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MODIFYING EFFECTS OF POLYOXYETHYLENE STEARATES ON THE RATE OF ACID-CATALYZED HYDROLYSIS OF ACETYLSALICYLIC ACID.

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ABSTRACT

The hydrolysis of acetylsalicylic Acid, ASA, in buffered solutions of polyoxyethylene stearates (Myrj 52, Myrj 53 and Myrj 59) has been studied at 37°C and over a pH range 1 through 2. The observed rate constant, K_{obs}, for ASA was found to be reduced markedly with an increase in Myrj concentration.

The distribution coefficient of ASA between the micellar and pseudo aqueous phases has been estimated. It was found to be parallel with both the length of POE chain and the hydrogen ion concentration. The data revealed that the hydrolysis of ASA occured mainly in the bulk aqueous phase, but at lower pH value, the contribution of hydrogen ion catalyzed reaction within the micelles becomes significant. The hydrolytic rate constant for ASA within the micelles, K_m, has been calculated and was found to increase in the following ranked order : Myrj 52 > Myrj 53 > Myrj 59.

INTRODUCTION

Since surface-active agents represent one of the most important groups of adjuvants, commonly employed in the pharmaceutical preparations, so, the drug-micelle interaction is of theoretical and practical importance. When surfactants are added into a dosage form, they have the ability to influence the drug solubility as well as its stability.

Hydrolysis of aspirin in aqueous solutions has been extensively investigated [1-4]. They estimated the overall first-order degradation rate constants as a function of pH value and they proposed various reaction mechanisms.

Attempts were made to suppress the hydrolysis of aspirin by incorporating anionic, cationic and nonionic surfactants[5]. The hydrolysis of undissociated form of aspirin was reduced by the three types of surfactants. On the other hand, the hydrolysis of the dissociated form was found to be minimized by the cationic type.

Also, the hydrolysis of aspirin was examined in bufferred solutions of cetomacrogol by Mitchell and Broadhead[6]. They found that the presence of cetomacrogol reduced the hydrolysis of aspirin.

Murthy and Rippie[7] studied the degradation of aspirin in polysorbate 80 solutions, and they found that the hydrolysis process occured to a significant extent within the micellar phase of the surfactant and the rate constant for the micellar degradation was one-fifth that in the aqueous phase.

Recently, an extensive investigation for the hydrolysis of aspirin in presence of different concentrations of polysorbates[8], cetyltrimethylammonium bromide, CTAB[9], and sodium lauryl sulfate[10] has been carried out. During these studies, the authors found that the observed rate constants were reduced, significantly, with an increase in surfactant concentration.

In the present work, a detailed study has been made on the stability of aspirin at 37°C in several concentrations of polyoxyethylene stearates, namely: Myrj 52, Myrj 53 and Myrj 59 over pH range 1 through 2. Aspirin was selected, here, as a representative example for those drugs which are characterised

by their low aqueous solubility and their tendency to be hydrolysed by the gastric fluid. Polyoxyethylene stearates, Myrjs, are characterised by having the same lipophilic portion and vary, mainly, in the length of polyoxyethylene portion, the hydrophilic moiety.

EXPERIMENTAL

Materials :

Acetylsalicylic acid, ASA, (USP grade), POE (40) stearate, Myrj 52, POE (50) stearate, Myrj 53 and POE (100) stearate, Myrj 59 (ICI, Chemical Inc., USA). Pure grade of ferric nitrate, salicylic acid (El-Nasr Pharm. Co., Egypt)

Buffer solutions :

Clark and Lubs (K Cl/H Cl) buffer was employed to prepare pH 1, 1.2, 1.4, 1.6, 1.8 and 2, in presence or absence of different concentrations of the tested POE stearates.

Kinetic procedure :

An accurate weight of ASA was dissolved in the aqueous buffer or buffered surfactant solution, at the required pH value so as to prepare 1 mg/ml of ASA solution. The prepared solutions were placed in a thermostatically controlled hot air oven operating at 37°C. Triplicate samples were withdrawn at the begining of the experiment and at suitable time intervals. The concentration of ASA retained at the specific time was calculated.

Analytical procedure :

One ml of the tested ASA solution was pipetted into a 25 ml volumetric flask, followed by the addition of one ml of iron test reagent [11] and the volume was completed to 25 ml with distilled water. The violet color developed was measured spectrophotometrically at 530 nm against blank similarly treated. The concentration of salicylic acid produced was calculated.

Knowing that each one mg of salicylic acid represents the hydrolysis of 1.304 mg of ASA. The concentration of ASA retained in the tested solution can be easily calculated.

RESULTS AND DISCUSSION

The acid-catalyzed hydrolysis of ASA was examined in 1,1.5, 2.5,5 and 10% POE stearates solutions at 37°C and 0.5 ionic strength. The pH of the tested solutions was adjusted at 1, 1.2,1.4,1.6,1.8 and 2. The hydrolysis of ASA was found to follow first-order kinetics either in absence or presence of the tested surfactants solutions. Typical results for ASA hydrolysis obtained by linear semilogarithmic plots of residual ASA versus time at pH 1 and in presence of different concentrations of Myrj 52, Myrj 53 and Myrj 59 are shown in Figures 1-3 respectively.

As illustrated in figures 1-3, the specific rate constant for hydrolysis of ASA at pH 1 was, markedly, decreased with an increase in the tested surfactant concentration. The effect of pH variation and the surfactant concentration on the observed rate constants, K_{obs}, of ASA is given in Table 1. Generally, the observed rate constants were found to decrease as the pH value and surfactant concentration were increased.

The retarding effect of surfactant for the hydrolysis of ASA is, presumably, due to the fact that the concentration a particular surfactant was varied in such a manner that the lowest concentration, 1%, was much higher than the corresponding critical micelle concentration, CMC.

This observation can be explained on the basis of the following assumptions :- in the acidic medium pH 1-2, most of aspirin molecules exist in an undissociated form, approximately 99.7% and 96.9% respectively.

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A part of these unionized molecules is capable to penetrate the micellar structure and get burried inside the micellar core. Under these conditions, it is possible to postulate that hydrogen ions will not be able to make contact with ASA molecules inside the micelles, and no hydrolytic cleavage will result. The ability of ASA to penetrate the micelles is likely affected by the pH value of the system as well as the HLB value of the tested surfactant.

