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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.

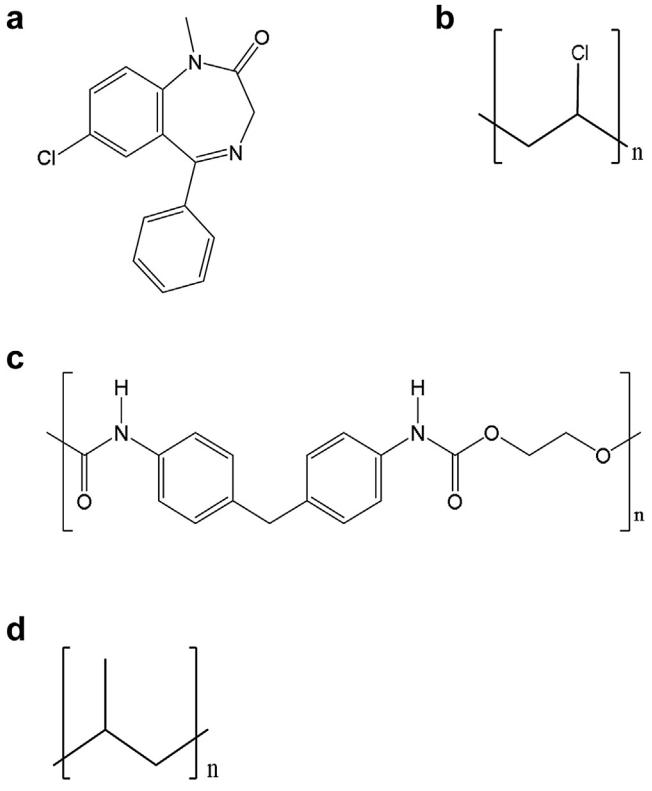

Fig. 1. Chemical structures of (a) diazepam and polymeric materials in IV administration sets: (b) PVC, (c) PU, and (d) PO (polypropylene).

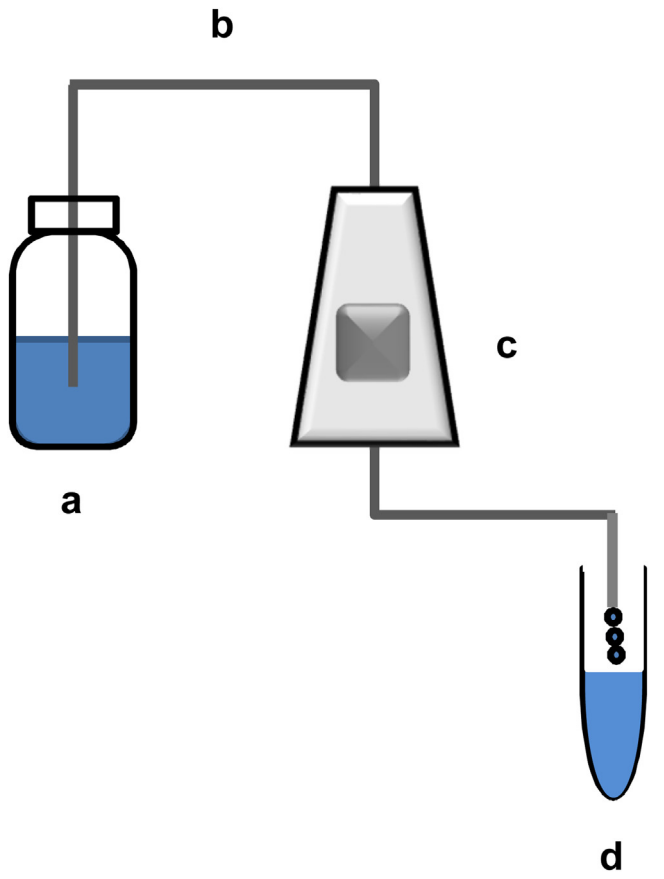

Fig. 2. Schematic diagram of the sorption kinetic study using an infusion pump: (a) diazepam diluted in 5% dextrose solution (Bottle), (b) tube of administration set (total 1 m in length), (c) infusion pump, and (d) diazepam passed through the tube.

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.