Drug Development and Industrial Pharmacy, 24(4), 385–388 (1998)

COMMUNICATION

Effects of Inorganic Salts on Solubilization of Estriol in an Aqueous Solution of Poly(ethylene oxide)/Poly(propylene oxide)/Poly(ethylene oxide) Triblock Copolymer

Yoshihiro Saito* and Takatoshi Sato

College of Pharmacy, Nihon University, 7-7-1, Narashinodai, Funabashi-shi, Chiba, 274, Japan

ABSTRACT

The effects of inorganic salts on the solubilization of estriol was studied in an aqueous solution of a poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide) triblock copolymer (Pluronic L-64). The solubility of estriol increased with increasing Pluronic L-64 and salt concentrations. Furthermore, two clear transition points corresponding to the polymolecular micelle formation and a pronounced change in micellar structure of Pluronic L-64 were found on the solubility curves. The effectiveness of inorganic salts for increasing solubility of estriol followed approximately the lyotropic or Hofmeister series, except Li^+.

INTRODUCTION

Poloxamers, i.e., triblock copolymers of the type poly(ethylene oxide)/poly(propylene oxide)/poly(ethylene oxide), available commercially under the trade name Pluronics, have been widely used as nonionic surfactants in pharmaceutical and cosmetic industries, since these copolymers have low toxicity and have the ability to form a clear solution in aqueous media (1,2). Recently, these copolymer micelles in aqueous solutions have attracted great attention, because they show interesting micellization and gelation behaviors (3–6). We have also reported the micellization and gelation of these copolymers in recent publications (7–10). The findings have suggested that the micelle and gel formations of these copolymers are greatly influenced by their concentration and temperature. Furthermore, we have reported that these copolymers have a significant function as a

---

*To whom correspondence should be addressed. Fax: +81-476-46-6581. e-mail: saitoyoshi@msn.com

sustained-release carrier for volatility of perfume compounds (11,12).

The solubilization behavior of drugs with surfactants in aqueous solutions is important in the pharmaceutical industry. However, there are few reports in the literature on solubility using these copolymers. As for the solubilization of drugs, only the solubility of indomethacin and diazepam by Lin et al. (13,14) and that of estriol (15) have been reported.

This study investigated the effects of inorganic salts on the solubilization mechanism of Pluronic L-64 (L-64) using estriol as a solubilizate.

EXPERIMENTAL PROCEDURES

Materials

L-64 was kindly donated by Asahidenka Kogyo K.K. (Tokyo, Japan) and was used as received. Some of the physicochemical characteristics of L-64 are summarized in Table 1. Estriol purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan) was of biochemical reagent grade and was used without further purification. The inorganic salts of the purest grade were obtained from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan). Distilled water per injection JP (Japanese Pharmacopoeia) was obtained from Otsuka Pharmacy Co., Ltd. (Tokyo, Japan).

Solubility Measurement

Excess quantities of the solid estriol were placed in 25-ml glass-stoppered test tubes together with 10-ml aliquots of sample solutions. The solutions were shaken for 24 hr at 30°C. This period was found to be sufficient for attaining equilibrium. After the equilibrium was established, sample solutions were filtered through Advantic GC-50 (0.45 μm) glass filter paper. Then, the samples were suitably diluted with methyl alcohol and assayed spectrophotometrically at a wavelength of 280 nm.

Table 1

Physicochemical Properties of Pluronic L-64

General formula	$EO_{13}PO_{30}\ EO_{13}$
Molecular weight	2900
Contents of EO (%)	40
Cloud point (°C)[a]	58 (1% Aqueous solution)
CMC_I (%)[b]	2.0×10^{-3}
CMC_{II} (%)[b]	7.6

[a] Technical information by Asahidenka Kogyo K.K.

[b] CMC_I and CMC_{II} are taken from a previous paper (7).