It is often possible to explain micellar catalysis or protection by making certain simplifications and assuming that only one substrate molecule is incorporated into a micelle, and that the aggregation number, N, of the micelle is independent on the substrate. There will be an equilibrium between the substrate, S, in solution and that in micelle, MS, (eq. 1)

$$\begin{array}{ccc} M + S & \overset{K}{\rightleftharpoons} & MS \\ \downarrow K_o & & \downarrow K_m \\ P & & P \end{array} \qquad \text{eq. 1}$$

where K_o and K_m are the rate constants for the formation of degradation products in the bulk of solution and in the micellar phase respectively and K is the distribution coefficient for ASA between the micellar and aqueous phases.

According to the literature[12], the apparent first order degradation rate constant, K_{obs}, is expressed as :

$$\left(\frac{1}{K_o - K_{obs}}\right) = \left(\frac{1}{K_o - K_m}\right) + \left(\frac{1}{K_o - K_m}\right)\left(\frac{1}{C_t - CMC}\right)\left(\frac{1}{K}\right) \qquad \text{eq. 2}$$

where; C_t is the total surfactant concentration, CMC; is the critical micelle concentration; K_{obs}, K_o, K and K_m were previously defined.

Equation 2 predicts that plots of $\frac{1}{(K_o - K_{obs})}$ against $\frac{1}{(C_t - CMC)}$ should give a straight line, from which it can be possible to obtain K_m and K values.

Plots of eq. 2 for the hydrolysis of ASA in presence of Myrj 52, Myrj 53 and Myrj 59 are shown in Figures 4-6 respectively. The values of K_m and K for various systems at different pH values are given in Table 1.

Figure 7 shows a marked dependency of K values on the pH of the bulk aqueous solution. Generally, the K values clearly decreased as the pH value was increased. In all the tested pH values, the K values can be arranged in the following ranked order : Myrj 59 > Myrj 53 > Myrj 52.

The dependency of K values on the type of Myrj used is clearly parallel to their chain length of the polyoxyethylene moiety for each surfactant as well as its HLB value. From the present study it could be concluded that the acid-labile ASA is significantly stabilized by incorporating the unionized species into the POE stearate micelles.

Figure 8 indicates that the K_{obs} for the hydrolysis of ASA at pH 1 is reduced appreciablly with an increase in surfactant concentration. Generally the more stabilizing effect was attained in presence of Myrj 59 followed by Myrj 53 and finally by Myrj 52. This observation can be explained on the basis that most of aspirin molecules are located inside the pallisade layer of the micelle and the extent of localization is proportional with the HLB value for each surfactant.

The rate of ASA hydrolysis inside the micelle, K_m, was also calculated at pH 1-2. The data are presented in Table 2 and Figure 9 where it can be seen that the rate of hydrolysis of

ASA in the micellar phase, K_m, is lower than that in the aqueous phase, K_o, and it decreases with an increase in pH value. It should be noted that the K_m values can't be neglected specially at the highly acidic medium, pH 1. The reaction occurring within the micellar pseudo-phase is presumably hydrogen ion attack since the hydroxyl catalyzed reaction as well as solvent, water, effect do not occur to a measurable extent at the lower pH values[7].

Also, it can be observed from Table 2 and Figure 9 that the K_m values are, almost, dependent on the type of Myrj used. Generally, the least K_m values were attained in the presence of Myrj 59 followed by Myrj 53 and finally Myrj 52, the same sequence of K_{obs}. This can be explained on the fact that as the POE units increased much of drug molecules will be transferred into the micellar phase. This will result in a protection of the drug molecules from attack by the hydrogen ion.

Table 1. Effect of pH Variation and Surfactant Concentration on the Over-all First Order Rate Constants, K_{obs}, of Aspirin Hydrolysis in Aqueous Solutions at 37°C.

Myrj Conc. %w/v	$k_{obs.}$; hr^{-1} X 10^4					
	pH 1.0	pH 1.2	pH 1.4	pH 1.6	pH 1.8	pH 2.0
			Myrj 52			
0	408	305	253	220	197	170
1.0	334	248	203	179	164	141
1.5	308	221	183	160	148	128
2.5	265	191	159	139	129	114
5.0	200	138	114	109	97	85
10.0	158	126	97	79	95	56
			Myrj 53			
1.0	323	243	202	173	159	137
1.5	280	216	179	157	142	122
2.5	252	189	157	137	122	108
5.0	191	146	120	100	91	78
10.0	137	105	80	66	62	55
			Myrj 59			
1.0	306	233	191	166	150	132
1.5	269	201	171	146	132	115
2.5	230	162	139	120	114	103
5.0	158	138	110	88	87	70
10.0	122	97	86	63	56	45

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Table 2. Parameters Interpreting the Effects of Myrjs on the Acid Hydrolysis of ASA at Different pH Values.

	Myrj 52			Myrj 53		Myrj 59	
pH	k_o (hr^{-1}) X 10^4	k_m (hr^{-1}) X 10^4	K	k_m (hr^{-1}) X 10^4	K	k_m (hr^{-1}) X 10^4	K
1.0	408	79	30.1	67	31.3	50	38.5
1.2	305	49	29.3	44	30.5	30	37.5
1.4	323	31	28.6	28	29.3	21	36.1
1.6	220	22	27.3	16	28.5	11	35.0
1.8	197	14	25.4	12	26.2	7	32.2
2.0	170	9	22.6	6	23.6	5	29.1

