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KINETICS OF ALKALINE HYDROLYSIS OF INDOMETHACIN IN THE PRESENCE OF SURFACTANTS AND COSOLVENTS

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ABSTRACT

The effect of nonionic and ionic surfactants as well as water-miscible cosolvents on the alkaline hydrolysis of indomethacin was investigated. Degradation in the presence and absence of surfactants was found to follow pseudo first-order kinetics. The nonionic surfactant, polysorbate 80, produced a 7-fold increase in the stability of indomethacin. The ionic surfactants, cetrimonium bromide, benzalkonium chloride and sodium lauryl sulphate, also resulted in an increase in the stability of indomethacin but to a lesser extent than polysorbate 80. The order of surfactants in increasing the stability of indomethacin was: polysorbate 80 > sodium lauryl sulphate > benzalkonium chloride > cetrimonium bromide. Polyethylene glycol 400 was found more effective than glycerin and propylene

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glycol in stabilizing indomethacin against alkaline degradation. Of all the surfactans and cosolvents used in the study, polyethylene glycol 400 produced the greatest stabilizing effect on indomethacin.

INTRODUCTION

Surfactants and cosolvents have been widely used in pharmacy to facilitate the formulation of poorly water-soluble drugs in solution dosage forms (1-5). They have also been used to increase the stability of drug substances (6-8). However, the presence of a surfactant may not always increase the stability of a drug (9-11). Moreover, the automatic replacement of water by a non-aqueous solvent may not necessarily result in enhanced stability (12).

Indomethacin is a slightly water-soluble drug which precludes its formulation in oral and parenteral solution dosage forms. Surfactants have been considered to promote its solubility (5, 13, 14) and stability (15, 16). Cosolvents have also been used to stabilize indomethacin (17).

The present study was undertaken to further investigate the usefulness of micellar systems and some commonly used water-miscible cosolvents for the stabilization of indomethacin aqueous solutions. This was achieved by studying the kinetics of the alkaline hydrolysis of indomethacin in the presence of various surfactants, namely polysorbate 80 (a nonionic surfactant) and sodium lauryl sulphate (an anionic surfactant), and cosolvents, namely polyethylene glycol 400, propylene glycol and glycerin.

MATERIALS AND METHODS

Materials

Polysorbate 80 (Sigma Chemical Co., St. Louis, MO., USA), sodium lauryl sulphate (SLS) (BDH Chemicals Ltd, Poole, England), benzalkonium chloride (Fluka AG, Buchs, West Germany), and cetrimonium chloride (Fluka AG, Buchs, West Germany, and cetrimonium bromide (Aldrich Chemical Co., Inc., Milwaukee, Wisconsin, USA) were laboratory grade. Polyethylene glycol (PEG 400) and propylene glycol (PG) (BDH Chemicals Ltd, Poole, England) were reagent grade. Sodium hydroxide (Vickers Laboratories Ltd., West York, England) was analytical grade. Indomethacin was kindly provided by the Jordan Pharmaceutical Manufactures, Na'ur, Jordan. Double-distilled water from an all-glass still was used throughout the study.

Apparatus

Shimadzu UV 240 Specrophotometer (Shimadzu Co, Kyoto, Japan) equipped with pr-1 Graphic Printer and TB-85 Thermo bath.

Methods

Kinetic Investigations

Stock solutions of indomethacin (40 ug/ml), 0.1 M sodium hydroxide, and 6% (w/v) surfactant solutions were prepared. The alkaline hydrolysis of indomethacin was conducted by placing 2 ml of stock indomethacin, 0.1 ml of sodium hydroxide, and 0.9 ml of distilled water in a 1 cm silica cell. The hydrolysis in the presence of the surfactant was carried under the same conditions except that 0.5 ml of the water was replaced

by the surfactant solution. the hydrolysis in the presence of PEG 400, glycerin and PG was performed under the same conditions except that the 0.9 ml of water was replaced by 0.9 ml of PEG 400, glycerin or PG. Blanks were prepared in the same way except that the 2 ml of stock indomethacin was replaced by 2 ml of water. All kinetic studies, in duplicate, were conducted in a spectrophotometer

Treatment of Data

The absorbance data obtained were used to calculate the concentration of indomethacin remaining at time t by reference to a standard curve. The percentage of unhydrolyzed indomethacin was then plotted against time on semilogarthmic paper. The observed first order rate constants, K_{obs}, were then calculated from the slopes of the straight lines using regression analysis. Correlation coefficients were between 0.9860 and - 0.9984.