RESULTS AND DISCUSSION

Figure 1 shows the effects of KCl and L-64 concentrations on the solubility of estriol in aqueous solution. The solubility of estriol increased with an increase in L-64 and KCl concentrations. Furthermore, two transition points were observed in the solubility curves and these transition points shifted remarkably to lower concentration with increasing KCl concentration. Previously, we found two clear discontinuities corresponding to critical micelle concentration (CMC_I) (at a low concentration) and CMC_{II} (at a high concentration) in the relationship between the surface tension and L-64 concentration (7). In addition, a monomolecular micelle was formed at CMC_I, while a polymolecular micelle appeared at CMC_{II}. Figure 2 shows the relationship between CMC_{II} obtained from fluorescence measurements using pyrene (16) and logarithm of the concentration where the two transition points appeared on the solubility curve as a function of KCl concentrations. The first transition point corresponded closely to CMC_{II} and a relationship was observed with polymolecular micelle formation. However, the second transition point was much higher than CMC_{II}, which was obtained from fluorescence measurement. In previous work, L-64 demonstrated a marked

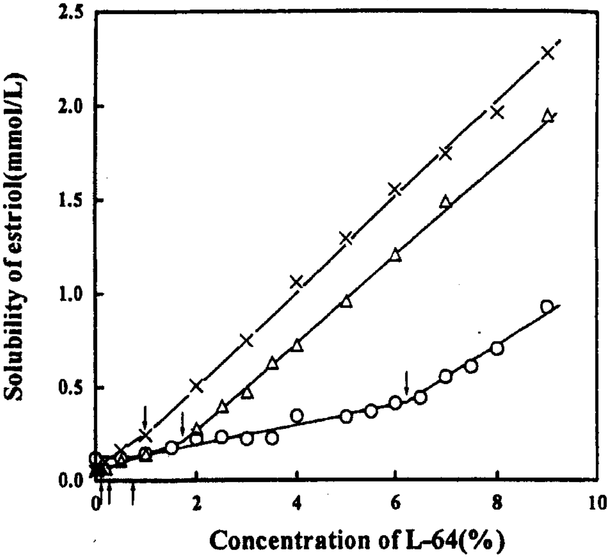

Figure 1. Solubility of estriol in aqueous solution of Pluronic L-64 containing KCl solution. Key: ○, without KCl; Δ, 0.5 mol/l KCl; ×, 1.0 mol/l KCl.

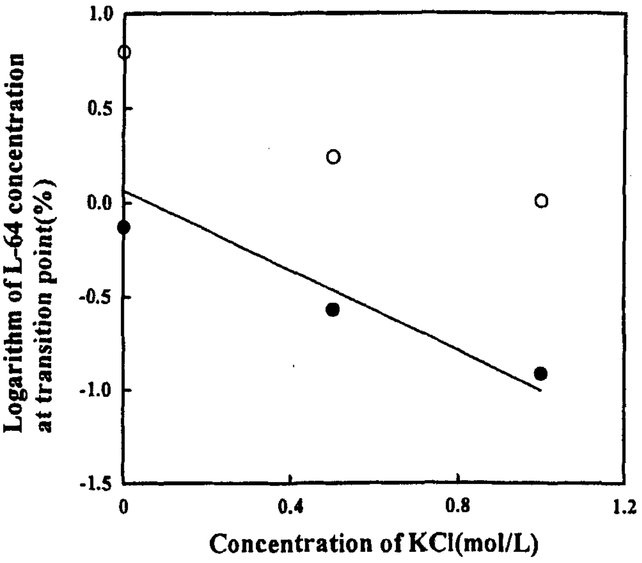

Figure 2. Relationship between Pluronic L-64 concentration at transition points and KCl concentrations. Key: —, CMC_{II} obtained from fluorescence measurement; ●, first transition point; ○, second transition point.

