Polyoxyethylene Tocopheryl Ethers;
A Series of Novel Surfactants from Tocopherol for FunctionalCosmetics.

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토코페롤에서 유도된 기능성 화장품용의 새로운 계면 활성제

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Abstract

A new and unique class of nonionic surfactants was synthesized by reacting biological α-tocopherol with ethylene oxide for functional cosmetics. The structures were confirmed by H^1-NMR, FT-IR, TLC and elemental analysis. POV and conjugated diene value study for EPO showed POE(n)TE had antioxidative effect similar to tocopheryl acetate.

Protective effect on cell membrane in photohemolysis of POE(5)TE, POE(10)TE and POE(18)TE were slightly lower than tocopherol but higher than nonoxynol-12, and POE(10)TE had UV absorption power comparable with tocopherol and homosalate. Biological activity of the hydrophobic group of the new surfactants make them unique and different from those of conventional nonionic surfactants.

Systematic safety evaluations of POE(n)TEs on the skin and eye proved that they are as safe as tocopherol. The results of physicochemical study showed POE(10)TE had the lowest CMC value, POE(18)TE had the maximum surface tension reduction and the highest foam volume and POE(n)TEs had various HLB values by the degree of ethoxylation.

The test results of technological and practical applications of these surfactants for cosmetics showed some POE(n)TEs were superior to conventional surfactants. POE(5)TE in W/O emulsions, POE(10)TE and POE(12)TE in O/W emulsions, POE(12)TE in dispersions, POE(18)TE in solubilizations and POE(50)TE in gelations were shown to be excellent, which was considered due to the structural characteristic and formation of liquid crystals of POE(n)TEs.

By the development and applications of these excellent multi-functional surfactants, innovative functional cosmetics were successfully formulated.

1. Introduction

The changes in consumer needs in recent years have created challenges to cosmetic manufacturers to invent and develop unique products.
There are a substantial number of recent publications dealing with innovative and provocative ideas of scientifically sound skin care which deserve attention.

The first of these concerns preventing UV-induced skin damage by controlling the formation of reactive oxygen species on or in the skin. The second subject deals with the interplay between topically-applied lipids and the water ecology of stratum corneum, and the use of such lipids to improve skin condition. These new concepts may inspire formulators to create novel skin care products.(1)

Age and the environment bring about a reduction in the metabolic activity of the skin and a consequent slowing down of cellular and extracellular renewal. The objective of functional cosmetology is thus to find active substance that take part in the metabolic processes of the cutis, providing it with stimulation to restore the youthful rate of biosynthesis and maintain reproduction of new skin cells.(2) Many biological substances can be candidate raw materials for the objective of functional cosmetology. Among them, tocopherol is one of the most attractive raw materials. Tocopherol has a function as a free radical scarvenger.(3,4) Free radicals are very reactive chemical species that participate widely in living processes. Free radical reactions are essential to life. But cell and tissue damage are resulted when free radicals exceed desirable levels. Tocopherol is considered to be essential for the stabilization of biological membranes.(5) When tocopherol is added to cosmetics, it provides protection against these destructive chemical particles that compromise the integrity of skin and hair and keep them looking their best. (6)

Much research work has always been carried out in order to obtain innovative surfactants with outstanding performances, suitable for cosmetics. The prime concern in selecting surfactants for use in cosmetic products is to maximize emulsifying, solubilizing and dispersing effects while preventing any adverse reaction on the epidermal cell structures.(7,8)

Surfactants are very important and indispensable in cosmetics, and very important especially in skin care products. They may react with the stratum corneum, so their safety and physiology are very important. One of the primary reasons for the use of nonionic surfactants in skin care products is their well-documented safety, particularly their excellent skin and eye tolerance.(9)

Our search for suitable raw materials to functional cosmetics led to the discovery of a new class of surfactants, polyoxyethylene tocopheryl ether[POE(n) TE], whose characteristics are connected with the structure of a biological tocopherol. The structures were confirmed by various methods.

The surface activities, chemical & biological properties, safety of these surfactants and their technological applications for cosmetics were studied. The development of these surfactants allow creation of innovative functional cosmetics.

2. Experimental

2.1 Preparation and Analysis

POE(n) TEs were prepared by reacting dl-α tocopherol with ethylene oxide in the presence of alkaline catalyst according to the autoclave method. (10) The reaction products were purified by Sephadex LH-20 (Pharmacia, Sweden) chromatography using chloroform/ methanol(1:1) if needed.(11) Every fraction was collected, and dragendorff positive frations were selected. The solvent was evaporated, and concentrated under reduced pressure. The resulting residue was a light yellow liquid to waxy appearance. The elemental analysis of POE(n)TEs was performed by Yanaco MT-2 CHN Corder (Yanaco, Japan). H^1-NMR spectra were recorded at 100 MH_z with tetramethylsilane as an internal standard using JEOL JNMMH-100 NMR Spectrometer (Jeol, Japan). FT-IR spectra were recorded by FTS-40 system (Bio-Rad Laboratories, Inc., U.S.A)

2.2 Physicochemical Properties

Tocopherol has characteristic unpleasant odor and dark brown color. Tocopherol is very unstable when exposed to air, light and UV. But its esters are more stable and generally used in cosmetics. Appearance and odor of POE(n)TEs are improved by the ethoxylation reaction. The more ethoxylated, the lighter color, the less odor and the better stability it has.

Surface tension by Du Nouy Tensiometer (Fisher Scientific., U.S.A) was measured for the aqueous solutions of 1.0 g/l concentration of POE(n)TEs. The physicochemical properties of POE(n)TEs are shown in Table 1. Hydrophilic-Lipophilic balance (HLB) values were obtained by the following equation.

$$HLB = E / 5$$

where E is equal to the weight percent of the hydrophilic moiety in the molecules, the quantity 5 simply being a scale factor to reduce the HLB values to a convenient value.(12)

We also compared the HLB values of POE(n)TEs with those of mixed surfactants of Polysorbate 60 (ICI, U.S.A)and Sorbitan sesquioleate (ICI, U.S.A)in a simple emulsion system which consisted of 50% liquid paraffin #70 (Witco, U.S.A), 47% water and 3% emulsifier.

2.3 Surface Activities

2.3.1 CMC and Surface Tension

In this study, CMC values were determined by Du Nouy method and dye absorption spectral measurement.

(1) Du Nouy Ring Method

The surface tension of the surfactant solutions in the range of $1x10^{-5}$ to $1x10^{-3}$ mol/l were measured by Du Nouy Tensiometer at 25° C. (13)

(2) Dye Absorption Spectral Measurement

Standard solution ($6.8x10^{-8}$ M) of Crystal violet analytical reagent (American Hospital Supply Corp., U.S.A) and POE(n)TEs were prepared.

A stock solution of the POE (n) TEs about the CMC was made up in a dye solution. Crystal violet and POE(n)TE were added to get various concentrations of the surfactants.

Ultraviolet absorption spectroscopy (Cecil Elegant Technology, Series CR-5500, Switzerland) was used for optical determination.

Table 1. Physicochemical Properties of POE(n)TEs

Characteristic	POE(5)TE	POE(10)TE	POE(12)TE	POE(18)TE	POE(50)TE
Appearance at 20° C	brownish yellow liquid	light yellow liquid	light yellow liquid	slightly yellow paste	slightly yellow solid
Odor	acceptable odor	a little odor	a little odor	nearly no odor	nearly no odor
Solubility 5% at R.T	oil soluble	almost water dispersible	scarcely water soluble	easily water soluble	easily water soluble
HLB values: (cal.) : (test)	6.8 6.8-7.2	10.1 10-10.5	11.0 11-11.5	13.0 13-13.5	16.7 17-17.5
Surface tension (dyne/cm) 1.0 g/l, at 25° C	50	46	43	41	49
CMC(mol/l) at 25° C	-	1.1×10^{-4}	1.3×10^{-4}	2.5×10^{-4}	9.0×10^{-4}

2.3.2 Foaming Properties

Dynamic foam test similar to Beh-James method was used for evaluating foam properties.(14,15)

In the apparatus employed, the foam is produced by subjecting 400ml of the 0.1% surfactant solution. Placed in a graduated test cylinder with a capacity of 2 *l* and provided with a stopper, cylinder is subject to rotation on a angled horizontal plane perpendicular to the axle of a motor revolving at 3000rpm for 1 min. The reading is taken immediately and 3 minutes after rotation.

