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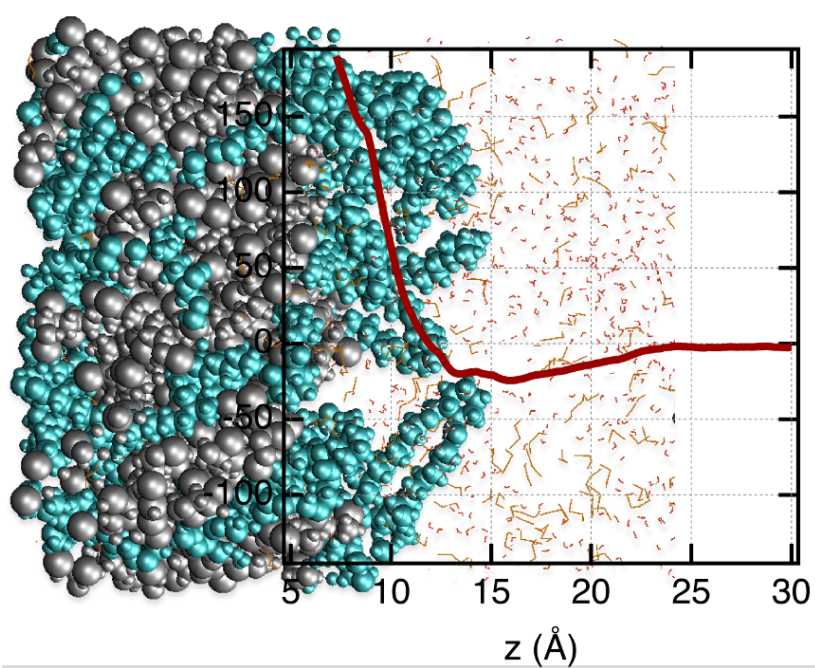


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1 Graphical Abstract

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4 Highlights

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- 7 • Long duration simulations showed plasticizer migration
8 from PVC surfaces

- 9 • Plasticizer migration was characterized and explained
10 from a thermodynamic perspective
11 item Molecular simulations helped rationalize the impact
12 of solvents on the interactions

- 13 • The adsorption of an active substance was function of the
14 interface properties

- 15 • Molecular simulations can be used to predict interactions
16 at a solid-liquid interface

Leaching of plasticizers from PVC medical devices : a molecular interpretation of experimental migration data

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Abstract

High pressure liquid chromatography (HPLC) experiments and molecular simulations were combined to investigate the leaching process of DINCH, DEHT and TOTM plasticizers from PVC materials. Methodologies based on statistical thermodynamics were used to rationalize the migration of the different plasticizers in water and ethanolic solutions from different free energy contributions. We extended this combined approach to the study of the adsorption of a model drug (diazepam) on different plasticized-PVC materials. The drug loss by sorption was investigated in different solutions and rationalized at an energy level. The combination of experiments and theoretical approaches proved to be effective for these sophisticated systems and processes for which various energy contributions are involved.

Keywords: Leaching of plasticizers, molecular simulations, HPLC experiments, molecular interpretation, molecular interactions

1. Introduction

Poly(vinyl chloride) (PVC) was first used for medical applications during World War II to replace medical devices (MD) made from glass, metal, ceramics, and rubber, which had the major drawback of being expensive, fragile and difficult to use. Since then, PVC medical devices have become ubiquitous thanks to their light weight, softness, low manufacturing cost, transparency, recyclability, water and chemical resistance and resilience [1, 2]. However, to make PVC soft and flexible, PVC must be mixed with plasticizers. For infusion tubings and transfusion bags, it is used with a high ratio of plasticizers [3, 4, 5].

The problem is that the plasticizers can escape from the polymer matrix, dissolve into the surrounding medium and contaminate it [3, 4, 6, 5, 7, 8, 9, 10, 11]. This raises the question of the interaction of plasticizers with blood and human tissues [12, 13, 14] and of their impact on human health. One plasticizer that used to be frequently used was di(2-Ethylhexyl)phthalate (DEHP), which was categorized in 2008 as CMR 1B (carcinogenic, mutagenic or toxic to reproduction) [15] and as an endocrine disruptor by the European Chemical Agency [16]. The use of DEHP in PVC medical devices is now limited to 0.1% by mass of plasticised material by the European Regulation N° 2017/245 on medical devices [17].

Alternative plasticizers like diisononyl phthalate (DINP), di(2-Ethylhexyl) terephthalate (DEHT/DEHTP), 1,2-cyclohexane dicarboxylic acid diisononyl ester (DINCH) or tris(2-Ethylhexyl)

trimellitate (TOTM/TEHTM) have therefore been used in the manufacturing of MDs [18]. Different experiments have been implemented to investigate the migration of these plasticizers from MDs in contact with fluids by using an approach based on a migration methodology comparable to that used in food industry [19, 4, 5]. These studies have shown a migration of all alternative plasticizers from infusion medical devices depending on the composition of the fluids in contact, and the conditions of the experiment as contact duration or temperature.

In order to gain an in-depth understanding of the mechanisms governing plasticizer leaching, high-level knowledge of the plasticization mechanism but also of the interactions that take place at the interface between the plasticized material and the solution in contact is needed [7]. Concerning the plasticization mechanism [20, 21, 22], various theories such as lubricity, gel, mechanistic and free volume theories [20, 21, 22] have been elaborated. Nevertheless, these theories remain phenomenological in nature and neglect the interactions at the molecular level which are essential for the design of new polymers and plasticizers but also for a better understanding of the mechanisms mentioned above.

One way of explaining this migration is to use molecular simulation [23], which relies on molecular interactions to generate microscopic configurations and statistical thermodynamics to calculate macroscopic quantities of interest. With this theoretical approach, it is possible to design a plasticized-PVC surface at the molecular scale and observe the conditions in which some plasticizers can escape from the surface in the time scale of the simulation, *i.e.*, at the microsecond scale. In this work, we completed these simulations by applying advanced methodologies

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74 that calculate free energy quantities and that informed us about
75 the spontaneous nature of the leaching process.

76 Recent applications of molecular simulations to plasticized
77 polymer materials have been successfully developed. For ex-
78 ample, the investigation of the performance of common phthal-
79 ates as plasticizers for PVC [24] was achieved using atomistic
80 models by calculating Young’s modulus, glass transition tem-
81 perature and structural properties at the molecular level. Molec-
82 ular dynamics simulations of a biopolymer starch/glycerol sys-
83 tem [22] were used to capture the transition region in the degree
84 of plasticization. Another recent work [25] has shown that it is
85 possible to rank plasticizers using molecular simulations by ex-
86 amining the depression of the glass transition temperature, ten-
87 sile strength and elastic modulus. We have also applied molec-
88 ular simulations and advanced methods of statistical mechanics
89 [26, 27] to study the sorption of drugs onto pure PVC [26] and
90 plasticized PVCs [27, 28] in order to interpret experiments at
91 the molecular level. These simulations have highlighted differ-
92 ent interaction strengths between drugs and the PVC surface as¹²⁶

93 a function of the nature of the plasticizer and of the drug (di-¹²⁷
94 azepam, paracetamol and insulin) in direct connection with the¹²⁸
95 analysis of experiments. These simulations used the concept of¹²⁹
96 potential of mean forces (PMF) [29, 30] to investigate the ad-¹³⁰
97 sorption process along the direction normal to the PVC surface.¹³¹

98 In this paper, we aim to combine experimental assays and¹³²
99 molecular simulations to investigate the migration of three plas-¹³³
100 ticizers (DINCH, DEHT and TOTM) from the PVC surface into¹³⁴
101 two different solutions (pure water and 50-50% ethanol-water¹³⁵
102 mixture). We completed this study by the study of the adsorp-¹³⁶
103 tion of diazepam onto plasticized-PVC in different media to in-¹³⁷
104 vestigate the impact of the types of interactions involved in the¹³⁸
105 solution on the strength of the adsorption.¹³⁹

