

Effects of Added Lower Alcohols on Solubilized Tocopherol Acetate Sorption to Polyethylene Film in Aqueous Solution¹⁾

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The effects of added lower alcohols on the sorption of tocopherol acetate (VEA) to polyethylene film were studied in an aqueous solution with polyoxyethylene cetyl ether used as a solubilizer. The sorption rate of solubilized VEA increased in inverse proportion to the dielectric constant of added lower alcohols. The increasing concentrations of lower alcohols resulted in turbidity of the VEA-surfactant system, *i.e.*, a reduction of the VEA solubilizing ability of the surfactant, followed by transparentization. An increase in ethanol concentration enhanced the sorption rate of solubilized VEA followed by a rate decrease. It also caused greater solubility of VEA in the absence of the surfactant, increasing the polarity of the surfactant micellar interior and causing disintegration of the micelles. Lower alcohols lessen the polarity of the solution in inverse proportion to the dielectric constant of the alcohols. Consequently, the alcohols may be responsible for weakening the hydrophobic binding between hydrophobic VEA and the hydrocarbon chain in the surfactant due to an increased affinity of VEA and the surfactant molecules for the bulk phase. We thus conclude that the sorption of solubilized VEA to polyethylene film is accelerated by thermodynamic labilization of VEA, but an increase in the VEA solubility in an aqueous-alcohol phase contributes to a decrease in the sorption rate.

Key words sorption rate constant; tocopherol acetate; polyethylene film; lower alcohol; polyoxyethylene cetyl ether; solubilization

Drug content in pharmaceuticals decreases through the process of sorption to plastics used for containers. It has been reported that nitroglycerin²⁾ and isosorbide dinitrate³⁾ are lost by sorption to intravenous infusion sets made from plastic. Soft contact lens composed of cross-linked polyhydroxyethyl methacrylate incorporates quaternary ammonium salts.⁴⁾ Drug sorption to plastics is affected by the structures of the plastics,^{3,5)} crystallinity⁶⁾ and surface hydrolysis.⁷⁾ Electron beam irradiation⁸⁾ and surfactant addition⁹⁾ have been conducted to reduce the sorption. Sorption behavior is regarded as partition phenomena of drugs between the plastic and bulk phase. Therefore, the suppression of sorption by additional surfactants may result from an increase in the distribution of drugs in the bulk phase by complex formation with additives. We reported that the sorption rate of tocopherol acetate (VEA, solubilized by polyoxyethylene alkyl ethers in an aqueous solution) to polyethylene varied with the solubilizing ability of the surfactants according to hydrophobic and hydrophilic group structures.¹⁾ The solubilizing capacity of non-ionic surfactants for hydrophobic agents changed according to temperature,¹⁰⁾ and the addition of electrolytes¹¹⁾ and lower alcohols.¹²⁾ These factors are presumed to affect the uptake of hydrophobic substances in aqueous surfactant solution into the plastics. Lower alcohols are often used for aqueous based pharmaceuticals as both solvent and solubilizer, along with non-ionic surfactants.

The present study is concerned with the sorption of hydrophobic drugs solubilized by non-ionic surfactants in aqueous solution. To clarify the effects of lower alcohols on sorption, an aqueous VEA solution with polyoxyethylene cetyl ether (PCE) and polyethylene film were used.

Experimental

Materials VEA (Eisai Co.) and PCE (Nikko Chemicals Co.) having 20 units of oxyethylene were of JP XII and The Japanese Cosmetic Ingredients, Second Edition grade, respectively. Pyrene (Wako Pure Chemical Industries), methanol, ethanol and isopropanol (Kokusan Chemical Works, Ltd.) were of analytical reagent grade. Propylene glycol and glycerin (Asahi Denka Kogyo Co.) were of JP XII grade. The VEA, PCE, lower alcohols and pyrene were used without further purification. Polyethylene was low density polyethylene film (UZ20100J, Mitsui Petrochemical Industries, Ltd.), containing trace amounts of erucic amide as a lubricant and silicon dioxide as a filler, with a thickness of 50 μm and a density of 0.920 g/cm³. All other reagents and solvents were of analytical reagent grade.