Foam height is an indication of foaming power and was recorded immediately (A) and after 3 min (B). Foam stability was calculated as ratio of B to A.

2.3.3 Adsorption

As an adsorbent synthetic zeolite 4A (Wako Pure Chem. Japan) powder of 200 mesh was used. Test solutions consisted of 5g of zeolite 4A and 50g of each surfactant solution whose concentrations vary from 0.001 to 0.15 wt% was made in 100ml volume of bottom flat flask, which was agitated for 1hr by oscillator and kept at 25° C for 48 hr for equilibrium. Equilibrium adsorption was evaluated by measuring the concentration of the solution after adsorption by the absorbances: POE(n)TEs at 289nm, Nonoxynol-12 at 278nm.

2.4 Chemical & Biological Properties

2.4.1 Measurement of Antioxidative Effect

Antioxidative effect of POE(n)TEs was examined using Evening Primrose Oil(EPO), which comprised more than 68% of linoleic acid and 7.5% γ-linolenic acid.(16) The purified POE(n)TEs and as reference Tocopheryl acetate, Tocopherol, and Nonoxynol 30 (Igepal CO-880, GAF, U.S.A) were added to the EPO as much as 0.1% and 1.0% and maintained in a constant temperature chamber of 50° C. After two and ten days, peroxide value (POV) for each sample was determined by iodometric titration as previously described (17). The results are expressed as μ mol peroxide g^{-1} sample. The amount of conjugated diene (CD) was also determined by measuring the absorbance at 234nm(18) with Cecil's computing double beam UV spectrophotometer.

2.4.2 Protective Effect on Cell Membrane

The blood collected from rabbit was centrifuged at 3000 rpm for 5 min to separate erythrocytes and serum, then washed and diluted with 0.9% saline phosphate buffer, pH 7.4 to prepare the erythrocyte suspension. The reaction mixture for photohemolysis determination consists of a test group containing 3.5ml of erythrocyte suspension, 50μl of ethanolic solution for each sample and a control group containing only 50μl of ethanol.

After the mixture was preincubated for 30 min at the dark place, 0.5ml of 1.5 X 10^{-6}M rose bengal was added and then sealed. The tubes were placed in 50 X 20 X 25cm rectangular hexahedron black box, and irradiated for 15 min by 20 watt fluorescence lamp at a distance of 5cm. The degree of hemolysis of the erythrocytes was measured by transmittance at 700nm with Spectronic 20D (Bausch & Lomb, U.S.A)

2.4.3 UV Absorption Ability ($E_{cm}^{\%}$)

POE(n)TEs, tocopherol and ascorbic acid were dissolved in 95% ethanol to reach 1x10^{-3} % concentration except ascorbic acid(Roche, U.S.A). it was dissolved in 50% ethanol. The UV absorption was recorded by Cecil's UV Spectrophotometer. $E_{cm}^{\%}$(290nm) was calculated from Beer-Lambert law.

2.4.4 Moisture Retention Ability

2.0 g of clean hair tresses were prepared and conditioned at 30℃, 60% RH, until they show contant weights. 5% solutions of POE(12)TE, POE(18)TE, glycerine(Dow, U.S.A.) and polysorbate 60(ICI, U.S.A) were made for absorption of water and each tress was soaked for 5 min in the test solutions. After removing over-absorbed solution, the weight of each tress was measured and kept it for desorption of water in a chamber of 30° C, and 60% RH. Moisture retention ability was evaluated by measuring the remaining water weight on the hair tress until equilibrium.

2.5 Safety Testing

The central question about the irritancy of any new raw material is whether it is likely to be less or more irritant than the raw material it is replacing in the formulation. So, the safety potential of POE(n)TEs was studied by comparison with various commercial surfactants.

2.5.1 Closed Patch Test on Human skin

Closed patch test was performed as Finn chamber patch method.(19) For 50 women aged from 20 to 50, 20 μl of sample solution was applied for 24 hr by the closed patch system on the inner surface of the forearm. The evaluation was carried out at 2 hr, 24 hr and 48 hr after removal.

2.5.2 Primary Skin Irritation

Primary skin irritation test as close patch was performed by a method of Federal Register (20). Six normal healthy Albino rabbits were used in this study. One square inch gauge patchs containing 0.5g of undiluted samples were applied intact and abraded skin suits on two groups of three rabbit each. The patches were secured for 24 hr and the exposure sites examined at 24 hr and 72 hr.

2.5.3 Primary Eye Irritation

Primary eye irritation was performed according to CTFA Safety Testing Guidelines (21). Six normal healthy Albino rabbits were used in this study. 0.1ml of 10% aqueous glycerin solution was instilled into the conjuntival sac and the lower lid was gently pulled away to form a cup and the 0.1ml of 10% aqueous solution of test material was inserted. The lids were held together for 1 sec. The contra-lateral eye serves as a control. The eyes were examined after 24 hr, 48 hr, 72 hr, 4 days and 7 days respectively.

The scores were recorded according to the Draize scoring ocular lesions (22) All tests were carried out in a room at 20 ± 2° C, 55± 4 % RH.

2.5.4 Acute Oral Toxicity

Acute oral toxicity test was performed according to the CTFA Safety Testing Guidelines.(21) White rats (Spraque-Dawly about 200g) grown for 8 weeks at 24° C and 50% RH room were used. The rats were divided into 2 groups and fasted for 18 hr before injecting the test materials. Each test materials was fed into 5 male and 5 female rats by the oral injector. After injecting the test materials all the toxic phenomena inclucling death were checked and recorded the mortality. After checking for 14 days, the rats were dissected and observed any pathological change of internal organs.

2.6 Technological Application to Cosmetics as Surfactants.

2.6.1 Emulsion

In this study very basic formulations were used to evaluate the properties of POE(n)TEs as emulsifier by comparing those of commercially available emulsifiers. Liquid paraffin(L.P. #70, Witco, U.S.A) was chosen as main component of oil phase with dimethicone(Dow Corning 200 fluid, Dow Corning, U.S.A) and water with propylene glycol were the water phase.

Also two or three different weights of liquid paraffin were used for evaluating the stabilities of the emulsions depending on the volume change of oil phase.

Emulsion stability can vary with both the kinds of emulsifiers and the amounts of emulsifiers used.(23) In order to know the basic properties of POE(n)TEs as emulsifiers, we have used proper amounts of emulsifiers for emulsion preparation.

(1) O/W Emulsion

The formulations used in this study are shown in Table 2.
After both oil phase with emulsifier and water phase were heated to 70° C, oil phase was added into water phase while homogenizing by T.K Homomixer (Tokushu Kikai, Japan) for 3 min, 5000 rpm.

After emulsification the mixture was cooled down to 30° C by slow agitation.

50 ml of emulsion sample was filled into test tube and then emulsion stability was evaluated by the volume ratio of the stable phase to total phase at 45° C incubator for 30 days.

(2) W/O Emulsion

The formulations used in this study are shown in Table 3. After both oil and water phases were heated to 70° C, water phase was added into oil phase while homogenizing with T.K. Homomixer for 3 min, 6000 rpm.

After emulsification the mixture was cooled down to 30° C by slow agitation. Stability was checked as the same way in O/W emulsion.

2.6.2 Solubilization

To compare the solubilization power of POE(18)TE with commercial solubilizer, two kinds of solubilizates and three different amounts of ethanol(Korean Ethanol, Korea) contents were used. One solubilizate is limonene oil which is fairly difficult to solubilize and the other is mixed perfume oil of α hexyl cinnamic aldehyde, lilial and musk ketone. Formulations are shown in Table 4. Preparations were made at 40° C and cooled down to 20° C rapidly. The degree of solubilization was determined by the transmittance (%) measurement at 700nm.

