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Simple and rapid analysis of endocrine disruptors in liquid medicines and intravenous injection solutions by automated in-tube solid-phase microextraction/high performance liquid chromatography

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Abstract

A simple and rapid method was developed for analyzing contamination of endocrine disruptors in liquid medicines and intravenous injection solutions. Endocrine disrupting compounds such as bisphenol A (BPA), alkylphenols and phthalates were quantitated by on-line in-tube solid-phase microextraction coupled with high performance liquid chromatography (in-tube SPME/HPLC) with UV detection. The liquid medicines and intravenous injection solutions could be used directly without any pretreatment, and the BPA, alkylphenols and phthalates in these solutions were automatically analyzed. The limits of quantification for these compounds were 1–10 ng/ml. Recoveries of these compounds spiked to the intravenous injection solutions was over 80%, except for some phthalates. Di-*n*-butyl phthalate (DBP) was detected at a concentration of 7–60 ng/ml in most intravenous injection solutions in plastic containers, but it was not detected in solutions in glass bottles. Diethyl phthalate, di-*n*-propyl phthalate, DBP and di-2-ethylhexyl phthalate (DEHP) were also detected in syrup, lotion and eye drops in plastic containers. On the other hand, BPA and alkylphenols were not detected at all in these solutions. DEHP contamination from an administration set increased when total vitamin formulation was added to the infusion solution. DEHP was easily leached from polyvinyl chloride tubing by polysorbate 80. The in-tube SPME/HPLC method is simple, rapid and automatic, and it provides a useful tool for the screening and determination of endocrine disruptor contamination in liquid medicines and intravenous injection solutions.

Keywords: In-tube solid-phase microextraction; Intravenous injection solutions; Automated sample preparation; Endocrine disrupting compound; Phthalates

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1. Introduction

Disposable plastic products are widely used for medical devices such as infusion solution bags, administration sets and containers of liquid medicines because of their flexibility, transparency and low cost compared with glassware. However, the additives in plastic products have recently attracted a great deal of public attention as several of these materials have been suggested to possess endocrine disrupting properties [1,2]; the additives can either mimic sex hormones or antagonize their effects, or affect them by more indirect mechanisms. Plasticizers, such as di-2-ethylhexyl phthalate (DEHP), are particularly high in polyvinyl chloride (PVC), which may contain up to 30%. And DEHP from medical packaging and equipment made of PVC has been reported to elute into intravenous injection solutions [3–5]. Although DEHP is a rodent liver carcinogen that acts through a mechanism thought to involve peroxisome proliferation [6], carcinogenicity by this mechanism is unlikely to be relevant to humans [7,8]. Several phthalates, DEHP, di-*n*-butyl phthalate (DBP), and benzyl butyl phthalate (BBP), are also teratogenic in animals [9,10]. Furthermore, administration of DBP and DEHP to pregnant rats interferes with normal fetal development in male offspring [11]. Regarding reproductive and developmental effects, phthalates vary in potency; DEHP is the most potent, and DBP and BBP are roughly an order of magnitude less potent [9–12]. Therefore, the medical packaging industry has minimized the use of phthalates by using polymers, such as polyethylene (PE), polypropylene (PP), and ethylene-vinyl acetate copolymer (EVA) instead of PVC. However, PVC is still used in tubing for administration sets because of a lack of a suitable substitute. Phthalates as plasticizers are also used in many applications, such as adhesives, printing inks and lacquers. Plasticizers are present in the printing inks used in flexible food packaging, and their migration into food has also been studied [13,14]. Although printing inks are not in direct contact with food, the plasticizers contained in inks can migrate into food through the packaging material or during storage of polymer reels. Phthalates such as DBP were found to originate from adhesives used in the joints of the packaging [15]. These studies suggested that phthalate contamination is derived not only from the plastics used in the containers but also from other sources. On the other hand, bisphenol A (BPA) and alkylphenols have been also used to stabilize and modify the characteristics and performance of polymers. BPA is used as a raw material to make polycarbonate plastics and to make epoxy adhesives and can coatings. Nonylphenol (NP) in packaging is produced by the oxidation of tris-nonylphenyl phosphite, an antioxidant/antiozonant, and is added to polymeric materials such as PVC, polyolefins and acrylics. Recently, some of these chemicals reported to have weak estrogenic activity [16,17], although their effects in animals and humans are far from clear. Therefore, it is important to assess contamination levels of these chemicals in liquid medicines and intravenous injection solutions stored in plastic containers. The establishment of a simple and rapid method for the identification and measurement of these chemicals is desired.

