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# Compatibility of Diazepam with Polypropylene Multilayer Infusion Container

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**Abstract:** Techflex®, a polypropylene-lined, multilayer infusion bag, was studied for its compatibility with diazepam, in comparison to the conventional infusion bag, Safeflex®, which is comprised of poly(vinyl chloride) (PVC). Diazepam was diluted in 0.9% sodium chloride isotonic solution and stored in the infusion bags for 24 h. To evaluate the sorption of diazepam into the infusion bags during storage, the concentration of the drug remaining in the bag was measured using gas chromatography-mass spectroscopy. The PVC bags exhibited a marked sorption of diazepam, with a drug loss reaching up to 90% of the initial concentration after 24 h of contact, whereas Techflex® inhibited the drug sorption, showing approximately 10%, under the same conditions. The differences in the sorption behaviors of the bags are discussed in terms of solubility parameters and crystallinities of the polymers.

*Keywords*: polypropylene, poly(vinyl chloride), diazepam, infusion, container, bag, multilayer, compatibility, crystallinity, solubility.

## Introduction

Poly(vinyl chloride) (PVC) infusion bags are commonly used for the infusion of drug admixtures due to their advantages, such as lightness, flexibility, and convenient storage, over the conventional glass containers; however, numerous studies have reported on the drawbacks of the PVC bags.[1] The major problem of the PVC bags for drug infusion purpose is that di-(2-ethylhexyl) phthalate (DEHP), the main plasticizer used in manufacturing PVC bags, can leach into the infusion solutions.[2-6] DEHP, when injected into the human patients, may have adverse effects on their bodies including chronic toxicities on the liver and the reproductive systems.[5-7] To overcome these problems, several types of non-PVC bags comprised of polyolefins, such as polyethylene and polypropylene (PP), have been developed.[1,2] Because these non-PVC products do not contain DEHP, concerns over leaching can be eliminated. Besides plasticizers, the other problem of the PVC infusion bags is the adsorption of drugs into the inner surfaces of the bags, thereby decreasing the infusion concentrations.[1] It is recognized that PVC causes the sorption of the lipophilic drugs, such as diazepam and nitroglycerine, whereas polyolefin materials are known to inhibit drug adsorption to a certain degree, the other strong point of polyolefin infusion bags over PVC bags.[1,8-10] However, the retardation behavior of drug sorption in the polyolefin bags remains yet unclear. The aim of this study was to evaluate the physico-chemical interactions between drugs and the polyolefin infusion bag. For this purpose, Techflex®, a newly developed multilayer infusion bag comprised of PP, and diazepam were respectively chosen as the polyolefin infusion bag and the lipophilic drug for intravenous administration, and the sorption behavior of diazepam in the multilayer bag was investigated and compared with that of the PVC bag. This paper dis-

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cusses the differences in the sorption behaviors of the two bags in terms of solubility parameters and crystallinities of the bag materials.

## Experimental

**Materials.** The conventional PVC infusion bag, Safeflex®, and a newly developed PP multilayer bag, Techflex®, consisting of three layers, PP, styrene-based rubber, and PP, were kindly provided by Choongwae Pharm (Seoul, Korea). Diazepam (Samjin Pharm, Seoul, Korea) and sodium chloride solution (Daihan Pharm, Ansan, Korea) were used for the preparation of the drug admixture.

**Preparation of Drug Admixture.** Drug admixture for the chromatographic analysis was prepared by dissolving 4 mg of diazepam in 100 mL of 0.9% sodium chloride solution (routine concentration in clinical practices).[1] For spectroscopic analysis, a series of diazepam/sodium chloride solutions of 0.04 to 1.2 mg/mL were prepared, infused, and stored in Safeflex® and Techflex® bags for 24 h in darkness at room temperature.

**Scanning Electron Microscopy (SEM).** For SEM analysis, the cross-sections of Safeflex® and Techflex® bags were frozen in liquid nitrogen, fractured, gold-sputtered, and observed under SEM (JSM-5410LV, JEOL, Tokyo, Japan).

