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# Diazepam sorption to PVC- and non-PVC-based tubes in administration sets with quantitative determination using a high-performance liquid chromatographic method

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ABSTRACT

Diazepam is highly sorbed to the plastic materials of administration sets for intravenous infusion. This can be detrimental as it should be delivered to the patient at the administered amount for efficacy and safety. We report here the sorption levels of diazepam onto various types of tubes in administration sets. The tube materials of the administration sets included polyvinylchloride (PVC) and the non-PVC materials such as polyurethane (PU) and polyolefin (PO) were used. Two conditions of diazepam administered in preclinical and clinical settings were tested using an infusion pump. Injections were prepared by diluting diazepam to 20 mg/500 mL and 10 mg/100 mL in 5% dextrose. Diluted diazepam solutions at the concentrations of 10 mg/100 mL and 20 mg/500 mL were separately delivered through 1 m of tubing at 1 mL/min for 1.05 and 4.05 h. Samples were analyzed using a high-performance liquid chromatography with UV detection. PVC- and PU-based tubes showed higher sorption of diazepam than did PO-based tubes. PO-based tubes delivered more than 90% of the administered diazepam. The results showed that PO-based tubes of administration sets have a promising potential to deliver hydrophobic drugs like diazepam with minimal sorption levels. In addition, the tube materials in administration sets may be one of the critical factors to ensure drug efficacy and safety.



## 1. Introduction

Diazepam is a benzodiazepine derivative (Fig. 1a) classified as a psychotic drug, is widely used to treat anxiety, insomnia, muscle spasm, and alcoholic withdrawal, and is also useful as a premedication for medical or dental procedures (Chen et al., 2011; Durrmeyer et al., 2010). In particular, diazepam has been studied as a treatment for epileptic seizure as a first-line anticonvulsant (Chen et al., 2011; Gholipour et al., 2009). Although diazepam is generally administered in an oral route, it should be administered as an intravenous (IV) infusion in the case of severe and urgent patient conditions like status epilepticus (Durrmeyer et al., 2010; Mehta et al., 2007; Singhi et al., 1998). For IV infusion, the delivered concentration of diazepam is a critical factor affecting patient disease status (Singhi et al., 1998). However, sorption of diazepam to the polymeric materials composing the administration sets is one of the limitations to drug safety and efficacy (Treleano et al., 2009).

Diazepam sorption, including adsorption and absorption, to administration sets and plastic bags during IV infusion has been reported (Jenke, 1993a,b; Martens et al., 1990; Roberts et al., 1991; Tchiakpe et al., 1995; Treleano et al., 2009). In administration sets, plastic tube materials affect drug sorption through physical and chemical interactions between tubes and drugs. Polyvinylchloride (PVC) (Fig. 1b) and non-PVC materials such as polyurethane (PU) (Fig. 1c) and polyolefin (PO) (Fig. 1d) are widely used as biocompatible polymers for administration sets. However, PVC tubes have leaching problems due to the use of plasticizers like di-(2-ethylhexyl) phthalate (DEHP), which is a reproductive toxicant (Arruda et al., 1989; Jenke, 1993a; Martens et al., 1990). In previous cases, DEHP was released from PVC tubes due to their interaction with surfactants, including in injections of poorly soluble drugs (Hanawa et al., 2003; Hanawa et al., 2000).

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To prevent drug sorption, multilayered materials with a layer-by-layer design have been developed as alternatives without plasticizers (Kambia et al., 2005; Treleano et al., 2009). These are composed of non-PVC materials, providing compatibility with drug and excipients in injection formulations. In particular, PO materials were developed to replace PVC materials in biomedical devices (e.g., drug containers, syringes, and administration sets) (Mason et al., 1981; Tchiakpe et al., 1995; Trissel et al., 2006). These materials minimize drug-medical device interactions during the administration of injections.

In this study, we investigated the sorption kinetics of diazepam to PVC or non-PVC tubes (PU and PO) in administration sets. For diazepam, two conditions of concentration and application time were monitored using a flow-through model of tubes with an infusion pump (Fig. 2). Diazepam concentrations in the samples were analyzed using a simple high-performance liquid chromatography (HPLC) with UV detection (Mercolini et al., 2009; Sruthi et al., 2013). Sorption profiles of diazepam were established to compensate the drug loss and to search for alternative materials for tubes of administration sets.

## 2. Materials and methods

### 2.1. Chemicals

Diazepam was obtained from Daewon Pharma., Co., Ltd. (Seoul, Korea). Diazepam injections (1 mg/mL, total 2 mL; Daewon diazepam injection®, Daewon Pharma. Co., Ltd., Hwaseong, Gyunggi, Korea) were purchased from Woori Pharm. Inc (Incheon, Korea). For the administration sets, PVC-, PU-, and PO-based tubes were kindly obtained from Polyscientech Co., Ltd. (Anseong, Gyunggi, Korea). Plasticizers such as phthalic acid esters were not used in the manufacturing process of non-PVC-based tubes.

