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Reducing the migration of di-2-ethylhexyl phthalate from polyvinyl chloride medical devices

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Abstract

We attempted to determine the processing conditions for decreasing the migration of phthalate esters, particularly di-2-ethylhexyl phthalate (DEHP), from polyvinyl chloride (PVC) products using a drug solvent after dilution based on the package insert. PVC sheets and PVC tubing were subjected to optical irradiation (ultraviolet (UV), visible light irradiation) and heat treatment to determine whether they are deteriorated by these treatments. UV irradiation to one side of the PVC sheet decreased the levels of DEHP migration from the sheets by almost 50%, although the amount of DEHP content in PVC sheet was observed no significant change. On the other hand, the levels of DEHP migrating from the inner surface of PVC tubing UV-irradiated from the outer surface were not decreased compared with the control. Therefore, the surface structure was examined by conducting Fourier transform infrared spectroscopy (FT-IR), electron spectroscopy for chemical analysis (ESCA) and static angle of contact measurement. In FT-IR analysis, we found that the UV-irradiated PVC sheets were exhibited broadened absorption bands with time. In ESCA analysis, the chlorine content was decreased and the oxygen content was increased with time in UV-irradiated PVC sheets. Moreover, the other treated PVC sheets shows no significant change compared with the non-UV-irradiated PVC sheet. Therefore, the surface structure of the UV-irradiated PVC sheet was changed. As a result, the migration of DEHP from PVC products can be decreased with simple treatment, such as UV-irradiation. This could be a useful method to develop novel PVC products.

Keywords: Di-2-ethylhexyl phthalate (DEHP); Polyvinyl chloride (PVC); Medical device; UV irradiation; Surface structure

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1. Introduction

Phthalate esters are widely used as industrial plasticizers. In particular, di-2-ethylhexyl phthalate (DEHP) is used in the manufacture of polyvinyl chloride (PVC) products and other plastics to achieve the desired softness, flexibility and stability for specific applications. PVC is employed in the production of floor tiles, food wrapping film, industrial tubing, and medical devices (Huber et al., 1996), and is the most widely used polymer because of its availability. In general, PVC products used in medicine contain up to 40% by weight of this plasticizer (Ljunggren, 1984); however, it has been reported that some species of phthalate esters including DEHP exhibit reproductive and developmental toxicity (Arcadi et al., 1998; Gray et al., 1999). DEHP is not chemically bound to the PVC polymer and may leach when a medical device is heated or when the PVC comes in contact with surrounding media, such as blood, serum, plasma, drugs and intravenously administered fluids. The migration of DEHP from PVC medical devices into the surrounding media has been reported to result in toxicity (Tickner et al., 2001; Yakubovich and Vienken, 2000; Hill et al., 2001). Extraction occurs either by leaching or after an extracting material (blood, IV fluid) diffuses into the PVC matrix and dissolves the plasticizer, which is relatively lipophilic (Rock et al., 1986). In Japan, the Ministry of Health, Labour and Welfare has set the tolerable daily intake (TDI) of DEHP at 40–140 μg/kg/day (MHLW, 2000) and the use of DEHP as a plasticizer has been regulated so that it cannot be used in the manufacture of, for example, infant toys and plastic gloves for handling food. DEHP has been reported to leach from PVC medical devices containing fat-soluble drugs to be administered orally. Depending on the conditions at the time of use, a patient may be exposed to high levels of DEHP through medical treatment (USFDA, 2001; Health Canada, 2002).

