In-Vitro and In-Vivo Studies on Ophthalmic Preparations of Xylocaine Hydrochloride,

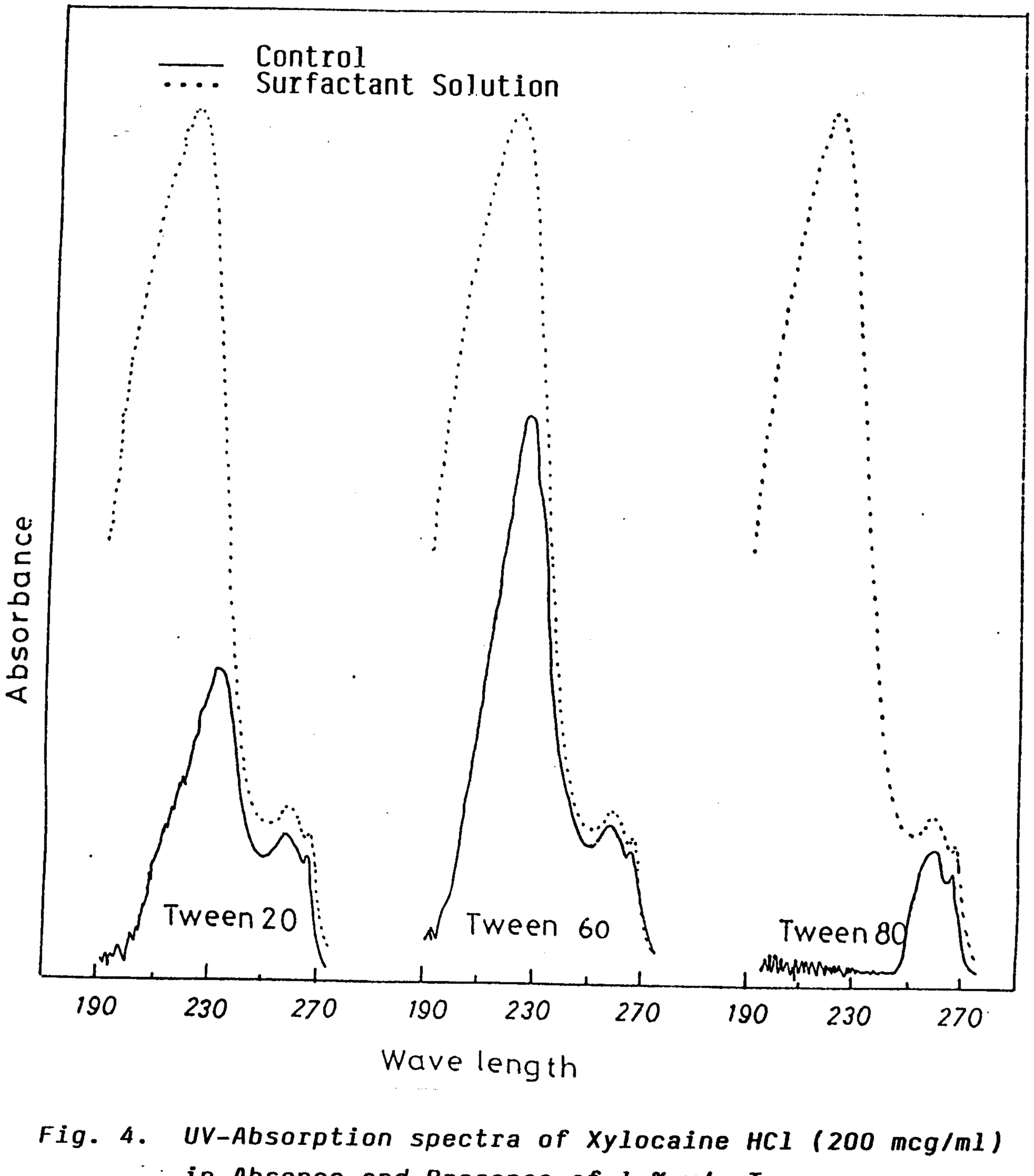


Fig. 4. UV-Absorption spectra of Xylocaine HCl (200 mcg/ml) in Absence and Presence of 1 % w/v Tweens.