The determination of phthalates, BPA and alkylphenols has been carried out by gas chromatography (GC) [18], GC/mass spectrometry (GC-MS) [19–23], high performance liquid chromatography (HPLC) [18,22,24–29] and LC-MS [22,29]. These methods involve a number of processes, including sampling, sample preparation, separation, detection, and data analysis. In general, more than 80% of the analysis time is spent on sampling and sample preparation steps, such as extraction, concentration, fractionation, and isolation. For the extraction of phthalates, BPA and alkylphenols from samples, solvent extraction by heating reflux, supercritical fluid extraction, liquid–liquid extraction, and solid-phase extraction have been used. However, most of these techniques are complicated and time-consuming, and they require expensive equipment. The use of complicated pretreatment methods may introduce errors, and the use of large volumes of organic solvents represents a significant health hazard to analysts and contributes to environmental pollution.

Recently, we developed a method for the determination of BPA, alkylphenols and phthalates in foods in contact with plastics by in-tube

solid-phase microextraction (SPME) coupled with HPLC [30]. In-tube SPME [31,32] is a microextraction and preconcentration technique for organic compounds in aqueous samples using an open tubular fused-silica capillary with an inner surface coating as the SPME device, which can be easily coupled on-line with HPLC and LC-MS [33–38]. In-tube SPME allows for convenient automation of the extraction process, which not only shortens the analysis time, but also provides better accuracy, precision and sensitivity relative to off-line manual techniques. In this paper, we report contamination levels of BPA, alkylphenols and phthalates in liquid medicines and intravenous injection solutions by in-tube SPME coupled with an HPLC photodiode array detection system. Using this method, we also studied the sources of these contaminants.

2. Experimental

2.1. Materials

Fig. 1 shows the endocrine disrupting compounds used in this study. Bisphenol A (BPA) and nonylphenol (NP) were purchased from Aldrich (Milwaukee, WI, USA). Octylphenol (OP), diethyl phthalate (DEP), di-*n*-propyl phthalate (DPP), di-*n*-butyl phthalate (DBP), di-*n*-amyl phthalate (DAP), di-*n*-hexyl phthalate (DHP), di-*n*-octyl phthalate (DOP), benzyl-*n*-butyl phthalate (BBP), dicyclohexyl phthalate (DCHP) and di(2-ethylhexyl) phthalate (DEHP) were purchased from Tokyo Kasei Kogyo (Tokyo, Japan). Each compound dissolved in methanol to make a stock solution at a concentration of 1 mg/ml. The solutions were stored at 4 °C and used after dilution with water to the required concentrations. Benzyl alcohol and polysorbate 80 (polyoxyethylene sorbitan monooleate) were purchased from Nacalai Tesque (Kyoto, Japan). Polyoxyethylated caster oil 60 (Emanon CH-60) was kindly provided by Kao Corporation (Tokyo, Japan). All solvents and water used in this study were of HPLC grade. All other chemicals were analytical grade.

2.2. Instrument and analytical conditions

The HPLC system used was a Model 1100 series (Agilent Technologies, Boeblingen, Germany), which consisted of a binary pump, an on-line degasser, an autosampler, a column compartment, a photodiode array detector (DAD), and an HP ChemStation. A Hypersil ODS (12.5 cm × 4.0 mm i.d., 5 μm particle size) from Agilent Technologies was used for the HPLC separation. HPLC conditions were as follows: column temperature, 40 °C; mobile phase and flow-rate, programmed by linear gradient of acetonitrile/water from 65 to 75% at 1.5 ml/min for a 5 min run, from 75 to 95% at 1.5–2.0 ml/min for a 5 min run and hold 95% at 2.0 ml/min for 2 min. UV detection was performed at 225 nm. UV spectra from 190 to 400 nm were also recorded for peak identification.

