Poly(ethylene oxide)/Poly(propylene oxide)/Poly(ethylene oxide) Triblock Copolymer as a Sustained-Release Carrier for Perfume Compounds

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ABSTRACT: The volatility behavior of perfume compounds in poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) copolymer was investigated by means of dynamic and static headspace analyses. Suppression of the volatility of perfume compounds by $EO_{105}PO_{27}EO_{105}$ copolymer was markedly greater than by polyethyleneglycol. This suppressive effect may be due to micelle and gel formation of $EO_{105}PO_{27}EO_{105}$ copolymer. $EO_{105}PO_{27}EO_{105}$ copolymer is expected to be useful as a novel sustained-release carrier that maintains constant release rates for the volatility of perfume compounds over a wide temperature range.

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KEY WORDS: $EO_{105}PO_{27}EO_{105}$ copolymer, headspace analysis, perfume compounds, solubilization, sustained-release carrier, volatility.

Perfume compounds are often added to industrial products, such as cosmetics, foods and medicines, and have desirable effects on our life and health. From a practical point of view, perfume compounds should be gradually released from these industrial products over a long time. Hence, many sustained-release carriers for perfume compounds, such as fixatives, microcapsules and cyclodextrins, have been developed (1).

Surfactants are also used as sustained-release carriers for perfume compounds. The functions of surfactants as sustained-release carriers have been reported by a few investigators (2,3) but are still not clearly understood. Recently, poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) (EO/PO/EO) triblock copolymers have received increasing attention because these surfactants have low toxicity compared with other nonionic surfactants and have the ability to form a clear solution in aqueous media (4,5). Previously, we reported the physicochemical properties of EO/PO/EO triblock copolymers in aqueous soluton (6–8). The findings suggested that these surfactants form micelles and gels in aqueous solution, and that the formation of micelles and gels is greatly influenced by concentration and temperature. Therefore, EO/PO/EO triblock copolymers may be useful as sustained-release carriers for perfume compounds.

In the present study, we examined the usefulness of a EO/PO/EO triblock copolymer as a sustained-release carrier for volatile perfume compounds.

EXPERIMENTAL PROCEDURES

Materials. Synthetic perfume compounds, 2-phenylethyl acetate (PA) and linalool (LL) from Tokyo Kasei Kogyo Co. Ltd. (Tokyo, Japan), and benzyl acetate (BA) from Wako Pure Chemical Industries Ltd. (Tokyo, Japan) were used without further purification. Table 1 shows the chemical structures, molecular weights, hydrophilic-lipophilic balance (HLB), and solubility in water (25°C) of the perfume compounds. The HLB values of perfume compounds were calculated by the method of Fujita (9). EO/PO/EO triblock copolymer (ADEKA® Pluronic F88) was manufactured and kindly donated by Asahidenka Kogyo K.K. (Tokyo, Japan), and purified by three precipitations from toluene/*n*-hexane (10). The physicochemical properties of EO/PO/EO copolymer are: general formula, $EO_{105}PO_{27}EO_{105}$ (^1H NMR); molecular weight, 10,800; m.p. (°C), 55; cloud point (°C), >100 (1% aq.); HLB, 28. Polyethyleneglycol 10,000 (PEG) was purchased from Merck-Schuchardt (Hohenbrunn, Germany) and was used as received. Other reagents were the purest grade of products supplied by Wako Pure Chemical Industries Ltd. (Tokyo, Japan). The water used in this study was water for injection JP (Japanese Pharmacopoeia) and was obtained from Otsuka Pharmacy Co. Ltd. (Tokyo, Japan).

Dynamic headspace analysis. To evaluate quantitatively the volatility of the perfume compounds from sample solutions at various temperatures, we assembled apparatus for collecting volatile perfume compounds, based on the dynamic headspace-gas sweep method (3,11), as shown in Figure 1. The 15 or 25% $EO_{105}PO_{27}EO_{105}$ aqueous solution (100 g), containing 5 mmol/kg of perfume compound, was loaded into the vessel (No. 8 in Fig. 1), which was stoppered by a silicon rubber cap, equipped with a thermocouple. Because the outer

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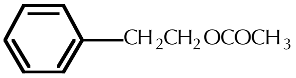
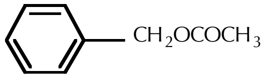
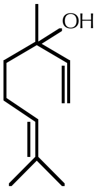
TABLE 1
Chemical Structure, Molecular Weight, HLB, and Solubility of Perfume Compounds

Perfume compounds	Chemical structure	Molecular weight	HLB	Solubility in water (mM)
Phenethyl acetate (PA)		164.20	3.75	7.7
Benzyl acetate (BA)		150.18	4.17	14.7
Linalool (LL)		154.25	5.20	10.2

jacket of this vessel was connected to a circulating thermostat-water bath, it was possible to evaluate the volatility of perfume compounds at various temperatures. The nitrogen gas, saturated with water, was passed through the surface of the sample solution in this vessel at a flow rate of 500 mL/min, and the eluted perfume compound from the sample solution was led into a cooling trap (–41°C).