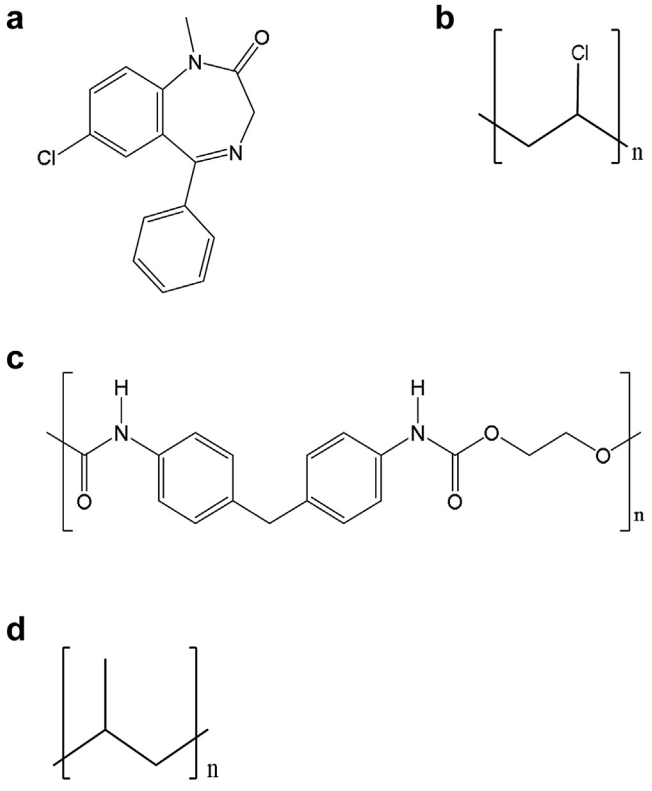


**Fig. 1.** Chemical structures of (a) diazepam and polymeric materials in IV administration sets: (b) PVC, (c) PU, and (d) PO (polypropylene).

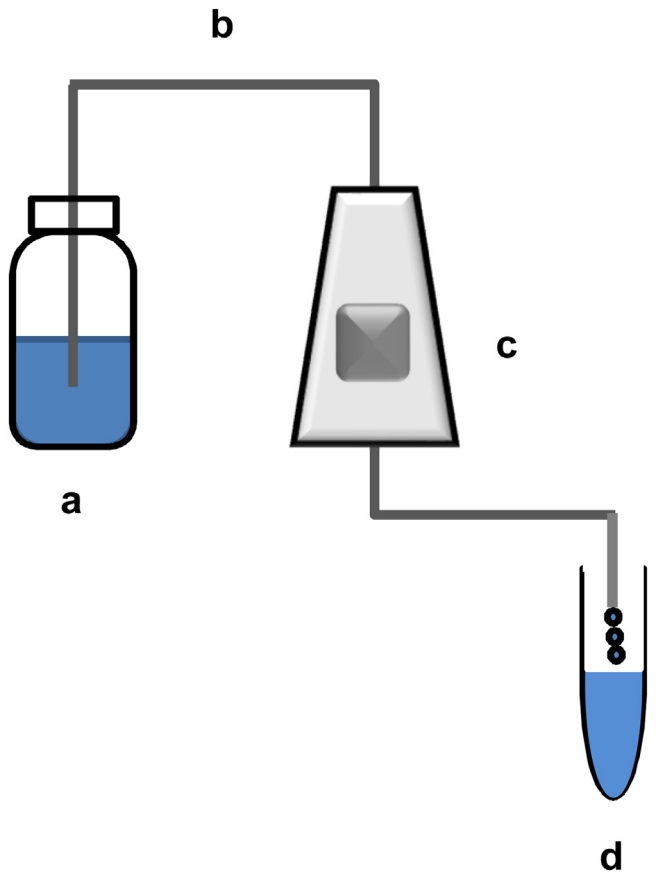


**Fig. 2.** Schematic diagram of the sorption kinetic study using an infusion pump: (a) diazepam diluted in 5% dextrose solution (Bottle), (b) tube of administration set (total 1 m in length), (c) infusion pump, and (d) diazepam passed through the tube.

Acetonitrile and methanol were obtained from Burdick and Jackson Co., Ltd. (MI, USA). Sodium dihydrogen phosphate was purchased from Sigma (St. Louis, MO, USA). Water was purified by a Milli-Q system (Millipore Corp., Bedford, MA, USA). All other chemicals and solvents were of analytical reagent grade.

