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# Investigation of the release behavior of DEHP from infusion sets by paclitaxel-loaded polymeric micelles

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**Abstract**

The current clinical formulation of paclitaxel (Taxol®) contains 1:1 blend of Cremophor® EL (polyethoxylated castor oil) and dehydrated ethanol. Cremophor® EL and dehydrated ethanol are well known to leach di-(2-ethylhexyl) phthalate (DEHP) from polyvinyl chloride (PVC) infusion bags and PVC administration sets. DEHP is a possible hepatotoxin, carcinogen, teratogen and mutagen. Long-term exposure to DEHP may cause health risks. As an alternative formulation for paclitaxel, paclitaxel-loaded polymeric micelles (PLPM), made of monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA) diblock copolymer, has demonstrated clear advantages over Taxol® in pharmacokinetics and therapeutic index. Paclitaxel in either PLPM or Taxol® formulations, diluted in 0.9% sodium chloride injection, was stable in the PVC infusion bags. The PLPM formulation significantly reduced the amount of DEHP extracted from PVC infusion bags and PVC administration sets. For PLPM diluted in 0.9% sodium chloride injection, the total amount of DEHP delivered over the simulated infusion period was 0.7 mg for 3 h and 2.0 mg for 24 h, which was less than 2.9% of the DEHP extracted by Taxol®. These results confirmed that there is negligible risk of DEHP exposure from diluted PLPM i.v. infusion using PVC infusion bags and PVC administration sets.


*Keywords:* Di-(2-ethylhexyl) phthalate; PVC; Paclitaxel (Taxol®); Polymeric micelles; mPEG-PDLLA

## 1. Introduction

Paclitaxel, a highly active anticancer agent, is effective for treatment of a variety of cancers including refractory ovarian cancer, breast cancer, non-small cell lung cancer, AIDS-related Kaposi's sarcoma, head and

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neck carcinoma and other cancers (Wani et al., 1971; Rowinsky et al., 1990; Holmes et al., 1995; Huizing et al., 1995; Rowinsky and Donehower, 1995; Wall and Wani, 1996). Due to poor solubility in water, paclitaxel (Taxol®) is currently formulated in a 1:1 blend of Cremophor® EL and ethanol (BMS, 2003). The Cremophor® EL formulation has severe pharmaceutical and pharmacological disadvantages: (1) it causes severe allergic reactions (Gregory and DeLisa, 1993; Kohler and Goldspiel, 1994); (2) diluted solution of Taxol® tends to precipitate over time (Straubinger, 1995); (3) Cremophor® EL is the principal determinant in the non-linear behavior of paclitaxel (Hurwitz et al., 1993; Schiller et al., 1994; Sonnichsen et al., 1994; Gianni et al., 1995; Sparreboom et al., 1996); (4) Cremophor® EL and ethanol are incompatible with components of some intravenous infusion sets in routine clinical use (Waugh et al., 1991). Both Cremophor® EL and ethanol are known to leach di-(2-ethylhexyl) phthalate (DEHP) from polyvinyl chloride (PVC) infusion bags and PVC administration sets (Calley et al., 1966). DEHP is suspected to be a hepatotoxin, carcinogen, teratogen and mutagen (Ganning et al., 1984; Hill et al., 2001). The Carcinogen Assessment Group of the US Environmental Protection Agency classified plasticizers such as DEHP as a "probable human carcinogen" (Schulz, 1989). Although the toxicity of DEHP remains low, long-term exposure of DEHP may pose risks to health (FDA, 2002).

