Limitation of the migration of plasticizers from medical devices through treatment with low-pressure cold plasma, polydopamine coating, and annealing.

Morgane Masse, Maude Jimenez, Stéphanie Genay, Alice Pettinari, Séverine Bellayer, Christine Barthelemy, Bertrand Décaudin, Nicolas Blanchemain, Pascal Odou

Limitation of the migration of plasticizers from medical devices through treatment with low-pressure cold plasma, polydopamine coating, and annealing

Morgane Masse[a,*], Maude Jimenez[b,c], Stéphanie Genay[a], Alice Pettinari[a], Séverine Bellayer[b], Christine Barthélémy[a], Bertrand Décaudin[a], Nicolas Blanchemain[d], Pascal Odou[a].

[a] Univ. Lille, CHU Lille, ULR 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, F-59000 Lille, France

[b] Univ. Lille, CNRS, INRA, ENSCL UMR8207, UMET - Unité Matériaux et Transformations, F-59000 Lille, France

[c] Institut Universitaire de France, 1 rue Descartes F-75005 Paris

[d] Univ. Lille, Inserm, CHU Lille, U1008 - Controlled Drug Delivery Systems and Biomaterials, F-59000 Lille, France

*Corresponding authors. E-mail address: morgane.masse@univ-lille.fr (M. Masse)

Keywords

- Plasticizer
- Migration test
- Cold plasma
- Poly(vinyl chloride)
- Coating
- Medical devices

Abstract

Poly(vinyl chloride) (PVC) is widely used in the manufacture of medical devices. The plasticizers added to PVC are potentially toxic for humans, likely to migrate, and thus unintentionally administered to patients. The objective of the present study was to reduce the migration of plasticizer (1,2-cyclohexanedicarboxylic acid, diisononylester (DINCH) or trioctyltrimellitate (TOTM)) from PVC by implementing a three-step surface treatment process: (i) pretreatment with low-pressure argon cold plasma, (ii) polydopamine coating, and (iii) post-treatment with cold plasma exposure or thermal treatment at 140°C.

Samples were then characterized in terms of the water contact angle (WCA) and the aspect in scanning electron microscopy. Plasticizer migration (n=5) was measured using an HPLC technique with ultraviolet detection and found to depend on the treatment and the plasticizer.

Plasticized PVC was hydrophobic, with a measured mean ± standard deviation WCA of 96.7 ± 3.6° for PVC-DINCH and 110.2 ± 5.8° for PVC-TOTM. Plasma post-treatment and thermal post-treatment were respectively associated with a mean decrease in migration of 38.3 ± 1.9% for DINCH and 61.5 ± 4.4% for TOTM.

Our results are promising with regard to limiting the migration of plasticizers into the patient's blood and thus enabling the development of safer medical devices.

1. Introduction

Infusion is defined as the regulated venous administration of drugs and/or physiological solutions for therapeutic or diagnostic purposes (ANSM, 2013). The medical devices used for infusion (such as infusion pumps and tubing) must be suitable with regard to the infused drug's physical-chemical properties; this is particularly necessary for drugs with a low therapeutic margin (e.g. catecholamine and insulin) and which are often administered with electric syringe pumps (Genay et al., 2015).

Infusion tubing is made of polymers like polyurethane (PU), polyethylene (PE), silicone, poly(vinyl chloride) (PVC) and PE/PVC coextrudate. PVC is the most widely used material for infusion tubing in clinical services, in view of its biocompatibility, sterilizability (using gamma radiation or ethylene oxide), and transparency (Chiellini et al., 2013). Plasticizers are added to PVC so that it is sufficiently flexible. However, the plasticizers are not strongly bound to the PVC; they can easily migrate into the infused products (nutrient mixtures, drug solutions, blood

products, etc.) and are thus unintentionally administered to the patient (Bernard et al., 2015). Unfortunately, some of these plasticizers are toxic. Indeed, the most commonly used plasticizer (di(2-ethylhexyl) phthalate (DEHP)) is currently classified as a category 1b carcinogenic, mutagenic and reprotoxic substance (Regulation (EC) No 1272/2008, 2008) and is an endocrine disruptor (Swan et al., 2015). In 2008, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) (SCENIHR, 2008) recommended the use of plasticizers other than DEHP; the most commonly used alternatives are trioctyltrimellitate (TOTM) and 1,2-cyclohexanedicarboxylic acid, diisononylester (DINCH) (Bourdeaux et al., 2016). In contrast to DINCH and its primary metabolites, TOTM and its primary metabolites are not toxic *in vitro* (Eljezi et al., 2017). However, several binding studies have shown that these alternative plasticizers have a high affinity for sex hormones (Kambia et al., 2019). They also migrate into drug solutions to varying extents (Bernard et al., 2015). This migration must be limited, to ensure the patients' safety during and after medication administration (Münch et al., 2018). A study conducted in a neonatal intensive care unit showed that newborns were exposed to plasticizers during care procedures, including transfusions, infusions, extracorporeal membrane oxygenation, and respiratory assistance (Bernard et al., 2021).

Unfortunately, the replacement of PVC in medical devices with another polymer is challenging (Simmchen et al., 2012) because PVC's mechanical characteristics (particular its elasticity and flexibility) are unequaled (Ito et al., 2005). One way of improving the safety of PVC consists in physical and/or chemical surface modifications that prevent plasticizer migration and maintain the bulk material's properties. Several researchers have described the use of surface modification approaches to limit the migration of DEHP from PVC: crosslinking with ultraviolet (UV) radiation (Ferri et al., 2012), treatment with low-pressure cold plasma (Audic et al., 2000), grafting of hydrophilic molecules (Lakshmi and Jayakrishnan, 1998), coatings (Bernard et al., 2014; Massard et al., 2012) and the incorporation of modified plasticizers (Raeisi et al., 2017).

Concerning the incorporation of modified plasticizers, the DEHP molecules were first grafted onto magnetic iron oxide (Fe_3O_4) nanoparticles in the presence of cyclodextrins (forming inclusion complexes). The modified plasticizer was then incorporated into PVC prior to manufacture of the tubing. Depending on the nanoparticle content, DEHP migration was 50 to 60% lower than for standard tubing (Raeisi et al., 2017). It was assumed that this reduction was

due to the formation of (i) dipole-dipole bonds between the polymer and the nanoparticles, and (ii) strong hydrogen bonds with DEHP.

Irradiation with UV or gamma radiation has been used to modify the outer surface of polymer-based medical devices, since a greater crosslinking rate at the surface would hinder the migration of plasticizers. Indeed, the surface treatment of PVC with 25, 50 or 100 Gy of gamma radiation was associated with a lower rate of DEHP migration from blood bags and tubing (Ferri et al., 2012). Similarly, Ito et al. (Ito et al., 2005) used UV radiation (52.5 $\mu W/cm^2$, for 1, 2 or 3 months) to obtain a 50% reduction in DEHP migration without changes in the PVC's mechanical properties (elasticity and tensile strength). The researchers reported that UV radiation modified the PVC's surface and reduced migration by reducing the chlorine content and increasing the oxygen content.

Lastly, surface grafting and surface coating have been investigated. For example, plasticized PVC sheets have been treated with an excess of Na-polyethylene glycol (PEG-4000) at 70°C. This resulting grafting of PEG chains reduced DEHP migration by around 30% and resulted in greater biocompatibility without modifying the PVC's mechanical properties (Lakshmi and Jayakrishnan, 1998). In another example, coatings have been applied to PVC. Special coatings (such as phospholipids and insulin) (Urban et al., 2016) were used to coat PVC cannulas for extracorporeal circulation. The coatings were intended to increase hydrophilicity and thus limit direct contact between the PVC surface and lipophilic blood components. Other coating molecules used with the intention of limiting the migration of plasticizers include ionically or covalently bound heparin (Hildenbrand et al., 2005), phospholipids (Münch et al., 2018), a sol-gel hybrid (titanium alkoxide and grafted alkoxysilane) (Bernard et al., 2014; Massard et al., 2012) and polydopamine (PDA). However, these coatings did not effectively limit the migration of DEHP.

PDA has been used to coat vascular stents (Sobocinski et al., 2014) and as a nanocarrier for drug loading (Mrówczyński, 2018) and shows very interesting characteristics. In particular, PDA increases surface hydrophilicity and biocompatibility (Wang et al., 2019) and adheres strongly to most substrates (Bernsmann et al., 2011). These putative advantages prompted us to use this coating in our surface modification.

Although there are many reports on the use of surface modifications to limit DEHP migration, very few studies have focused on limiting the migration of alternative plasticizers. To the best of our knowledge, only one study looked at the use of low-pressure argon cold plasma for limiting bis(2-ethylhexyl) adipate (DEHA) migration in food films (Audic et al., 2000). However, the decrease in migration was not documented over time, and the DEHA content is lower in food films (~25%) than in medical devices (~35%).

