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Research Article

Micellar Solubilization of Timobesone Acetate in Aqueous and Aqueous Propylene Glycol Solutions of Nonionic Surfactants

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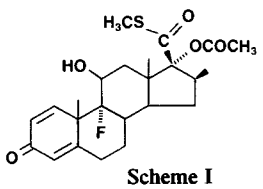
The micellar solubilization of timobesone acetate, a novel topical corticosteroid, was studied in aqueous and aqueous propylene glycol solutions of 1 to 5% nonionic surfactants at 25°C. The surfactants used were polyoxyethylene (POE) sorbitan monofatty acid esters (polysorbates), fatty acid esters (Myrj), and fatty alcohol ethers (Brij), as well as sucrose monolaurate (Crodesta SL40). The increase in the solubility of timobesone acetate in the micellar solutions was dependent on the type and concentration of surfactant. The solubilizing capacity of the surfactant micelles and the distribution coefficient of timobesone acetate in aqueous micellar solutions were found (1) to increase with increasing length of the hydrophobic fatty acid group; (2) to increase according to the structure of the hydrophilic group in the order of POE sorbitan ester, sucrose ester, POE ester, and POE ether; (3) to be unaffected by the increase in POE chain length; and (4) to tend to decrease in surfactant containing unsaturated fatty acid groups. In aqueous propylene glycol solution, the solubilizing capacity increased slightly, i.e., up to 1.5-fold in 50% propylene glycol solution, for the ester-type surfactants (polysorbates and Myrj). But this increase was not observed in the ether-type surfactant (Brij) solution. The distribution coefficient decreased logarithmically with increasing concentrations of propylene glycol in the solution. This was caused by the logarithmic increase in the timobesone acetate solubility in the bulk phase, while the solubility in the micellar phase was practically unchanged. The results support the equilibrium distribution model of micellar solubilization.

KEY WORDS: timobesone acetate; topical corticosteroid; micellar solubilization; solubility; solubilizing capacity; distribution coefficient.

INTRODUCTION

Timobesone acetate, which is chemically 17β-methylthiocarbonyl - 9α-fluoro-11β, 17α-dihydroxy - 16β - methylandrosta-1, 4-diene-3-one 17-acetate (I), is a novel topical corticosteroid useful for relieving the inflammatory manifestations of corticosteroid responsive dermatoses (1). Preliminary studies in animals indicate that this class of corticosteroids, which are the thiol ester of etianic acid derivatives, have high topical antiinflammatory activity but low systemic activity due to their rapid metabolism in the liver to the inactive etianic acid derivatives (2). The topical activity and bioavailability of timobesone acetate from cream and ointment have been demonstrated by vasoconstriction assay in comparison with several commercially available high-potency corticosteroid preparations (3).



Scheme I

To develop an oil-in-water emulsion-type cream formulation, it is essential to determine the solubility of timobesone acetate in the oil and water phases. This information can be used to optimize the delivery and to prevent the uncontrolled cyrstallization of the drug. Since nonionic surfactants are used to stabilize the emulsion system, the solubility study in the water phase must be directed to the micellar solubilization of timobesone acetate in the water phase, which may contain a cosolvent and humectant, such as propylene glycol.

Micellar solubilization of drugs in surfactant solution has been investigated extensively, and several comprehensive reviews on this subject have been published (4–8). The solubilization of steroids by surfactant micelles has been reported by several investigators (9–12). However, all these studies were conducted in aqueous solution to elucidate the mechanism and extent of solubilization. No study of micellar solubilization of corticosteroid has ever been conducted in aqueous cosolvent solution. The purpose of this study was to investigate the solubilization of timobesone acetate in various nonionic surfactant solutions and, more importantly, to elucidate the effect of a cosolvent propylene glycol on the solubilization phenomena.