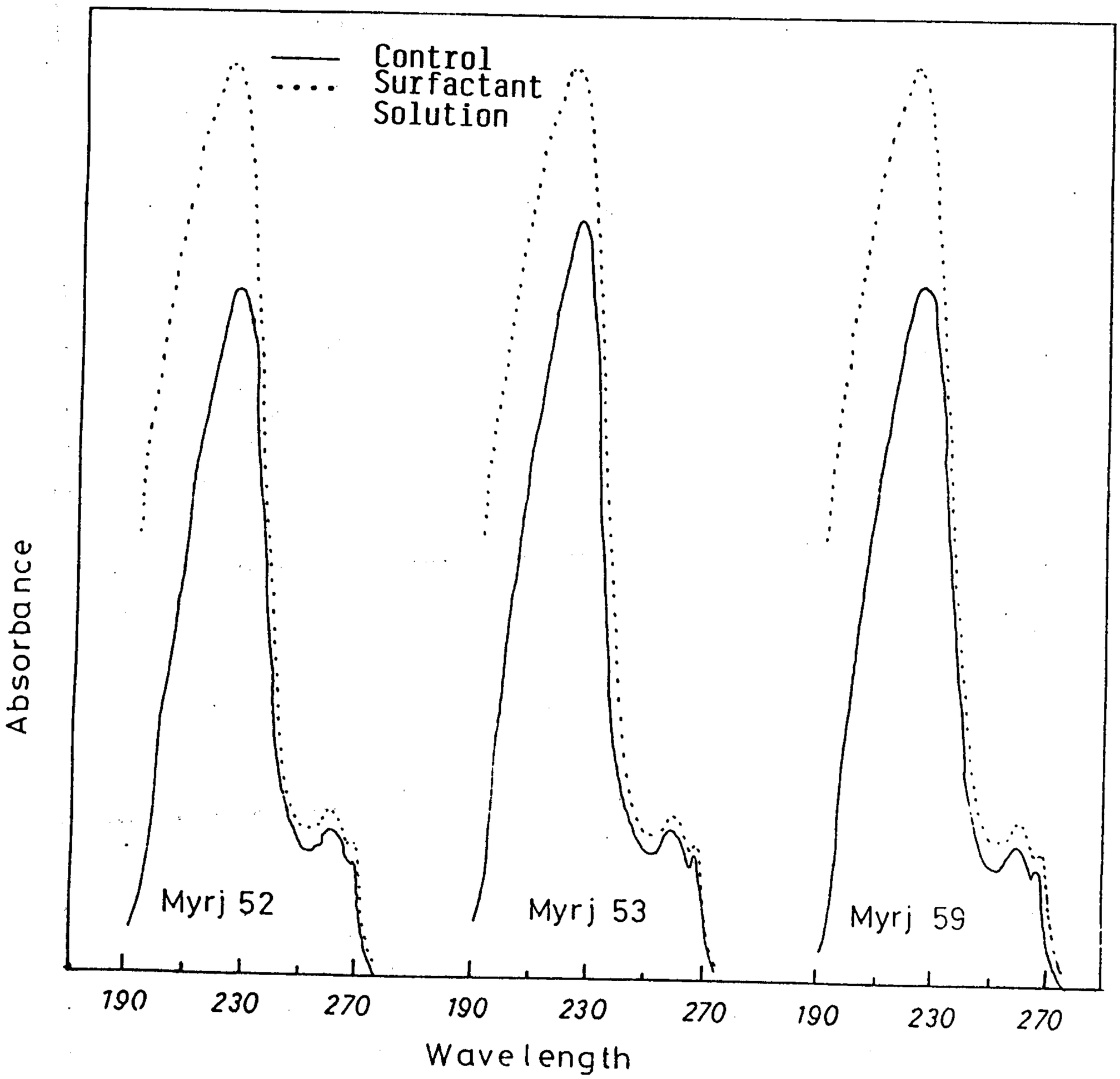


Fig. 5. UV-Absorption Spectra of Xylocaine HCl (200 mcg/ml) in Absence and Presence of 1% w/v Myrjs.

