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Investigation of the release behavior of diethylhexyl phthalate from the polyvinyl-chloride tubing for intravenous administration

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Abstract

The release behavior of diethylhexyl phthalate (DEHP) from a polyvinyl-chloride (PVC) tube, which is part of an intravenous administration set, was investigated with the coexistence of polysorbate 80 (Tween 80) in various solutions such as physiological saline (PS), distilled water for injection (DWI) and glucose solution (TZ). The cumulative amount of DEHP released after 5 h was in the following order; PS, DWI > 50% TZ. From a comparison of the amount of released DEHP and the critical micelle concentration (CMC) of various solutions, the lower the CMC of the solution, the higher the amount of DEHP released from the PVC tubing. When the concentration of Tween 80 was kept constant at 1 mg/ml, the cumulative amount of DEHP released with a flow rate 90 ml/h was higher than that at 60 ml/h. These results suggest that the release of DEHP from the PVC tubing is closely correlated with the interaction of Tween 80 and DEHP such as the formation of micelles, the collision of micelles against the surface of the PVC tubing and the diffusion properties of DEHP and/or Tween 80 in the liquid medium.

Keywords: Diethylhexyl phthalate; PVC tube; Polysorbate 80; Critical micelle concentration; Release behavior; Micelle

1. Introduction

In the actual practice of medical treatment, infusion therapy is universally applicable as an

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important dosage form which can avoid the first-pass effect of medicine for the digestive tract and liver and can quickly provide an accurate dosage. Polyvinyl chloride (PVC) is the most widely used material in the intravenous administration set (IAS). In order to provide moderate pliability and desirable strength to PVC plastic tubing, diethylhexyl phthalate (DEHP) is used as a plasticizer. There are many reports concerning the release of DEHP from PVC tubing when certain type of fluids come in contact with PVC (Craig et al., 1997; Nuijen et al., 1999). Kawano et al. (1992, 1993) demonstrated that the coexistence of polyoxyethylene castor oil (CO 60) contained in the injection material as an emulsifier accelerated the release of DEHP from the IAS. Peters and Cook (1973) demonstrated that DEHP is teratogenic in rats. David et al. (1999) also demonstrated that DEHP promoted the proliferation and hepatomegaly associated with hepatocellular tumorigenesis. Though the influence of DEHP within the human body has not yet being made clear, the intake of DEHP in the human body through IAS should be avoided. DEHP has been designated as an environmental disrupting chemical by The Japanese Ministry of Health and Welfare (1998). However, there are few reports in the literature concerning the relationship between the release behavior of DEHP from IAS and the coexistence of additives for injections such as surfactants, salt and sugar (Stephen and Lawrence, 1993).

For this investigation, we selected polysorbate 80 (Tween 80) as a model surface-active agent. Tween 80 is also well-known as an amphiphilic surface-active agent as well as HCO 60, which is the commonly used emulsifier in the formulation of various pharmaceutical dosage forms increasing the solubility of water insoluble drugs (Martin, 1993).

The objective of this investigation was to determine the relationship between the release behavior of DEHP from the PVC tubing and the concentration of Tween 80 in various solutions such as distilled water for injection (DWI), physiological saline (PS) or various concentrations of glucose solutions (TZ).

2. Experimental section

2.1. Materials

Polysorbate 80 (Tween 80) was procured from Sigma (St Louis, MO). Diethylhexyl phthalate (DEHP) and di-*n*-pentyl phthalate were from Kanto Chemical Co., Inc. (Tokyo, Japan). Distilled water for injection (DWI), physiological saline (PS) and glucose solution (TZ) were of JP grade. The TERUFUSION® intravenous administration set (IAS, Terumo, TS-A256PK027, Tokyo, Japan) was used.