The primary objective of the present study of PVC substrates was to reduce the migration of TOTM and DINCH by combining physical surface modifications with PDA coating. To this end, we (i) pretreated with cold plasma the native PVC surface, (ii) applied a PDA coating plasma and (iii) used cold plasma or thermal treatment (140°C) to crosslink the PDA coatings and create a physical barrier that might prevent plasticizer migration.

The PVC films were characterized after each treatment step. Plasticizer migration was analyzed using an in-house HPLC-UV technique that can detect and quantify all the plasticizers used in medical devices in a single run (Masse et al., 2017).

2. Materials and methods

2.1. Products and consumables

PVC pellets containing 30% DINCH or 35% TOTM were provided by Cair LGL (Lissieu, France). The pure plasticizers used for calibration were DINCH (BASF, Houston, Etats-Unis), benzylbutylphtalate (BBP), and TOTM (Sigma-Aldrich, St. Quentin Fallavier, France). For the PDA coating, trishydroxymethylaminomethane buffer (TRIS®, Sigma Life Science, St-Quentin, France) and dopamine (Sigma, Issy-Les-Moulineaux, France) were purchased. Absolute ethanol (VWR Chemicals, Fontenay sous-bois, France) was used for the migration study. Acetonitrile (ACN) (HiPerSolv Chromanorm®) and tetrahydrofuran (THF) (HiPerSolv Chromanorm®) were purchased from VWR (Fontenay-sous-Bois, France). All solvents were HPLC grade.

2.2. Preparation of plasticized PVC films

Fifteen grams of PVC pellets plasticized with 30% DINCH or 35% TOTM were deposed in a specific mold (10 x 10 x 0.1 cm^3) and placed in a press (Polystat 200T, Servitec, Wustermark, Germany) at 10 kN and 170°C for 10 minutes, to obtain 0.8-mm-thick sheets. The sheets were cut into rectangles (3 x 1 cm), placed between two sheets of non-adhesive paper,

introduced into the press (with no pressure) at 170°C for one minute and then exposed to a pressure of 15 kN for one minute. Films (0.2 mm in thickness) were obtained, and disk-shaped samples (diameter: 10 mm) were cut out and stored at room temperature (RT) in a desiccator before use.

2.3. Treatment of PVC

2.3.1. Cold plasma treatment

Low-pressure cold plasma was generated in a plasma chamber (Europlasma CD1200-400 COMBI MC; Dressler radiofrequency generator, 13.56 MHz (Europlasma, Pessac, France)) with 100% argon (Air Liquid Creative Oxygen, Paris, France) at 500 watts.

The different plasma conditions used are summarized in Table 1, according to a prespecified experimental design for which various parameters were studied: electric field power (in watts), treatment duration (in seconds) and flow rate (expressed in standard cubic centimeters per minute – SCCM). Argon was chosen to treat the samples because it reportedly produces crosslinked surfaces that most effectively reduce plasticizer migration (Audic et al., 2000). Fig.1 shows possible PVC rearrangements after argon plasma treatment.

Table 1
Low-pressure argon cold plasma conditions

	Flow rate in standard cubic centimeters per minute (SCCM)	**Duration (seconds)**
Plasma condition 1 (P1)	100	180
Plasma condition 2 (P2)	850	60
Plasma condition 3 (P3)	500	60

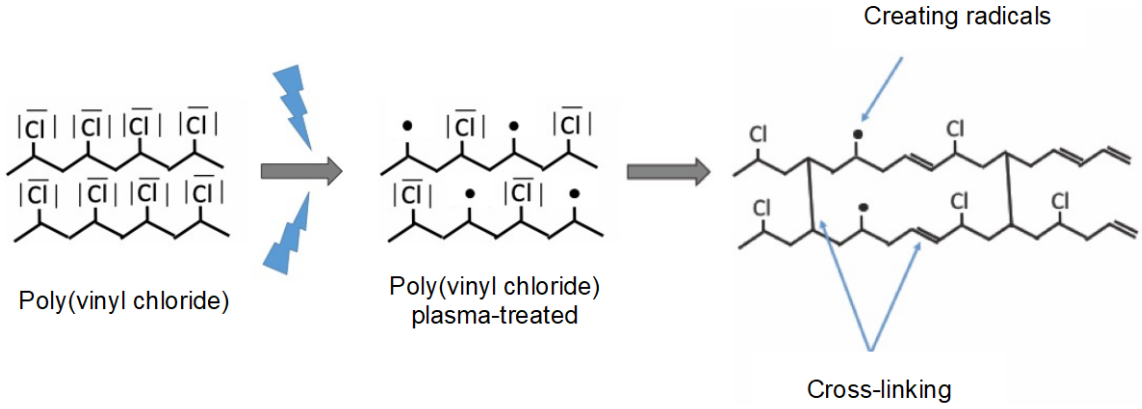


Fig. 1. Examples of PVC rearrangements after argon plasma treatment

2.3.2. Polydopamine coating

The PVC disks (whether pretreated with cold plasma or not) were placed in a vial containing 5 mL of 2 mg/mL dopamine solution in a 10 mM Trizma buffer adjusted to pH 8.5 with NaOH (VWR, Fontenay-sous-Bois, France). PDA was obtained by oxidative polymerization of dopamine upon contact with the TRIS® aqueous buffer (Fig. 2). The reaction was performed in an orbital shaker (IKA-KS 260 basic, Dutscher, Brumath, France) at RT and 400 rpm for 16 hours (Sobocinski et al., 2014). The PVC disks coated with PDA were placed in a beaker of ultrapure water and exposed to ultrasound for 5 minutes, in order to remove PDA not linked to the disk. The samples were dried in an oven (ED 400, Binder, Tuttlingen, Germany) at 60°C for 5 minutes and stored at RT in a desiccator before use.

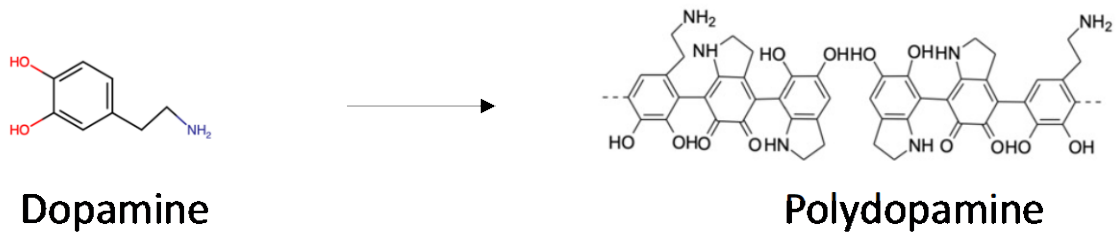


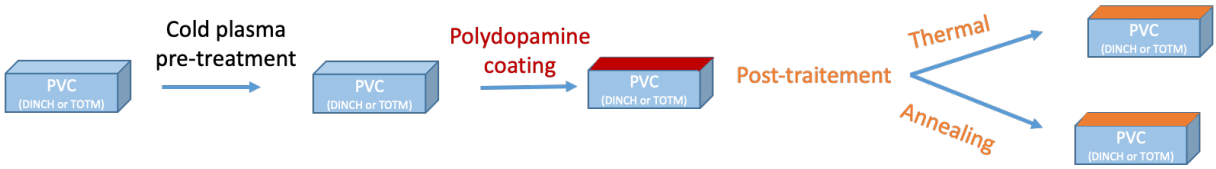
Fig. 2. Representation of the polymerization of dopamine into PDA.

220 *2.3.3. Post-treatments*

Some samples were post-treated to try to crosslink the PDA layer and thus create a physical barrier that might prevent the migration of plasticizers (Table 2). Two post-treatment approaches were considered: (i) thermal annealing (A) in an oven at 140°C for 1 hour, and (ii) 225 exposure to low-pressure argon cold plasma. Each disk's plasma post-treatment was always the same as its plasma pretreatment: for example, disks initially treated with P1 were always post-treated with P1, etc.. Each experiment designed to limit plasticizer migration was carried out for both PVC-DINCH and PVC-TOTM (Table 2 and Fig. 3).

230 **Table 2**
Summary of experiments and the associated sample names.

Experiment	Sample name
Nontreated PVC sample	NT
PDA-coated PVC sample	PDA
Cold plasma pretreatment	P1 / P2 / P3
Cold plasma pretreatment + PDA coating	P1+PDA / P2+PDA / P3+PDA
Cold plasma pretreatment + PDA coating + plasma post-treatment	P1+PDA+P1 / P2+PDA+P2 / P3+PDA+P3
Cold plasma pretreatment + PDA coating + thermal annealing (A)	P1+PDA+A / P2+PDA+A / P3+PDA+A



235

Fig. 3. Summary of the PVC treatments.