**Gas Chromatography/Mass Spectroscopy (GC/MS).** At specified time intervals from 1 to 24 h, the bags were agitated, and the admixtures were directly sampled from both Safeflex® and Techflex® bags up till the end of the storage period. All samples were freeze-dried and dissolved in methanol (J.T. Baker, Phillipsburg, NJ, USA) before used for GC/MS analysis. Deuterium-labeled phenanthrene-d10 (10 μg/mL; Supelco, Bellefonte, PA, USA) was prepared as the internal standard. Working standard solutions of diazepam were prepared in methanol (1-100 μg/mL) and stored at -20 °C prior to use. GC/MS analysis was performed using an Agilent 6890 Plus gas chromatograph equipped with a 5973N mass selective detector quadrupole mass spectrometer system (Hewlett-Packard, Palo alto, CA, USA). A DB-5 MS capillary column (30 m×0.25 mm i.d., 0.25 μm film thickness, 5% diphenyl-95% dimethylsiloxane phase; J&W Scientific, Folsom, CA, USA) was used. The GC oven temperature was maintained at 100 °C for 1 min, ramped to 275 °C at 20 °C per min, maintained for 1 min, then to 300 °C at 5 °C per min, and finally maintained for 1 min. The sample was injected in the split mode at the splitting ratio of 1:2. The temperatures of the GC injection port and the MS interface were set at 290 and 300 °C , respectively. The mass selective detector was run in the electron impact mode, with the electron energy at 70 eV. The instrumental parameters were set at 300 μA filament emission current and multiplier voltage of 2,200 V. The mass spectrometer was operated in a full-scan mode between 35 and 650 amu. For monitoring and confirmation analysis, the selected ion monitoring mode was used, with the dwell time of each ion set at 50 ms.

**Fourier Transform Infrared Spectrometry/Attenuated Total Reflectance (FTIR/ATR).** After given periods of the admixture contact, the samples were cut into 4×4 cm strips and washed three times with deionized water for a total of 15 min. The washed strips were then cut into 1×4 cm pieces and vacuum-dried for 5 h. A qualitative analysis of the diazepam sorption in the samples was performed using an FTIR/ATR (Nicolet AVATAR 360, Thermo Fisher Scientific, Waltham, MA, USA). Thirty-two scans were averaged at the resolution of 4 $cm^{-1}$.

**Differential Scanning Calorimetry (DSC).** Crystallinity of the infusion bags was measured by DSC using a TA instrument (DSC-7, Perkin-Elmer, Waltham, MA, USA), at the heating rate of 10 °C/min from -30 to 250 °C under the stream of $N_2$ gas. The melting temperature was determined from the peak of the melting endotherm. The crystallinity was calculated using the following equation:

$$\text{Crystallinity (\%)} = (\Delta H_m / \Delta H^o) \times 100$$

The melting enthalpy ($\Delta H_m$) value was determined based on the second scan of the DSC analysis, and that of the 100% crystalline phase ($\Delta H^o$) was confirmed from the literature.[11,12]

## Results and Discussion

**SEM Images of the Micro Sectional View of Infusion Bags.** Figure 1 shows the SEM images of the micro section of the infusion bags; the cross-section of Safeflex® film exhibits the conventional style PVC monolayer, whereas that of Techflex® shows triple layers tightly welded together with different thicknesses. The thickness of the layers is one of the important factors to consider in manufacturing the multilayer non-PVC infusion bags, because it affects the softness of the bags. Although rubbery phase adhesives were commonly used as the mid-layers to compensate for the toughness of the polyolefin films, desirable physical properties could only be accomplished when a very thin outer layer was entangled to the rubbery phase; thus, the outer layer of Techflex® is far thinner than the inner layer.

