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1 **Fluorination of PVC medical devices to prevent plasticizers migration**

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4

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10 **Abstract**

11 Medical devices (MD) are often made of plasticized polyvinylchloride (PVC). However,
12 plasticizers may leach out into infused solutions and expose the patients to a toxic risk. The
13 aim of the present work is to fluorinate plasticized PVC tubular MDs to create a barrier layer
14 on their internal surface, and to study the impact of such a chemical treatment on the
15 migration of the plasticizers. Following fluorination by pure molecular fluorine, the physico-
16 chemical characterization of these modified MDs was carried out using various spectroscopic
17 and microscopic techniques or tensile tests, evidencing the formation of covalent C-F bonds
18 on the surface of the treated samples without modification of their mechanical and optical
19 properties. The migration of plasticizers from fluorinated MDs was assessed using gas
20 chromatography coupled with mass spectrometry and was found considerably decreased in
21 comparison with the pristine MDs. After 24 hours, the amount of tri-octyltrimellitate
22 plasticizer (TOTM) detected in migrates from fluorinated MDs was even lower than the limit
23 of quantification. Complementary cytotoxicity assays were performed according to the ISO

24 EN 10993-5 standard, showing that the new fluorinated material does not cause a cytotoxic
25 effect on L929 cells.

26 **Keywords:**

27 Plasticizer, PVC, migration, fluorination, polymer, cytotoxicity.

28

29 ***1. Introduction***

30 Polyvinyl chloride (PVC) is widely used in the production of tubular medical devices (MDs)
31 as infusion lines, feeding tubes and tubings, umbilical catheters, MDs for respiratory
32 assistance, dialysis and other extracorporeal circulation and blood bags due to its many
33 benefits such as transparency, excellent performance, and low cost. Nevertheless, PVC is
34 highly rigid, and plasticizers are added to improve its softness and flexibility. Since the latter
35 are not covalently bound to the PVC matrix, they can be released into the human body when
36 used in a MD [1,2]. The migration of these plasticizers poses a public health problem for
37 some compounds such as phthalates. This is well exemplified by di-(2-ethylhexyl) phthalate
38 (DEHP), commonly used as a plasticizer in PVC medical devices. DEHP has been shown to
39 be reprotoxic and presents a potential danger for patients [3]. For such reasons, it was
40 classified as a CMR1b (Cancerigen Mutagen or Reprotoxic) risk substance under the
41 Classification Labeling and Packaging (CLP) Regulation [4], due to its effect on reproduction
42 and fertility. In addition, it was also classified among endocrine disruptors [5]. The addition of
43 DEHP to PVC in the purpose of manufacturing a MD is now restricted according to
44 European Regulation 2017/745 of the European Parliament and of the Council of 5 April
45 2017 relating to medical devices [6]. Unless justified, its weight ratio is limited to 0.1% of
46 DEHP.

47 In this context, several solutions are possible such as the substitution of PVC by other
48 materials like polyethylene (PE), polypropylene, polyurethane or silicon. Depending on the
49 applications, substitution may not always be possible for functional reasons and because the
50 required performance of the MD is not achieved. Some manufacturers have had to resort to
51 alternative solutions to DEHP-plasticized PVC and have substituted DEHP with other
52 plasticizers such as DEHT (di-(2-ethylhexyl) terephthalate), TOTM (tri-octyltrimellitate),
53 DINP (di-(isononyl) phthalate), DINCH (1-di(isononyl)cyclohexane-1,2-dicarboxylic acid),
54 DEHA (di-(2-ethylhexyl) adipate) or ATBC (acetyltri-n-butyl citrate). Like DEHP, these
55 plasticizers are only blended and not covalently bound to PVC and have the ability to migrate
56 from the MD into the fluid contained inside (blood, infused drug), though less than DEHP,
57 therefore exposing the patient to their contact [7–9]. Some of these plasticizers do not seem to
58 be free from risks [10].

59 The search of innovative methods in order to limit migration of plasticizers is in progress, and
60 surface crosslinking and grafting or the use of plasticizers covalently bonded to PVC [11] in
61 particular have been attempted. However, these techniques are usually expensive, and their
62 efficiency has not proved optimal. The best solution in terms of simplicity and performance
63 would therefore be a surface treatment of MDs already on the market.

64 The fluorination of polymers appears as a potential innovative solution in this purpose. Its
65 feasibility on an industrial scale is notably recognized through the use of molecular fluorine as
66 reagent in direct fluorination processes. Thus, a few companies (Air Products and Chemicals
67 Inc, Solvay Chemicals, Pelchem ...) developed their own fluorine-based surface treatments
68 processes to improve the barrier properties, friction coefficient and printability of polymers.
69 In particular, direct fluorination of the inner wall of fuel tanks and containers for the
70 automotive industry has been studied [12–15] and has indeed been shown to prevent the
71 diffusion of non-polar or low-polarity substances.

72 In this study, the sidewall of commercialized PVC-plasticized MDs was fluorinated by direct
 73 fluorination with a view to prevent plasticizers release. Should this strategy prove successful
 74 in terms of anti-migration, fluorination could be considered as a potential surface treatment of
 75 MDs only under the condition that it does not result in cytotoxicity through the release of
 76 fluorinated molecules, which may arise from decomposition of the polymer, from side-
 77 products (e.g. HF resulting from the conversion of C-H bonds into C-F), or from fluorination
 78 of the plasticizer. The durability of the C-F bonds formed is also questionable in order to
 79 avoid migration of fluorinated species from the MD. The present work aims to answer these
 80 questions through plasticizer migration tests, cytotoxicity and mechanical properties
 81 investigations as well as the study of the nature of fluorinated groups grafting onto the
 82 polymer during fluorination.

83

84 **2. Materials and methods**

85 **2.1. Samples**

86 The MDs used for this study were infusion sets, selected on the basis of their two different
 87 plasticizers respective content: tri-octyltrimellitate (TOTM) and di-(2-ethylhexyl) terephthalate
 88 (DEHT) (Figure 1), as announced by their manufacturer. The characteristics of the chosen
 89 MDs are summarized in table 1.

Designation	MD1	MD2
Supplier	B Braun Medical	Codan
Reference	866704	714021
Batch	17F29F8SPB	A64017
Inner diameter (mm)	2.5	3.0
Thickness (mm)	0.8	0.8
Announced plasticizer	DEHT	TOTM
Quantity of plasticizer (weight %) ^a	40 ± 1	37 ± 1

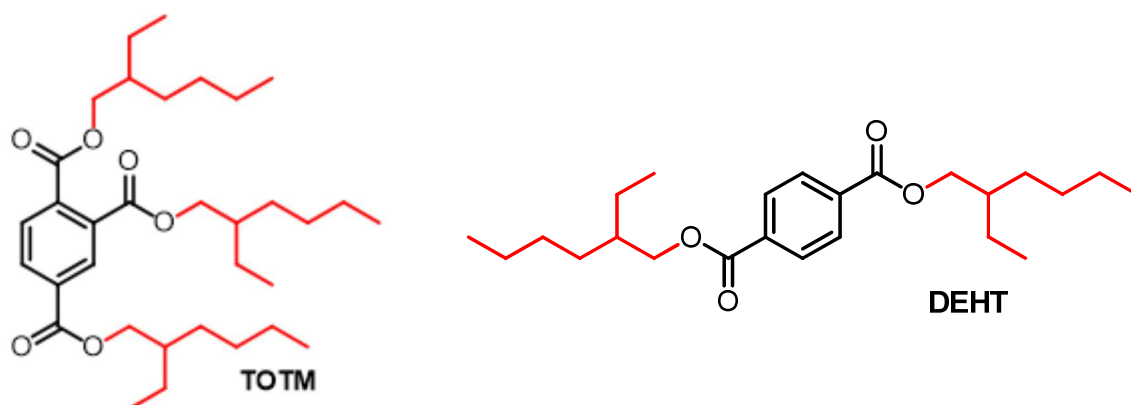
90 ^a: See section 2.5

91

Table 1: Characteristics of the PVC tubings used.

92

93



94

95

Figure 1: TOTM and DEHT structures

96

2.2. Fluorination

97 Fluorination by pure molecular fluorine F_2 was conducted in static mode. Gaseous fluorine
98 was purchased from Solvay Fluor (purity 98-99% v/v). 10 cm-long tubular samples were
99 placed in a closed passivated nickel reactor. The reactor was evacuated up to 10^{-3} mbar and F_2
100 injected up to a pressure of 200 mbar. After reaction for 30 min, the reactor was flushed with
101 N_2 for 2h (gas flow of 50 mL/min). Because HF molecules may result from the conversion of
102 C-H bonds into C-F, the fluorinated MDs were outgassed in primary vacuum (10^{-3} mbar) for 2
103 h in order to eventually remove these molecules as well as by-products such as CF_4 , C_2F_6
104 from their surface. The fluorinated samples are named F-MD1, F-MD2 in the following.

105

2.3.Characterization

107 A comprehensive set of physico-chemical measurements was carried out through
108 complementary techniques and at different scales to characterize the fluorinated layer formed,
109 using solid state Nuclear Magnetic Resonance (NMR), X-ray Photoelectron Spectroscopy
110 (XPS), Fourier transform infrared spectroscopy (FTIR) in the Attenuated Total Reflection
111 (ATR) mode, Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM).

112 A NICOLET 5700 (Thermo Electron) spectrometer was used to record IR spectra using the
113 ATR mode. 128 scans with a 4 cm^{-1} resolution were collected to acquire each spectrum
114 between 400 and 4000 cm^{-1} .

