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Research Papers

THE HYDROLYSIS OF INDOMETHACIN IN AQUEOUS SOLUTIONS OF POLYSORBATES

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SUMMARY

The effect of surfactants on the rate of hydrolysis of indomethacin is reported for homologous series of polyoxyethylene (20) sorbitan fatty acid esters (polysorbates). The degradation of the solubilized drug follows a first-order process in which the rate decreases with the increasing surfactant concentration. The increasing length of hydrophobic chain of surfactant molecule has little effect on the rate of reaction. The solubilized solutions of indomethacin can be stored for at least one year. The influence of pH on the solubilizing power of polysorbate 80 is also studied.

INTRODUCTION

In a pharmaceutical formulation it is often desirable to prepare a clear liquid in a pH range at which the drug exists in an insoluble form or is unstable. In such cases the phenomenon of micellar solubilization is used not only to improve the solubility of poorly soluble drugs, but also for protecting them against degradative processes such as hydrolysis (Riegelman, 1960; Nogami et al., 1960; Sheth and Parrot, 1967; Meakin et al., 1971; Hamid and Parrot, 1971) and autooxidation (Mitchell and Wan, 1964; Amin and Bryan, 1973). A commonly offered general explanation for the mechanism of drug stabilization in the presence of surfactants is that presumably the attacking species cannot readily contact the solubilized compound buried in the interior of the micelle (Fendler and Fendler, 1970; Cordes and Dunlap, 1969).

The present study was undertaken to further investigate the usefulness of micellar systems for the stabilization of chemically unstable drugs in aqueous pharmaceutical preparations.

Indomethacin was selected as the object of this investigation, because this compound is practically insoluble in water and in spite of its greater solubility in alkaline solutions is unstable under these conditions (Krasowska, 1974; Hajratwala and Dawson, 1977). More-

over, as reported previously (Krasowska, 1976, 1978) non-ionic surfactants increase the solubility of indomethacin and its analogues in aqueous solutions, especially when used at high concentration.

The aim of the present work was to find out whether these high concentrations would slow the rate of hydrolysis to an extent that would increase the shelf-life of indomethacin significantly and whether the difference in the hydrophobic chain length in polysorbate molecule exerts any influence on the degradation rate.

MATERIALS AND METHODS

Materials

The following were used: 2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-3-indolyl]acetic acid [1], polyoxyethylene(20)sorbitan monolaurate (polysorbate 20). polyoxyethylene-(20)sorbitan monopalmitate (polysorbate 40); polyoxyethylene(20)sorbitan monostearate (polysorbate 60); polyoxyethylene(20)sorbitan monooleate (polysorbate 80) [2].

All surface active agents were commercial lots which were used without further purification. The other reagents were analytically pure. The water used throughout the study was double distilled from an all still glass.

Buffer composition

pH 6.0 KH_2PO_4, 0.0583 + $Na_2HPO_4 \cdot 12\,H_2O$, mol · liter^{-3} 0.008325
pH 7.0 KH_2PO_4, 0.0246 + $Na_2HPO_4 \cdot 12\,H_2O$, mol · liter^{-3} 0.0409
pH 8.0 KH_2PO_4, 0.00373 + $Na_2HPO_4 \cdot 12\,H_2O$, mol · liter^{-3} 0.0629
pH 9.0 $Na_2B_4O_7 \cdot 10\,H_2O$ + 0.0425 + HCl, 0.015

Ionic strength of the buffers was held constant at 0.2 by the addition of KCl.

Solubility studies at different pH values

The apparent solubility of the indomethacin in buffered aqueous solutions of polysorbate 80 was studied for pH values 6.0, 7.0 and 8.0. The experiments were performed at 25°C in the same way as reported earlier (Krasowska, 1976). The values at pH 2.2 obtained previously were used for comparison.

It is clear from the results shown in Fig. 1 and Table 1 that at pH values 7.0 and 8.0 the concentration of indomethacin in solubilized solutions as high as 0.5–1% and 0.9–1.5%, respectively, could be obtained in the presence of 2.5–10% of surfactant.

