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Investigation of the release behavior of diethylhexyl phthalate from polyvinyl chloride tubing for intravenous administration based on HCO60

Takehisa Hanawa [a,*], Naoko Endoh [a], Fumi Kazuno [a], Masahiko Suzuki [a], Daisuke Kobayashi [b], Mutsuko Tanaka [c], Kenji Kawano [c], Yasunori Morimoto [b], Shin'ichiro Nakajima [d], Toshio Oguchi [a]

[a] *Department of Pharmacy, Faculty of Medicine, University Hospital, University of Yamanashi, 1110 Shimokato, Tamaho, Yamanashi 409-3898, Japan*
[b] *Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0248, Japan*
[c] *Faculty of Pharmaceutical Sciences, Niigata College of Pharmacy, 5-13-2 Kamishinei, Niigata 950-2081, Japan*
[d] *Clinical Trial Guidance Department, Organization for Pharmaceutical Safety and Research, 3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan*

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Abstract

The release behavior of diethylhexyl phthalate (DEHP) from polyvinyl chloride (PVC) tubing, which composes materials in an intravenous administration set (IAS), was investigated using polyoxyethylated hydrogenated castor oil (HCO60) in physiological saline (PS), distilled water for injection (DWI), and ribose, fructose, and glucose (TZ) solutions. The amount of DEHP released increased with increasing HCO60 concentration, and the cumulative amount of DEHP released after 4 h increased in the following order: 50% TZ < DWI = PS. At HCO60 levels above and below critical micelle concentration, no significant increase in the amount of DEHP released was observed; the release of DEHP appeared due to molecular interactions between DEHP and HCO60 molecules rather than the solubilization of DEHP into micelles. The release behavior of DEHP was affected by the addition of sugars. The amount of DEHP released decreased with an increase in the mean numbers of equatorial OH groups *n*(e-OH) per molecule in the following order: glucose [*n*(e-OH); 4.6] < fructose (3.0) < ribose (2.1). Molecular mobility of HCO60 was assumed to be restricted by interaction with the sugar molecule and/or the extent of microscopic viscosity. Interaction of HCO60 with the sugar, the difference in the mode, and/or the extent of molecular interaction between sugar and HCO60 appeared to induce the difference in release behavior, while the increase in the number of water molecules needed to hydrate sugar molecules seemed to decrease the amount of free water, thus allowing microscopic viscosity to increase and to restrict the mobility of HCO60. These results suggest that the release of DEHP from PVC tubing is closely associated with the interaction of DEHP with HCO60, and related to the molecular mobility of HCO60 in solution.

Keywords: Diethylhexyl phthalate; PVC tubing; HCO60; Release behavior; Sugars; Number of equatorial OH groups

* Corresponding author. Tel.: +81-55-273-9810; fax: +81-55-273-6672.
E-mail address: t-hanawa@yamanashi.ac.jp (T. Hanawa).

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1. Introduction

In the actual practice of medical treatment, infusion therapy is widely used to deliver an accurate dosage and avoid first-pass effects of medication in the digestive tract and liver. Polyvinyl chloride (PVC) is the most widely used material in intravenous administration set (IAS). PVC products obtain their pliability and strength through the addition of diethylhexyl phthalate (DEHP) as a plasticizer. Previously, we reported that isosorbide dinitrate and/or cinnamic acid adsorb into IAS (Nakajima et al., 1985; Nakazawa et al., 1988). Furthermore, water-insoluble drugs, such as miconazole, cyclosporin, and tacrolims, are adsorbed into IAS concurrently with the release of DEHP (Kawano et al., 1992, 1994; Suzuki et al., 2000). Also in other reports, the release of DEHP from PVC is able to be determined by high-performance liquid chromatography (HPLC) analysis (e.g. Hata et al., 2001; Niino et al., 2001).