MATERIALS AND METHODS

Materials. All materials were obtained commercially

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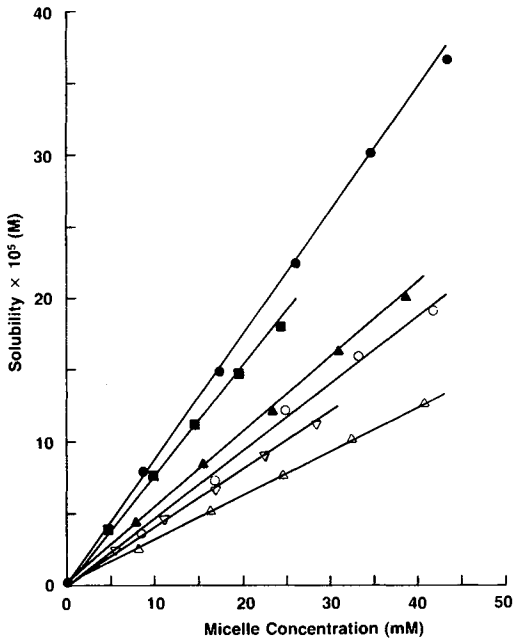

Fig. 1. Solubility of timobesone acetate in aqueous micellar solution of POE 20 sorbitan monolaurate (△) and monostearate (▲), POE 40 stearate (■), POE 23 lauryl ether (○), POE 20 stearyl ether (●), and sucrose monolaurate (▽) at 25°C.

and used as received: polyoxyethylene (POE) 20 sorbitan monolaurate (polysorbate 20) and monooleate (polysorbate 80) from Mazer Chemicals, Inc.; POE 20 sorbitan monopalmitate (polysorbate 40) and monostearate (polysorbate 60), POE 40 stearate (Myrj 52) and 100 stearate (Myrj 59), POE 23 lauryl ether (Brij 35), and POE 20 cetyl ether (Brij 58), stearyl ether (Brij 78), and oleyl ether (Brij 98) from ICI Americas, Inc.; sucrose monolaurate (Crodesta SL40) from Croda, Inc.; and propylene glycol, USP, from VWR. Timobesone acetate was obtained from the Institute of Organic Chemistry, Syntex Research. The chemicals and reagents used in the high-performance liquid chromatographic (HPLC) assay were reagent grade.

Solubility Studies. An excess of timobesone acetate was added to 3 ml of the surfactant–water or surfactant–propylene glycol–water solution being investigated. After 1 min of sonication, the suspension was equilibrated for 4 days with rotary mixing in a 25°C water bath. Preliminary studies indicated that equilibrium solubility was achieved within this period of mixing. The suspensions were filtered through a Gelman GA-6 filter (pore size, 0.45 μm), and the timobesone acetate concentration was determined by HPLC. Each study was conducted in duplicate or triplicate.

Analytical Method. The assay of timobesone acetate was carried out using an HPLC system consisting of a Micromeritics Model 728 autoinjector, Altex Model 110A pump, Kratos Spectroflow 757 spectrophotometric detector, and Spectra Physics SP 4270 computing integrator. The following reverse-phase HPLC conditions were used: column, Whatman Partisil ODS 3 (25 × 0.46 cm, 10 μm); mobile phase, acetonitrile/water (60/40, v/v); flow rate, 1 ml/min; detection, 254 nm; and retention time, 6 min.

RESULTS AND DISCUSSION

The solubilities of timobesone acetate in aqueous nonionic surfactant solutions as a function of micelle concentration are representatively depicted in Fig. 1. In all of the surfactant solutions, the solubility of timobesone acetate increased linearly with increasing micelle concentration, which is the surfactant concentration subtracted by the critical micelle concentration (CMC). The values of the CMC were taken from the literature and range from 0.004 m*M* for POE 20 cetyl ether (Brij 58) (13) to 0.34 m*M* for sucrose monolaurate (14). These values were relatively small compared to the surfactant concentrations used in this study (5–40 m*M*). The increase in solubility was dependent on the type and concentration of the surfactants. POE 20 stearyl ether (Brij 78) afforded the highest increase in solubility, while POE 20 sorbitan monolaurate (polysorbate 20) afforded the lowest.