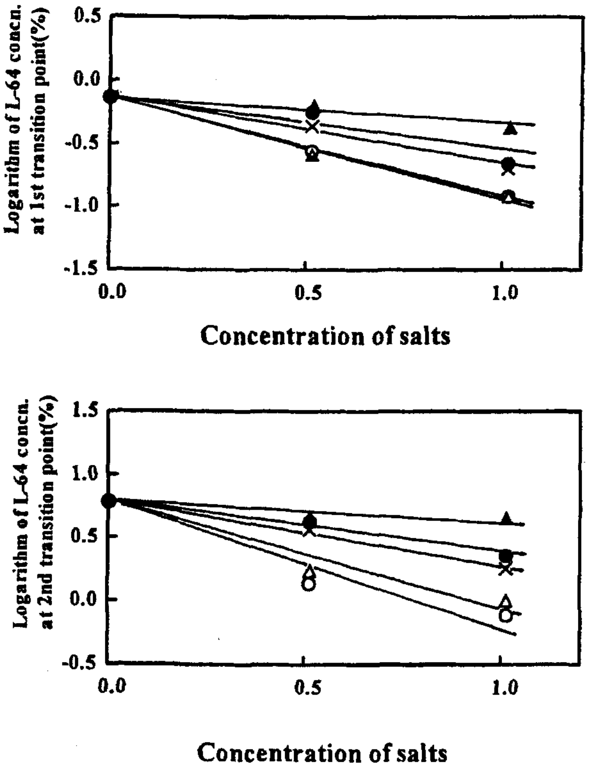

Figure 3. Effects of added salts on Pluronic L-64 concentration at first and second transition points. Key: ○, NaCl; Δ, KCl; ×, KBr; ●, LiCl; ▲, KI.

increase in micellar size and aggregation number at remarkably higher concentration than CMC_{II} (7). The appearance of the second transition point on the solubility curve may be related to a pronounced change in micellar structure since the concentration corresponding to the change in micellar structure is similar to the concentration at the second transition point.

Figure 3 shows the relationship between logarithm of the L-64 concentration at two transition points and the salt concentration. The plots formed an approximately straight line for all kinds of salts. The salt effect on the first transition point gave approximately the same order as that of the second transition point. The effectiveness of the inorganic salts in lowering these transition points follows the lyotropic or Hofmeister series of the anions for a given cation (K^+), namely $Cl^- > Br^- > I^-$. Conversely, for a given anion (Cl^-), the cation order observed was as follows: $Na^+ \geq K^+ > Li^+$. This order is also at variance with the lyotropic or Hofmeister series in which Li^+ precedes Na^+. However, the same salt orders are observed in lowering the CMC and cloud point of nonionic surfactants (17,18). This behavior may be related to the salting in of nonionic surfactants due to the complex formation between either linkages of oxyethylene chain and Li^+ (19). From these results, it may be concluded that the hydration factor plays an important role in bringing about changes in the first and second transition points. The hydration of the oxyethylene chains of polyoxyethylated nonionic surfactant is brought about through the formation of hydrogen bonds between the ether oxygen and water molecules. The addition of the inorganic salt shifts the equilibrium toward the dehydration side, with the result that the solubility of L-64, and consequently these transition points are lowered (20).

Micellar solubilization can be treated as a process in which the water-insoluble material is partitioned between an aqueous phase and a micellar phase. The apparent partition coefficient (K_M) associated with this process is expressed by Eq. (1).

$$K_M = [E_M]/[E_{NM}] \tag{1}$$

where $[E_M]$ is the concentration of estriol in the micelle and $[E_{NM}]$ is the concentration of estriol in the nonmicellar phase. The slope of the solubilization isomers expressed on a molar basis gives the values for $[E_M]$. The number of moles of estriol solubilized per mole of water gives the values for $[E_{NM}]$. Furthermore, the standard free energy change (ΔG_s^0), when one mole of estriol transfers from the solution to the micelle, is given:

$$\Delta G_s^0 = -R \cdot T \cdot \ln K_M \quad (2)$$

where R is the gas constant and T is the absolute temperature. K_M values and ΔG_s^0 values are given in Table 2. The K_M values increased with an increase in concentration of inorganic salts and became remarkably high after the second transition point. ΔG_s^0 values reflected the results of K_M, and were negative, indicating spontaneous solubilization. The rise in solubility of estriol after the second transition point may be the result of the formation of a larger micelle, capable of entrapping more estriol. Bahadur et al. reported that the effect of inorganic salts on the increase in micellar aggregation number of L-64 is the order KF > KCl > KBr following the lyotropic or Hofmeister series (21). The effectiveness of inorganic salts for increasing the K_M as shown in Table 2 follows the lyotropic or Hofmeister series, except Li^+. Consequently, it is thought that the growth of L-64 micelle by the addition of inorganic salts is responsible for the increase of the solubilizing ability.

