

KINETICS OF ASPIRIN HYDROLYSIS IN AQUEOUS SOLUTION
OF SURFACTANTS I:NON - IONIC SURFACTANTS.

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ABSTRACT

The kinetics of aspirin hydrolysis were studied in the presence of different concentrations of polysorbates and at a variety of pH range. The aspirin hydrolysis in the presence of polysorbates followed first-order kinetics and the observed rate constants at different pH values and in the presence of the surface-active agents were calculated. The surfactant effect ratio (SER) was calculated and found to be decreased as the surfactant concentration was increased. The micellar rate constant, K_m , for the drug in the presence of the tested surfactants at a given pH value as well as the distribution coefficient, K , of aspirin between the micellar and the aqueous phases were estimated. From the results obtained, it could be observed that the K_m and K values are markedly influenced by the pH^m value of the system. The study revealed that the surfactants are not only used to solubilize those poorly water soluble compounds but also to increase their stability in aqueous solutions.

INTRODUCTION

It is well known that the micellar solubilization phenomenon is not only responsible for improving the solubility of the slightly water-soluble drugs, but also for protecting them against decomposition¹⁻⁵. It has been postulated, that micellar solubilization usually takes place through one of the following mechanisms: a) association of the drug molecules within the micellar core, b) penetration into the palisade layer of the micelle and c) adsorption by the micellar surface.¹ If the solubilized drug molecules are localized in the hydrophobic interior part of the micelle, then the hydrolytic species, H^+ and OH^- , are not ready to come in contact with them and subsequently the rate of decomposition is reduced^{6,7}. The degree of penetration of a solubilized drug molecule, through the micelle, is usually affected by the ionic nature as well as the pH value of the system.

The modifying effect of surfactants on the reaction rate constants of organic compounds results from the fact, that the drug is partly associated with the micelle which exhibits different environmental conditions from that of the bulk of the solution. For those micellar solubilized drugs, it is assumed that the drug molecules are distributed between the micellar and the aqueous phases with a constant distribution coefficient, and therefore the rate constant for the solubilized drug is really different from that of the free drug.

It has been noted, that surface active agents modify the rate of organic reactions and their influence on the drug stability attracts the attention in the field of the pharmaceutical formulations^{3,8-10}. If the drug molecules are localized

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in the micellar core, the rate of degradation will be retarded irrespective of the ionic nature of the surface active agent. For the ionic surfactants it has been postulated, that if the drug is localized in the hydrophilic portion of the micelle and close enough to the surface, then electrostatic effects between the surface and the ionic species of water are operative. Sometimes, the drug molecules are adsorbed on the surface of the micelle, then the nature of the charge on the micelle would be the major factor for determining the hydrolytic rate. Therefore, it would be predicted, that when the micelle surface is positively charged, then the hydroxyl ion will be attracted. The electrostatic theory cannot, however, account for the decrease in the rate of the base-catalysed hydrolysis of esters caused by cetrimide¹¹.

The hydrolysis of aspirin aqueous solution has been extensively investigated¹²⁻¹⁸. The most complete investigation was carried out by Edwards¹² who demonstrated, that the apparent rate constant for the hydrolysis of aspirin at different pH values is actually a composite of six rate constants. Each one is associated with one of the hydrolytic reactions depending on hydrogen ion, hydroxyl ion or water reacting with either molecular or ionic aspirin.

Due to the interest in this field of pharmaceutical research, it was decided to study the stability of aspirin in presence of some selected polysorbates. These surface active agents are characterized by having the same hydrophilic part and differ mainly in the number of carbon atoms of the hydrophobic portion. So, this kinetic study was carried out so as to find out a relationship between the hydrolytic rate constant and the polysorbate structure as well as its concentration at different pH values.

EXPERIMENTAL

Materials:

Aspirin^a, polysorbate 20^b, polysorbate 40^b, polysorbate 80^b, pure grades of ferric nitrate, hydrochloric acid, mercuric chloride, potassium chloride, glycine, sodium hydroxide, citric acid and dibasic sodium phosphate.

Apparatus:

- 1- A constant temperature water bath held at $35^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$.
- 2- Self recording double beam spectrophotometer (Pye-Unicam).
- 3- Digital pH meter (Pye-Unicam).