115 ^{19}F NMR measurements were performed using a Bruker Avance spectrometer, at a working
116 frequency of 282.2 MHz . A magic angle spinning (MAS) probe (Bruker) operating with a 2.5
117 mm rotor was used, allowing a 30 kHz spinning rate. For MAS spectra, a simple sequence
118 was performed with a single $\pi/2$ pulse length of $4\text{ }\mu\text{s}$. ^{19}F chemical shifts were externally
119 referenced with respect to CF_3COOH (its chemical shift $\delta_{^{19}\text{F}}$ is -78.5 ppm vs CFCl_3).

120 XPS spectra were measured with a Phi system equipped with a hemispherical analyzer and Al
121 $\text{K}\alpha$ line radiation (1486.6 eV). Curve fitting was carried out with Gaussian/Lorentzian product
122 functions (G/L mixing ratio of about 0.7) of similar FWHM over a given energy range. The
123 relative sensitivity factors of F and O with respect to C were preliminary adjusted from
124 polymers as standards in order to better account for the transmission function of the
125 hemispherical analyzer (pass energy 20 eV). No preliminary ion-etching or charge
126 compensation were used. Special attention was given to properly correct binding energies
127 with respect to charging effects in our non-conducting samples, and all spectra were
128 referenced against the position of the C_{1s} peak from non-halogenated carbons at 285.0 eV ,
129 mostly from the samples themselves or of adventitious origin.

130 Changes in the surface composition of samples were also investigated by a Zeiss SUPRA
131 55VP Scanning Electron Microscopy (SEM) coupled with EDX microanalysis. The energy of
132 the electron beam was fixed to 3 keV . The samples were held with double-sided carbon
133 adhesive tape, deposited on a metallic support. Due to the insulating nature of the surface, a
134 thin carbon coating was preliminary performed on the samples to increase conductivity and
135 avoid samples charge effects. Fluorination is known to increase the roughness of polymers
136 and SEM images were acquired to investigate this point in addition to AFM experiments

137 (Bruker Innova) in tapping mode, performed in order to acquire surface topography images
138 and to extract surface roughness information following fluorination.
139 Contact angles were recorded using an Attension Theta Lite Optical Tensiometer with an
140 imaging source camera. Liquid drops were directly deposited on the surface of the MDs and
141 F-MDs with a micrometric-screw syringe. Two reference liquids were used: water and
142 diiodomethane. Their polar and dispersive components are reported in the literature [16]. The
143 angle measurement was done with the ImageJ software and repeated at least 3 times with each
144 liquid. To determine the polar and dispersive components and the total surface energy, the
145 conventional Owens-Wendt method [17] was used. Other contact angle measurements were
146 carried out using the same method with a 50/50 ethanol/water (v/v) mixture instead of water
147 as well as the pure plasticizer DEHT for MD1 and F-MD1 or TOTM for MD2 and F-MD2.

148

149 ***2.4. Mechanical studies***

150 Tensile testing of the pristine and modified MDs was carried out on a Dynatech 1.5 device,
151 according to ISO 527. Samples were tested at room temperature, using a load cell of 500 daN.
152 The mechanical properties were assessed from the stress-strain curves; the tensile modulus E_t ,
153 stress at break σ_b , and strain at break ϵ_b have been evaluated.

154 Shore A hardness was measured on pristine and fluorinated MDs using a Bareiss BS61
155 durometer, according to ISO 868.

156

157 ***2.5. Evaluation of plasticizers migration***

158 The total quantity of plasticizers initially present in each PVC tubing was determined by gas
159 chromatography coupled with mass spectrometry (GC-MS) Clarus500 (Perkin Elmer) after
160 total solvent extraction (CHCl_3), using the method described by Bourdeaux et al [18].

161 To evaluate the plasticizers migration, a simulant is needed that can mimic a lipophilic drug
162 infused through the tubing. Indeed, lipid components increase the ability of drugs to extract
163 plasticizers from PVC [19,20]. We chose an ethanol / water (50/50) (v / v) mixture as a
164 simulant, for its ability to reflect foods with a lipid component, as earlier suggested by
165 Bernard et al. [21].

166 The amount of TOTM or DEHT released was analyzed in a similar way by GC-MS, after
167 solid/liquid extraction from the simulant over different periods of time. 600 μ L of the thus
168 obtained solution was taken and added to 600 μ L of a 2 μ g/mL benzylbutylphthalate (BBP)
169 solution (internal standard) in chloroform for liquid/liquid extraction of the released amount
170 of plasticizer. After homogenization during 30 s (20 Hz vortex), the samples were
171 centrifugated at 3500 rpm for 5 min. Finally, the chloroform phase was taken for analysis by
172 GC-MS, always according to the method described by Bourdeaux et al [18]. For each
173 experiment, assays were performed in triplicate.

174

175 ***2.5.1. Static migration conditions***

176 Static migration assays were performed by soaking 10 cm of the MD in the simulant up to 96
177 h and samples were collected after 1h, 2h, 4h, 8h, 24h, 48h, 36h and 96h immersion to be
178 analyzed.

179 ***2.5.2. Dynamic migration conditions***

180 Based on clinical practices, assays were performed under a 1 mL/h flow rate for 24 hours,
181 commonly used for drug administration. The syringes were filled with the ethanolic simulant
182 and the tubing set on the syringe. The other end of the tubing was connected to a collecting
183 tank. An initial purge was made with 5 mL of simulant; this sample corresponds to zero in
184 time T_0 . This purge volume is eliminated, and the migration kinetics start from T_0 . The

185 experiment was conducted for 24 hours and samples were taken after 1h, 2h, 4h, 8h and 24h
186 from the collecting tank.

187 **2.5.3. Expression of the results**

188 The initial amount of each plasticizer in the tubing samples was expressed in weight percent
189 (mean % \pm standard deviation).

190 The amounts of each plasticizer released into the simulant were expressed using the mass (μg)
191 of the plasticizer released into the simulant divided by the MD surface in contact with the
192 simulant (dm^2).

193 After dynamic migration, the quantities of released plasticizer were then expressed in
194 mg/kg/24h . The transformation of the data from $\mu\text{g}/\text{dm}^2$ to $\text{mg}/\text{kg/24h}$ is based on the
195 following clinical assumption *i.e.* "1 adult weighing 60 kg is likely to receive 2 L of
196 medication per day infused through 13 dm^2 of tubing, 1 L of medicinal solution infused per
197 6.5 dm^2 of plasticized PVC tubing" as described by Bernard et al. [21].

198 **2.6. MDs Toxicity**

199 **2.6.1. Cytotoxicity tests**

200 The cytotoxicity of the MDs was investigated before and after fluorination using the MTT test
201 (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) according to the EN ISO 10
202 993-5 standard design for the biocompatibility of MDs. The tests were performed on both
203 MDs and their extracts after dynamic migration (the last 24-hour sampling).

204 **2.6.1.1. Cell culture**

205 L929 cells were cultured in 24-wells plates (without plasticizers) (Thermo ScientificTM Biolite
206 24 Well) with Dulbecco's modified Eagle Medium (DMEM) supplemented with 10% of fetal

207 calf serum (SVF), 100 IU/mL of penicillin and 100 µg/mL of streptomycin (complete
208 DMEM) at 37 °C with 5% of CO₂.

209 **2.6.1.2. MTT assay procedure**

210 For the viability assay of the fluorinated MDs, cells were seeded in triplicate at 10⁴ cells/well.
211 After 24 h, the media were removed and replaced by: (i) control conditions with 100 µL of
212 complete medium, (ii) round samples of tubing (5 mm) already cut and sterilized by hydrogen
213 peroxide *gas plasma* (Sterrad®) added with 100 µL of complete medium, (iii) 100 µL of
214 extracts after dynamic migration which was evaporated and taken up by the culture medium
215 containing 1% of dimethylsulfoxide (DMSO), (iiii) control DMSO conditions with the
216 complete medium supplemented with 1% of DMSO. Cells were then incubated and MTT
217 assay and quantification on the viability percentage were carried out after 24 hours.

218 The MTT reagent was used at a concentration of 5 mg/mL in phosphate saline buffer (PBS).
219 At the end of the cell cultures, the media were removed, and 30 µL of the MTT reagent were
220 added to each well. Cells were then incubated for 3 h at 37 °C with 5% of CO₂. The MTT
221 reagent was removed and 200 µL of DMSO were added to each well. After 1 h of formazan
222 dissolution, the optical density (OD) of each well was measured at 570 nm
223 (spectrophotometer Spark® TECAN).

224 **2.6.1.3. Statistical analysis**

225 The experiments performed in triplicate were repeated at least twice and the outcomes of each
226 MD are reported. Differences in viability percentages between the control conditions and the
227 test conditions were analysed using the Mann-Whitney non-parametric test.

228 **2.6.2. Search for fluorinated derivatives**

229 To verify whether fluorinated compounds can migrate from the fluorinated MDs, tests under
230 conditions of total plasticizer extraction were carried out. The detection of potential
231 fluorinated compounds in the extract thus obtained was then carried out by ^{19}F NMR. For
232 each fluorinated MD, a 10 cm sample was placed in a volumetric flask with QSP 100 mL of
233 deuterated chloroform (CDCl_3) to make a complete extraction. After 2 hours, 2 mL were
234 taken and the ^{19}F NMR spectra were carried out on the liquid phase with a Bruker Avance 400
235 MHz spectrometer.