Table 2. Formulations of O/W Emulsion (wt %)

Ingredient \ Formula	1	2	3
Liquid paraffin	50.0	80.0	80.0
Dimethicone	0.1	0.1	0.1
Emulsifier*	3.0	3.0	5.0
Propylene Glycol	5.0	5.0	5.0
D.I.Water	To 100.0	To 100.0	To 100.0

Emulsifier*

1: POE(10)TE, 2: POE(12)TE, 3: Polysorbate 85(ICI, U.S.A)

4: Polysorbate 60 / Sorbitan Sesquioleate (35:65)

5: Polysorbate 60 / Sorbitan Sesquioleate (50:50)

6: Polysorbate 60 / Sorbitan Sesquioleate (60:40)

Table 3. Formulations of W/O Emulsion (wt %)

Ingredient \ Formula	1	2	3
1. Liquid paraffin	20.0	50.0	80.0
2. Dimethicone	0.1	0.1	0.1
3. Emulsifier*	4.0	4.0	4.0
4. Propylene glycol	5.0	5.0	5.0
5. D.I. Water	To 100.0	To 100.0	To 100.0

Emulsifier*
1: POE(5)TE, 2: Polysorbate 60 / Sorbitan Sesquioleate(10:90)
3: Polysorbate 60 / Sorbitan Sesquioleate(15:85)
4: Polysorbate 60 / Sorbitan Sesquioleate(25:75)

Table 4. Formulations of Solubilization (wt %)

Ingredient\Formula	1	2	3	4	5	6
1. Propylene Glycol	5.0	5.0	5.0	5.0	5.0	5.0
2. Solubilizer*	1.0	1.0	1.0	1.0	1.0	1.0
3. Ethanol	15.0	50.0	15.0	15.0	25.0	50.0
4. Perfume						
1) Limonene	0.3	0.8	-	-	-	-
2) Mixed perfume	-	-	0.5	0.7	1.0	2.0
5. D.I. Water	To 100	To 100	To 100	To 100	To 100	To 100

Solubilizer*

1: POE(18)TE, 2: Nonoxynol - 12 (Nihon Emulsion, Japan),
3: Polysorbate 80 4: Choleth-24 (Amerchol, U.S.A)
5: PEG(60) Hydrogenated Castor Oil (Nikko, Japan)

2.6.3 Dispersion

TiO_2 C47-056(Sun Chem. U.S.A.) being a widely used pigment was selected for dispersion preparation. The formulations to evaluate the dispersing power of POE(n)TE and commercial dispersing agents are shown in Table 5.

Dispersions were made by melting the dispersing agent in propylene glycol, followed by adding the others in the beaker, and agitating for 3min at 50° C and cooling down to 30° C. Dispersion was evaluated by the volume ratio of dispersed volume to total volume.

2.6.4 Gelation

Formulations for gelation test are shown in Table 6. Gel was made by dissolving the gelling agents in propylene glycol at 50° C and agitation was continued for 10 min after adding all the ingredients. Gelation was evaluated for the hardness which was measured by Rheometer(Fudo, Japan) at 30℃, 200g, 2 cm/sec and adaptor #3. Two gelling agent concentrations were used in this test.

Table 5. Formulations of Dispersion (wt %)

Ingredient \ Formula	1	2
1. Propylene glycol	5.0	5.0
2. Ethanol	-	5.0
3. Dimethicone	0.1	0.1
4. Dispersing agent*	2.0	2.0
5. TiO_2	5.0	5.0
6. D.I. Water	To 100.0	To 100.0

Dispersing agent*
1: POE(10)TE, 2: POE(12)TE, 3: Polysorbate 85, 4: Polysorbate 80
5: Polysorbate 60 / Sorbitan Sesquioleate(60:40)
6: Polysorbate 60 / Sorbitan Sesquioleate(70:30)

Table 6. Formulations of Gelation (wt %)

Ingredient \ Formula	1	2	3
1. Propylene glycol	5.0	5.0	10.0
2. Ethanol	5.0	5.0	10.0
3. Gelling agent*	20.0	20.0	30.0
4. Tocopherol	-	1.0	4.0
5. D.I.Water	To 100	To 100	To 100

Gelling agent* 1: POE(12)TE, 2: POE(50)TE, 3: Choleth-24

3. Results and Discussion

3.1 Analysis of POE(n)TEs

The reaction products of POE(n)TEs are, in reality, a mixture of derivatives of the tocopherol moiety containing different molecular proportions of ethylene oxide units and a wide range of molecular weights.(24) Alkaline catalysts are generally used for ethoxylation reaction (Fig. 1).

The distribution of each individual product was visualized by TLC using dragendorff reagent (Fig. 2). The H^1-NMR spectra were shown in Fig. 3. In the spectrum for tocopherol, peak for $-CH_2-CH_2-$ or $-CH_3$ appears at 1.17-1.30δ three peaks for $-CH_3$ of phenyl at 2.80δ and peak for -OH of trimethylphenol at 4.1δ. In the spectra for POE(n)TEs, the peak at 4.1δ disappears while peak for -OH of the end ethylene oxide at 4.8δ, the peak at 3.7δ is due to the oxyethylene unit.(25) The peak at 3.7δ is much stronger due to an increased moles of ethylene oxide added. The FT-IR spectra are shown in Fig. 4. The strong band in 1100 - 1150 cm^{-1} and the weak band in 3320 - 3500 cm^{-1} indicate the existence of polyoxyethylene chain substituted on tocopherol. The band in the region of 1100 - 1150 cm^{-1} has been known to depend on the nature of oxyethylene linkage.

The difference between found and calculated elemental anlaysis data was in the range of 0.5% and they showed good accordance. Elemental analysis data showed good agreement with the data of H^1-NMR and FT-IR spectra, also support the presence of polyoxyethylene chain added to tocopherol.

3.2 Surface Activities

3.2.1 Critical Micelle Concentrations(CMC) and Surface Tension

Micellization is the property that surfactants have of forming colloidal-sized cluster in solution, this is an important and fundamental property of surfactants. Micellization is a mechanism alternative to adsorption at the interfaces for removing lyophobic groups from contact with the solvent, thereby reducing the free energy of the system. CMC is the concentration at which micellization occurs.(26) For nonionic polyoxyethylenated alcohols and alkylphenols in aqueous medium, empirical relationships have been found between the CMC and the number of oxyethylene units R in the molecule, in the form

$$\log CMC = A' + B'R$$

Where A' and B' are constants for a particular temperature and hydrophobic group. (26) It is seen that CMC values of the surfactants increase with increasing oxyethylene chain length, as expected from above equation.

Fig.5(b) shows that the CMC values for POE(n)TEs follow separate lines parallel to each other, indicating that the effects of the structure of the long-chain oxyethylene group are represented by the slope B', which seems to be related to the homologus series. As shown in Fig.5, the longer the length of oxyethylene chain, the higher the CMC of POE(n)TEs. In Table 1, the surface tension and CMC value of POE(n)TEs are shown.

The characteristic changes of the absorption spectra were observed in the dye surfactant interacting system with varing concentrations of POE(12)TE and POE(18)TE. At CMC, the absorption spectra were changed to bathochromic shift.

This is due to the immobilization of dye incorporated into the micellar region. It has been shown that the absorption spectra of dye molecule being incorporated in the micelle provide information about the micellar properties.

The spectral behaviors of Crystal violet in aqueous solution with varing concentrations of POE(12)TE and POE(18)TE are shown in Fig. 5(a). POE(12)TE has lower CMC than POE(18)TE, that means the dye can be incorporated more rapidly into the micelle of POE(12)TE than that of POE(18)TE as the concentration increase.

3.2.2 Foaming Property

Another important property of surfactants is their foaming property. Foaming property of surfactant solutions can be assessed by either dynamic, static, or semistatic method. In the dynamic method the foam lamellae, because of the agitation, remain thick and are susceptible to instantaneous rupture unless protected by the surface elasticity of the films.
According to the study of Schick and Beyer both foam formation and foam stability pass through a maximum when the adduct contains 13 oxyethylene unit.(27) This maximum is termed the critical hydrophile hydrophobe balance(CHHB). The dynamic foam test results are shown in Table 7. Among POE(n)TEs, POE(18)TE has maximum foam volume. This result was well agreed with the previous data.

Table 7. Foam Volume and Foam Stability of 0.1% Surfactant Solution at 25° C

Surfactant	Foaming Volume initial	Foaming Volume 3 min	Foam Stability (%)
POE(5)TE	460	457	99.5%
POE(10)TE	470	467	99.3%
POE(12)TE	580	570	98.3%
POE(15)TE	520	516	99.2%
POE(18)TE	790	780	98.7%
POE(30)TE	780	770	98.7%
POE(50)TE	630	610	96.8%
Nonoxynol-12	810	800	98.8%

3.2.3 Adsorption

The adsorption of nonionic surfactants on solid surface is the basis for the chemical applications of these substances. One important area of application of nonionic surfactants, where adsorption and wetting play a decisive role, is dispersion of pigment in a liquid media. A characteristic property surfactants have is their tendency to aggregate in solution or at interfaces. This property results in an increase in surfactant concentration at the solid/liquid interface in comparision to the bulk concentration.