David et al. (1999) demonstrated that DEHP promoted the proliferation and hepatomegaly associated with hepatocellular tumorigenesis. Therefore, the European Union banned the use of DEHP in toys and restricted the daily intake to 37 μg/kg per day. In Japan, the Ministry of Health and Welfare (2000) issued a notice restricting the oral tolerable daily intake (TDI) of DEHP to 40–140 μg/kg per day. Meanwhile, Center for Devises and Radiological Health (CDRH) and U.S. Food and Drug Administration (FDA) assessed the risk posed by exposure of patients to DEHP from the data of critical studies (CDRH, 2001). Foe example, AdvaMed (2001) study made available the results of a 21-day repeat intravenous dose study of DEHP in neonatal (3–5-day old) rats. At the end of the 21-day dosing period, testicular atrophy and hepatomegaly were observed in neonatal rats following daily intravenous exposure to DEHP at 300 mg/kg per day. Furthermore, histopathological examination of the testes of animals in the 300 mg/kg per day dosing group revealed a decrease in a diameter of the seminiferous tubules and a mild depletion of germinal epithelial cells. Although testicular atrophy persisted at the end of the recovery period, histopathological changes were not seen in the recovery group previously exposed to a DEHP dose of 300 mg/kg per day for 21 days. The no-observed-adverse-effect-level (NOAEL) proposed in the AdvaMed study was 60 mg/kg per day. In addition to investigating organ weight changes and conducting a histopathological examination of tissues, AdvaMed (2001) also performed a functional assessment of male reproductive capacity (sperm count, sperm motility and sperm morphology) in DEHP exposed rats at the end of the recovery period. No effect on any of these parameters was observed in the recovery group of animals. From the results of AdvaMed and the other critical studies, CDRH and FDA proposed the parenteral tolerable intake (TI) of DEHP was 0.6 mg/kg per day. As described above, although the effects of DEHP on humans are not fully understood, its intake through IAS should be avoided.

We previously demonstrated that the release of DEHP from IAS was promoted by the presence of injection additives such as surfactants (Hanawa et al., 2000; Muramatsu et al., 2000). Tanaka et al. (2001) demonstrated that estimating the extent of DEHP dissolution was possible under several drip conditions, using an aqueous solution of polyoxyethylated caster oil (HCO60). However, the details of the release mechanism of DEHP have not been elucidated.

For this investigation, we chose HCO60 as a model surface-active agent. HCO60 is a well-known amphiphilic surface-active agent similar to Tween 80, which is a commonly used emulsifier in the formulation of various pharmaceuticals, used to increase the solubility of water-insoluble drugs such as paclitaxel, miconazole, cyclosporine, tacrolimus and enocitabine. The objective of this study was to determine the relationship between the release behavior of DEHP from IAS and the concentration of HCO60 in various liquids such as DWI, PS, and sugar solutions, and to clarify any differences in release behavior of DEHP into various sugar solutions.

2. Experimental

2.1. Materials

Polyoxyethylated hydrogenated caster oil (HCO60) was procured from Nihon Surfactant Kogyo KK (Tokyo, Japan). DEHP and di-*n*-pentyl phthalate were procured from Kanto Chemical Co., Inc. (Tokyo, Japan). Physiological saline (PS), distilled water for injection (DWI), and 50% glucose solution (50% TZ) were of JP grade. D(−)-Ribose (Rib) and fructose

(Fru) were procured from Wako Pure Chemical Industries Ltd. (Osaka, Japan). PVC tubing from the TERUFUSION® IAS (Terumo, TS-A256PK027, Tokyo, Japan) was used in the experiments. Acetonitrille, methanol and distilled water of high purity HPLC grade were altogether supplied commercially by Kanto Chemical Co., Inc. and used without further purification.

2.2. Measurement of DEHP

DEHP concentrations in the sample solutions were determined by HPLC under the following conditions: column, Shodex® C18M-4D (4.6 mm i.d. × 150 mm length, Showa Denko Co., Ltd., Tokyo, Japan); mobile phase, 60:100:25 acetonitrile/methanol/distilled water; elution rate, 1.5 ml/min; internal standard (IS), di-*n*-pentyl phthalate; detector, SPD-10AVP (225 nm, Shimadzu Co., Kyoto, Japan); pump, LC-10AdVP (Shimadzu Co.), column oven, CTO-10AVP (Shimadzu Co.); and calculator, C-R8A (Shimadzu Co.). The resulting retention times of IS and DEHP under the chromatographic conditions were approximately 2.8 and 7.9 min, respectively. Calibration curve was constructed by plotting the peak area of the DEHP to IS against the concentration of DEHP. The data were fitted to least squares linear regression and the linearity of the standard curve was found ($r > 0.995$). Limit of detection (LOD) and limit of quantitation (LOQ) were 0.02 and 0.22 μg/ml, respectively.