Composition of Buffer Solutions Used:

pH	Buffer used
1, 1.4. and 1.8	(Clark and Lubs) ¹⁹ K Cl/H Cl
2.4, 3, 4, 5, 6 and 7,	(McIlvaine): Disodium phosphate/ Citric acid mono-hydrate ²⁰
8 and 9	(Sorensen) ²¹ Glycine/Na OH

Kinetic Study:

The amount of aspirin necessary to prepare 1 mg/ml solution was accurately weighed, transferred into a volumetric flask and completely dissolved in either buffer alone or in buffer containing an increasing surfactant concentration up to 10% w/v. The solvents used for preparing aspirin solutions were preheated to about 35°C before use. A portion of aspirin solution, about 25 ml, was transferred into a stoppered tube and the tube was placed immediately in a thermostatically controlled water bath operated at $35^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$. The temperature of aspirin solution was followed until it reached 35°C . The time was recorded and considered to be the initial time. One ml

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- a) USP grade
 - b) ICI Chemical Inc., USA.

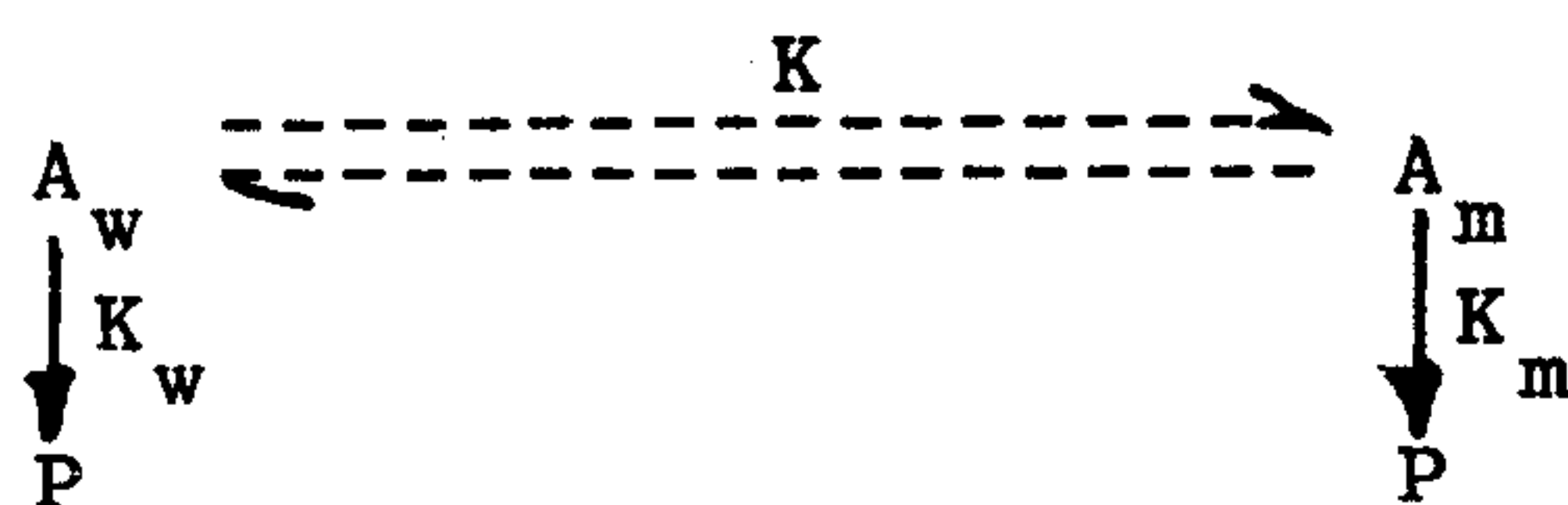
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sample of aspirin solution was withdrawn at the starting time and at suitable time intervals and analyzed for its salicylic acid content.

It is well known that one mole of aspirin is hydrolyzed into one mole of salicylic acid and one mole of acetic acid. The amount of salicylic acid formed was determined colormetrically by measuring the absorbance at 530 nm and in the presence of Trinder reagent²². The absorbance of the samples was measured against a blank similarly treated. It is a fact that the hydrolysis of aspirin does not stop during the period from the sampling time to that time at which the absorbance was measured. Therefore, it is necessary to fix the time between the sampling and absorbance reading to minimize the error that results from the hydrolytic process of aspirin during this period. Each kinetic study was made in duplicate and the average concentration of aspirin retained was calculated. It should be noted that the ionic strengths of the drug solutions were adjusted at 0.5.