### 2.2. Determination of diazepam

Diazepam was analyzed using the HPLC method with UV detection. Diazepam was dissolved in methanol at the concentration of 1 mg/mL as a stock solution. It was diluted to 20 μg/mL and then 2:1 serially diluted with methanol to 0.3125 μg/mL as a standard solution. Samples were filtered using syringe filters (PTFE 0.45 μm, Whatman, GE Healthcare, Germany) prior to HPLC injection. After filtration, 10 μL of blank and standard solutions (0.3125, 0.625, 1.25, 2.5, 5.0, 10.0, and 20.0 μg/mL) were directly injected to the HPLC system (Agilent 1260, Agilent, Santa Clara, CA, USA) equipped with a $C_{18}$ column (1.5 mm × 250 mm, 5 μm, Shiseido, Japan). The mobile phase was a mixture of acetonitrile, methanol, and sodium phosphate buffer (29:47:24, v/v/v), which was adjusted to pH 3.1 with phosphoric acid. The flow rate was 0.1 mL/min. Diazepam was detected at 232 nm. The retention time and average peak areas were recorded and analyzed using ChemStation software (Rev.B.04.03, Agilent Technologies, Santa Clara, CA, USA). Total run time was 10 min for each sample.

#### 2.2.1. Specificity

The peak of diazepam was monitored to determine if it was separated from other peaks in the chromatogram.

*2.2.2. Linearity*

The concentrations for calibration curves of diazepam were prepared in the range of 0.3125–20.0 μg/mL with a 2:1 serial dilution. Calibration curves were constructed by plotting average peak areas against concentrations, and a regression equation was computed.

*2.2.3. Filtering efficiency*

The filtering efficiency of diazepam was calculated as a percentage of the concentration of filtered to unfiltered sample. The samples were measured in triplicate.

*2.3. Sorption kinetic study*

Diazepam sorption to tubes of administration sets was kinetically monitored in this study. Diazepam injections were diluted into bottled 5% dextrose solution (JW Pharmaceutical, Seoul, Korea) at the concentrations of 20 mg/500 mL and 10 mg/100 mL. The diluted diazepam solutions were prepared in bottles to prevent sorption of diazepam to plastic bags. PVC-, PU-, and PO-based tubes of administration sets were used to compare the sorption kinetics of diazepam to different types of polymers. After loading the tubes with the diluted diazepam solutions for 3 min, the administration sets were connected to an infusion pump (Terumo infusion pump, Terumo Medical Corp., USA). The diluted diazepam solutions were delivered through the tubes at a flow rate of 1 mL/min. Samples were collected in amber vials at various time points. The samples were appropriately diluted, and 10 μL of diluted sample was directly injected into the HPLC system. Analysis of diazepam was performed as mentioned above.

*2.3.1. Case #1*

- Diazepam concentration: 20 mg/500 mL.
- Sampling points: 0.05, 0.30, 0.55, 1.05, 2.05, and 4.05 h.

*2.3.2. Case #2*

- Diazepam concentration: 10 mg/100 mL.
- Sampling points: 0.05, 0.30, 0.55, and 1.05 h.

*2.4. Statistical analysis*

All results are expressed as mean ± SD. Statistical analysis was performed using Student's *t*-test and analysis of variance (ANOVA). A p value less than 0.05 was considered significant.

## 3. Results

*3.1. Analysis of diazepam*

*3.1.1. Specificity*

Fig. 3 shows the representative chromatograms of diazepam. Compared with methanol used as a blank (Fig. 3a), the peak of diazepam was detected at 8.2 min of retention time in the chromatogram (Fig. 3b and c). Fluctuations in retention time in the chromatograms occurred within 1 min based on the changes in temperature and column performance.

*3.1.2. Linearity*

Calibration curves of diazepam were plotted in the concentration range of 0.3125–20 μg/mL (Fig. 4). The curve showed excellent linearity and correlation coefficient. The mean regression equation of six replicated calibration curves was y = 629.7274 (±4.0531) x + 45.9062 (±35.3773) (y = diazepam concentration, x = peak area) with an r-square of 0.99.

