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1 **Mechanical clamp stress on PVC infusion tubing: impact on the surface degradation**

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16 **Abstract**

17 Several commercial infusion tubes made of plasticized PVC were shown to present a layer of
18 bloomed species on their internal wall (lubricants and stabilizers), which are poorly soluble in
19 water. During infusion, tubes are crushed and pinched to regulate the flow. The impact of
20 mechanical stress on these layers infusion was studied.

21 Device inner surfaces were characterized by AFM in order to put into evidence surface
22 degradations before and after infusion. This was correlated with a global and local IR
23 analysis.

24 Because of the clamp stress, the deposits were damaged. Thus, injecting water into the
25 damaged tubing increased the layer degradation. Rolling clamp and pinch clamp may have
26 very different effects on the inner layer morphology and degradation and this may be
27 modulated by the initial layer morphology.

28 Injecting water into clamp stressed tubing may increase the risk of detaching parts of the
29 internal layer and be a supplementary factor of particulate contamination for the patient.

30 **Keywords**

31 PVC - Mechanical stress - Surface degradation - Blooming - Particulate contamination —
32 Atomic force microscopy

33 **Introduction**

34 Infusion is a very common act in hospitals. Its benefits are widely recognized for the patient
35 in particular in emergency cases, for unconscious patients and for the nutrition of critically ill
36 patients. Infusion is performed by using transparent flexible tubing mostly made in plasticized
37 PVC. This PVC contains several additives such as plasticizers but also stabilizers and
38 lubricants. In a previous paper ¹, we showed that the internal walls of several PVC infusion
39 tubes were covered by a layer made of additives that bloomed and crystallized onto the PVC
40 surface (metallic stearates and bis amide lubricant). Water contact eroded this layer and we

41 suspected it to conduct to a particulate contamination of the infused solution. This particulate
42 contamination is potentially harmful to the patient: depending on the particle's size and
43 shape, on the patient's health and age, it may damage different organs; it may lead to a
44 thrombo-embolization or to the formation of granulomas^{2 3 4 5}. Moreover, during the infusion,
45 mechanical stress on the tubing can occur because of the use of clamps. Pinch and slide
46 clamps are used to stop the flow by pinching very locally the tubing (fig 1a). Roller clamps
47 are equipped with a small roller which allows the tube to be more or less crushed in order to
48 incrementally occlude it (fig. 1b). This allows a regulation of the flow rate by defining the size
49 of the tubing lumen. Both kinds of clamps can be found on the same set (fig 1c). The aim of
50 this paper was to characterize the effect of both kinds of clamp stresses on the layers found
51 on the internal wall of PVC infusion tubes and the consequences of water injection into the
52 tubing after this stress: we suspected it may lead to a potential higher and faster degradation
53 of the layer with a higher risk of particulate contamination. Indeed, the effect of repeated
54 compression of plastic tubing was studied in the case of hemodialysis circuit⁶; because of
55 the high and complex stress exerted by the peristaltic pump, cracks were observed on the
56 plastic surface and particles were then shed from these defects because of the shear stress
57 exerted on the inner wall of the tubing^{7 8 9 10}. These particles may then be injected into the
58 bloodstream. This complication is well known in dialysis when using silicone tubing and is
59 called spallation; it was studied by several authors mainly between 1980 and nowadays; it
60 can be implicated in brain dysfunction, granulomatosis hepatitis, macrophage
61 activation... long-term treated patients could show up to 250 mg of silicone particles lodged in
62 organs because of the use of silicone tubing^{11 12}. But, the PVC used to replace it produces
63 particles too: they were mainly below 5 μm in diameter but they can reach 50 μm ¹³.
64 Moreover, in another publication, Madsen et al.¹⁴ advised against the stripping of PVC
65 infusion sets with a pair of scissors, by compressing the tubing between the thumb and a
66 scissor blade, a clinical practice used to manage with flow malfunctions: because of this, an
67 increased number of particles (5 to 100 μm) in the infused liquid were detected.

68 In a first part, after having discussed the structure and homogeneity of the tube internal
69 lumen surface, the impact of the different kinds of clamps on the additive layer's morphology
70 will be described and then the impact of water injection on damaged layers will be discussed.