2.3. In-tube solid-phase microextraction

As shown in Fig. 2, Supel-Q PLOT capillary column (60 cm × 0.32 mm i.d., 12 μm film thickness, Supelco, Bellefonte, PA, USA) was used as the in-tube SPME device. It was placed between the injection loop and injection needle of the autosampler. The injection loop was retained in the system to avoid fouling of the metering pump. Capillary connections were facilitated by the use of a 2.5 cm sleeve of 1/16 in. polyetheretherketone (PEEK) tubing at each end of the capillary (1 in. = 2.54 cm). A PEEK tubing internal diameter of 330 μm was found to be suitable to accommodate the capillary used. Normal 1/16 in. stainless steel nuts, ferrules and connectors were then used to complete the connections. The autosampler software was programmed to control the in-tube SPME extraction, desorption and injection. Vials (2 ml) were filed with 1 ml of sample for the extraction, and set into the autosampler programmed to control the SPME extraction and desorption technique. In addition, 1.5 ml each of methanol and water in 2-ml autosampler vials with septum was set on the autosampler. The capillary column was washed and conditioned by two repeated draw/eject cycles (40 μl each) of these solvents, and then a 50-μL air plug was drawn prior to the extraction step. The extraction of

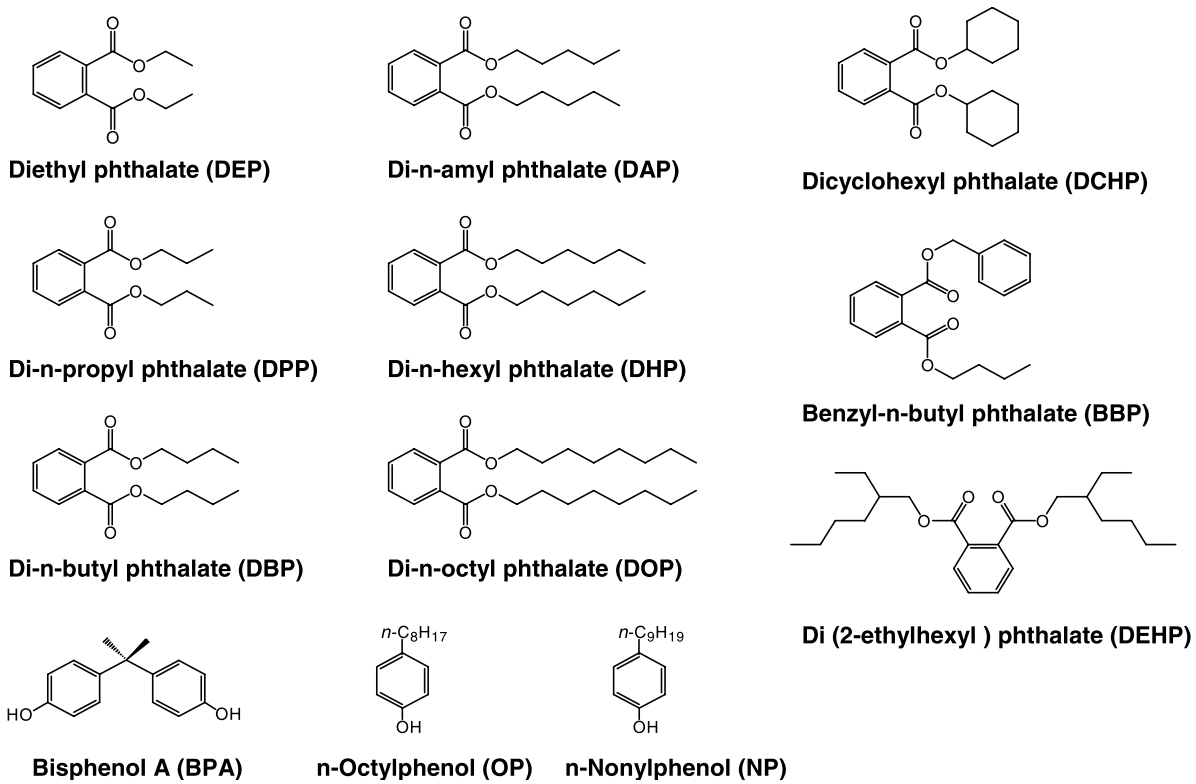

Fig. 1. Chemical structures of BPA, alkylphenols and phthalates used in this study.