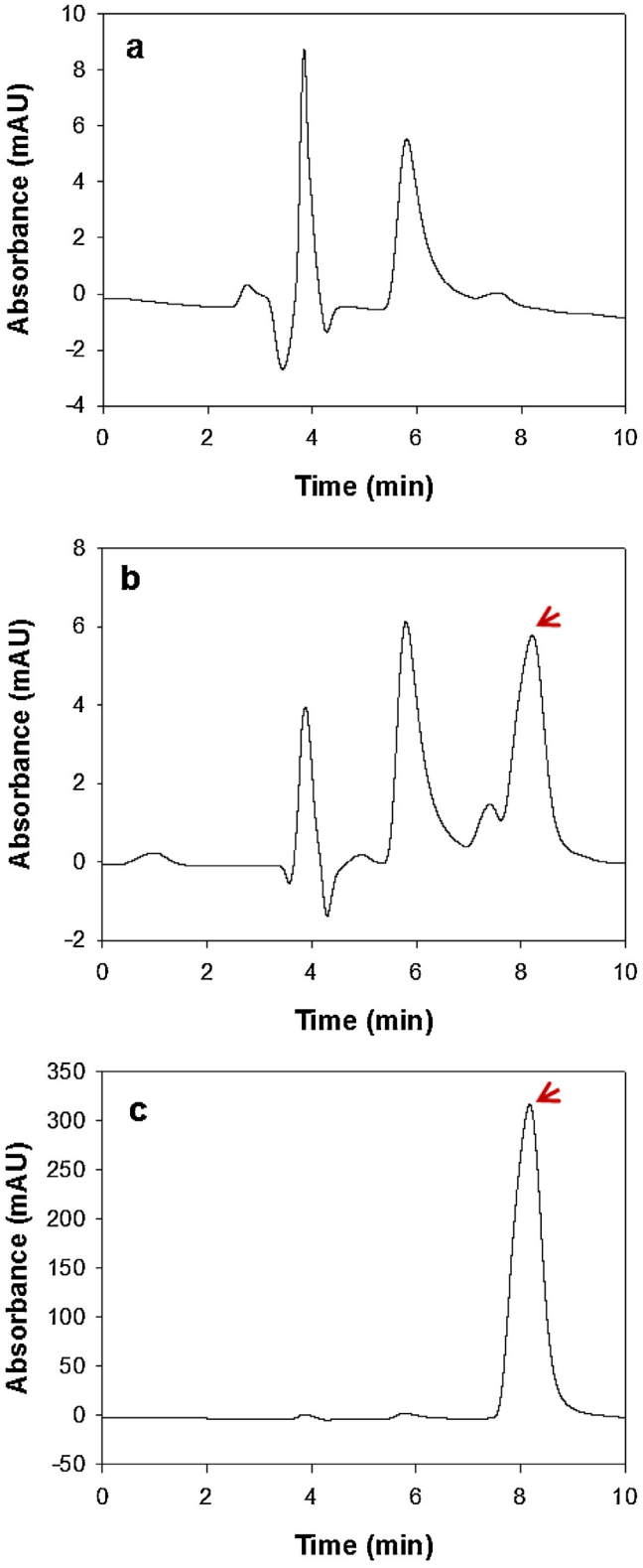


**Fig. 3.** Representative chromatograms of (a) blank and diazepam at the concentrations of (b) 0.3125 μg/mL as the limit of quantification (LOQ) and (c) 20 μg/mL as the highest concentration. Red arrows represent the diazepam peaks at 8.2 min in the chromatograms. Methanol was used as a blank sample. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

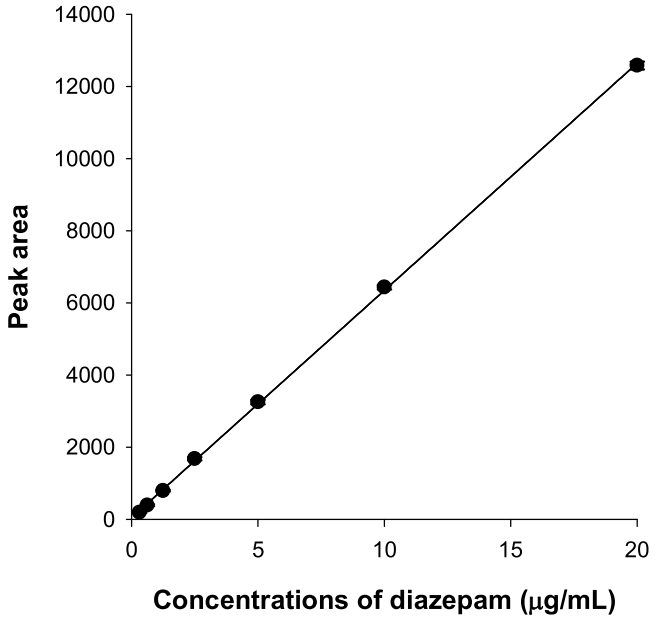


**Fig. 4.** Calibration curve of diazepam in the concentration range of 0.3125–20.0 μg/mL. The equation of the calibration curve was y = 629.7274 (±4.0531)x + 45.9062 (±35.3773) with r-square value of 0.99. The results are expressed as mean ± SD (n = 6).