To overcome the disadvantages of the current Taxol® formulation, a variety of Cremophor® EL-free formulations including parenteral emulsion, mixed micelles, water-soluble prodrugs, complexes with cyclodextrin, liposomes, microencapsulation systems and polymeric micelles are being developed (Singla et al., 2002). Although the alternative approaches have shown promises in replacing the Cremophor® EL-based vehicle, most of these systems are still at the early stages of research and are far away from use in humans. Among the alternative formulations of paclitaxel, polymeric micelles using biodegradable amphophilic diblock copolymer offer a great deal of advantages over other colloidal systems and conventional dosage forms. Diblock copolymers with biodegradable core-forming blocks have been widely researched for hydrophobic drug delivery (Kwon et al., 1994, 1995; Piskin et al., 1995; Hagen et al., 1996; Inoue et al., 1998; Kim et al., 1998; Kwon, 1998; Yokoyama et al., 1998; Yu et al., 1998; Jones and Leroux, 1999; Yokoyama et al., 1999; Kataoka et al., 2000). The hydrophobic core of polymeric micelles serves as a non-aqueous environment for the drug and the hydrophilic shell interacts with the biological milieu and affects the pharmacokinetic and disposition of the block polymer. Drug delivery using polymeric micelles was recently reviewed by Kwon (2003).

We have developed a polymeric micellar system to deliver paclitaxel using a low molecular weight, non-toxic and biodegradable amphiphilic diblock polymer, monomethoxy poly(ethylene glycol)-block-poly(D,L-lactide) (mPEG-PDLLA). The physicochemical properties, pharmacokinetics, biodistribution and toxicity of mPEG-PDLLA micelles have been reported previously (Zhang et al., 1996; Burt et al., 1999; Liggins et al., 2000; Kim et al., 2001; Liggins and Burt, 2002; Chi et al., 2003). In comparison to Taxol®, paclitaxel-loaded polymeric micelle (PLPM) has proven to have higher antitumor efficacy, lower toxicity and preferable pharmacokinetic patterns (Kim et al., 2001). In order to move PLPM to clinical use, it was necessary to evaluate the stability of PLPM in clinical settings and the compatibility of PLPM with infusion sets. In this note, we assessed the stability of PLPM diluted by 0.9% sodium chloride injection and investigated the releasing behavior of DEHP extracted by PLPM in simulated i.v. infusions.

## 2. Experimental

### 2.1. Materials

Paclitaxel (Genexol®) was obtained from Samyang Genex Co. (Seoul, Korea). Taxol® was purchased from Bristol-Myers Squibb (NJ, USA) via a local pharmacy in Korea. mPEG-PDLLA was synthesized from D,L-lactide (Boehringer Ingelheim KG, Ingelheim Germany) and monomethoxy poly(ethylene glycol) (NOF Co., Tokyo, Japan) through ring opening polymerization (Deng et al., 1990; Zhu et al., 1990). Cremophor® EL was supplied by BASF Aktiengesellschaft (Ludwigshafen, Germany). 0.9% sodium chloride injection (USP) was supplied in PVC infusion bags (Highflex, Choongwae Pharma Co., Seoul, Korea). PVC administration sets were provided by Green Cross Medical Co. (Seoul, Korea). DEHP (99%) and dehydrated ethanol

were purchased from Sigma–Aldrich Co. (MO, USA). Methanol and acetonitrile (HPLC grade) were supplied by Fisher Scientific (NJ, USA). Purified deionized water was prepared by the Milli-Q plus system from Millipore Co. (MA, USA).