BPA, alkylphenols and phthalates onto the capillary coating was performed by 20 repeated draw/eject cycles of 40 μl of sample at a flow rate of 100 μl/min with the six-port valve in the LOAD position (Fig. 2A). After washing the tip of the injection needle by one draw/eject cycle of 2 μl of methanol, the extracted compounds were desorbed from the capillary coating with mobile phase flow. Then the compounds were transported to the LC column by switching the six-port valve to the INJECT position (Fig. 2A), and detected by the DAD system. To ensure low backgrounds from phthalates and other contaminants, all glasswares containing autosampler vial used for analysis were washed with glass-distilled methanol and then dried at 100 °C overnight prior to use.

2.4. Determination of BPA, alkylphenols and phthalates in sample solutions

Syrup, lotion and eye drops were purchased from a local pharmacy. Six kinds of intravenous injection solutions (electrolyte solution, physiological saline, xylitol solution, maltose solution, glucose solution, and total amino acid solution) in plastic or glass containers were purchased from medical suppliers. Glucose solution and physiological saline were analyzed in December 2001 and July 2002, respectively, and the other intravenous injection solutions were analyzed in June 2001. Samples of 1 ml were put into 2-ml autosampler vials with septa. BPA, alkylphenols and phthalates in the samples were measured directly by the on-

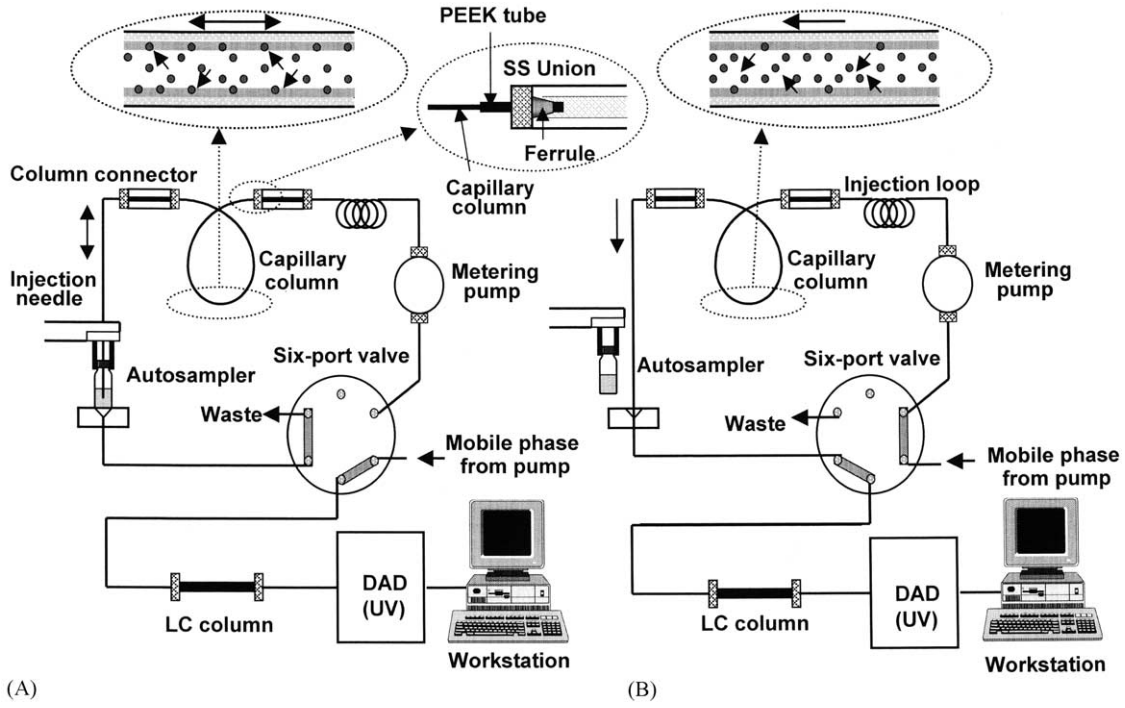

Fig. 2. Schematic diagram of automated in-tube SPME/HPLC-DAD system. (A) Extraction step, (B) desorption step.

line in-tube SPME/HPLC method described above.