It is generally accepted (15,16) that solubilization of a non-micelle-forming compound can be treated in terms of an association equilibrium between the solutes and the micelles in a micellar solution. Thus,

$$D_w + M \overset{K_m}{\rightleftarrows} D_m$$

Table I. Solubilizing Capacity of Surfactant Micelles and Distribution Coefficient of Timobesone Acetate in Aqueous Micellar Solutions

Surfactant	Solubilizing capacity (mmol/mol)	Distribution coefficient (mM^{-1})
POE 20 sorbitan monolaurate (polysorbate 20)	3.1 (0.1)[a]	5.19
POE 20 sorbitan monopalmitate (polysorbate 40)	4.7 (0.3)	7.88
POE 20 sorbitan monostearate (polysorbate 60)	5.2 (0.2)	8.58
POE 20 sorbitan monooleate (polysorbate 80)	5.1 (0.4)	8.43
POE 23 lauryl ether (Brij 35)	4.7 (0.4)	7.82
POE 20 cetyl ether (Brij 58)	7.7 (1.3)	12.8
POE 20 stearyl ether (Brij 78)	8.4 (0.3)	14.1
POE 20 oleyl ether (Brij 98)	7.5 (0.6)	12.6
POE 40 stearate (Myrj 52)	7.3 (0.3)	12.2
POE 100 stearate (Myrj 59)	6.9 (0.7)	11.6
Sucrose monolaurate (Crodesta SL40)	3.9 (0.1)	6.5

[a] ±95% confidence limit.

where D_m and D_w are, respectively, the drug solubilized in the micellar and bulk water phases; M is the micelles; and K_m is the distribution coefficient of drug between the micellar and the bulk phases.

Accordingly, the following relationships are derived:

$$K_m = \frac{S_m}{S_w M} \quad (1)$$

$$S_t = S_m + S_w = K_m S_w M + S_w \quad (2)$$

where S_m and S_w are, respectively, the solubilities of the drug in the micellar and bulk phases; M is the concentration of micelles; and S_t is the total solubility of the drug in the micellar solution.

Therefore, a plot of S_t vs M [Eq. (2)] will give a straight line with an intercept of S_w and a slope of $K_m S_w$, which is the solubilizing capacity of the micelles. The slopes were determined by linear regression, and their 95% confidence limits were calculated. The distribution coefficient K_m can then be calculated from the slope and S_w.

Table I lists the solubilizing capacity of the surfactant micelles and the distribution coefficient of timobesone acetate between the micellar and the bulk phases of aqueous micellar solutions. For the polysorbate and Brij series, the solubilizing capacity and, thus, the distribution coefficient increased with increasing length of the fatty acid from laurate to stearate. Because of its hydrophobic property, timobesone acetate was expected to be solubilized in the hydrophobic core of the micelles. The more hydrophobic core of stearate micelles would favor greater interaction with timobesone acetate leading to a higher solubilizing capacity.

Comparing surfactants with the same fatty acid chain length, it was apparent that the structure of the hydrophilic group affected the extent of solubilization. Thus, for surfactants containing laurate, the solubilizing capacity increased in the order of POE 20 sorbitan, sucrose, and POE 23 ether. Similarly, for surfactants with palmitate or stearate, the ether-type surfactants (Brij) have a higher solubilizing capacity than the sorbitan (polysorbate) or ester-type (Myrj) surfactants. Factors that could account for these phenomena are the hydrophilicity of the hydrophilic group and the geometric consideration of the packing of the monomer into the micelles. The relatively linear structure of the ether-type surfactants appears to favor the formation of a more hydrophobic environment and larger micelles with a higher solubilizing capacity.

The length of the POE chain did not affect the solubilizing capacity of the micelles, as shown by POE 40 stearate and POE 100 stearate. Statistical analysis of the two slope values indicated that they were not significant at the 95% confidence level. This confirms that solubilization occurred in the hydrophobic core but not in the hydrophilic mantle layer of the micelle.

Surfactants containing an unsaturated fatty acid group showed a lower solubilizing capacity than the corresponding saturated fatty acid, e.g., POE 20 oleyl ether vs POE 20 stearyl ether. The difference was statistically significant. The same phenomenon was observed in the solubilization of dimethylaminobenzene in micellar solution of potassium oleate as compared to potassium stearate (17). This is due to the *cis* configuration of oleic acid, which affords less effective hydrophobic interaction than the linear stearic acid group in the formation of micelles. Interestingly enough, this effect was not observed in the sorbitan ester surfactants (polysorbate 80 vs polysorbate 60). Apparently, the bulky sorbitan group could have accommodated the *cis* configuration of oleic acid without causing any effect in the micellar structure.

