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Non-PVC(폴리올레핀) 수액용 튜브 내면에서의 약물흡착 거동 – PVC 및 PU 수액튜브와의 비교

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Drug Adsorption Behavior of Polyolefin Infusion Tube Compared to PVC and PU

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초록: PVC 재질로 만들어진 기존의 수액백과 튜브는 가소제인 DEHP(diethylhexyl phthalate)를 함유하고 있어 정맥 주사 시에 가소제의 용출과 약물 흡착이라는 심각한 취약점을 내재하고 있다. 본 연구에서는 폴리올레핀 재질로 만들어진 non-PVC 수액튜브(가소제 미포함)를 개발하고, 이들 튜브 내면에서의 약물 흡착 거동을 기존의 PVC 및 PU 재질의 수액 튜브와 비교 검토하므로써, 수액 주사 시 약물 흡착으로 인한 약효 감소 효과를 최소화 가능한 방안을 도출하고자 한다. 4가지의 non-PVC 수액튜브는 폴리에틸렌(PE), 폴리프로필렌(PP), syndiotactic 1,2-폴리부타다이엔(PB)과 스타이렌-에틸렌(SE)의 공중합 탄성체를 사용하여 압출하여 제조하였으며, 이들은 기존의 PVC 수액튜브의 기계적 특성과 동등한 물성을 나타내었다. 아울러 제조된 폴리올레핀 재질의 4가지 수액튜브들은 기존의 PVC 및 PU 재질의 수액튜브 대비 우수한 약물흡착 방지 효과를 나타내었다. 따라서 이들은 약물흡착 방지용 수액튜브뿐 아니라 DEHP의 용출 위험이 배제된 안전한 수액튜브로서 임상 적용 가능할 것이다.

Abstract: PVC (polyvinyl chloride) intravenous fluid bags and tubes that contain DEHP (diethylhexyl phthalate) as a plasticizer have several associated disadvantages for intravenous injections. We investigated the drug absorption behaviors on the inner surface of an infusion tube that consisted of commercialized PVC/PU (polyurethane). We developed a non-PVC (polyolefin) tube in order to improve the efficacy of this drug administration method. We prepared four types of non-PVC (polyolefin) infusion tubes using a polyethylene (PE), polypropylene (PP), syndiotactic 1,2-polybutadiene (PB), and styrene-ethylene (SE) copolymer elastomers were prepared using a single screw extruder. The four types of manufactured non-PVC (polyolefin) infusion tubes had good mechanical properties that were equivalent to PVC tube properties. The four types of prepared non-PVC (polyolefin) infusion tubes also prohibited drug absorption when compared to the commercialized PVC and PU tubes. Therefore, based on the results of this study, prepared non-PVC (polyolefin) tubes are good candidates for infusion because they prevent drug absorption and the release of DEHP.

Keywords: non-PVC, polyolefin, infusion tube, drug absorption, partition coefficient.

Introduction

PVC (polyvinyl chloride) intravenous fluid bags and tubes that contain DEHP (diethylhexyl phthalate) as a plasticizer have several associated disadvantages for intravenous injections. First, the release of DEHP from infusion bags occurs during storage and undesired toxic effects can affect a patient's well-being and health after the injection.[1-4] Second, DEHP release is accelerated by surfactants in anticancer agent solutions and released DEHP reduces the stability of hydrophobic Taxol solutions in long-term storage conditions.[5,6] Third, the active ingredients of drugs that comprise an infusion solution are easily adsorbed on the surface of the PVC infusion bag,

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which results in a decreased drug efficacy during the hours of infusion. Drug efficacy can decrease by up to 50%, 15-25% and 13-20% for chlormethiazole, isosorbide dinitrate and diazepam, respectively during long term storage.[7,8]

Therefore, many researchers have worked to develop non-PVC materials that can be used for infusion bags to overcome these challenges. Although an infusion tube that connects to the infusion bag is essential for drug administration, less effort has been focused on developing non-PVC (DEHP-free) and non-absorptive materials for infusion tubes.