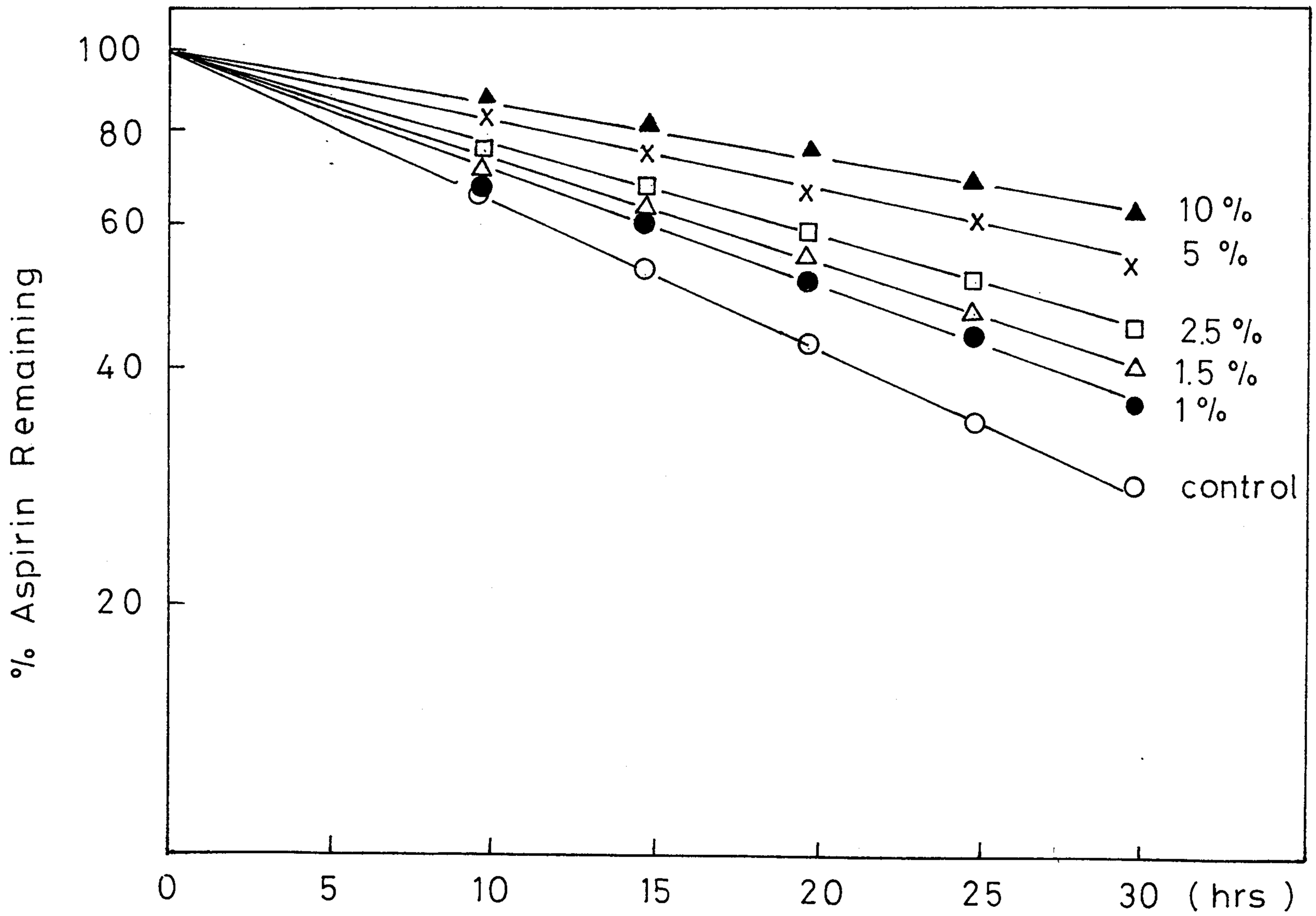

Figure 1. Effect of Increasing Concentration of Myrj 52 on the Hydrolytic Rate of Aspirin Solution at pH 1 and 37° C.

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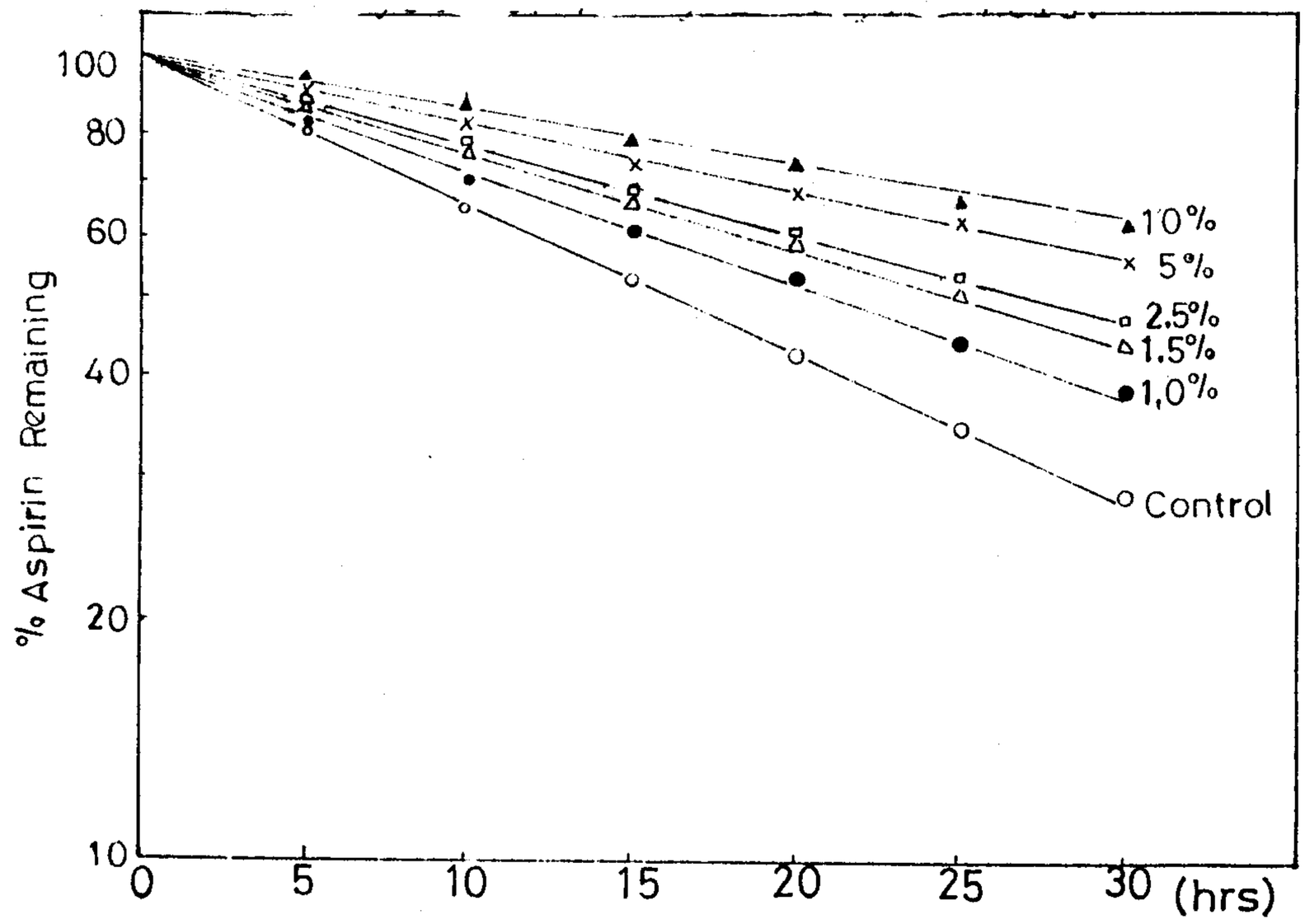