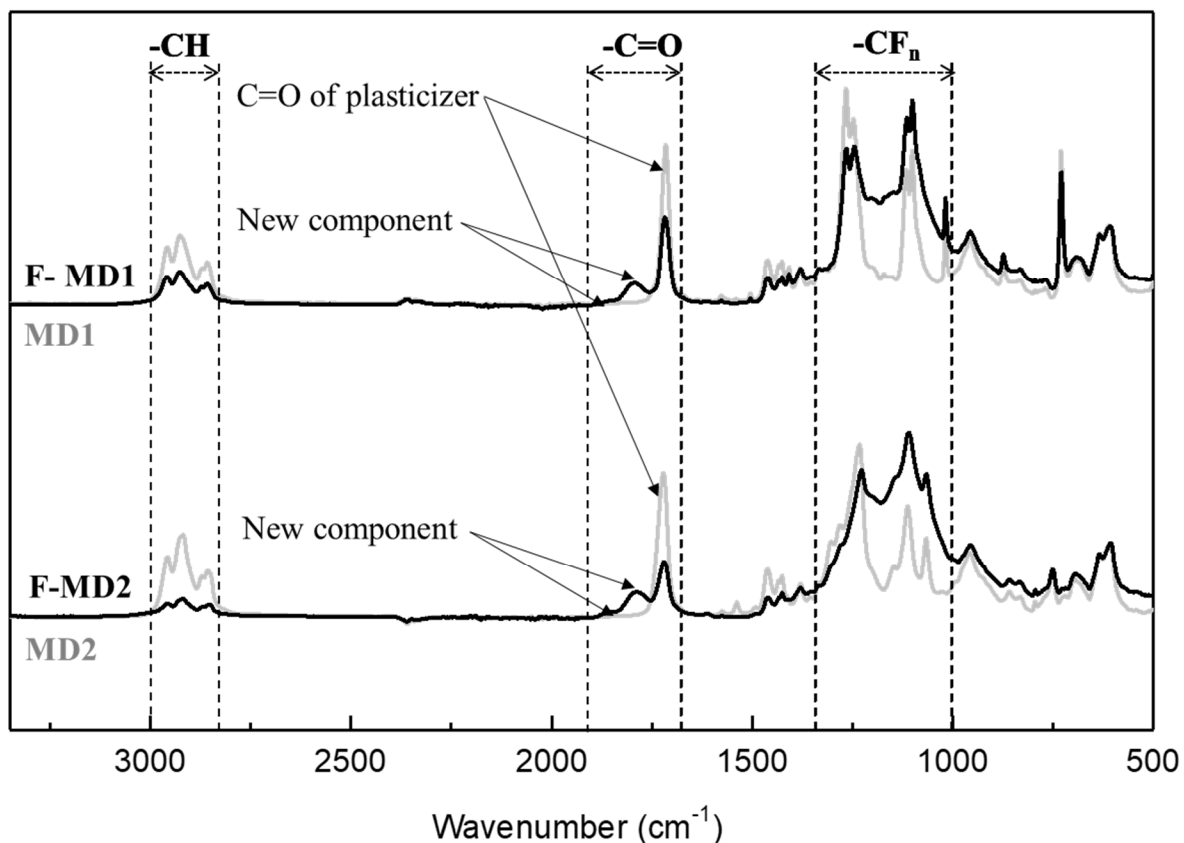
236 **3. Results**

237 **3.1. Characterization of the fluorinated MDs**

238 FTIR spectra recorded from the MDs before and after fluorination are presented in Figure 2
239 and other spectra recorded from pure plasticizers are reported in supplementary data Figure
240 A1. To confirm the reproducibility of fluorination, FTIR spectra was performed on a
241 fluorinated F-MD1 cutted in different places and the results are reported in supplementary
242 data Figure A2.

243 Figure 2 evidences a marked difference between MDs and F-MDs. A broad band over the
244 $1000\text{--}1300\text{ cm}^{-1}$ range appears for the fluorinated samples, resulting from the overlapping of
245 signals that can be assigned to the different absorption contributions of CF_n moieties
246 vibrations, *i.e.* CHF, CF_2 , CF_3 . FTIR spectra also show a decrease in the intensities of the CH
247 and CH_2 groups, suggesting that some H atoms are substituted by F atoms. Moreover, a
248 decrease in the contribution of the carbonyl group of the plasticizers (1724 cm^{-1}) was noticed
249 after fluorination, evidencing that the amount of plasticizer might be lower at the surface level
250 of the MDs following fluorination. An additional component emerging around 1790 cm^{-1}
251 followed by another weak band at 1860 cm^{-1} seem to bear witness for the formation of a new
252 oxygenated functional group. According to the Spectral Database for Organic Compounds
253 (SDBS), the corresponding signals could be attributed to the anhydride function or to a new

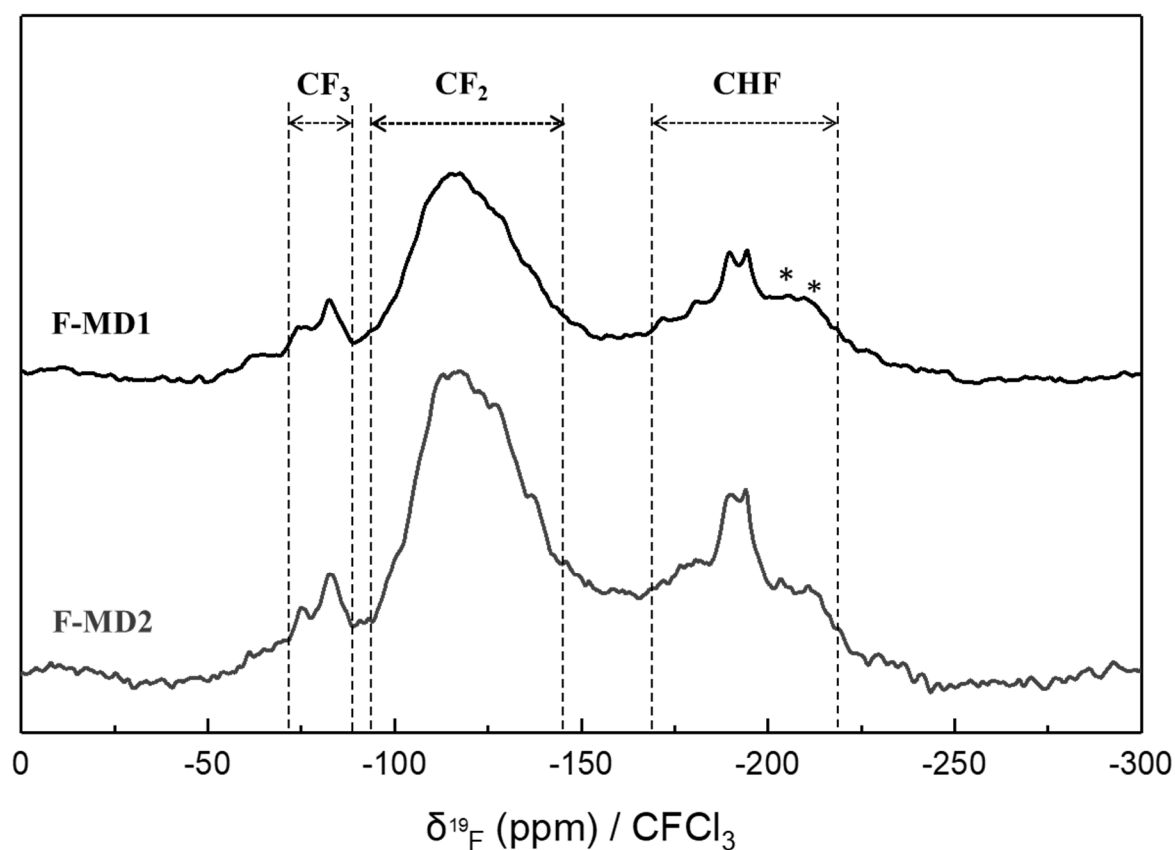
254 fluorinated ester. They may also be related to the formation of the acyl fluoride group FCO
255 [22,23]. Such a chemical change is explained by the post-reactivity of samples after their
256 fluorination, owing to the presence of radical species, which arise from C-H or C-C bond
257 cleavage. Some of those radicals are still present following fluorination and react with O₂ and
258 H₂O upon re-exposure to air atmosphere [22,23].



259
260 **Figure 2. FTIR spectra in ATR mode of pristine (grey) and fluorinated (bold black)**
261 **MDs.**

262
263 ¹⁹F NMR measurements (Figure 3) were performed in order to identify the different
264 fluorinated groups appearing in the treated MDs. Several broad bands covering the well-
265 known typical chemical shift range of CHF, CF₂ and CF₃ groups can be clearly distinguished
266 [24–26]. -CHF groups exhibit chemical shifts close to -198, -211 and -222 ppm vs CFCl₃
267 according to their more or less fluorinated environment. CF₂ groups were related to bands in
268 between -173 and -113 ppm, while signals at -81 and -74 ppm were assigned to CF₃ groups.