Preparation of Solubilized VEA Solution VEA was added to liquefied PCE on a water bath at about 80°C and mixed. The mixture was solubilized in distilled water, followed by the addition of lower alcohols. The concentrations of VEA and PCE were adjusted to 0.1 mg/ml and 1.0 mg/ml, respectively. After the solubilized VEA solution was maintained at 25°C for 24 h, transmittance of the solution was measured spectrophotometrically at 610 nm and a solution layer thickness of 10 mm using a spectrophotometer (model UV-2100, Shimadzu Co.).

Sorption Measurement of VEA to Polyethylene The solubilized VEA solution with lower alcohols (70 ml) was poured into a glass bottle, followed by immersing polyethylene film with 2.1 g (*ca.* 287 cm²) into the solution. After sealing, the glass bottle was stored at 60°C. VEA concentration in the stored solution was determined once a week by HPLC (model LC100, Yokogawa Electric Co.) under the following conditions: reversed-phase column (Inertsil ODS-2 4.6 \times 150 mm, GL Sciences, Inc.); detection (UV at 284 nm); mobile phase (methanol: water = 49:1, v/v); flow rate of 1.0 ml/min; temperature at 50°C.

Solubility Measurement of VEA in Aqueous Ethanol Solution Excess VEA was added to an aqueous ethanol solution (0–90% (v/v)), followed by shaking in a sealed test tube. After being maintained at 25°C for 7 d, the solution was centrifuged (10000 $\times g$, model SCR18B, Hitachi Koki Co.) at 25°C. VEA concentration in the aqueous-ethanol phase was determined by HPLC.

Ultrafiltration An ultrafiltration unit, (Ultrafree CL-LCC, Nihon Millipore Co.) with a nominal cutoff molecular size of 5000, and centrifugal filtration technique were used. Pyrene dissolved in ethanol (1.0 $\times 10^{-2}$ M) was diluted stepwise with water, followed by adding the pyrene solution to the solubilized VEA solution with ethanol. After being

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poured into the unit (2 ml), the solubilized VEA solution with ethanol (0–70% (v/v)) and pyrene (0 or 1.0×10^{-6} M) was ultrafiltered at 25 °C. The first ultrafiltrate and remainder were rejected, owing to adsorption of the solutes on the ultrafiltration unit. VEA, PCE and pyrene concentrations in the second ultrafiltrate were determined by HPLC under the above (VEA) and following (PCE and pyrene) conditions. PCE: column (Asahipak GS-510 7.6 \times 500 mm, Asahi Chemical Industry Co.); detection of refractive index (model SE-51, Showa Denko Co.); mobile phase (methanol: water = 99: 1, v/v); flow rate, 1.0 ml/min at room temperature. Pyrene: reversed-phase column used for VEA determination; fluorescence detection (model RF-530, Shimadzu Co.); emission and excitation wavelengths of 380 and 338 nm, respectively; mobile phase (methanol: water = 4: 1, v/v); flow rate of 1.0 ml/min; temperature at 50 °C.

Evaluation of Pyrene Fluorescence Intensity Fluorescence spectra of pyrene were taken with a fluorescence spectrophotometer (model RF-540, Shimadzu Co.) at 25 °C and at an excitation wavelength of 338 nm. The aqueous pyrene solutions (1.0×10^{-6} M) with ethanol (ca. 0–60% (v/v)), PCE (0 or 1 mg/ml) and VEA (0 or 0.1 mg/ml) prepared in a similar manner with ultrafiltration were stirred to stabilize the solution for fluorescence measurement at 25 °C for 24 h. The fluorescence measurement was repeated three times. The ratio of pyrene fluorescence intensity at the first peak (ca. 374 nm) compared to third peak (ca. 385 nm) was defined as I_1/I_3 .

Results and Discussion

Sorption of Solubilized VEA to Polyethylene Figure 1 shows typical changes in VEA in the solubilized solution with PCE. Little change in VEA concentration was observed in the absence of polyethylene. The presence of polyethylene caused a decrease in VEA which was accelerated by ethanol. Similar results were obtained for other lower alcohol systems. The VEA amount obtained by the extraction of polyethylene film agreed approximately with the loss from the stored solution.¹⁾ The sorbed quantity of VEA to polyethylene film was thus taken as the quantity of VEA which had disappeared in the solubilized solution.