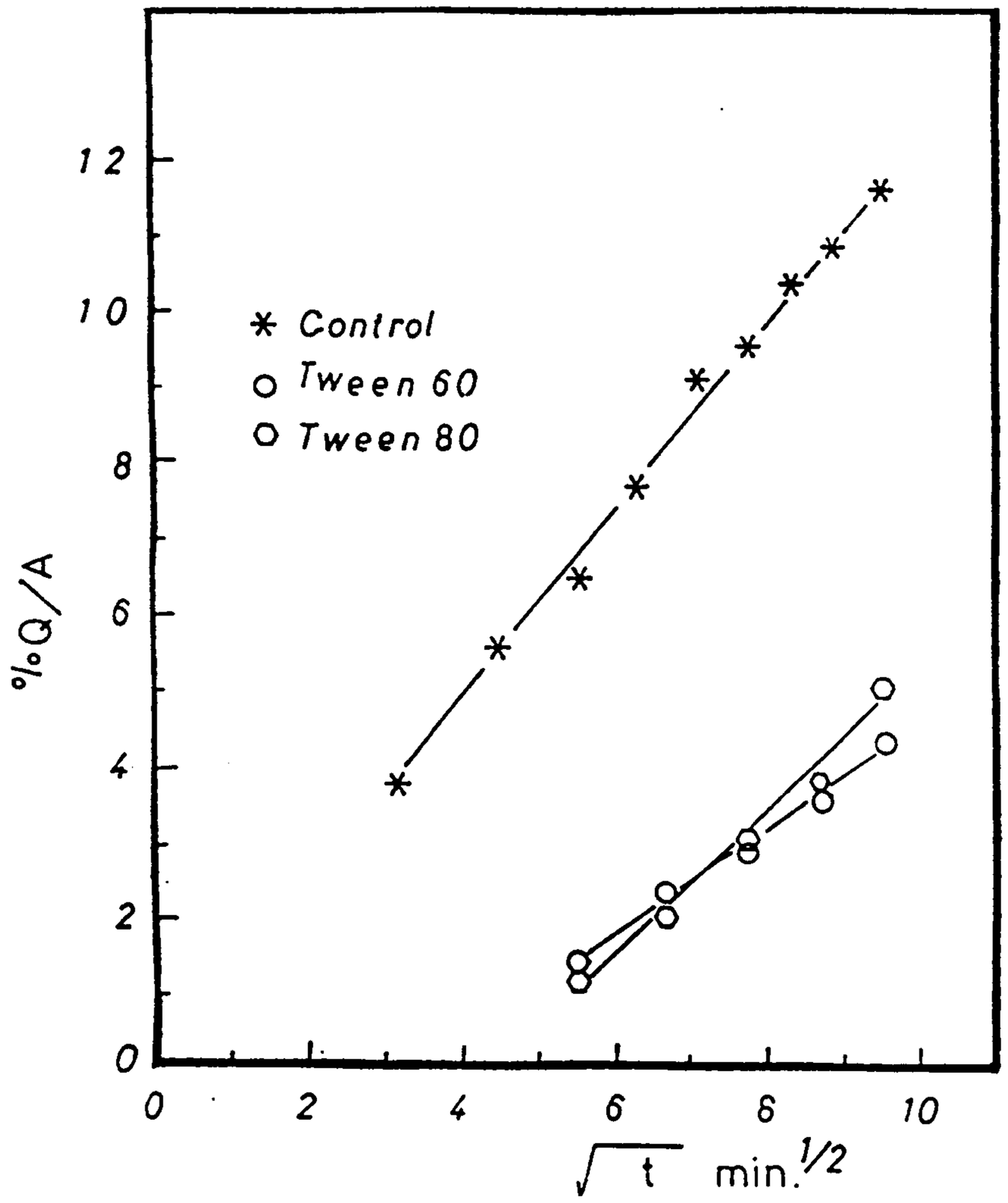


Fig. 6. Diffusion of Xylocaine HCl from Simple o/w Emulsions Preparad by Tweens.