2.3. Evaluation of a dripped solution from PVC tubing

Concentrations of HCO60 solutions ranging from 0.03 to 10 mg/ml were prepared in DWI, PS, or 50% TZ. One meter of PVC tubing was clipped from the IAS and attached to the infusion pump (TERUFUSION® infusion pump model: TE-112, Tokyo, Japan). A sample was collected at intervals from the drops forming at a rate of 60 ml/h.

2.4. Scattered light intensity measurement

Measurements of scattered light intensity were performed at 25 °C with a Fiber-Optics Particle Analyzer (Otsuka Electronics, KK, FSL-1000) equipped with a solid-state laser (100 mW) as the light source. All measurements were made at a wavelength of 532 nm and a measurement angle of 90°. Samples of surfactant solutions at various concentrations were used for light scattering measurements after removal of dust by filtration. Benzene (Dojin Chemical Laboratory, KK) was used as the reference substance.

2.5. Determination of HCO60 solubility into various sample solutions

A measured amount (2.0 ml) of DEHP was added to various HCO60 sample solutions (20 ml) and incubated at 25±0.1 °C for 24 h. After the incubation, sample solution was centrifuged at 3000 rpm for 510 min, the amount of DEHP dissolved in the aqueous phase was determined.

2.6. Statistical analysis

All results are presented as the mean ± S.D. The significance of difference was analyzed by the use of the paired *t*-test, and a significance level of less than 5% was considered significant.

3. Results and discussion

3.1. Release behavior of DEHP from PVC tubing

Fig. 1 illustrates the release behavior of DEHP from the PVC tubing in DWI, PS, and 50% TZ. In all cases, the amount of DEHP released increased linearly after a slight lag time, suggesting that the rowed that the release of DEHP from the PVC tubing follows zero-order release kinetics. In contrast, the release of DEHP from the PVC tubing into PS and DWI without HCO60 was less than the LOD. The PVC tubing used in this study contains approximately 35% DEHP (i.e. the weight of the PVC tubing was 7.0 g/m and contained approximately 2.45 g DEHP). As shown in Fig. 1, the cumulative amount of DEHP released up to 4 h in DWI containing 5.0 mg/ml of HCO60 was 776 μg, equivalent to 0.01% of the quantity contained in the whole PVC tubing. The release of DEHP occurred at the inner surface of the PVC tubing, and the diffusion of DEHP through the PVC tubing and the reduction of DEHP in the PVC was disregarded. In a previous study, we estimated the amount of DEHP