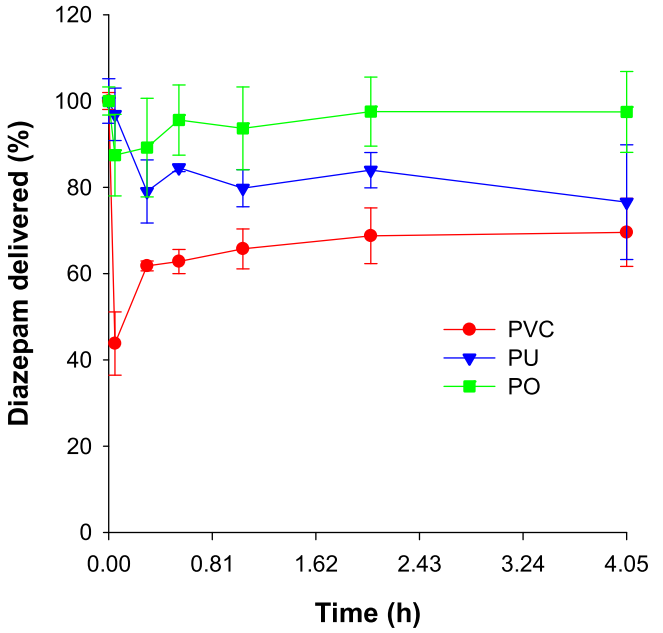


**Fig. 5.** Case #1: Profiles of diazepam sorption to PVC- and non-PVC tubes. Diazepam concentration was used at 20 mg/500 mL. Diazepam solution was passed through PVC-, PU-, and PO-based tubes at a fixed flow rate of 1 mL/min. Samples were collected at 0.05, 0.30, 0.55, 1.05, 2.05, and 4.05 h. Sorption profiles were plotted as diazepam delivered (%) vs. time (h). The results are expressed as mean ± SD (n = 3).

*3.1.3. Filtering efficiency*

Comparing filtered with unfiltered samples in triplicate, the filtering efficiency of diazepam was higher than 90%. Diazepam was filtered with a minimal loss, suggesting that filtering is a suitable tool for preparation of samples. Table 1 lists the filtering efficiencies of the different diazepam concentrations.

*3.2. Sorption kinetics of diazepam to tubes*

We kinetically determined the sorption profiles of diazepam to PVC- or non-PVC-based tubes in administration sets. For this purpose, two infusion conditions of diazepam were used at the fixed flow rate of 1 mL/min. In case #1, the diazepam concentration was low at 20 mg/500 mL and was monitored for 4.05 h. In case #2, the diazepam concentration was 10 mg/100 mL, which was relatively high. Sorption in case #2 was monitored for 1.05 h.

*3.2.1. Case #1*

In case #1, we used a diazepam concentration of 20 mg/500 mL diluted with 5% dextrose solution and monitored the sorption profiles of diazepam to tubes (Fig. 5). We confirmed the high diazepam sorption to PVC- and PU-based tubes with delivery levels equilibrated to 70% and 77%, respectively. Although PO-based tubes demonstrated sorption in the early phase up to 0.55 h, they delivered higher than 90% of the administered diazepam after sorption equilibrium.

**Table 1**
Filtering efficiencies of diazepam (n = 3).

| Diazepam (μg/mL) | Filtered/Unfiltered (%) |
|---|---|
| 20.0 | 99.1 ± 2.3 |
| 10.0 | 92.0 ± 1.8 |
| 5.0 | 96.9 ± 0.7 |
| 2.5 | 95.6 ± 1.3 |
| 1.25 | 90.7 ± 1.9 |
| 0.625 | 95.8 ± 2.8 |
| 0.3125 | 94.9 ± 3.0 |

*3.2.2. Case #2*

Because the low concentration of diazepam showed a high sorption level, we investigated the sorption level at the high concentration of diazepam of 10 mg/100 mL (Fig. 6). In the case of PVC-based tubes, the delivered diazepam level after 0.05 h was reduced to 76% and was further reduced to 62% at 0.30 h. In the same time, delivered diazepam levels in PU-based tubes were reduced to 81% and 74% after 0.05 h and 0.30 h, respectively. However, in PO-based tubes, delivered diazepam levels were maintained over 90% throughout the test period.

## 4. Discussion

Diazepam as an anticonvulsant (Fig. 1a) can be delivered to patients using an administration set in a severe disease state like status epilepticus. In such cases, the sorption of diazepam to materials of the administration sets can be detected (Martens et al., 1990; Mason et al., 1981). This sorption includes both adsorption on the surface materials and absorption into polymer matrices (Treleano et al., 2009). Avoidance of such sorption is critical to properly deliver drugs to patients (Arruda et al., 1989; Cloyd et al., 1980). Herein, we reported the diazepam sorption with PVC- (Fig. 1b) and non-PVC-based tubes (Fig. 1c–d) in administration sets. A flow-through model of tubes was used after preloading the injectable solutions with an infusion pump. Tubes were loaded for 3 min before starting the tests. All tubes were 1 m long to exclude the effect of tube length on the drug sorption (Fig. 2). In addition, the tubes did not contain other components (e.g., in-line filters, Y-tube with cap, etc.) to eliminate other factors potentially affecting sorption in administration sets.