RESULTS AND DISCUSSION

The rate of aspirin hydrolysis was followed at 35°C, at a variety of pH values and in the presence of surfactant concentrations, from 1 - 10 % w/v. The surfactants used in this study were : polysorbate 20 (PS 20), polysorbate 40 (PS 40) and polysorbate 80 (PS 80). The modifying effect of surfactants on the rate of aspirin hydrolysis results from the fact that the reaction rate of the solubilized aspirin inside the micelle differs from that in the bulk phase. The decomposition of aspirin in an aqueous surfactant solution, above the respective CMC, could be represented as:



where A_w and A_m represent the concentrations of aspirin in the aqueous and micellar phases respectively; K_w and K_m are the rate constants for the hydrolysis of aspirin in aqueous and micellar phases respectively and K is the distribution coefficient of aspirin between the micellar and aqueous phases.

It was shown, that for a given pH value and at a definite surfactant concentration, a plot of the logarithm of the residual concentration of aspirin versus the sampling time was linear (not shown). The K_m values at different pH values and various surfactant concentrations were estimated by application of the following equation²³.

$$K_{obs.} = \frac{1 - V}{K} \left(\frac{K_w - K_{obs.}}{V} \right) + K_m \quad (\text{Eq. 1})$$

where $K_{obs.}$ is the observed rate constant related to the total amount of aspirin in the total volume. V is the volume fraction of the micellar phase, K and K_m were previously defined. When the volume fraction is small, Eq. 1 could be rearranged in the following manner:

$$K_{obs.} = \frac{1}{K} \left(\frac{K_w - K_{obs.}}{V} \right) + K_m \quad (\text{Eq. 2})$$

From Eq. 2, when $k_{obs.}$ is plotted versus $\left(\frac{K_w - K_{obs.}}{V} \right)$

a straight line will be obtained with a slope equal to $-\frac{1}{K}$ and an intercept equal to k_m .

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The effect of different concentrations of PS 20, PS 40 and PS 80 on the rate of aspirin hydrolysis at a variety of pH values is tabulated in Tables 1-3. From these tables it could be observed that as the surfactant concentration was increased at a given pH value. The SER is the ratio between $K_{obs.}$ and K_w . The half-life periods were found to be lengthened as the surfactant concentration was increased. The half-life at pH 2.4 and in the presence of 10% surfactant solution was about double that in absence of the surfactant. The half life was found to be increased as the pH value was increased from pH 1 - pH 2.4 and then was decreased as the pH value was increased to pH 9. From tables 1-3, it can be observed that the half life of aspirin at pH 1 is greater than that at pH 9. This observation could be explained on the basis that at pH 1, the distribution coefficient of aspirin between the micellar and aqueous phases is much greater than that at pH 9. Accordingly, a significant amount of the drug was associated within the micellar core. Those solubilized aspirin molecules, inside the micellar core, are protected from attack by the H^+ species. On the other hand, at pH 9 a greater amount of aspirin is present in an ionized form and the distribution coefficient will be reduced. Therefore, most of aspirin molecules are present in the aqueous phase and they are ready to be attacked by the hydroxyl ions.

The observed decrease in the SER with an increase in the surfactant concentration could be explained on the basis that as the surfactant concentration was increased, the micellar volume fraction was increased and it would be seemed logic to expect that the decrease in the SER values is at least partly due to the less polar nature of the micellar phase.

It was clearly observed from Figs. 1-3 that plots, based on Eq. 2 were satisfactory linear for the different polysorbates used. The values of the rate of aspirin hydrolysis associated with the micellar phase K_m , as well as the distribution coefficient of aspirin between the micellar and the aqueous phases, K , derived from the intercepts and slopes of the lines in Figs. 1-3 have been calculated by the least square method and are given in Table 4. From this table it could be seen that the K_m values were found to be decreased from pH 1 to pH 2.4 and as the pH values were increased, the k_m values were found to be increased. This behaviour was observed for all the polysorbates used. The K_m value at a given pH value was found to be dependent on the type of polysorbate used. It is well known that polysorbates are characterized by having the same hydrophilic portion and differ mainly in the hydrophobic one, so it could be concluded, that K_m value is markedly dependent on the hydrophobic portion of each polysorbate used. At pH 2.4 the polysorbates tested could be ranked in a decreasing order according to K_m values as follows : PS 80 > PS 40 > PS 20. This finding was parallel to the HLB values of these surfactants.

