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Migration of plasticizers from poly(vinyl chloride) and multilayer infusion bags using selective extraction and GC–MS

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ABSTRACT

Flexible poly(vinyl chloride) (PVC) is widely used in the pharmaceutical industry for the manufacture of medical devices (tubes, probes, bags, primary packaging, etc.). The objective of the present study was to develop a procedure to evaluate the migration potential of nine plastic additives in aqueous infusion bags (NaCl 0.9% and glucose 5%): five phthalates, one adipate, two alkylphenols, and benzophenone. Two types of materials were analyzed: (i) new and outdated plasticized PVC (containing 40% of diethylhexyl phthalate DEHP); and (ii) tri-laminate polyethylene-polyamide-polypropylene, a multilayer material presumably exempt from DEHP. In addition, we evaluated the migration of plasticizers from PVC raw materials (film and grain) under controlled conditions to compare the migration levels according to Regulation 2011/10. Solid phase extraction and liquid-liquid extraction with gas-chromatography coupled to mass spectrometry were used in all tests. The migration of DEHP in PVC grain exceeded the maximum regulated level of 5000 μg/kg, whereas the levels were much lower in films. In new PVC bags, DEHP was the only compound detected at 4.31 ± 0.5 μg/L in NaCl 0.9% and 4.29 ± 0.25 μg/L in glucose 5% serums, whereas the levels increased 10 times in three-year shelf-life bags. In multilayer bags, DEHP was not found but instead, two plasticizers were detected namely dibuthylphthalate (DBP) and diethylphthalate (DEP) at 0.7 ± 0.1 μg/L and 4.14 ± 0.6 μg/L, respectively. These plasticizers are not mentioned as additives allowed in materials intended for parenteral use (European Pharmacopoeia 8.0, 3.1.5. and 3.1.6.). Caprolactam was tentatively identified and could have stemmed from the polyamide of the multilayer composite. The levels of phthalates remained low but not negligible and might constitute a risk to public health in the case of reiterative infusions.

1. Introduction

Invented more than a century ago, plastics have invaded all the fields of activity because of their unique properties (physical, mechanical, thermal, electrical and optical) and multiple functionalities. According to the European Markets for Plastics, more than 38% are used in food packaging sector and for pharmaceutical conditioning [1]. Different types of plastics are employed in the conditioning of pharmaceutical products, poly(vinyl chloride) (PVC) being the most widely used. PVC has good mechanical, electric, chemical, thermal properties and represents 11% of the plastics market, among which 15% is used for packaging [2]. In certain applications, plasticizers, and phthalates in particular, are added to the PVC resin in order to confer its unique characteristics of flexibility, malleability and durability. The French National Institute for Industrial Environment and Risks (INERIS) [3] indicates that more than 90% of the phthalate production is used as plasticizers for PVC among which, 50% is diethytlhexylphthalate (DEHP). Indeed, in the last 30 years, DEHP has been considered as the standard product of the plasticizers' market [4] as it is valued for the unique mechanical properties which confer to the PVC and in addition, it presents a very good quality to price ratio [5].

The European Directive 2005/84/EC forbade phthalates as additives in PVC and in other plastic materials used in toys and in nursery articles which can be placed in the mouth of the child [6]. In the pharmaceutical domain, Directive 2007/47/CE has put into force in March 2010 questions as to the use of phthalates in medical devices and suggested to use alternative plasticizers, less toxic and more strongly bound to PVC to reduce leaching [7]. However, and paradoxically, DEHP remains authorized by the European Pharmacopoeia in the polymer resins for medical devices, such as the catheters, transfusion bags, probes, ventilation pipes

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and nutritional supports [8]. Not chemically bound to PVC, DEHP migrates in a pervasive way to the surrounding media [4]. This plastic additive is classified as toxic reproductive class 1B by Regulation EC, N°1272/2008 [9] and constitutes a risk in the case of ingestion. To minimize children exposure, a ban, enforced since July 1st 2015, is only imposed for pipes used in pediatrics, neonatal and maternity devices [10]. However, other plasticizers are used to replace DEHP such dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DBP), butyl benzyl phthalate (BBP) and bis (2-ethylhexyl) adipate (DEHA). In addition, technical nonylphenol (NP) and 4-*tert*-octylphenol (OP) can be used as antioxidants in plastic polymers and benzophenone as an additive to protect plastics from ultraviolet radiation. All of these additives are toxicologically active but yet, compared to DEHP, there is little information on their migration potential from medical devices and the effects they may cause in humans [11].

Infusion bags used in the packaging of parenteral aqueous solutions are made of PVC containing 40% DEHP (according to pharmacopoeia). The most common bags used as vehicles are NaCl 0.9% and glucose (mainly 5 and 10% but also at 20, 30 and 50%) for intravenous nutrition. The capacity of the bags can range from 100 to 1000 mL. During the manufacturing process, the infusion bags are subjected to vapor sterilization at a temperature of 121 °C during 20 min, which favors the release of DEHP [12,13]. Since the 1990s, there has been scientific evidence on the migration of DEHP or other phthalates from PVC bags containing the surfactant polysorbate 80 [14], cyclosporine [15], taxol [16], teniposide [17], miconazole [18] or lipophilic infusion media [19]. By intravenous route, phthalates become fully bioavailable and have been localized in human tissues [20], in urine [21], and in blood [22,23]. Toxicological studies point out that phthalates perturb the endocrine system, being able to distort the fertility [24]. Specifically, DEHP is classified by the statutory food-processing authorities as a toxic substance for the reproduction category IB, with a Tolerable Daily Intake (TDI) of 50 μg/kg/day [25]. However, its migration potential in aqueous solutions has not been widely studied, even though they represent the main vehicle in intravenous treatments.