Many studies have been reported on the release behavior of DEHP from PVC medical devices under various conditions (Hanawa et al., 2000; Jenke, 2001; Faouzi et al., 1995), because it is essential that the exposure be precisely determined in order to evaluate its significance as an integral part of the risk assessment of DEHP to human health. However, the quality change of PVC products during storage has been not estimated so far. It is possible that the content and release behavior of DEHP may be influenced by optical irradiation and temperature change during storage. Moreover, in this study, a DEHP migration test using PVC products treated with optical irradiation (visible and ultraviolet) and heating as external factors during storage was performed using a drug solvent for injection after dilution to the required concentration based on the package insert. In addition, the surface structure was examined by conducting Fourier transform infrared spectroscopy (FT-IR), electron spectroscopy for chemical analysis (ESCA) and static angle of contact measurement. When the PVC products were irradiated with UV, degradation occurred (Takeishi and Okawara, 1970). The tensile test was also performed as PVC products may deteriorate due to irradiation and heat treatment. The results of this study led to the development of processing conditions for decreased DEHP migration from PVC products, and provided novel information relevant to risk assessment and product development.

2. Materials and methods

2.1. Materials and chemicals

The test materials were a medical PVC sheet (1 cm × 3 cm, thickness: 0.4 mm) used in the manufacture of blood bags, and PVC tubing (length 10 cm, i.d. 2.13 mm) used for the transfusion, infusion, and donation of blood.

The drug solvent used for the DEHP migration tests was Sandimmun® (250 mg cyclosporine per ampoule (5 ml), Novartis Pharma Co., Tokyo, Japan). It is used for injection after dilution with 50 mg/ml glucose to the required concentration (0.5 mg/ml as cyclosporine concentration) based on the package insert.

Phthalate esters, di-2-ethylhexyl phthalate and DEHP-d_4, were purchased from Kanto Chemical Co. (Tokyo, Japan). Hexane, anhydrous sodium sulfate, a sodium salt of DEHP analytical grade, analytical grade diethyl ether, and HPLC grade distilled water were used in the experiments.

2.2. Pretreatment of PVC sheet and tubing

2.2.1. Control

A PVC sheet maintained in the shade and at room temperature was used as a negative control.

2.2.2. Heat treatment

The PVC sheets were kept at temperatures of 4, 37 and 60 °C for 1 week, 2 weeks, 1 month, 2 months and 3 months. The positive control was a PVC sheet kept at 100 °C for 25 days.

2.2.3. Optical irradiation

The embossed side is the outer surface of a blood bag. Some PVC sheets were irradiated with visible light using fluorescent lamp placed at a distance of 75 cm. On the other hand, the other PVC sheets were irradiated UV-ray using UV germicidal lamp placed at distance of 60 cm (UV intensity: 52.5 $\mu W/cm^2$) in clean-bench. These PVC sheets were irradiated for 1 week, 2 weeks, 1 month, 2 months or 3 months. After irradiation, the samples were stored in the shade. The positive control for visible light irradiation was a PVC sheet exposed to sunlight for approximately 1 year. The positive control for UV irradiation was a PVC sheet irradiated with a 254-nm UV lamp at a distance of 3 cm for 25 days. PVC tubing cut to a length of 10 cm was irradiated with a 254-nm UV lamp at a distance of 3 cm for 14 days.

2.3. GC–MS

A Hewlett-Packard HP 6890 Series GC system equipped with an auto-injector (Agilent Technologies, Palo Alto, CA) and a JMS700 spectrometer (JEOL, Tokyo, Japan) were used for gas chromatography-mass spectrometry (GC–MS). Chromatographic separations were performed with a BPX-5 fused silica capillary column (25 m × 0.22 mm i.d., film thickness: 0.25 μm, SGE Japan, Kanagawa, Japan).

A sample (2 μl) was injected in the pulsed splitless mode. The injector temperature was 260 °C. Helium was used as the carrier gas at a flow rate of 1 ml/min. The column temperature was programmed from 120 to 300 °C (held for 2 min) at a rate of 10 °C/min. The electron impact (EI)-mass spectrum was recorded at 70 eV for qualitative analysis, and ions of *m/z* 149.024 (DEHP) and 153.049 (DEHP-d_4) were selected as quantitative ions in selective ion monitoring (SIM) analysis (resolution = 5000) using the lock and check method of calibrating standard ions (*m/z* 168.989 of PFK). Quantitative analysis of each sample was repeated five times for calibration curves and twice for the other samples. The preparation of calibration curves and the calculation of quantitative data were performed using computer software TOCO, version 2.0 (total optimization of chemical operations), applying the function of mutual information (FUMI) theory (Hayashi and Matsuda, 1994; Hayashi et al., 1996, 2002; Haishima et al., 2001).