### 2.2. Preparation and characterization of mPEG-PDLLA block copolymer and PLPM

mPEG-PDLLA copolymers were synthesized by ring opening polymerization of D,L-lactide in the presence of poly(ethylene glycol) using stannous octoate as a catalyst (Deng et al., 1990; Zhu et al., 1990). PLPM was prepared by a solid dispersion technique, conveniently modified to increase micelles stability (Zhang et al., 1996). Briefly, paclitaxel (30 mg) and mPEG-PDLLA (150 mg) were dissolved in 2.0 ml of acetonitrile. After 5 min of stirring, the organic solvent was evaporated on a rotary evaporator to obtain a transparent gel matrix. The resulting transparent gel matrix was dissolved by addition of water at 60 °C to obtain a transparent paclitaxel-incorporated micellar solution. The solution was filtered through a 0.22 μm filter and lyophilized by a freeze dryer system (Labconco, USA) to obtain dried PLPM. The structure and composition of the block copolymer and PLPM in $CDCl_3$ or $D_2O$ were determined by a 300 MHz $^1H$ NMR instrument (Bruker DRX-300, Germany). The molecular weight and molecular weight distribution of mPEG-PDLLA diblock copolymer were determined by gel permeation chromatography (GPC: Waters model 150C ALC/GPC, MA, USA). The critical micelle concentration (CMC) of the mPEG-PDLLA diblock copolymer was determined by monitoring the fluorescence changes of pyrene in the copolymer solution (Yamamoto et al., 2002).

### 2.3. Analysis of DEHP and paclitaxel by HPLC

The concentrations of DEHP were determined by HPLC based on the method developed by Waugh et al. (1991) using a HP1100 series system (Agilent Technologies, Palo Alto, USA). Chromatographic separation was achieved using a CAPCELL PAK (4.6 mm × 150 mm, 5 μm particle size, C8, Shiseido, Japan) at 25 °C. The mobile phase consisted of methanol/1% acetic acid (85:15) with a flow rate of 1.0 ml/min. The eluent was monitored at 254 nm with UV detection. The analysis of paclitaxel was modified based on the method by Waugh et al. (1991). Chromatographic separation was achieved using a Curosil PFP column (4.6 mm × 250 mm, 5 μm particle size, Phenomenex, USA). The mobile phase consisted of 55% deionized water and 45% HPLC grade acetonitrile with a flow rate of 1.5 ml/min. The eluent was monitored at 227 nm with UV detection.

### 2.4. Statistical analysis

All results are presented as the mean ± S.D. The significance of difference was analyzed by the use of the Student's *t*-test, and a significance level of less than 5% was considered significant.

## 3. Results and discussion

### 3.1. Characterization of PEG-PDLLA copolymer and PLPM

The composition of mPEG-PDLLA block copolymer was determined by $^1H$ NMR spectroscopy (Fig. 1). The weight ratio of the mPEG block and PDLLA block in the copolymer was obtained based on the characteristic protons of PDLLA at 5.2 ppm and PEG (3.6 ppm) on the $^1H$ NMR spectrum. The weight ratio of the block copolymer was determined as 2000 (mPEG) to 1740 (PDLLA), which leads to a number molecular weight (Mn) of the copolymer as 3740. Consistent with the $^1H$ NMR characterization, the weight molecular weight (Mw) of the mPEG-PDLLA diblock copolymer was 4189 as determined by GPC. The molecular weight distribution of the mPEG-PDLLA diblock copolymer is 1.12. High resolution $^1H$ NMR spectroscopy has often been employed to analyze the microstructure of polymer chains in solution (Kim et al., 1998; Shin et al., 1998; Ha et al., 1999; Kim et al., 1999; Kim and Lee, 2001). The characteristic NMR peaks of both PLA and mPEG showed up in $CDCl_3$, while in $D_2O$, the mPEG peaks were still present but the intensity of the PLA peaks was dramatically reduced (Fig. 1). $CDCl_3$ is a good solvent for both PLA and mPEG; thus, the diblock copolymer did not form micellar structures in this solvent. In $CDCl_3$, the protons from both PLA and mPEG segments are easily accessible and the movement of PLA and mPEG was not