71 **Material and methods**

72 Material

73 Different PVC tubes were used for this study. These tubes were chosen because, as we
74 shown in a previous paper ¹, they had internal layers with very distinct morphologies. For the
75 AFM studies, tubes were cut in 10 cm long parts. The tubes came from the following kinds of
76 infusion sets: Infusomat® Space line (old reference with DEHP as a plasticizer), Intrafix®
77 SafeSet (BBraun, Germany) and Volumat® Line (Fresenius Kabi, Germany). Intrafix®
78 contains DEHT as a plasticizer and Volumat® line contains TOTM. The dimensions of the
79 tubes are given in table 1 and were very similar; typical plasticizer ratios were between 37
80 and 40% (see ref). Typical commercial tubes for infusion are made in relatively soft materials
81 with a shore A index between 65 and 80. For this study, a same production batch was used
82 for each reference.

	Infusomat	Intrafix	Volumat
Internal diameter (mm)	3	3	3
External diameter (mm)	4.1	4.1	4.1

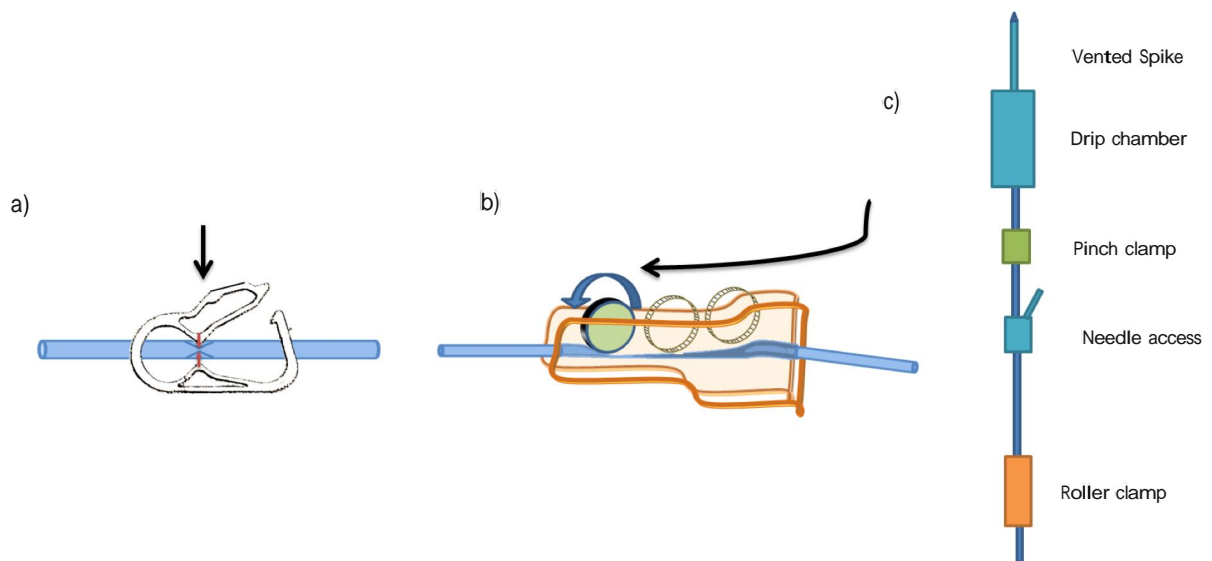
83 Table 1: dimensions of the tubes used

84 Mechanical stress

85 Stress was applied by using a rolling clamp or by using a pinch clamp. To insure that the
86 analyzed region by AFM corresponds to a stressed one, the pinch clamp and the roller were
87 used on the whole length of the cut tube part. In both case compressive stress was applied
88 on the tube. In the case of the roller clamp, the tube was progressively crushed on a large
89 portion of the tubing to reach a maximum stress when the flow is completely blocked. The
90 roller uniformly compresses the tube sides to confine its cross-section. For the pinch clamp,

91 the compression stress was exerted locally by the two jaws and shear stress can occur if
92 their edges are misaligned.

93 To study the impact of a clamp stress in a case of an infusion act, the tubing was first
94 stressed by the clamps and then an infusion by gravity act was mimicked by infusing 40 ml
95 of filtered water (Direct Q UV ultrapure water type 1). After letting the sample dry, it was
96 analyzed. For this study, only Infusomat® and Intrafix® tubes were analyzed.