269 Hence, the confirmed presence of such fluorinated groups supports the C-F bonds response
270 observed with IR spectroscopy after fluorination. The CF₂ and CF₃ groups arise from a
271 perfluorination mechanism, involving the complete substitution of H atoms in some places.
272 The presence of CF₃ terminations may also indicate that a C-C bond cleavage, induced by
273 molecular fluorine, occurs in some places. CF₃ is then a good indicator of polymer
274 decomposition and the present data evidence its moderate amplitude in our operating
275 conditions. Interestingly, the relative intensities of each area allow to establish the average
276 functional composition in fluorinated groups through the whole thickness of the fluorinated
277 surface layer (Table 2), from which an average fluorination degree of the fluorinated
278 segments can be deduced.
279

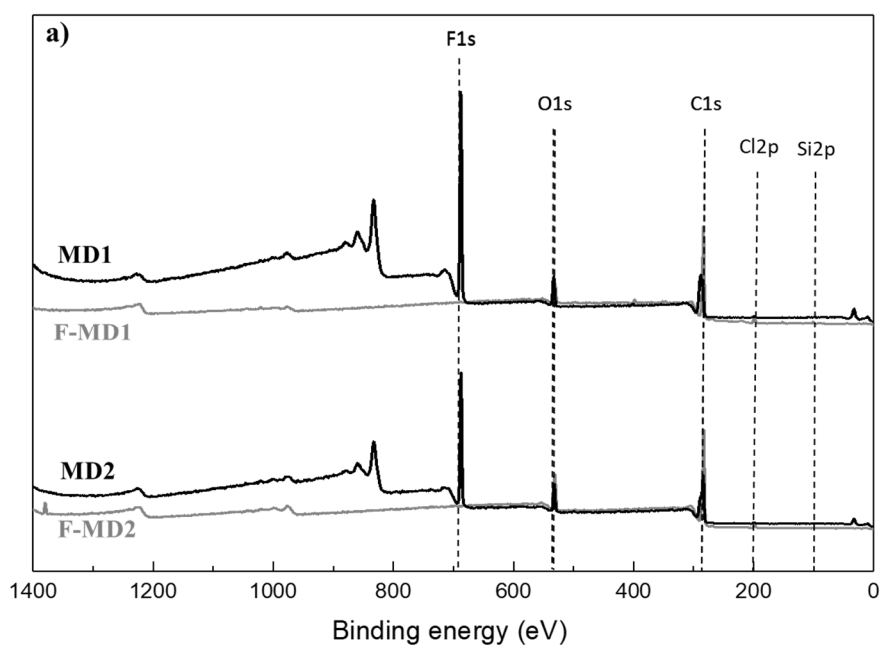


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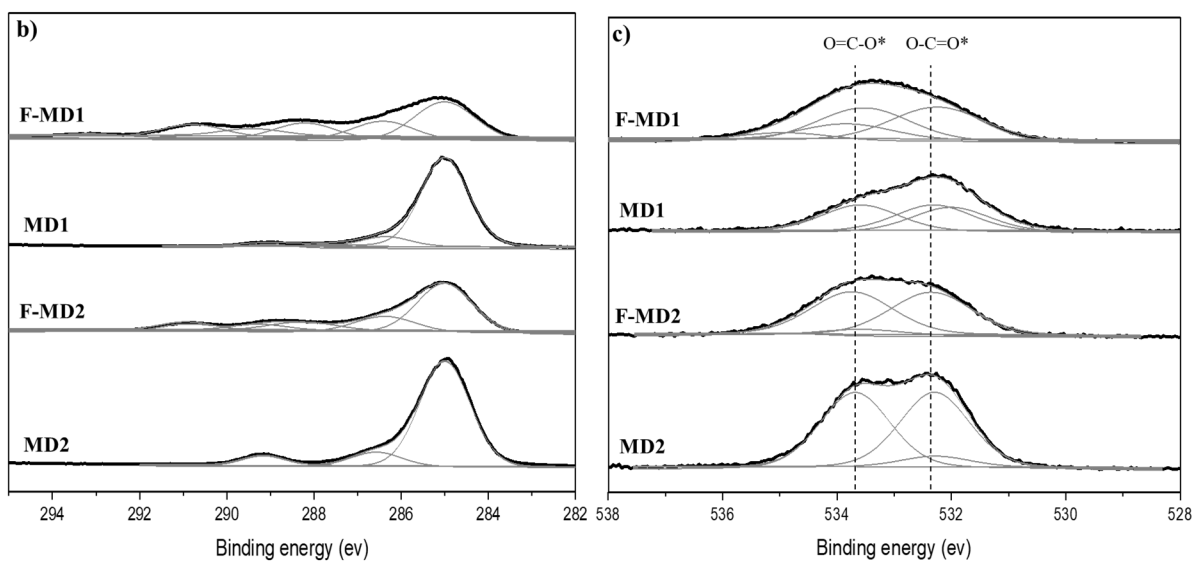
Figure 3. ¹⁹F NMR MAS (30 kHz) spectra of the fluorinated MDs.

282 The survey, C_{1s} and O_{1s} XPS spectra obtained from the fluorinated samples are displayed in
283 Figure 4. The main elements identified are C and O, with F in addition in the case of a
284 fluorinated sample. A Cl contribution at binding energy of 200 eV arises from the PVC matrix
285 each time. The weak intensity of the related signal is due either to the well-known degradation
286 of chlorinated polymers under X-ray exposure [27,28], or to Cl substitution by F during the
287 treatment. Some additional signals of low intensity can be associated with the presence of
288 small quantities of industrial additives, generally added to MDs during manufacturing.
289



290

291



292

293 **Figure 4. a) Survey, b) C_{1s}, c) O_{1s} XPS spectra of the pristine and fluorinated MDs.**

294 For MD1 and MD2, the O_{1s} spectrum has been initially split into two contributions

295 corresponding respectively to the C=O (O-(C=O*)-C) and C-O (O*-(C=O)-C) of the ester

296 group present in each plasticizer. As both signals should be of equal magnitude, an additional

297 contribution to the fit is necessary that may be attributed to Si-O-Si induced by the presence

298 of small quantities of industrial silicone additives to MDs, as confirmed in the survey spectra.

299 After fluorination, for F-MD1 and F-MD2, the overall profile of the O_{1s} spectra is found to

300 shift to higher core energies, as a third additional contribution adds to the two initial peaks of

301 the ester function. This highly likely arises from O in an electronegative environment, owing

302 to the presence of F in its vicinity following fluorination (-CF₂-O, O=C-F or CF₂-COO) but

303 may also result from the creation of the anhydride function upon or after fluorination, in

304 compliance with the conclusions drawn from the IR spectra analysis.

305 F_{1s} spectra (Figure A3 in supplementary data) confirmed the existence of covalent C-F bonds,

306 as determined in all the fluorinated samples from previous characterization techniques.

307 The C_{1s} signal can be deconvoluted into six peaks. The signal of the carbon engaged in the

308 ester group can be distinguished near 289 eV. From standard tables and literature data

309 dedicated to fluorinated polymers [29], the characteristics of CHF, CF₂-CH₂ and CF₂-CF₂
 310 groups can be identified, supporting the ¹⁹F NMR data.
 311 Variations in the nominal composition of the outer surface following fluorination, established
 312 from the elements area ratios considering relative sensitivity factors, is summarized in Table
 313 2. The relative intensities of the C_{1s} contributions also allows to assign a functional formula to
 314 the outer surface of the fluorinated layer. It is interesting to compare data in Table 2 extracted
 315 from the NMR and XPS techniques, respectively. Indeed, data from NMR consist of an
 316 average throughout the bulk, whereas XPS focuses on the upper atomic layers only.

317
318

319

Fluorinated Sample	NMR		XPS			
	Average fluorination degree of fluorinated segments in the bulk ^a	CF ₂ /CHF	Average fluorination degree of fluorinated segments at the surface ^b	CF ₂ /CHF	Functional formula at the surface	Surface chemical composition ^c
MD1	CF _{1.6}	1.25	CF _{1.51}	1.06	C _{0,596} (O-C=O) _{0,077} (CHF) _{0,159} (CF ₂) _{0,168}	C ₁ F _{0,49} O _{0,12}
MD2	CF _{1.6}	0.98	CF _{1,49}	0.95	C _{0,715} (O-C=O) _{0,064} (CHF) _{0,113} (CF ₂) _{0,107}	C ₁ F _{0,35} O _{0,13}

320 ^a equal to $F/C = (1 + 2x + 3y) / (1 + x + y)$ with $x = CF_2 / CHF = (1/2 I_{CF_2} / I_{CHF})$ and $y = CF_3 / CHF =$
 321 $(1/3 I_{CF_3} / I_{CHF})$

322 ^b equal to $F/C = (n+2p)/(n+p)$ deduced from the functional formula C_m(CHF)_n(CF₂)_p(COO)_q