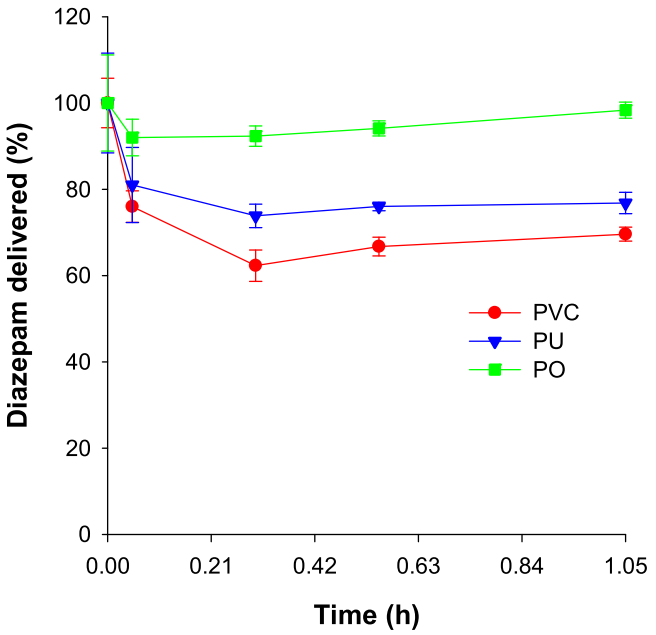


**Fig. 6.** Case #2: Profiles of diazepam sorption to PVC- and non-PVC tubes. A high concentration of diazepam was used at 10 mg/100 mL to mimic the initial dose for the treatment of status epilepticus. Flow rate was fixed at 1 mL/min. Samples after passing through the tubes were collected at 0.05, 0.30, 0.55, and 1.05 h. Sorption profiles of diazepam using PVC-, PU-, and PO-based tubes were plotted as drug delivered (%) vs. time (h). The results are expressed as mean ± SD (n = 3).

For drug sorption on polymer matrices of tubes, several phenomena have been investigated including partitioning of drugs between the polymer and contact media, which is related to the hydrophobicity of injectable drugs (Jenke, 1993b; Treleano et al., 2009). Drugs delivered through the tubes of administration sets equilibrate between the polymeric materials of the tubes and the injectable media. Because of this, the partition coefficient and log P of a drug are major factors that can explain drug sorption to polymeric tubes. Drug sorption is also affected by the structure-based polarity and molecular weight of the polymers used in administration sets (Farid et al., 2016). Furthermore, chemicals such as phthalic acid ester plasticizers may leach from PVC-based tubes due to their interaction with components in the injections (Hanawa et al., 2000). Leaching of chemicals from the tubes can induce toxicity (Erythropel et al., 2014; Wu et al., 2014) and lead to drug loss (Kim et al., 2005; Zhang et al., 2015). The extent of drug sorption is not easily predicted in administration sets since they are dynamic systems, however it can be explained by several factors including partitioning, diffusion, leaching, hydrophobicity, and other drug properties.

PVC-based polymeric tubes of administration sets and bags for containers are reported to have safety problems for drug sorption (Martens et al., 1990; Roberts et al., 1991; Van Dooren, 1991). Many drugs including diazepam (e.g., nitroglycerin, isosorbide dinitrate, etc.) have sorption to PVC-based polymers. The sorption levels of drug to PVC-based polymers are more than 50%. Thus, non-PVC materials are extensively used as alternatives to avoid the problems of PVC (Treleano et al., 2009; Trissel et al., 2006). In IV products including administration sets and IV tubing, the products consisting of PVC with plasticizers have recently begun to be replaced with PVC-free or DEHP-free polymeric materials. The PU and PO used in this study not only have advantages of mechanical properties such as elasticity, transparency, and hardness, but also avoid drug sorption and plasticizer leaching. Commercial products made of PU and PO are already used in administration tubes and bags as well as syringes and catheters for IV products (Kambia et al., 2005; Trissel et al., 2006).

Diazepam in pharmaceutical dosage forms, plasma, and tissues is usually monitored with a HPLC method (Behnoush et al., 2015; Mercolini et al., 2009; Sruthi et al., 2013). To quantify the diazepam concentration and calculate the sorption levels to tubes of administration sets, we analyzed the drug using a simple HPLC method with UV detection. Diazepam was specifically and reproducibly detected (Fig. 3) with linearity in the concentration range of 0.3125–20 μg/mL (Fig. 4). In addition, filtering loss of diazepam at the various concentrations was lower than 10% (Table 1). The method developed in this study was successfully applied to diazepam sorption tests.