106 The paper is organized as follows: Section 2 contains the
107 description of the experimental and computational procedures.¹⁴⁰
108 In section 3, we discuss the experimental results in line with the¹⁴¹
109 macroscopic properties provided by molecular simulations and¹⁴²
110 we characterize the drug adsorption by the description of local¹⁴³
111 arrangements close to the PVC surface. We conclude in Section¹⁴⁴
112 4.¹⁴⁵

113 2. Experimental and computational procedures

114 2.1. Experimental studies

115 The leaching studies were conducted to evaluate the migra-¹⁵¹
116 tion of the plasticizers from the tubings during static contact¹⁵²
117 with a solution of diazepam diluted to 20 µg/mL in two differ-¹⁵³
118 ent solutions (water and a 50-50% ethanol-water mixture), in¹⁵⁴
119 order to analyse the effect of the solution on the leaching. The¹⁵⁵
120 ethanol-water (50/50 v/v) solution is known for its ability to¹⁵⁶
121 reflect lipophilic drugs [19] based on models proposed by regu-¹⁵⁷
122 lation EU 10/2011 on plastic materials and articles intended to¹⁵⁸
123 come into contact with food [31, 32, 33]. Adsorption studies¹⁵⁹
124 were conducted in the same conditions to study the effect of the¹⁶⁰
125 solution and the presence of plasticizers on drug adsorption.¹⁶¹

Table 1: Description of the tubings

Tubing	M_{plast} (%)	Length (cm)	Inner \varnothing (mm)
PVC-DINCH	31	55	4
PVC-DEHT	30	55	4
PVC-TOTM	37	55	4

Table 2: Limits of quantification and detection of the plasticiz-
ers.

Plasticizers	LOQ (µg mL ⁻¹)	LOD (µg mL ⁻¹)
DINCH	10	5
DEHT	1	0.1
TOTM	0.5	0.1

2.2. Materials

Three types of plasticized PVC tubings were studied, all pro-
vided by Cair LGL (Lissieu, France). The tubings were made
with different plasticizers: DINCH (CAS 166412-78-8), DEHT
(CAS 6422-86-2), and TOTM (CAS 3319-31-1). The manu-
facturer targeted the same shore hardness for all tubings, so the
mass fraction of the plasticizer depends on the plasticizer as
summarized in Table 1. These results were obtained after anal-
ysis by GC-MS following the method published by Bourdeaux
et al.[34]

For the initial filling of the tubings with the tested solutions,
we used 50 mL polypropylene syringes (BD Plastipak, Spain,
ref 300865), and an electric syringe pump at a flow rate of 1200
mL/h.

2.3. Reagents

Two reagents were used, both of HPLC grade: acetonitrile,
99.9% purity (Reidel-de Haën, Germany) and ethanol, 99.8%
purity (Riedel-de Haën, Germany). Water was purified using
a U12 pack ultrapure water system (VWR international SAS,
Fontenay sous Bois, France). For the contact study, the ethanol-
water mixture was prepared at 50-50% by volume.

2.4. Instrumental analysis

Plasticizer quantification was performed using a liquid chro-
matography system (LC2010A HT HPLC) equipped with an
UV detector (Shimadzu, Marne la Vallée, France). The station-
ary phase used for the separation of plasticizers was a C8 col-
umn (Kinetex 100 mm × 4.6 mm; 2.6 µm) from Phenomenex
(Le Pecq, France) combined with a guard cartridge (2 mm × 4.6
mm ; same stationary phase). The mobile phase was a mixture
of water and acetonitrile delivered at a flow-rate of 2 mL min⁻¹.
The analytical conditions[35] are adapted to our chromatogra-
phy system, and the limits of quantification (LOQ) and of detec-
tion (LOD) are established in Table 2. The exactitude profiles
calculated as described by Hubert et al.[36, 37] are presented in
Figure S1 (Supplementary Information) for the three plasticiz-
ers.

2.5. Study design

Each tubing was first washed with the solution, filled and closed manually at both extremities using clamps, and then stored in a climatic chamber (Binder, model KBF240, GmbH Tuttingen, Germany) at 25 °C and 60% residual humidity. The plasticizer concentrations were measured right after filling the syringes (T0), and after the following contact times : 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 4 h, 6 h and 24 h. Three independent tubings were used ($n = 3$) for each experimental condition and time-point, thus corresponding to a total of 54 tubings for each plasticizer.

2.6. Computational procedures

The three plasticizers and the PVC chains were modeled by using the all-atom general Amber force field (GAFF2) [38]. The atomic partial charges were calculated at the B3LYP/6-31++g(d,p) [39, 40] level using Cioslowki's atomic polar tensor (APT) method [41, 42, 43]. These calculations were carried out using the Gaussian16 [44] package. The water molecules were described by using the TIP4P2005 model [45]. The GAFF2 model is quite universal and has been applied to many chemically different systems whereas the TIP4P2005 and TraPPE force fields have been shown to successfully reproduce a significant number of thermodynamic properties.

The molecular dynamics simulations were performed with the LAMMPS package [46]. For the integration of the equation of motion we used the standard velocity-Verlet algorithm with a timestep of 2 fs. The SHAKE algorithm [47] was used to constrain all the C-H bonds of all molecules, the O-H bonds and the HOH angle of water molecules. The Lennard-Jones crossing parameters were calculated using the Lorentz-Berthelot rules. The Nose-Hoover thermostat and barostat algorithms [48] were used to maintain the temperature at 300 K and the pressure at 1 atm. For the repulsion-dispersion interactions, the cutoff radius was fixed to 12 Å. The periodic boundary conditions were applied in the three directions. The electrostatic interactions were handled with the Particle-Particle-Particle-Mesh (PPPM) 3D method [49].

For the three plasticizers, we modeled a surface plasticized at 37 % in mass. The design of the plasticized PVC was modeled using 18 short chains of 50 monomers to obtain a good homogenization of the plasticizers. The number of molecules of plasticizers depended on the mass of the plasticizer used. These properties are given in Table S2 (Supplementary Information) along with the simulated density of each system. To construct the surface, a box of size $50 \times 50 \times 50 \text{ \AA}^3$ with the plasticizers homogeneously distributed was modeled, and each PVC chain was constructed step by step in order to propose random equilibrium chain configurations. The resulting configuration was relaxed in the NPT ensemble with increasing temperature up to 600 K, the system was then maintained at this temperature for 1 ns and then cooled to 300 K with a ramp of 1 ns. The final configuration was obtained after NVT runs at 300 K.

The systems were composed of a polymeric surface and a solution of :

- Water : 5000 water molecules

- Ethanol-water : 3000 water + 930 ethanol molecules

Classical molecular dynamics simulations were performed with an equilibration period of 500 ps. Structural and thermodynamic properties were calculated during the acquisition phase of 500 ns. We plotted in Figure S2 (Supplementary Information) the evolution as a function of time of the temperature, total, kinetic and potential energies over the last 150 ns of the simulation of the PVC-TOTM system to show what we did not observe any drift of these properties over these long NVT-simulations.

To compute the PMF profiles, the harmonic biasing method Umbrella sampling (US) [50, 51] allows an efficient sampling by applying a bias along the reaction path, and is thus an interesting method for values of the reaction coordinates for which the PMF is unfavorable. With the US method, the Hamiltonian is modified by the addition of a weighting function that takes a quadratic form with the spring constant k equal to $0.11 \text{ kJ mol}^{-1} \text{ \AA}^{-2}$. The Weighted Histogram Analysis Method (WHAM) [52] was used to recover the unbiased free energy profile $\Delta G(z)$.

For the PMF calculations, the NVT statistical ensemble was computed over 200 ns with a constant PVC surface $S = L_x L_y = 50 \times 50 \text{ \AA}^2$ at 300 K. The PMF profiles correspond then to the free energy profile $\Delta F(z)$ along a chosen reaction coordinate. The reaction coordinate was defined as a z -coordinate : the difference between the z -positions of the center of mass of a molecule of plasticizer and the PVC surface. The maximum value of the reaction coordinate was set to 35 Å. The Helmholtz free energy $\Delta F(z)$ was set to zero for the largest separation distance between the molecule and the polymeric surface.