The distribution coefficient of aspirin between the micellar and the aqueous phases, K , was found to be pH-dependent and its value was found to be decreased with an increase in the pH value. This could be explained on the basis that as the pH values were increased, the amount of ionized aspirin was increased. The affinity of these ionized molecules of aspirin to be associated with the micellar core is limited and therefore the distribution coefficient, K , was reduced.

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Table 1: Effect of Polysorbate 20 Concentration and pH Variation on the SER Value and $t_{1/2}$ for Aspirin Hydrolysis at 35° C.

pH	Concentration of Polysorbate 20, % w/v											
	0	1	2.5	5	7.5	10						
	k_w^{-1} $\text{hr}^{-1} \times 10^4$	$t_{1/2}$ (hr)	SER* $\times 10^3$	$t_{1/2}$ (hr)	SER $\times 10^3$	$t_{1/2}$ (hr)	SER $\times 10^3$	$t_{1/2}$ (hr)	SER $\times 10^3$	$t_{1/2}$ (hr)	SER $\times 10^3$	$t_{1/2}$ (hr)
1	408	17	867	19.6	777	21.9	700	24.2	635	26.8	581	29.2
1.4	195	35.5	871	40.8	769	46.2	697	51	620	57.3	579	61.3
1.8	92	75.3	869	86.6	771	97.6	695	108.3	620	121.6	576	130.8
2.4	67	103.4	865	119.5	746	138.6	686	150.7	567	182.4	627	216.6
3	115	60.3	921	65.4	852	70.7	791	76.2	748	80.6	730	82.5
4	238	29.1	865	33.6	815	35.7	790	36.9	752	38.7	731	39.8
5	294	23.6	867	27.2	810	29.1	782	30.1	731	32.3	724	32.5
6	311	22.3	884	25.2	829	26.9	788	28.3	749	29.7	723	30.8
7	334	20.8	898	23.1	832	24.9	787	26.4	751	27.6	724	28.6
8	332	20.9	918	22.7	867	24.1	831	25.1	795	26.3	774	27
9	435	15.9	942	16.9	903	17.6	878	18.1	846	18.8	839	19

* Surfactant Effect Ratio = k_{obs} / k_w .

Table 2 : Effect of Polysorbate 40 Concentration and pH Variation on the SER Value and $t_{1/2}$ for Aspirin Hydrolysis at 35°C.

pH	Concentration of Polysorbate 40, % w/v															
	0		1		2.5		5		7.5		10					
	k_w^{-1} (hr ⁻¹) x 10 ⁴	$t_{1/2}$ (hr)	SER * x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)				
1	408	17	875	19.4	772	22	662	25.7	632	26.9	596	28.5				
1.4	195	35.5	862	41	753	47.1	651	54.6	615	57.8	254	64.2				
1.8	92	75.3	869	86.6	771	97.6	619	121.6	586	128.3	543	138				
2.4	67	103.4	865	119.5	761	135.9	597	173.3	537	192.5	462	223.5				
3	115	60.3	913	66	852	70.7	739	81.5	713	84.5	670	90				
4	238	29.1	886	32.8	840	34.7	756	38.5	735	39.2	731	39.8				
5	294	23.6	884	26.7	799	29.5	741	31.8	721	32.7	704	33.5				
6	311	22.3	893	24.9	836	26.7	755	29.5	740	30.1	688	32.4				
7	334	20.8	898	23.1	823	25.2	748	27.7	727	28.5	700	29.6				
8	332	20.9	903	23.1	840	24.8	759	27.5	738	28.3	723	28.9				
9	435	15.9	873	18.2	781	20.4	680	23.4	655	24.3	616	25.8				

* Surfactant Effect Ratio = k_{obs} / k_w

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Table 3: Effect of Polysorbate 80 Concentration and pH Variation on the SER Value and $t_{1/2}$ for Aspirin Hydrolysis at 35°C.