Kinetic investigations

The amount of indomethacin necessary to produce 0.01% w/v solution was weighed into a volumetric flask and dissolved in buffer alone or in buffer containing an increasing concentration of surfactant up to 10% w/v.

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[1] Metindol (Indomethacin), kindly supplied by Pharmaceutical Works 'Polfa' (Poland), m.p. 155–157°C.

[2] Marketed as Tween 20, 40, 60, 80 – Atlas Chemie GmbH, Essen, G.F.R.

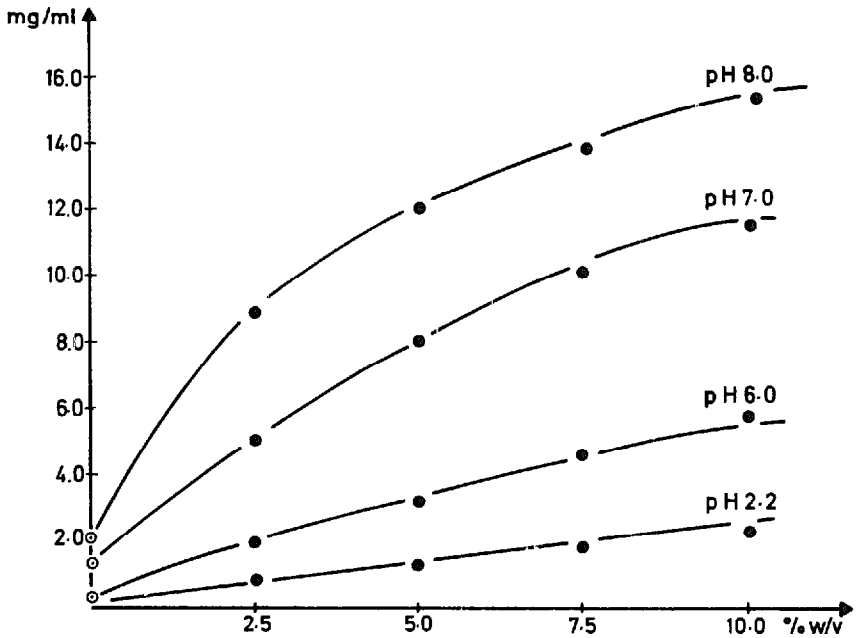

Fig. 1. The effect of pH on the degree of solubilization of indomethacin in aqueous solutions of polysorbate 80.

The solutions containing polysorbate 80 buffered to pH 7.0, 8.0 or 9.0 were subjected to kinetic analysis at 70, 80 and 90°C. In the case of other polysorbates used, the solutions buffered to pH 8.0 were investigated at one temperature (80° C) exclusively. Samples were withdrawn at suitable time intervals, cooled in an ice bath and assayed spectro-

TABLE 1

EFFECT OF pH VARIATION ON THE DEGREE OF SOLUBILIZATION OF INDOMETHACIN AND THE VALUE OF PARTITION COEFFICIENT *K* BETWEEN MICELLAR AND AQUEOUS PHASES

Concentration of polysorbate 80% w/v	Solubility of indomethacin % w/v			
	pH 2.2 [a]	pH 6.0	pH 7.0	pH 8.0
0	0.001	0.012	0.077	0.21
2.5	0.06	0.206	0.496	0.871
K	2422	665	225	130
5.0	0.119	0.327	0.79	1.18
K	2486	554	196	99
7.5	0.150	0.465	1.01	1.40
K	2149	545	176	83
10.0	0.230	0.580	1.18	1.55
K	2546	527	160	72

[a] According to Krasowska (1976).

photometrically for intact indomethacin as described previously (Krasowska et al., 1973; Krasowska, 1974). Each kinetic run was made in duplicate and no significant differences in rates were observed.

RESULTS AND DISCUSSION

The percentage residual concentration of indomethacin was calculated for each period of heating and 1 g% concentration–time plot was constructed as illustrated in Fig. 2. The degradation behaviour is observed to follow first-order kinetics.

The values for apparent rate constants k_{obs} obtained from these curves by means of a least squares regression analysis were averaged and are shown in Table 2.