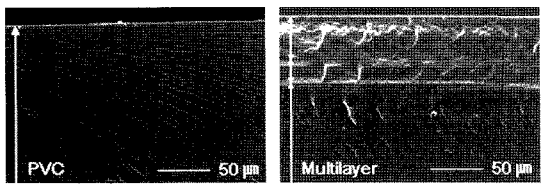


**Figure 1.** SEM images (×500) of sectional structure of PVC and multilayer bag. In the multilayer bag, outer layer, middle layer and inner layer appeared from the top to the bottom.

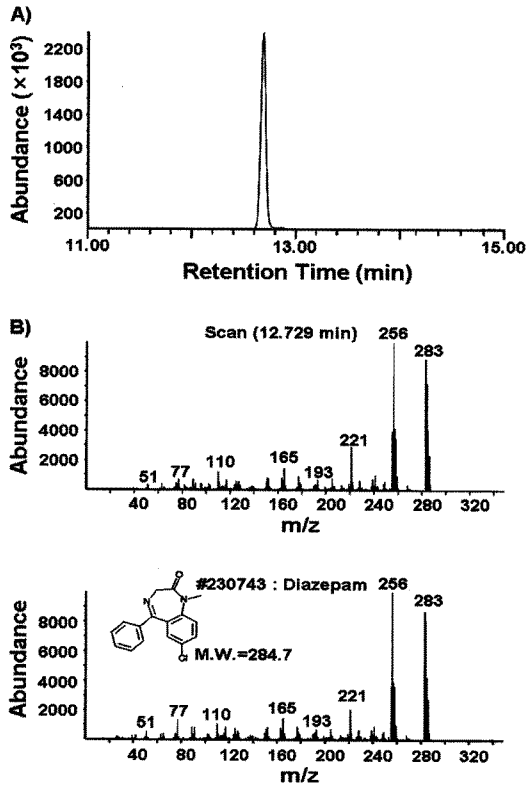


**Figure 2.** Total ion chromatograms of diazepam in the GC/MS scan mode; (A) diazepam initial concentration, (B) mass spectrum of diazepam in the sample and result from the library searching.

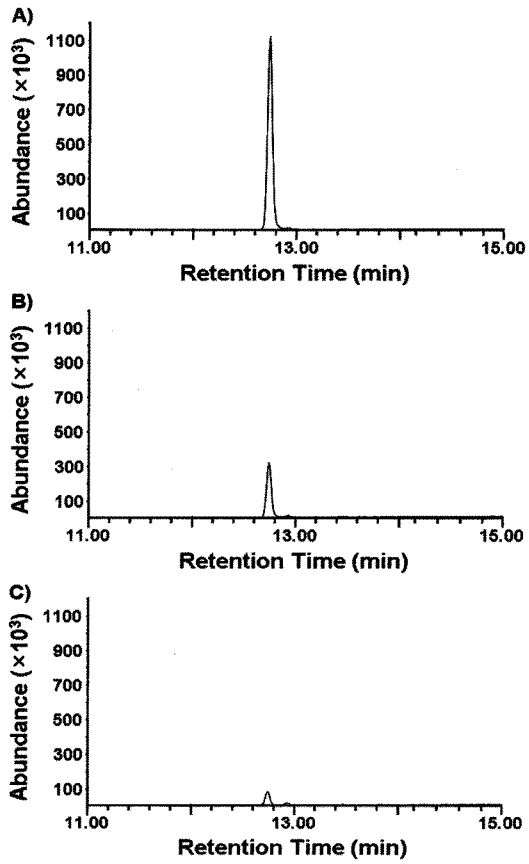


**Figure 3.** GC/MS results of diazepam stored in PVC bags. (A) diazepam stored in PVC bag during 1 h, (B) diazepam stored in PVC bag during 8 h, (C) diazepam stored in PVC bag during 24 h.