pH	Concentration of Polysorbate 80, % w/v															
	0		1		2.5		5		7.5		10					
	k_w hr ⁻¹ x 10 ⁴	$t_{1/2}$ (hr)	SER* x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)	SER x 10 ³	$t_{1/2}$ (hr)				
1	408	17	875	19.4	772	22	661	25.7	632	595	28.5					
1.4	195	35.5	866	41	753	47.1	651	54.6	615	553	64.2					
1.8	92	75.3	869	86.6	771	97.6	620	121.6	587	543	138.6					
2.4	67	103.4	630	119.5	554	135.9	434	173.3	391	336	223.5					
3	115	60.3	913	66	852	70.7	739	81.5	713	670	90					
4	238	29.1	886	32.8	840	34.7	756	38.5	743	731	39.8					
5	294	23.6	884	26.7	799	29.5	741	31.8	721	704	33.5					
6	311	22.3	894	24.9	836	26.7	755	29.5	739	688	32.4					
7	334	20.8	898	23.1	823	25.2	748	27.7	727	700	29.6					
8	332	20.9	903	23.1	840	24.8	759	27.5	738	723	28.9					
9	435	15.9	873	18.2	781	20.4	680	23.4	655	616	25.9					

* Surfactant Effect Ratio = k_{obs} / k_w .

Table 4: Parameters Interpreting the Effects of Polysorbates on the Hydrolysis of Aspirin at a Variety of pH Values and 35°C .

pH	Surfactant					
	PS 20		PS 40		PS 80	
	k_m, hr^{-1} $\times 10^4$	K	k_m, hr^{-1} $\times 10^4$	K	k_m, hr^{-1} $\times 10^4$	K
1	180	28.6	188	30.1	196	30.8
1.4	75	27.5	80	28.2	85	27.5
1.8	28	24.8	34	25.5	40	26
2.4	15	19.7	19	23.2	22	23.6
3	55	16.7	60	21.3	68	21.5
4	155	43.3	163	54.1	167	63.3
5	185	32.7	190	47.6	195	51.6
6	188	26	201	41.3	210	43.3
7	192	24.3	208	37.7	224	40.2
8	205	19.6	212	34.3	238	34.8
9	290	13.2	216	32.1	342	32.7