3. Results and discussion

3.1. Plasticizer migration

3.1.1. In water

The study of the plasticizers' migration was approached by means of long molecular dynamics simulations. These simulations were carried out over a period of 0.5 μs for DINCH, DEHT and TOTM plasticizers in water. Fig. 1 shows the density profiles of the PVC chains, plasticizers and water molecules calculated in the last nanosecond of the simulation. Figure S3 (Supplementary Information) shows the same profiles but only calculated over the first nanosecond. The comparison between these profiles calculated on different time intervals should be able to demonstrate whether certain plasticizers can migrate into the solutions that were tested during the studied time-frame. The profiles of Fig. 1 establish an homogeneous distribution of plasticizers inside the PVC matrix but also that the PVC-water interfacial region is also populated by plasticizer molecules. However, the density profiles of Fig. 1 do not show the presence of plasticizer molecules in the bulk water phases (regions characterized by a constant density profile of about 1000 kg m^{-3}), thus suggesting that no migration took place during the simulation timescale. The density profiles of all the individual plasticizer molecules shown in Figure S4 (Supplementary Information) confirm that no plasticizer molecule was located deeper in water than the position of the Gibbs dividing

271 surface, defined here as the inflection point of the density pro-
 272 files of solvent molecules. The plasticizers furthest from the
 273 PVC surface remain in contact with the PVC, presenting a few
 274 parts of the molecule in the interfacial region. The water density
 275 profiles exhibit a progressive decay near the PVC surface indi-
 276 cating that the interfacial region which extends over about 10 Å
 277 is made up of PVC chains, plasticizers and water molecules and
 278 extend over about 10 Å.

279 In addition, the analysis of the profiles of Figure S3 and S5
 280 (Supplementary Information) over the first nanosecond of sim-
 281 ulation shows that the profiles did not change much over half³²⁷
 282 a microsecond confirming the fact that no major migration of³²⁸
 283 plasticizers from the PVC surface occurred in water over this³²⁹
 284 time interval. ³³⁰

285 We used the HPLC method to detect any release of plasticiz-³³¹
 286 ers (DINCH, DEHT and TOTM) in the solution in contact with³³²
 287 plasticized PVC tubings. During the contact study, no release³³³
 288 of plasticizers was detected, even after 24 hours of contact for³³⁴
 289 all plasticizers. The experimental results confirm the hypothe-³³⁵
 290 sis based on molecular simulation that there is no (or beneath³³⁶
 291 the detection threshold of the analytical method that was used)³³⁷
 292 release of plasticizers when PVC tubings are in contact with an³³⁸
 293 aqueous solution. ³³⁹

294 3.1.2. In ethanol-water solution ³⁴¹

295 The static contact study was conducted with an ethanol-water³⁴²
 296 (50/50 v/v, containing 20 µg/mL of diazepam) solution to anal-³⁴³
 297 yse the release of plasticizers. Fig.2 shows the evolution over³⁴⁴
 298 time (in minutes) of the concentration of plasticizers during³⁴⁵
 299 static contact with different tubings. For the three plasticizers,³⁴⁶
 300 we can see a significant increase in the plasticizer concentration³⁴⁷
 301 during the first 30 minutes of contact after which the concentra-³⁴⁸
 302 tion seems to stabilize around a threshold value: 58 µg mL⁻¹³⁴⁹
 303 for DINCH, 23 µg mL⁻¹ for DEHT and 4 µg mL⁻¹ for TOTM.³⁵⁰
 304 The experimental part highlighted the differences in leaching³⁵¹
 305 between tubings, as PVC DINCH tubings released the biggest³⁵²
 306 quantity of plasticizers, PVC DEHT released near 3 times less³⁵³
 307 plasticizers, and PVC TOTM showed a very low leaching ca-³⁵⁴
 308 pacity compared to the other two. ³⁵⁵

309 To interpret these experimental results of plasticizer leach-³⁵⁶
 310 ing, we propose now to analyze the density of plasticizers, PVC³⁵⁷
 311 and solvent molecules calculated in the ethanol-water solution³⁵⁸
 312 during 500 ns. Fig. 3 displays the profiles of the last nanosec-³⁵⁹
 313 ond of simulation whereas Figures S4 and S5 (Supplementary³⁶⁰
 314 Information) inform us about the density profiles of the first³⁶¹
 315 nanosecond. The density profiles of each plasticizer molecule³⁶²
 316 in the ethanolic solution are given for completeness in Figures³⁶³
 317 S5 and S6. First, Fig. 3 establishes that the interface has be-³⁶⁴
 318 come disorganized over time, revealing density profiles of water³⁶⁵
 319 and alcohol molecules that are much less consistent with a step³⁶⁶
 320 function density profile of a solid-liquid interface. We can even³⁶⁷
 321 observe that a small fraction of ethanol and water molecules³⁶⁸
 322 were able to penetrate the PVC matrix, indicating favorable in-³⁶⁹
 323 teractions between the PVC chains and ethanol molecules, ir-³⁷⁰
 324 respective of the type of plasticizer used here. Interestingly, by³⁷¹
 325 analyzing the density profiles of DINCH and DEHT, it can be³⁷²
 326 noticed that they are no longer equal to zero in the bulk ethanol³⁷³

Table 3: Leaching ratio in ethanol-water solution: molecular simulation versus experiments [19]

Tubing	Leaching ratio	
	Simulation	Experiments
PVC-DINCH	0.094 ±0.01	0.12
PVC-DEHT	0.041 ±0.01	0.036
PVC-TOTM	0.008 ±0.01	0.006

solution, thus indicating a migration of these two plasticizers. The phenomenon seems to be less pronounced for TOTM. By comparing these observations with the profiles calculated over the first nanosecond (see Figure S6, Supplementary Information), an evolution over time in the shape of these profiles and the structure at the interface can be clearly seen. Indeed, during the first nanosecond, the density profiles of water and alcohol molecules showed a typical solid-liquid interface profile, with a predominance of ethanol molecules occupying this interfacial zone. As for plasticizers, they were homogeneously distributed within the PVC (see Figure S6 and Figure S7, supplementary Information).

The change in the shape of the density profiles over half of microsecond is very impressive, illustrating the onset of the plasticizer’s migration in an ethanolic solution. The analysis of the density profiles calculated after 500 ns (see Figure S8, supplementary Information) shows that on average 7-8 out of 80 DINCH molecules had migrated from the PVC whereas only 3-4 out 86 DEHT molecules left the PVC. At most 1 out 62 TOTM molecules escaped from the PVC material over the simulated period. These simulations establish an approximate degree of leaching ranging from 1 to about 9 %.

First, the simulation confirms the migration of the plasticizers at the molecular level, in agreement with the experimental results. Quantitatively, the values of leaching ratios listed in Table 3 agree well between simulation and experiments for DINCH and DEHT plasticizers. It should be pointed out that the uncertainty in the calculation of the leaching ratio for these both plasticizers is based on more or less one molecule, which corresponds then to ±0.01 on the leaching ratio. For TOTM, the low experimental ratio of 0.006 indicates that less than one molecule (0.4 molecule of TOTM on average) migrates into the solution if we consider 62 TOTM molecules. This would mean multiplying the number of TOTM molecules by 3 and the simulation time by about 9 to obtain a quantitative value. This computational effort becomes too large to simulate the material over half a microsecond. For the PVC-TOTM system, it is therefore clear that the system-size simulated here does not allow a quantitative assessment of the leaching ratio. However, it is remarkable to note that the trends highlighted experimentally between the plasticizers is well reproduced by the simulation. Different typical configurations extracted from the MD simulations are shown in Fig. 4 and give an idea of the leaching at a molecular scale. These snapshots allow the visualization of the plasticizer migration in ethanol-water versus water, and are coherent with the density profiles.