2.4. Migration test

The migration of DEHP from PVC sheets was examined in 5 ml of Sandimmun® prepared according to the instructions on the package insert. PVC sheets, which were irradiated or heat-treated were kept in test tubes and extraction was carried out by shaking at room temperature for 1 h. A 0.1 ml aliquot of the extract was pipetted into another test tube, and 2 ml of distilled water and 5 ml of diethyl ether containing 50 ng/ml DEHP-d_4 were added. The mixture was then subjected to extraction with shaking for 10 min. After centrifugation at 3000 rpm for 10 min, the organic phase was collected and dehydrated with anhydrous sodium sulfate, and subjected to GC–MS analysis.

PVC tubing cut to 10 cm length was used in the DEHP migration test, and filled with Sandimmun® (tube length, 8 cm; capacity, 0.285 cm^3; and surface area, 5.35 cm^2). The tubing was subjected to extraction with shaking at room temperature for 1 h. The extract was transferred into another test tube and treated in the same manner as that for PVC sheets.

2.5. Determination of DEHP compounds in PVC sheet by GC–MS

A PVC sheet sample (0.02 g) was dissolved in 20 ml of THF by soaking overnight at room temperature. A 0.1 ml aliquot of the solution was pipetted out and diluted with 2.0 ml of diethyl ether. A 0.1 ml aliquot was obtained, mixed with 50 ng/ml DEHP-d_4 (1 ml) and diethyl ether (8.9 ml), and then analyzed by GC–MS.

2.6. Analysis of surface structure

2.6.1. Infrared spectrometry

A JIR-SPX 200 (JEOL, Tokyo, Japan) was used for FT-IR spectroscopy coupled with attenuated total reflection (ATR) analysis. To analyze the PVC sheets, we used a germanium crystal, and the incidence angle was set at 45°.

2.6.2. Electron spectroscopy for chemical analysis

ESCA measurements were performed using an ESCA-3200 (Shimadzu, Kyoto, Japan). Only the inner side of the blood bag was measured for the heat treatment group and the visible light irradiation group, whereas both sides of the blood bag were measured for the UV irradiation group.

2.6.3. Static angle of contact

A solution of Sandimmun®, prepared according to the instructions on the package insert, was added dropwise to PVC sheets. After 120 s, the width and height of the droplet were measured with a G-1-1000 (ERMA, Tokyo, Japan). The static angle of contact with Sandimmun® was computed as follows:

$$L^2 = \left(\frac{w}{2}\right)^2 + (L-h)^2$$

$$\sin\delta = \left(\frac{w/2}{L}\right)$$

L is radius of droplet (mm); w is width of droplet (mm); h is height of droplet (mm); and (δ) static angle of contact.

Only the inner side of the blood bag was measured for the heat treatment group and the visible light irradiation group, whereas both sides of the blood bag were measured for the UV irradiation group.

2.7. Tensile test

A PVC sheet (0.7 cm × 3 cm, center width: 0.4 cm, thickness: 0.04 cm) was used as the sample (Fig. 1). Measurements were performed using an Autograph AG-20 kNG (Shimadzu, Kyoto, Japan) at a speed of 40 mm/min.

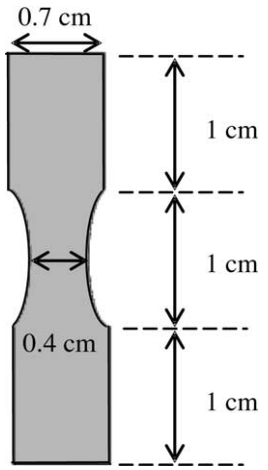

Fig. 1. The PVC sheet used in the tensile test A PVC sheet: 0.7 × 3 cm, center width: 0.4 cm, thickness: 0.04 cm.