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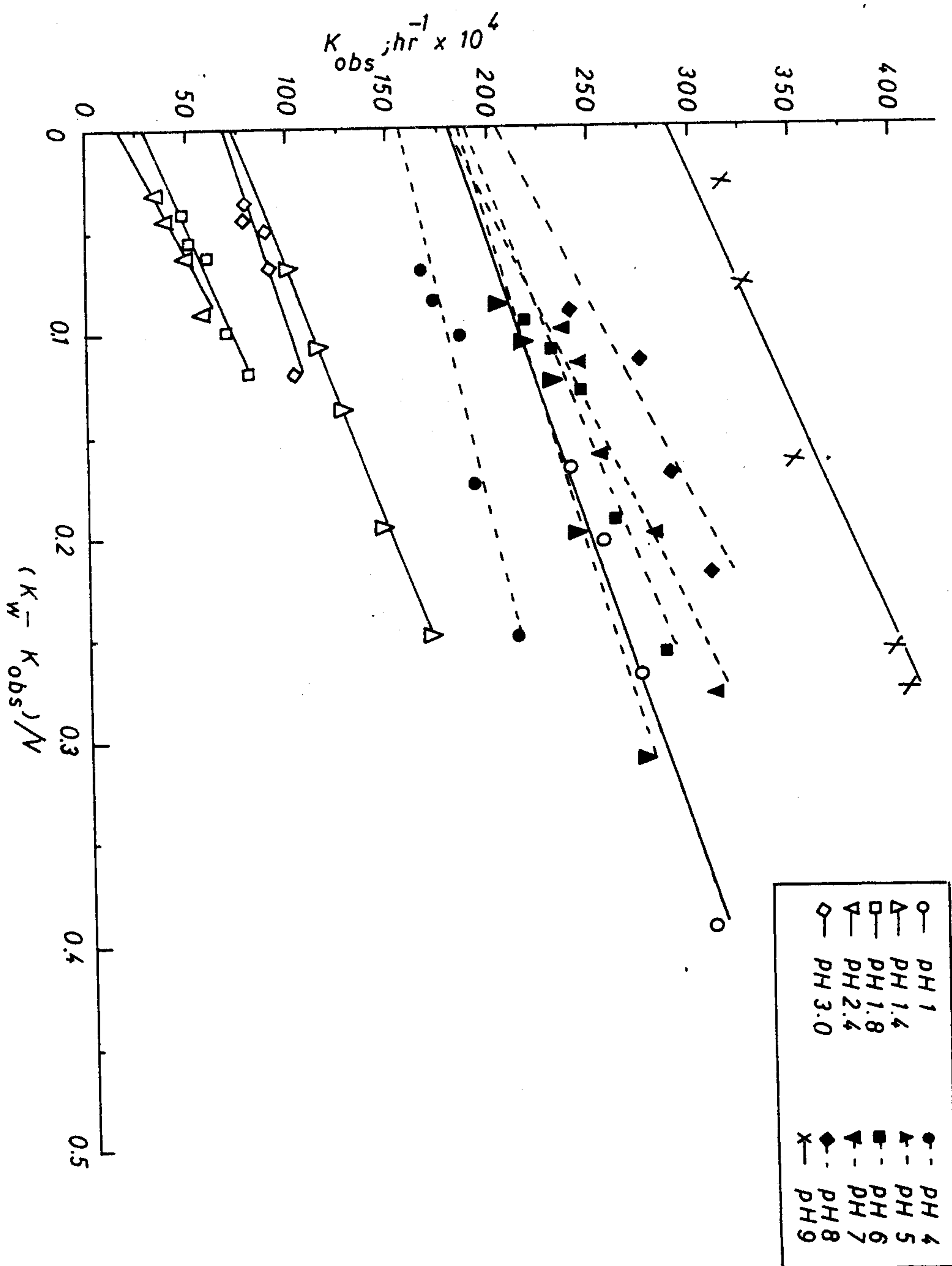


Figure 1 : Plots of the Observed Rate Constants Against $(K_w - K_{obs})/V$ for the Hydrolysis of Aspirin at 35°C and a Variety of pH Values in the Presence of Different Concentrations of Polysorbate 20.