2.5. *Migration test from PVC administration set by nutrients and formulation components*

Migration of phthalates from a PVC administration set was examined by measuring the concentration of phthalates in intravenous injection solution or in its total vitamin formulation solution before and after passing the solutions through the administration set. Total vitamin formulation (Sorvita, Fuso Pharmaceutical Industry, Osaka, Japan) contains thiamine hydrochloride (5 mg), sodium riboflavin phosphate (5 mg), pyridoxin hydrochloride (3 mg), cyanocobalamine (0.03 mg), nicotinamide (20 mg), folic acid (1 mg), biotin (0.2 mg), ascorbic acid (100 mg), pantenol (12 mg) as a water-soluble vitamin, retinal palmitate (2500 IU vitamin A), cholecarciferol (200 IU vitamin D), tocopherol acetate (15 mg), menatetrenone (2 mg) as a fat-soluble vitamin, and other additives such as benzyl alcohol (20 mg), polysorbate 80 (20 mg) and polyoxyethylated castor oil 60 (80 mg). These organic solvent and surfactants are used as solubilizing agent for fat-soluble vitamins. Intravenous injection solutions (200 ml) with and without total vitamin formulation were passed through administration sets at a flow-rate of 2 ml/min, then 1 ml of flow-through liquid or untreated solution was put into 2-ml autosampler vials and analyzed by in-tube SPME/HPLC. Administration set consists of needle, PVC tube (100 cm $\times$ 3 mm i.d.), plastic (polyolefins) drip chamber, roller clamp and flash tube. Migration of phthalates from PVC administration tube was examined by shaking a section of the tubing with the organic solvent and surfactant found in the total vitamin formulation. The solvent and surfactant were used at the same concentrations that were found in the vitamin formulation. The PVC administration tube (0.5 g) was placed in 20 ml of polysorbate 80 (0.1 mg/ml), polyoxyethylated castor oil 60 (0.4 mg/ml), or benzyl alcohol (0.1 mg/ml) in 100-ml Erlenmeyer flasks with screw-caps, and the mixture was shaken at 100 rpm for 2 h at 25 °C using a

round-trip shaker. Samples of 0.1 ml of the liquids and 0.9 ml of distilled water were put into 2-ml autosampler vials, and analyzed by in-tube SPME/HPLC.

3. Results and discussion

3.1. Analysis of BPA, alkylphenols and phthalates by in-tube SPME/HPLC

BPA, alkylphenols and phthalates were well separated within 12 min on a Hypersil ODS column using acetonitrile/water as a mobile phase. In-tube SPME of BPA, alkylphenols and phthalates was optimized as described in our previous study [30]. A porous polymer type capillary column, Supel-Q PLOT, gave superior extraction efficiency as compared with the liquid phase type capillary column, Omegawax 250, DB-17 and DB-1. The amount of compounds extracted depends on the extraction time and rate. The optimum in-tube SPME conditions were 20 draw/eject cycles of 40 μl of sample at a draw/eject rate of 100 μl/min using a Supel-Q PLOT capillary column. The extracted compounds were easily desorbed from the capillary by mobile phase flow, and no carry-over was observed because the capillary column was washed and conditioned by draw/eject cycles of methanol and mobile phase prior to extraction. Air plugging before the extraction step was carried out to prevent not only sample mixing but also desorption of analyte from the capillary coating by the mobile phase during the ejection step. BPA, alkylphenols and phthalates showed excellent responses in UV detection at 225 nm, and detection limits to give signal-to-noise ratios of 3 under our HPLC-DAD conditions were 0.1–4.0 ng/ml. The in-tube SPME method showed 18–125 times higher sensitivity than the direct injection method, because these compounds in the sample solution were concentrated in the capillary column during draw/eject cycles. A linear relationship was obtained for each compound in the concentration range 1–500 ng/ml (six-point calibration). The correlation coefficients were 0.991–0.999, and relative standard deviations were 1.8–18.4% ($n = 3$). The extraction and desorption of BPA, alkylphenols and phthalates by the in-tube SPME/HPLC method were automatically accomplished within 35 min, and automatic analysis of about 40 samples per day was also possible by overnight operation.