Figure 2. Effect of Increasing Concentration of Myrj 53 on the Hydrolytic Rate of Aspirin Solution at pH 1 and 37° C

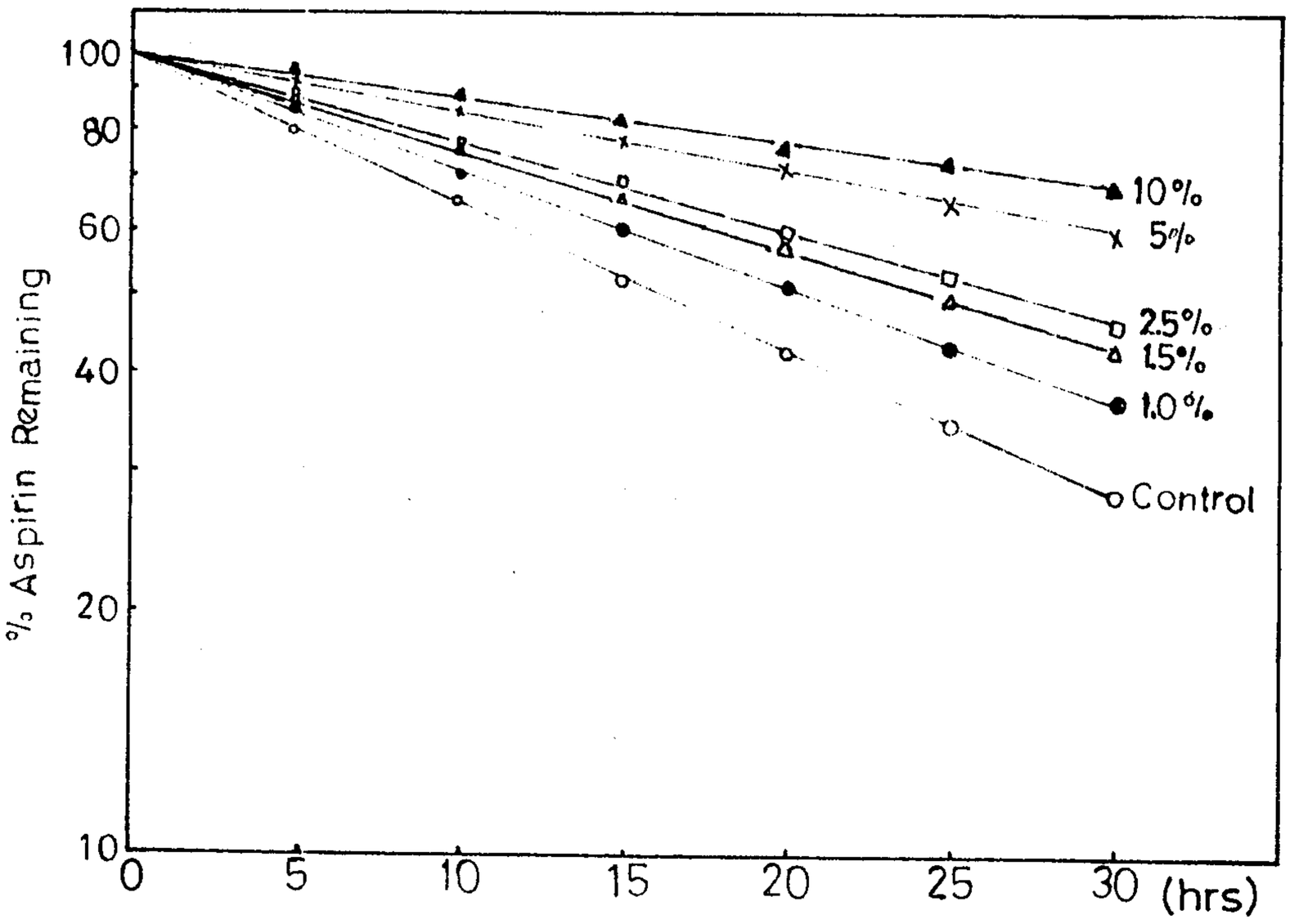

Figure 3. Effect of Increasing Concentration of Myrj 59 on the Hydrolytic Rate of Aspirin Solution at pH 1 and 37°C.