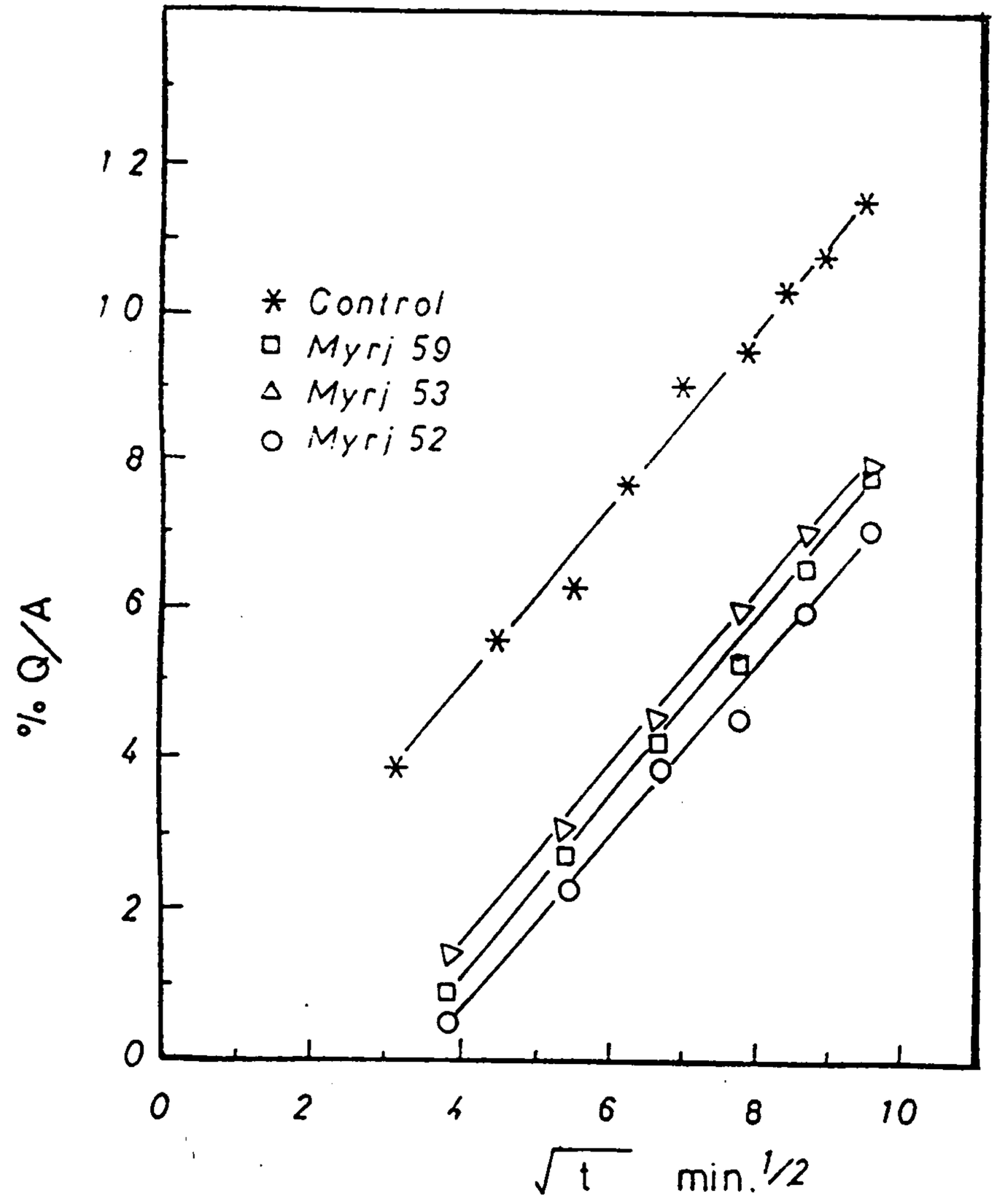