The above may indicate the partition of VEA between the polyethylene and PCE micellar phase due to the insoluble character of VEA in water. A relatively long time may be required for equilibrium of the VEA partition. In this study, the sorption rate of VEA to polyethylene film was determined by the approximation of VEA in the solubilized system as

$$A = A_0 \cdot \exp(-k \cdot t) \quad (1)$$

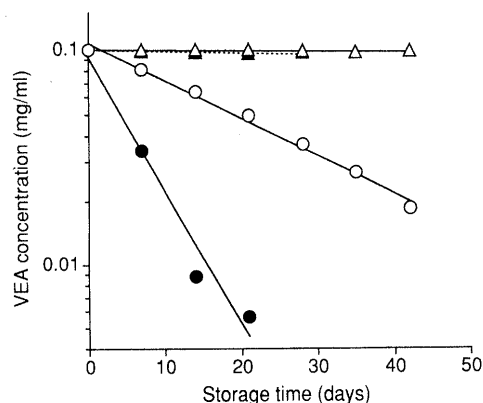


Fig. 1. Changes in VEA Concentration in Solubilized Solution with PCE in the Presence (○, ●) or Absence (△, ▲) of Polyethylene Film at 60 °C

○ and △, without ethanol; ● and ▲, with ethanol of 5% (v/v).

where A and A_0 are VEA concentrations in the aqueous phase after and before storage, respectively, k is the apparent constant of the VEA sorption rate (d^{-1}) and t is the storage time (d). The approximation was carried out using VEA data of linear ranges.

Effects of Various Lower Alcohols on the Sorption Rate of VEA Table 1 shows k to polyethylene in the presence of various lower alcohols of 5% (v/v). The increase in k in the PCE-VEA system was caused by the addition of every alcohol in the low concentration ranges used for aqueous based pharmaceuticals.^{13,14)} It also increased according to the carbon numbers of univalent alcohols and decreased with the numbers of the hydroxyl group of the alcohols having a glycerol skeleton. Figure 2 shows the relationship between k and the dielectric constant of the lower alcohols or water in the literature.¹⁵⁾ An increase in k was inversely proportional to the dielectric constant of added lower alcohols.

The addition of lower alcohols increased the critical micelle concentration (CMC) of non-ionic surfactants.¹²⁾ Polarity of the aqueous-alcohol phase is related to the dielectric constant of the added alcohols, since this constant represents the polarity of a substance. The increase in CMC may possibly be due to a weakening of the hydrophobic binding between surfactant molecules. VEA molecules may be incorporated into the PCE micellar interior by hydrophobic interaction.¹⁾ Consequently, a variation in the sorption rate of VEA may be attributed to changes in the characteristics of PCE-VEA micelles due to the

Table 1. The Apparent Partition Coefficient of VEA in Solubilized System to Polyethylene in the Presence of Various Lower Alcohols of 5% (v/v) at 60 °C

Alcohols	k (d^{-1})
Control ^{a)}	0.0385
Methanol	0.111
Ethanol	0.157
Isopropanol	0.210
Propylene glycol	0.0958
Glycerin	0.0563

a) Free from alcohol.

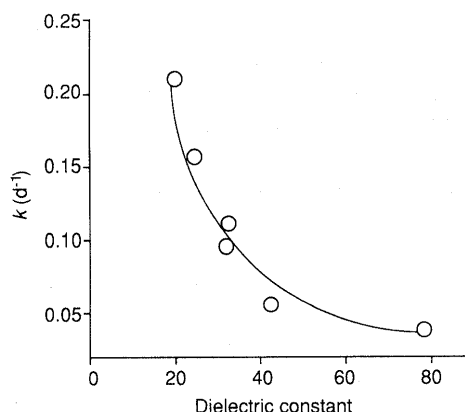


Fig. 2. Relationship between k of VEA in the Solubilized System to Polyethylene at 60 °C and the Dielectric Constant of Added Lower Alcohols and Water

Dielectric constant at 25 °C except for propylene glycol at 20 °C.¹⁵⁾ Regression line: $Y = 9.10X^{-1.29}$, $r = 0.973$ (Y = apparent sorption rate constant, X = dielectric constant).