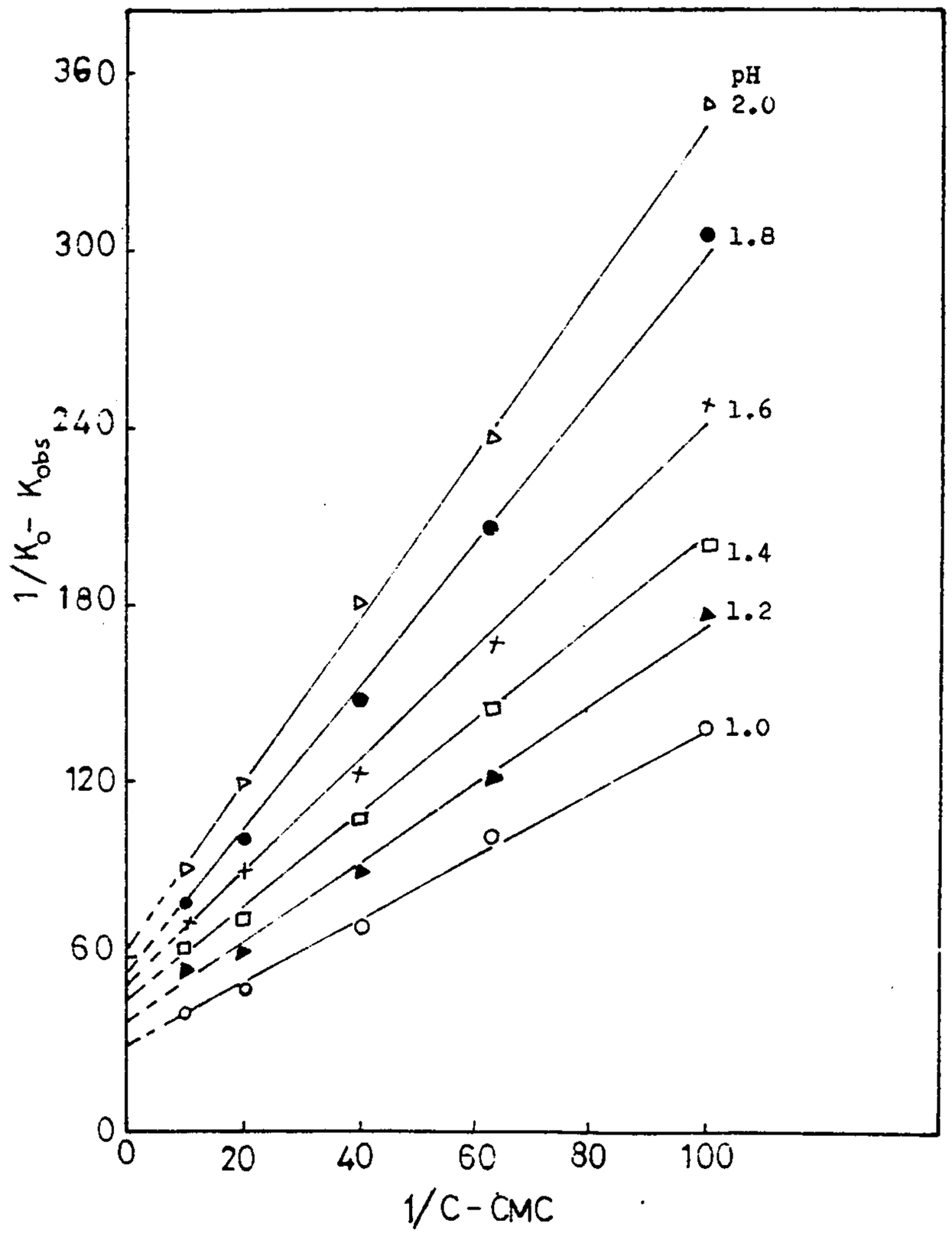

Figure 4. Double Reciprocal Plots According to Eq. 2 for the Hydrolysis of Aspirin in Presence of Myrj 52 at 37°C.