3. Results and discussion

3.1. Determination of DEHP released from PVC products by GC–MS

First, the background was analyzed in order to examine the accuracy of the GC–MS method. When 50 ng/ml DEHP-d_4 with diethyl ether solution was used as the internal standard, 0.93 ± 0.31 ng/ml DEHP (n = 5) was detected in the internal standard. The DEHP background peaks in the internal standard solution were trace levels (S_0). In addition, the precision (SD) was expressed as SD_0. The limit of detection (LOD) and the limit of quantification (LOQ) of DEHP were calculated using S_0 and SD_0; LOD ($S_0 + 3 \times SD_0$) and LOQ ($S_0 + 10 \times SD_0$) were 1.9 and 4.0 ng/ml, respectively. A calibration curve was obtained for the peak ratio of DEHP to DEHP-d_4 versus the DEHP concentration level. The response was found to be linear in the validated range with a correlation coefficient (r) exceeding 0.999. Furthermore, the 95% confidence interval calculated by TOCO was sufficiently narrow to determine the amount of DEHP released from the PVC products. We found that this GC–MS method could be used for DEHP analysis with high accuracy.

The levels of DEHP that migrated from the PVC sheets were then determined, and the time course is shown in Fig. 2. Heat treatment and optical irradiation were each performed for 1 week, 2 weeks, 1 month, 2 months, and 3 months. At 2 months, the levels of DEHP migrating into Sandimmun® were slightly decreased by heat treatment and visible light irradiation, however no remarkable change was observed between the treatments, or between those treatments and their respective positive controls. The level of DEHP migration from the heat-treated PVC sheets has decreased the temperature-dependent. The most possible factor for the temperature-dependent, the sublimation/vaporization was occurred by heat treatment in

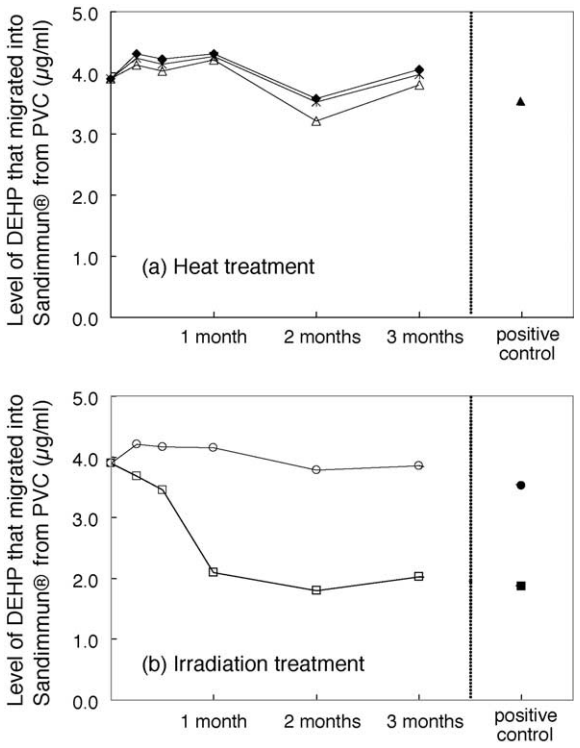

Fig. 2. Level of DEHP migrating into Sandimmun® injection from PVC sheet samples. (a) Heat treatment: PVC sheets were kept at 4 °C (♦); 37 °C (*) and 60 °C (△). Heated positive control: PVC sheets were kept at 100 °C for 25 days (▲). (b) Irradiation treatment: PVC sheets were irradiated with visible light (◯) and UV (□). The visible irradiated positive control (●) was irradiated with sunlight for approximately 1 year. The UV-irradiated positive control (■) was irradiated with a UV lamp at 254 nm (3 cm, 25 days). The quantitative data were performed using computer software TOCO, Version 2.0 (Total Optimization of Chemical Operations), applying the function of mutual information (FUMI) theory.