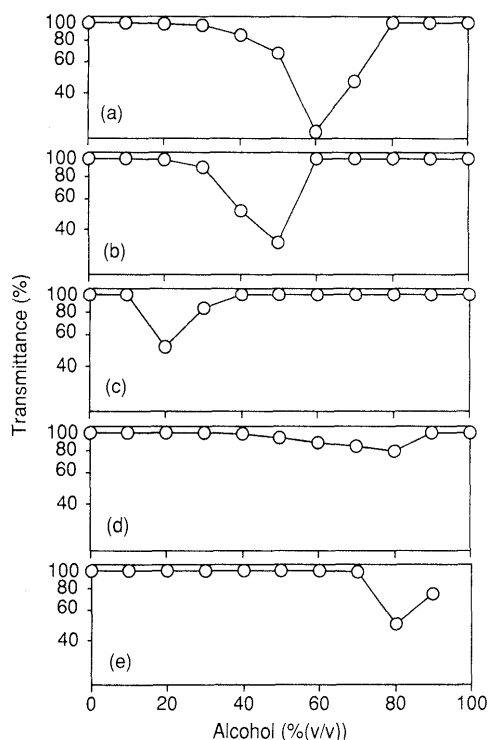


Fig. 3. Changes in Turbidity of PCE-VEA System due to Lower Alcohol Addition at 25 °C

(a) methanol, (b) ethanol, (c) isopropanol, (d) propylene glycol and (e) glycerin.

alcohols.

Change in VEA Solubilizing Ability of PCE by Various Lower Alcohols Defined as the maximal quantity of transparently solubilized VEA per one gram of PCE, the change in VEA solubilizing capacity of PCE (0.56 g of VEA per 1.0 g of PCE) was not found to be affected by lower alcohols of 5% (v/v). However, increasing the concentrations of the lower alcohols resulted in turbidity of the PCE-VEA system, followed by transparentization, as shown in Fig. 3. In the case of ethanol, turbidity of the system increased with added proportions of the alcohol, followed by minimum solubilization of VEA at 50% (v/v). The PCE-VEA system was observed to revert again to transparentization above 50% (v/v) ethanol. Increases in the carbon number and hydroxyl groups of the alcohols may have caused the system to have become turbid at low and high concentrations, respectively. Figure 4 shows the effects of ethanol concentration on VEA solubility in the absence of PCE, along with a variation in the transmittance of the PCE-VEA system. VEA solubility in the aqueous ethanol solution was small below 40% (v/v) ethanol, while above this concentration, it rapidly increased.

The turbidity in the solubilized system, *i.e.*, transformation from a solubilization to an emulsification, is evidence of a decrease in the solubilizing ability of PCE. The decrease in the dielectric constant of the added alcohols and the increase in concentration contribute to a decrease in the polarity of the bulk phase. A decrease in the polarity of the bulk phase is thus responsible for a decrease in the solubilizing ability of PCE. The micellization of a surfactant is depressed by the addition of ethanol due to increasing the affinity of the surfactant for the bulk phase,

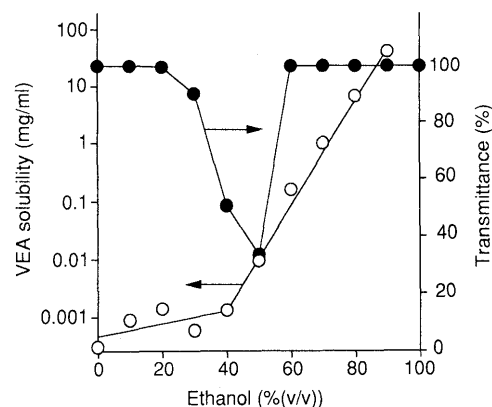


Fig. 4. Effects of Ethanol on VEA Solubility (○) in the Absence of PCE and on Turbidity of the PCE-VEA System (●) at 25 °C

Transmittance is the same as in Fig. 3b.