The adsorption isotherms of polyoxylethylene alkylphenol are of the Langmuir type and the plateau heights decrease with increasing number oxyethylene units.(27)

Fig.6 shows the adsorption isotherms of POE(n)TEs. Adsorption decreases according to the increase of ethylen oxide chain length of the POE(n)TEs. This is well agreed with the previous results. The plateau region commenced at or near the CMC generally.

It is assumed that POE(n)TEs appeared to show surface saturation in the vicinity of the CMC of the adsorbate with an orientation of the adsorbate flatwise.

3.3 Chemical & Biological Properties

3.3.1 Antioxidative Property of POE(n)TEs

The degree of oxidation of EPO in the presence of POE(n)TEs was measured by both peroxide value and conjugated diene values and listed in Table 8 and Table 9. The addition of POE(n)TEs to EPO as substrate resulted in the retardation of the oxidative deterioration of the oil.

Peroxide values were determined by iodometric titration, and the antioxidative activities were investigated by UV absorbance of the oil at 234nm. POE(5)TE, POE(10)TE and POE(15)TE showed a higher antioxidative effect than control itself but not higher than tocopherol. Increasing the hydrophilicity of POE(n)TEs caused decreasing the antioxidative activity against the oil. We suggest that the chemical affinity between the substrate and antioxidative compound is very important for preventing the oxidation of the oil.(28)

In oil system, antioxidative activities were affected not only by the electron density at the ether linkage but also by the solubility for oil. It will be necessary to increase the solubility in the oil to enhance the antioxidative activity (29).

3.3.2 Protective Effect of POE(n)TEs on Cell Membrane in Photohemolysis

The effect of POE(n)TEs and other references on the cell membrance against singlet oxygen is shown in Fig.7. POE(n)TEs suppressed the singlet oxygen induction. At certain concentration, some monomers of POE(n)TEs were incorporated into the lipid bilayers of red cell membranes without causing any appreciable hemolysis. The monomers and micelles could interact with membranes

Table 8. Peroxide Values(μmol peroxide/g)

Sample	After 2 days	After 10 days
Control(EPO)	32.70	157.77
EPO + Tocopherol (0.1%)	20.04	60.54
EPO + Tocopheryl acetate (0.1%)	25.18	143.50
EPO + POE(10)TE (0.1%)	26.58	148.44
EPO + POE(10)TE (1.0%)	24.88	142.90
EPO + Nonoxynol-30 (1.0%)	28.28	177.71

*Each sample contains wt% of material in EPO.

Table 9. Conjugated Diene Values

Sample	A_{234}	A_{234} ratio*(%)
EPO + Tocopheryl acetate (0.1%)	0.708	65.6
EPO + Tocopheryl acetate (1.0%)	0.650	60.2
EPO + Tocopherol (0.1%)	0.347	32.0
EPO + POE(5)TE (0.1%)	0.760	70.4
EPO + POE(10)TE (0.1%)	0.810	75.0
EPO + POE(15)TE (0.1%)	0.800	74.1
EPO + POE(5)TE (1.0%)	0.695	64.4
EPO + POE(10)TE (1.0%)	0.745	69.0
EPO + POE(15)TE (1.0%)	0.758	70.0
Control(EPO)	1.080	100.0

*Each sample contains wt% of material in EPO.

$$A_{234}\ \text{ratio}^{*} = \frac{A_{234}\ \text{of sample}}{A_{234}\ \text{of control}} \times 100$$

of red cells in different way. At higher concentration, the surfactant can dissolve the lipid bilayer of membranes and may be diluted with some lipid components of red cells. The antioxidative and cell membrane protection activities in photohemolysis of tocopherol had been considered to be caused by the phenolic hydroxyl group in its molecule (30). However we suggest that not only the phenolic hydroxy group but ether linkage is also responsible for the activity of tocopherol. It was well documented in the relation between the structures of 1,3-dioxaindan derivatives and their activities which have no phenolic hydroxy group but ether linkage. (31,32)

They supposed that radical scavenging activities of these compounds with no phenolic hydroxy group arose by the electron density at the ether linkage.

In the case of POE(n)TEs, we assume the free radical activity was due to the increased density at 1-position of chromanyl ring caused by electron donating effect of ethylene oxide substitution at para position as well as oxyethylene group.

Another possible mechanism for protective effect on cell membrane in photohemolysis supports the polyethylene oxide radical formation by irradiation.

One radical spot on polyoxyethylene was distributed along the chain as $\cdot\cdot\text{-O-}\dot{\text{C}}\text{H-CH}_2\text{-O-}\cdots$. The hydrogen atom arisen from polyethylene oxide maybe terminate free radical chain reaction. (33,34,35)

3.3.3 UV Absorption of POE(n)TEs

The UV absorption of POE(n)TEs was compared with that of tocopherol, ascorbic acid and homosalate as referance.

As shown in Fig.8, there was a little reduction of extinction coefficient($E_{cm}^{\%}$) after adding ethylene oxide chain to tocopherol. $E_{cm}^{\%}$

was also decreased when ethylene oxide chain was added. Fig. 8 shows the E_{cm}^{*} of POE(10)TE and various compounds for comparison. POE(10)TE has higher E_{cm}^{*} than ascorbic acid but not tocopherol.

3.3.4 Moisture Retention Ability

Skin health is directly influenced by the moisture content of the stratum coneum and the moisture in hair also plays a critical role in its physical and cosmetic properties. The horny layer of skin contains a relatively small amount of water, only 10 to 15% by weight. This gives functioning and flexbility of the horny layer. An ideal moisturizer should have high moisture retention ability at low outside humidity levels.(36) In this study, in order to evaluate moisturizing effect of the POE(n)TEs at low humidity, moisture retention ability was studied and calculated by the following equation for POE(n)TEs, glycerine and Polysorbate 60.

$$\text{Moisture Retention Ability(\%)} = \frac{W_o - W_l}{W_o} \times 100$$

where W_o = Weight of water on the hair at initial time

W_l = Weight of water loss on the hair at given time

The test results of moisture retention ability using hair tress at 30°C, 60% RH, are shown in Fig. 9. POE(12)TE showed better moisture retention ability than the others. This maybe comes from characteristic structure of POE(n)TE which has high water holding capacity and gel-like structure at 5% aqueous solution.

3.5 Safety Data

3.5.1 Human Patch Tests

The results of human patch tests are shown in Table 10.

POE(18)TE shows slight irritation reaction but the other POE(n)TEs show no reaction. POE(n)TEs show much less irritation rate than Polysorbate 60 and Nonoxynol-12. This means almost all POE(n)TEs are very safe materials.

3.5.2 Primary Skin Irritation

The test results of primary skin irritation are shown in Table 11. All POE(n)TEs show practically non-irritating index (PII) which is lower scores than that of Polysorbate 60 which showed minimally irritating. This means that all POE(n)TEs are very safe raw materials.

Table 10. Results of Human Patch Test

Item	Irritation Reaction Rate (n=50)		
Sample \ Hour	4hr	48hr	mean
POE(5)TE	0	0	0
POE(10)TE	0	0	0
POE(12)TE	0	0	0
POE(18)TE	0.8	0	0.4
POE(50)TE	0	0	0
Tocopherol	0	0	0
Polysorbate 60	1.7	0	0.8
Nonoxynol-12	1.7	0	0.8
Squalane	0	0	0

Table 11. Results of Primary Skin Irritation Test

Item	Primary Irritation		
	Score		PII
Sample \ hour	24hr	72hr	
POE(5)TE	7	2	0.38
POE(10)TE	9	3	0.50
POE(12)TE	12	2	0.58
POE(18)TE	13	3	0.59
POE(50)TE	11	3	0.50
Tocopherol	10	0	0.42
Polysorbate 60	14	4	0.75
Nonoxynol-12	14	4	0.75

3.5.3 Primary Eye Irritation

The results of primary eye irritation test of 10% aqueous solution are shown in Table 12. POE(n)TEs show very low PII which means they are non-irritating and considered very safe.