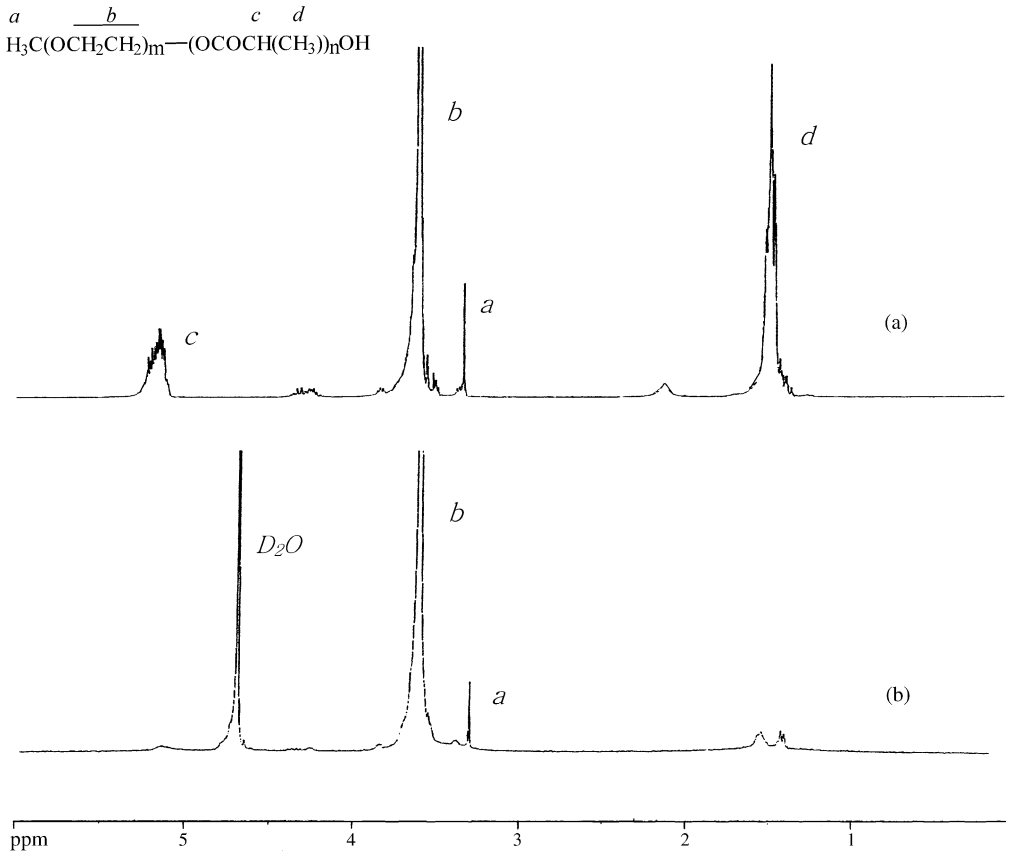


Fig. 1. $^{1}$H NMR spectra of mPEG2-PDLLA diblock copolymer in $CDCl_3$ (a) and $D_2O$ (b).

restricted. In $D_2O$, the expansion of the PLA peaks in Fig. 1 revealed scattered smaller peaks resulting from oligomers of PDLLA. This indicated that the movement of PLA was restricted due to the high viscosity of the PLA core. In $CDCl_3$, the characteristic proton peaks of paclitaxel were still present in presence of the mPEG-PDLLA diblock copolymer (Fig. 2). However, when paclitaxel and the diblock copolymer were mixed in $D_2O$, most of the proton peaks of paclitaxel disappeared suggesting a transition of microenvironment (Fig. 2).

The CMC of the mPEG-PDLLA diblock copolymer was determined using pyrene as a fluorescence probe to detect the formation of the micelles (Kim et al., 1999). A CMC value of approximately 0.007 mg/ml was obtained for the mPEG-PDLLA diblock copolymer. The CMC value of the copolymer is much lower than that of many low molecular weight surfactants, suggesting that the polymeric micellar system can still retain micelle-like structures in much diluted solutions.