2.2. Evaluation methodology of dripped solution from the PVC tubing

The Tween 80 sample solution was prepared as follows: a definite weight of Tween 80 (0.05–1.0 g) was dissolved in PS, 50% TZ and DWI, respectively. One meter of polyvinyl chloride (PVC) tube was clipped from the IAS and attached to the infusion pump (TERUFUSION® infusion pump model: TE-112, Tokyo, Japan). The sample solution was collected at suitable intervals from the drops dripping at the rate of 60 or 90 ml/h.

2.3. Measurement of DEHP

The DEHP concentration in the sample solution was determined with high-performance liquid chromatography (HPLC). The HPLC conditions were as follows: column, Shodex® C18-5A (4.6 mm i.d. × 150 mm length, Showa Denko Co., Ltd., Tokyo, Japan); mobile phase, acetonitrile/methanol/distilled water = 60:100:25; elution rate, 1.5 ml/min; internal standard, di-*n*-pentyl phthalate; detector, UVIDEC 100-IV (225 nm, Japan Spectrophotometer, Inc., Tokyo, Japan).

2.4. Determination of DEHP content in the PVC tubing

One gram of PVC tubing was completely dissolved with tetrahydrofuran, and a 2-ml portion of the solution was diluted with 48 ml of methanol. After centrifuging (3500 rev./min for 10 min), the aliquot of the solution was removed and

the DEHP concentration was determined as described above.

2.5. Measurement of the surface tension of Tween 80 sample solutions

The surface tensions of Tween 80 sample solutions were determined with a Whilhelmy-type surface tensiometer (Kyowa Interface Science Co., Model CBVP-A3) using a platinum plate at 25 ± 0.1°C.

3. Results and discussion

3.1. Release behavior of DEHP from PVC tubing in various solutions

Fig. 1 illustrates the release behavior of DEHP from the PVC tubing in PS, 50% TZ and DWI. The cumulative amount of DEHP released increased linearly, suggesting that the release of DEHP from the PVC tubing follows a zero-order release. One meter of PVC tubing used in this study contains approximately 2.2 g of DEHP; even if the concentration of Tween 80 was 2.0 mg/ml, the cumulative amount of the DEHP released after 5 h as shown in Fig. 1b was only 864 μg which is equivalent to 0.04% of the total amount of DEHP contained in the PVC tubing used in this investigation. Therefore, it seemed likely that the physicochemical properties of the PVC tubing may not be influenced by the loss of DEHP throughout this investigation. In the light of the above observation, by allowing the sample solutions to flow through PVC tubing, it appeared to maintain an apparent sink condition at the surface of PVC tubing. This may account for the linear increase of the cumulative amount of the DEHP released.

Fig. 2 illustrates the effect of the concentration of Tween 80 against the cumulative amount of DEHP released from the PVC tubing after 5 h. In the cases of both PS and 50% TZ, the amount of DEHP released increased as the concentration of Tween 80 increased. When the concentration of Tween 80 was 2 mg/ml, the cumulative amount of DEHP released into the DWI was 841 μg which is approximately equal to the amount found in PS. The overall results indicated that the cumulative amount of DEHP released in 50% TZ was lower than the amount in PS and/or DWI. On the other hand, when the release behavior of DEHP from the PVC tubing into PS and/or DWI without