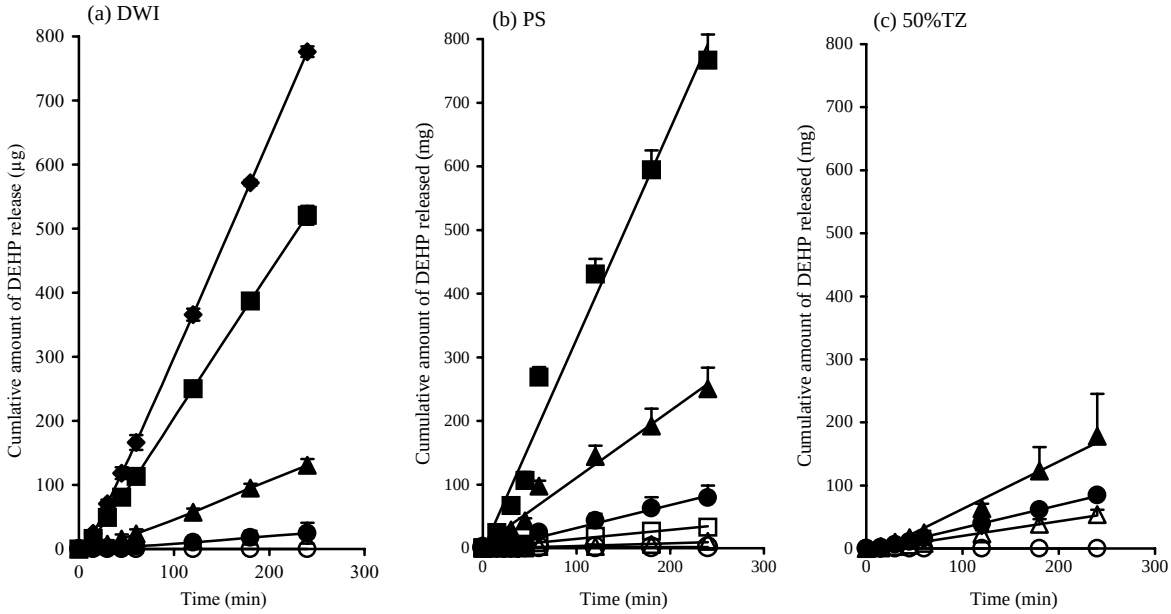

Fig. 1. Release profiles of DEHP from PVC tubing in various solutions: (a) HCO60 concentration in DWI at 0.01 mg/ml (○), 0.1 mg/ml (●), 0.5 mg/ml (▲), 3 mg/ml (■), 5 mg/ml (◆); (b) HCO60 concentration in PS at 0.03 mg/ml (○), 0.05 mg/ml (△), 0.08 mg/ml (□), 0.125 mg/ml (●), 0.6 mg/ml (▲) 6.0 mg/ml (■); (c) HCO60 concentration in 50% TZ at 0.1 mg/ml (○), 2.5 mg/ml (△), 5 mg/ml (●), 10 mg/ml (▲). Data are expressed as mean ± S.D. ($n = 3$).

intake by patients during the infusion of an injection containing HCO60 using PVC tubing through an equation predicting the amount of DEHP released from PVC tubing in DWI:

$$D_{\text{total}} = 4.09RH\sqrt{C_H}\left(T - \frac{0.755R^2H}{S}\right) \quad (1)$$

where D_{total} is total amount of DEHP released (μg), R is the inner diameter of PVC tubing (cm), H is the length of the tube (cm), T is the total number of hours of infusion (h), and S is drip rate (ml/h) (Tanaka et al., 2001). Although this formula is applicable only for DWI, the calculated value of 758 μg corresponded well with the value obtained in this study. In practice, many different factors, including HCO60, other solubilizing agents, fats, oils, and temperature may contribute to the release of DEHP from PVC tubing. Further investigation needs to be conducted on the release behavior into PS and TZ.

Because sink conditions were maintained within the tube while sample solution flowed, the release of DEHP was thought to progress by zero-order kinetics and the amount of DEHP released to increase linearly. When the cumulative amount of DEHP released by 4 h of contact with each sample solution was compared, no difference was found between DWI and PS; the existence of sodium chloride did not affect release behavior. In contrast, the amount of DEHP released into 50% TZ was low compared to other sample solutions, suggesting that the presence of glucose molecule affects release of DEHP.

3.2. Relationship between critical micelle concentration (CMC) of HCO60 and release behavior of DEHP

It is well known that the physicochemical properties of solutions containing surfactants change dramatically before and after the CMC (Martin, 1993). Amphiphilic surface-active agents such as Tween 80, which form micelles, increase the solubility of water-insoluble drugs. We investigated the effect of micelle formation of HCO60 on the release behavior of DEHP. Fig. 2 illustrates the relationship between scattered-light intensity ratio ($I_{\text{sample}}/I_{\text{benzene}}$) and the HCO60 solution concentration. CMC values were determined for the inflection point of each curve as shown in Table 1. CMCs of PS, 10% TZ, and DWI