### 3.2. Stability of paclitaxel in i.v. infusion solutions using PVC bags

The stability of paclitaxel has been evaluated for diluted PLPM both in storage and during simulated infusion runs. The stability of PLPM diluted in 0.9% sodium chloride injection in PVC infusion bags was tested over a period of 24 h. Paclitaxel in polymeric micelles at a nominal concentration of 0.6 mg/ml was stable at ambient temperature under fluorescence light. There was no significant difference between paclitaxel concentration at time zero and any subsequent time points. The test solution of PLPM appeared slightly bluish. The bluish appearance continued without pre-

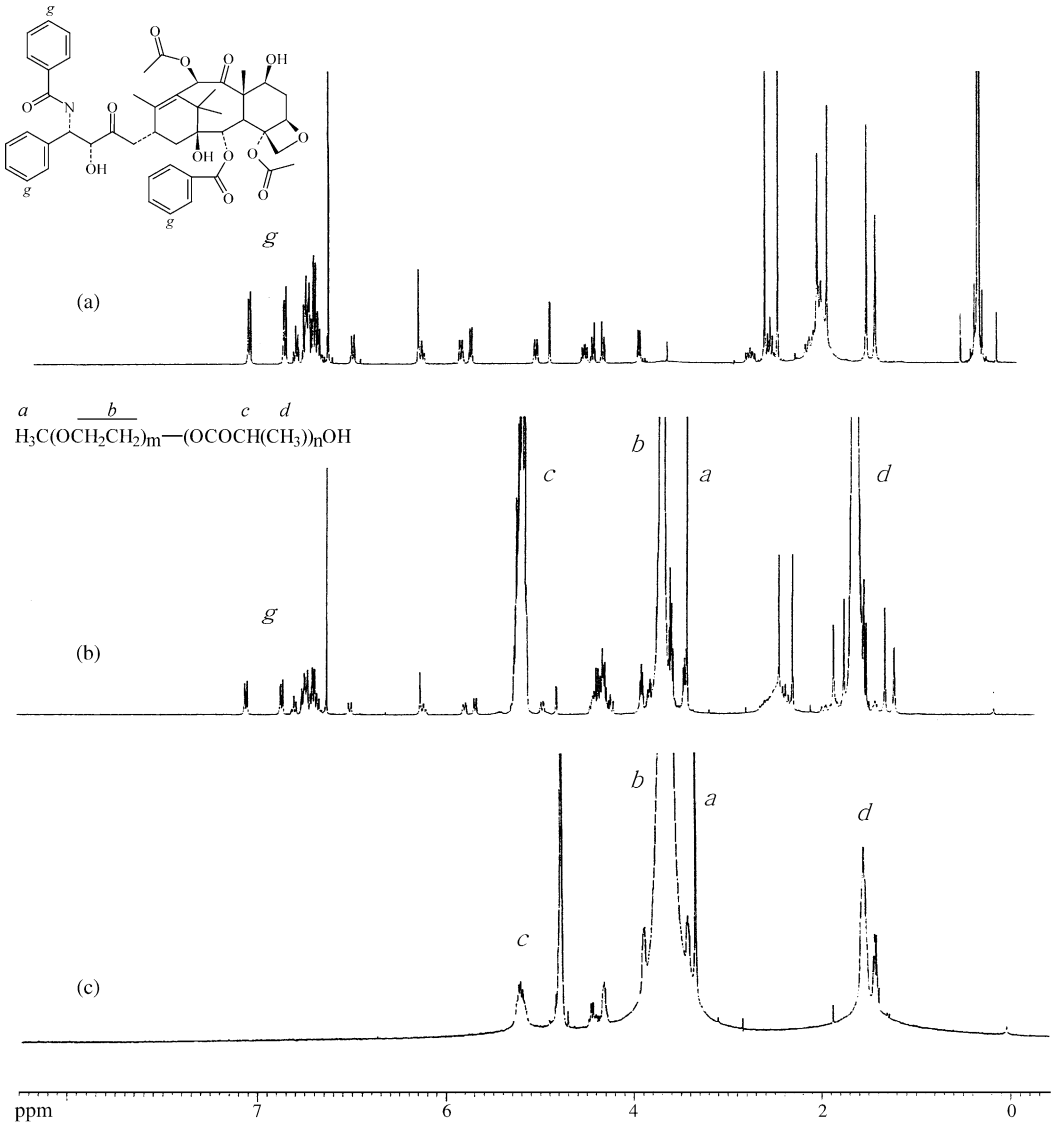


Fig. 2. $^{1}$H NMR spectra of paclitaxel in $CDCl_3$ (a) and PLPM using mPEG-PDLLA diblock copolymer in $CDCl_3$ (b) and $D_2O$ (c).