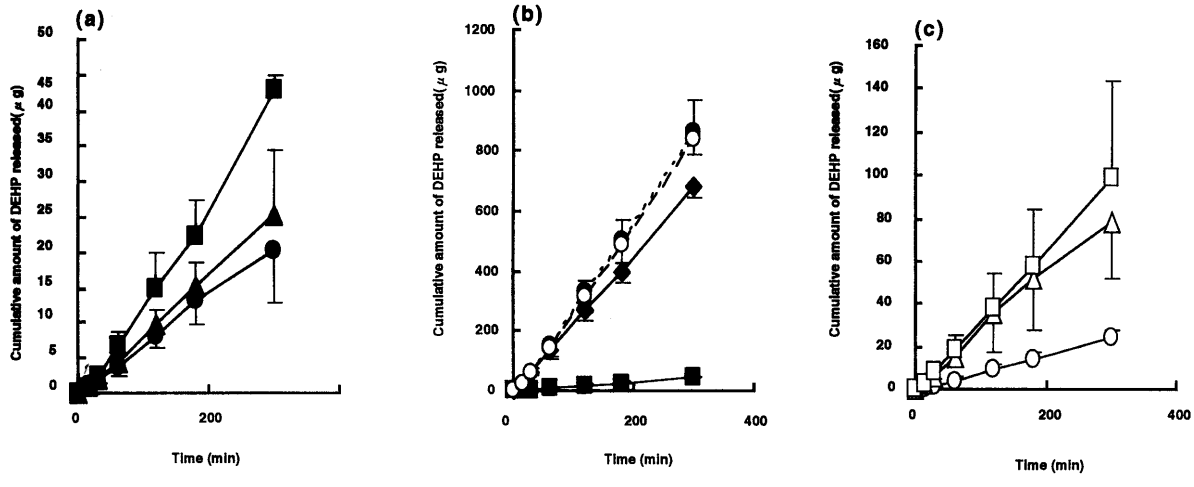

Fig. 1. Release profile of DEHP from PVC tubing. (a) The concentrations of Tween 80 in PS were ●, 0.01 mg/ml; ▲, 0.02 mg/ml; ■, 0.03 mg/ml. (b) The concentrations of Tween 80 in PS were ■, 0.03 mg/ml; ◆, 1.0 mg/ml; ●, 2.0 mg/ml; ○, 2.0 mg/ml of Tween 80 in DWI. (c) The concentrations of Tween 80 in 50% TZ were ○, 0.04 mg/ml; △, 0.4 mg/ml; □, 2.0 mg/ml; the data are expressed as mean ± S.D. ($n = 3$).

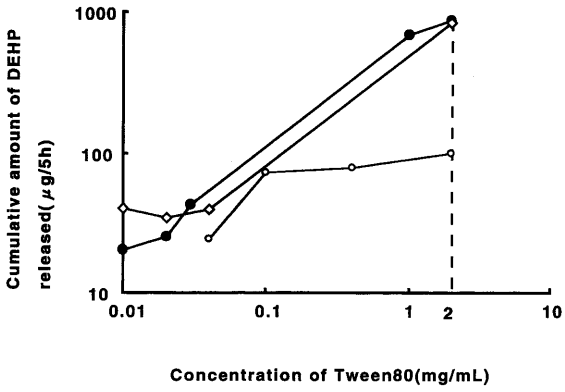

Fig. 2. Effect of Tween 80 on the release of DEHP from PVC tubing; ●, PS; ▲, DWI; ○, 50% TZ; the data are expressed as mean ± S.D. ($n = 3$).

adding Tween 80 was investigated by the GC-MS measurement, the detected concentration of DEHP were under its limiting concentration, i.e. 0.5 ng/ml (data not shown).

In order to investigate the release behavior of DEHP from the PVC tubing for a longer period, PS or 50% TZ containing 2 mg/ml of Tween 80 was circulated through PVC tubing for 30 days (Fig. 3). Even with the long-term circulation, dissolution equilibrium was not established in both

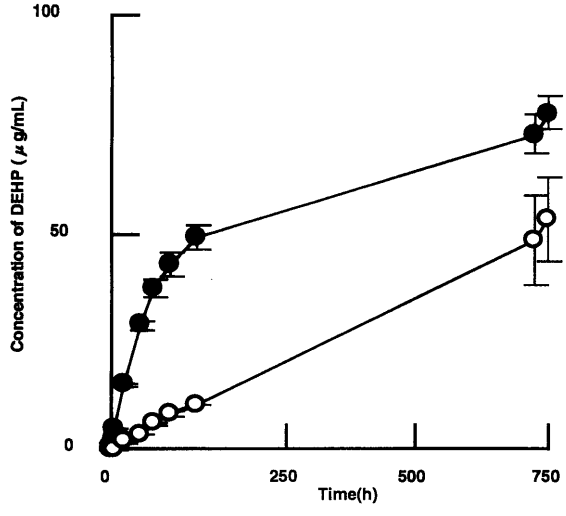

Fig. 3. Dissolution behavior of DEHP from PVC tubing into PS or 50% TZ; ●, PS; ○, 50% TZ, the concentration of Tween 80 was 2 mg/ml; the data are expressed as mean ± S.D. ($n = 3$).