323 ^c from relative XPS intensities of each element

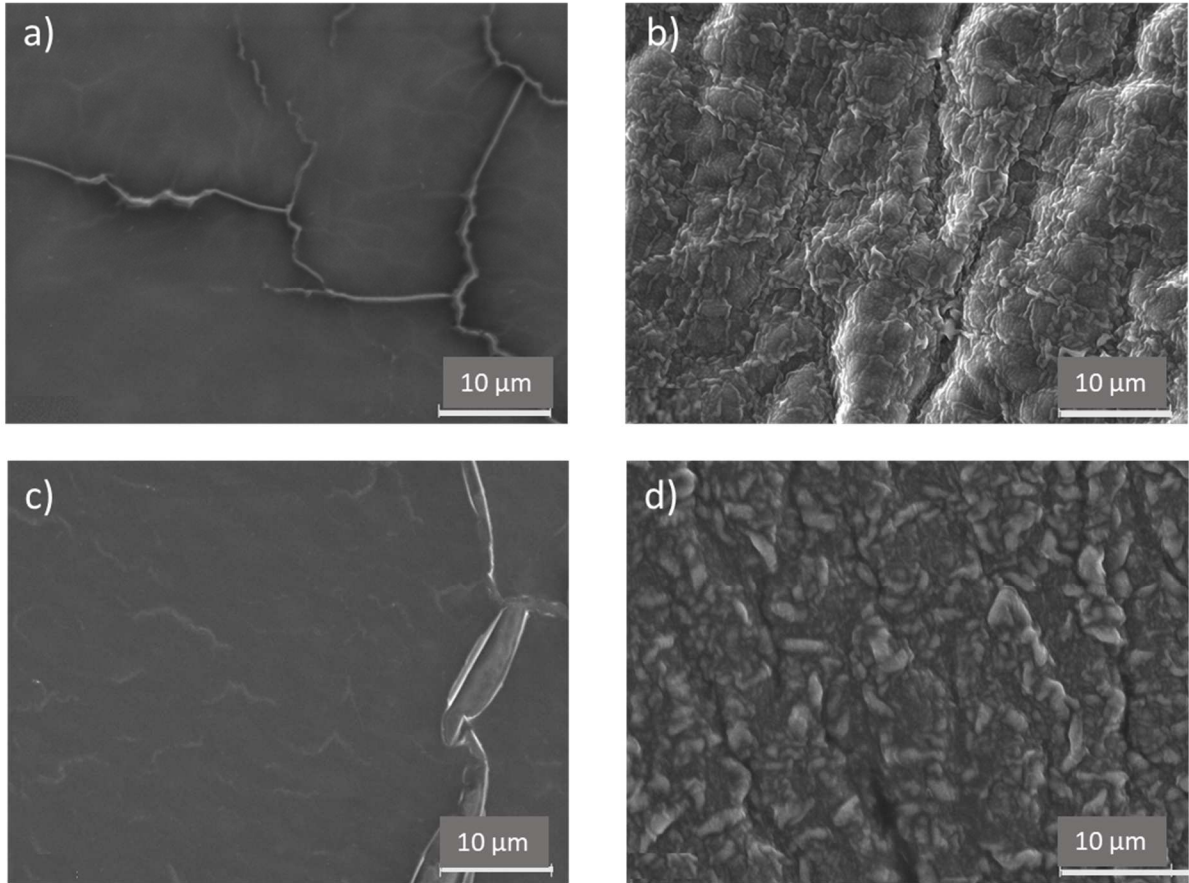
324 **Table 2: Fluorinated MDs surface composition and the CF₂/CHF ratios**

325
 326 Comparison of the data shows that both the CF₂/CHF ratio and the average F/C of the
 327 fluorinated units is higher in the whole fluorinated thickness (NMR data) than in its upper
 328 atomic layers (as seen by XPS). This finding leads to admit that at the extreme surface, a
 329 region in contact with a large quantity of gaseous fluorine, perfluorination is quickly followed
 330 by volatilization induced by hyperfluorination. This favors the persistence of the under-
 331 fluorinated units CHF to the detriment of the perfluorinated units CF₂. Oppositely,

332 fluorination of the internal volume takes place following kinetically limited diffusion of
333 fluorine in the bulk and is therefore less aggressive with regard to the lower amount of
334 fluorine involved locally. This phenomenon ensures the conservation of the perfluorinated
335 units CF_2 . Also, the occurrence of fragmentation, upon fluorination, into small volatile
336 molecules is greater in compounds of finite dimensions and it is therefore highly likely that at
337 the surface, the decomposition is greater for the plasticizer molecules than for the
338 macromolecular polymer matrix. A probable surface deficit in perfluorinated plasticizers
339 could well explain the observed inversion of the CF_2/CHF ratio from the outer to the inner
340 levels of the fluorinated layer.

341 To investigate the influence of fluorination on the polymers surface texture, scanning electron
342 microscopy was performed. The images are shown in Figure 5 with $\times 1000$ magnification in
343 order to point out how fluorination modified the initial smooth morphology. The marked
344 changes observed unambiguously evidence that fluorination causes notable etching of the
345 surface of the MDs. The strong oxidizing power of elemental fluorine is known to induce
346 chemical scissoring of alkyl chains through perfluorination, resulting in the elimination of
347 volatile fluorinated short chain compounds and subsequent loss of material [13,30,31].

348

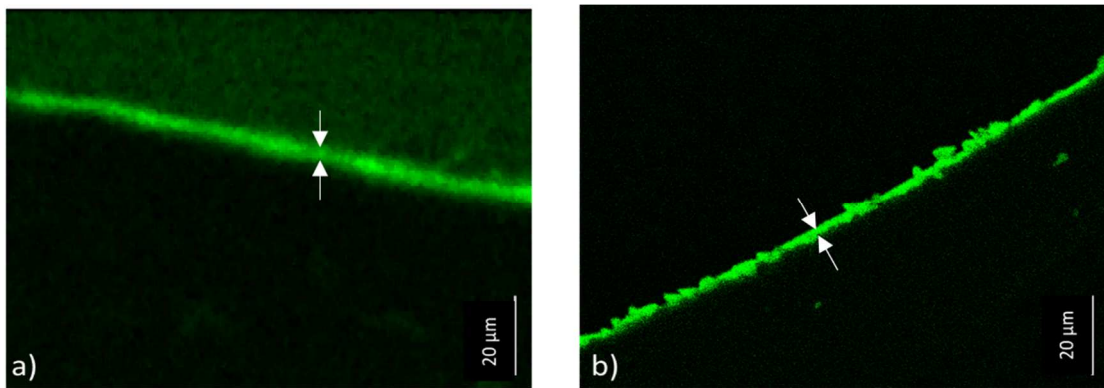


349

350 **Figure 5. SEM images of the MDs before and after fluorination: a) MD1, b) F-MD1, c)**
 351 **MD2, d) F-MD2.**

352

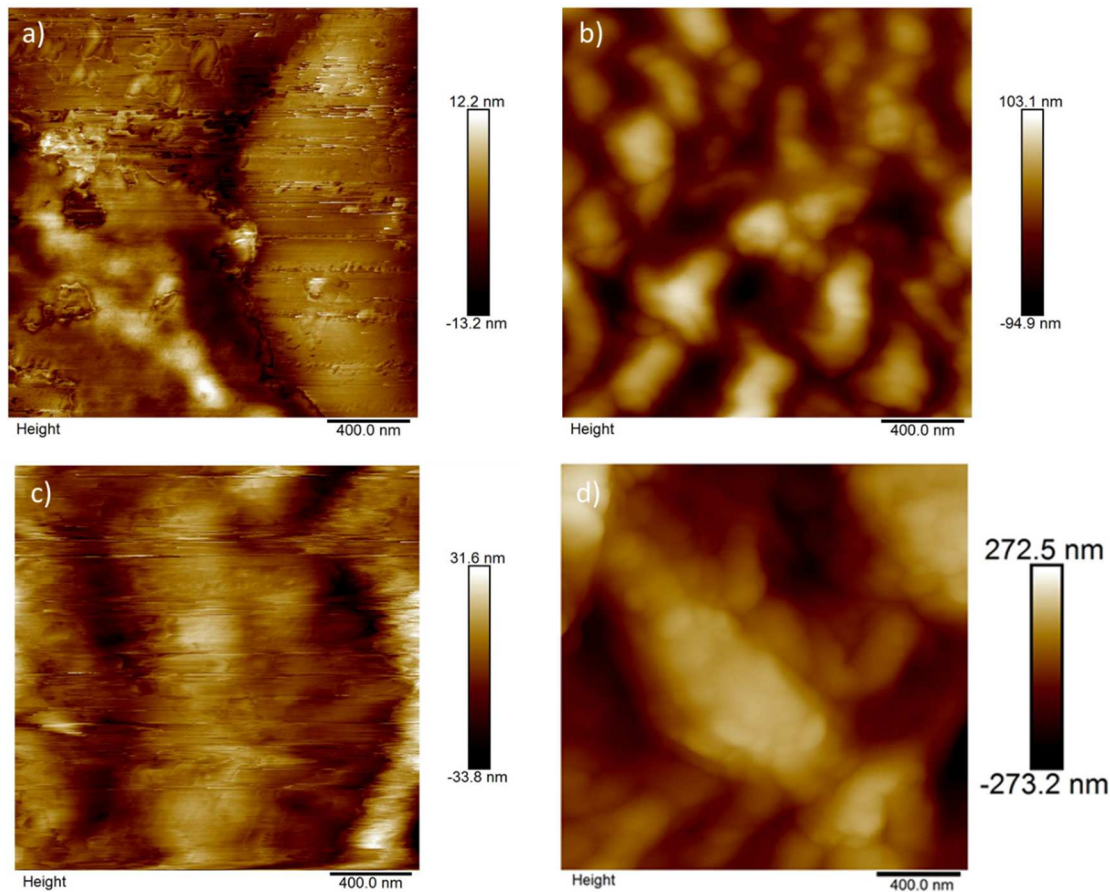
353 Complementarily, elemental mapping through EDX microanalysis allowed to estimate the
 354 thickness of the fluorinated layer in all samples around 1-4 μm , as shown in figure 6. The
 355 mapping was carried out on cross sections of cut F-DMs, exposing the whole wall thickness
 356 to the electron beam.



357

358 **Figure 6. SEM-energy dispersive X-ray F map showing its distribution in the scanned area**
 359 **of the MD wall; a) F-MD1, b) F-MD2. (Colored)**

360 The former surface texture analysis was further extended with the help of AFM, so as to
 361 quantify enhancement of the rugosity, the latter being well-known to affect the wettability of
 362 surfaces by liquids. The recorded AFM images obtained are shown in Figure 7 and the
 363 roughness parameters measured in Table 3.