3.2. Determination of BPA, alkylphenols and phthalates in sample solutions

Using the in-tube SPME/HPLC method, BPA, alkylphenols and phthalates in several liquid medicines and intravenous injection solutions in plastic or glass containers were analyzed to examine endocrine disruptor contamination. As shown in Fig. 3, some phthalates were detected in these samples. The limit of quantification of BPA, alkylphenols and phthalates in the intravenous injection solutions was 1–10 ng/ml. As shown in Table 1, the recoveries of BPA, alkylphenols and phthalates spiked to intravenous injection solutions were above 80%, except for some phthalates. DBP was detected at concentrations of 7–60 ng/ml in most of the intravenous injection solutions in plastic containers, but it was not detected in the same solutions in glass bottles (Table 2). DEP, DPP, DBP and DEHP were also detected in syrup, lotion and eye drops in plastic containers (Table 3), but BPA and alkylphenols were not detected in these solutions. In addition, the DBP concentration tended to be high in the intravenous injection solutions, which have longer storage periods. Furthermore, the intravenous injection solutions in plastic bottles with paper labels held in place with adhesive tended to show higher concentrations of DBP in comparison with those in plastic bottles directly printed with ink. These results suggest that DBP in label adhesives contaminated the infusion solutions by passing through the plastic.

3.3. Migration test from PVC administration set by nutrients and formulation components

As shown in Fig. 4, the level of DBP did not increase in the intravenous injection solution upon addition of total vitamin formulation before and after passing these solutions through the administration set. DEHP was detected in the intravenous

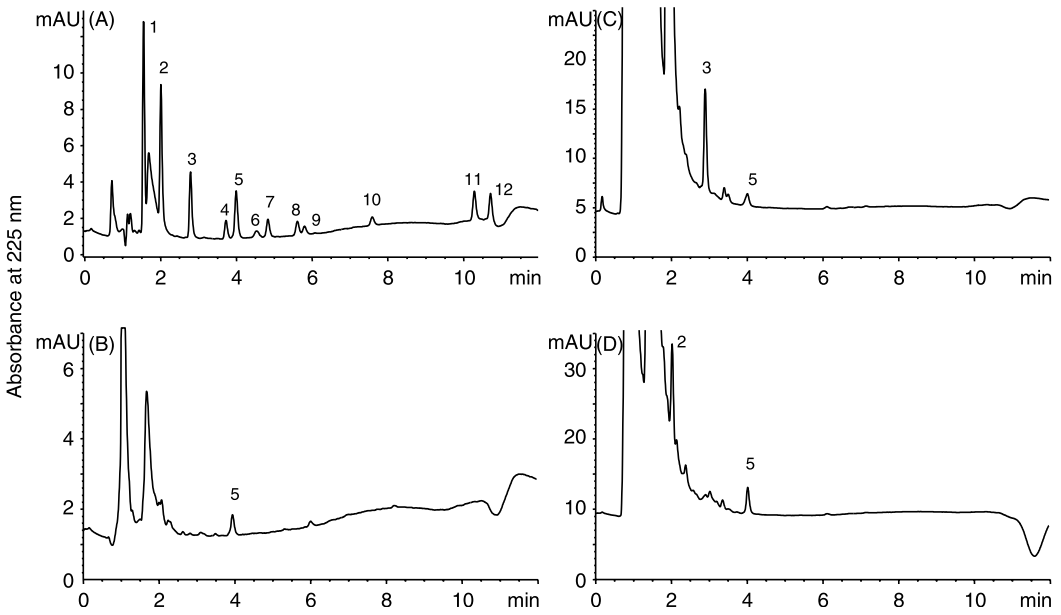

Fig. 3. Chromatograms from standard solution and samples by in-tube SPME/HPLC. (A) Standard solution (50–500 ng/ml), (B) intravenous injection solution, (C) syrup, (D) eye drops. Peak: 1 = BPA, 2 = DEP, 3 = DPP, 4 = BBP, 5 = DBP, 6 = OP, 7 = NP, 8 = DAP, 9 = DCHP, 10 = DHP, 11 = DEHP, 12 = DOP. HPLC conditions: see Section 2.