In our previous paper,[9] we reported about developing clinically-available non-PVC infusion tubes made of polyolefin and investigated their biological safety under *in vitro* and *in vivo* conditions. In this study, we investigated the drug absorption behaviors on the inner surface of a commercialized PVC/PU (polyurethane) infusion tube and developed non-PVC (polyolefin) tubes in order to improve the efficacy of drug infusion in the clinical condition.

The absorptive interactions of nitroglycerin, isosorbide dinitrate, and chlormethiazole hydrochloride (Figure 1) were investigated using the PVC/PU and non-PVC (polyolefin) infusion sets. In addition, we compared the partition coefficients of these drugs with water and organic solvents to identify a suitable non-PVC material that can be used for a clinically-effective infusion system.

Chlormethiazole hydrochloride (an antipsychotic drug), isosorbide dinitrate (prevents angina attacks), and nitroglycerin (used for the treatment of angina and cardiac failure) were selected as model drugs and their absorption behaviors were studied using PVC/PU and non-PVC infusion tubes for a predetermined circulating time.

Experimental

Materials. Polyethylene (PE), polypropylene (PP), syndiotactic 1,2-polybutadiene (PB), and styrene-ethylene (SE) copolymer elastomers were used as materials for the non-PVC (polyolefin) infusion set. The PE elastomer (Infuse®, melt index (g/min, 190 ºC, 2.16 Kg); 5.0) and PP elastomers (Vistamaxx®, melt index (g/min, 190 ºC, 2.16 Kg); 3.0) were obtained from Dow Chemical Co., Ltd. (Midland, MI, USA) and ExxonMobil Chemical Co., Ltd. (Houston, TX, USA), respectively. PB elastomer (syndiotactic 1,2-polybutadien, melt index (g/min, 150 ºC, 21.2 N); 3.0) was obtained from JSR Corporation (Japan Synthetic Rubber Corporation, Tokyo, Japan) and SE elastomer (ethylene-styrene copolymer graft ethylene-styrene-diene copolymer, melt index (g/min, 200 ºC, 10 Kg); 4.0) was obtained from Denki Kagaku Kogyo Co., Ltd. (Denka Co., Ltd., Kyoto, Japan). Four types of non-PVC (polyolefin) tubes were prepared. A polyolefin-1 tube was made from a PE elastomer/PB blend. A polyolefin-2 tube was made from a PP elastomer/PB blend. A polyolefin-3 tube was made from a PE elastomer/PP elastomer/PB blend and a polyolefin-4 tube was made of SE only.

As a control, a commercialized PVC tube (Becton Dickinson (BD) Co., Ltd., Franklin Lakes, NJ, USA) and two kinds of commercialized non-PVC tubes; a PU tube for an intravenous (IV) set from Tianjin Hanaco Medical (THM) Co., Ltd., (Tianjin, China) and a PB tube for an IV set from Nipro Corporation (Osaka, Japan), were used in the drug absorption experiments. Chlormethiazole hydrochloride, isosorbide dinitrate, and nitroglycerin were purchased from Sigma-Aldrich Chem. Co. (St. Louis, MO, USA) and used without purification for the *in vitro* drug absorption experiments.

Tube Manufacturing. A single screw extruder (K-tek, Inchon, Korea) was used to manufacture the non-PVC (polyolefin) tubes in a clean room (class 10000) environment. The tube extrusion conditions included screw temperatures of 130 and 160 ºC, an extrusion rate of 30 m/min. The four types of manufactured non-PVC (polyolefin) tube samples had inner diameters (ID) of 2.4-2.8 mm and outer diameters (OD) of 3.7-4.1 mm. The commercialized PVC and non-PVC (PB, PU) tubes had IDs of 2.5-2.8 mm and ODs of 3.8-4.1 mm.