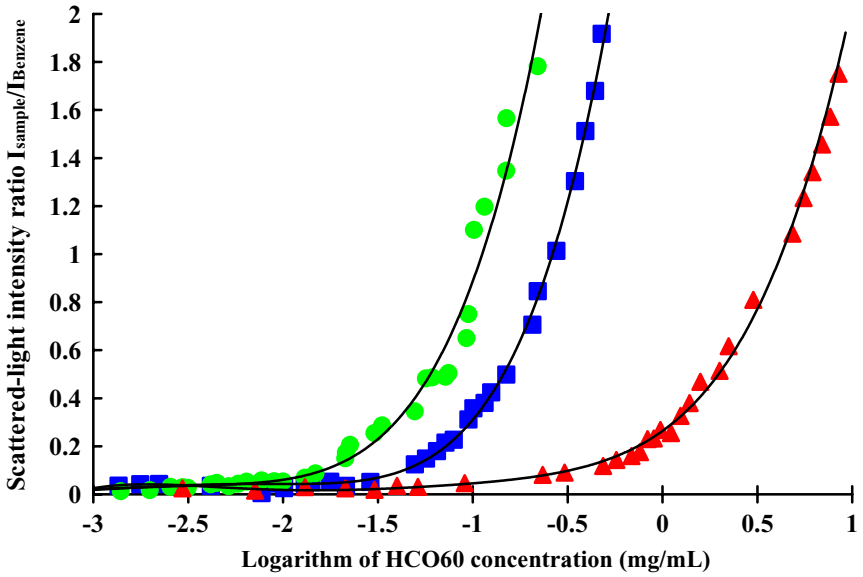

Fig. 2. Change in scattered light intensity by HCO60 aqueous solutions as a function of surfactant concentrations at 25 °C: (▲), 50% TZ; (●), PS; (■), DWI.

were 0.02, 0.028, and 0.039 mg/ml, respectively. The addition of electrolytes is known to lower the CMC of amphiphilic surface-active agents. In addition, the presence of sodium chloride lowers the CMC compared with that of DWI (Martin, 1993). Achara et al. (1999) demonstrated that the addition of various amounts (1.8–9.0%, v/v) of carbohydrate, such as glucose, sucrose, maltose, or galactose, to a solution containing various ionic- or non-ionic surfactants lowered the CMC. They proposed that, due to hydrophobic interactions, "icebergs" form around the non-polar tails of surfactant molecules, which need to unite for micelle formation. In the presence of carbohydrates, water–water interaction is replaced by water–sugar interaction; therefore, the chances of iceberg formation to protect the monomers decrease. As a consequence, micelle formation is favored and the CMC is reduced. Our results agree with these proposals. However, in the case of 50% TZ, the CMC was 0.52, which is 18.6 times that found for 10% TZ, likely due to the viscosity difference of the sample solutions. The viscosity of 50% TZ is 6.195 mPa s (data not shown), which restricts the mobility of HCO60 molecules that form the micelles. This effect may be due to structure changes induced by the hydration of glucose, and/or molecular interactions between water, glucose, and HCO60 molecules. In other words, the fraction of non-dissociated water increases with hydration of glucose molecules. The concentration of HCO60 in non-dissociated water was lower in TZ solutions, indicating that the CMC in TZ solution increased with an increase to 50% TZ.

Table 1
Critical micelle concentration (CMC) of various solutions

Solution	CMC (mg/ml)
DWI	0.04
PS	0.02
50% TZ	0.52

Fig. 3a illustrates the effect of concentration of HCO60 with cumulative amount of DEHP released from PVC tubing after 4 h. Release behavior into DWI and PS was similar; the amount of DEHP released increased with HCO60 concentration. The overall results indicated that the cumulative amount of DEHP released in 50% TZ was lower than the amounts released into PS and DWI. Fig. 3b depicts the relation between the cumulative amount of DEHP released and the relative concentration of HCO60 in each solution. As compared with the increased rate of DEHP release below and above the CMC, it hardly changed,