Table 12. Results of Primary Eye Irritation Test

Item	Primary Irritation Index(PII)					
Sample \ Hour	1hr	24hr	48hr	72hr	4days	7days
POE(5)TE	2	0	0	0	0	0
POE(10)TE	2	0	0	0	0	0
POE(12)TE	3	0	0	0	0	0
POE(18)TE	2	0	0	0	0	0
POE(50)TE	3	0	0	0	0	0
Polysorbate 60	3	0	0	0	0	0
Nonoxynol-12	6	0	0	0	0	0

3.5.4 Acute Oral Toxicity

The test results of acute oral toxicity are shown in Table 13. LD_{50} of POE(n)TEs are more than 5g/kg. This means all POE(n)TEs are non-toxic or very safe and not classified as toxic materials.

These results were well agreed with the acute oral LD_{50} data for POE(n)TEs by Korea Research Institute of Chemical Technology (KRICT) Toxicology Center. (37)

Table 13. Results of Acute Oral Toxicity Test

Item	Acute Oral LD_{50}
POE(5)TE	> 5g/Kg
POE(10)TE	"
POE(12)TE	"
POE(18)TE	"
POE(50)TE	"

3.6 Technological Applications for Cosmetics as Surfactants.

3.6.1 Emulsion

It has long been recognized that in homologous series of surfactants there is a point or range in which the polarity of the molecule, i.e., the relation between the contributions of the polar hydrophilic head and the nonpolar lipophilic tail is optimal for a specific emulsion. Griffin defined this potarity of nonionic surfactants in terms of empirical quantity, which he termed the hydrophile lipophile balance, or HLB.(27) In this study, we tested the stabilities of O/W emulsion with POE(10)TE and POE(12)TE by comparing with those of commercial excellent emulsifiers having similar HLB values.

(1) O/W Emulsion Stability

In Table 14, stability test results of O/W emulsions are shown. When oil content is over than 76%, it becomes very difficult to make stable O/W emulsion with 3% of ordinary emulsifiers.

The stability was evaluated by measuring the stable portion of the emulsion, total volume-(drained volume + coalesced volume).(38) Emulsion stability was expressed by the following equation.

$$\text{Emulsion Stability}(\%) = \frac{\text{Total Volume} - (\text{Drained Volume} + \text{Coalesced Volume})}{\text{Total Volume}} \times 100$$

Formula 1 with 50% of liquid paraffin # 70, all emulsifiers showed fairly good emulsion stability. But in Formula 2 with 80% of liquid paraffin #70 and 3% emulsifier contents only emulsifiers POE(10)TE and POE(12)TE can make stable emulsions. In Formula 3, the other emulsifiers can not make stable emulsions even at the concentration of 5%. Emulsions of Formula 2 with POE(10)TE and POE(12)TE were viscous liquid emulsion but emulsions of Formula 3 with POE(10)TE and POE(12)TE were gel-like creams.

Among the emulsifiers tested in this study, POE(10)TE and POE(12)TE showed better emulsion stability than the other commercial emulsifiers. We assume this was due to a formation of liquid crystal in the emulsion system. It has gel-like consistancy, which is important for stabilization of emulsions. (39)

Liquid crystals in Formula 2 and 3 with POE(10)TE and POE(12)TE were observed and are shown in Fig.10 (a). Polarized light microscope with filter and camera was used for observing the liquid crystal. The formation of liquid crystal at low concentration of 3% and 5% of POE(10)TE and POE(12)TE is a very unique and interesting property, which maybe comes from the characteristic molecular structures and association configuration of POE(10)TE and POE(12)TE.

Table 14. Results of O/W Emulsion Stability(%) Test

Item Emulsifier \ Formula	Emulsion Stability (%) 1	 2	 3
POE(10)TE	100	100	100
POE(12)TE	75	100	100
Polysorbate 85	80	NO	NO
Polysorbate 60/Sorbitan Sesquioleate(35:65)	90	NO	NO
Polysorbate 60/Sorbitan Sesquioleate(50:50)	76	NO	NO
Polysorbate 60/Sorbitan Sesquioleate(60:40)	68	NO	NO

* NO: No stable emulsion was formed. Emulsion was separated just after emulsification.

(2) W/O Emulsion Stability

In Table 15, stability test results of W/O emulsion are shown. The stability was evaluated and expressed the same way as in O/W emulsion. POE(5)TE shows a little better emulsion stability than commercial surfactant mixtures.

Table 15. Results of W/O Emulsion Stability(%) Test

Item Emulsifier Formula	Emulsion Stability (%) 1	 2	 3
POE(5)TE	98	93	98
Polysorbate 60 / Sorbitan Sesquioleate(10:90)	92	95	95
Polysorbate 60 / Sorbitan Sesquioleate(15:85)	97	90	76
Polysorbate 60 / Sorbitan Sesquioleate(25:75)	95	91	60

3.6.2 Solubilization

Solubilization is a particular mode of dissolving substances that are insoluble in a given medium. While this definition has the virtue of not being restricted to the solubilization of insoluble or sparingly soluble organic substances in water by the addition of suitable surfactant, it involves the previous presence of a colloidal solution whose aggregates or particles take up and incorporate within or upon themselves the otherwise insoluble material.(27) Surfactant molecules form micelles in aqueous solution when the concentration exceeds a specific value called CMC.

In general little or no solubilization occurs until the CMC is reached indicating that the solubilization molecules are taken up in some way by the micelles. The majority of solubilization studies here focused on organic solubilizates in dilute aqueous surfactant solutions.(27)
The results of solubilizing effect test are shown in Table 16.

In Formula 1, 2 and 4 with 15% ethanol, only POE(18)TE and Polysorbate 80 showed higher solubilizing effect than the others. In Formula 2 and 6 with 50% ethanol, only POE(10)TE and PEG(60) hydrogenated castor oil showed better solubilizing effect.

In the case of limonene solubilization POE(18)TE showed better solubilizing effect. For solubilization of mixed perfume oil POE(18)TE also showed better solubilizing effect than the others.

These results show that POE(18)TE has very large solubilizing capacity that can be applied to various types of formulations. These may be due to that POE(18)TE has somewhat small CMC value, 2.5×10^{-4}, or large micelle size and has a constant good configuration for solubilization when made micelles.

Table 16. Results of Solubilization Transmittance(%) Test

Item Emulsifier \ Formula	Transmittance(%) 1	 2	 3	 4	 5	 6	 mean
POE(18)TE	95.0	92.0	99.5	99.8	98.8	100.0	97.5
Nonoxynol-12	26.5	2.6	95.5	100.0	1.5	92.1	53.0
Polysorbate 80	93.4	28.1	94.2	68.7	0.1	9.7	49.0
Choleth-24	3.8	0.7	93.2	0.2	0.1	0.5	16.4
PEG(60)hydro. castor oil	7.8	90.3	99.0	0.4	94.2	100.0	65.2

3.6.3 Dispersion

Nonionic surfactants can have profound effects on the colloid stability of particle dispersions. The use of low molecular weight surfactant to stabilize colloidal dispersions is widely practiced.

The stability to aggregation of a colloidal dispersion and conditions for instability can be quite well described in terms of the potential energy of interaction between pairs of particles. Moreover, changes in colloidal stability, brought about by the addition of a nonionic surfactant are by and large considered to be a consequence of the adsorption of surfactant molecules on the particle surfaces, the adsorbed layers serving to modify this interaction energy. In general, nonionic surfactant adsorb strongly at very dilute solution concentrations and saturation coverage on the particle surfaces in more or less complete in the neighborhood or somewhat above the surfactant CMC.(27)

We evaluated and expressed the dispersion power by the following equation.

$$\text{Dispersion power (\%)} = \frac{\text{Pigment Dispersed Volume}}{\text{Total Dispersion Volume}} \times 100$$

The test results of dispersion are shown in Table 17. POE(12)TE showed better dispersion ability than the others. We suppose that this maybe come from the properties of POE(12)TE being adsorbed strongly in the dilute solution and having high saturation coverage on the particle surface.

Table 17. Results of Dispersion Power(%) Test

Item Dispersing agent \ Formula	Dispersion Power(%) 1	 2
POE(10)TE	18.4	17.2
POE(12)TE	69.2	26.7
Polysorbate 80	18.9	14.2
Polysorbate 85	21.1	17.6
Polysorbate 60/Sorbitan Sesquioleate(60:40)	12.6	16.7
Polysorbate 60/Sorbitan Sesquioleate(70:30)	12.6	16.7

3.6.4 Gelation

A gel is a mixture, one component of which is a fluid, homogeneous down to substantially colloidal dimensions, capable of resisting a finite shear force.(40)

This difinition defines a gel in terms of two important operational phenomena: first, a gel may contain a substantial portion of liquid component; second, it is characterized by an extremely high viscosity and is, indeed, a semi-solid.(41) The hardness of the gels are shown in Table 18.