Drug Absorption. We used 2 mg of chlormethiazole hydrochloride dissolved in 100 mL of a 0.9% NaCl solution to create the drug solutions for UV spectrometry absorption testing (SINCO S-4100 UV-Vis spectrophotometer, Sinco Co., Ltd., Seoul, Korea). Then 1.5 mL of nitroglycerin and 6 mg of isosorbide dinitrate were dissolved in 100 mL of a 10% aqueous ethanol solution.[10] The chemical structures of the drugs are shown in Figure 1. The four types of prepared non-PVC (polyolefin) tubes and three types of control tubes were mounted on micro tubing pump (EYELA MP-3N, Tokyo Rikakikai Co., Ltd., Tokyo, Japan). The lengths of the seven tubes were adjusted to 70-120 cm depending on the inner diameter and the inner surface area of the tubes that contacted the drug solution was held constant at 75 cm^2. The circulating rate of the drug solutions through the seven kinds of tubes was controlled between 1.2-3.0 mL/min to achieve a constant volume current. The different inner diameters of the tubes were considered and adjustments were made. The drug absorption behavior was evaluated by measuring the UV absorbance differences of the

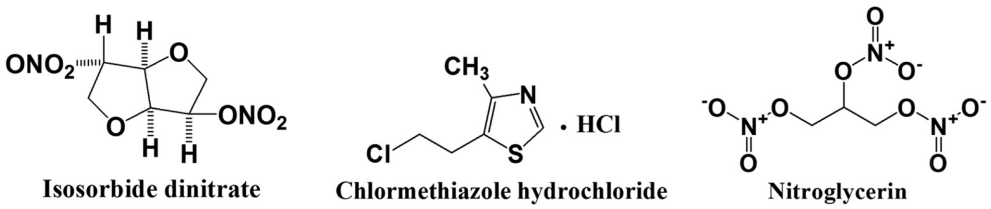

Figure 1. Chemical structures of model drugs.

circulating drug solutions at predetermined time intervals (every 30 min and 1 hr during the first and second half of the circulation time span, over a total of 8 hrs).

Results and Discussion

Tube Manufacturing. The cross-sectional shape of the manufactured non-PVC (Polyolefin-3) tube and control tubes (PB, PVC, and PU) are shown in Figure 2. PB (Nipro), PU (THM), and PVC (BD) tubes were manufactured from single PB, PU, and PVC resins, respectively, and they possessed a homogeneous phase, which was confirmed with a digital camera (Figure 2) and optical microscope (data not shown). The Polyolefin-3 tube was made of a multi-component polymer resin (PE elastomer/PP elastomer/PB blend), but the cross-sectional morphology also had a homogeneous phase similar to the PB, PU, and PVC tubes. This demonstrates that the manufactured Polyolefin-3 tube showed good miscibility in the multi-component polymer resin, and especially Polyolefin-4 tube showed similar mechanical properties (hardness, tensile strength, elongation, and compression recovery) after the tubing process compared to PVC properties (Table 1). This means that the olefin infusion tubes can be overcome their weak points such as less elasticity and low compression set property through above mentioned processing and blending conditions.

Drug Absorption. The time-dependent drug concentrations were changed during the absorption experiments where the circulation rate was controlled to maintain a fixed quantity of flow at 2 mL/min.

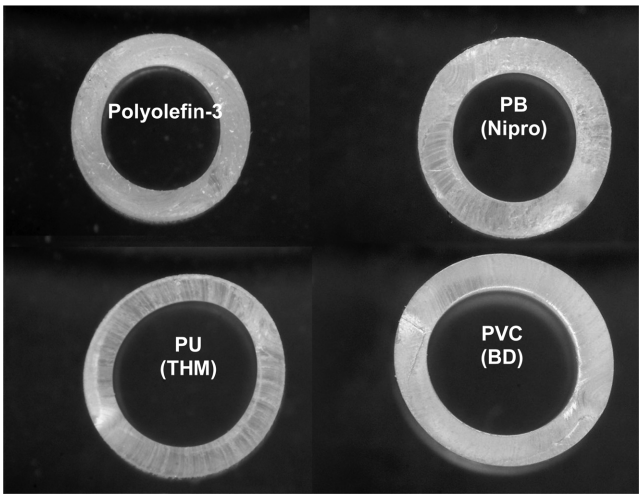

Figure 2. Cross-sectional morphology of prepared (Polyolefin-3) and commercialized infusion tubes (PB, PU, and PVC).