2.4. Scanning electron microscopy (SEM)

240 The PDA coatings (applied to both DINCH-PVC and TOTM-PVC films) were observed by SEM (Hitachi SU 5000, Hitachinaka, Japan; 5 kV; magnification: ×3300) with detector secondary electrons (SE) and total vacuum was caried out. Samples were cut and carbon coated using Baltec SCD005 sputter coater.

245

2.5. Goniometry

Immediately after the treatment, the water contact angle (WCA) was measured with ultrapure water on a goniometer (DSA 100, Krüss, Hamburg, Germany). Three drops of water (calibrated volume: 2.0 µL) were deposited on each sample, and the WCA (in degrees) was measured immediately three times for each drop (i.e. n = 9 angle measurements for each sample, expressed as the mean ± standard deviation (SD)). A Shapiro-Wilk test was carried out to check that the data were normally distributed. The results obtained for nontreated PVC (PVC-NT) and treated PVCs were compared in a non-parametric Kruskal-Wallis test. The threshold for statistical significance was set to $p<0.05$.

2.6. FTIR

FTIR-ATR analyses were performed using a Perkin Elmer (Villebon sur Yvette,France) "Spectrum one" infrared spectrometer. Some analyses were carried out by attenuated total reflection with a monoreflective diamond crystal. Wave number scanning for each sample was performed between 500 and 4000 cm^{-1}.

2.7. Extraction study

The plasticizers (DINCH and TOTM) contained in PVC pellets, sheets and films were extracted, in order to determine the exact concentration of plasticizer (in %, mass/mass) contained therein (Radaniel et al., 2014) (n = 5). Approximately 25 mg of a PVC sample were accurately weighed and dissolved by contact with 900 µL THF and 100 µL BBP (the internal standard) for one hour. The concentrations of BBP added were adjusted to match the dilutions of the PVC sample prior to chromatographic analysis, so that a target BBP concentration of 1 µg/mL was always obtained. Next, 500 µL of the mixture were added to 500 µL of methanol, to precipitate the PVC. After 5 minutes of centrifugation (centrifuge 5415R, Eppendorf, Le Pecq, France) at 13000 rpm, the supernatant was diluted in ACN according to each plasticizer's UV absorbance (Lecoeur et al., 2015). Thus, the dilution was 1:10 for DINCH (with low UV absorbance) and 1:500 for TOTM.

The micropipette tips (Eppendorf® loretention, VWR) and the centrifuge microtubes (Eppendorf®, VWR) were made of plasticizer-free plastic. To minimize cross-contamination and environmental contamination, glass materials (vials, beakers, HPLC vials, etc.) were washed with THF, washed with methanol and rinsed with ultrapure water before use.

2.8. The migration study

2.8.1. Validation of the migration method

The analytical method was validated in accordance with the guidelines issued by the French Society of Clinical Pharmacy (SFPC) /Group of Evaluation and Research for Protection in Areas Under Control (GERPAC) (SFPC, GERPAC, 2013).

For TOTM, a 500 µg/mL stock solution was prepared by accurately weighing 50 mg TOTM and diluting the compound in 100 mL ACN. Next, a 60 µg/mL diluted solution was prepared by dilution in 100% absolute ethanol. Lastly, diluted solutions (range: 0.9 to 30 µg/mL) were then prepared by diluting the diluted solution with absolute ethanol/ultrapure water (50/50, v/v).

For DINCH, a 10 mg/mL stock solution was prepared by accurately weighing 500 mg DINCH and diluting the compound in 50 mL ACN. Next, a 400 µg/mL diluted solution was prepared by dilution in 100% absolute ethanol. Lastly, diluted solutions (range: 50 to 200 µg/mL) were prepared by diluting the diluted solution with absolute ethanol/ultrapure water (50/50, v/v).

2.8.2. Migration of plasticizers

We studied the migration of plasticizer from both untreated disks and treated disks (n=5). The weight of each disk was checked before the test. The migration simulant was a mixture of water and absolute ethanol (50/50, v/v) ("Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food," n.d.). Disks were exposed for 24 hours and 72 hours, which correspond respectively to the maximum of intravenous infusion times for lipid and non-lipid drug solutions. Plasticizer migration was quantified directly in the simulant after contact with the PVC. The simulant was stored in a cabinet (Binder) at +40°C, in order to simulate the temperature inside an incubator used to care for newborns in hospital. The migration parameters were chosen in accordance with the European Commission's guidelines (Commission Regulation No 10/2011).

Each TOTM-plasticized PVC disk was then placed in an Eppendorf® centrifuge tube (Eppendorf® LoBind microcentrifuge DNA tube, volume = 1.5 mL, Eppendorf®, Fontenay-sous-Bois, France) containing a mixture of 500 µL ultrapure water and 500 µL absolute ethanol. In the literature, DINCH is described as the plasticizer that migrates most readily (after DEHP) (Faessler et al., 2017). This is why larger volumes of simulant (10 mL) were used to avoid

saturation of the simulant solution. Thus, 5 mL of ultrapure water and 5 mL of absolute ethanol were brought into contact with DINCH disks in closed glass vials.

The closed Eppendorf® tubes (containing PVC-TOTM) or glass vials (containing PVC-DINCH) were placed at +40°C prior to the HPLC-UV plasticizer assay (Masse et al., 2017).

The plasticizer migration results were presented as the mean ± SD plasticizer mass/disk mass, expressed as a percentage. The migration results for PVC-NT and treated PVC samples were compared by applying a Kruskal-Wallis test with Bonferroni's correction. Beforehand, a Shapiro-Wilk test was carried out to check that the data were not normally distributed. All statistical analyses were performed with XLSTAT software (version 16.15, Addinsoft, Paris, France).

3. Results

3.1. Measurement of the plasticizer content of nontreated PVC samples

The THF extraction of DINCH and TOTM from nontreated PVC took account of the extraction yields reported for this method (91 ± 1.8% for DINCH and 100 ± 0.5% for TOTM) (Radaniel et al., 2014). The extracted percentages of TOTM and DINCH were similar for the pellets, sheets and films and agreed with the data given by the supplier: 35% for TOTM and 30% for DINCH (Table 3). There was no loss of plasticizer during the production of the films.

Table 3
The mean ± SD % plasticizer content in PVC pellets, sheets and films, measured using an HPLC-UV assay (n = 5 per type of sample).

Plasticizer	Sample	% plasticizer (g/100 g PVC)
TOTM	Pellets	31.3 ± 4.4%
	Sheet	32.2 ± 1.5%
	Film	35.5 ± 2.0%
DINCH	Pellets	29.1 ± 3.0%
	Sheet	30.3 ± 2.8%
	Film	30.5 ± 2.2%

3.2. Surface characteristics of the PVC samples

The samples pretreated with cold plasma and coated with PDA were brown in color. When PVC was coated with PDA alone (i.e. in the absence of plasma pretreatment), the samples were weakly colored; this indicated poor adhesion of PDA to PVC and justified the use of plasma pretreatment to promote the binding of PDA to PVC.

3.2.1. Scanning electron microscopy

SEM images of functionalization revealed the presence of PDA nanoparticles, in line with the literature data (Fig. 4) (Dreyer et al., 2012; Jiang et al., 2011). For sample P2+PDA+R, the wrinkling of the film is probably due to heat.