PS and 50% TZ. In the case of PS, the concentration of DEHP increased significantly at the initial circulating period, while in the case of 50% TZ, this concentration increased linearly but was overall lower than that of PS. This is of interest in that in spite of the same concentration of Tween 80; the release profiles differ from each other with the variety of the solution.

3.2. Critical micelle concentration of Tween 80 in various solutions

Tween 80 is well-known as an amphiphilic surface-active agent. When present in a liquid medium at low concentrations, the amphiphiles exist separately and are of such a size as to be subcolloidal and to interact with hydrophobic surface or drugs. Therefore, it might increase the dissolution rate of water insoluble drugs. As the concentration is increased, Tween 80 forms micelles above the critical micelle concentration (CMC) acting as a solubilizer to increase the apparent solubility of drugs. This investigation also attempted to determine the CMC of Tween 80 in PS, DWI and TZ by using the surface tensiometer because the relationship between the release behavior of DEHP and CMC of Tween 80 in various liquid medium seemed to be indispensable. The measurement of surface tension permits the investigation of the interaction between amphiphilic substances and may provide information on the formation of the micelle (Saito and Sato, 1992). Fig. 4 illustrates the relationship between the surface tension and the concentration of Tween 80 varied in liquid medium solutions. CMC values were determined as an inflection point of each curve as shown in Table 1. It is known that adding electrolytes lowers the CMC of amphiphilic surface-active agents and also the existence of sodium chloride seems to lower the CMC compared with that of DWI (Martin, 1993). Furthermore, as compared with PS, the CMC values of 30 and 50% TZ are assumed to be about 3.5 and 10 times that of PS, respectively. This seems to be attributed to the change of the structure of water related to the hydration of glucose and/or the molecular interaction between the water molecules and the glucose molecules and

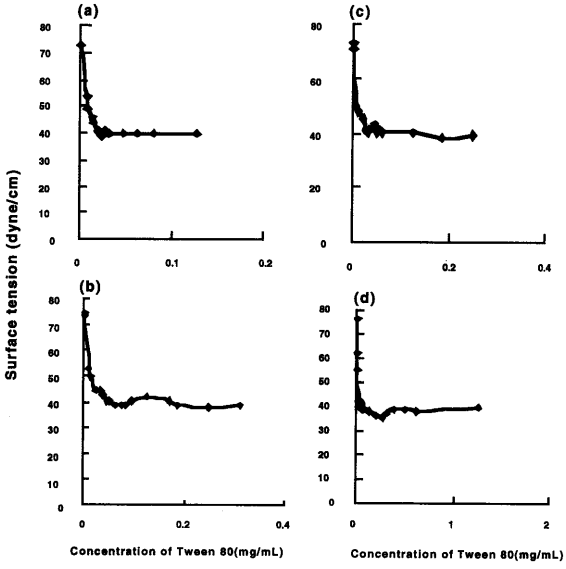

Fig. 4. Surface tension of Tween 80 in various solutions. (a) PS; (b) DWI; (c) 30% TZ; (d) 50% TZ. The data are expressed as mean ± S.D. ($n = 3$).

Tween 80 molecules. In other words, the fraction of the non-dissociated water is considered to increase by the hydration between glucose molecules and the water molecules. The concentration of Tween 80 in non-dissociated water was apparently lowered in TZ solutions; it can therefore be presumed that the CMC in TZ solution increased with an increase in TZ concentration. Therefore, the difference in the release behavior of DEHP as shown in Fig. 3 seems to be due to the difference in the mode of micelle formation between PS and 50% TZ.