PVC sheet. On the other hand, the significant change on migration was observed in UV-irradiated PVC sheets. The levels of DEHP migrating from the PVC sheets showed a time-dependent decrease in the UV irradiation group. At 1 month after UV irradiation, the level of DEHP migrating from the PVC sheet was reduced to approximately half that of the negative control. No significant change was observed thereafter, even if irradiation was continued. In addition, the level of DEHP migrating from the PVC sheet after UV irradiation over 3 months was not different from that of the positive control. We hypothesized that the reduction by half of the DEHP level has caused by UV-irradiated sides. We thought the UV-irradiated side (outer surface) of PVC sheet induces suppression in DEHP migration, and inner surface of PVC sheet dose not influence in migration. In order to confirm this hypothesis, we examined the PVC tubing that was able to distinguish outer and inner surface. The outer surface of the PVC tubing was subjected to strong UV irradiation. Subsequently, the level of DEHP migrating from the inner surface of the PVC tubing was determined. As a result, it was found that the level of DEHP released from the inner surface of the PVC tubing was almost the same as that of the negative control PVC tubing. It was concluded that the inner surface of the PVC tubing was not influenced by UV irradiation from the outside, since there was no change in the levels of DEHP released when compared with the control.

3.2. DEHP content examination

The DEHP content in the PVC sheets subjected to heat treatment or optical irradiation was determined. No significant difference in the DEHP content was found between the heat treatment groups and the visible light irradiation group. The positive controls of the two groups had almost the same DEHP content. On the other hand, the DEHP content in the UV-irradiated PVC sheets decreased slightly with time (Table 1). The most possible factor for the time-dependent, the sublimation/vaporization was occurred by UV-irradiated PVC sheet.

The rate of decrease in the DEHP content of the UV-irradiated PVC sheet was not equivalent to that of the level of migration. Therefore, the level of the suppression of DEHP migration was more remarkable than that of decreasing-content of DEHP.

3.3. Surface analysis

3.3.1. Surface analysis by FT-IR

FT-IR with ATR spectra was obtained from PVC sheets subjected to optical irradiation or heat treatment. Fig. 3a shows a characteristic absorption band at 635 cm^{-1}, due to C–Cl stretching vibration from PVC. We also observed absorption due to C–H from the aromatic compound and the carbonyl group from DEHP at 742 and 1720 cm^{-1}, respectively. Furthermore, an absorption band due to the alkane C–H bond from PVC and DEHP was found at nearly 1250 cm^{-1}.

Table 1
DEHP content in PVC sheet samples (w/w, %)

	4 °C	37 °C	60 °C	Visible light	UV light
1 week	31.2 ± 0.09	31.9 ± 0.61	33.2 ± 0.35	34.1 ± 1.65	36.2 ± 2.14
2 weeks	32.6 ± 0.44	33.3 ± 0.25	31.7 ± 0.03	34.8 ± 1.36	34.7 ± 3.32
1 month	32.9 ± 0.39	34.2 ± 0.45	35.0 ± 1.11	34.1 ± 0.85	33.7 ± 5.11
2 months	33.2 ± 0.12	33.9 ± 0.25	33.3 ± 0.43	32.8 ± 0.18	29.4 ± 0.63
3 months	33.8 ± 0.04	32.9 ± 0.26	30.9 ± 0.34	29.5 ± 4.05	27.1 ± 0.37

Negative control samples: 36.0 ± 2.60%; positive control samples subjected to heat treatment: 32.4 ± 0.45%; positive control samples irradiated with visible light: 32.6 ± 0.70%; positive control samples irradiated with UV: 30.8 ± 0.53%.

The FT-IR spectra of the heated-treated and visible light-irradiated PVC sheets were almost the same as that of the negative control. The spectrum was rectified using software because the ATR spectrum depended on the wavelength to calculate the areas of the characteristic absorption bands for DEHP or PVC. When the area ratios for the heat-treated or visible light-irradiated PVC sheets were compared with those of the negative control, no clear change was seen. On the other hand, as shown in Fig. 3b–f, the UV-irradiated PVC sheets were found to exhibit broadened absorption bands with time. These results led us to hypothesize that UV irradiation caused a change in the surface structure. The FT-IR spectrum of the non-UV-irradiated side was the same as that of the negative control, indicating that there was no change in the surface structure.