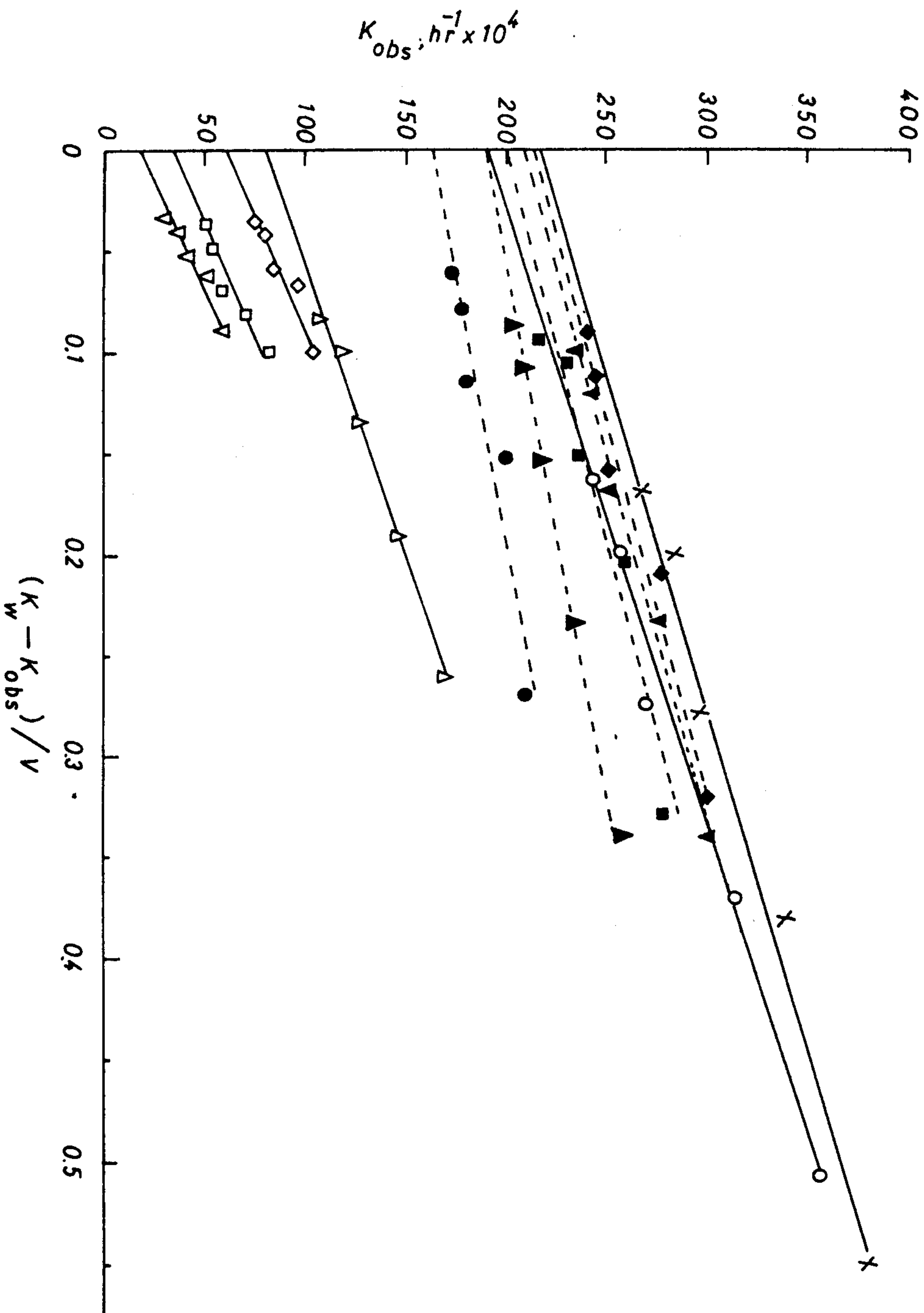


Figure 2: Plots of the Observed Rate Constants Against $(K_w - K_{obs})/V$ for the Hydrolysis of Aspirin at 35°C and a variety of pH Values in the Presence of Different Concentrations of Polysorbate 40.
Key: as Fig. 1.

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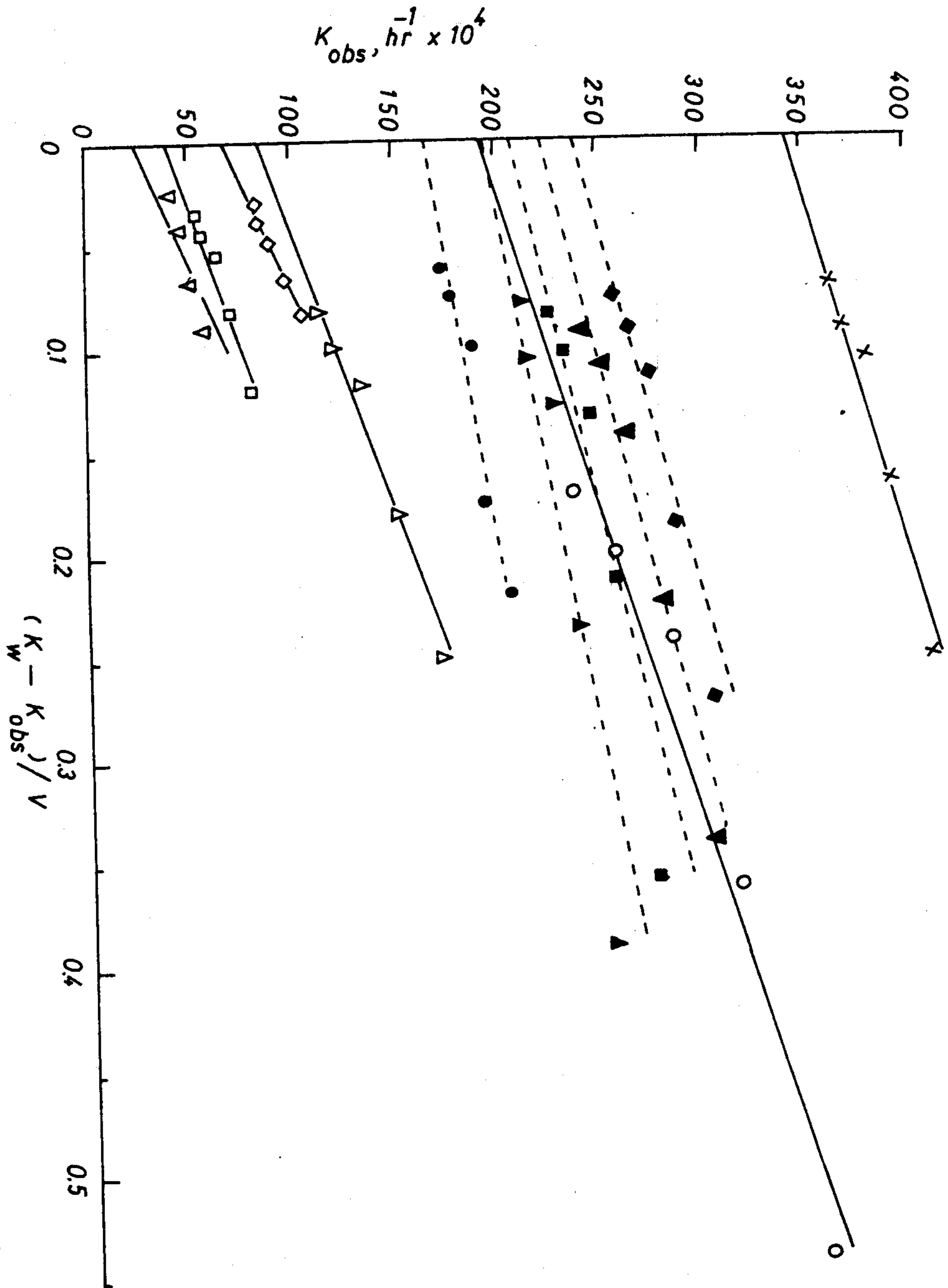