The perfume compound collected in the cooling trap was diluted to 25 mL with acetone that contained 1-decanol for LL, or 1-dodecanol for PA, and BA as internal standards. This acetone solution was analyzed with a Shimadzu Co. (Tokyo, Japan) model GC-14B gas chromatograph, equipped with a flame-ionization detector. A 1 m × 3 mm i.d. glass column packed with PEG-20M was used. The injection and detection temperatures were kept at 250°C, and the column temperature was 130°C for LL, and 150°C for PA and BA. Nitrogen gas was used as carrier gas, and the flow rate of this gas was kept at 30 mL/min. The sample volume was adjusted to 5 µL, and then the sample was injected into the gas chromatograph. The area of each peak was measured by a Shimadzu Chromatopac C-R6A integrator.

Static headspace analysis. The solubilization equilibrium constant (K_s) of each perfume compound was determined by means of the static headspace analysis reported by Morgan *et al.* (12). $\mathrm{EO}_{105}\mathrm{PO}_{27}\mathrm{EO}_{105}$ aqueous solution (10 mL), containing a perfume compound of various concentrations, was placed into a sample vial (19.3 mL), sealed airtight with a silicon septum, and allowed to equilibrate in a water bath at 25°C before injection into the gas chromatograph. Approximately 500 µL of vapor of perfume compound above the solution was drawn out from the vial with the gas-tight syringe. The sample volume was adjusted to 400 µL, and then the sample was injected into the gas chromatograph. The column temperature was 105°C for LL, and 110°C for PA and BA. Other conditions of the gas chromatograph were similar to those described above.

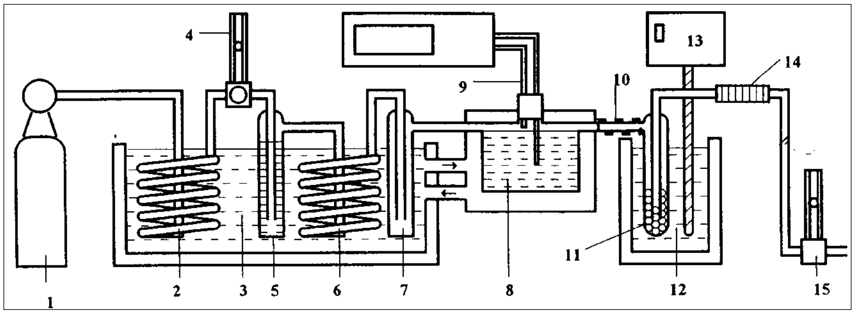


FIG. 1. Dynamic headspace apparatus for collecting perfume compounds from sample solution: 1, N_2 carrier gas (500 mL/min); 2, copper tube (10 m); 3, circulating thermostat; 4, flow meter with needle valve; 5, gas-washing bottle (water); 6, rubber tube (6 m); 7, trap; 8, sampler (silicon rubber cap); 9, thermocouple with voltmeter; 10, ribbon heater; 11, cooling trap (glass beads); 12, Dewar flask (ethanol: –41°C); 13, cooler; 14, drying tube ($CaCl_2$); 15, flow meter.

RESULTS AND DISCUSSION

We determined the perfume compound concentration in the solution at each sweep time from the material balance between the mass of perfume compound initially added in the sample solution and the mass of perfume compound volatilized. A linear relationship was observed between the logarithm of the perfume compound remaining in the solution and sweep time for all perfume compounds. This means that the volatilization rate of the perfume compound shows first-order dependence on the concentration of the perfume compound in the solution. We evaluated the volatility of each perfume compound from a rate constant of volatilization (*k*) determined from the slope of the straight line.