364
 365 **Figure 7. AFM images of the internal surface of the tubings before and after fluorination:**
 366 **a) MD1, b) MD1 F₂, c) MD2, d) MD2 F₂. (Colored)**

	MD1	F-MD1	MD2	F-MD2
R _a (nm)	5.1 ± 0.3	71.2 ± 0.7	27.8 ± 0,5	55.0 ± 1.3
R _q (nm)	6.8 ± 0.4	92.4 ± 0.5	33.1 ± 0.8	72.4 ± 1.9

367 **Table 3: Evolution in the roughness parameters deduced from AFM imaging of the pristine**
 368 **and fluorinated samples.**

369 Modification of the roughness on the treated surfaces is clearly highlighted. The magnitude
 370 determined for the pristine tubings is increased by a factor of 10 and 2, following fluorination

371 of MD1 and MD2, respectively. The phase images recorded by AFM (Figure A4 in
372 supplementary data) show a well differentiated contrast. This color contrast could reveal
373 contamination deposits discontinuous thin films; and could be related to an organic material
374 of different chemical nature. AFM images also revealed the disappearance, after fluorination,
375 of this organic compound initially present on the non-fluorinated MD. This could be a
376 contamination linked to the manufacturing process or an additive added to the MD during
377 manufacture. As observed in XPS spectra, the Si element appearing in XPS for virgin MD and
378 disappearing after fluorination: high affinity for silicon of molecular fluorine means it can be
379 eliminated in the volatile SiF₄ form.

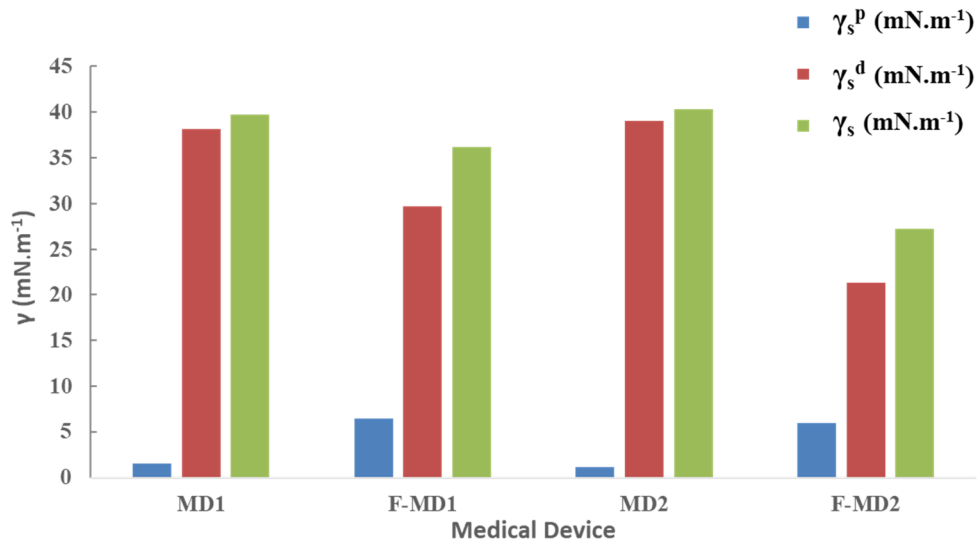
380 Polar (γ_s^p), dispersive (γ_s^d) and total (γ_s) surface tension of the MDs and F-MDs are
381 represented in Figure 8. The surface energy of the MDs decreases after fluorination with an
382 increase in the polar component compared to the dispersive component. The polar character
383 was found enhanced due to the formation of specific polar groups of the C=O type on the
384 surface of the MDs, as discussed before based on the FTIR data. During the fluorination
385 process, some of the C-C and C-H on the PVC surface can be broken during the fluorination;
386 this phenomenon results in the presence of dangling bonds (radicals) which are not fully
387 saturated by fluorine. Moreover, COF groups can be formed. Both radicals and COF groups
388 react with O₂ and water molecules when the tubings are exposed to air after the fluorination
389 process. Those both post-reactivities can result in the formation of polar functional groups,
390 including carbonyl groups (C=O). The presence of these polar groups increases the polarity of
391 the surface compared to unmodified PVC. The formation of polar groups on the surface of
392 fluorinated PVC can also be explained by the concept of bond polarity and electronegativity.
393 Fluorine is highly electronegative, and its introduction onto the PVC surface can lead to the
394 redistribution of electron density in the adjacent carbon atoms. This redistribution can create

395 partial positive charges on the carbon atoms, making them more susceptible to oxidation and
396 the formation of polar groups, such as carbonyl (C=O) functionality.

397 When fluorine gas reacts with the surface of plasticized PVC, it replaces some of the
398 hydrogen atoms in the polymer with fluorine atoms. This substitution creates a surface rich in
399 fluorine atoms, which are highly electronegative, leading to a decrease of the polar component
400 of surface tension (γ_s^p). This is the main reason for the decrease of the total energy surface.
401 Whatever the polymer and because of the reactivity of F_2 gas, fluorination (i.e. formation of
402 covalent C-F bonds) competes with decomposition. In this latter phenomenon, gaseous
403 species are evolved such as CF_4 , C_2F_6 , ... and the surface is etched. Because plasticizer
404 molecules are present and exhibit a reactivity towards F_2 which is expected higher than the
405 polymer, the etching could be important (see AFM section). Those changes affect the
406 dispersive component of surface tension (γ_s^d) which decreases.

407 Contact angles with the liquid pure plasticizers could not be measured, the drop spreading
408 quickly on the surface of the MDs, fluorinated or not. The contact angles measured with the
409 water-ethanol mixture did not show a significant difference after fluorination of the MDs, as
410 shown in Table 4.

411



412

413 *Figure8. (a) Polar, dispersive, and total surface energy of medical devices before and after*
 414 *fluorination. (Colored)*

415

416

Sample	Contact angle (°)	
	Pristine MD	Fluorinated MD
MD1	67 ± 0.3	62 ± 1.3
MD2	66 ± 1.2	62 ± 2.2

417

Table 4: Contact angles with the water/ethanol mixture (50/50) (v/v).

418

419 **3.2.Mechanical properties**

420 The mechanical properties of the MDs used are listed in Table 5, including tensile modulus

421 (E_t), stress at break (σ_b), strain at break (ϵ_b) and Shore A hardness. For all samples, the results

422 indicate that fluorination has no significant effect on the mechanical characteristics of the

423 MDs. This point is of importance for clinical application. The location of fluorinated layer on

424 the outmost surfaces only, as seen by SEM-EDX, allows the bulk properties to be maintained.

425 Minimal differences observed over the fluorinated samples are due to sampling fluctuations.

426 The transparency of PVC plasticized tubing was carefully assessed following the process of

427 fluorination, and the results confirmed that the tubing retained its visual transparency. This

428 important finding ensures that the fluorinated tubing can be effectively utilized in clinical
 429 settings. By maintaining their transparency, these tubings allow for easy monitoring of fluid
 430 flow and detection of any potential contaminants. The ability to visually inspect the tubing is
 431 crucial for ensuring the safety and efficiency of medical procedures in clinics, providing
 432 healthcare professionals with a reliable tool for patient care.

433

Samples	MD1	F-MD1	MD2	F-MD2
E_t (MPa)	14.93 ± 0.25	15.10 ± 0.10	14.90 ± 0.10	15.07 ± 0.23
σ_b (MPa)	13.70 ± 0.26	13.27 ± 0.35	15.50 ± 0.61	16.10 ± 0.10
ϵ_b (MPa)	227.77 ± 15.60	216.47 ± 10.57	293.03 ± 20.24	332.40 ± 7.11
Shore A hardness	79.8 ± 1.8	79.5 ± 1.2	79.5 ± 1.4	79.7 ± 1.2

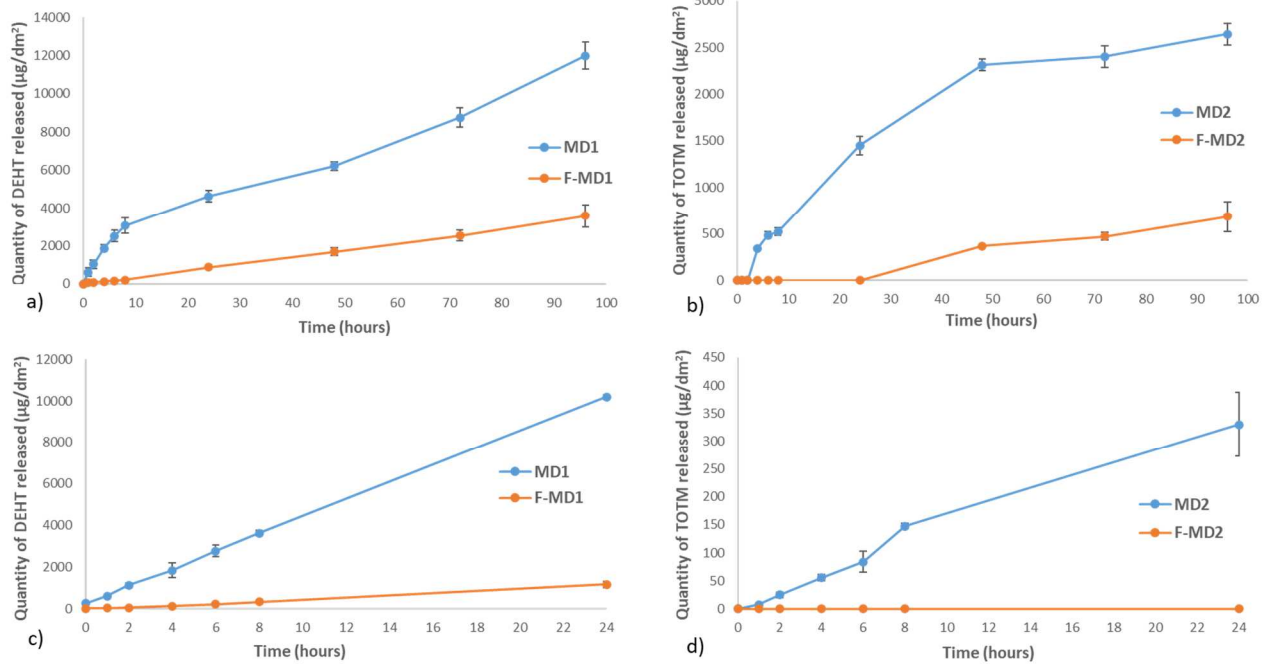
434

Table 5: Mechanical properties of the MDs.