Next, we tested diazepam sorption to tubes of administration sets. Factors considered in the sorption tests were composition of tubes in administration sets (PVC, PU, and PO) and diazepam concentrations (high and low). Flow rate and the length of the tubes were fixed. In all cases, there was diazepam sorption to the tubes, however PO-based tubes delivered more than 90% of the administered diazepam. Sorption of diazepam administered at a low concentration (20 mg/500 mL) increased up to 0.55 h and then reached equilibrium (Fig. 5). PVC- and PU-based tubes showed higher sorption levels than PO-based tubes. Diazepam administered at a high concentration (10 mg/100 mL) was also sorbed to PVC- and PU-based tubes. However, the sorption level to PO-based tubes was reduced (Fig. 6). The level of sorption was highest in PVC-based tubes, lower in PU-based tubes, and lowest in PO-based tubes.

The pattern of outflow concentration of diazepam can be explained using nonlinear regression with a convection-interfacial resistance-diffusion model with the tubing preloaded with solution (Roberts, 1996). Drugs delivered through tubes of administration sets partition to polymeric tubes early on during infusion and then equilibrate after diffusion of adsorptive drugs from the tubes (Roberts, 1996). Log P is an important value that can explain how a drug will interact with polymers in the tubes. Drugs with a high log P value are likely to partition to polymeric tubes of administration sets. Indeed, the physicochemical nature of polymers in tubes is a critical factor that can be used to prevent an interaction with injectable drugs (Treleano et al., 2009). The sorption levels of diazepam, a lipophilic drug with a high log P value of 2.82 (Mercolini et al., 2009), were different based on the tube material. For this reason, alternatives without toxicity and sorption capacity have been developed using various polymeric materials and designs to block the interaction of inner tube surface and contact infusion media (Kambia et al., 2005; Trissel et al., 2006). In this study, PO-based tubes showed a relatively low sorption potential compared with PVC- and PU-based tubes. The results showed that PO can minimize the interaction with diazepam as it passes through the tubes and suggest that diffusion and partition of active ingredients on the surface and polymer matrix of PO tubes can be equilibrated with reduced drug loss compared to PVC- and PU-based tubes (Roberts, 1996).

## 5. Conclusion

We confirmed diazepam sorption profiles in PVC- and non-PVC-based tubes of administration sets using an infusion pump in two preclinical and clinical conditions of diazepam uses. A simple HPLC method with UV detection was developed and successfully applied for the determination of diazepam in injection solutions. In this study, PVC- and PU-based tubes showed high sorption of diazepam, whereas PO-based tubes delivered more than 90% of the administered diazepam. The results suggest that PO-based

tubes of administration sets are a promising alternative to deliver hydrophobic drugs like diazepam with minimal sorption.

## Conflict of interest

No conflict of interests to declare.