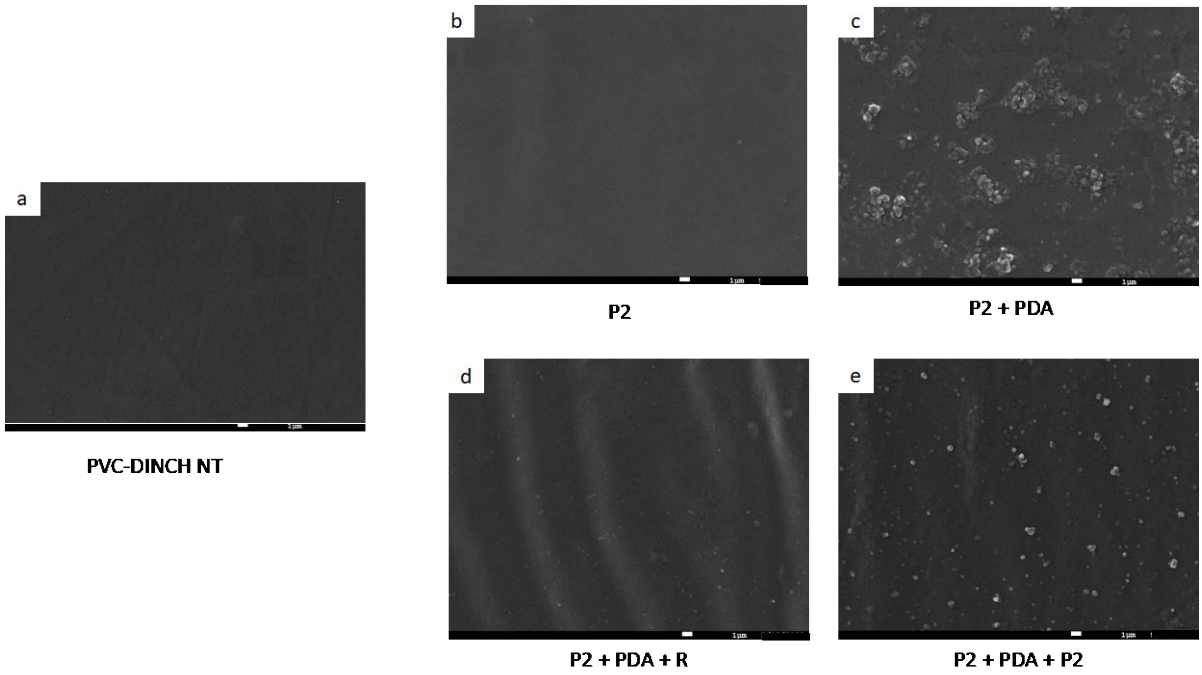


Fig. 4. Scanning electron micrographs of native PVC-DINCH NT (a), PVC-DINCH pretreated with cold plasma (P2) (b), PVC-DINCH pretreated with cold plasma and then coated with PDA (P2 + PDA) (c), PVC-DINCH pretreated with cold plasma, coated with PDA and annealing (P2 + PDA + R) (d), PVC-DINCH pretreated with cold plasma, coated with PDA and plasma (P2 + PDA + P2) (e). Magnification: × 3300.

3.2.2. Wettability

Native PVC-TOTM is hydrophobic, with a mean WCA of 110.2 ± 5.8° in our experiment (Fig. 5A). Low-pressure cold plasma treatment with argon increased the surface wettability. Indeed, P1, P2 and P3 treatments gave WCAs of 71.5 ± 5.1°; 73.2 ± 2.0° and 73.0 ± 7.9°, respectively. The addition of PDA to plasma-pretreated disks led to lower WCAs: 65.0 ± 3.3° for P1+ PDA; 62.3 ± 8.0° for P2+ PDA, and 60.8 ± 1.8° for P3+ PDA. After A at 140°C, WCA increased to 73.8 ± 3.2°, 89.5 ± 1.5° and 84.6 ± 6.3° for P1+PDA+A; P2+PDA+rA and P3+PDA+A, respectively. After plasma post-treatment, WCAs of 66.0 ± 3.4°; 69.0 ± 6.0° and 72.3 ± 8.0° were observed for P1+PDA+P1; P2+PDA+P2 and P3+PDA+P3, respectively; the samples were more hydrophilic than when thermal A was used.

PVC-DINCH NT presented a WCA of 96.7 ± 3.6° (Fig. 5B). As observed for TOTM, low-pressure argon cold plasma treatment led to a more hydrophilic surface, with WCAs of 59.1 ± 0.9°; 55.6 ± 0.7° and 65.5 ± 4.6° for P1, P2 and P3, respectively. The addition of PDA was associated with a less slightly hydrophilic surface: 67.8 ± 2.6°; 64.6 ± 4.6° and 77.9 ± 5.2°

for P1+PDA, P2+PDA, and P3+PDA, respectively. Thermal A and plasma posttreatment resulted in a hydrophobic polymer surface, with WCAs similar to those measured for PVC-NT.

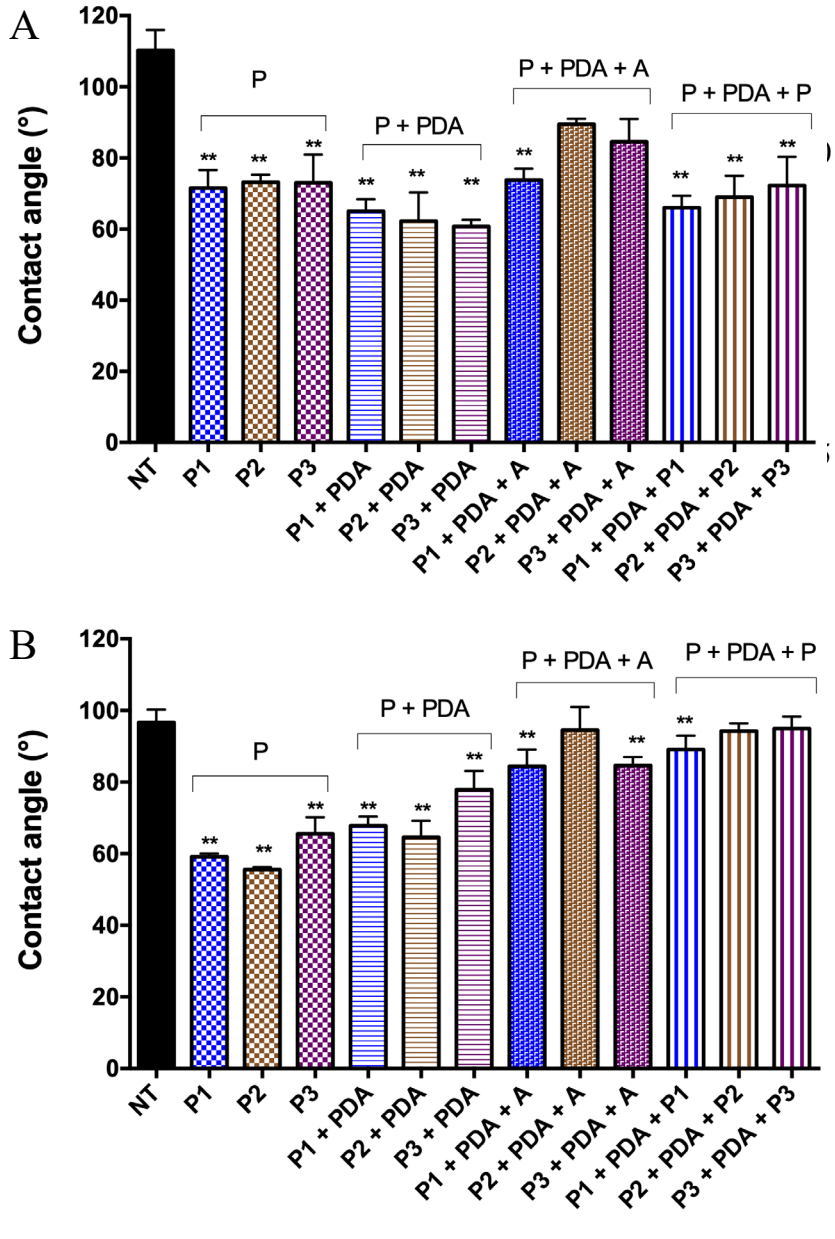


Fig. 5. Water contact angles of nontreated and treated PVC-TOTM disks (A) and PVC-DINCH (B) disks, n = 9. ** $p < 0.0001$.

3.2.3. FTIR

The PDA layer can be observed through OH groups (bands around 3500 cm-1) and C=C groups (band around 1600 cm-1) for all three PDA-coated samples (P2+PDA, P2+PDA+R and P2+PDA+P2). Infrared spectrum of PVC-TOTM and PVC-DINCH are summarized in supplementary data (figure 1 and 2 for TOTM and DINCH, respectively).

3.3. Plasticizer migration

3.3.1. Validation of the analytical method

The validation parameters for the HPLC-UV method are summarized in Table 4. The validated ranges enabled us to quantify plasticizer migration. The detected concentrations of TOTM were lower than those of DINCH; this was expected, since TOTM is known to migrate less than DINCH (Bernard et al., 2015; Faessler et al., 2017).

Table 4
Validation parameters of TOTM and DINCH migration ranges.

Plasticizer	Concentration range	r^2	LOD	LOQ
TOTM	1 – 30 µg/mL	0.9990	0.7 µg/mL (0.0018%)	0.9 µg/mL (0.0023%)
DINCH	50 – 200 µg/mL	0.9910	15 µg/mL (0.038%)	30 µg/mL (0.075%)

LOD: limit of detection; LOQ: limit of quantification.

3.3.2. Migration study

3.3.2.1. TOTM migration

The migrated amount of TOTM in PVC NT was 0.035 ± 0.008% after 24 hours in the simulant and 0.054 ± 0.005% after 72 hours (Fig. 6). The various plasma conditions did not appear to influence TOTM migration; the migrated amount of TOTM was 0.037 ± 0.004%, 0.024 ± 0.002 and 0.026 ± 0.005% for P1, P2 and P3, respectively, after 24 hours of incubation. Cold plasma alone (migration: 0.029 ± 0.002% and 0.055 ± 0.004% after 24 and 72 hours, respectively for all conditions plasma) or combined with PDA coating (0.027 ± 0.001% and 0.047 ± 0.003% after 24 and 72 hours, respectively) did not significantly reduce migration.