Figure 3 shows the absorption behaviors of chlormethiazole hydrochloride on the PVC, PU, and various polyolefin tubes. Chlormethiazole hydrochloride (pKa, 3.2) is a well-known drug which is water-soluble and very hydrophilic, and also exists in its ionized form in infusion solution conditions. The measured pH of chlormethiazole hydrochloride is 4.06 in the 0.9% NaCl aqueous solution. Because of the affinity between the ionized chloride group in chlormethiazole, chlorinated

Table 1. Non-PVC and PVC Infusion Tube Mechanical Properties

Tube samples	Hardness	Tensile strength at break (MPa)	Elongation (%)	Elastic modulus (MPa)	Compression set (%)
Polyolefin-1	78A	12.3	1,120	30.8	39.0
Polyolefin-2	79A	13.1	890	35.2	42.0
Polyolefin-3	78A	12.7	960	33.8	40.8
Polyolefin-4	76A	25.9	520	8.0	34.5
PB(Nipro)	79A	10.3	764	12.1	32.2
PU(THM)	75A	40.8	980	12.4	26.5
PVC(BD)	80A	26.9	372	13.9	34.8

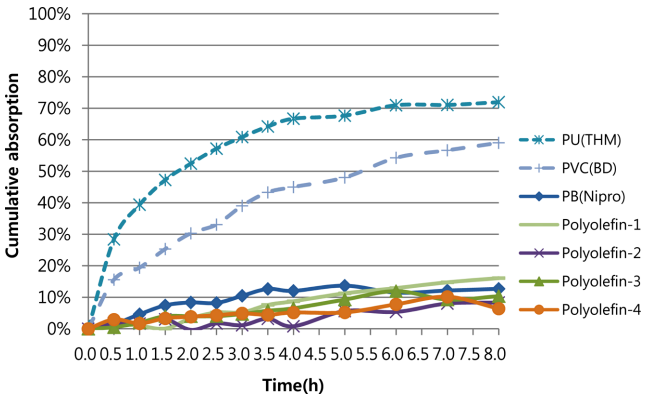

Figure 3. Chlormethiazole hydrochloride absorption behaviors on the inner surface of the tubes at room temperature.

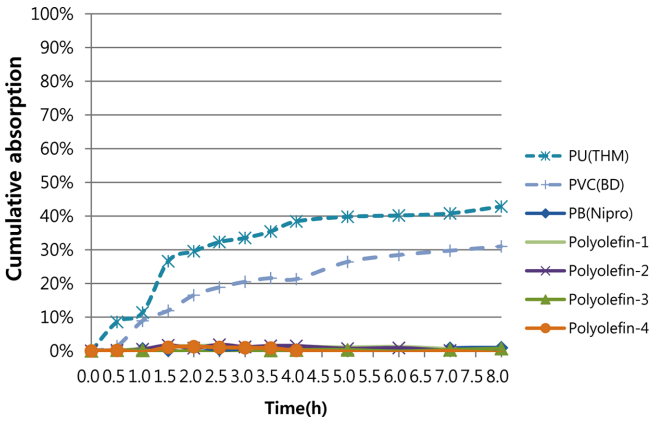

Figure 4. Isosorbide dinitrate absorption behaviors on the inner surface of the different tubes at room temperature.

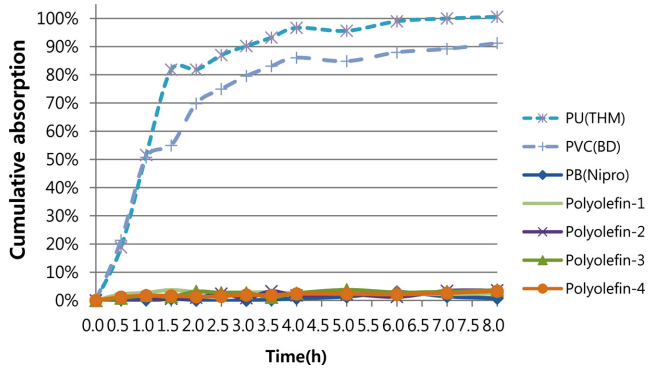

Figure 5. Nitroglycerin absorption behaviors on the inner surface of the different tubes at room temperature.