**Quantitative Study of Diazepam Sorption of Infusion Bags.** A typical total ion chromatogram of diazepam extracted from a sample is shown in Figure 2(A). The diazepam peak appeared at 12.729 min of the retention time, and no significant interferences were observed in the total ion chromatogram. The mass spectrum of diazepam in the sample and those obtained from library search are shown in Figure 2(B). The mass spectral characteristic ions of diazepam were respectively selected at *m/z* 256 and 283 for quantification and confirmation. The peak areas of diazepam in the PVC bags decreased with increasing storage time (Figure 3); however, in the case of the multilayer samples, little difference was found in the peak areas between the initial and the final admixture solutions up until 24 h of storage (Figure 4). To quantify the amount of the adsorbed diazepam, the ratio of the peak areas of diazepam and phenanthrene-d10, the internal standard, was calculated. A calibration curve was generated using the least-squares linear regression analysis in the range of 1 to 100 μg/mL, with the correlation coefficient for diazepam being 0.993. Figure 5 shows the changes in the concentration of diazepam as a function of time in the PVC and the multilayer bags during 24 h storage. The concentration of diazepam remaining in the PVC bag decreased rapidly to 55% within 1 h, then to 9% at 24 h. On the other hand, approximately 10% drug loss was found in the multilayer bags after 24 h. Based on the clinical regulations, compatibility of the plastic containers with drugs can be defined as the concentration representing 90-105% of the initial drug concentration;[1] thus, the multilayer bags tested in the present study were more compatible with diazepam than the PVC bags for 24 h.

**FTIR Study for Diazepam Sorption on the Surfaces of Infusion Bags.** Because the loss of drugs in the infusion bags is thought to be caused by the adsorption and/or the diffusion of the drugs into the inner layers of the bags; surface analysis of the inner layers of the bags for the adsorbed drugs can be an important tool in providing evidences. Figure 6 shows the FTIR/ATR spectra of diazepam and the inner surfaces of the infusion bags. The characteristic IR band at 1683 $cm^{-1}$, attributed to the imine groups (C=N) in

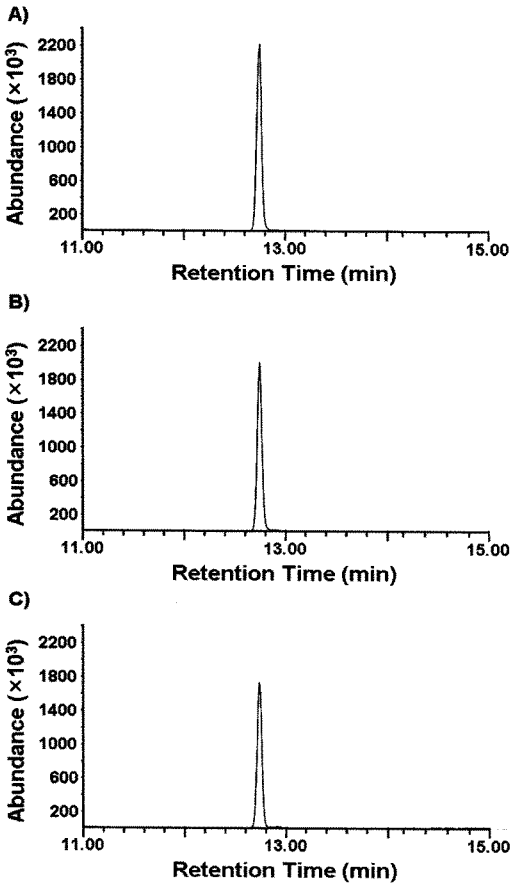


**Figure 4.** GC/MS results of diazepam stored in multilayer bags. (A) diazepam stored in the multilayer bag during 1 h, (B) diazepam stored in multilayer bag during 8 h, (C) diazepam stored in multilayer bag during 24 h.