97

98 Figure 1: a) pinch clamp that allows stopping the flow by pinching the tube between two jaws
99 b) roller clamp: the drawing shows the movement of the roller along the tube which it crushes
100 progressively to regulate the flow rate c) example of placement of clamps on a standard
101 primary set (Volumat®VLST22)

102

103 AFM

104 *Tapping mode*

105 The analyses were performed with an Innova AFM (Bruker, Palaiseau, France). The
106 tapping mode in air was used (cantilever frequency= 320 kHz, stiffness= 42 N/m, NCHV
107 probe from Bruker). At least six different areas of each sample (a sample corresponds to a
108 10 cm long part of a tube) were imaged using a scan rate between 0.5 and 1 Hz. Three
109 samples were used for each tube analyzed: one for studying the non-stressed state, one for

110 studying the impact of pinch clamp and another one for studying the impact of roller clamp.
111 For the impact of water injection, three samples of another tube were used (one for the non-
112 stressed state, one for the stressed tube before infusion and the last one for the stressed
113 tube after infusion).

114 *Force imaging mode*

115 The AFM used was a Nanowizard III (JPK Instruments AG, Berlin, Germany) using
116 Quantitative Imaging® (QI) mode which is a force curve imaging mode. Force distance curve
117 was realized for every pixel of the image. The probes were CSC 37 (Micromasch, stiffness
118 around 0.35 N/m). The stiffness data were calculated from the slope of the force versus
119 scanner elongation curves in the repulsive regime. For every point, the maximum applied
120 force (set-up value) to the sample was 2nN. This analysis was used for studying the impact
121 of water injection on stressed tubes because by using adhesion and stiffness measurements
122 it is possible to easily identify the areas where the additive layer was removed. It was indeed
123 showed in a precedent paper¹ that polymer surface was softer but has a higher interaction
124 with the tip as compared to the bloomed additive layer.

125 **FTIR-ATR**

126 The spectrometer apparatus was a Perkin Elmer (Courtaboeuf, France) Spectrum Two used
127 in the ATR (Attenuated Total Reflection) mode with a diamond crystal (500 to 4000 cm⁻¹) and
128 a LiTaO₃ (lithium tantalate) MIR detector with a SNR of 9,300:1. 8 scans were performed
129 with a resolution of 4 cm⁻¹, The inner surfaces of each sample were analyzed at least on 10
130 different points of the surface. For FTIR studies, 20 cm long tube samples were used: for
131 each condition (stressed, not stressed, pre and post infusion), two different tubes were
132 analyzed, and, for each tube, infusion was realized on two different parts of the same tube

133 IR nanospectroscopy, AFM IR

134 NanoIR2 (Anasys Instruments, CA USA) was used; the AFM microscope is combined with
135 an infrared pulsed tunable laser to perform infrared analysis under the AFM tip. The laser
136 was a multi-chip quantum cascade laser QCL (MIRCAT, Daylight solution, CA USA) ranging
137 from 1530 cm^{-1} to 1850 cm^{-1} , The repetition rate of this source is tunable (1 kHz to 500 kHz)
138 and was chosen to match the contact resonant frequency of the AFM cantilever. The beam
139 was focused from the top side of the sample onto the AFM cantilever. A gold coated probe
140 was used (MikroMasch : HQ:CSC38/Al-BS-50 - spring constant 0,03 N/m - resonance
141 around 190 kHz).