Figure 2 shows the effect of propylene glycol on the solubilization of timobesone acetate in aqueous propylene glycol micellar solutions. Alcohols and glycols are known to weaken the formation of micelles by increasing the solvent power of the solution and, thus, decreasing the hydrophobic interaction within the micelle. This effect will increase the CMC of the surfactant. It has been reported (18) that the CMC of POE alkyl phenols in 50% ethylene glycol solution increased by eightfold compared to that in water. Similarly, the CMC of POE lauryl ethers were 1.4-fold higher in 12% *n*-propanol solution than in water (19). Although the CMCs of the surfactants were expected to increase in the presence of propylene glycol, the increase was relatively small compared to the concentrations of surfactants used in this study. More importantly, the increase in the CMCs had a negligible effect on the slope of the plots in Fig. 2, from which the

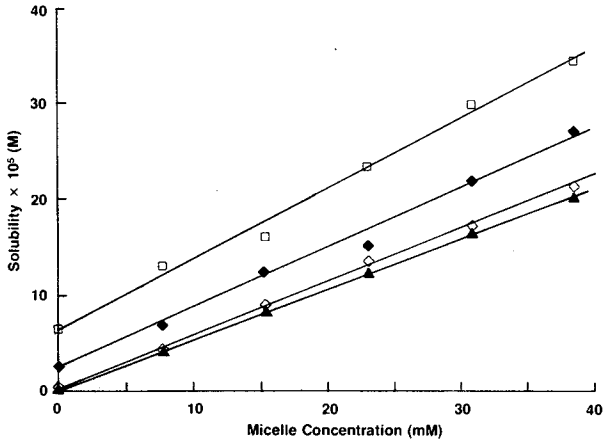

Fig. 2. Solubility of timobesone acetate in aqueous micellar POE 20 sorbitan monostearate solution containing 0% (▲), 20% (◇), 40% (◆), and 50% (□) propylene glycol.

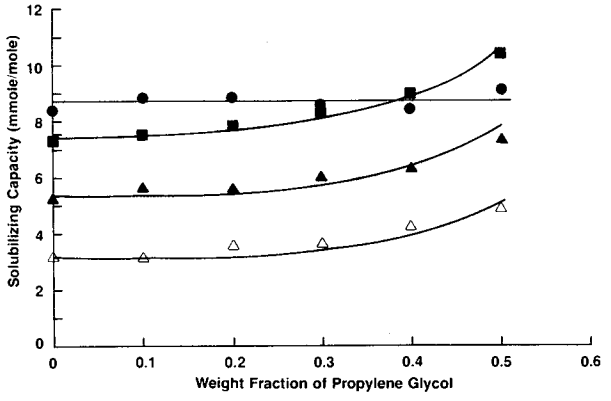

Fig. 3. Solubilizing capacity of POE 20 sorbitan monolaurate (△) and monostearate (▲), POE 40 stearate (■), and POE 20 stearyl ether (●) micelles in solution with increasing weight fractions of propylene glycol.

Table II. Solubility of Timobesone Acetate in Aqueous Propylene Glycol Solutions Containing Various Weight Fractions of Propylene Glycol at 25°C

f^a	Solubility × 10^5 (M)
0.0	0.06
0.2	0.34
0.4	2.60
0.6	20.9
0.8	129.0
1.0	497.2

[a] Weight fraction of propylene glycol.

solubilizing capacity and distribution coefficient were obtained.

Figure 3 shows the solubilizing capacity of four representative surfactant micelles in solutions containing increasing fractions of propylene glycol. For the ester-type surfactants (polysorbate and Myrj), the solubilizing capacity began to show a gradual increase in 20% propylene glycol solution and continued to increase up to 1.5-fold in 50% propylene glycol solution. However, the ether-type surfactant (Brij) showed practically no change in its solubilizing capacity in solutions containing up to 50% propylene glycol.

For the micellar system of aqueous propylene glycol solution, Eq. (1) can be rewritten as

$$\log K_m = \log \frac{S_m}{M} - \log S_f \qquad (3)$$

where S_f is the solubility of drug in the bulk aqueous solution containing f fraction of propylene glycol.