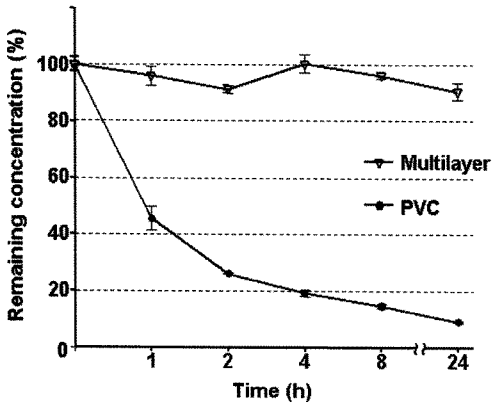


**Figure 5.** Remaining concentration of diazepam as a function of time in PVC and multilayer bags (n = 3).

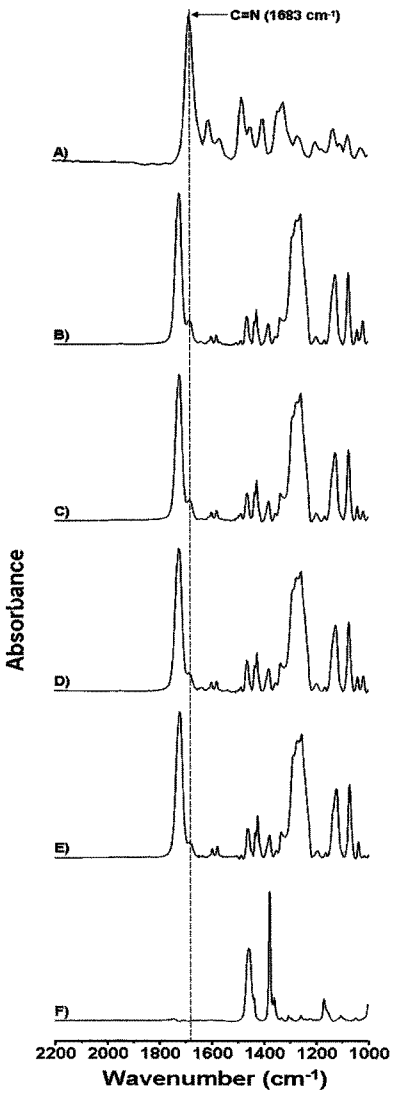


**Figure 6.** FTIR spectra of the diazepam, diazepam stored in infusion bag during 24 h. (A) FTIR spectrum of diazepam, (B-E) diazepam stored in PVC bag (according to 1.2, 0.8, 0.4 mg/mL, 40 μg/mL concentration), (F) diazepam stored in multilayer bag. The small peak at 1683 $cm^{-1}$ appeared due to C=N group of diazepam on the surface of PVC.

diazepam, is shown in Figure 6(A). The intensity of this band increased with the increasing concentration of diazepam in the drug admixtures (Figure 6(C-E)), an indication that Safeflex® may have an affinity for diazepam adsorption and/or has sufficient space for easy diffusion of diazepam into the film surface. In the case of Techflex®, however, no spectral changes were observed.

**Table I. Solubility Parameters of Drug and Infusion Bag**

| Material | Solubility Parameters ($\delta_1$ or $\delta_2$) | $\lvert\delta_1 - \delta_2\rvert$ |
|---|---|---|
| Diazepam | 25.4 ($\delta_1$) | 0 |
| PVC | 19.4 ($\delta_2$) | 6.0 |
| PP | 16.6 ($\delta_2$) | 8.8 |

**Solubility Parameters.** In addition to the problems of diazepam sorption, numerous studies have reported that lipophilic drugs, such as fentanyl citrate, clomipramine hydrochloride, nitroglycerin, chlorpromazine, and wafarin sodium, also trigger the sorption, resulting in the decreased drug concentration.[1,9,13] In terms of the mechanism of the drug sorption in the infusion bag, dissolution ability of the drugs into the inner layer material was considered as the main factor. Thus, the solubility parameters of the drugs and the materials needed to be further evaluated.