The dependence of k_{obs} on temperature is described by an Arrhenius plot as shown in Fig. 3.

The apparent activation energies calculated from the least squares slopes of the observed first-order rate constants versus reciprocal of absolute temperature, as well as the magnitude of other related parameters, are shown in Table 2.

A comparison of the observed k values calculated for aqueous buffer solutions alone and in the presence of polysorbate 80 shows that the rate of indomethacin hydrolysis is reduced appreciably with increasing surfactant concentration. The increase in stability is also evident from increase of apparent activation energies as well as free enthalpy values.

Table 3 contains the values of k at 20°C and $t_{0.1}$ – the times required for 10% degradation of the drug in the polysorbate 80 solution stored at room temperature. From

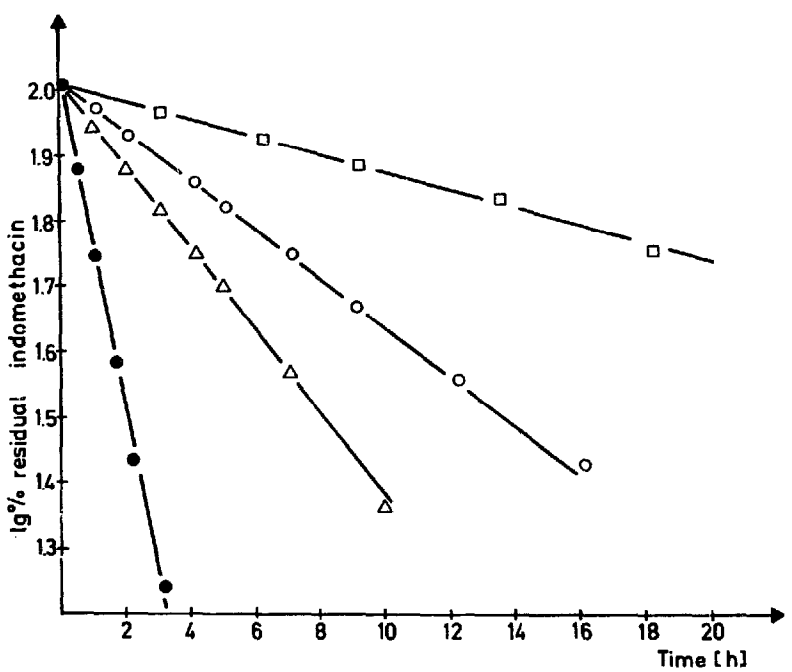

Fig. 2. Typical apparent first-order plot for hydrolysis of indomethacin in the absence and presence of polysorbate 80 in phosphate buffer at 80°C; u = 0.2. 0%, •; 2.5%, △; 0.5%, ○; 10%, □.

TABLE 2

APPARENT FIRST ORDER RATE CONSTANTS ($k_{obs} \cdot 10^6$, s^{-1}) AND RELATED PARAMETERS FOR THE INDOMETHACIN DEGRADATION IN THE PRESENCE AND ABSENCE OF POLYSORBATE 80

Parameter	Surfactant concentration % w/v											
	pH 7.0				pH 8.0				pH 9.0			
	0	2.5	5.0	10.0	0	2.5	5.0	10.0	0	2.5	5.0	10.0
$k_{70°}$	11.47 [a]	2.00	1.04	0.464	58.3	12.59	6.92	2.46	441.7	145.4	79.45	37.0
$k_{80°}$	30.45	5.52	2.69	1.33	182.7	39.71	24.0	7.93	820.2	340.2	205.7	111.9
$k_{90°}$	80.73	15.20	7.99	4.30	418.3	104.8	53.78	23.0	1803.0	733.9	471.7	274.0
$\Delta Ha^{\neq}$ kJ · K^{-1} mol^{-1}	101.50	104.75	105.71	116.82	102.07	110.30	112.60	116.05	72.96	84.07	92.49	103.98
$\Delta H^{\neq}$ [b] kJ · K^{-1} mol^{-1}	98.64	101.89	102.85	113.96	99.22	107.45	109.74	113.19	70.11	81.22	89.64	101.13
lg A [c]	10.51	10.25	10.12	11.45	11.31	11.89	11.98	12.06	7.75	8.96	9.98	11.40
$\Delta S^{\neq}$ [d] J · K^{-1} mol^{-1}	−53.14	−58.16	−61.35	−35.13	−37.94	−37.16	−32.26	−23.49	−105.98	−82.83	−63.28	−36.12
$\Delta F^{\neq}$ [e] kJ · K^{-1} mol^{-1}	116.87	121.85	123.88	126.01	112.23	120.19	118.52	121.25	106.45	109.63	111.35	113.52

[a] According to Krasowka (1974).