Table II lists the solubility of timobesone acetate in aqueous propylene glycol solutions containing various fractions of propylene glycol (20). According to Yalkowski and Rubino (21), S_f is related to the fraction of propylene glycol as

$$\log S_f = \log S_w + f(\log S_c - \log S_w) \qquad (4)$$

where S_c is the solubility of drug in pure propylene glycol. A plot of log S_f vs f should be linear with a slope of [log S_c − log S_w]. This is shown in Fig. 4 (right ordinate) for timobesone acetate in aqueous propylene glycol solution. This regression line was drawn by using the data in Table II. The slope of this line is 4.03 (Table III), which is very close to the value of 3.92 calculated from [log S_c − log S_w]. This confirms that Eq. (4) is a valid relationship. Inserting Eq. (4) into Eq. (3) gives

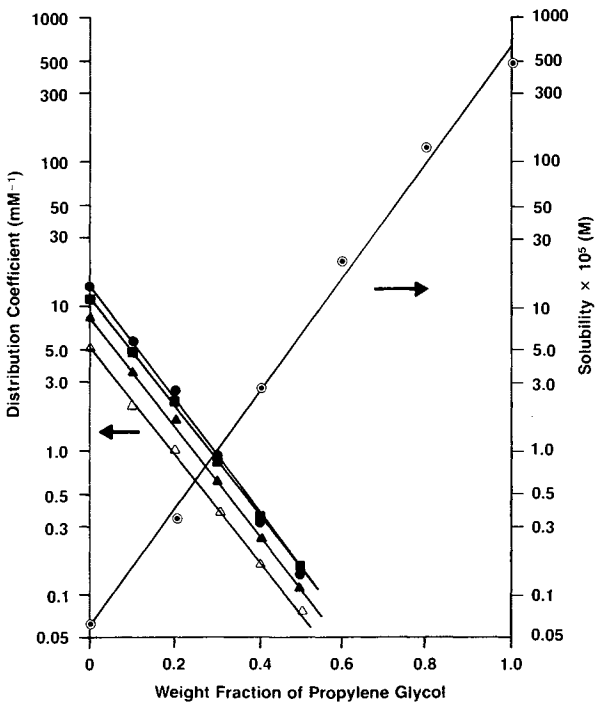

Fig. 4. Solubility (⊙) and distribution coefficient of timobesone acetate in, respectively, nonmicellar and micellar solutions of POE 20 sorbitan monolaurate (△) and monostearate (▲), POE 40 stearate (■), and POE 20 stearyl ether (●) with increasing weight fractions of propylene glycol.

$$\log K_m = \log \frac{S_m}{S_w M} - f(\log S_c - \log S_w) \qquad (5)$$

Therefore, in order to conform with the equilibrium distribution model, a plot of log K_m vs f should give the same slope of [log S_c − log S_w] as that of log S_f vs f, but with a negative sign. Figure 4 (left ordinate) shows the plots of log K_m (distribution coefficient) vs f for timobesone acetate in the four representative micellar solutions, and their slopes are given in Table III. For Brij 78, the slope (−4.07) is essentially the same as the slope of the nonmicellar solubility line (+4.03) but with an opposite sign. This suggests that the decrease in the distribution coefficient with increasing fractions of propylene glycol was entirely due to the increase in timobesone acetate solubility in the bulk aqueous propylene glycol solution, while the solubility in the micellar phase did not change (Fig. 3). For polysorbate 20, polysorbate 60, and Myrj 52, up to an 8% decrease in the absolute value of the slopes was observed as a result of the slight increase in the

Table III. Slopes of Regression Lines of the Solubility and Distribution Coefficient of Timobesone Acetate in, Respectively, Nonmicellar and Micellar Solutions with Increasing Weight Fractions of Propylene Glycol

A. Nonmicellar solution	Slope, log S_f vs f
No surfactant	+4.03
B. Micellar solution	Slope, log K_m vs f
POE 20 sorbitan monolaurate (polysorbate 20)	−3.70
POE 20 sorbitan monostearate (polysorbate 60)	−3.83
POE 40 stearate (Myrj 52)	−3.80
POE 20 stearyl ether (Brij 78)	−4.07

solubilizing capacity of the micelles with increasing fractions of propylene glycol. These results confirm the validity of the relationship given by Eqs. (1) and (3) and, thus, support the equilibrium distribution model of micellar solubilization.

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