The aim of the present study is to develop a procedure to determine the migration potential of plastic additives from PVC materials used in the manufacture of aqueous infusion bags used as vehicles of pharmaceutical products. The specific objectives were: (i) to determine the migration of plasticizers from raw materials (film and grain) used in the manufacture of medical infusion devices, and (ii) to determine the levels of plasticizers in aqueous infusion solutions containing NaCl 0.9% and glucose 5% conditioned in new and outdated plasticized PVC bags (containing up to 40% of DEHP) and in multi-layer bags (presumably exempt from DEHP). Although in this study special attention was given to DEHP because it is the only plasticizer that is allowed by the pharmaceutical regulations, other plasticizers have also been included as they can be potential replacements of DEHP.

2. Materials and methods

2.1. Standards and reagents

Phthalates Mix 525 (500 ng/μL each, in methanol) containing dimethyl phthalate (DMP), diethyl phthalate (DEP), di-n-butyl phthalate (DBP), butyl benzyl phthalate (BBP), bis (2-ethylhexyl) adipate (DEHA) and bis(2-ethylhexyl) phthalate (DEHP) was from Supelco (Bellefonte, PA, USA). Technical nonylphenol (NP) was obtained from Riedel-de Häen (Seelze, Germany) as a solid technical mixture of isomers. 4-*tert*-octylphenol (OP) as a solid was supplied by Supelco (Bellefonte, PA, USA) and benzophenone (BP) as a solid was purchased from Sigma-Aldrich (St. Louis, MO). Anthracene-d10 used as surrogate standard, was from Dr. Ehrenstrofer (Germany) as a solution of 10 ng/μL in cyclohexane.

200 mg Oasis HLB solid phase extraction (SPE) cartridges were from Waters (Milford, MA, USA) and were used with a Baker vacuum system (Product No. 7018-94; J.T. Baker, Deventer, the Netherlands). Chromatography-grade methanol, dichloromethane, acetone, n-hexane, ethyl acetate and HPLC water were purchased from Merck (Darmstadt, Germany). Nitrogen for drying with 99.995% of purity was from Air Liquid (Barcelona, Spain). NaCl and glucose reagents were purchased from Merck (Darmstadt, Germany) and solutions were prepared in Milli-Q water at a concentration of 0.9% and 5%.

2.2. Migration assays of plasticizers from raw material (grain and film)

The migration study was performed on the raw material in the form of grain (3.5 ± 10% mm of diameter) and film (sheets of 220 μm of thickness) used for the manufacture of tubing and bags for infusion, respectively. Migration tests were carried out according to the existing regulations used in the food industry (Directive 2011/10/EU) [26]. An amount of 1.5 g of raw material, in the form of grain or film (previously cut into pieces of 2×2 cm^2) was introduced into pre-cleaned Pyrex flasks, 100 mL of mineral water (in glass bottle) were added and flasks were capped using Teflon septa protected with aluminum foil to prevent contact with plastic cap. Three types of migration assays were performed: (i) incubation in an ultrasonic apparatus (Selecta, Barcelona) during 30 min; (ii) incubation in a laboratory oven (Radiber SA, Barcelona, Spain) at 40 °C during a period of 10 days; (iii) steam sterilization in an autoclave (Selecta, Barcelona) at a temperature of 121 °C for a period of 20 min, simulating the actual conditions used during infusion bags manufacturing. According to Directive 2011/10/EU [26], water is the most appropriate medium to simulate the aqueous infusion solutions of NaCl and glucose. Similar conditions were reported in the pharmacopoeia 8.0 and 3.1.14 for the assessment of the overall migration of contaminants from the PVC material for parenteral use [27]. Extraction of the contaminants from the water was carried out by both LLE and SPE methods. Samples were prepared in triplicate for each migration condition to compare and validate the results. The extraction procedure is depicted in Section 2.4.

2.3. Analysis of plasticizers in NaCl and glucose bags

NaCl and glucose infusion bags were supplied by the Algerian manufacturing of infusion solutions. Two types of 500 mL bags were studied: (i) plasticized PVC bags with approximately 40% of DEHP and (ii) multilayer (MLP) bag consisting of polypropylene (PP), polyamide (PA) and high density polyethylene (HDPE) joined together by means of polyurethane (PU) adhesive. For PVC bags, two types were tested, a newly manufactured one (PVCnew) which expired in 2017 (at the time the study was performed) and another already expired in 2014 (PVCexp). The expired bag had been kept for 3 years in the real conditions of use according to ICH (International Conference of Harmonization) of Technical Requirements for the Registration of Pharmaceuticals for Human Use [28]. Outdated bags permitted to confirm with certainty the origin of phthalates in serum due to migration from the PVC after a long contact time. On the other hand, multilayer bags analyzed are supposed to be free of DEHP (according to the requirements of pharmacopoeia). Three bags of each category were analyzed.

2.4. Analytical methodology

Two extraction protocols were developed for the analysis of plasticizers in the migration assays using mineral water as simulant