Figure 2 shows the effects of $EO_{105}PO_{27}EO_{105}$ concentration on the volatility of BA as a function of temperature. The volatility of BA in 25% $EO_{105}PO_{27}EO_{105}$ solution was less than that in 15% $EO_{105}PO_{27}EO_{105}$ solution. This shows that the volatility of BA can be controlled in spite of elevated temperatures by the selection of $EO_{105}PO_{27}EO_{105}$ concentration. For 15% $EO_{105}PO_{27}EO_{105}$ concentration, one breakpoint (↓ in Fig. 2) was observed in the volatilization curve of BA, while for 25% $EO_{105}PO_{27}EO_{105}$ concentration, two breakpoints (↑ in Fig. 2) appeared. EO/PO/EO copolymers form micelles and gels in aqueous solution at a certain concentration and temperature (6–8). The solution temperature at which micelles start forming is defined as a critical micellization temperature (CMT), whereas that at which gels start forming is defined as the critical gelation temperature (CGT). Previously, we investigated the CMT and CGT at various $EO_{105}PO_{27}EO_{105}$ concentrations by such physicochemical techniques as surface tension, differential scanning calorimetry (DSC), and viscosity methods (8). The CMT of 15% $EO_{105}PO_{27}EO_{105}$ was 32.8°C, while the CMT and CGT of 25% $EO_{105}PO_{27}EO_{105}$ were 21.6 and 41.1°C, respectively. The breakpoints in the volatilization curves are in close agreement with the CMT and CGT at each concentration of $EO_{105}PO_{27}EO_{105}$.

Figure 3 shows the *k* for three perfume compounds from 25% PEG and $EO_{105}PO_{27}EO_{105}$ aqueous solutions as a function of temperature. PEG is the component of the hydrophilic part of $EO_{105}PO_{27}EO_{105}$ micelle, and most perfume compounds are solubilized in the hydrophilic part of the micelles formed by nonionic surfactants (13). Also, PEG is widely used as a fixative to control the volatility of perfume compounds (1). In PEG aqueous solution, the volatility of any perfume compound increases greatly with temperature, while in $EO_{105}PO_{27}EO_{105}$ aqueous solution, it is approximately constant in spite of the temperature increase; that is, the volatility of perfume compounds was only slightly suppressed by PEG compared with $EO_{105}PO_{27}EO_{105}$. This is because self-association of PEG does not occur in aqueous solution with an increase in the temperature. On the other hand, $EO_{105}PO_{27}EO_{105}$ in aqueous solution forms micelles at a temperature above CMT and exhibits a dramatic change in viscosity at a higher temperature (CGT), revealing thermoreversible gelation. These conformational changes (monomer → micelle → gel) with an increase in temperature may contribute to the suppression of the volatility of perfume compounds.

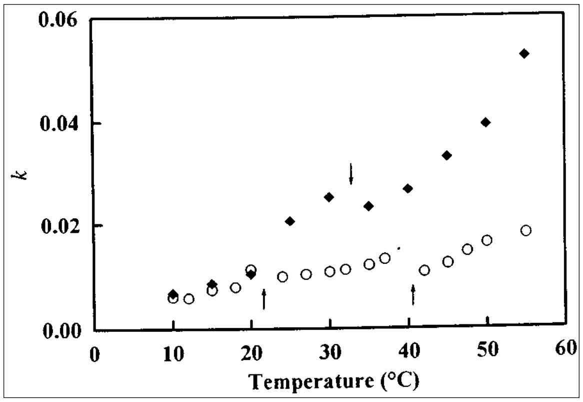


FIG. 2. Release profiles of benzyl acetate from $EO_{105}PO_{27}EO_{105}$ (ethylene oxide/propylene oxide/ethylene oxide) aqueous solutions as a function of temperature: ◆, 15% $EO_{105}PO_{27}EO_{105}$; ○, 25% $EO_{105}PO_{27}EO_{105}$; *k*, rate constant of volatilization.