hydrocarbon chains in PVC and the polarized chemical structure of PU, this drug is easily attached and absorbs with PVC and PU polymers rather than an absorption process, which normally occurs instantaneously under saturation conditions.[11] In comparison, the hydrophobic polyolefin tubes (Polyolefin-1, Polyolefin-2, Polyolefin-3, Polyolefin-4, and PB (Nipro)) had a lower absorption tendency. However, there was still more absorption compared to the nitroglycerin and isosorbide dinitrate conditions which are demonstrated in Figures 4 and 5. The affinity of chlormethiazole to the hydrophobic substrates is due to the low partition coefficient to octanol-water (2.12) of chlormethiazole compared to nitroglycerin (41.8) and isosorbide dinitrate (20.6).[12,13] These conditions have been demonstrated in the results of M. G. Lee's early research.[14]

Figures 4 and 5 show the absorption behaviors of isosorbide dinitrate and nitroglycerin on the PVC, PU and various polyolefin tubes. Isosorbide dinitrate and nitroglycerin are water-soluble lyophilic drugs and were dissolved in a 10% ethanol (as a co-solvent) aqueous solution. Their partition coefficients to PVC-water were 38.7 (isosorbide dinitrate) and 115.2 (nitroglycerin). The absorption behavior of isosorbide dinitrate was nearly half of nitroglycerin. A comparison of the data shown in Figures 3 and 4 indicates that the partition coefficients of chlormethiazole and isosorbide dinitrate to PVC-water were 41.0 and 38.7, respectively; however, the chemical absorption behaviors were very different and the absorption of chlormethiazole was nearly twice of isosorbide dinitrate. This can be explained as a difference of the absorption mechanism. As previously mentioned, chlormethiazole absorption corresponds to the simple absorption mechanism but isosorbide dinitrate mechanism is strongly related to the other absorption mechanism which includes the relative permeation of the drug into the tube surface.

Therefore, firmly adhered isosorbide dinitrate molecules prevent additional absorption-desorption exchange of drug molecules, which consequently occurs in absorption process on the PVC tube inner surface. In addition, complete isosorbide dinitrate absorption also occurred with the temperature change from 4 to 60 °C.[13]

The absorption behaviors of nitroglycerin and isosorbide dinitrate to the PVC tube are shown in Figures 4 and 5, and, based on the absorption mechanism, the behaviors were highly variable. This may be attributable to the difference of the PVC-water partition coefficients of the two drugs and their diffusion coefficients in PVC. Such an affinity difference to PVC originates from the chemical structures of nitroglycerin (having 3 nitro groups) and isosorbide dinitrate (having 2 nitro groups). In another report,[15] the substitution of an -NO_2 group with an -OH group increased the chance of forming a hydrogen bond between a drug and aqueous solution, which resulted in a

reduced affinity of a drug to the PVC tube surface. This demonstrates that the -NO_2 group affects the absorption behavior of drugs on PVC tubes.

In comparison, adsorbed drugs (nitroglycerin and isosorbide dinitrate) were not observed in the polyolefin tubes because their partition coefficients to polyolefin-water are very low and nearly equivalent (0.3).[13]

Conclusions

The four kinds of prepared non-PVC (polyolefin) infusion tubes were made of polyethylene (PE), polypropylene (PP), syndiotactic 1,2-polybutadiene (PB), and styrene-ethylene (SE) copolymer elastomers by using a single screw extruder. These four types of prepared non-PVC (polyolefin) infusion tubes had good mechanical properties that were equivalent to the properties of a PVC (BD) tube. The four prepared non-PVC (polyolefin) infusion tubes also prohibited drug absorption behaviors when compared to the commercialized PVC (BD) and PU (THM) tubes. The drug affinity differences between PVC/PU and polyolefin tubes were related to their partition characteristics. Therefore, the prepared non-PVC (DEHP-free) tubes are good candidates for infusion sets because they prevent drug absorption and the release of DEHP.

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