injection solution after but not before the solution passed through the administration set. Moreover, DEHP contamination significantly increased in the intravenous injection solutions when total vitamin formulation was added. To identify the source of DEHP contamination, the migration of phthalates from PVC administration tubing was examined by shaking tubing with the organic solvent and surfactant components of the total vitamin formulation. As shown in Fig. 5, DEHP is easily eluted from PVC tube by polysorbate 80 (included as a solubilizing agent in the formulation). The DEHP migration with polyoxyethylated castor oil 60 or benzyl alcohol was low or undetectable. The increase in the DEHP migration caused by vitamins was not observed. These results

Table 1
Recoveries of phthalates spiked to intravenous injection solution

Phthalate	Spiked (ng/ml)	Recovery (%), mean ± S.D.[a]	Spiked (ng/ml)	Recovery (%), mean ± S.D.[a]
BPA	20	97.7 ± 7.2	100	112.4 ± 2.2
DEP	20	105.1 ± 8.3	100	115.7 ± 2.9
DPP	20	86.3 ± 10.7	100	98.7 ± 3.5
BBP	20	69.4 ± 8.8	100	79.4 ± 3.7
DBP	20	106.6 ± 9.6	100	92.5 ± 3.6
OP	20	81.4 ± 11.0	100	92.1 ± 3.6
NP	20	86.1 ± 15.4	100	99.7 ± 4.8
DAP	100	80.1 ± 11.6	500	88.3 ± 3.5
DCHP	100	79.2 ± 7.8	500	83.0 ± 4.9
DHP	100	101.8 ± 10.8	500	114.1 ± 14.1
DEHP	200	98.2 ± 7.3	1000	82.4 ± 11.0
DOP	200	98.1 ± 4.9	1000	76.2 ± 9.0

[a] $n = 3$.

Table 2
Contents of DBP in several intravenous injection solutions

Intravenous injection solution	Volume (ml)	DBP (ng/ml)[a]	Container	Label
Electrolyte solution A	200	17.7±6.9	PE bottle	Adhesive paper
	500	20.3±3.7	PE bottle	Adhesive paper
Electrolyte solution B	500	7.6±3.2	PE bag	Printed ink
Electrolyte solution C	500	11.9±3.8	PP bottle	Adhesive paper
Physiological saline A	100	58.9±6.6	PE bottle	Adhesive paper
Physiological saline B	200	20.1±1.6	PE bottle	Adhesive paper
	250	7.4±1.5	PE bag	Printed ink
Xylitol solution	500	28.4±4.3	PE bottle	Adhesive paper
Maltose solution	500	8.0±2.9	EVA bag	Printed ink
Glucose solution	200	49.2±4.3	PE bottle	Adhesive paper
	500	12.5±0.6	PE bag	Printed ink
Total amino acid solution A	200	ND[b]	Glass bottle	Adhesive paper
Total amino acid solution B	200	ND	Glass bottle	Adhesive paper

[a] Mean±S.D. ($n = 3$).
[b] Not detectable.

indicate that DEHP can be readily leached out of the PVC administration tube by surfactant in the drug formulation. Therefore, formulations that elute DEHP should be prepared in non-PVC containers and administered through non-PVC tubing.

4. Conclusions

The automated in-tube SPME/HPLC method used in this study can perform continuous extraction of BPA, alkylphenols and phthalates from aqueous samples followed by HPLC-DAD analysis. This method is simple, rapid, selective and sensitive for analysis of BPA, alkylphenols and phthalates. It can also be directly applied to the analysis of liquid medicines and intravenous injection solutions without any pretreatment. Using this method, the contamination levels were measured, and the origins of phthalates were found. We believe that this method provides a useful tool for the screening and determination of BPA, alkylphenols and phthalate contamination in liquid medicines and intravenous injection solutions in plastic containers.