[b] For temperature 343 K, according to the equation $\Delta H^{\neq} = \Delta Ha^{\neq} - RT$.

[c] In accordance with the expression $\lg k = \Delta Ha/2.303\ RT$.

[d] In accordance with the expression $S^{\neq} = 2.303\ R\ [\lg A - \lg k\frac{k \cdot T}{h}]$.

[e] According to the equation $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$.

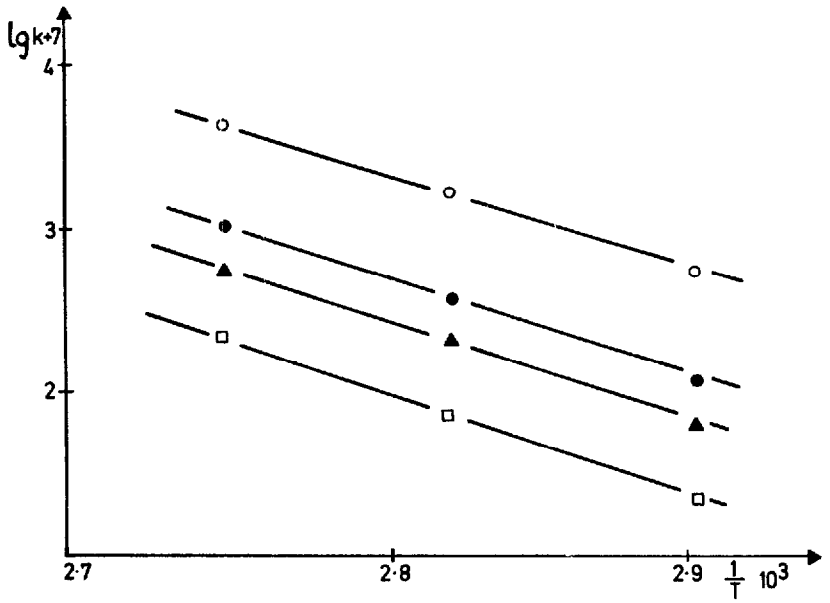

Fig. 3. Arrhenius plot showing temperature dependence of hydrolysis of indomethacin in the presence of various concentration of polysorbate 80 (pH 8.0). 0%, ○; 2.5%, ●; 5%, ▲; 10%, □.

these data it is apparent that the shelf-life of indomethacin in solubilized systems increased markedly for each pH value, and at pH 7.0 the solubilized solution could be stored for at least one year.

The modifying effect of a surfactant on the rate of hydrolysis is usually explained on the basis of a two-phase model of solubilized systems and the distribution of the drug between the aqueous and micellar phases. The postulation is made in this model that the rate in the micellar phase is smaller than the rate in the bulk phase, because the drug is firmly incorporated into the non-ionic micelle and protected by it from attacking ions. From this model information more quantitative in character can be obtained by relating the observed rate constant to the postulated contributing rate constants in micellar and

TABLE 3

APPARENT FIRST ORDER RATE CONSTANTS ($k_{obs} \cdot 10^9$, s^{-1}) AND 10% DEGRADATION TIMES ($t_{0.1}$) FOR INDOMETHACIN DECOMPOSITION AT 293 K IN THE PRESENCE OF VARIOUS CONCENTRATIONS OF POLYSORBATE 80

Surfactant concentration % w/v	pH 7.0		pH 8.0		pH 9.0	
	k	$t_{0.1}$	k	$t_{0.1}$	k	$t_{0.1}$
0	26.76	45 days	131.5	9 days	5650	5 h
2.5	3.84	316 days	17.36	70 days	960	30 h
5.0	1.89	644 days	8.32	146 days	318	3.8 days
10.0	0.43	7.7 years	2.41	504 days	74.5	16 days

bulk phases as represented by the following equation:

$$k_{obs} = k_o F_o + k_m F_m$$

where k_m and k_o are rate constants in the micellar and bulk phases, respectively, and F_o and F_m are fractions of drug present in the micellar and bulk phases. Knowledge of the partition coefficient of a drug between these two phases is fundamental in such considerations.