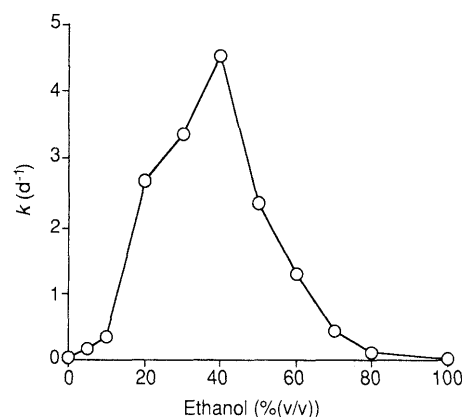


Fig. 5. Change in k of VEA in Solubilized System to Polyethylene in the Presence of Ethanol at 60 °C

and a greater concentration inhibits micelle formation.¹⁶⁾ Such alcohol effects may be the reason for a lowering of the VEA solubilization, *i.e.*, for the turbidity of the PCE-VEA system. Transparentization of the PCE-VEA system continued after turbidity, possibly due to the rapid increase in VEA solubility in the aqueous-alcohol phase.

Effects of Ethanol on the Sorption Rate of VEA Figure 5 shows changes in k in the presence of ethanol. In contrast to the lowered transmittance of the PCE-VEA system, k increased with ethanol when the ethanol level was 0–40% (v/v). The increase in ethanol may contribute to the thermodynamic labilization of VEA because of the emulsification, resulting in greater k . The increase in ethanol would cause a greater affinity of VEA for the aqueous-ethanol phase as well, thus leading to lower k at high concentrations of ethanol. The above combined effects probably result in maximum k with an increase in ethanol.

A rise in temperature contributes to an increase in the micellar mass, aggregation number and solubilizing ability of non-ionic surfactants in water,¹⁰⁾ possibly due to a decrease in the affinity of the surfactant molecules for the bulk phase, owing to a reduction in hydrogen bonding between hydrophilic oxyethylene chains and water. The ethanol concentration at maximal k (40% (v/v) at 60 °C) was different from that at the maximal turbidity of the PCE-VEA system (50% (v/v) at 25 °C). The effects of

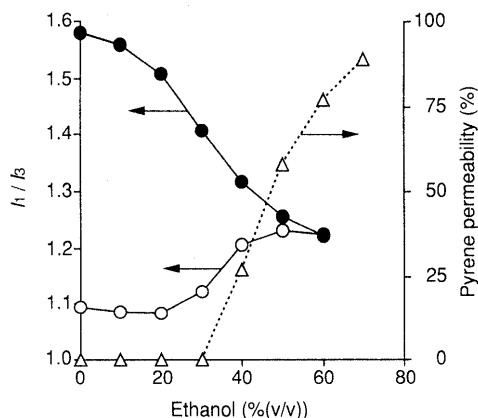


Fig. 6. Effects of Ethanol on I_1/I_3 (○, ●) and Permeability of Pyrene (△) Passing through an Ultrafiltration Membrane at 25 °C

○ and △, with PCE and VEA; ●, without PCE and VEA. Each point of I_1/I_3 represents the mean of three measurements.

temperature on the characteristics of the PCE-VEA micelles in the presence of ethanol are unknown, whereas it is almost certain that differences in temperature cause a difference of ethanol concentration between inflection points of k and turbidity of the system.

Effects of Ethanol on PCE Micellar Structure Fluorescence probing is useful for examining surfactant micellar properties, since fluorescence intensity of the vibronic bands depends on solvent polarity.¹⁷⁾ I_1/I_3 , obtained from the pyrene fluorescence spectra, increases with the increasing polarity of a pyrene environment in micelles,¹⁸⁾ and pyrene molecules are situated in the interface between the oxyethylene mantle and hydrophobic core, *i.e.*, in the palisade layer, in polyoxyethylene nonylphenyl ether micelles.¹⁹⁾

Figure 6 shows the effects of increasing the concentration of ethanol on I_1/I_3 and the permeability of pyrene molecules passing through the ultrafiltration membrane. I_1/I_3 in the PCE-VEA system was smaller than that in the aqueous ethanol solution, but the same at 60% (v/v) of ethanol. Although I_1/I_3 decreased with ethanol in the absence of PCE and VEA, its value in the presence of PCE and VEA increased with ethanol at 30% (v/v) or above. The ultrafiltration membrane completely prevented the permeation of pyrene molecules at 30% (v/v) ethanol or below. A steep increase in permeability was observed above this concentration.