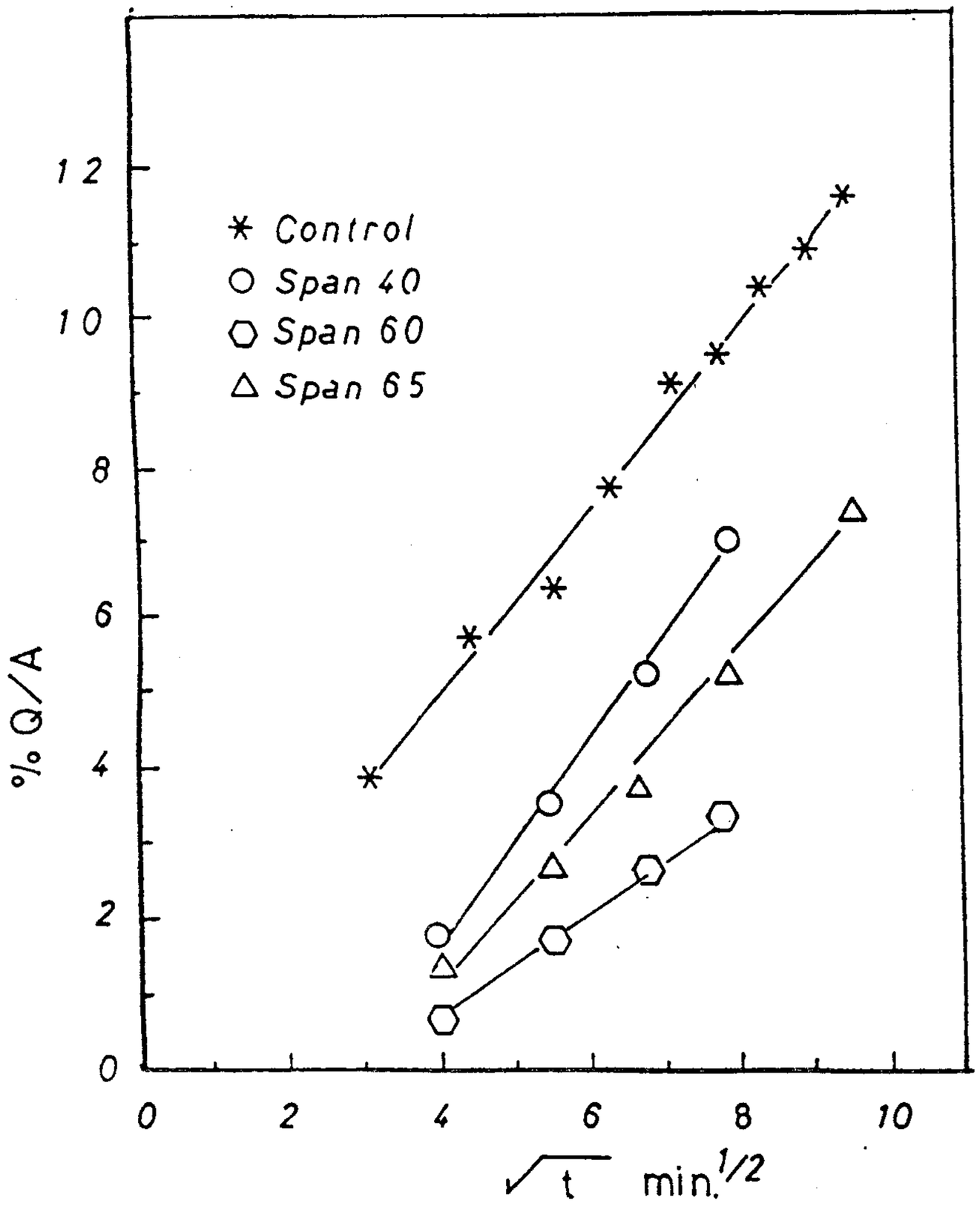