In contrast, thermal A (TOTM migration: 0.013 ± 0.002% and 0.018 ± 0.001% after 24 and 72 hours, respectively) and plasma post-treatments other than P3+PDA+P3 at 24h (0.015 ± 0.001% and 0.022 ± 0.002% after 24 and 72 hours, respectively) were associated with significantly lower migration of TOTM ($p < 0.0001$). The percentage decreases (relative to PVC-NT) observed for thermal and plasma post-treatments after 24 and 72 hours (except for P3+PDA+P3 condition after 24h) were respectively 63%, 67%, 57% and 59%.

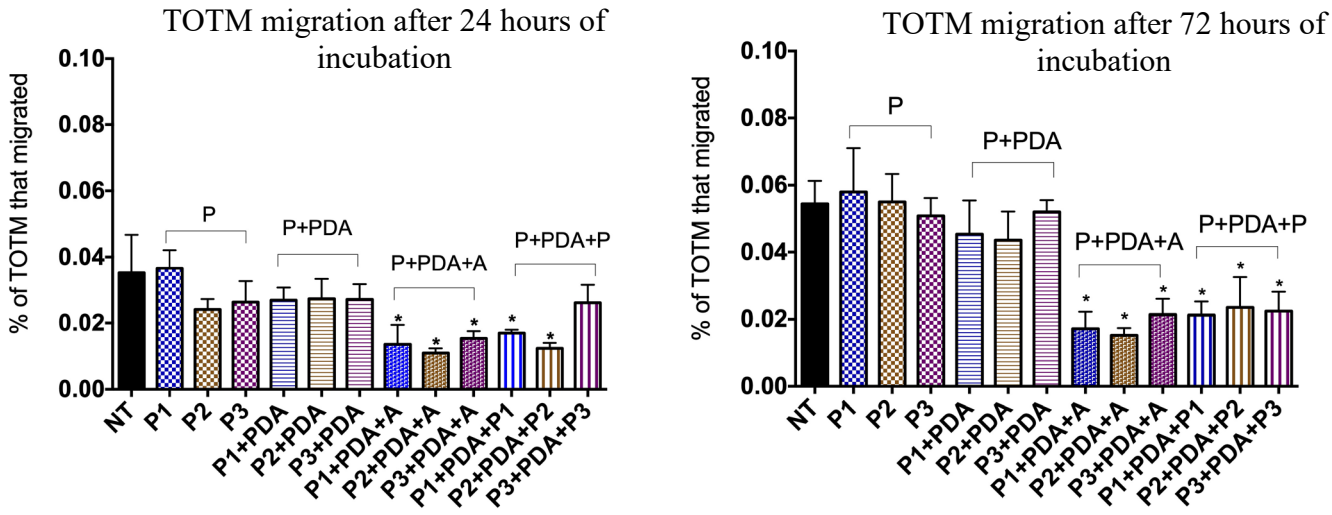


Fig. 6. The percentage of TOTM that had migrated after 24 hours and 72 hours of incubation (n = 5). p with Bonferroni correction= 0.0006; * $p < 0.0001$.

3.3.2.2. DINCH migration

The amount of DINCH migration from PVC NT was 2.70 ± 0.23% after 24 hours and 3.01 ± 0.31% after 72 hours (Fig. 7). As observed for TOTM, plasma alone did not significantly reduce DINCH migration: after 24 hours, the values were 2.02 ± 0.06%; 2.44 ± 0.24% and 2.45 ± 0.18% for P1, P2 and P3, respectively. When averaging P1 to P3, the mean amount of DINCH migration was 2.31 ± 0.31% after 24 hours and 3.02 ± 0.49% after 72 hours. As observed for plasma treatment alone, P+PDA did not significantly reduce DINCH migration (2.09 ± 0.32% and 2.42 ± 0.30% after 24 and 72 hours, respectively, when averaging P1 to P3). Annealing (except for condition 2) was associated with significantly less DINCH migration after 24 hours (1.87 ± 0.14% for P1 and P3). The treatment sequence that gave the greatest relative reduction in migration was P+PDA+P: 1.67 ± 0.31% after 24 hours and 1.87 ± 0.28% after 72 hours, i.e. a 38% decrease relative to PVC-NT.

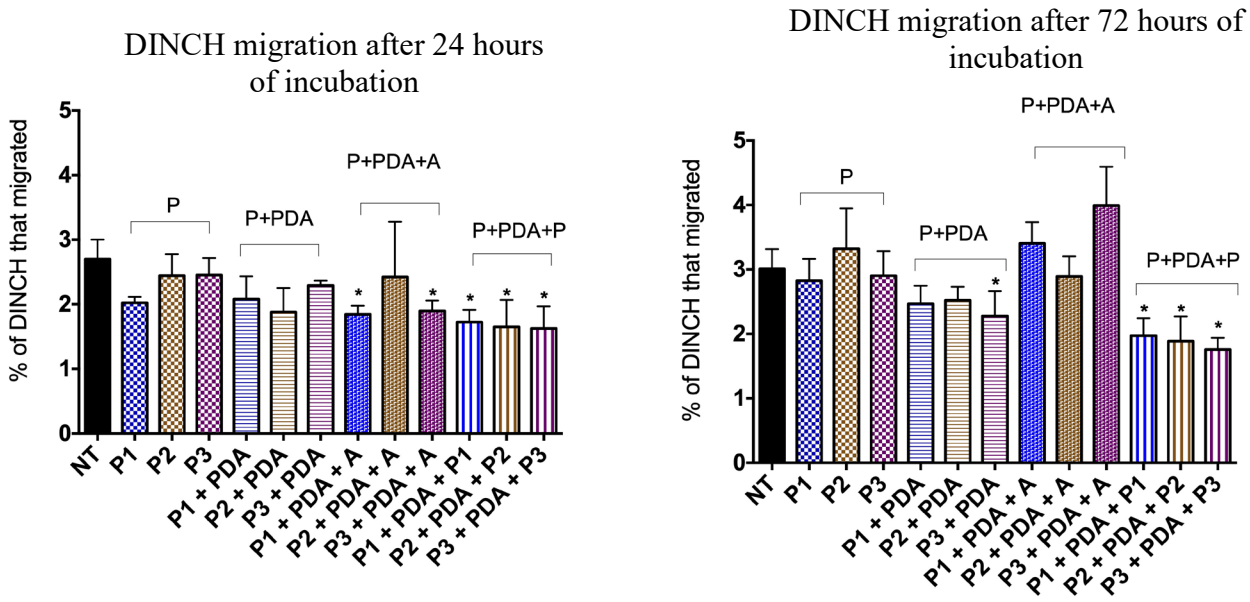


Fig. 7. The percentage of DINCH that had migrated after 24 hours and 72 hours of incubation (n = 5). p with Bonferroni correction = 0.0006. * $p < 0.0001$.

4. Discussion

The migration of plasticizers from PVC-containing medical devices is a major problem in the clinic. Indeed, these toxic molecules can migrate from medical devices and be unintentionally administered to the patient. At present, the substitution of PVC with other materials is not always possible because the substitutes do not have equivalent mechanical and/or physical-chemical properties. Thus, the objective of the present study was to find one or more surface treatments that reduced plasticizer migration. Here, we tested combinations of low-pressure cold plasma pretreatment, PDA coating, and thermal or cold plasma post-treatment. For DINCH and TOTM, the combination of the three treatments was associated with significantly lower migration: about 40% less for DINCH and 60% less for TOTM. The best combination depended on the plasticizer: the inclusion of a cold plasma post-treatment was most effective for DINCH, whereas thermal post-treatment was most effective for TOTM.

These differences in the reduction of TOTM vs. DINCH migration can be explained by the compounds' physical-chemical properties and the study's methodology. Indeed, the two plasticizers different greatly in terms of the migration rate, which was 77 times higher for DINCH than TOTM after 24 hours of incubation and 55 times higher after 72 hours. One explanation for these different behaviors might relate to the wettability induced by the plasticizer. PVC is a hydrophobic material: the WCA of pure PVC powder was 81.6 ± 2.7° (Zhang et al., 2015). The nature and percentage of the added plasticizer seems to influence the WCA, with the values of 110 ± 5.8° for PVC-TOTM and 96.7 ± 3.6 for PVC-DINCH. In general, the WCA increases with the plasticizer contents: 81.6 ± 2.9 for 30% m/m PVC-acetyltributylcitrate (ATCB) and 95.9 ± 2.7° for 70% m/m PVC-ATCB, in a literature report (Zhang et al., 2015). Although TOTM and DINCH have a log P of 5.94 and 10, respectively, the WCAs for PVC-TOTM were higher than those found with PVC-DINCH because the TOTM content (35%) was higher than the DINCH content (30%). Another hypothesis put forward is that since DINCH is more hydrophobic, it will consume more hydrophobic C-Cl functions with PVC and the surface will be less hydrophobic.