cipitation over the entire test period (24 h). The stability of paclitaxel in PLPM and Taxol® formulation was also tested during a simulated i.v. infusion using PVC infusion bags and PVC administration sets. Paclitaxel in PLPM and Taxol® diluted in 0.9% sodium chloride injection was stable over the entire simulated i.v. infusion period (Table 1). There was no significant difference between paclitaxel concentration at time zero and any subsequent time points for both PLPM and Taxol®. Paclitaxel from either Taxol® or PLPM was eluted as a sharp peak on the HPLC profile and dilution in 0.9% sodium chloride injection caused no degradation of paclitaxel. The experimental settings for the stability study simulate the normal clinical practice. These results showed that paclitaxel in sodium chloride injection diluted PLPM were visually and chemically stable and adsorption of paclitaxel to PVC infusion bags was negligible.

Table 1
Stability of paclitaxel in PLPM and Taxol® during 24 h-simulated i.v. infusion after dilution to nominal concentration of 0.6 mg/ml in i.v. infusion solutions containing 0.9% sodium chloride injection in PVC infusion bags

| Paclitaxel concentration (mg/ml) | % Initial concentration ($n = 3$, mean ± S.D.)[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Nominal | Actual | 1 h | 2 h | 3 h | 6 h | 8 h | 12.5 h | 24 h |
| Taxol® | 0.6 | 0.56 | 100.5 ± 0.1 | 99.5 ± 0.1 | 99.9 ± 0.5 | 99.9 ± 0.2 | 100.3 ± 0.2 | 100.2 ± 0.4 | 100.8 ± 0.3 |
| PLPM[b] | 0.6 | 0.53 | 100.3 ± 0.2 | 101.4 ± 0.5 | 99.8 ± 1.1 | 100.4 ± 0.5 | 100.6 ± 0.3 | 99.8 ± 0.4 | 98.0 ± 0.4 |

[a] Paclitaxel concentration taken at time zero were designated as 100.0%.
[b] PLPM: paclitaxel-loaded polymeric micelles.

### 3.3. Extraction of DEHP from PVC containers and PVC administration sets

The releasing behavior of DEHP by PLPM was investigated during infusion runs in comparison to Taxol®. The concentration of DEHP leached from the PVC bag and administration set containing Taxol® at 0.6 mg/ml and Taxol®-vehicle corresponding to the formulation with Taxol® at 0.6 mg/ml were ranging from 73 to 171 μg/ml throughout the 24 h-simulated i.v. infusion. The amount of DEHP leached from PVC infusion sets increased with time of exposure to Taxol® and Taxol®-vehicle. The total amount of DEHP delivered with Taxol® over the 24 h of infusion was 83–86 mg (Fig. 3). Fig. 3 also showed that the extraction of DEHP by Taxol® was mainly due to the vehicle. In case of the 3 h-simulated i.v. infusion, the total amount of DEHP delivered with Taxol® was 23–27 mg for 3 h (Fig. 3). Under the same conditions, PLPM extracted much less DEHP. For PLPM at 0.6 mg/ml, the concentration of DEHP leached from PVC infusion sets was insignificant at the end of the simulated infusion for either 3 or 24 h. The total amount of DEHP delivered with PLPM over the 24 h was about 2.0 mg. In case of the 3 h-simulated infusion, the total amount of DEHP delivered was around 0.7 mg for 3 h (Fig. 3).