In the next section, we aim to use advanced algorithms of sta-

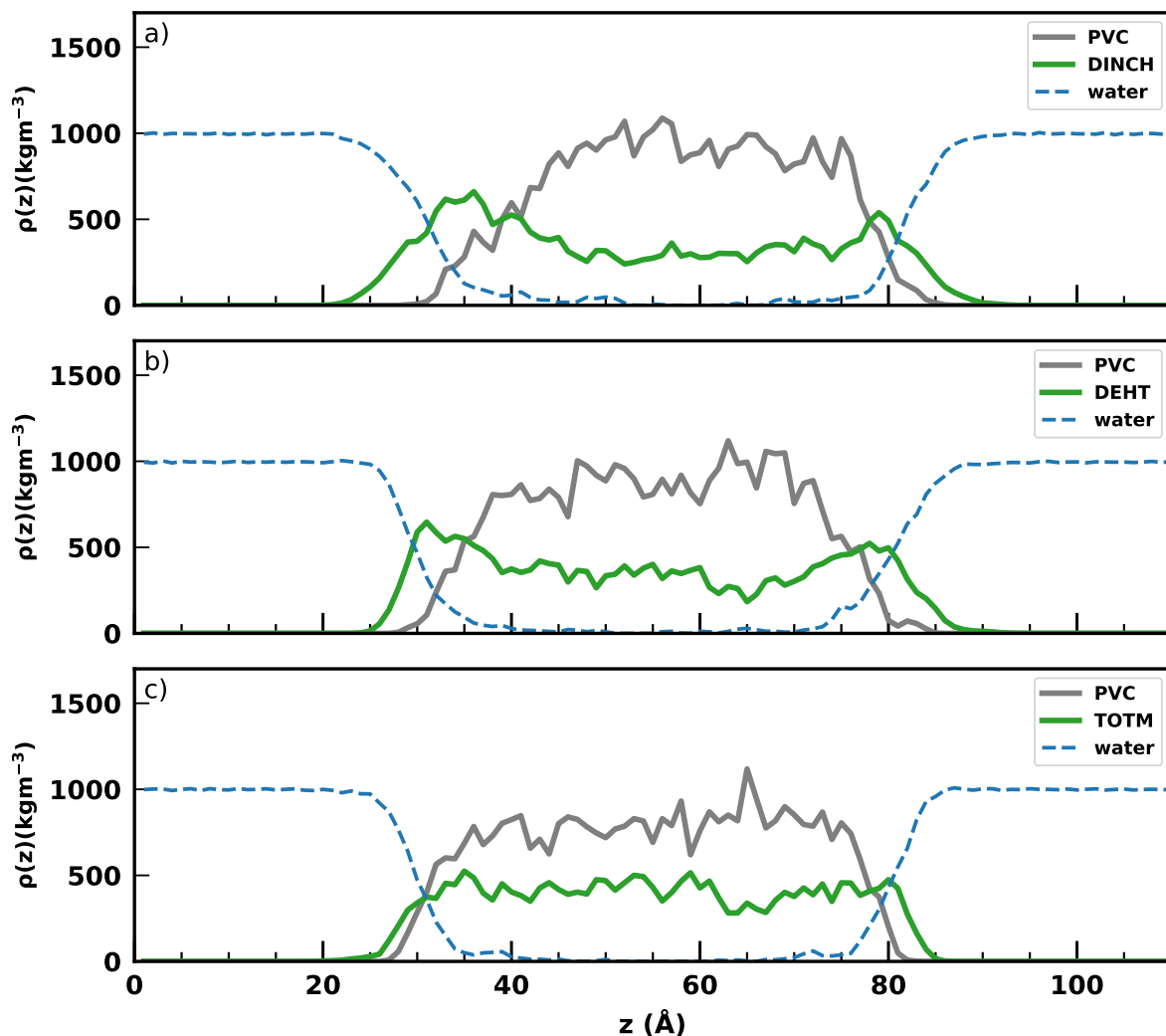


Figure 1: Density profiles of PVC chains, plasticizer and water molecules along the direction normal to the surface over the last nanosecond (499..500) ns of the simulation; a) DINCH; b) DEHT and c) TOTM.

374 tistical thermodynamics to calculate a free energy profile along³⁹¹
 375 the separation distance between the material and the plasticizer³⁹²
 376 in order to explain the leaching process.

377 3.1.3. Thermodynamics

378 The analysis of the density profiles shows a possible migra-³⁹⁷
 379 tion, but the absence of migration over 0.5 microseconds (for³⁹⁸
 380 example in the case of the aqueous solution) does not mean that³⁹⁹
 381 it cannot occur on a time scale greater than that of the sim-⁴⁰⁰
 382 ulation. To support these results and gain an insight into the⁴⁰¹
 383 molecular causes of the migration phenomenon, it is important⁴⁰²
 384 to evaluate the free energy of the plasticizer as a function of its⁴⁰³
 385 position relative to the surface. This type of calculation can then⁴⁰⁴
 386 provide information on the spontaneous nature of the leaching.⁴⁰⁵
 387 The diffusion of plasticizer molecules inside the PVC was not⁴⁰⁶
 388 considered by this PMF calculation due to the cost of the sim-⁴⁰⁷
 389 ulation to reach the relaxation of the material and investigate⁴⁰⁸
 390 the sampling of the polymer matrix by the plasticizer. We only

393 considered the start of migration when the plasticizer was on
 394 the PVC surface. We then performed a set of simulations at a
 395 given z -position of the plasticizer's center of mass. For each
 396 value of z , we calculated a free energy $\Delta F(z)$. This allowed
 397 us to obtain a free energy profile along the direction normal to
 398 the non-plasticized PVC surface. As z is relatively large, the
 399 plasticizer does not interact with the surface and $\Delta F(z) = 0$.
 400 When the free energy profile exhibits a free energy minimum
 401 at the interfacial zone, it means that the interaction between the
 402 plasticizer and the non-plasticized PVC surface is thermody-
 403 namically favorable and therefore that the plasticizer migra-
 404 tion is unfavorable.

We present in Fig. 5 the free energy profiles of each plas-
 ticizer in vacuum, water, ethanol-water and ethanol solutions.
 The values of the free energy minimum (ΔF_{\min}) are given in Ta-
 ble 4. The free energy profiles calculated in vacuum in Fig.5a
 show that the net interaction between the plasticizer and the
 non-plasticized PVC surface is very favorable with well-depths

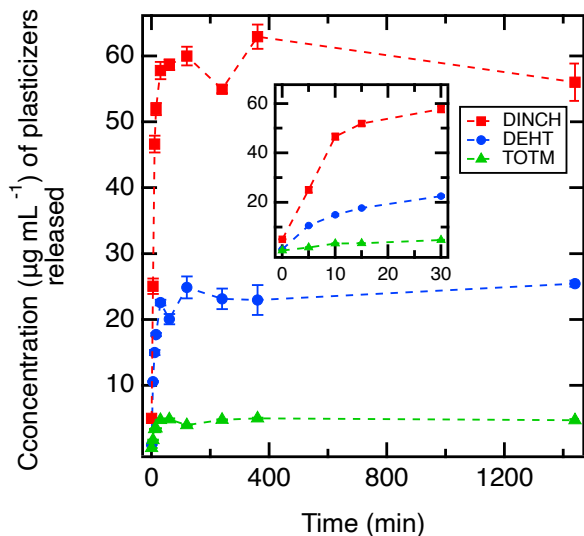


Figure 2: Quantity of plasticizers released during static contact of different plasticized-PVC tubings with an ethanol-water (50/50 v/v) solution as a function of time in minutes. The inset shows a close-up view over the first thirty minutes ($n=3$, mean \pm SD)

of around $-129 \pm 2 \text{ kJ mol}^{-1}$ between the different plasticizers. The calculation of these free energy curves in water shows well-depths that are shallower than in vacuum, with values ranging from -82 to -60 kJ mol^{-1} . In ethanol-water mixtures, the well-depths are even shallower than in water with a reduction by almost half. Very interestingly, the free energy minima are close to zero in pure ethanol solution as shown in Table 4. These free energy values clearly indicate that the leaching of plasticizer away from the polymer surface costs a lot of free energy in vacuum. This energy cost is lower in water, but considerably reduced in ethanolic solutions. From a leaching viewpoint, it means that the free energy barrier to overcome during plasticizer desorption process has been almost reduced to zero in ethanol. In ethanol-water solutions, the free energy cost which is lower than 30 kJ mol^{-1} is clearly coherent with the experimental measurements of DINCH and DEHT leaching. For TOTM, the free energy penalty of 42 kJ mol^{-1} leads to a weak migration of TOTM molecules. These simulations agree with the threshold value of 30 kJ mol^{-1} established in Ref.26. The free energy costs listed in Table 4 for the ethanol-water solution respect the quantities of plasticizers released of Fig. 2. It is now interesting to identify the energy contributions that could explain this free energy balance.