Table 3
Contents of phthalates in several liquid medicines

Liquid medicine	Content (ng/ml)/mean±S.D. ($n = 3$)			
	DEP	DPP	DBP	DEHP
Syrup	ND[a]	138.9±4.3	29.0±1.5	ND
Lotion	ND	ND	ND	ND
Eye drops A[b]	178.6±17.2	ND	116.9±19.1	ND
Eye drops B	ND	ND	17.1±5.1	ND
Eye drops C	ND	ND	15.2±0.8	ND
Eye drops D	ND	ND	142.1±4.4	112.6±26.9

[a] Not detectable.
[b] Main components of A, B, C and D are ketotifen fumarate, glutathione, sodium azulene sulfonate and pranoprofen, respectively.

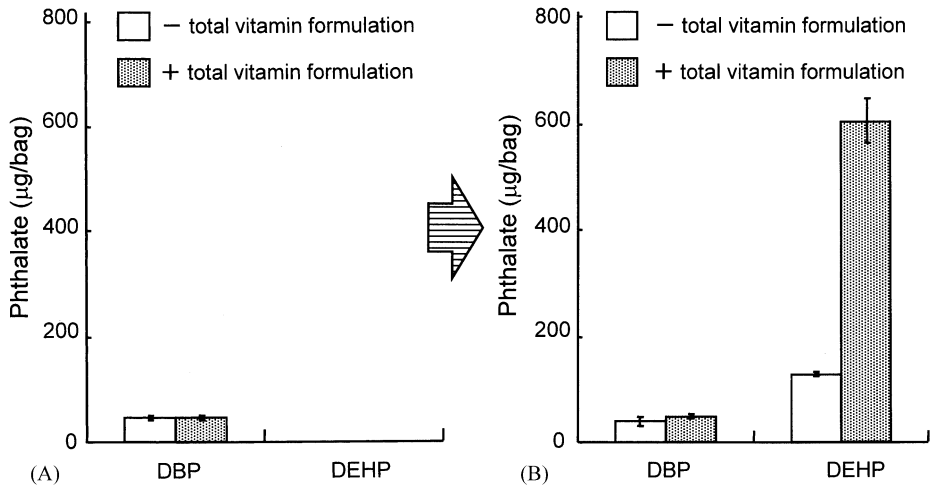

Fig. 4. Effects of the addition of total vitamin formulation to intravenous injection solution on the migration of phthalates from the administration set. (A) Intravenous injection solution before passing through administration set, (B) intravenous injection solution after passing through administration set.

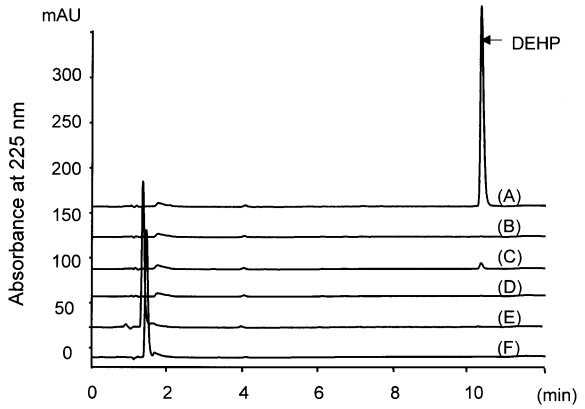

Fig. 5. Migration of phthalates from PVC administration tubing into several solvents. (A) 0.1 mg/ml polysorbate 80 in water+PVC administration tube, (B) 0.1 mg/ml polysorbate 80 in water, (C) 0.4 mg/ml polyoxyethylated castor oil 60 in water+PVC administration tube, (D) 0.4 mg/ml polyoxyethylated castor oil 60 in water, (E) 0.1 mg/ml benzyl alcohol in water+PVC administration tube, (E) 0.1 mg/ml benzyl alcohol in water.

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