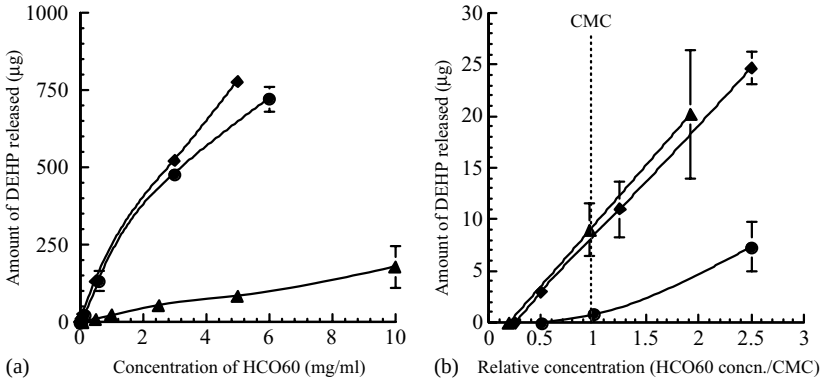

Fig. 3. Release behavior of DEHP from PVC tubing into DWI, PS, or 50% TZ below or above CMCs. (a) Effect of HCO60 on the release of DEHP from PVC tubing. (b) Relationship between relative concentration of HCO60 and amount of DEHP released. (◆), DWI; (●), PS; (▲), 50% TZ; (- - -), CMC. Data are expressed as mean ± S.D. ($n = 3$).

indicating that the existence of CMC does not affect release behavior. Lim and Chen (1974) investigated the solubility of aspirin in various surfactant solutions above and below the CMC values, and found that apparent aspirin solubility increased above the CMC. Lim and Chen stated that, although the mechanism for the effects of the surfactants on aspirin solubility cannot be fully explained, micelle size and shape likely play a prominent role in producing the observed solubilizing effects. In our previous study about the release behavior of DEHP from PVC tubing during the administration of enteral nutrition, an Ensure Liquid® (EL) solution, the mechanisms of DEHP release into EL solution comprise the following: (a) DEHP on the surface of the PVC membrane dissolves into EL solution, which displays some degree of lipophilicity, and then (b) DEHP distributes into corn–oil particles in the EL solution (Tanaka et al., 2002). In addition, the release of DEHP from the surface of the PVC membrane leads to (c) diffusion of DEHP throughout the PVC membrane (PVC/DEHP). The repetition of steps (a), (b) and (c) results in the release of DEHP over a prolonged period of time. Under those conditions, process (a) seems to be the rate-determining step. Also in this study, increase of the amount of DEHP released with increase in the concentration of HCO60 added seems to be due to the dissolution of DEHP on the surface of the PVC tubing resulting from the detergent effect and/or the improvement of the solubility of the lipophilic agents due to monomolecular interaction between DEHP and HCO60.

As mentioned above, the release of DEHP was restricted by addition of glucose, which is of interest for avoiding intake of DEHP into the human body through PVC tubing in clinical practice.

3.3. Effect of the types and concentration of sugar on release behavior of DEHP

To examine the effect of adding sugar on DEHP release behavior, various concentrations (10–70%, w/w) of glucose solutions were passed through PVC tubing (Fig. 4). For both 10 and 30% TZ, the presence of glucose significantly affected DEHP release behavior. In contrast, no difference in release behavior with and without glucose was observed in 50 and 70% TZ. The relation between glucose concentration and the release of DEHP in the presence of HCO60 was investigated (Fig. 5). Although the solubility of DEHP rose with an increase in HCO60 concentration, solubility decreased when the concentration of glucose was high. Furthermore, it appeared that the concentration of DEHP was under its LOD without addition of HCO60. These results indicate that the presence of glucose molecules lowered the solubility and the amount of DEHP released.

3.4. Release behavior of DEHP in sugar solutions

The release behavior of DEHP from PVC tubing in solutions of ribose, fructose, and glucose was investigated to determine if the release behavior of DEHP

