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Development of a simple method for predicting the levels of di(2-ethylhexyl) phthalate migrated from PVC medical devices into pharmaceutical solutions

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Abstract

This study deals with the development of a simple method for predicting the elution levels of di-2-ethylhexyl phthalate (DEHP) from medical devices made of polyvinyl chloride (PVC) by using the physicochemical properties of pharmaceutical injections as a marker. GC-MS analysis showed that the release of DEHP from medical grade PVC product was concentration-dependently increased by extraction with two kinds of lipophilic injections (Sandimmun® and Prograf®) and three kinds of surfactants (HCO-60, Tween® 80, and SDS). The solubility of lipophilic pigments such as Sudan III, methyl yellow, and 1,4-diamino-anthraquinone against these solutions were also increased in a concentration-dependent manner, in which methyl yellow showed the highest response regarding the increase of optical density (O.D.). Further, electrical conductivity and static contact angle to the PVC sheet of the solutions were also increased or decreased in the same manner. As a result of the comparative study, significant correlation was found between DEHP release levels and these three physicochemical properties, particularly methyl yellow solubility, of the solutions tested. To evaluate the relationship in detail, DEHP release levels from PVC tubing and methyl yellow solubility of 53 injections used in gynecologic and obstetric fields were determined. None of the hydrophilic medicines showed any significant release of DEHP, and all showed low solubility of methyl yellow. On the other hand, the lipophilic medicines releasing a large amount of DEHP showed high solubility of methyl yellow (greater than O.D. 0.8). These

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results indicate that a significant proportional relationship exists between DEHP release potency and methyl yellow solubility of pharmaceutical solutions, and the risk of DEHP exposure to the patients administered pharmaceuticals through transfusion set could be easily predicted by the solubility test without complicated elution tests of DEHP using GC-MS or LC-MS.

Keywords: DEHP; PVC; Medical device; Prediction; Risk assessment

1. Introduction

Phthalate esters, and DEHP in particular, have been extensively used as plasticizers due to the increased flexibility of PVC a plastic polymer used in a wide array of products including medical devices such as tubings, intravenous bags, blood containers, and catheters. DEHP is easily eluted from PVC products into not only foods but also pharmaceuticals and body fluids that come in contact with the plastic, and the migrated DEHP is directly and/or indirectly introduced into the human body (Allwod, 1986; Loff et al., 2000; Tickner et al., 2001). Some phthalates including DEHP are considered to be a toxic compound exhibiting effects similar to those of endocrine disruptors in rodents; they have antiandrogenic effects in male rats during the development of the male reproductive system and the production of normal sperm (Poon et al., 1997; Lamb et al., 1987; Tyl et al., 1988), and decrease the 17β-estradiol level in blood in female rats (Davis et al., 1994). General toxicity of DEHP has been well evaluated, and so far the result of risk assessment to human health indicates that this compound is relatively safe to humans. However, because the reproductive and developmental toxicity of DEHP to the human body is not well understood, it has recently been suggested that precautions be taken to limit the exposure of humans, particularly that of high risk patient groups such as male neonates, male fetuses, and peripubertal males, to DEHP. The concern is that DEHP's potency might have adverse effects on humans similar to those demonstrated on young rodents.

Taking the above into consideration, several agencies and official organizations in the world individually evaluated the safety of DEHP released from PVC products (Center for Devices and Radiological Health, 2001; Health Canada, 2002), and the Japanese Ministry of Health, Labor and Welfare (JMHLW) restricted the oral tolerable daily intake (TDI) value to 40–140 μg/kg/day.

It is very important that the exposure amount be exactly determined to conduct a risk assessment of the effect of DEHP on human health. Although some studies on the elution of DEHP from PVC medical devices have been performed as one of the JMHLW projects (Haishima et al., 2004; Inoue et al., 2003a,b; Takatori et al., 2004), it is not easy to identify the release behavior of DEHP from the variety of PVC products used in Japan by elution test under conditions that are the same as or similar to those of medical use. In addition, analytical methods having high sensitivity, precision, selectivity of quantitative ions, and low background, such as tandem LC-MS, high resolution GC-MS, and column-switching LC-MS methods, are required to determine DEHP for clinical assessment. Thus, regardless whether an investigation is in vivo or in vitro, the release test of DEHP is at present time-consuming and labor-intensive.

Jenke (2001) reported that the chemical compatibility assessment considers two distinct yet complementary mechanisms by which a device and its contacted solution can interact. These mechanisms include the migration of a chemical component out of the device and into the contacted solution (leaching) and the sorption of contained solution components by the device (binding). Alternatively, the product/device interaction can be modeled based on a rigorous scientific assessment of the physicochemical processes. Such models are based on the linear correlation of polymer/solution interaction constants with solvent/water partition coefficients (Nasim et al., 1972; Pitt et al., 1988; Hayward et al., 1990; Kenley and Jenke, 1990; Jenke, 1991; Jenke et al., 1991; Atkinson and Duffull, 1991; Roberts et al., 1991; Jenke et al., 1992). In addition, it is known that extraction occurs either by leaching or after an extracting material such as blood and pharmaceutical solutions diffuses into the PVC matrix and dissolves the plasticizer, which is relatively lipophilic. In consideration of these issues, we suspected that the release behavior of DEHP from PVC medical devices may be predicted from the physicochemical properties of