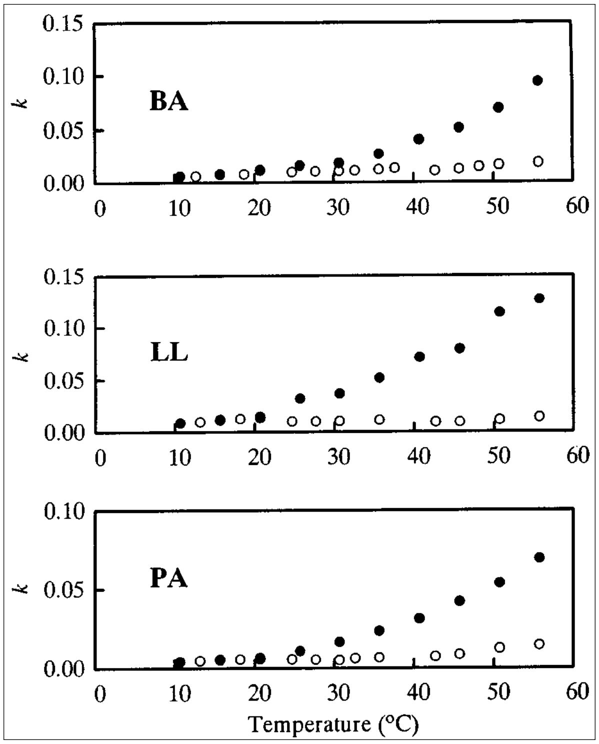


FIG. 3. Release profiles of perfume compounds from $EO_{105}PO_{27}EO_{105}$ and polyethyleneglycol (PEG) aqueous solutions as a function of temperature: ●, 25% PEG; ○, 25% $EO_{105}PO_{27}EO_{105}$; BA, benzyl acetate; LL, linalool; PA, 2-phenylethyl acetate. See Figure 2 for other abbreviations.

Furthermore, we examined the difference in volatility of the three perfume compounds. Here, we evaluated the volatility of each perfume compound by using the ratio of k in the $EO_{105}PO_{27}EO_{105}$ aqueous solution and k in the PEG aqueous solution ($k_{EO/PO/EO}/k_{PEG}$). In this manner, the difference in vapor pressure of each perfume compound is canceled.

Figure 4 shows the relationship between $k_{EO/PO/EO}/k_{PEG}$ of each perfume compound and temperature. At a low temperature (in the monomer region), there is no difference between $k_{EO/PO/EO}$ and k_{PEG} (i.e., $k_{EO/PO/EO}/k_{PEG} \approx 1$) because $EO_{105}PO_{27}EO_{105}$ does not form micelles in aqueous solution. However, the $k_{EO/PO/EO}/k_{PEG}$ in the micelle region decreased with an increase in temperature. This is thought to be due to the marked change in micellar structure with increased temperature (8). On the other hand, the $k_{EO/PO/EO}/k_{PEG}$ in the gel region was not altered by the increase in temperature. This may be because there is no significant change in the gel structure with increased temperature. Besides, it is obvious that the volatility of perfume compounds in the micelle and gel regions is controlled in the order of LL > PA > BA, thus a difference in volatility among the three perfume compounds was recognized in the micelle and gel regions.

When a perfume compound solubilized into the micelle volatilizes from the surfactant solution, it appears to volatilize *via* micelle phase → bulk phase → vapor phase (2). The volatilization rate of perfume compounds from the bulk phase to the vapor phase is proportional to its vapor pressure; the vapor pressure of a perfume compound is also proportional to its concentration in the bulk phase (Henry's law); therefore, the volatilization rate of perfume compound appears to be in proportion to the concentration of perfume compound in the bulk phase, and the perfume compound in the bulk phase is in equilibrium with the perfume compound in the micelle phase. Consequently, the volatilization rate of perfume compound solubilized in the surfactant solution depends on the distribution of the perfume compound between the bulk and the micelle phases. The static headspace analysis method has been used for studying the solubilization of organic compounds by surfactant micelles (12,14,15); therefore, the K_s of the perfume compounds between the bulk and the micelle phases was calculated by this method.

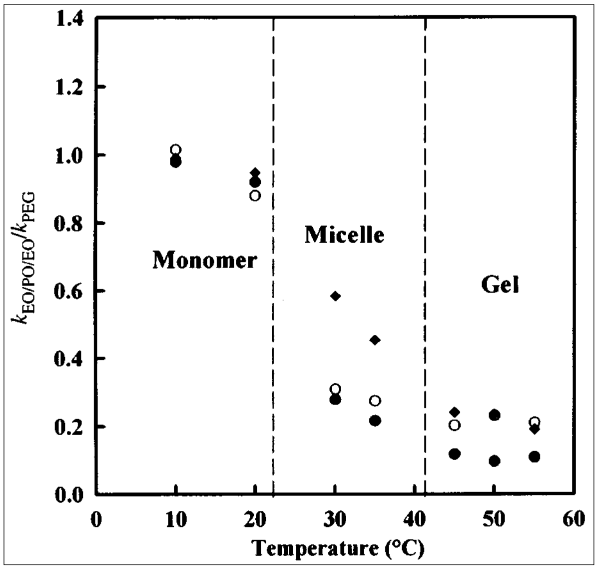


FIG. 4. Release profiles of perfume compounds as a function of temperature: ●, LL; ○, PA; ◆, BA. See Figures 2 and 3 for abbreviations.

First, we determined the concentration of perfume compound in the vapor phase ($C_{p,vap}$) by gas chromatography, and we determined the concentration of perfume compound in solution ($C_{p,sol}$) from the material balance between the concentration of perfume compound initially added in the solution ($C_{p,tot}$) and the concentration of perfume compound in the vapor phase.