Based on this statement several authors (Tong et al., 1965; Smith et al., 1974; Winterborn et al., 1974) derived equations enabling the k_m value to be calculated. The proposed equations, however, are not valid for every hydrolysis condition, which may be due to simplifications and assumptions made in their derivation or the neglecting of some factors involved in the process.

The instability of indomethacin under experimental conditions applied in this investigation (alkaline medium, high temperature) made it impossible to determine the partition coefficient by solubility studies, but as can be seen from the data for 25°C (Fig. 1, Table 1), the values of K vary strongly with surfactant concentration, especially in more alkaline medium. Therefore, due to the lack of accurate values of the partition coefficient the mathematical treatment reported by Tong et al. (1965) and Smith et al. (1974) could not be applied in this study.

The equation derived by Winterborn et al. (1974), enabling the partition coefficient to be obtained from kinetic studies, when applied to the data obtained in this investigation, led to physically impossible negative values of k_m. This confirmed the similar results obtained by Dawson et al. (1977) and others (Lippold et al., 1972).

Therefore, an approximate quantitative measure of the effect of the surfactant on the degradation rate was expressed in terms of the ratio k_{obs}/k_o (where k_o is the value of the rate constant in the absence of polysorbate 80) and the results are given in Table 4.

One can see from these results that the ratio falls with increasing surfactant concentration. At pH 7.0 or 8.0 its value is more or less stable when the same concentrations at different temperatures are compared. At more alkaline conditions (pH 9.0) this regularity is no longer observed.

TABLE 4

THE EFFECT OF POLYSORBATE 80 AND pH VARIATION ON THE RATIO $k_{obs}:k_0$ FOR INDOMETHACIN DECOMPOSITION

Temperature (K)	Surfactant concentration, % w/v								
	pH 7.0			pH 8.0			pH 9.0		
	2.5	5.0	10.0	2.5	5.0	10.0	2.5	5.0	10.0
343	0.174	0.091	0.040	0.216	0.119	0.042	0.329	0.179	0.084
353	0.181	0.09	0.044	0.217	0.131	0.043	0.414	0.250	0.136
363	0.188	0.099	0.053	0.250	0.128	0.055	0.407	0.262	0.152

TABLE 5

APPARENT FIRST-ORDER CONSTANTS FOR INDOMETHACIN DECOMPOSITION ($k_{obs} \cdot 10^6$, s^{-1}) IN POLYSORBATE SOLUTIONS (pH 8.0, μ 0.2, TEMP. 353 K)

Surfactant	Surfactant concentration, % w/v		
	2.5	5.0	10.0
Tween 20	48.5	23.3	9.5
Tween 40	55.5	31.5	10.3
Tween 60	56.1	26.5	10.5
Tween 80	39.71	24.0	7.9

It is very likely that a subsequent decrease in the ratio, observed when the polysorbate concentration increases, could also be associated with decrease of polarity of the reaction medium. Such a high surfactant concentration as used in this study is followed, of course, by a larger micellar phase volume, and it would seem logical to expect that the decrease in the rate of hydrolysis is at least partly due to the less polar nature of the micellar phase. As was shown in a previous paper (Krasowska, 1974), the rate of indomethacin hydrolysis is markedly reduced by lowering the dielectric constant of the reaction mixture. Increasing solubilizing power of polysorbates connected with an increasing length of hydrophobic chain in the polysorbate molecule (Krasowska, 1976) does not reflect in the same manner the degree of protection from alkaline hydrolysis of indomethacin. This can be seen from the k_{obs} values in Table 5.

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