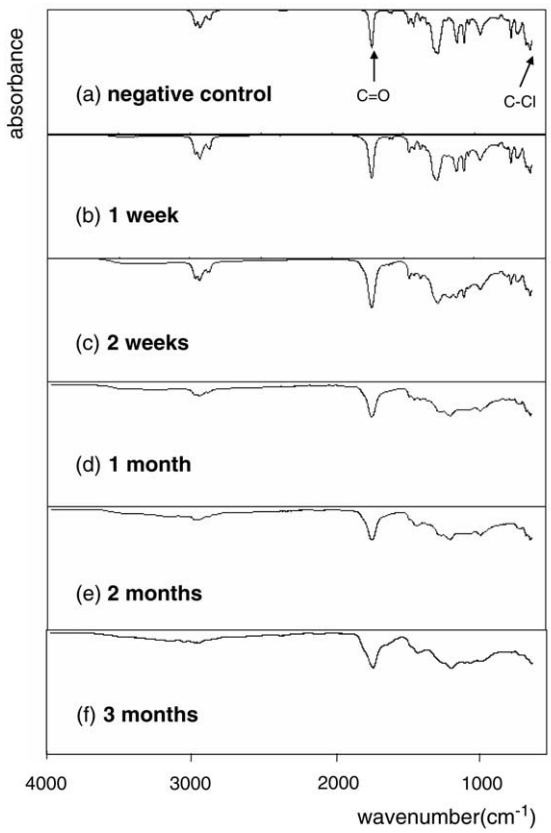

Fig. 3. FT-IR spectra of UV-irradiated and negative control PVC sheets FT-IR spectra of PVC sheets: negative control (a); and those irradiated with UV light for 1 week (b); 2 weeks (c); 1 month (d); 2 months (e) and 3 months (f).

3.3.2. Surface analysis by ESCA

Surface analysis of the PVC sheets was carried out and carbon, oxygen, chlorine and silicon were found on the sheet surface. As shown in Fig. 4a, the surface structure of the PVC sheets was not influenced by heat treatment or visible light irradiation because the composition ratio was maintained. On the other hand, in the UV-irradiated PVC sheets (Fig. 4b), the chlorine content was decreased and the oxygen content was increased with time. For the inner surface of the UV-irradiated PVC sheets, the composition ratio was hardly changed compared to the negative control in the period of 1 week to 1 month. However, after 2 months, the composition ratio was not changed at all compared with the negative control.

3.3.3. Surface analysis by static angle of contact measurement

In order to evaluate the affinity of the PVC sheets and the actual concentration of the Sandimmun® injection, we measured the static angle of contact. The static angle of contact was 37.1 ± 0.84 and 53.4 ± 0.93° for the outer and inner surfaces of the non-treated PVC