The heat generated during the mixing of a drug with a polymer, caused by adsorption and diffusion, can be approximated as follows:

$$\Delta H = \upsilon_1 \upsilon_2 (\delta_1 - \delta_2)^2$$

where $\delta$ is the solubility parameter, and subscripts 1 and 2 refer to drug and materials, respectively. Strong interaction between the drug and the infusion bag can be expected if $|\delta_1 - \delta_2|$ is less than 3.5-4.0. This approach to the diffusibility and the solubility of the polymers has been extensively used in the fields of polymer chemistry.[14,15] The values of $\delta_1$ and $\delta_2$ of the materials used in the present study were calculated using Burrell and Hoy's equation (Table I):[14,16]

$$\delta = \frac{\rho \Sigma E}{M}$$

where values of $E$ are summed over the structural configuration of the repeating unit in the polymer chain, with repeat molecular weight $M$ and density $\rho$.

The difference between the solubility parameter of diazepam and PVC was 6.0, whereas that of diazepam and PP was much higher at 8.8. This implies the diffusion of diazepam into PVC is much easier than that into PP. However, because $|\delta_{Diazepam} - \delta_{PVC}|$ value of the PVC bag was beyond the range of easy diffusion, favored diffusion of the drug into the PVC bag can hardly be expected. Therefore, further studies on the chain characteristics of the polymers, such as crystallinity, amorphousness, and glassiness, are necessary to clarify the diffusion mechanism of the drug into the bag materials.

**Crystallinity of the Inner Layer Material.** Figure 7 shows the DSC thermogram of the infusion bags. The melting temperature of the PVC bag was 45.03 °C . In the multilayer bag, three melting temperature peaks appeared at 47.06, 128.56, and 165.02 °C, respectively corresponding to each layer of the multilayer bag, elastomeric alloy (tie layer), PP of the inner layer, and PP of the outer layer. The crystallinity of Safeflex® was determined to be 0.96%, and this extremely amorphous characteristic of the PVC film can be attributed to the large amount of DEHP incorporated between the PVC main chains. As reported by the manufacturer, Safeflex® contains, as a plasticizer, around 53-63% DEHP.[17] This high concentration of DEHP may induce the loosening of the intermolecular bond, resulting in the production of an amorphous structure, which, in turn, facilitates the diffusion of the diazepam molecules into the bag.[9] On the other hand, the crystallinity of the inner layer of Techflex® was 17.79%. Considering the crystalline structure, together with its poor affinity for diazepam, there is little possibility that diazepam infuses into Techflex®.

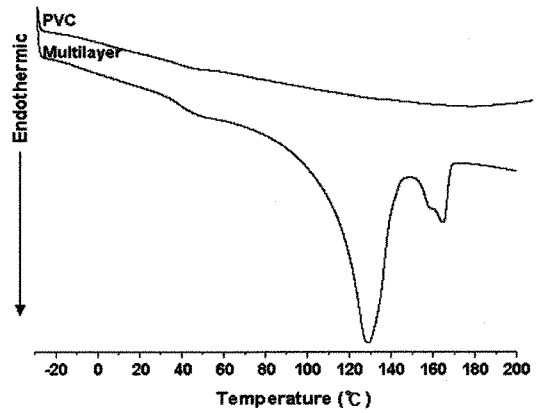


**Figure 7.** DSC curves of PVC and multilayer bags. Three melting points appeared in the multilayer bag, which indicate that the multilayer consisted of three materials.

## Conclusions

Techflex®, a newly developed PP-lined multilayer infusion bag, was studied for its compatibility with diazepam, comparatively with the conventional infusion bag, Safeflex® comprised of PVC. FTIR and GC studies showed that the concentration of diazepam in the 0.9% sodium chloride solution remained practically unchanged in the Techflex® infusion bags for 24 h, whereas the admixtures stored in the Safeflex® bags showed a significantly high sorption. These results can be attributed to the differences in the crystallinities and the solubility parameters between the two polymers. Although the present study indicates Techflex® is superior to the PVC bags, further studies should be conducted with additional drugs and solvents to confirm the safety and efficacy of the newly developed infusion bag.

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