Table 1
Critical micelle concentration of various solutions

Solution	CMC (mg/ml)
PS	0.024
DWI	0.031
30% TZ	0.074
50% TZ	0.247

3.3. The relationship between the release of DEHP from PVC tubing and the formation of micelles of Tween 80

Fig. 5a shows the relationship between the cumulative amount of DEHP released and the concentration of Tween 80 added in PS or 50% TZ. In both PS and 50% TZ, the release of DEHP accelerated below the CMC. In order to clarify the effect of the CMC on the release behavior of DEHP, we attempted to rewrite the x-axis of Fig. 4 into the relative concentration of Tween 80 to the CMC in each solution. Fig. 5b depicts the relationship between the cumulative amount of DEHP released and the relative concentration of Tween 80 in each solution. In the case of PS, though the slope of the cumulative amount of released DEHP was small below the CMC, a pronounced increase was observed at above the concentration of CMC. Whereas in the case of 50% TZ as opposed to the case of PS, a marked change was scarcely observed above the CMC, the slope of the cumulative amount of the DEHP released significantly increased below the CMC. In both cases of PS and 50% TZ studied in this investigation, the acceleration of the release of DEHP was observed below the CMC. This suggests that the release of DEHP is caused by the wetting or detergency effect of Tween 80 and/or a molecular interaction between DEHP and Tween 80. Whereas in the case of PS, the formation of micelle and the solubilization of DEHP into the micelle is assumed to contribute to the increase of the cumulative amount of DEHP released above the CMC.

Fig. 6 illustrates the cumulative amount of DEHP released from PVC tubing up to 5 h at the various flow rates and concentrations of Tween 80 above the CMC in PS. At the flow rate of 90 ml/h, the cumulative amount of DEHP released increased with an increase in the added concentration of Tween 80. On the other hand, when the concentration of Tween 80 was kept constant at 1 mg/ml, the cumulative amount of DEHP released with a flow rate 90 ml/h was higher than that at 60 ml/h. In the case of PS, these results indicate that the concentration of Tween 80 flowing through the PVC tubing seems to be not as sig-

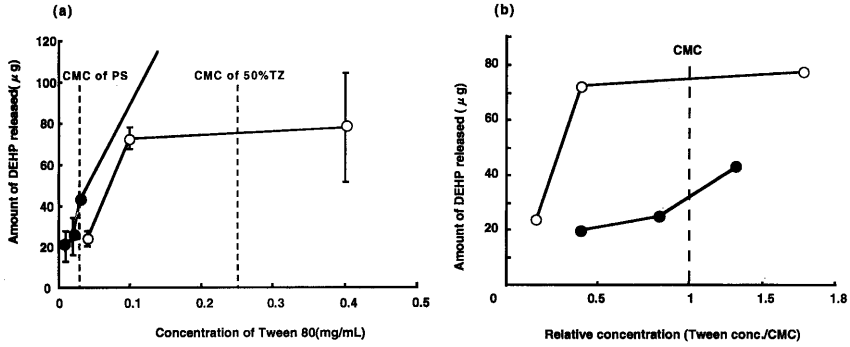

Fig. 5. Release behavior of DEHP from PVC tubing into PS or 50% TZ below or above their CMCs. (a) Effect of Tween 80 on the release of DEHP from PVC tubing; (b) Relationship between relative concentration of Tween 80 and amount of DEHP released. ●, PS; ○, 50% TZ; dotted lines show the CMC of each solution; the data are expressed as mean ± S.D. ($n = 3$).