One hypothesis to explain the differences in plasticizer migration is that the plasticizer has more affinity with the external environment than with PVC. DINCH has a higher log P than TOTM, DINCH will have more affinity with an external lipophilic medium than TOTM. However, the difference in migratory behavior between TOTM and DINCH might also be explained by the plasticizers' physical-chemical characteristics. Indeed, TOTM has a higher molecular weight than DINCH (546.80 g/mol and 424.70 g/mol, respectively) and - due to the presence of its three alkyl chains - has a much larger steric footprint. Our results are in line with *in vitro* studies (Bernard et al., 2015) in which DINCH migrates more than TOTM after 24 hours of incubation (3.52 ± 0.47% and 0.20 ± 0.05%, respectively) by gas chromatography assay supplemented by a flame ionization detector method.

In contrast to the report by Bernard *et al.* (Bernard et al., 2015) (in which the TOTM migration rates after 24 and 72 hours of testing were similar), we found that TOTM migration changes over time. The same was also observed for DINCH, which continued to migrate at 72 hours. Moreover, our migration percentages for both TOTM and DINCH were lower than those reported by Bernard *et al.* after 24 and 72 hours of incubation (respectively 0.20 ± 0.05% and 0.28 ± 0.04% for TOTM, and 3.52 ± 0.47% and 3.30 ± 0.27% for DINCH). One possible explanation for this interstudy disparity is the methodology used by Bernard *et al.* (i.e. a 30 cm

length of PVC tubing weighing about 2 g, and a large volume (125 mL) of simulant. In our study, the samples weighed about 40 mg and the volume of simulant was just 1 mL for TOTM and 10 mL for DINCH. Although the initial plasticizer contents in the samples were similar in the two studies (30% for DINCH and 35% for TOTM), plasticizer migration processes are probably not identical in tubes vs. disks.

Even when used at a low concentration, plasticizers still migrate. In order to limit this phenomenon, we thought to coat PVC samples with PDA. However, if the PVC was not pretreated, the PDA coating did not adhere properly and so was easily removed. Therefore, we implemented a low-pressure cold plasma process prior to the PDA coating; this increased PDA adhesion through the formation of unstable, reactive radicals (Audic et al., 2000). The PDA coating was then applied directly to the PVC.

For both TOTM and DINCH, plasma treatment alone did not appear to affect plasticizer migration. However, low-pressure argon cold plasma treatment increased the surface wettability. Plasma treatment causes chlorine loss, so the chlorine:carbon ratio decreases and the oxygen:carbon ratio increases (Hankett et al., 2012). The generation of oxygenated groups (hydroperoxides, carbonyls, hydroxyls, carboxyls, etc.) might be due to reactions of the PVC's carbons with oxygen in the air following the plasma treatment (Khorasani and Mirzadeh, 2007). Our results do not confirm or invalidate literature data on other plasticizers. For example, Zhang et al. showed that compared with oxygen plasma treatment, argon cold plasma treatment appeared to favor the migration of the plasticizer ATBC (Zhang et al., 2015). According to these researchers, argon plasma might split PVC chains and cause molecular rearrangements and the loss of terminal methyl groups. These changes would result in a decrease in the interactions between the PVC chains and ATBC and thus would facilitate the latter's migration. In contrast, Audic et al. (Audic et al., 2000) stated that argon is most effective at reducing DEHA migration by inducing cross-linking and degradation. In our study of two other plasticizers (DINCH and TOTM), we could not draw clear conclusions about the effect of argon plasma pretreatment on plasticizer migration.

Low-pressure cold plasma and PDA coating (P+PDA) probably formed a barrier that limited plasticizer migration. The coating of PDA on plasma-pretreated disks led to a reduction in the WCA: the PDA's amine groups made the surface more hydrophilic. However, the migration

reduction was small for both plasticizers after 24 and 72 hours (respectively 0.027 ± 0.001% and 0.047 ± 0.003% for TOTM and 2.09 ± 0.32% and 2.42 ± 0.30% for DINCH, on average.

We therefore added a post-processing step (thermal treatment at 140°C or low-pressure argon cold plasma treatment) to try to cross-link the PDA layer and form a physical barrier that might limit plasticizer migration. Depending on the post-treatment used, a significant decrease in migration of both TOTM and DINCH was observed.

After A at 140°C, the WCA was higher and so the surface was less hydrophilic. Indeed, A causes cross-linking of the PDA by the formation of indole derivatives that reduce the number of amine groups (Luo et al., 2013).

For DINCH, post-treatment with cold plasma limited the migration: 1.67 ± 0.31% and 1.87 ± 0.28% after 24 and 72 hours, respectively, which correspond to a 38% decrease in migration relative to PVC-NT. Thermal post-treatment was not associated with any particular improvement – even after 72 hours. Indeed, the amount of DINCH migration at 72 hours was even higher than that observed for PVC-NT (3.43 ± 0.61% vs 3.02 ± 0.49%, respectively). We hypothesized that thermal post-treatment caused DINCH to migrate to the surface and thus increased migration. Indeed, Hankett et al. (Hankett et al., 2012) have reported that post-thermal treatment caused DEHP to migrate to the surface of the sample. Given that DEHP and DINCH are both small molecules (molecular weight: 390.6 for DEHP and 424.6 g/mol for DINCH), they can migrate easily to the surface.

In contrast, thermal post-treatment did not appear to facilitate the migration of TOTM to the surface because the value fell by more than 60%. This is probably due the fact that TOTM tends to migrate less than DINCH. Moreover, TOTM has a higher molecular weight (546.8 g/mol) than DINCH and DEHP, and so A has less impact on the plasticizer's migration to the surface. Migration of plasticizers cannot be reduced solely by modifying the hydrophilicity and lipophilicity of the surface, other parameters must also be taken into account, such as polarity, volatility, molecular weight and steric hindrance.

In hospitals, a large number of PVC medical devices are used in the treatment of patients; the latter are therefore exposed extensively to plasticizers. A study carried out in a neonatal intensive care unit found that 44 different PVC-containing medical devices were used. The plasticizer content in the PVC is these devices ranged from 36% to 48% m/m. Another study of cardiovascular resuscitation showed that the levels of TOTM released were 31.8 ± 2.3 under static conditions, 39.0 ± 0.5 under low-flow-rate conditions, and 10.1 ± 0.3 µg/mL under high-

flow-rate conditions. These high migration rates were mainly due to the extracorporeal membrane oxygenation cannulas, which contain blood and held at body temperature. By applying the treatments described in our study, we suggest these levels could be lowered to 12.72 µg/mL under static conditions, 15.6 µg/mL under low-flow-rate conditions and 4.04 µg/mL mg/L under high-flow-rate conditions. Similarly, Faessler et al. (Faessler et al., 2017) showed that DINCH migrated at concentrations of 5.8 ± 0.11 µg/mL (with Intralipid 20%) and 5.1 ± 0.4 µg/mL (with ClinOleic 20%). Our treatments might decrease this migration to 3.48 and 3.06 µg/mL, respectively.

This study was carried out on plasticized PVC film. For industrial use, many parameters in terms of diffusion of plasma inside the tube, sterilization and brown coloration (Lee et al., 2007) will have to be adjusted to transpose the functionalization processes to tubes.

5. Conclusion

Our results showed that a combination of surface treatment (low-pressure cold plasma), PDA coating, and surface post-treatments (with cold plasma or heat) significantly limited plasticizer migration from PVC (by about 40% and 60% for DINCH and TOTM, respectively). Low-pressure cold plasma pretreatment of the PVC was mandatory: otherwise, the PDA coating did not adhere. PDA coating alone did not prevent plasticizer migration. However, the post-treatment of PDA-coated PVC favored cross-linking and led to a decrease in plasticizer migration. The extent of the migration also depended on the plasticizer's molecular weight. DINCH has a low molecular weight (like DEHP) and migrates more easily than TOTM; this explains why the treatments intended to reduce migration were less effective for DINCH. Our results are promising with regard to limiting the migration of plasticizers into the patient's blood and thus enabling the development of safer medical devices. Before this approach can be validated for use in medical devices, additional studies (particularly mechanical testing and ageing studies) are required.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Highlights

- Plasticizers migration from PVC can be toxic for patient.
- Migration is different according to the plasticizer type
- Plasma alone does not reduce plasticizers migration
- Polydopamine coating combined with plasma and annealing limit migration

References

Audic, J.-L., Poncin-Epaillard, F., Reyx, D., Brosse, J.-C., 2000. Cold plasma surface modification of conventionally and nonconventionally plasticized poly(vinyl chloride)-based flexible films: Global and specific migration of additives into isooctane. J. Appl. Polym. Sci. 79, 1384–1393. https://doi.org/10.1002/1097-4628(20010222)79:8<1384::AID-APP50>3.0.CO;2-H