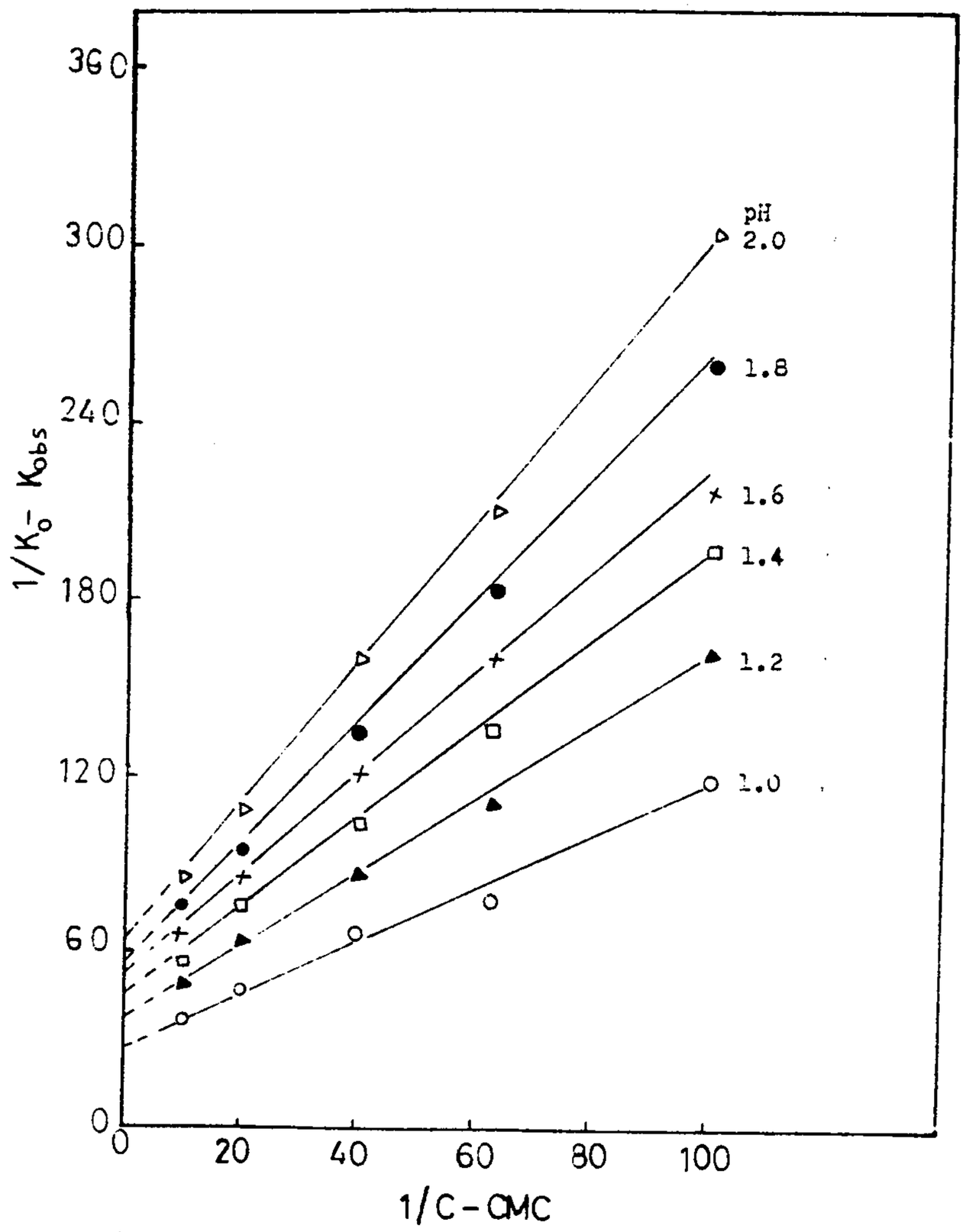

Figure 5. Double Reciprocal Plots According to Eq. 2 for the Hydrolysis of Aspirin in Presence of Myrj 53 at 37°C.

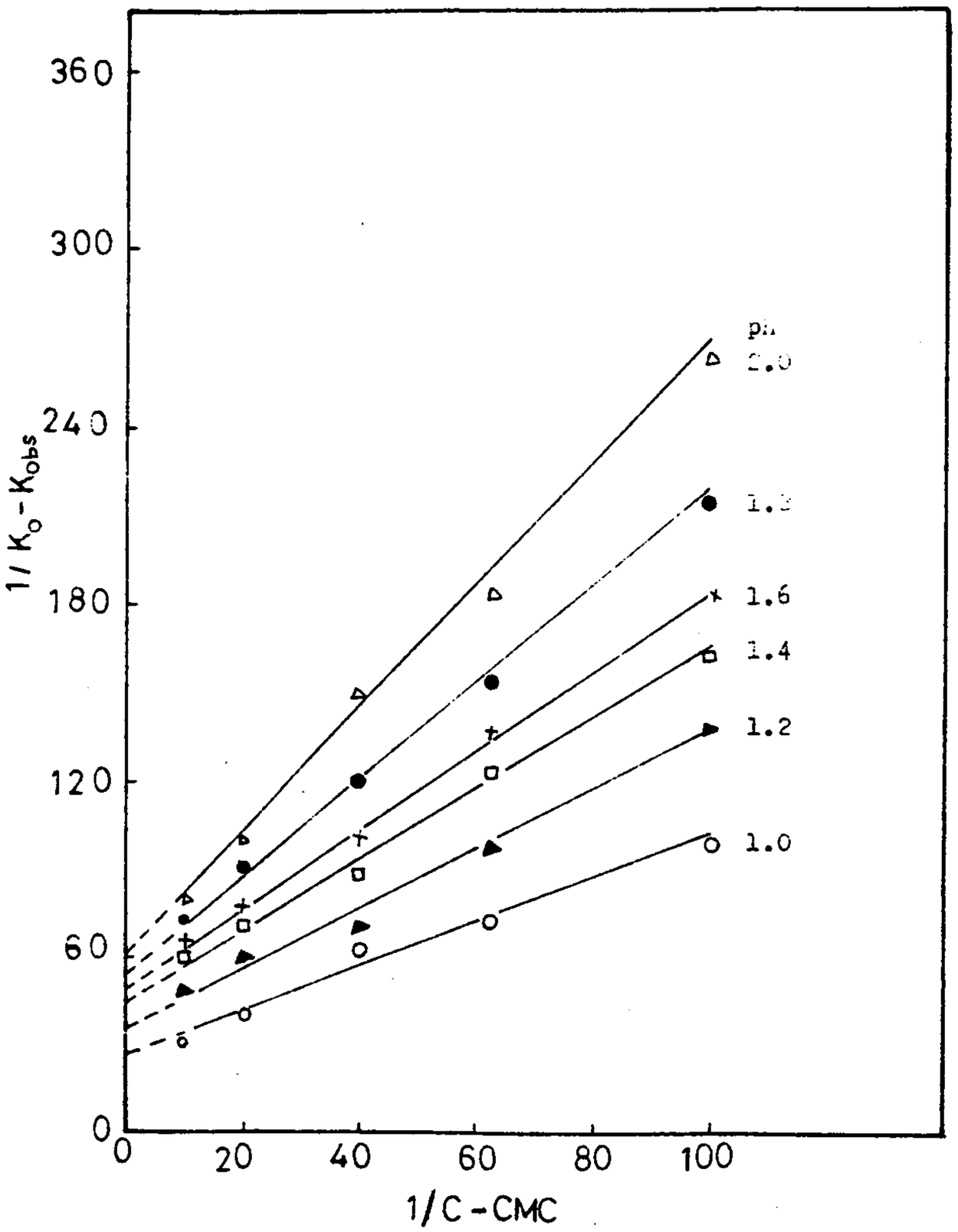

Figure 6. Double Reciprocal Plots According to Eq. 2 for the Hydrolysis of Aspirin in Presence of Myrj 59 at 37°C.