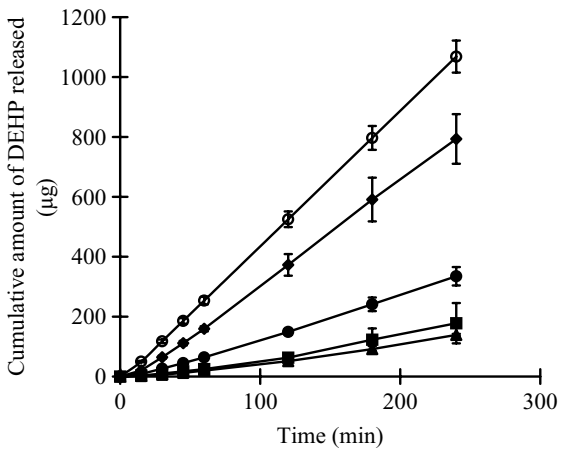

Fig. 4. Effect of TZ concentration on the release of DEHP from PVC tubing: (○), DWI; (◆), 10% TZ; (●), 30% TZ; (■), 50% TZ; (▲), 70% TZ. The concentration of HCO60 is 10 mg/ml. Data are expressed as mean ± S.D. ($n = 3$).

was affected by the physicochemical properties of the sugar. Fig. 6 shows the cumulative amount of DEHP released after 4 h in various sugar solutions containing 10 mg/ml of HCO60.

The cumulative amount of DEHP released after 4 h increased significantly in the following order: glucose < fructose < ribose. The limited release of DEHP into some sugar solutions may be due to the restricted mobility of the interactions of HCO60 with DEHP as a result of hydrogen bonding between the sugar and HCO60. Therefore, differences in the mode and/or extent of molecular interactions between the sugar and HCO60 induced changes in release behavior as shown in Figs. 4 and 6.

We focused on the differences in the hydration properties of sugar molecules to clarify our results. Although a sugar molecule contains many hydroxyl groups that can hydrogen bond with surrounding water molecules, the hydroxyl groups are not equivalent. Uedaira and Uedaira (1980) demonstrated that different sugars affected the thermal denaturation of lysozomes. Differential scanning calorimetry studies revealed that the denaturation temperature was closely associated with the mean number of equatorial OH groups per molecule [n(e-OH)]. Because equatorial hydroxyl groups e-OH on sugar molecules are able to hydrate surrounding water molecules, lysozomes are more stable in aqueous sugar solutions having large n(e-OH) values. Furthermore, from ^{17}O NMR studies, Uedaira and Uedaira demonstrated that the n(e-OH) values of ribose, fructose, and glucose were 2.1, 3.0, and 4.6, respectively. As shown in Fig. 6, the cumulative amount of DEHP released increased with an increase in n(e-OH). These results are consistent with the results shown in Fig. 4, and suggest that an increase in the number of water molecules

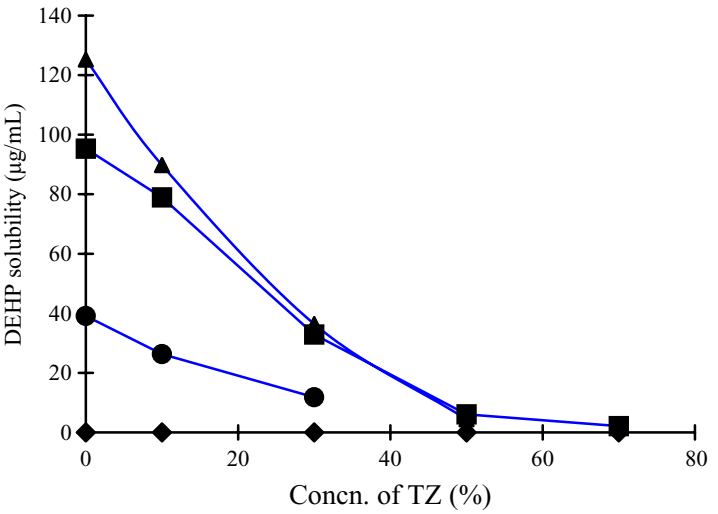

Fig. 5. Effect of TZ concentration on the solubility of DEHP in the presence of HCO60. HCO60 concentration is 10 mg/ml (▲), 5 mg/ml (■), 1 mg/ml (●), 0 mg/ml (◆). Data are expressed as mean ± S.D. ($n = 3$).