Figure 3: Plots of the Observed Rate Constants Against $(K_w - K_{obs}) / V$ for the Hydrolysis of Aspirin at 35°C and a Variety of pH Values in the Presence of Different Concentrations of Polysorbate 80.
Key : as Fig. 1.

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معدلات تميؤ الاسبرين فى محلول المنشطات السطحية

١ - منشطات السطح الغير متأيننة

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الولايات المتحدة الامريكية

تم فى هذا البحث دراسة معدل تميؤ الاسبرين فى المحاليل المنظمة عند ارقام هيدروجينية مختلفة تراوحت بين ١ - ٩ وكذا فى وجود تركيبات مختلفة (١ - ١٠ % و / ح) من عديد سوربات ٢٠ ، عديد سوربات ٤٠ وعديد سوربات ٨٠ فى نفس المحاليل المنظمة وعند نفس الارقام الهيدروجينية المستخدمة . وتمت الدراسة عند درجة حرارة ٣٥° م وتركيز أيونى ه ر . أثبتت الدراسة ان تميؤ الاسبرين قد اتبع تفاعلا من الرتبة الاولى . ومن نتائج البحث تم حساب معدلات تميؤ الاسبرين فى وجود او غياب المنشطات السطحية المستخدمة بتركيزاتها المختلفة وعند الارقام الهيدروجينية المستخدمة . وايضا تم حساب النسبة بين معدل تميؤ الاسبرين فى وجود المنشطات السطحية وفى حالة عدم وجودها . ولقد اتضح من الدراسة انه كلما زيد تركيز المنشط السطحى كلما انخفضت قيمة هذه النسبة . وتم ايضا حساب معدل تميؤ الاسبرين داخل الشباك المختلفة لعديدات السوربات المستخدمة وكذا معامل توزيع الاسبرين بين الوسط المائى والشباك . واتضح ان معدل التوزيع يعتمد على قيمة الاس الهيدروجينى المستخدم . ومن الدراسة لوحظ ان فترة نصف العمر للاسبرين قد ارتفعت بزيادة تركيز المنشط السطحى المستخدم . ومن الدراسة ثبت ان المنشطات السطحية لا تستخدم فقط فى عملية تذويب المركبات الشحيحة الذوبان فى الماء بل زيادة درجة ثباتها .

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