RESULTS AND DISCUSSION

Results

The hydrolysis of indomethacin in alkaline solutions was found to follow pseudo first-order kinetics (Fig.1). The K_{obs} obtained from the slope of the curve was 2.18×10^{-2} min^{-1} and the half life ($t_{0.5}$) was 31.8 min. The effect of the nonionic surfactant, polysorbate 80, and the ionic surfactants, cetrimonium bromide and benzalkonium chloride (cationic), and sodium lauryl sulphate (anionic) on the alkaline hydrolysis of indomethacin is depicted in Fig. 1. It is obvious that the degradation follows pseudo first-

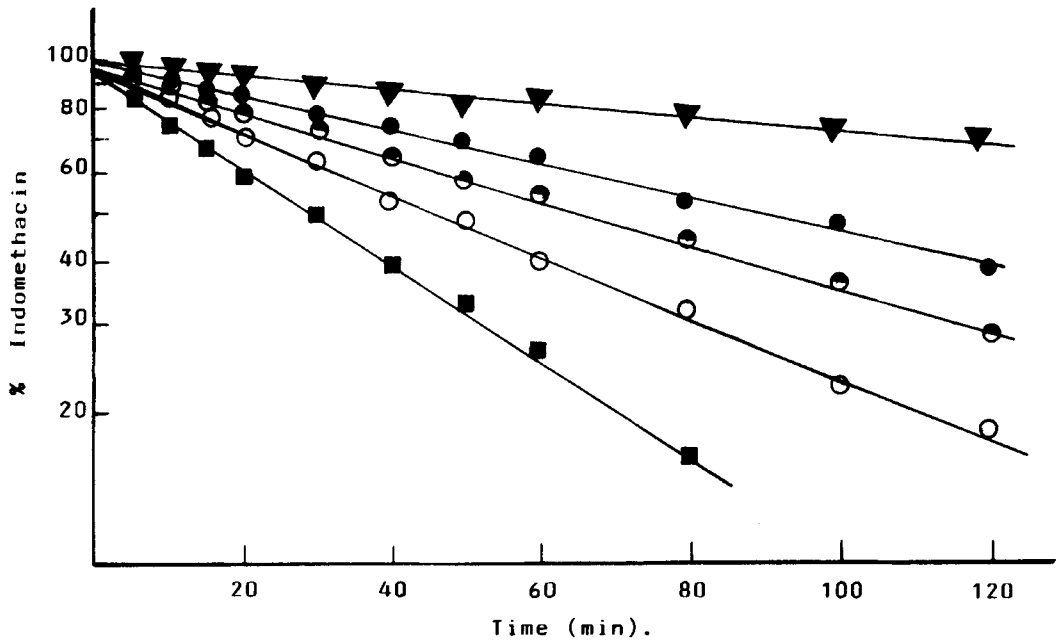

FIGURE 1

Effect of surfactants on the alkaline hydrolysis of indomethacin. ■ NaOH only; ○ 1% cetrimonium bromide; ◓ 1% benzalkonium chloride; ● 1% sodium lauryl sulphate; ▼ 1% polysorbate 80.

order kinetics. The K_{obs} obtained from the curves are shown in Table 1. A comparison of the K_{obs} values in the absence and in the presence of surfactants demonstrates that the rate of indomethacin degradation is appreciable in the following order: polysorbate 80 > sodium lauryl sulphate > benzalkonium chloride > cetrimonium bromide. Polysorbate 80 produced a 7-fold increase in the stability of indomethacin.

TABLE 1

The observed rate constants and the half-lives for the alkaline hydrolysis of indomethacin in the presence of surfactants.

Surfactant	K_{obs} (min^{-1})	$t_{0.5}$ (min)
Polysorbate 80	3.026×10^{-3}	229.0
Sodium lauryl sulfate	7.830×10^{-3}	88.5
Benzalkonium chloride	1.017×10^{-2}	68.1
Cetrimonium bromide	1.412×10^{-3}	49.1

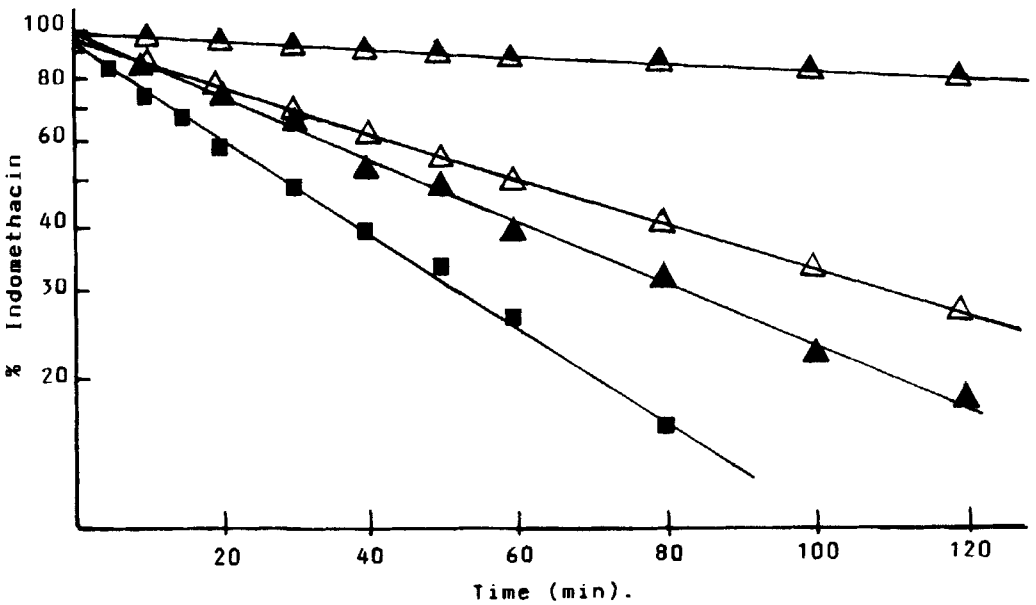

FIGURE 2

Effect of consolvents on the alkaline hydrolysis of indomethacin. ■ NaOH only; ▲ 30% glycerin; △ 30% propylene glycol; ▲ 30% PEG 400.