142 The spectra were collected with 1 cm^{-1} spectral resolution.

143 SEM

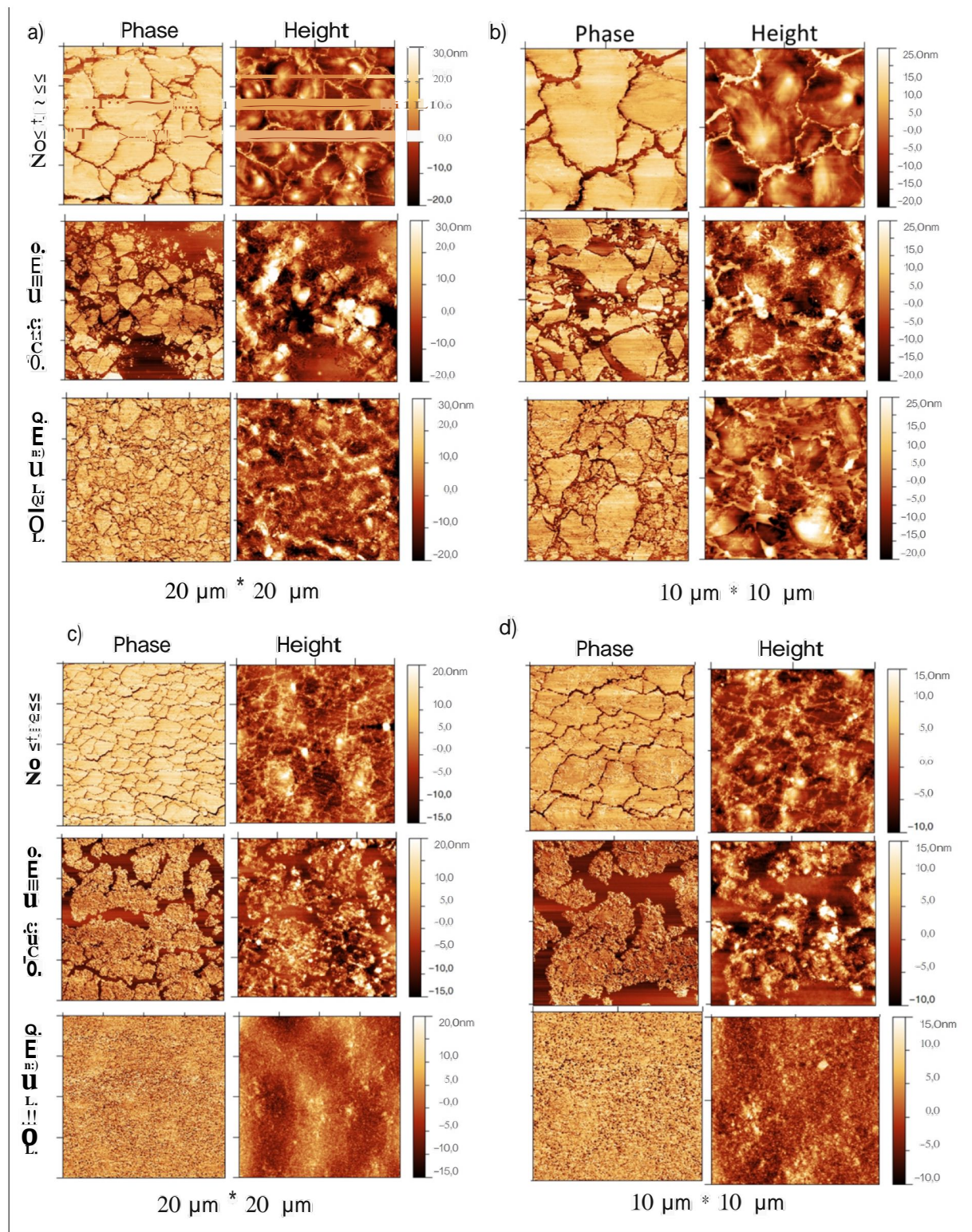
144 A FlexSEM 3000 (Hitachi) was used in back scattered electron mode (15 keV) to image the
145 internal lumen surface of the tube

146 **Results and discussion**

147 Initial texture of the layer

148 As already mentioned in a previous paper ¹, the morphology of the inner layer was very
149 different depending on the tubing reference. But the topography was quite uniform along
150 the same tubing with very consistent images, especially at the 20*20 or 10*10 μm^2
151 scales. However textures might vary depending on the commercial batch: even if the
152 structures of the different batches have a quite high degree of similarity, discrepancies
153 were observed between batches and even between tubes of the same batch; this may
154 come from small variations in the production process or in the aging of the sample (time
155 between production and analysis, temperature...).That is why, for more convenience and
156 accuracy, we compared the impact of stress and infusion only on several parts of a same
157 tube for AFM studies.

158 As we mentioned above, compared to the morphologies observed in a precedent
159 publication¹, we observe similar but not identical structures. For the Intrafix® sample (fig
160 2.a.b) big ovoid and smooth nodules (20-30 nm high) were still present (mostly-around 3-
161 6 μm in length and 2 μm in width), surrounded with thin protrusions (less than 0.2 to 1 μm
162 wide and between 20-50 nm high) ; the rms roughness was equal to 9.5 ± 0.6 nm for R_q
163 and 7 ± 0.5 nm for R_a ($20 \times 20 \mu\text{m}^2$). For Volumat®, a kind of network of protrusions (5-10
164 nm high and less than 1 μm wide) was observed but the layer was less uniform and
165 smooth than the samples previously analyzed from another batch (fig 2.c d): the
166 roughness was 6.3 ± 1.4 nm for R_q and 4.6 ± 1.1 nm for R_a ($20 \times 20 \mu\text{m}^2$).