POE(50)TE has excellent gelling property, high hardness and good transparency which can be considered to have good solubilizing effect. We assume this maybe due to the characteristic property of POE(50)TE.

We assume that the excellent gelling property of POE(50)TE was caused by the formation of liquid crystal. The formation of liquid crystal in Formula 3 with POE(50)TE was observed with a polarized light microscope and the results are shown in Fig.10(b). At high concentration POE(50)TE are easily oriented to make a stable form of lyotropic liquid crystals in the solution.(42)

Table 18. Results of Gelation Hardness(g) Test

Item	Hardness(g)		
Gelling agent \ Formula	1	2	3
POE(12)TE	5.0	30.0	3.0
POE(50)TE	17.0	37.0	72.0
Choleth-24	NO	3.0	4.0

※ NO: No gel was formed. Low viscous liquid was obtained.

4. Conclusion

We have successfully developed a new and unique class of nonionic surfactants, POE(n)TEs, from biological tocopherol. The systematic study revealed following properties important for innovative and functional cosmetics.

Overall safety evaluations of human patch test, primary skin irritation, primary eye irritation test and acute oral toxicity test of POE(n)TEs proved that they were as safe as tocopherol and much safer than polysorbates 60 and nonoxynol-12 known as safe.

By measuring POV and conjugated diene value for POE(n)TEs, it was found that POE(n)TEs had significant antioxidative effects which were similar to that of tocopheryl acetate. This is a very new and unique property of POE(n)TEs as surfactants.

The test results of photohemolysis using rabbit erythrocyte showed that POE(n)TEs have very good protective effects on cell membrane. The effect of POE(n)TEs was slightly inferior to that of tocopherol but better than conventional surfactant, nonoxynol-12.

UV absorption test showed POE(n)TEs had very similar capacity to tocopherol and homosalate. And POE(12)TE was found to have much higher moisture retention ability than glycerine.

The tests for technological and practical application for basic cosmetics were carried out. POE(10)TE and POE(12)TE showed excellent O/W emulsion stability, especially at high amounts of oil, they have incomparably better O/W emulsion stability than conventional polysorbate 60/sorbitan-sesquioleate mixed emulsion system having similar HLB value. Also POE(5)TE showed good W/O emulsion stability. Occurance of liquid crystals in the emulsion systems with POE(10)TE and POE(12)TE greatly contributed to the emulsion stability.

POE(18)TE had excellent solubilizing power in the various formulations. It showed unique constant solubilizing power but conventional solubilizers did not. This was considered due to the solubility, low CMC value of 2.5×10^{-4} mole/l and the high affinity of lipophilic region of POE(18)TE with the solubilizate in the solution.

Better dispersion power of POE(12)TE than the other dispersing agents was considered to come from the favorable adsorption property. In gelation test POE(50)TE showed excellent gelling power, which was superior to conventional gelling agent, Choleth-24. The strong gel structure seemed to result from the formation of highly ordered liquid crystals, which had lamellar structure.

From these results, it was found that POE(n)TEs contributed much more improved safety, chemical and biological effect and stability to cosmetics than conventional surfactants. We think the development and applications of these unique surfactants allowed creation of innovative functional cosmetics.

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요 약

기능성 화장품을 위한 일련의 새롭고 독특한 비이온 계면활성제들을 생리활성물질인 α-Tocopherol 과 에칠렌옥사이드의 반응에 의해서 제조하였다. 반응 생성물의 구조는 H^1-NMR, FT-IR, 원소분석, TLC를 통해 확인하였다. EPO에 대한 POV 와 CDV 연구에서 POE(n)TEs는 모두 토코페릴아세테이트와 유사한 항산화효과를 나타

내었다. 그러나 POE(5)TE, POE(10)TE, POE(18)TE의 광용혈에 대한 세포막보호효과는 Control에 비해 높은 결과를 나타내었다. POE(10)TE의 자외선흡수능은 Homosalate와 유사하게 나타났다. Primary Skin Irritation, Primary Eye Irritation 및 Acute Oral Toxicity 테스트결과 POE(n)TEs의 안전성이 입증되었다.

POE(n)TEs의 계면화학연구에서는 POE(10)TE가 가장낮은 CMC값을 나타내었고, POE(18)TE는 Maximum surface tension reduction 과 최대 Foam volume을 보였다. 화장품의 실질적인 응용을 위한 테스트 결과 W/O유화에서는 POE(5)TE, O/W유화에서는 POE(10)TE 와 POE(12)TE, 분산에서는 POE(12)TE, 가용화에서는 POE(18)TE, 겔화에서는 POE(50)TE가 우수하였는데, 이것은 POE(n)TEs의 구조적특성과 Liquid Crystal형성에 기인한 것으로 여겨진다.

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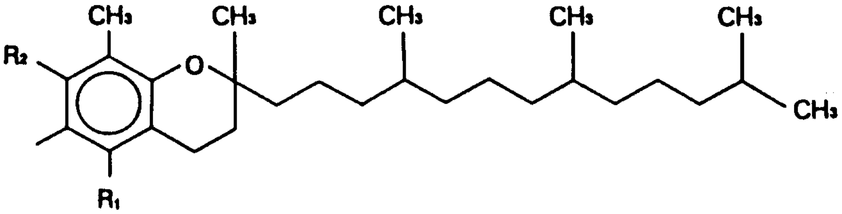
Fig 1. Preparation Scheme of POE(n)TEs

$$\mathrm{ROH} + \mathrm{E.O} \xrightarrow[\Delta,\ \text{Pressure}]{\text{Catalyst}} \mathrm{ROCH_2CH_2OH}$$

$$\mathrm{ROCH_2CH_2OH} + (n\text{-}1)\ \mathrm{E.O} \xrightarrow[\Delta,\ \text{Pressure}]{\text{Catalyst}} \mathrm{RO(CH_2CH_2O)\ nOH}$$

R represents Tocopheryl group



	R_1	R_2
α -Tocopherol	$-CH_3$	$-CH_3$
β -Tocopherol	$-CH_3$	-H
γ -Tocopherol	-H	$-CH_3$
δ -Tocopherol	-H	-H

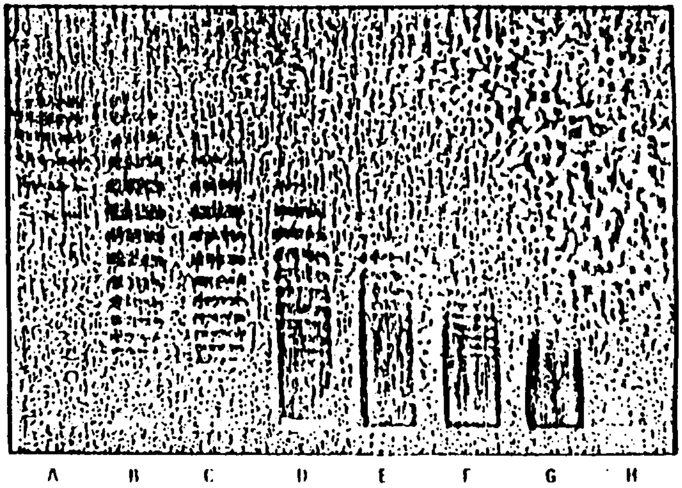
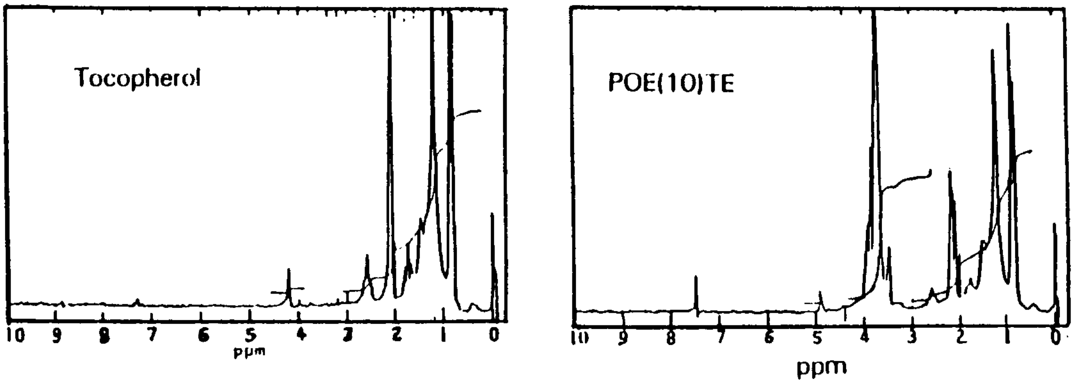