Pyrene permeation through the membrane describes dissolution of the fluorescent from the micellar interior to the aqueous-ethanol phase. The site of pyrene in the PCE-VEA system is considered to be as follows: the pyrene molecules exist in the PCE micelles at 30% (v/v) ethanol or below, and they are partly distributed in the aqueous-ethanol phase above this concentration. The I_1/I_3 difference below 60% (v/v) of ethanol was thus due to the difference in polarity between the aqueous-ethanol phase and the hydrocarbon-like micellar interior. An increase in the distribution of pyrene into the aqueous-ethanol phase may cause I_1/I_3 to increase above 30% (v/v) ethanol in the presence of PCE and VEA. An increase in I_1/I_3 around 30% (v/v) ethanol in the VEA solubilizing system suggests an increase in micellar inner polarity near

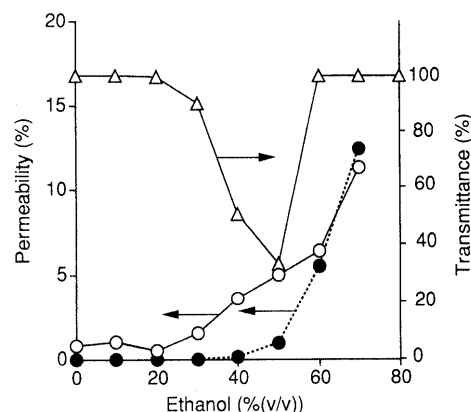


Fig. 7. Changes in Permeability of PCE (○) and VEA (●) in a Solubilized System Passing through an Ultrafiltration Membrane, and the Turbidity of the PCE-VEA System (△) as a Function of Ethanol at 25 °C

Transmittance is the same as in Fig. 3b.

the site of pyrene because all pyrene molecules exist in the micelles. The increase in micellar inner polarity may be due to the penetration of water into the micelles by weakening hydrophobic binding between PCE molecules. This variation may be also caused by a 5% addition of the alcohols in proportion to the dielectric constant, since a decrease in the dielectric constant of the alcohols is responsible for increasing k . Few studies have reported on the effect of added alcohols to the solubilizing systems by non-ionic surfactants. It is evident that increasing the polarity in the micellar interior results in thermodynamic labilization of hydrophobic VEA situated in the micellar hydrocarbon core.

Figure 7 shows the effects of increasing concentrations of ethanol on the permeability of VEA and PCE in the solubilized system passing through the ultrafiltration membrane, along with variations in the transmittance of the PCE-VEA system. Slight elution of PCE was observed at low concentrations of ethanol, followed by an increase in membrane permeability with increasing ethanol. The permeation of VEA through the membrane was less than the identification limits in the range of 0–30% (v/v) ethanol, followed by an increase.

An ultrafiltration technique makes it possible to separate macromolecules from solution, and solutes with low molecular weights show free passage. The molecular weights of VEA (472.75) and PCE monomers (nominal weight of 1122) are sufficiently less than the cutoff size of the membrane (5000), whereas the apparent mass of PCE-VEA micelles and its emulsion droplets may be much larger than the cutoff size. Enhanced PCE and VEA permeation thus suggests the disintegration of micelles or emulsion droplets. However, the free passage of PCE or VEA was not observed until the tolerant limit of the ultrafiltration membrane for ethanol. This discrepancy indicates that VEA molecules form some aggregates with PCE to possibly differ from the micelles and emulsion droplets, in spite of the transparentization of the PCE-VEA solution.

Conclusion

The addition of lower alcohols to VEA solubilized solution with PCE results in lowering the polarity of the aqueous-alcohol phase. Lowering the polarity of the bulk phase causes a weakening of the hydrophobic binding between hydrophobic VEA and hydrocarbon chains in PCE due to the greater affinity of the surfactant and VEA molecules. Consequently, the sorption of VEA to hydrophobic polyethylene may be accelerated by the alcohols at relatively low concentrations. High concentrations of the lower alcohols increase in the VEA distribution in the aqueous-alcohol phase. The incorporation of VEA into polyethylene film may thus be concluded to be depressed by the greater affinity of the VEA molecules for the aqueous alcohol phase. These findings are useful for the design of aqueous-based pharmaceuticals with solubilized hydrophobic drugs packed into plastic containers.

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