167

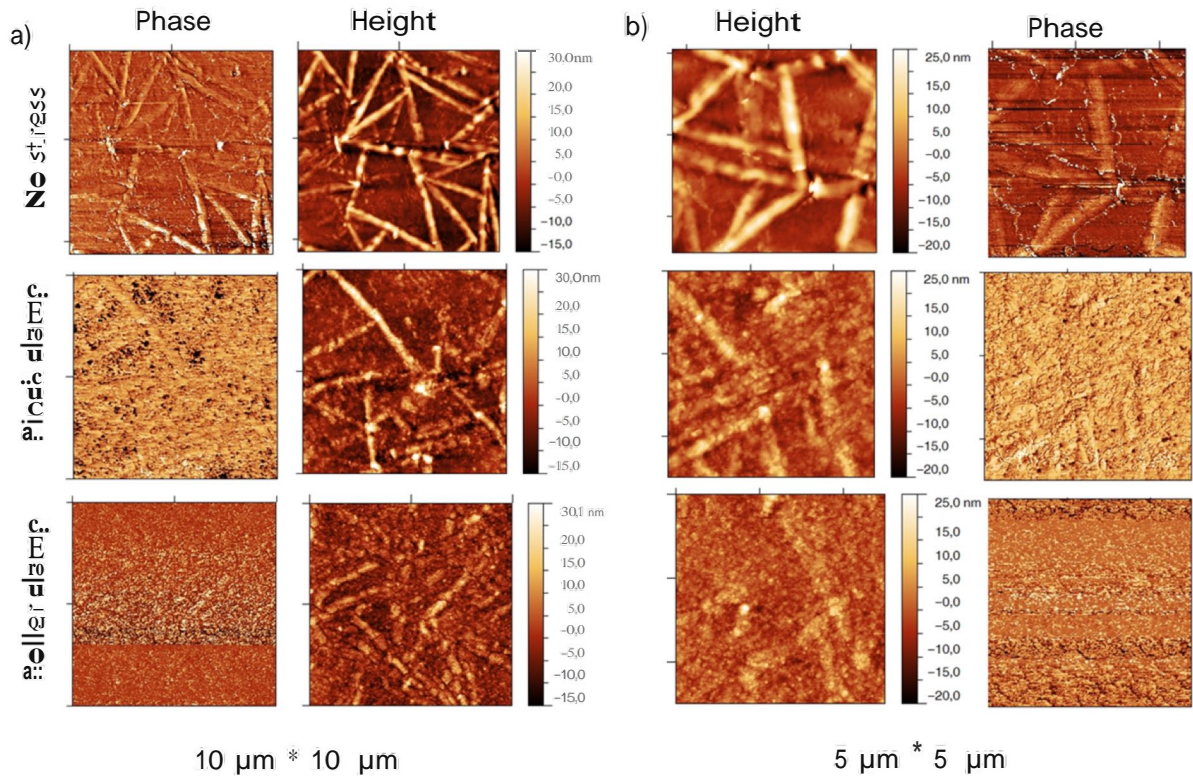
168

169 **Figure 2:** AFM images (height and phase) in tapping mode of the internal layer a) of the