435

436 **3.3. Plasticizer migration**

437 After evidencing the covalent grafting of fluorine atoms, the physico-chemical modifications
 438 of the surface and the maintaining of mechanical properties, the effect of a 1 μm fluorinated
 439 layer on plasticizers migration must be investigated. Figure 9 shows the results of the
 440 migration assays (static and dynamic) of the plasticizers from our PVC MDs.



441

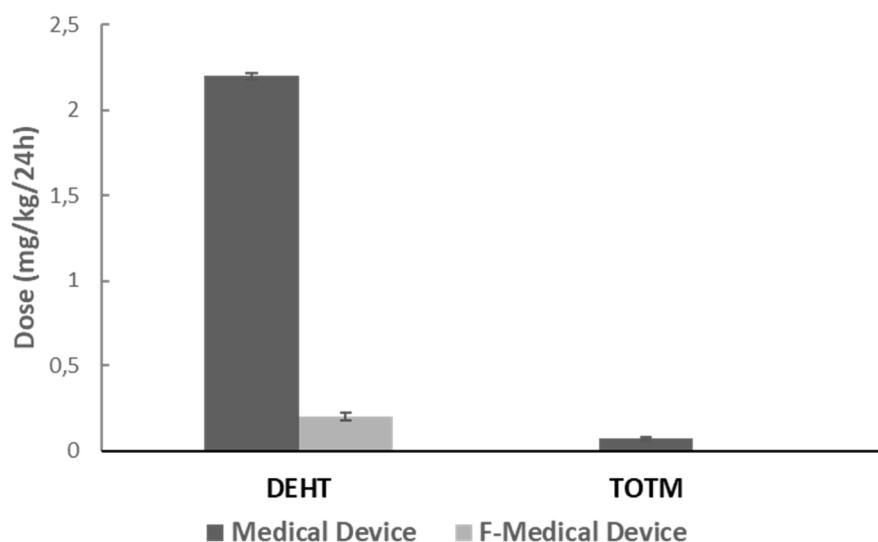
442 **Figure 9. Quantity of plasticizers released during migration assays per dm² from MDs,**
 443 **before and after fluorination: static migration conditions for MD1 (a), MD2 (b), dynamic**
 444 **migration conditions for MD1 (c), MD2 (d), (n = 3; mean ± standard deviation). (Colored)**

445 After fluorination, the quantity of plasticizer released into the simulant drastically decreased
 446 in both migration conditions and regardless the MDs tested. After 24 hours, the amount of
 447 TOTM detected was lower than its limit of quantification (LOQ) of 0.5 µg/mL [18], in
 448 migrates from F-MD2. After 24 hours in the dynamic assays, the quantity of DEHT released
 449 from the fluorinated MD was 8 times less for MD1 (from 10188.64 ± 94.99 µg/ dm² to
 450 1171.97 ± 137.48 µg/ dm²).

451 The evolution of the released doses following fluorination, expressed in mg/kg/24h, is
 452 complementarily presented in Figure 10.

453

454



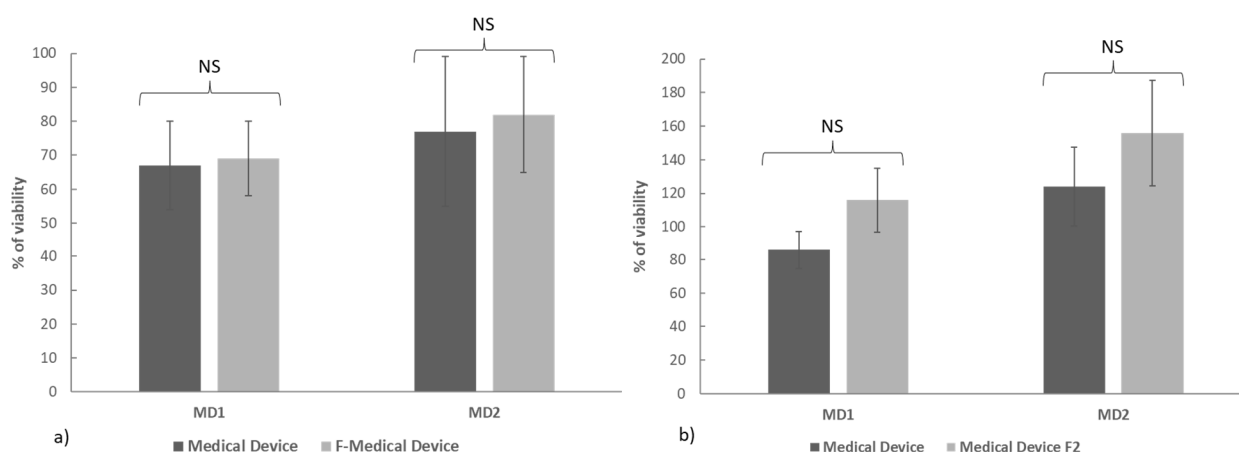
455

456 **Figure 10. Quantity of plasticizer released after 24 hours of dynamic migration assay**
 457 **(mg/kg/24h).**

458 Released quantities found for DEHT and TOTM (PVC) were 2.2 ± 0.02 , 0.07 ± 0.01
 459 mg/kg/24h, respectively. After fluorination, the DEHT quantity decreased to 0.2 ± 0.02
 460 mg/kg/24h whereas TOTM was not quantifiable.

461 3.4. Toxicity

462 Figure 11 shows the results of viability tests performed on L929 cells cultured in the presence
 463 of the plasticized-PVC MDs or their migrates after 24 hours of contact.



464

465 **Figure 11. Cytotoxicity tests of the MDs (a) and their migrates (b). Outcomes of the cell**
 466 **viability analysis using MTT assay. L929 cells were seeded at 10^4 cells/well and cultured for**
 467 **24 hours. NS: not significant $p > 0.05$.**

468 According to viability tests after 24 hours, the MDs and their released plasticizers were found
469 to be not cytotoxic compared with the control containing only L929 cells with culture
470 medium. No difference in cytotoxicity was observed between fluorinated and non-fluorinated
471 MDs ($p > 0.05$).

472 The ^{19}F NMR spectra (Figure A5 in supplementary data) recorded on the various chloroform
473 extracts of the fluorinated MDs did not show characteristic peaks of fluorinated bonds, which,
474 according to the sensibility of ^{19}F NMR, proves the absence of fluorinated compounds
475 detectable in the solutions analyzed.

476 **4. Discussion**

477 Our work attempted to study the prevention of plasticizers migration from plasticized PVC
478 MDs *via* surface modification using fluorination. The characterization of the MDs evidences
479 no modification of their bulk properties after fluorination, especially the mechanical
480 properties, including flexibility and transparency, which proves that the fluorinated MDs will
481 keep the same functional qualities as the non-fluorinated ones. After successfully fluorinating
482 our infusion sets, the migration of plasticizers from such fluorinated tubings has been found
483 significantly reduced in comparison with the pristine plasticized PVC tubings. Cytotoxicity
484 tests have shown that the new fluorinated material does not cause a cytotoxic effect on L929
485 cells.

486 Accordingly, fluorination seems to be an efficient method of tackling the problem of
487 plasticizers release from already marketed PVC-made MDs.

488 Such results probably stem from to the cumulation of several effects.

489 The first hypothesis for interpreting the benefits associated with surface fluorination consists
490 in considering the fluorinated thickness as a diffusion barrier to plasticizers, which would
491 result from a reduced chemical affinity between the non-fluorinated core plasticizers and their
492 surface halogenated counterpart. The contact angle measurements using the plasticizers
493 showed a spread of the drop on the fluorinated surface and do not, however, support such a
494 hypothesis. In addition, during our migration tests, the release at the beginning is greatly
495 reduced by the action of fluorination but the plasticizers seem to start to migrate more quickly
496 after a few hours, although the quantity released is always lower than that found from non-
497 fluorinated MDs. This phenomenon does not corroborate the above hypothesis either. A
498 second interpretation may consist of a plasticizer depletion at the surface of the MDs,
499 following partial consumption by fluorine or a depletion of the soluble form of the plasticizer
500 due to its chemical transformation. The plasticizers present inside the PVC matrix thus

501 continue to migrate, but from the depth of the tubing, temporarily slowing their occurrence in
502 the liquid phase. The resulting gradient in plasticizer content may therefore cause a retarding
503 effect, which can only be temporary. Without other effects, this gradient is then not sufficient
504 to explain long term decrease in plasticizer release.