Bernard, L., Bouattour, Y., Masse, M., Boeuf, B., Decaudin, B., Genay, S., Lambert, C., Moreau, E., Pereira, B., Pinguet, J., Richard, D., Sautou, V., For The Armed Study Group, null, 2021. Association between Urinary Metabolites and the Exposure of Intensive Care Newborns to Plasticizers of Medical Devices Used for Their Care Management. Metabolites 11, 252. https://doi.org/10.3390/metabo11040252

Bernard, L., Cueff, R., Breysse, C., Décaudin, B., Sautou, V., 2015. Migrability of PVC plasticizers from medical devices into a simulant of infused solutions. Int. J. Pharm. 485, 341–347. https://doi.org/10.1016/j.ijpharm.2015.03.030

Bernard, L., Cueff, R., Massard, C., Blavignac, C., Awitor, K.O., Chopineau, J., Sautou, V., 2014. Hybrid sol gel coating: A solution to prevent interactions between plasticized poly(vinyl chloride) and injectable drugs? J. Appl. Polym. Sci. 131, n/a-n/a. https://doi.org/10.1002/app.40145

Bernsmann, F., Ball, V., Addiego, F., Ponche, A., Michel, M., Gracio, J.J. de A., Toniazzo, V., Ruch, D., 2011. Dopamine-melanin film deposition depends on the used oxidant and buffer solution. Langmuir ACS J. Surf. Colloids 27, 2819–2825. https://doi.org/10.1021/la104981s

Bourdeaux, D., Yessaad, M., Chennell, P., Larbre, V., Eljezi, T., Bernard, L., Sautou, V., 2016. Analysis of PVC plasticizers in medical devices and infused solutions by GC–MS. J. Pharm. Biomed. Anal. 118, 206–213. https://doi.org/10.1016/j.jpba.2015.10.034

Chiellini, F., Ferri, M., Morelli, A., Dipaola, L., Latini, G., 2013. Perspectives on alternatives to phthalate plasticized poly(vinyl chloride) in medical devices applications. Prog. Polym. Sci. 38, 1067–1088. https://doi.org/10.1016/j.progpolymsci.2013.03.001

Commission Regulation (EU) No 10/2011 of 14/01/11 on plastic materials and articles intended to come into contact with foodstuffs available at: https://eur-lex.europa.eu/legal-content/FR/TXT/?uri=CELEX%3A02011R0010-20140324[cited 03 June 2018], n.d.
Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food, n.d.

Dreyer, D.R., Miller, D.J., Freeman, B.D., Paul, D.R., Bielawski, C.W., 2012. Elucidating the structure of poly(dopamine). Langmuir ACS J. Surf. Colloids 28, 6428–6435. https://doi.org/10.1021/la204831b

Eljezi, T., Pinta, P., Richard, D., Pinguet, J., Chezal, J.-M., Chagnon, M.-C., Sautou, V., Grimandi, G., Moreau, E., 2017. In vitro cytotoxic effects of DEHP-alternative plasticizers and their primary metabolites on a L929 cell line. Chemosphere 173, 452–459. https://doi.org/10.1016/j.chemosphere.2017.01.026

Faessler, D., McCombie, G., Biedermann, M., Felder, F., Subotic, U., 2017. Leaching of plasticizers from polyvinylchloride perfusion lines by different lipid emulsions for premature infants under clinical conditions. Int. J. Pharm. 520, 119–125. https://doi.org/10.1016/j.ijpharm.2017.01.046

Ferri, M., Marcella, F., Chiellini, F., Federica, C., Pili, G., Giorgio, P., Grimaldi, L., Luca, G., Florio, E.T., Pili, S., Stefania, P., Cucci, F., Francesco, C., Latini, G., Giuseppe, L., 2012. Di-(2-ethylhexyl)-phthalate migration from irradiated poly(vinyl chloride) blood bags for graft-vs-host disease prevention. Int. J. Pharm. 430, 86–88. https://doi.org/10.1016/j.ijpharm.2012.03.039

Genay, S., Décaudin, B., Scoccia, S., Barthélémy, C., Debaene, B., Lebuffe, G., Odou, P., 2015. An in vitro evaluation of infusion methods using a syringe pump to improve noradrenaline administration. Acta Anaesthesiol. Scand. 59, 197–204. https://doi.org/10.1111/aas.12439

Hankett, J.M., Zhang, C., Chen, Z., 2012. Sum frequency generation and coherent anti-Stokes Raman spectroscopic studies on plasma-treated plasticized polyvinyl chloride films. Langmuir ACS J. Surf. Colloids 28, 4654–4662. https://doi.org/10.1021/la2045527

Hildenbrand, S.L., Lehmann, H.-D., Wodarz, R., Ziemer, G., Wendel, H.P., 2005. PVC-plasticizer DEHP in medical products: do thin coatings really reduce DEHP leaching into blood? Perfusion 20, 351–357. https://doi.org/10.1191/0267659105pf836oa

Ito, R., Seshimo, F., Haishima, Y., Hasegawa, C., Isama, K., Yagami, T., Nakahashi, K., Yamazaki, H., Inoue, K., Yoshimura, Y., Saito, K., Tsuchiya, T., Nakazawa, H., 2005. Reducing the migration of di-2-ethylhexyl phthalate from polyvinyl chloride medical devices. Int. J. Pharm. 303, 104–112. https://doi.org/10.1016/j.ijpharm.2005.07.009

Jiang, J., Zhu, Liping, Zhu, Lijing, Zhu, B., Xu, Y., 2011. Surface characteristics of a self-polymerized dopamine coating deposited on hydrophobic polymer films. Langmuir ACS J. Surf. Colloids 27, 14180–14187. https://doi.org/10.1021/la202877k

Kambia, N.K., Séverin, I., Farce, A., Moreau, E., Dahbi, L., Duval, C., Dine, T., Sautou, V., Chagnon, M.-C., 2019. In vitro and in silico hormonal activity studies of di-(2-ethylhexyl)terephthalate, a di-(2-ethylhexyl)phthalate substitute used in medical devices, and its metabolites. J. Appl. Toxicol. 39, 1043–1056. https://doi.org/10.1002/jat.3792

Khorasani, M.T., Mirzadeh, H., 2007. Effect of oxygen plasma treatment on surface charge and wettability of PVC blood bag—In vitro assay. Radiat. Phys. Chem. 76, 1011–1016. https://doi.org/10.1016/j.radphyschem.2006.10.002

Lakshmi, S., Jayakrishnan, A., 1998. Migration resistant, blood-compatible plasticized polyvinyl chloride for medical and related applications. Artif. Organs 22, 222–229.

Lecoeur, M., Décaudin, B., Guillotin, Y., Sautou, V., Vaccher, C., 2015. Comparison of high-performance liquid chromatography and supercritical fluid chromatography using evaporative light scattering detection for the determination of plasticizers in medical devices. J. Chromatogr. A 1417, 104–115. https://doi.org/10.1016/j.chroma.2015.09.026

Lee, H., Dellatore, S.M., Miller, W.M., Messersmith, P.B., 2007. Mussel-inspired surface

chemistry for multifunctional coatings. Science 318, 426–430. https://doi.org/10.1126/science.1147241

Luo, R., Tang, L., Zhong, S., Yang, Z., Wang, J., Weng, Y., Tu, Q., Jiang, C., Huang, N., 2013. In vitro investigation of enhanced hemocompatibility and endothelial cell proliferation associated with quinone-rich polydopamine coating. ACS Appl. Mater. Interfaces 5, 1704–1714. https://doi.org/10.1021/am3027635

Massard, C., Bernard, L., Cueff, R., Raspal, V., Feschet-Chassot, E., Sibaud, Y., Sautou, V., Awitor, K.O., 2012. Photopolymerizable hybrid sol gel coating as a barrier against plasticizer release. Prog. Org. Coat. 75, 116–123. https://doi.org/10.1016/j.porgcoat.2012.04.005

Masse, M., Genay, S., Feutry, F., Simon, N., Barthélémy, C., Sautou, V., Décaudin, B., Odou, P., Group, for the A.S., 2017. How to solve the problem of co-elution between two compounds in liquid chromatography through the first UV derivative spectrum. A trial on alternative plasticizers to di(2-ethylhexyl) phthalate. Talanta 162, 187–192. https://doi.org/10.1016/j.talanta.2016.10.029

Mrówczyński, R., 2018. Polydopamine-Based Multifunctional (Nano)materials for Cancer Therapy. ACS Appl. Mater. Interfaces 10, 7541–7561. https://doi.org/10.1021/acsami.7b08392

Münch, F., Höllerer, C., Klapproth, A., Eckert, E., Rüffer, A., Cesnjevar, R., Göen, T., 2018. Effect of phospholipid coating on the migration of plasticizers from PVC tubes. Chemosphere 202, 742–749. https://doi.org/10.1016/j.chemosphere.2018.03.136

National Agency for the Safety of Medicines and Health Products (ANSM). Analysis of drug sales in France in 2013., n.d.