In addition, it was necessary to assess the amount of DEHP extracted from the PVC administration sets alone. Fig. 4 indicates the respective effects of using glass containers and PVC administration sets on the total amount of DEHP extracted by Taxol® or PLPM. Infusion of Taxol® using a PVC administration set and a glass infusion container extracted 28 mg of DEHP over 24 h, which accounted for one-third of the total

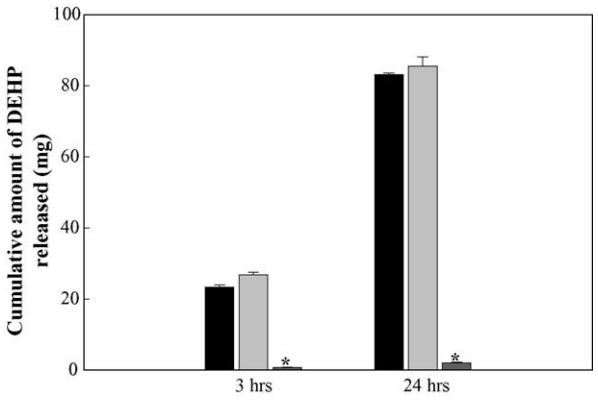


Fig. 3. The cumulative release of DEHP from PVC infusion bags and PVC administration sets containing PLPM, Taxol® and Taxol®-vehicle during 24 h-simulated i.v. infusion after dilution to nominal paclitaxel concentration of 0.6 mg/ml (Taxol®-vehicle; corresponding to paclitaxel injection 0.6 mg/ml) in i.v. infusion solutions containing 0.9% sodium chloride injection. Total volume was approximately 500 ml. Data are presented as mean ± S.D. ($n = 3$). $^{*}P < 0.05$. *Key:* (■) Taxol®; (□) Taxol®-vehicle; (■) PLPM.

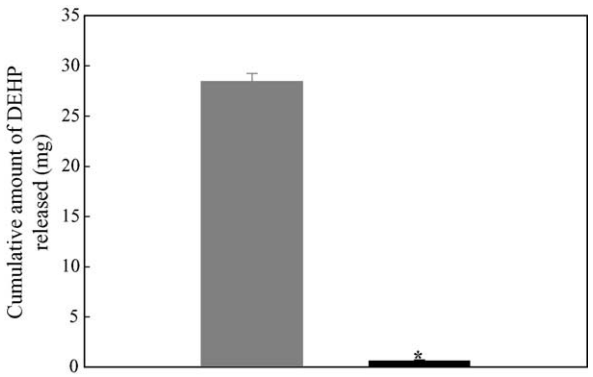


Fig. 4. The cumulative release of DEHP from glass infusion containers and PVC administration sets containing PLPM and Taxol® during 24 h-simulated i.v. infusion after dilution to nominal paclitaxel concentration of 0.6 mg/ml in i.v. infusion solutions containing 0.9% sodium chloride injection. Total volume was approximately 500 ml. Data are presented as mean ± S.D. ($n = 3$). $^{*}P < 0.05$. *Key:* (■) PLPM; (■) Taxol®.

amount of extracted DEHP when both PVC container and PVC administration set were used. When a PVC administration set is used with a glass infusion container, the amount of DEHP extracted by PLPM is negligible.

These results confirmed previous findings and showed that Taxol®-vehicle contributed the majority of the DEHP extracted from PVC infusion bags and PVC administration sets. Absence of Cremophor® EL and ethanol in the polymeric formulation significantly reduced the amount of DEHP extracted from PVC infusion bags and administration sets. During the 24 h infusion period, the amount of DEHP leached by PLPM was less than 2.9% of that by Taxol®, suggesting that there is little risk of DEHP exposure from diluted PLPM i.v. infusion using PVC infusion bags and PVC administration sets. This added extra advantage using the mPEG-PDLLA micellar system to deliver paclitaxel.

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