To do so, we propose to calculate the difference $\Delta F_{\min}^{\text{solution}} - \Delta F_{\min}^{\text{vacuum}}$ listed in Table 4. This difference is always positive and increases from water to ethanol solutions. These positive values indicate that the interaction of the plasticizer with the PVC at the interface is less favorable in solution than in vacuum. Indeed, if the difference is more positive, the adsorption of the plasticizer onto the PVC surface is less favored and

therefore the possibility of plasticizer migration out of the interface is increased. The migration of the plasticizer involves its desorption from the PVC surface, the adsorption of solvent molecules that replace the plasticizer on the PVC surface and the gradual solvation of the plasticizer as it migrates into the solution. First, the desorption of the plasticizer is measured by the opposite of ΔF_{\min} . Second, to calculate the other free energy contributions, it is necessary to design a thermodynamic cycle in which the reactants and products are in solution and in vacuum [53]. From this thermodynamic cycle, it can be deduced that the free energy difference $\Delta F_{\min}^{\text{solution}} - \Delta F_{\min}^{\text{vacuum}}$ sums two contributions: one resulting from the adsorption of solvent molecules initially in bulk solution and replacing the plasticizer molecule on the PVC surface and one other coming from the gradual solvation of plasticizer as it returns to the solution. This free energy difference can be expressed as

$$\Delta F_{\min}^{\text{solution}} - \Delta F_{\min}^{\text{vacuum}} = -\Delta F_{\text{ads-solv}} - \Delta F_{\text{solv-plast}} \quad (1)$$

where $\Delta F_{\text{solv-plast}} \approx -\frac{1}{2}\Delta F_{\text{des}}$ and $\Delta F_{\text{ads-solv}}$ are the free energies of solvation of the plasticizer after migration and of adsorption of solvent molecules on the PVC surface after plasticizer migration, respectively.

To evaluate the solvation of the plasticizer, we evaluated the desolvation of plasticizers in ethanol and in water in a system devoid of a PVC surface by developing an alchemical transformation. In this case the free energy of solvation is the opposite of the desolvation free energy calculated in the alchemical transformation. The reader is redirected to the reference 53 for a comprehensive description of the methodology. We accumulate the free energy attribute during the process of desolvation of the plasticizer and the solvent molecules. This is achieved by progressively turning off the intermolecular interactions between the plasticizer and the solvent molecules. The initial state contains all the intermolecular interactions between the solvent and plasticizer molecules whereas these intermolecular interactions become equal to zero in the final state. The intermediate states represented by the coupling parameter λ correspond to alchemical systems with intermolecular interactions which are a weighting of the interactions of the initial and final states. The reader is directed to the Supplementary Information for a description of the operational expression used in the calculation.

Fig. 6 represents the cumulative free energy of desolvation during the different steps λ of the desolvation process. The final point, corresponding to the free energy of desolvation is reported in Table 5 for each plasticizer. Interestingly, we observe that the cost of desolvation of each plasticizer ranges from 98 to 118 kJ mol^{-1} in ethanol, from 95 to 128 kJ mol^{-1} in ethanol-water and from 66 to 88 kJ mol^{-1} in water. This means that the plasticizer solvation during its migration into the liquid solution is thermodynamically favored and becomes even more favorable in ethanol-water and ethanol solutions in which the energetic cost fell below -100 kJ mol^{-1} . This solvation attribute explains why the plasticizer molecules prefer to be solvated by ethanol than by water. If we assume that half of the solvation layer is recovered during the migration into bulk solution,

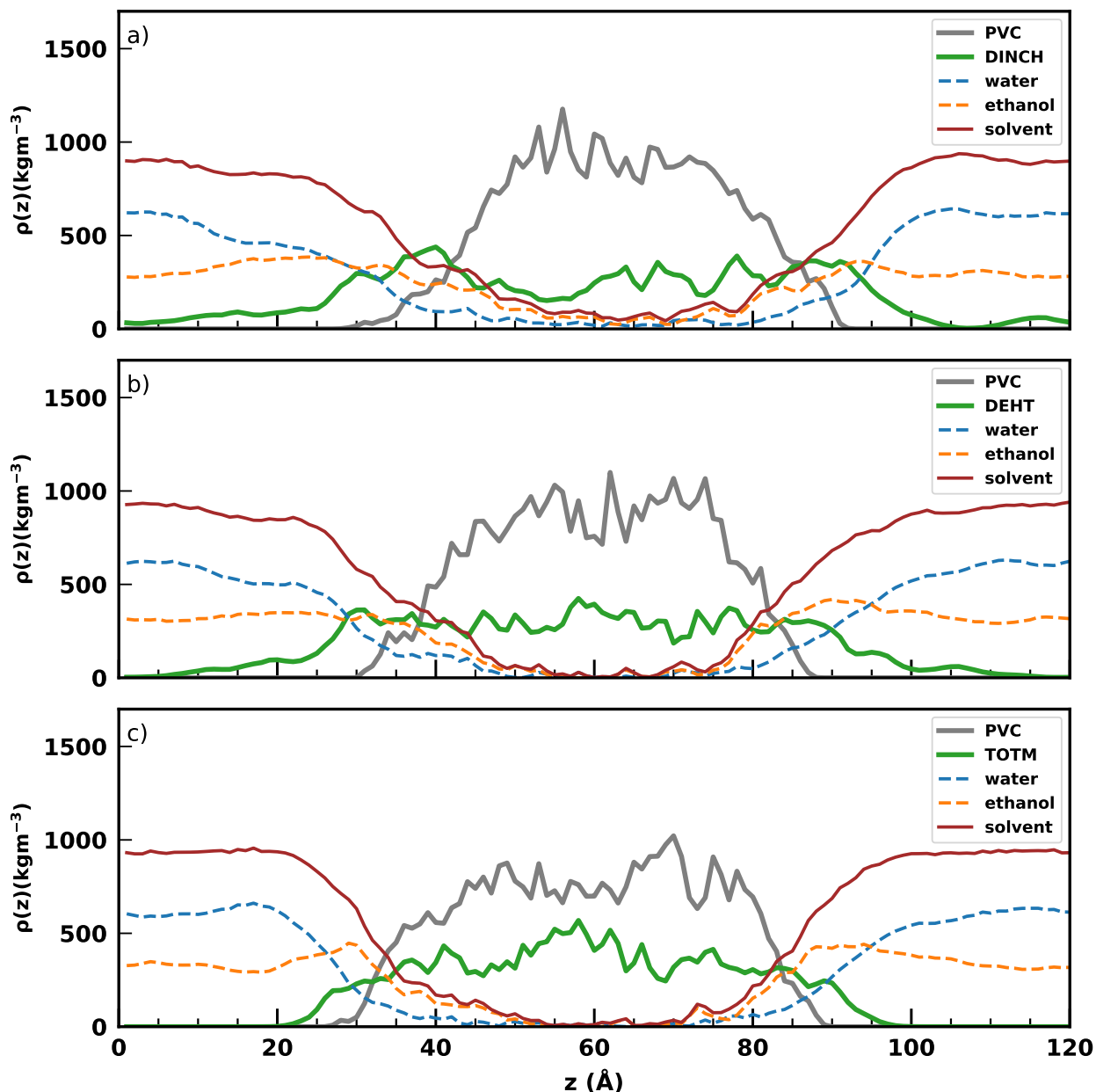


Figure 3: Density profiles of PVC chains, plasticizer, water and ethanol molecules in a 50/50 ethanol/water (v/v) solution along the direction normal to the surface over the last nanosecond (499.500) ns of the simulation; a) DINCH; b) DEHT and c) TOTM.