Radaniel, T., Genay, S., Simon, N., Feutry, F., Quagliozzi, F., Barthélémy, C., Lecoeur, M., Sautou, V., Décaudin, B., Odou, P., ARMED study group, 2014. Quantification of five plasticizers used in PVC tubing through high performance liquid chromatographic-UV detection. J. Chromatogr. B Analyt. Technol. Biomed. Life. Sci. 965, 158–163. https://doi.org/10.1016/j.jchromb.2014.06.027

Raeisi, A., Faghihi, K., Shabanian, M., 2017. Designed biocompatible nano-inhibitor based on poly(β-cyclodextrin-ester) for reduction of the DEHP migration from plasticized PVC. Carbohydr. Polym. 174, 858–868. https://doi.org/10.1016/j.carbpol.2017.06.105

Règlement (CE) No 1272/2008 du parlement européen et du conseil du 16 décembre 2008 relatif à la classification, à l'étiquetage et à l'emballage des substances et des mélanges, modifiant et abrogeant les directives 67/548/CEE et 1999/45/CE et modifiant le règlement (CE) no 1907/2006, disponible sur : http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:fr:PDF, n.d.

Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR), Opinion on the safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonate and other groups possibly at risk. European Committee, 2008. Disponible sur :http://ec.europa.eu/health/archive/ph_risk/committees/04_scenihr/docs/scenihr_o_008.pdf, n.d.

SFPC, GERPAC. Methodological guidelines for stability studies of hospital pharmaceutical preparations 2013 http://www.gerpac.eu/IMG/pdf/guide_stabilite_anglais.pdf (accessed August 2022)., n.d.

Simmchen, J., Ventura, R., Segura, J., 2012. Progress in the Removal of Di-[2-Ethylhexyl]-Phthalate as Plasticizer in Blood Bags. Transfus. Med. Rev. 26, 27–37. https://doi.org/10.1016/j.tmrv.2011.06.001

Sobocinski, J., Laure, W., Taha, M., Courcot, E., Chai, F., Simon, N., Addad, A., Martel, B., Haulon, S., Woisel, P., Blanchemain, N., Lyskawa, J., 2014. Mussel inspired coating of a biocompatible cyclodextrin based polymer onto CoCr vascular stents. ACS Appl. Mater. Interfaces 6, 3575–3586. https://doi.org/10.1021/am405774v

Swan, S.H., Sathyanarayana, S., Barrett, E.S., Janssen, S., Liu, F., Nguyen, R.H.N., Redmon, J.B., TIDES Study Team, 2015. First trimester phthalate exposure and anogenital distance in newborns. Hum. Reprod. Oxf. Engl. 30, 963–972. https://doi.org/10.1093/humrep/deu363

Urban, K., Redford, D., Larson, D.F., 2016. Insulin binding to the cardiopulmonary bypass biomaterials: Perfusion. https://doi.org/10.1177/0267659107081632

Wang, H., Lin, C., Zhang, X., Lin, K., Wang, X., Shen, S.G., 2019. Mussel-Inspired Polydopamine Coating: A General Strategy To Enhance Osteogenic Differentiation and Osseointegration for Diverse Implants. ACS Appl. Mater. Interfaces 11, 7615–7625. https://doi.org/10.1021/acsami.8b21558

Zhang, X., Li, Y., Hankett, J.M., Chen, Z., 2015. The molecular interfacial structure and plasticizer migration behavior of “green” plasticized poly(vinyl chloride). Phys. Chem. Chem. Phys. PCCP 17, 4472–4482. https://doi.org/10.1039/c4cp05287k

Supplementary data

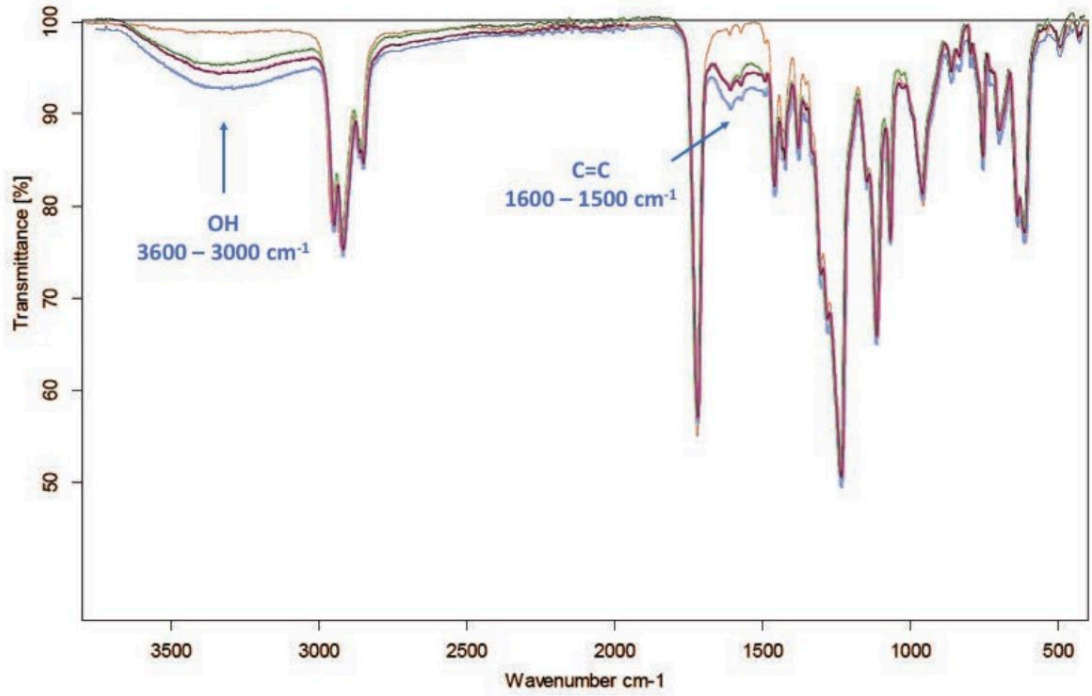


Figure 1: infrared spectrum of PVC-TOTM treated with P2 (orange), P2+PDA (blue), P2+PDA+R (green) and P2+PDA+P2 (red).

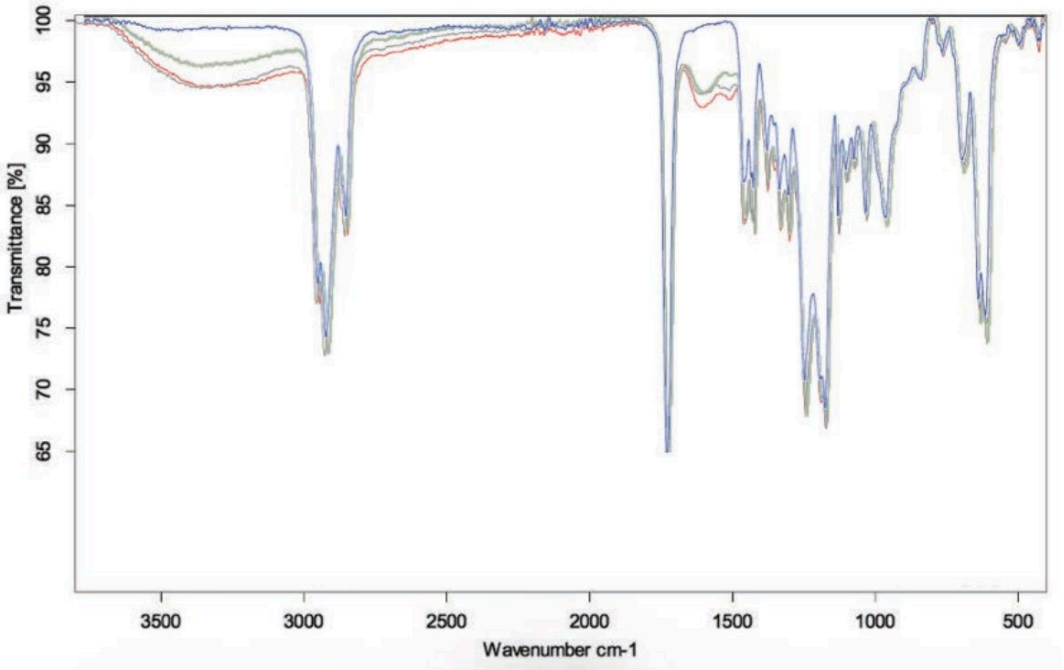


Figure 2: infrared spectrum of PVC-DINCH treated with P2 (orange), P2+PDA (blue), P2+PDA+R (green) and P2+PDA+P2 (red).