Fig. 7. Diffusion of Xylocaine HCl from Simple o/w Emulsions Prepared by Myrjs.



ig. 8. *Diffusion of Xylocaine HCl from Multiple w/o/w Emulsions Prepared by Span 40,60 or 65 and Tween 60.*

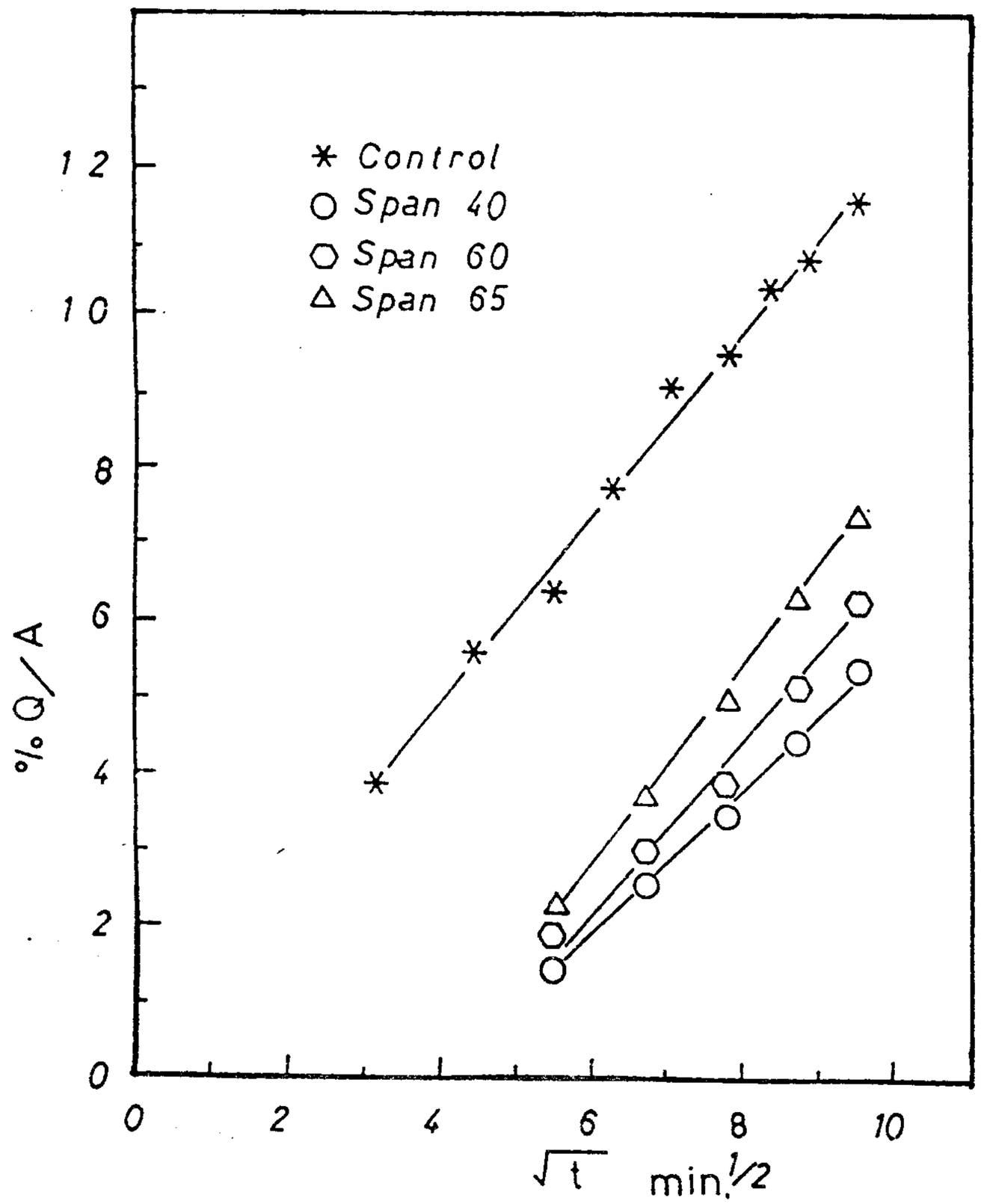


Fig. 9. *Diffusion of Xylocaine HCl from Multiple w/o/w Emulsions Prepared by Span 40, 60 or 65 and Myrj 52.*

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" دراسات معملية وحيوية على مستحضرات ايدروكلوريد الزيلوكين الرمدية "

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* قسم الرمد ـ كلية الطب ـ جامعة أسيوط ـ جمهورية مصر العربية .

استخدم فى هذا البحث عدد من المنشطات السطحية المحبه والكارهة للماء وذلك لتحضير مستحلبات بسيطه o/w ومستحلبات متعدده w/o/w . تم دراسة الديلزه الديناميكية لايدروكلوريد الزيلوكين من محلوله المائى ومحاليل المنشطات السطحيه وكذا من المستحلبات البسيطه والمستحلبات المتعدده ، وأثبتت التجارب أن انتقال العقار من خلال الغشاء السلوفانى المعيارى يتبع ميكانيكية الانتشار المحكوم .

وأثبتت التجارب أن عملية الانتشار تعتمد على نوعيه المنشط السطحى المستخدم وكذا على نوعية المستحلب وعموما فان تواجد العقار داخل شباك المنشط السطحى أو المستحلب يقلل من معدل انتشاره من خلال الغشاء السلوفانى .

لقد اجريت تجارب على عينات من المرضى كل عينه عباره عن ٢٥ مريضا من العيادات الخارجية وذلك لحساب أطول وقت ممكن يحدثه العقار كمخدر موضعى على أعين المرضى . فى هذا البحث استخدمت ستة مستحضرات عباره عن اثنين من المستحلب البسيط وأربعة من المستحلب العديد .

ولقد تم مقارنه وقت التأثير لهذه المستحضرات بوقت التأثير لمحلول العقار المائى عند نفس التركيزات . ووجد أن أطول وقت ينتج من استخدام المستحلب العديد والذى استخدم فيه سبان ٦٠ كمنشط محب للزيت ، ميرج ٥٢ كمنشط سطحى محب للماء .

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