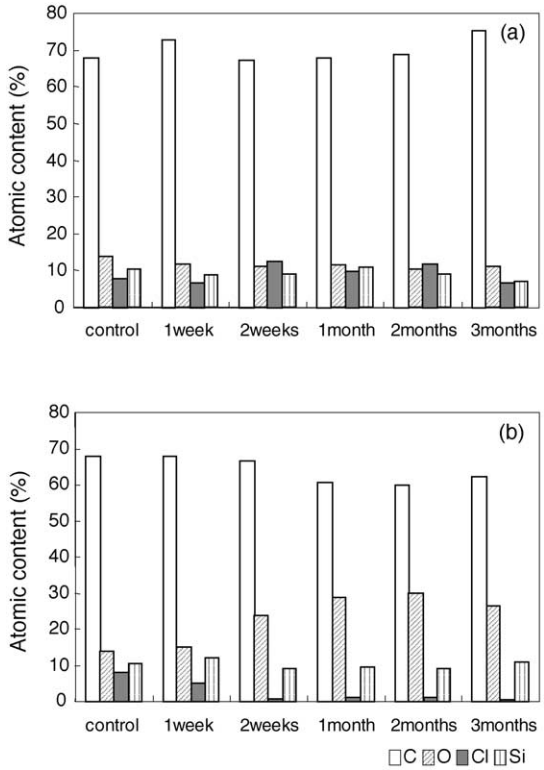

Fig. 4. Elemental analysis of PVC sheets by ESCA: (a) typical bar graph of PVC sheet samples subjected to heat treatment or visible light irradiation, and negative control and (b) bar graph of PVC sheet sample subjected to UV irradiation.

sheets, respectively. We hypothesize that the difference in the contact angle is due to differences in the embossed processing of the outer and inner surfaces (Fig. 5c (control) and Fig. 5b (control)). As shown in Fig. 5, the static angle of contact of the PVC sheets using the Sandimmun® injection as the wetting agent was not affected by either heat treatment or visible light irradiation (Fig. 5a). On the other hand, the static angle of contact of the inner surface of the UV-irradiated PVC sheets was decreased with time (Fig. 5b). In addition, the static angle of contact of the inner surface of the UV-irradiated positive control PVC sheets was almost the same as that of the inner surface of the PVC sheets UV-irradiated for 3 months. On the other hand, the static angle of contact of the outer surface of the UV-irradiated PVC sheets was increased markedly from the control to 3 months (Fig. 5c).

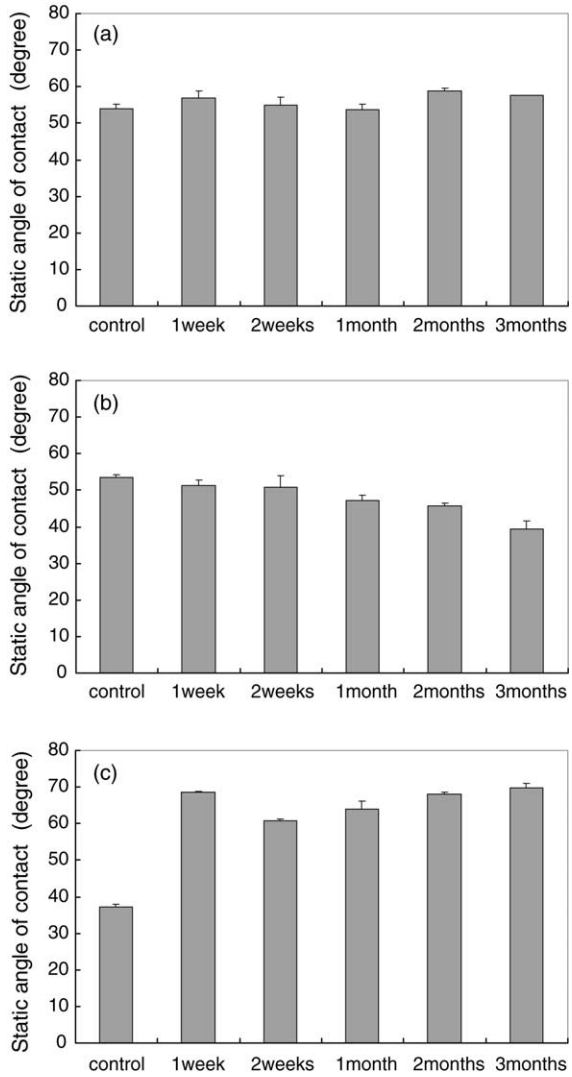

Fig. 5. Static angle of contact of PVC sheet samples Sandimmun® injection was used to determine the static angle of contact of PVC sheets subjected to heat treatment or optical irraditation. Typical bar graph of PVC sheet samples subjected to heat treatment or visible light irradiation. Bar graph of PVC sheet samples subjected to UV irradiation. The static angle of contact obtained by the inner surface of PVC sheet. Bar graph of PVC sheet samples subjected to UV irradiation. The static angle of contact obtained by the outer surface of PVC sheet.