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## References

Arruda, W.O., Brito Filho, D., Rosa, S.L., Fontoura, P.S., Cardoso Mde, A., 1989. Factors affecting diazepam availability from intravenous admixture solutions. Arquivos de neuro-psiquiatria 47, 291–294.
Behnoush, B., Sheikhazadi, A., Bazmi, E., Fattahi, A., Sheikhazadi, E., Saberi Anary, S. H., 2015. Comparison of UHPLC and HPLC in benzodiazepines analysis of postmortem samples: a case-control study. Medicine (Baltimore) 94, e640.
Chen, W.B., Gao, R., Su, Y.Y., Zhao, J.W., Zhang, Y.Z., Wang, L., Ren, Y., Fan, C.Q., 2011. Valproate versus diazepam for generalized convulsive status epilepticus: a pilot study. Eur. J. Neurol. 18, 1391–1396.
Cloyd, J.C., Vezeau, C., Miller, K.W., 1980. Availability of diazepam from plastic containers. Am. J. Hosp. Pharm. 37, 492–496.
Durrmeyer, X., Vutskits, L., Anand, K.J.S., Rimensberger, P.C., 2010. Use of analgesic and sedative drugs in the NICU: integrating clinical trials and laboratory data. Pediatr. Res. 67, 117–127.
Erythropel, H.C., Maric, M., Nicell, J.A., Leask, R.L., Yargeau, V., 2014. Leaching of the plasticizer di(2-ethylhexyl)phthalate (DEHP) from plastic containers and the question of human exposure. Appl. Microbiol. Biotechnol. 98, 9967–9981.
Farid, O., Mansour, F., Habib, M., Robinson, J., Tarleton, S., 2016. Investigating the sorption influence of poly(vinyl alcohol) (PVA) at different crosslinking content. J. Environ. Chem. Eng. 4 (1), 293–298.
Gholipour, T., Rasouli, A., Jabbarzadeh, A., Nezami, B.G., Riazi, K., Sharifzadeh, M., Dehpour, A.R., 2009. The interaction of sildenafil with the anticonvulsant effect of diazepam. Eur. J. Pharmacol. 617, 79–83.
Hanawa, T., Muramatsu, E., Asakawa, K., Suzuki, M., Tanaka, M., Kawano, K., Seki, T., Juni, K., Nakajima, S., 2000. Investigation of the release behavior of diethylhexyl phthalate from the polyvinyl-chloride tubing for intravenous administration. Int. J. Pharm. 210, 109–115.
Hanawa, T., Endoh, N., Kazuno, F., Suzuki, M., Kobayashi, D., Tanaka, M., Kawano, K., Morimoto, Y., Nakajima, S., Oguchi, T., 2003. Investigation of the release behavior of diethylhexyl phthalate from polyvinyl chloride tubing for intravenous administration based on HCO60. Int. J. Pharm. 267, 141–149.
Jenke, D.R., 1993a. Modeling of solute sorption by polyvinyl chloride plastic infusion bags. J. Pharm. Sci. 82, 1134–1139.
Jenke, D.R., 1993b. Evaluation of varîous solvent systems for modelîng solute sorption with plasticîzed polyvinyl chlorîde materials. J. Pharm. Sci. 82, 617–662.
Kambia, N.K., Dine, T., Dupin-Spriet, T., Gressier, B., Luyckx, M., Goudaliez, F., Brunet, C., 2005. Compatibility of nitroglycerin, diazepam and chlorpromazine with a new multilayer material for infusion containers. J. Pharm. Biomed. Anal. 37, 259–264.
Kim, S.C., Yoon, H.J., Lee, J.W., Yu, J., Park, E.S., Chi, S.C., 2005. Investigation of the release behavior of DEHP from infusion sets by paclitaxel-loaded polymeric micelles. Int. J. Pharm. 293, 303–310.
Martens, H.J., De Goede, P.N., Van Loenen, A.C., 1990. Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. Am. J. Hosp. Pharm. 47, 369–373.
Mason, N.A., Cline, S., Hyneck, M.L., Berardi, R.R., Ho, N.F., Flynn, G.L., 1981. Factors affecting diazepam infusion: solubility, administration-set composition, and flow rate. Am. J. Hosp. Pharm. 38, 1449–1454.
Mehta, V., Singhi, P., Singhi, S., 2007. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. J. Child Neurol. 22, 1191–1197.
Mercolini, L., Mandrioli, R., Iannello, C., Matrisciano, F., Nicoletti, F., Raggi, M.A., 2009. Simultaneous analysis of diazepam and its metabolites in rat plasma and brain tissue by HPLC-UV and SPE. Talanta 80, 279–285.
Roberts, M.S., Kowaluk, E.A., Polack, A.E., 1991. Prediction of solute sorption by polyvinyl chloride plastic infusion bags. J. Pharm. Sci. 80, 449–455.
Roberts, M.S., 1996. Modeling solute sorption into plastic tubing during organ perfusion and intravenous infusions. J. Pharm. Sci. 85, 655–665.
Singhi, S., Banerjee, S., Singhi, P., 1998. Refractory status epilepticus in children: role of continuous diazepam infusion. J. Child Neurol. 13, 23–26.
Sruthi, A., Tejaswi, P., Thanuja, N., Sudheer Kumar, D., Vivek Sagar, P., 2013. Simple RP-HPLC method for estimation of diazepam in tablet dosage form. J. Pharm. Res. 6, 140–144.
Tchiakpe, L., Airaudo, C.B., Abdelmalik, O.M., Gayte-Sorbier, A., Verdier, M., Guerri, J., 1995. Stedim 6 and Clearflex, two new multilayer materials for infusion containers. Comparative study of their compatibility with five drugs versus glass flasks and polyvinyl chloride bags. J. Biomater. Sci. Polym. Ed. 7, 199–206.
Treleano, A., Wolz, G., Brandsch, R., Welle, F., 2009. Investigation into the sorption of nitroglycerin and diazepam into PVC tubes and alternative tube materials during application. Int. J. Pharm. 369, 30–37.
Trissel, L.A., Xu, Q.A., Baker, M., 2006. Drug compatibility with new polyolefin infusion solution containers. Am. J. Health Syst. Pharm. 63, 2379–2382.
Van Dooren, A.A., 1991. PVC as pharmaceutical packaging material. A literature survey with special emphasis on plasticized PVC bags. Pharm. Weekblad. Sci. Ed. 13, 109–118.
Wu, Q., Zhang, N., Shen, Y., Jia, Y., Lei, W., 2014. Influence of polyvinyl chloride infusion extension tube on propofol injection pain: a randomised controlled study. Eur. J. Anaesthesiol. 31, 663–668.
Zhang, H., Yang, F., Shen, G., Yang, Y., Tang, Y., 2015. Comparison of the release behaviors of di (2-ethylhexyl) phthalate and tri(2-ethylhexyl) trimellitate from the polyvinyl-chloride infusion set into pharmaceutical solutions. Chin. J. Chromatogr./Zhongguo hua xue hui 33, 522–529.