Table 4: Free energy (ΔF_{\min}) values in kJ mol^{-1} obtained from the minimum of the PMF curves calculated in different environments (vacuum, water, ethanol-water and ethanol). The difference between the free energies calculated in the solution and in vacuum ($\Delta F_{\min}^{\text{solution}} - \Delta F_{\min}^{\text{vacuum}}$) is shown in brackets. The standard deviations [26] are estimated to be within 3 kJ mol^{-1} .

	$\Delta F_{\min} (\Delta F_{\min}^{\text{solution}} - \Delta F_{\min}^{\text{vacuum}})$			
	vacuum	water	ethanol-water	ethanol
DINCH	-129	-60 (69)	-24 (105)	-3 (126)
DEHT	-128	-52 (76)	-27 (101)	-1 (127)
TOTM	-131	-82 (49)	-42 (89)	-5 (126)

Table 5: Desolvation free energy contributions (ΔF_{des}) (kJ mol^{-1}) of the plasticizers calculated in water and ethanolic solutions. The standard deviations are estimated to be within 2 kJ mol^{-1} .

	ΔF_{des}		
	water	ethanol-water	ethanol
DINCH	70	100	104
DEHT	66	95	98
TOTM	88	128	118

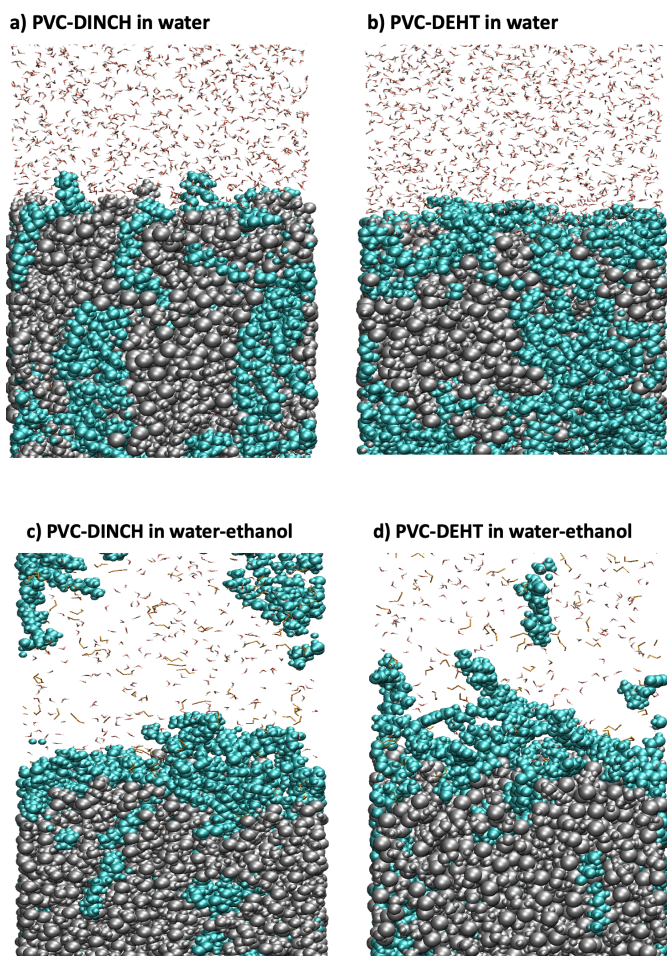


Figure 4: Typical configurations of plasticized PVC surfaces in a) and b) water and in c) and d) ethanol-water solutions at the end of simulations of 500 ns with DINCH and DEHT plasticizer molecules. The plasticizer molecules are coloured in cyan and the PVC atoms in grey.

the plasticizer leaching allows an energetic gain between -44 and -33 kJ mol^{-1} in water and between -59 and -49 kJ mol^{-1} in ethanol. In the water-ethanol mixture, the gain ranges from -64 to -47 kJ mol^{-1} .

We focus now on the adsorption of solvent molecules which replace the plasticizer on the PVC surface. To calculate this contribution, we rely on Eq.1. Indeed, the replacement at the PVC surface of the plasticizers by solvent molecules, leading therefore to the adsorption of these solvent molecules, is thermodynamically favorable as it yields a free energy gain (calculated here through $\Delta F_{\text{ads-solvent}}$ by Eq.1) between -43 and -5 kJ mol^{-1} in water and between -78 and -67 kJ mol^{-1} in ethanol. In the ethanol-water solution, the free energy gain is within a range of -55 to -25 kJ mol^{-1} .

To summarize, the calculation of different energy contributions establishes that the migration of plasticizers in ethanolic solutions is energetically favored due to favorable free energy contributions coming from both the solvation of plasticizers by the ethanol molecules during the migration process and the adsorption of the solvent molecules which replace the plasticizer on the PVC surface. These free energy contributions support the conclusions drawn from the analysis of density profiles, namely that migration is favoured in ethanolic solutions.

3.2. Drug adsorption

The question now is how the adsorption of the drug is modified by the nature of the solution and the presence of released plasticizers in the solution. We used a previously published HPLC method [27] to detect any loss by sorption of diazepam with different plasticized-PVC surfaces in water and ethanol-water solutions. Figure 7 shows the evolution over time (in minutes) of the concentration of diazepam during static contact with different plasticized-PVC tubings in both solutions. Firstly, it can be clearly seen that the loss of diazepam is radically different in water or ethanol-water solutions. Indeed, a significant loss by sorption in water with a remaining concentration of about 5% of the initial concentration in solution after 400 min of contact was noted. The amount of adsorbed drug when in solution in water was slightly less with the TOTM tubings (by about 2%), but we did not observe any significant difference between DINCH and DEHT plasticizers. Secondly, in ethanol-water solutions, the loss by sorption was attenuated. Indeed, after 400 min, in the ethanol-water solution, a fraction of