Table 2

Apparent Partition Coefficient (K_M), and Free Energy Change (ΔG_s^0) for Estriol by Pluronic L-64 in Aqueous Salt Solutions at 30°C

Salt	K_M ($\times 10^{-3}$)	ΔG_s^0 ($kJ \cdot mol^{-1}$)
Without salt	6.02	-21.9
	(18.9)	(-24.8)
0.5 mol/l NaCl	49.5	-27.2
	(64.1)	(-27.9)
1.0 mol/l NaCl	53.1	-27.4
	(70.2)	(-28.1)
0.5 mol/l KCl	29.0	-25.9
	(55.2)	(-27.5)
1.0 mol/l KCl	53.9	-27.4
	(67.3)	(-28.0)
0.5 mol/l LiCl	20.7	-25.0
	(33.7)	(-26.3)
1.0 mol/l LiCl	41.9	-26.8
	(56.1)	(-27.5)
0.5 mol/l KBr	24.1	-25.4
	(38.3)	(-26.6)
1.0 mol/l KBr	41.9	-26.8
	(56.2)	(-27.5)
0.5 mol/l KI	9.61	-23.1
	(27.1)	(-25.7)
1.0 mol/l KI	9.99	-23.2
	(29.7)	(-25.9)

The numbers in parentheses indicate the parameters of estriol after the second transition point.

REFERENCES

1. S. Miyazaki, C. Yokouchi, T. Nakamura, N. Hashiguchi, W. M. Hou, and M. Takada, Chem. Pharm. Bull., 34, 1801 (1986).
2. S. Miyazaki, Y. Ohkkawa, M. Takada, and D. Attwood, Chem. Pharm. Bull., 40, 2224 (1994).
3. Z. Zhou and B. Chu, Macromolecules, 20, 3089 (1987).
4. N. K. Reddy, P. J. Fordham, D. Attwood, and C. Booth, J. Chem. Soc., Faraday Trans., 86, 1569 (1990).
5. G. Wanka, H. Hoffmann, and W. Ulbricht, Colloid Polym. Sci., 268, 101 (1990).
6. K. Pandya, P. Bahadur, T. N. Nagar, and A. Bahadur, Colloids Surf. A, 70, 219 (1993).
7. Y. Saito, Y. Kondo, M. Abe, and T. Sato, Yakugaku Zashi, 114, 325 (1994).
8. K. Miura, Y. Saito, T. Horiuchi, Y. Kondo, M. Abe, and T. Sato, J. Soc. Cosmet. Chem. Japan, 29, 28 (1995).
9. Y. Saito and T. Sato, Hyomen, 33, 617 (1995).
10. K. Suzuki, Y. Saito, T. Horiuchi, Y. Tokuoka, M. Abe, and T. Sato, J. Soc. Cosmet. Chem. Japan, 30, 330 (1996).
11. Y. Saito, K. Miura, Y. Tokuoka, Y. Kondo, M. Abe, and T. Sato, J. Dispersion Sci. Technol., 17, 567 (1996).
12. K. Suzuki, Y. Saito, Y. Tokuoka, M. Abe, and T. Sato, J. Am. Oil Chem. Soc., 74, 55 (1997).
13. S. Y. Lin and Y. Kawashima, Pharm Acta Helv., 60, 339 (1985).
14. S. Y. Lin and J. C. Yang, Acta Pharm. Technol., 33, 222 (1987).
15. Y. Saito, Y. Kondo, M. Abe, and T. Sato, Chem. Pharm. Bull., 42, 1348 (1994).
16. Y. Saito and T. Sato, private communication.
17. A. Ray and G. Nemethy, J. Am. Chem. Soc., 93, 6787 (1971).
18. H. Schott, J. Colloid Interface Sci., 43, 150 (1973).
19. K. Deguchi and K. Meguro, J. Colloid Interface Sci., 50, 223 (1975).
20. W. U. Malik and S. M. Saleem, J. Am. Oil Chem. Soc., 45, 670 (1968).
21. P. Bahadur, K. Pandya, M. Almgren, P. Li, and P. Stilbs, Colloid Polym. Sci., 271, 657 (1993).