TABLE 2

The observed rate constants and the half-lives for the alkaline hydrolysis of indomethacin in the presence of cosolvens.

Cosolvent	K_{obs} (min^{-1})	$K_{0.5}$ (min)
Glycerin	1.438×10^{-2}	48.2
Propylene glycol	1.047×10^{-2}	66.2
PEG 400	1.695×10^{-3}	408.8

The effect of the cosolvents, PEG 400, PG, and glycerin, on the alkaline hydrolysis of indomethacin is shown in Fig. 2. The observed rate constants obtained from the curves are shown in Table 2. It is clearly demonstrated that the hydrolysis follows pseudo first-order kinetics. PEG 400 was found to be more effective than PG and glycerin in stabilizing indometahcin against alkaline degradation. The 60% PEG 400 concentration produced a several folds increase in the stability of indomethacin over the 30% concentration. Propylene glycol was found to be more effective than glycerin.

Discussion

The alkaline hydrolysis of indomethacin is shown in Fig. 1. It is evident from the figure that the hydrolysis follows a pseudo first-order kinetics. The K_{obs} value

as obtained from the figure was found to be $2.18X10^{-2}$ min^{-1}. A similar value was obtained by Hajratwala and Dawson (18). The figure also shows the hydrolysis of the drug in solutions of polysorbate 80, SLS, cetrimonium bromide and benzalkonium chloride at concentrations (1%) above the critical micelle concentration. It can be noted from the figure that the hydrolysis in these surfactant solutions followed a pseudo first-order kinetics. The stabilizing effect of the surfactants varied with the nature of the surfactant used as reflected by the K_{obs} values (Table 1). Polysorbate 80 resulted in the most profound increase in stability. This could be attributed to the entrapment of indomethacin molecules into the interior of the micelle. This reduces the accessibility of the drug molecule to the hydroxyl ions in solution and therefore reduces the rate of hydrolysis of the drug. As the micelle is nonionic and the drug molecule in negatively charged due to the ionization of the carboxylic group, the primary mechanism of interaction between the drug and the micelle is hydrophobic in nature and of the van der Waals type. Accordingly, the drug will be oriented in such a way that the carboxylic group will be toward the aqueous phase and the rest of the molecule in the micelle interior.

Sodium lauryl sulphate as indicated from the K_{obs} values prduced a lesser degree of stability of indomethacin than polysorbate 80. This could be due to the reduction of the degree of incorporation of the drug into the micelle interior owing to the electrostatic repulsion between the negatively charged micelle and the negatively charged drug molecule (19).

Benzalkonium chloride and cetrimonium bromide produced a lesser degree of stabilization of indomethacin against alkaline hydrolysis than either polysorbate 80 or SLS. This can be tentatively attributed to the strong electrostatic attraction between the drug and the cationic micelle resulting in location most of the charged drug molecules at the surface of the micelle as compared to those in the interior of the micelle (9). Therefore, the hydroxyl ions have a free access to the drug molecules. Hence the rate of hydrolysis is increased in the presence of benzalkonium chloride and centrimonium bromide as compared to polysorbate 80 or SLS. The difference in the K_{obs} values of cetrimonium bromide and benzalkonium chloride may be attributed to the surface pH, dielectric constant (19) and the degree of aggregation of the micelle, and drug-micelle interaction (20).

The effect of the cosolvents on the alkaline hydrolysis of indomethain is depicted in Fig. 2. It is obvious from the figure that the hydrolysis follows a pseudo first-order kinetics. The K_{obs} values shown in Table 2 indicate that PEG 400 produced the greattest stabilizing effect.

Propylene glycol and glycerin although increased the stability of indomethacin but their effect was less than that of PEG 400 The marked effect of PEG 400 may be attributed, in part, to its low dielectric constant ($\epsilon < 32.0$). Since indomethacin is negatively-charged under the alkaline conditions of the study, and as its degradation is catalyzed by hydroxyl ions, the rate of hydrolysis will decrease in a medium of low ϵ

as conferred by PEG 400 (21). On the other hand, the rate is enhanced in a medium of high ϵ as conferred by glycerin (ϵ = 4.25) (22). This explains the ineffectiveness of glycerin in stabilizing indomethacin against alkaline hydrolysis.

Although the dielectric constant of PG (ϵ = 32.0) is not significantly different from that of PEG 400, its effect in reducing the alkaline hydrolysis of indomethacin is intermediate between PEG 400 and glycerin. The difference in effectiveness between PG and PEG 400 may be attributed to differences in the orientation of solvent molecules around indomethacin molecules and the magnitude of increase in the dielectric constant near the drug molecules over that in the bulk of solution (21).

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