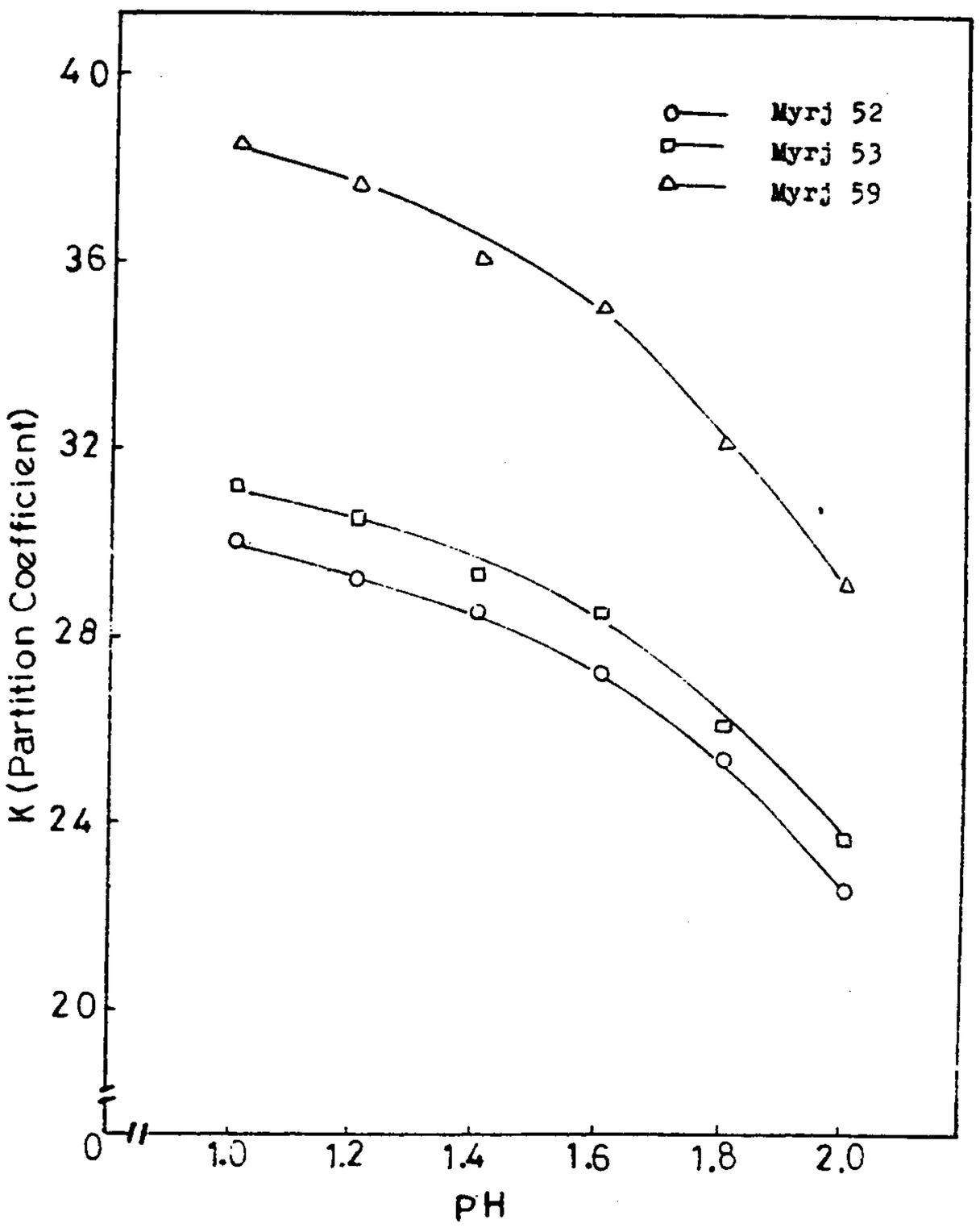

Figure 7. Apparent Distribution Coefficients for Partitioning of Aspirin between the Micellar and Aqueous Phases of Myrj 52, Myrj 53 and Myrj 59 solutions at 37°C; Plotted as a Function of pH.

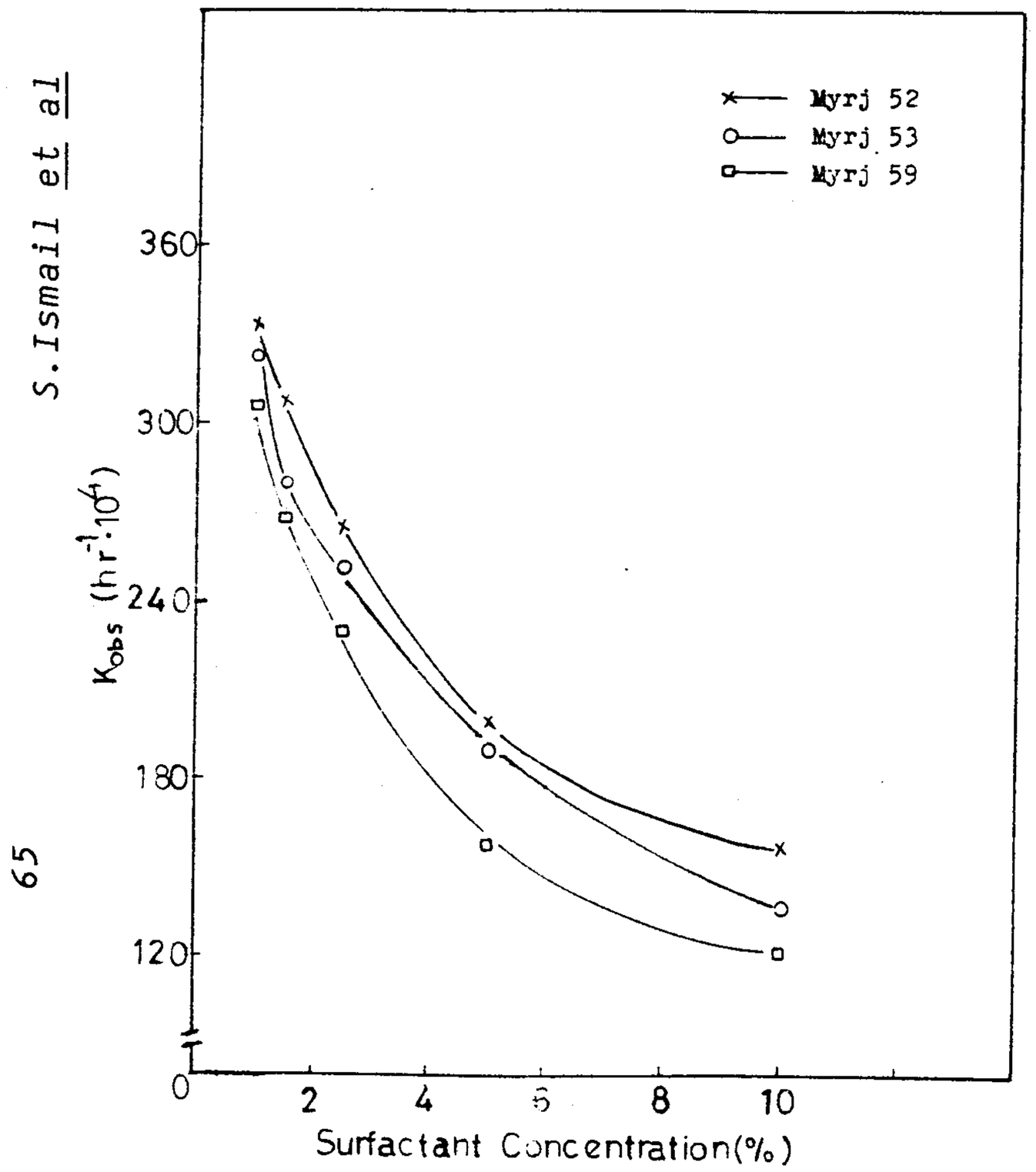

Figure 8. Effect of Surfactant concentration on the K_{obs} for the Hydrolysis of Aspirin at pH 1 and 37°C