505 The afore-mentioned radical mechanism of fluorination can involve partial crosslinking at the
506 level of the surface layer, even in its thickness. This phenomenon, by securing the chains of
507 the constituents to each other, reduces their respective mobility and therefore their
508 interdiffusion, while limiting the dissemination of other components between these same
509 chains which have become more difficult to separate from each other.

510 In addition, the conversion of C-H into C-F during fluorination results in a higher chemical
511 diffusion barrier because of the difference in size between H and F. The new bonds create
512 steric hindrance preventing plasticizers to pass through. Fluorination is commonly used to
513 treat the surface of polymers, in order to enhance their hydrophobicity and barrier property
514 against multiatomic molecules, like hydrocarbons [12,32].

515 Finally, the post-fluorination surface observed by microscopy requires consideration of a
516 possible additional contribution. Indeed, the significant increase in roughness is likely to limit
517 the contact surface of the internal wall of the tubing with a flowing fluid. Thus, the chemical
518 erosion caused by the action of fluorine could therefore be an effective limiting factor to the
519 diffusion of plasticizers.

520 The chemical structures and polarities of plasticizers play a crucial role. These characteristics
521 determine their interactions with the polymer they are mixed with. Polarity and, consequently,
522 solubility are the main physicochemical properties that influence the migration of plasticizers
523 from the PVC matrix. Plasticizers with a positive Log P (partition coefficient of a molecule
524 between n-octanol and water) will migrate towards lipophilic liquids, while molecules with a

525 negative Log P will preferentially migrate towards hydrophilic solutions. The plasticizers
526 studied here have a positive Log P and are therefore more likely to migrate towards lipophilic
527 liquids. Longer alkyl chains or non-polar branches originating from polar structural units
528 increase the hydrophobicity of the molecule and reduce its solubility in aqueous
529 environments, thus limiting its migration in these media [34]. DEHT and TOTM have side
530 chains of 8 carbon atoms.

531 The overall oxygen-carbon ratio, therefore, provides a good reflection of migratory power.
532 Both DEHT and TOTM contain the same polar ester group but with varying degrees of
533 aliphatic side groups. Thus, according to Rie Ito's study [7], the steric hindrance and high
534 molecular weight of TOTM limit its migration compared to other plasticizers.

535 All migration tests clearly showed the decrease in plasticizers release. However, the simulant
536 used (ethanol-water mixture 50/50 (v/v)) is a very efficient extractor and the quantity released
537 is overestimated. For the dynamic mode migration tests, we tested one flow rate (1mL / hour)
538 in all experiments. The application of a lower flow rate may extract more plasticizer at each
539 time of the kinetic, regardless of the plasticizer and type of device, as demonstrated in [8].

540 Several other strategies have been developed to prevent plasticizers migration from PVC MDs
541 into physiological fluids, using either an additional external coating or radiochemical
542 treatment. For the first route, according to the work of Münch et al., a phospholipid coating of
543 the PVC matrix does not reduce plasticizers migration. On the contrary, it may lead to a
544 slightly increased release of TOTM and DEHP from PVC tubes [35]. Fei et al. have studied
545 the barrier effect of a SiO_x coating deposited by plasma on a plasticized PVC film and found
546 that the migration of DEHP from such a film was remarkably lower than for the control
547 sample [36]. Messori et al. prepared α - ω -triethoxysilane terminated poly(ethylene oxide)
548 (PEO-Si) samples by the sol-gel approach. These hybrids were used as coatings for flexible
549 PVC tubes and have shown a reduction of plasticizer leaching from PVC MDs [37]. However,

550 one main drawback of the latter methods can be a strong evolution in the mechanical
551 properties and drastic alteration of the surface of treated PVC. The Young's modulus of a
552 hybrid coated PVC is indeed approximately 50 times higher than that of an untreated polymer
553 [38]. Our fluorination strategy is then a serious advantage at that level. Furthermore, the
554 delamination of surface coatings may occur under mechanical stress, while fluorination
555 results in a continuous layer with a fluorine gradient, i.e. without polymer/coating interface.
556 Fluorination is then again one major benefit regarding adherence problems

557 Several studies reported the use of β -cyclodextrin as a solution to prevent the release of
558 plasticizers from PVC [39–43], due to its known sequestering capacity against hydrophobic
559 molecules. A comprehensive study on the prevention of plasticizers migration was conducted
560 by Raeisia et al., by synthesizing a new nano-inhibitor derived from grafting a poly(β -
561 cyclodextrin-ester) network to magnetic nanoparticles. This method effectively reduces the
562 migration of DEHP from PVC while preserving the mechanical properties [41], but contrarily
563 to one step gas/solid fluorination, this treatment involves several stages of synthesis and
564 cannot have the same relevance with respect to production scale-up necessary for MDs
565 already commercialized.

566 Structural changes in the polymer matrix have also been assessed so as to induce barrier
567 properties towards plasticizers. As reported by Marcella et al., irradiation with gamma-ray
568 reduces the release of DEHP from blood bags [44], for instance. However, none of the related
569 studies ever attempted to verify whether plasticized PVC retains the mechanical properties
570 sought by suppliers to manufacture MDs and whether the modified material can be cytotoxic.

571 Some further advantages of fluorination may be detailed here. This treatment could be
572 performed at the industrial scale [14] without toxic solvent (as a gas/solid reaction) and then
573 with a low environmental footprint. Articles of any shape may be treated. Stable covalent C-F
574 bonds are formed, allowing long term enhancements of plasticizer barrier properties and no

575 fluorinated by-product released from the MD into the fluid is to be feared, whatever the
576 contact time.

577 The cytotoxicity test performed in our study was according to the EN ISO 10 993-5 standard
578 designed for the biocompatibility of MDs. This standard is rather intended for implantable
579 MDs to evaluate materials and provide assurance that a commercialized MD can be used on
580 patients. We used this standard to demonstrate that fluorination has no additional cytotoxic
581 effect, and the new fluorinated infusion sets can therefore be commercialized for medical use.
582 However, the endocrine disrupting effect of the migrates has not been studied in our work and
583 could occur even from the small quantities that we detected, implying further work in parallel
584 before complete final approval.

585 *5. Conclusion*

586 A new technical solution emerges from the present study to avoid or at least to strongly limit
587 the migration of plasticizers from PVC-plasticized medical devices. The fluorination
588 treatment developed here as an anti-migration barrier brings a real improvement without
589 change of the overall mechanical properties because the reaction focuses on the outmost
590 surface. Following assays in dynamic mode, conditions closest to clinical practice, the
591 quantity of DEHT released after 24 hours from the fluorinated MD dropped by a factor of 8
592 and up to below the LOQ for TOTM. Neither cytotoxicity nor the release of fluorinated
593 fragments or HF from the surface fluorinated layer is evidenced with fluorinated MDs.
594 Optimization of the process is now essential to obtain MDs that can be manufactured on an
595 industrial scale. This will consist in fluorinating the internal surface of the tubing only, since
596 this is the surface that will be in contact with the products to be administered to patients. It
597 will be necessary to modelize the adsorption of drugs or active ingredients on a fluorinated
598 surface to assess whether there is a risk of loss of these molecules. Modeling can be carried
599 out using model of fluoropolymers such as polytetrafluoroethylene (PTFE) or polyvinylidene

600 difluoride (PVDF). Finally, complementary investigations need to be conducted in parallel to
601 verify the absence of endocrine disruptor effects of migrates, which can follow non-
602 monotonic curves and be present at very low doses. Further work on highly promising
603 fluorine-treated MDs is under way with a view to certify a total absence of health risk.

604

605

606 ***Data availability***

607 The experimental data required to reproduce the findings from this study will be made
608 available to interested investigators upon request.

609

610 ***Credit authorship contribution statement***

611 Imen Dhifallah: Conceptualization, Investigation, Methodology, Project administration,
612 Supervision, Validation, Writing - original draft. Daniel Claves: Conceptualization,
613 Investigation, Methodology, Supervision, Validation, Writing - original draft. Nicolas Batisse:
614 Investigation, Methodology, Writing - original draft. Regis Cueff: Investigation, Validation,
615 Methodology. Anne-Francoise Sapin: Investigation, Validation, Methodology. Yassine
616 Bouattour: Investigation, Methodology, Writing - original draft. Elodie Petit: Investigation,
617 Methodology. Marc Dubois: Conceptualization, Data curation, Methodology, Project
618 administration, Supervision, Validation, Writing - original draft. Valérie Sautou:
619 Conceptualization, Data curation, Methodology, Project administration, Supervision,
620 Validation, Writing - original draft.

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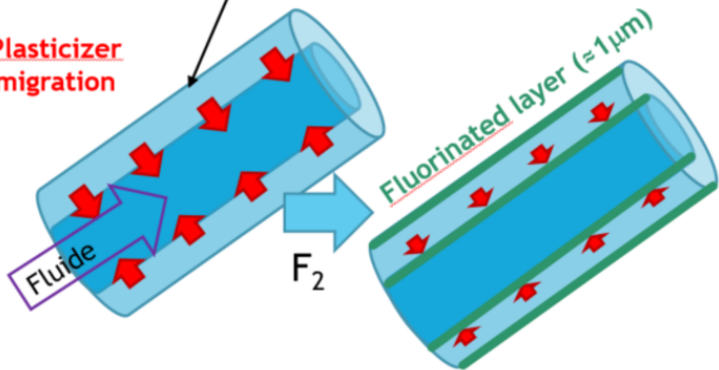
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Plasticized PVC
medical device



Plasticizer
migration



Migration
quantification