The concentration of perfume compound in the micelle phase ($C_{p,mic}$) is represented by the difference between the $C_{p,sol}$ and the concentration of perfume compound in the bulk phase ($C_{p,bulk}$) by the following equation:

$$C_{p,mic} = C_{p,sol} - C_{p,bulk} \qquad [1]$$

A first-order equation was fitted to the data (perfume activity vs. perfume concentration in water), and this function was used to calculate the $C_{p,bulk}$ from a measured perfume activity in the sample solution. Furthermore, the mole fraction of perfume compound in the micelle (X_p) is represented by the following equation:

$$X_p = C_{p,mic}/[C_{p,mic} + (C_{surf,tot} - C_{surf,CMC})] \qquad [2]$$

where $C_{surf,tot}$ is the total concentration of surfactant, $C_{surf,CMC}$ is the monomer concentration of surfactant; thus ($C_{surf,tot} - C_{surf,CMC}$) means the micellar concentration of surfactant.

K_s of perfume compound in aqueous micellar solution is defined as follows:

$$K_s = X_p/C_{p,bulk} \qquad [3]$$

Figure 5 shows the relationship between the square root of the derived K_s values ($K_s^{1/2}$) and the mole fraction of perfume compound in the $EO_{105}PO_{27}EO_{105}$ micelle. As shown in Figure 5, $K_s^{1/2}$ decreased monotonously with the increase of X_p for all perfume compounds. The decrease in $K_s^{1/2}$ with increasing X_p is similarly observed for solubilization isotherms of perfume compounds by other surfactants (16). The reason for this may be that the perfume compounds compete for adsorption sites in the vicinity of the hydrophilic parts of micelles, so that the addition of more and more of the perfume compound leads to monotonically decreasing values of $K_s^{1/2}$ as X_p increases (17). Also, the values of $K_s^{1/2}$ were always LL > PA > BA in the region of all X_p. This means that perfume with a larger $K_s^{1/2}$ value is solubilized more readily into the $EO_{105}PO_{27}EO_{105}$ micelle. This tendency is in agreement with the order of $k_{EO/PO/EO}/k_{PEG}$ in the micelle and gel regions. Consequently, the volatility of perfume compounds from the $EO_{105}PO_{27}EO_{105}$ micellar solution appears to be governed mainly by the solubilization equilibrium constant. The

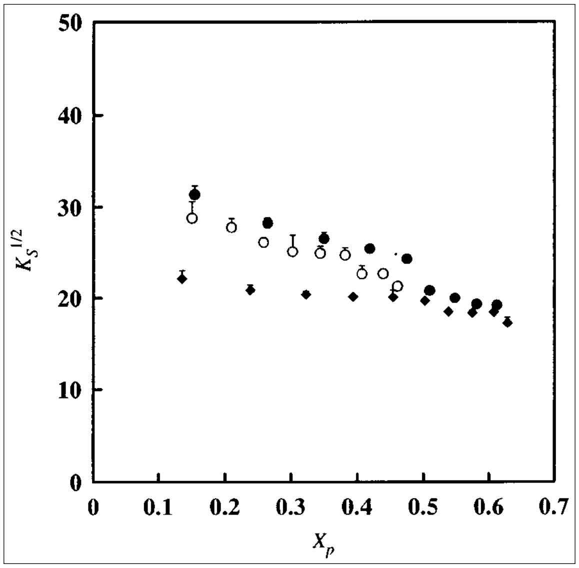


FIG. 5. Dependence of solubilization equilibrium constants for perfume compounds in $EO_{105}PO_{27}EO_{105}$ micelles on intramicellar mole fraction of perfume compounds: ●, LL; ○, PA; ◆, BA. Each point represents the mean ±SD of three experiments; K_s, solubilization equilibrium constant; X_p, mole fraction of perfume compound in the micelle. See Figures 2 and 3 for other abbreviations.

volatilization mechanism of the perfume compounds from the gel cannot be explained at the present time because the solubilization of perfume compounds in the gel is complicated. However, Mortensen *et al.* (18) reported that the formation of gel by EO/PO/EO copolymers is associated with the close packing of the micelles with weak interparticle interactions and is constructed from a cubic array of micellar subunits. Therefore, the volatilization mechanism of perfume compounds from the $EO_{105}PO_{27}EO_{105}$ gel may be similar to that from the micelle.

From the results of this study, we have concluded that $EO_{105}PO_{27}EO_{105}$ copolymer has a significant function as a sustained-release carrier for the volatility of perfume compounds.

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