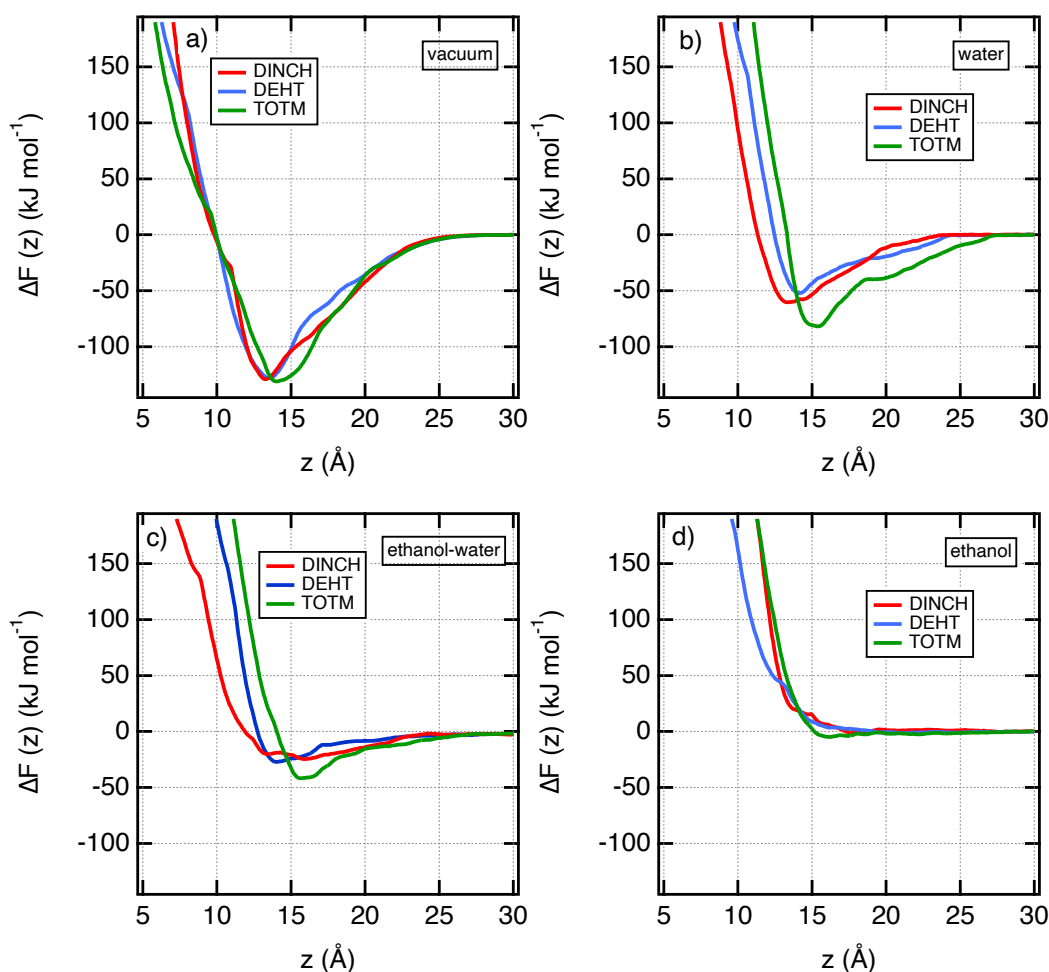


Figure 5: Free energy profiles $\Delta F(z)$ along the z -direction for the adsorption process from solution to the surface of pure PVC for different plasticizers in different environments a) vacuum, b) water, c) 50/50 ethanol-water solution and d) ethanol.

535 the drug concentration ranging from 32 % to 17 % was adsorbed⁵⁵⁶
 536 on the PVC compared to 95 % in water. This experimental data⁵⁵⁷
 537 can be interpreted in the light of the analysis of the free en-⁵⁵⁸
 538 ergy profiles shown in Figure 8. All plasticized PVC surfaces⁵⁵⁹
 539 are modeled with the same mass fraction as PVC TOTM (37%)⁵⁶⁰
 540 tubings used in the experimental part. ⁵⁶¹

541 Actually, the free energy profiles correspond to the process of⁵⁶²
 542 adsorption on the plasticized-PVC surface in water and ethanol-⁵⁶³
 543 water solutions. From these curves, we can extract the free en-⁵⁶⁴
 544 ergy minimum and calculate a free energy of adsorption which⁵⁶⁵
 545 is in fact a little different from the minimum of the free energy⁵⁶⁶
 546 curve since it considers an exponential average over the states⁵⁶⁷
 547 populating the region around the minimum. The free energy⁵⁶⁸
 548 of adsorption is calculated using Eq. S20 of the Supplemen-⁵⁶⁹
 549 tary Information and is given in Table 6. In ethanol-water so-⁵⁷⁰
 550 lutions, the free energy profiles showed minima around a value⁵⁷¹
 551 close to -23 kJ mol^{-1} whereas the corresponding free energies⁵⁷²
 552 of adsorption were of about -18 kJ mol^{-1} . These low values of⁵⁷³
 553 free energy of adsorption (already reported in previous studies⁵⁷⁴
 554 [26, 27, 28]) seem to indicate that no significant drug loss by⁵⁷⁵
 555 sorption can be observed when the free energy minimum is less⁵⁷⁶

negative than -30 kJ mol^{-1} . Indeed, these negative values of free
 energy confirm that the adsorption is thermodynamically possible
 (and therefore can possibly happen experimentally) but that the
 drug-PVC interaction is not strong enough to induce a drastic
 loss by sorption. In ethanol-water, the experiments show a
 medium loss of diazepam, meaning that molecular simulations
 can show intermediate adsorption phenomenon for ΔF_{\min}
 ranging from -20 to -30 kJ mol^{-1} . This is not the case for
 the adsorption of diazepam in water for which the calculated
 free energy minima range from -65 to -38 kJ mol^{-1} and
 experiments show a drastic drug loss by sorption. This means
 that the nature of the solution plays a major role in determining
 the strength of the adsorption. We recall that the free energy
 minimum in vacuum [27] is equal to -108 , -152 and -91 kJ mol^{-1}
 for the adsorption of diazepam in plasticized-PVC with
 DINCH, DEHT and TOTM plasticizers. The free energy of
 desolvation of diazepam in water and ethanol is given in the
 Supplementary Information. The free energy curves of
 desolvation are shown in Figure S9 (Supplementary Information).
 We observed that the free energy of desolvation is higher in
 ethanol than in water. The fact that the adsorption is less
 favored in ethanol-water can be in part

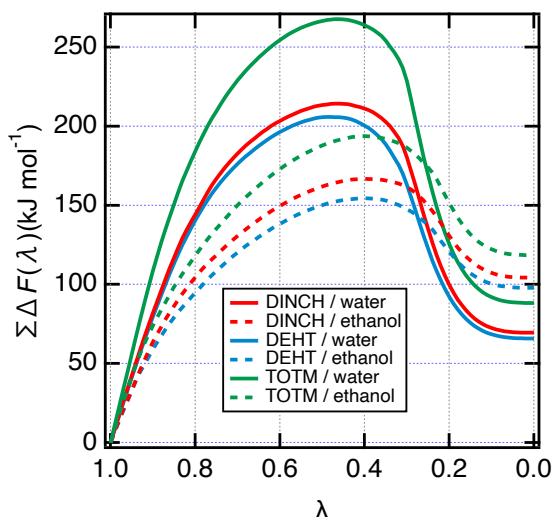


Figure 6: Cumulative $\Delta F(\lambda)$ free energy values as a function of the coupling parameter λ calculated in the desolvation process of the three plasticizers both in water and in ethanol solutions. The curves calculated in ethanol-water solutions are not shown for clarity. We used the Finite Difference Thermodynamic Integration method to calculate $\Delta F(\lambda)$. See Section 3 of the Supplementary Information.

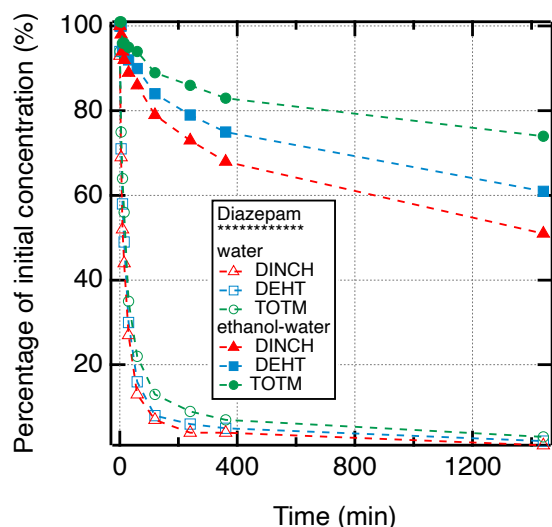


Figure 7: Evolution of diazepam concentrations in static contact with plasticized PVC tubings compared to initial concentrations. The error bars on the concentrations values are less than 1% and cannot be read with the scale used.

577 explained by a more unfavorable desolvation free energy con- 596
 578 tribution in the ethanol-water media. We show here that it is 597
 579 possible to explain the adsorption of diazepam by examining 598
 580 the interactions between all the species at the molecular scale 599
 581 and that the process of adsorption requires the investigation of 600
 582 different energy contributions. This discovery could have pro- 601
 583 found implications as in the future it might be possible to pre- 602

584 dict drug interactions with various surfaces and materials, thus
 585 reducing the need for long, costly and sometimes complex ex-
 586 periments.

Table 6: Free energy minimum and free energy of adsorption values (kJ mol^{-1}) calculated from the PMF curves corresponding to the adsorption of diazepam on plasticized-PVC surfaces, in water and ethanol-water solutions. The free energy of adsorption are calculated by using Eq. S7 of the Supplementary Information.