Fig 2. TLC patterns after Dragendorff Reagent Spray; Spot color: red-orange color; Mobile phase: Ethyl acetate/Acetone/water (50:50:6); A: POE(5)TE, B: POE(10)TE, C: POE(12)TE, D: POE(18)TE, E: POE(21)TE, F: POE(30)TE, G: POE(50)TE, H: Tocopherol



(a)

(b)

3. H^1-NMR Spectra of α-Tocopherol and POE(10)TE in $CDCl_3$ solution

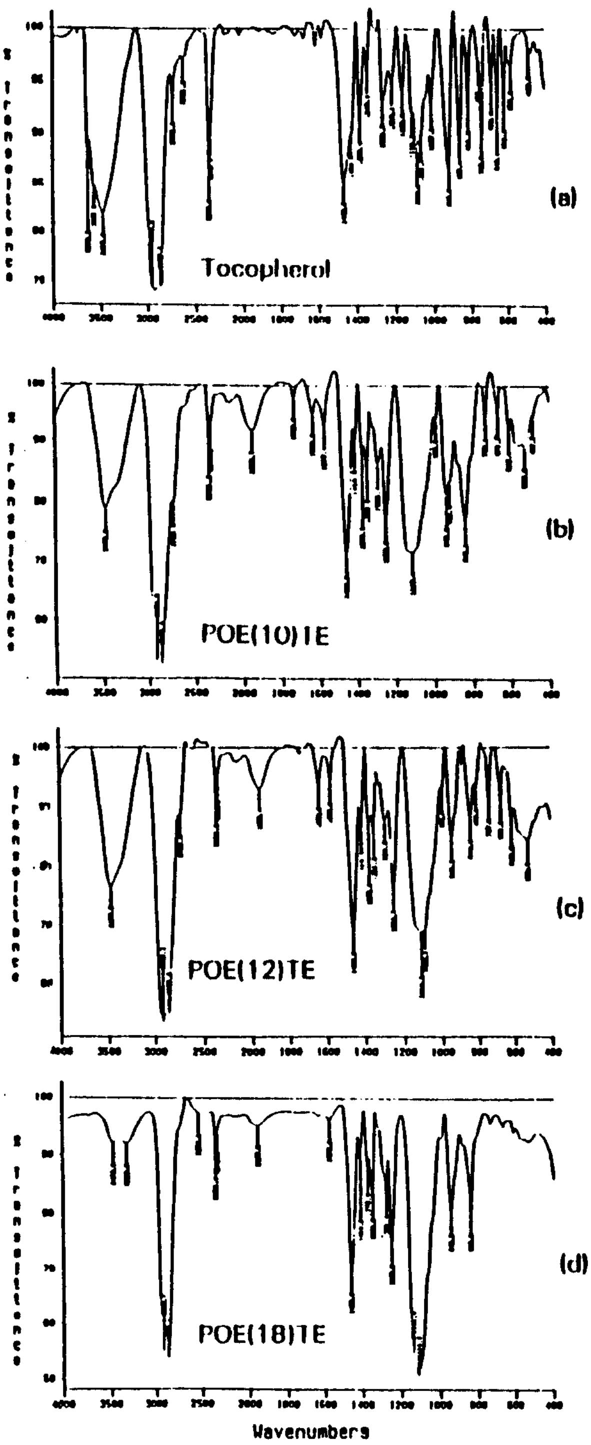


Fig 4. FT-IR spectra of POE(10)TE, POE(12)TE, POE(18)TE, and Tocopherol

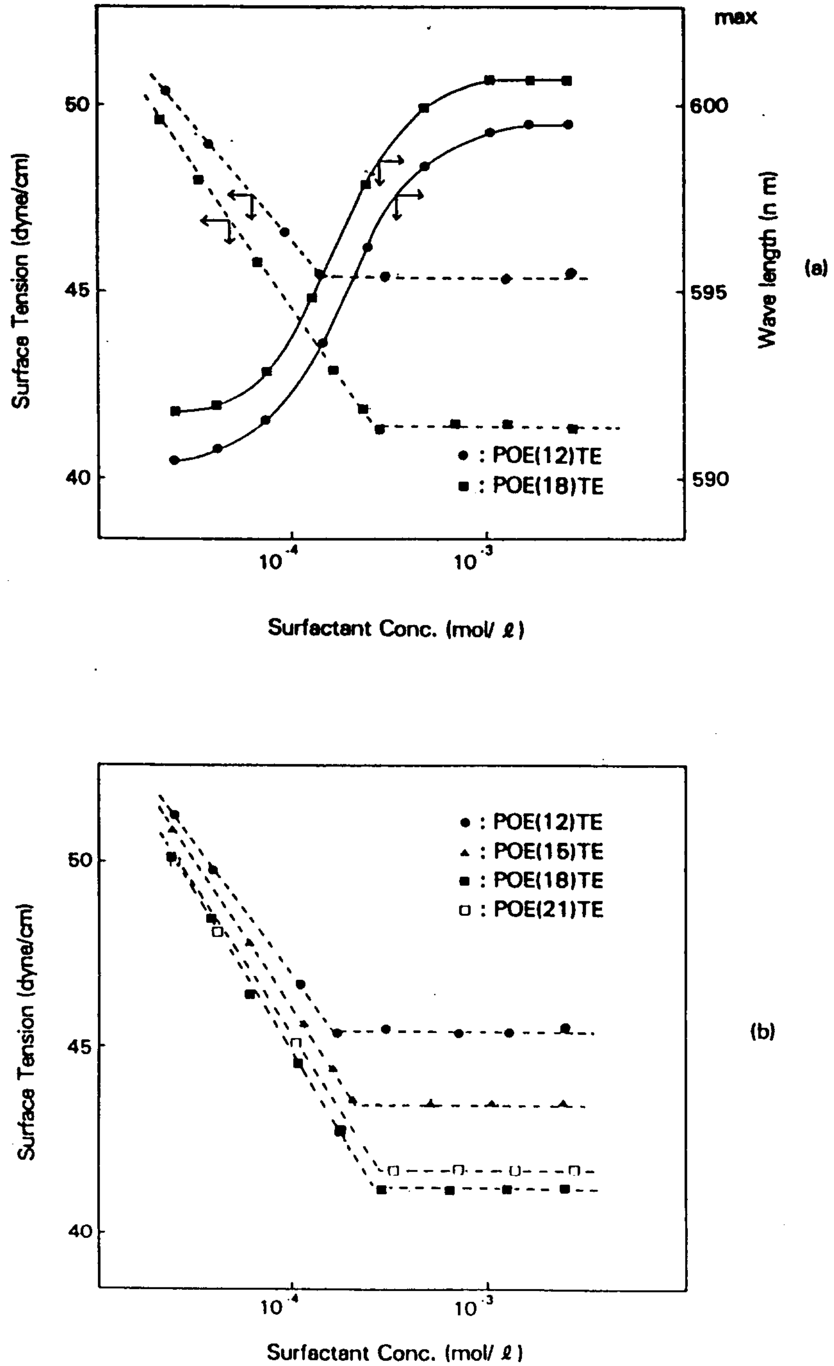


Fig 5. The CMC determination by Surface Tension Method and Dye Absorption Spectral Measurement.