Therefore, surface structure of the heat-treated PVC sheets and visible light irradiated PVC sheets did not change with time. On the other hand, surface structure of the UV-irradiated PVC sheets was markedly changed.

Table 2
Maximum force to break the PVC sheets for tensile test

	4 °C	37 °C	60 °C	Visible light	UV light
1 week	37.03 ± 1.68	36.54 ± 1.15	37.64 ± 2.01	36.63 ± 1.32	37.59 ± 0.86
2 weeks	36.12 ± 1.34	36.92 ± 0.52	36.20 ± 0.80	36.97 ± 1.12	36.28 ± 0.67
1 month	36.12 ± 1.07	36.86 ± 2.13	36.46 ± 1.39	36.70 ± 1.69	35.73 ± 0.76
2 months	37.84 ± 1.93	36.43 ± 2.14	36.08 ± 1.56	37.03 ± 0.39	36.43 ± 0.52
3 months	36.76 ± 1.48	36.28 ± 2.04	36.52 ± 0.81	36.86 ± 1.77	36.76 ± 1.05

($n = 4$) Negative control samples: 36.37 ± 0.78 N; positive control samples subjected to heat treatment: 37.28 ± 0.92 N; positive control samples irradiated with visible light: 37.11 ± 1.33 N; positive control samples irradiated with UV: 33.07 ± 2.88 N.

3.4. Tensile test

Flexibility and stability are some of the reasons why PVC products are used widely. In order to examine the deterioration of PVC products subjected to heat treatment or optical irradiation, the tensile strength and elasticity were measured. The maximum force to break the PVC sheets ranged from 33.1 ± 2.9 to 37.8 ± 1.9 N regardless of treatment (Table 2).

Therefore, there were no notable changes in the tensile strength and elasticity of the PVC sheets when heat treatment or optical irradiation was applied.

4. Conclusions

The DEHP content and the surface structure of the PVC products, and the levels of DEHP migrating from them were measured in order to determine the influence of external factors on PVC products during storage. In addition, a tensile test was carried out to determine the tensile strength and elasticity of the PVC products. It was hypothesized that UV irradiation led to changes in the surface structure, and that change was responsible for the decreased levels of DEHP migrating from the PVC products using a drug solvent diluted according to the package insert.

In order to clarify the change in the surface structure, we examined the surface by ESCA. In UV-irradiated PVC sheets, we observed that the hydrogen chloride level was decreased and oxidation proceeded with time. Similarly, in the FT-IR spectra, we observed that the absorption band characteristic of C–Cl stretching vibration from PVC and the C–H band from the aromatic compound were decreased with time. In addition, the absorption bands in the FT-IR spectra were found to broaden with time. PVC oxidation and crosslinking were surmised to explain these events. Based on these results, the UV irradiation of PVC products induced a decrease in the levels of DEHP migration, and the PVC products maintained their features, such as flexibility and stability. Some studies have reported the decreased DEHP release from PVC products by modifying the surface structure of the products under various conditions such as UV-irradiation with sodium azide as an enhancer for absorbing UV-energy, gamma-ray irradiation, in an aqueous solution containing water-soluble compounds such as methacrylic acid, and gas plasma treatment under reduced pressure (Jayakrishnan et al., 1995; Krishnan et al., 1991). In comparison with these techniques, the simple UV-irradiation method described in this study seems to have a great advantage, because it can be performed easily under atmosphere conditions without reagents or special instruments.

Today, the medical device industry is searching for a substitute for DEHP as a plasticizer. Our results suggest that the levels of DEHP migrating from a PVC product can be reduced by easy surface treatment without changing the type of plasticizer. This could be useful method to develop novel PVC products, if other safety aspects are confirmed. Possible biological changes should not be ignored, since increased oxygen content on the surface could have an important impact on the activation of the clotting system and complements. A detailed investigation is in progress in our laboratory to develop novel PVC products.

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