	ΔF_{\min}	ΔF_{ads}^o	ΔF_{\min}	ΔF_{ads}^o
	water		ethanol-water	
DINCH	-38	-34	-24	-18
DEHT	-65	-58	-23	-18
TOTM	-41	-35	-23	-18

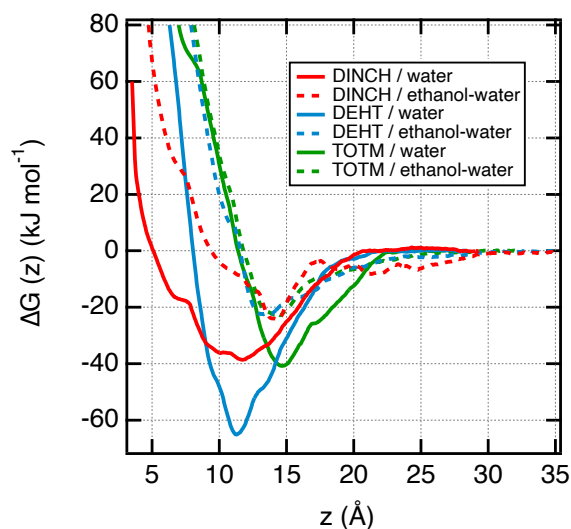


Figure 8: Free energy profiles of the interaction of diazepam onto different plasticized PVC surfaces calculated along the z -coordinate in water and in ethanol-water solutions.

587 Whereas the strength of the adsorption can be explained by
 588 means of the calculation of the free energy profile, the struc-
 589 tural description of the adsorption region can be carried out
 590 by standard molecular dynamics simulations. The density pro-
 591 files obtained normal to the surface are given in Figure 9. For
 592 the interaction of the diazepam with the DINCH-PVC surface
 593 in ethanol-water, we observe for example in Figure 8a that
 594 the interface region is populated by the drug diazepam, water,
 595 ethanol, DINCH molecules and PVC chains. It is clear that the
 drug is more solvated by ethanol than by water in line with the
 values of free energy of desolvation of diazepam (see Table 5).

In the case of water (see Figure 9b), the adsorption region
 is more structured and the z -position of the drug coincides
 with that of the Gibbs dividing surface of water. From a structural
 point of view, the adsorption in water differs significantly from
 that in ethanol-water where ethanol molecules penetrate the in-

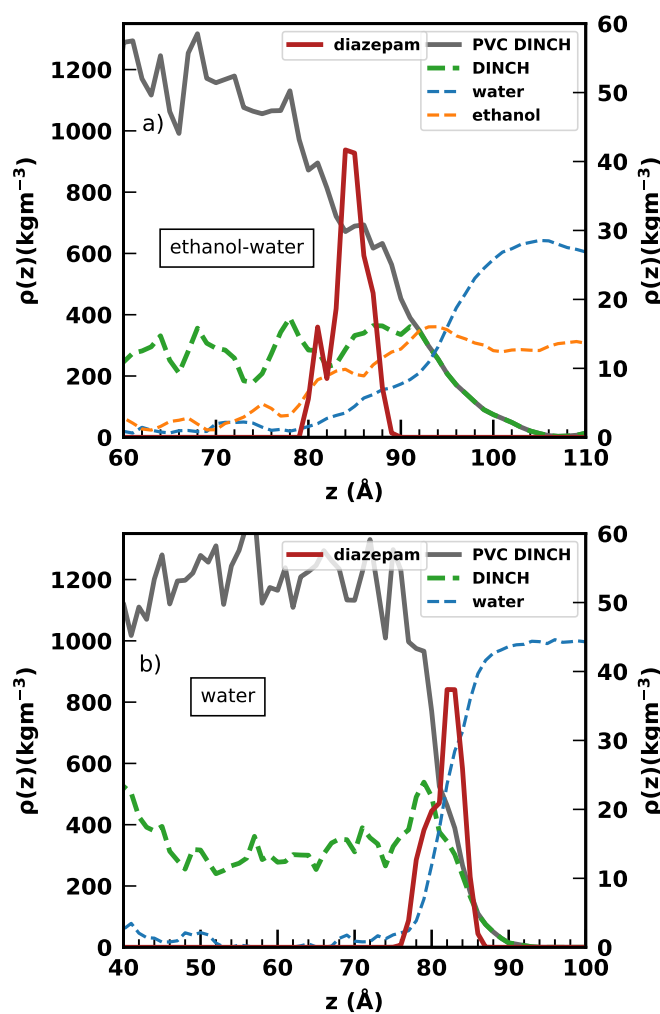


Figure 9: Density profiles of PVC DINCH, DINCH, water, ethanol and diazepam in the interfacial region in a) ethanol-water and b) water solutions calculated during the course of the simulation over 500 ns. The right axis shows the density of diazepam.

interfacial zone. Nevertheless, the fact that diazepam adsorption is energetically stronger in water does not induce specific structural properties noticeable on the density profiles of Figure 9.

4. Conclusions

The first objective of our study was to verify whether it was possible to observe plasticizer migration such as what is experimentally known to happen for plasticized medical infusion devices. In order to detect plasticizer leaching, we used an HPLC assay to measure the concentration of the plasticizers released into different solutions. For ethanol solutions, we observed the migration of the plasticizers with leaching ratios ranging from 0.006 to 0.12 for TOTM, DEHT and DINCH molecules, respectively. We completed these experiments by doing molecular simulations over a relatively long time scale covering half a

microsecond. The analysis of these molecular dynamics simulations confirmed the migrations of plasticizers in ethanol and ethanol-water solutions and no detectable leaching in water which suggests the driving role of molecular interactions in this process. The trends observed in the experimental leaching ratios are also well correlated by molecular simulations. The use of statistical thermodynamics enabled us to calculate potentials of mean force along the direction normal to the non-plasticized PVC surface of the three plasticizers in water, ethanol-water and ethanol solutions. The comparison of the different PMF curves in the three environments and the analysis of the desolvation curves of plasticizers in water and ethanol led us to rationalize the migration of plasticizers from an energy point of view, thus showing the predominant role played by the molecular interactions between the plasticizer and the solvent in the migration process.

We extended the coupling between experiments and simulations to the adsorption of a drug (diazepam) on plasticized-PVC surfaces. We clearly demonstrated that the loss of drug by sorption is significantly reduced in ethanol-water compared to water solutions. Molecular simulations supported this observation by calculating the potential of mean force as a function of the separation distance between the drug and PVC surface. The simulated free energy of adsorption confirmed that the adsorption of diazepam in ethanolic solutions is weaker than in water. This is due to the fact that the drug is much more solvated in ethanolic solution leading to a unfavorable free energy contribution of desolvation upon adsorption and making as a consequence the adsorption less favorable. We found that the ethanol-water mixture is a good solvent for plasticizers and diazepam. It prevents excessive adsorption of the drug but can lead to the migration of plasticizers such as DINCH and DEHT.

The combination of simulation and experiments has proved to be a very effective approach for the investigation of plasticizer leaching and the energetic characterization of drug adsorption. The maturity of this approach should enable us in the near future to design/select the material and plasticizer to limit the migration of plasticizers and the adsorption of the drugs onto medical devices.

Credit author statement

Meriem Sahnoune Millot: Investigation, Conceptualization, Writing-Original Draft preparation, Writing - Reviewing and Editing **Julien Devémy:** Methodology, Software **Jérémy Pinguet:** Investigation **Philip Chennell:** Investigation, Conceptualization, Writing - Reviewing and Editing **Alain Dequid:** Methodology, Conceptualization, Writing - Reviewing and Editing **Valérie Sautou:** Supervision, Conceptualization, Project administration, Writing - Reviewing and Editing **Patrice Malfreyt:** Supervision, Conceptualization, Writing-Original Draft preparation, Writing - Reviewing and Editing

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have ap-

670 peared to influence the work reported in this paper.

671 Data availability

672 Data will be made available on request.

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686 sity.

687 Supplementary materials

688 Exactitude profiles. Description of the systems in terms of
689 number of plasticizer molecules, PVC chains and density. Den-
690 sity profiles of the individual plasticizer molecules over differ-
691 ent time periods. Theory and operational expressions for the
692 calculation of the free energy contributions. Free energy desor-
693 ption curves of diazepam in water and ethanol solutions. The-
694 ory and expressions for the calculation of the free energy of
695 adsorption.

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