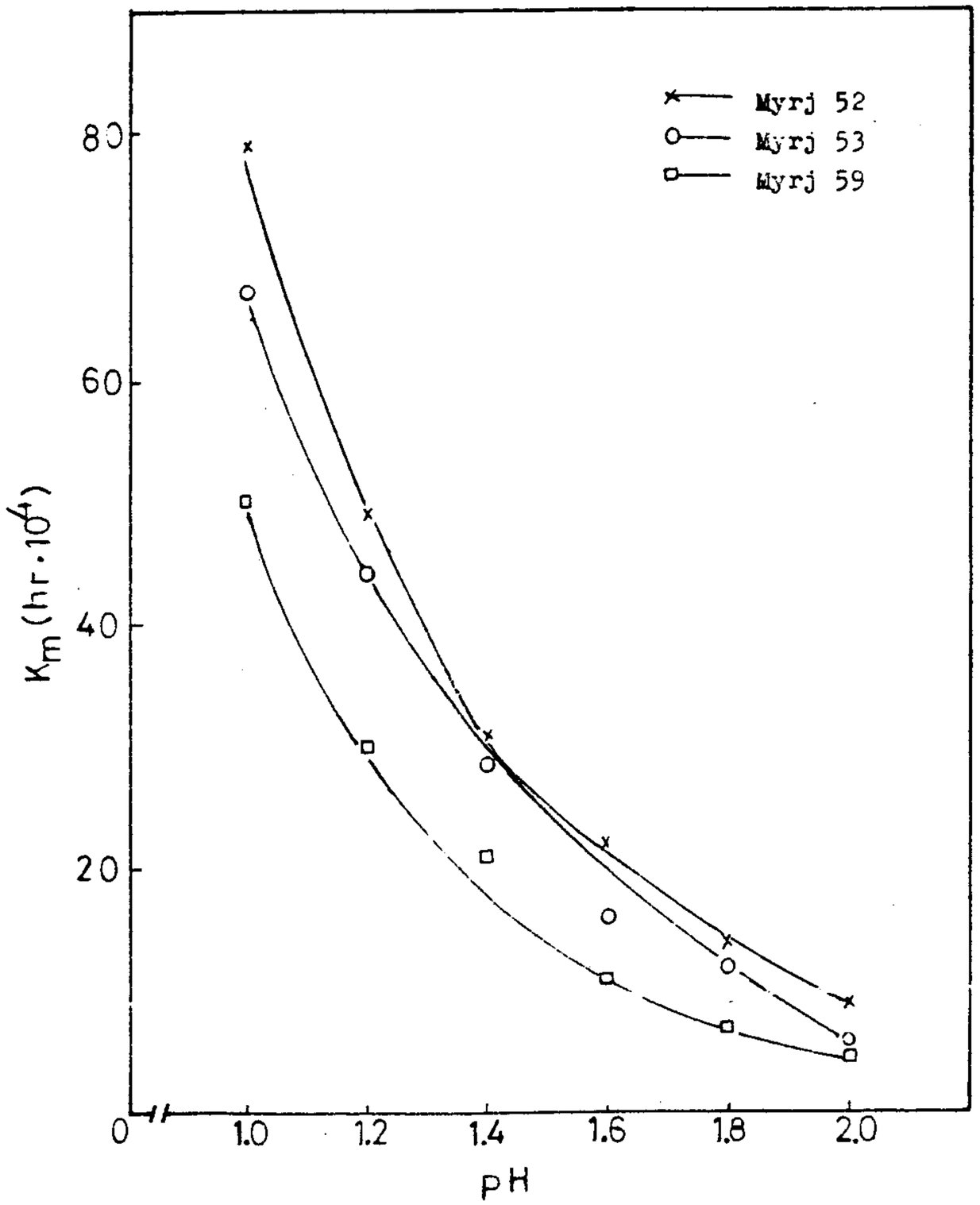

Figure 9. Effect of pH Variation on the Hydrolytic Rate Contant of Aspirin Within the Micelles of Polyoxyethylene Stearates, K_m, at 37°C.

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التأثيرات المتحورة لاستيرات عديده أوكسيد الايثلين على معدل تميؤ حمض الاستيل سلسيليك فى الوسط الحمضى

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قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة أسيوط ـ مصر

تمت دراسة التحلل المائى لحامض الاستيل سلسيليك فى المحاليل المنظمه لاستيرات عديده أوكسيد الايثلين (ميرج ٥٢ ، ميرج ٥٣ ،ميرج ٥٩) عند درجة حراره ٣٧ م وفى مدى الاس الايدروجينى ١ ـ ٢ وقد وجد أن ثابت معدل التحلل الظاهرى يقل بوضوح مع زيادة تركيز الميرجات .

وقد تم تقنين معامل التوزيع للاسبرين بين وسط الشباك والوسط المائى وقد وجد أنه يتناسب طرديا مع عدد وحدات أوكسيد الايثلين وكذلك مع تركيزات ايونات الايدروجين وقد وجد أن التحلل المائى يحدث بصوره رئيسية فى الوسط المائى . وعند الاس الايدروجينية المنخفضة فانه لايمكن اغفال ثابت معدل التحلل المائى داخل الشباك ووجد أن هذا المعدل يعتمد أيضا على نوع المنشط السطحى المستخدم . ويمكن ترتيب ثوابت معدل التميؤ داخل الشباك على النحو التالى .

ميرج ٥٢ > ميرج ٥٣ > ميرج ٥٩ .

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