nificant as the amount of Tween 80 passed through the PVC tubing, and the amount of DEHP released might be determined by the amount of micelles which entrap the DEHP into the inner phase. Therefore, we measured the release behavior of DEHP when the amount of Tween 80 passed through PVC tubing was constant. Fig. 7 illustrates the release behavior of DEHP released from the PVC tubing under several conditions. The total amount of Tween 80 passed through the PVC tubing was kept constant at 180 mg in the first three columns from the left side of Fig. 7 and 450 mg in the last two columns. In both cases, irrespective of the fact that the total amount of Tween 80 passed through the PVC tubing being kept constant, the cumulative amount of DEHP released at a flow rate of 90 ml/h was higher than that at 60 ml/h. This phenomenon suggests that other factors relative to the flow rate such as the collision of the micelles against the surface of the PVC tubing, diffusion properties of DEHP and/or Tween 80 in the liquid medium seemed to affect the release behavior of DEHP.

4. Conclusion

The release behavior of DEHP from PVC tubing was affected by the presence of Tween 80. The amount of DEHP released increased with the increase of Tween 80. Furthermore, various solutions also affected the release behavior of DEHP and the CMC within these solutions. At a concentration level of Tween 80 below the CMC, the release of DEHP from the PVC tubing seemed to be caused by the wetting or detergency effect of Tween 80 and/or the molecular interaction between DEHP and the Tween 80. Whereas at a concentration level of Tween 80 above the CMC in PS, the formation of micelles appeared to promote the release of DEHP from the PVC tubing. Furthermore, the collision of micelles against the surface of the PVC tubing and the diffusion properties of DEHP and/or Tween 80 in the liquid medium seemed to affect the release behavior of

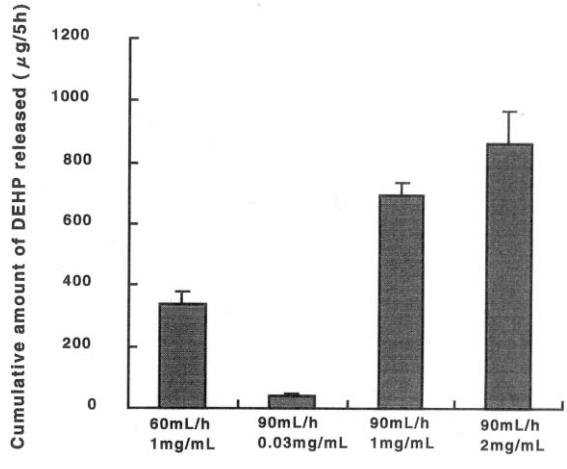

Fig. 6. Cumulative amount of DEHP released from PVC tubing at various flow rates and concentrations of Tween 80; the data are expressed as mean ± S.D. ($n = 3$).

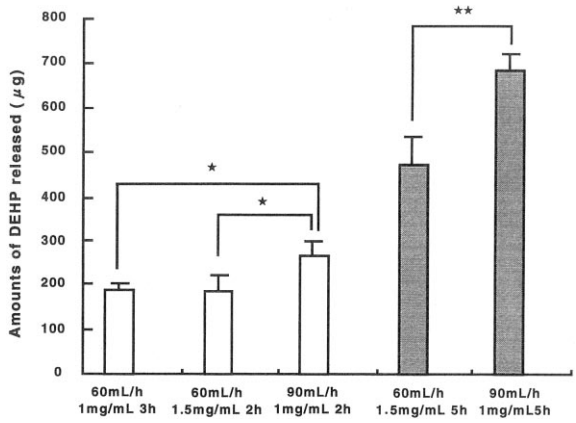

Fig. 7. Release of DEHP from PVC tubing in several conditions. The total amounts of Tween 80 passed through PVC tubing were 180 mg (no pattern) or 450 mg (dotted pattern). The data are expressed as mean ± S.D. ($n = 3$); $^{\star}P < 0.05$; $^{\star\star}P < 0.01$.

DEHP. The release behavior of DEHP from the PVC tubing might be explained by taking the diffusion out of the drug from the surface of the device composed of the polymer matrix for instance. We believe further detailed investigation of the release behavior of DEHP under various CMC values and flow rates of the solubilizer in various solutions will reveal ways to minimize the release of DEHP.

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