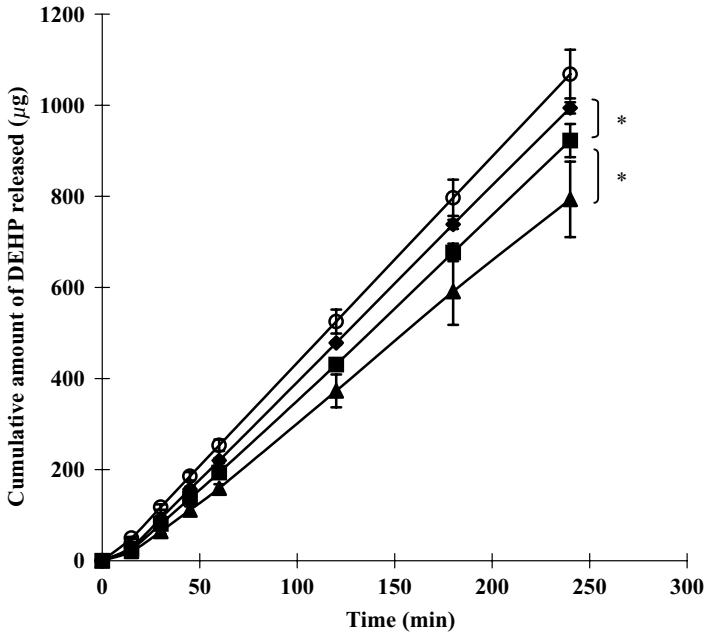

Fig. 6. Release of DEHP from PVC tubing into the various sugar solutions: (○), DWI; (◆), 10% ribose; (■), 10% fructose; (▲), 10% TZ. HCO60 concentration is 10 mg/ml. Data are expressed as mean ± S.D. ($n = 3$). $^{*}P < 0.05$.

that hydrate a sugar molecule cause an increase in viscosity of the solution. As a result, the mobility of HCO60 molecule is restricted, lowering the release of DEHP. Furthermore, molecular interactions between the sugar and HCO60 also is influenced by the hydration characteristics of the sugar molecule; the number of HCO60 molecules interacting with the sugar molecules increased with an increase in *n*(e-OH); the mobility of HCO60 may restrict the release and dissolution of DEHP simultaneously. Table 2 shows the solubility of DEHP in 10% ribose, 10% fructose, and 10% TZ. Although the concentration of HCO60 was 10 mg/ml in each solution, the solubility of DEHP was 10% ribose = 10% fructose > 10% TZ. The differences in solubility were likely due to the differences in the hydration properties of sugar molecules as described above.

Table 2
Solubility of DEHP in various sugar solutions

Solution	Solubility (μg/ml)
10% ribose	102.7 ± 6.3
10% fructose	102.1 ± 7.2
10% TZ	89.8 ± 3.1

The data are expressed as mean ± S.D. ($n = 3$). Each solution contains HCO60 (10 mg/ml).

Although the details of the molecular interactions between the sugar and HCO60, and the changes in microscopic viscosity caused by addition of the sugar are not fully understood, these phenomena are likely to be intricately related.

4. Conclusions

In conclusion, the amount of DEHP released increased with HCO60 concentration. At concentrations of HCO60 below and above the CMC, DEHP release did not increase significantly; the release of DEHP depended upon molecular interactions between DEHP and HCO60 rather than dissolution of DEHP into HCO60 micelles. DEHP release behavior was affected by the presence of sugar. The amount of DEHP released decreased as the mean number of equatorial OH groups *n*(e-OH) per molecule increased in the following order: glucose [*n*(e-OH); 4.6] < fructose (3.0) < ribose (2.1). The molecular mobility

of HCO60 was restricted by its interactions with sugar molecules and the microscopic viscosity. Molecular interactions between the HCO60 and the sugar affected DEHP release behavior, while an increase in the number of water molecules needed to hydrate the sugar decreased the amount of free water, thus allowing microscopic viscosity to increase and restrict HCO60 mobility. In this study, the maximum amount of DEHP released at once was 776 μg, and it was lower than the parenteral TI (0.6 mg/kg per day) proposed by FDA in the case a man with a weight of 60 kg. However, there is no change in DEHP being a foreign substance for the human body, and inflow inside of the body should be avoided. These results obtained in this study suggest that substances can restrict the release of DEHP from PVC tubing, thus preventing the intake of DEHP into the human body.

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