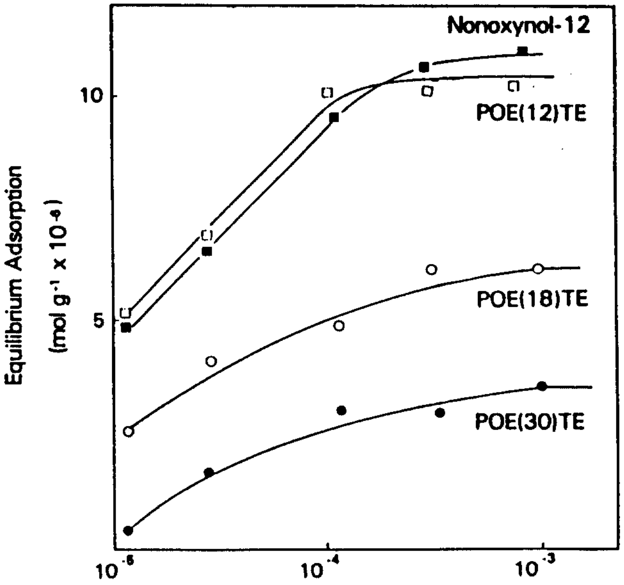


Fig 6. Equilibrium Concentration (mol/ℓ)
Adsorption Isotherms of POE(n)TEs

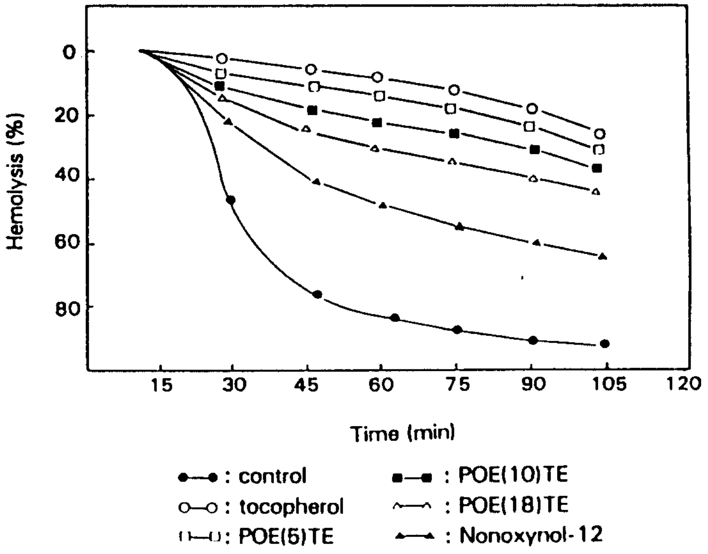


Fig 7. Effect of POE(n)TEs on the Rose-Bengal sensitized
Photohemolysis of Rabbit Erythrocytes.
(Conc. 1.3 x 10^{-4} W/V %)

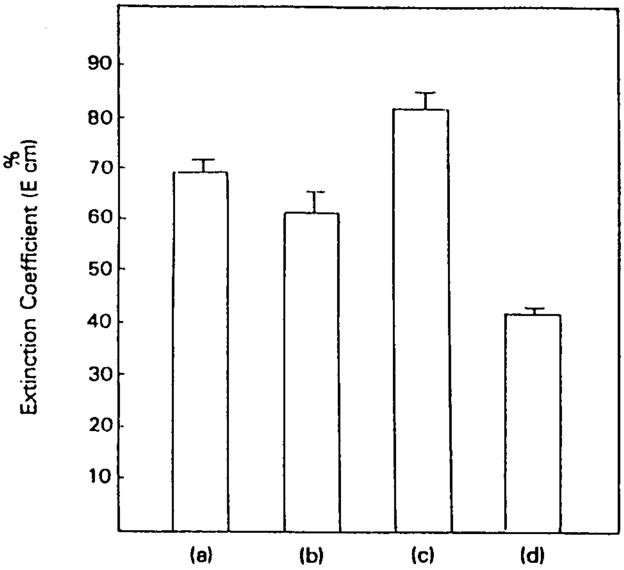


Fig 8. E%cm (extinction) Values of Tocopherol, POE(10)TE, Homosalate in 95% ethanol, and Ascorbic acid in 50% ethanol. [Tocopherol: (a), POE(10)TE: (b), Homosalate: (c), Ascorbic acid: (d)]

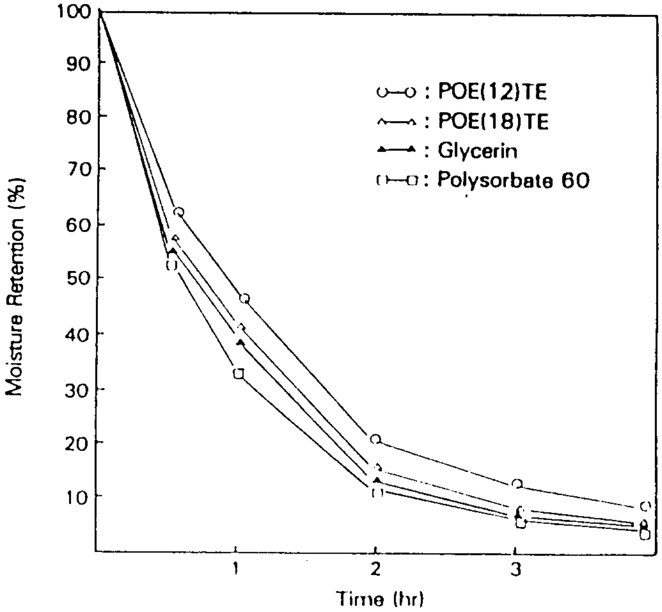


Fig 9. Moisture Retention Ability

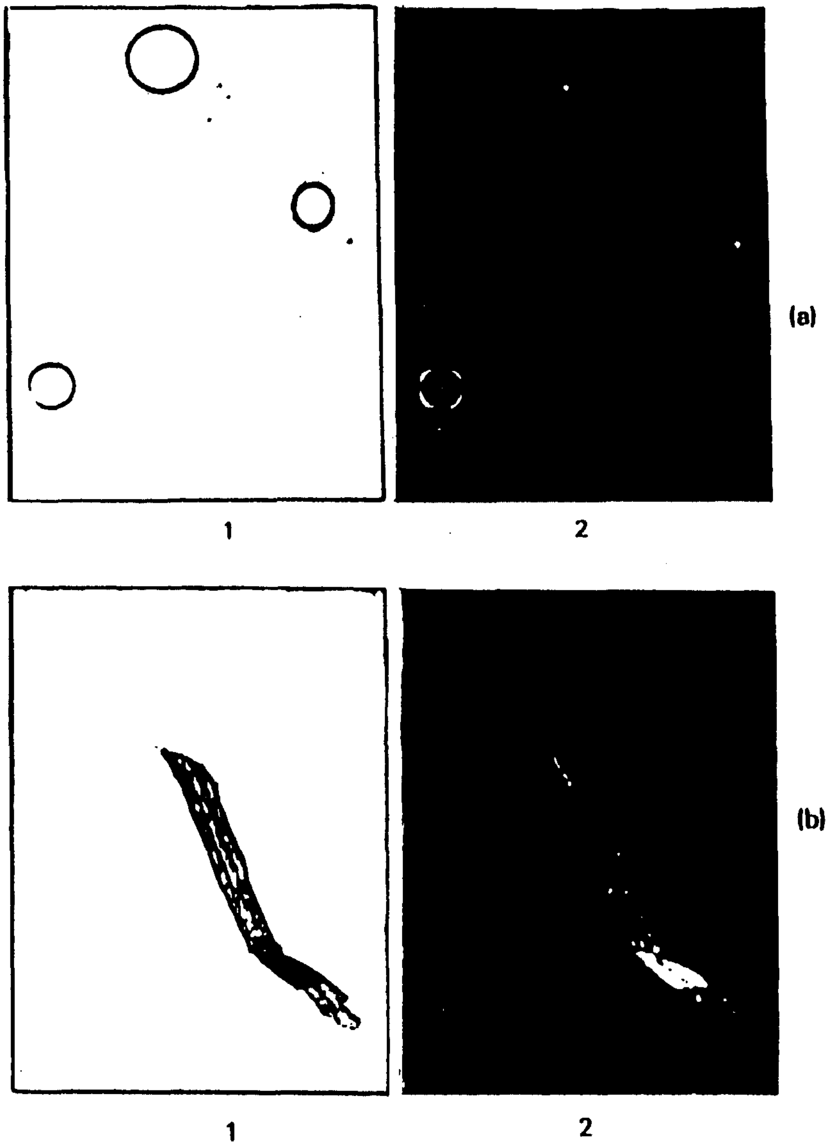


Fig 10. Photomicrographs of O/W Emulsion in Table 2 (formula 3 with POE(10)TE) and Gel in Table 6 (formula 3 with POE(50)TE) (X200)
(a) O/W Emulsion (1: ordinary light, 2: polarized light)
(b) Gel (1: ordinary light, 2: polarized light)