170 Intrafix® tube 20*20 μm^2 . b) of the Intrafix® tube 10*10 μm^2 c) of the Volumat® tube 20*20

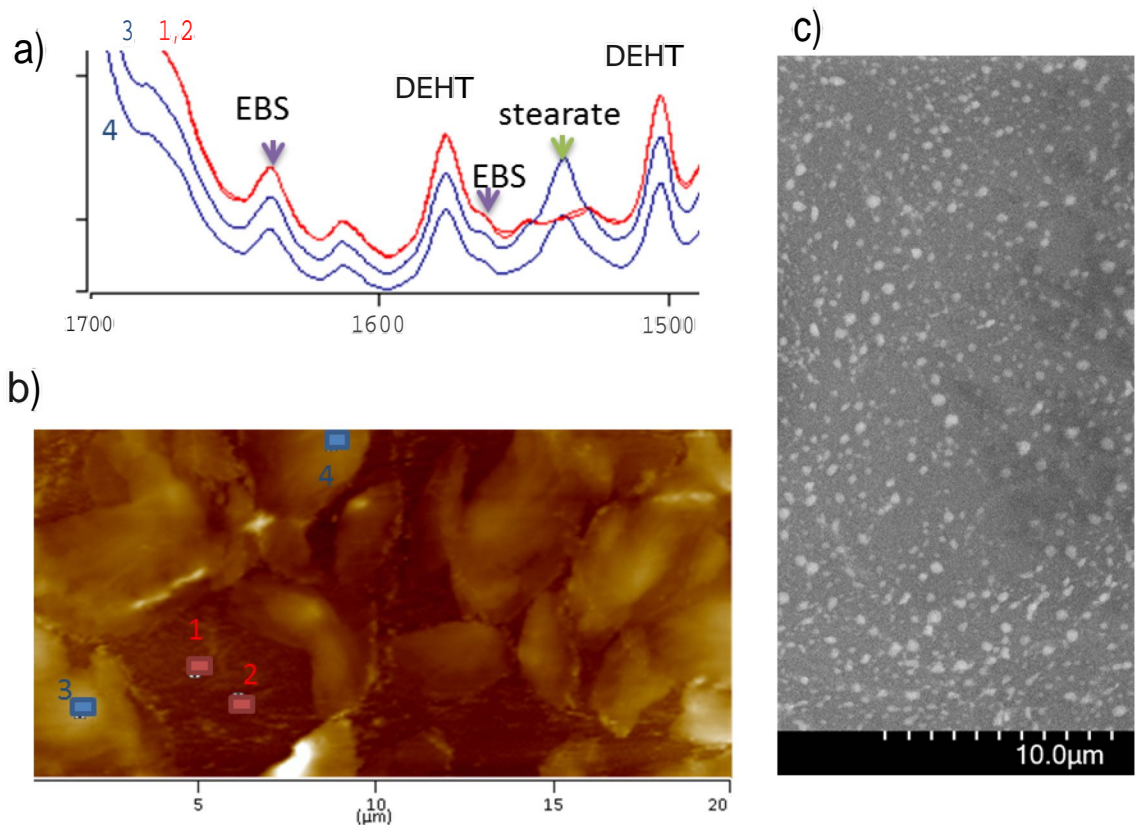
171

172 For Infusomat® the layer shows the same kind of needle- like structure previously
 173 observed but with a lower density of these needles (fig 3). The rms roughness of the
 174 surface was 7.1 ± 1 nm for R_q and 5.3 ± 0.9 nm for R_a ($10 \times 10 \mu\text{m}^2$).



175
 176 **Figure 3:** AFM images in tapping mode (height and phase) of the internal layer of the
 177 Infusomat® tube. Scan sizes are either a) $10 \times 10 \mu\text{m}^2$ or b) $5 \times 5 \mu\text{m}^2$

178
 179 It was previously showed that these layers were made of bis-amide lubricant (EBS) and
 180 of zinc and calcium stearates ¹, which are additives contained in PVC able to bloom and
 181 recrystallize onto the surface. The repartition of the different compounds however is not
 182 easy to characterize because of the small thickness of the bloomed layer. Thanks to the
 183 Intrafix® tube analysis by nanoIR and SEM backscattered electrons (fig. 4), it is however
 184 possible to see that the composition of the layer may change very locally, with some area
 185 much or less rich in metallic stearates.



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Figure 4: a) Local IR spectra obtained on the surface of Intrafix using IR

nanospectroscopy, AFMIR b) AFM height image of the surface with dots corresponding

to the spectra c) backscattered electrons SEM image of Intrafix intern lumen. Three

contrasted zones appear in the images; the brighter correspond to the higher atomic

numbers; the different area may be due to the repartition of Zn stearates ($Z_{Zn}=30$),

calcium stearates ($Z_{Ca}=20$) and lubricant (only C, O and N atoms)

193

Impact of pinch and roller clamps

194

The topography (roughness and texture) was impacted by the mechanical stress but

195

it may differ depending on the initial layer topography and on the nature of the clamp

196

used. For example, the pinch clamp has a trend to increase the roughness (fig 5.a.b)

197

and to locally dislocate the layer with significant parts of it that were clearly detached from

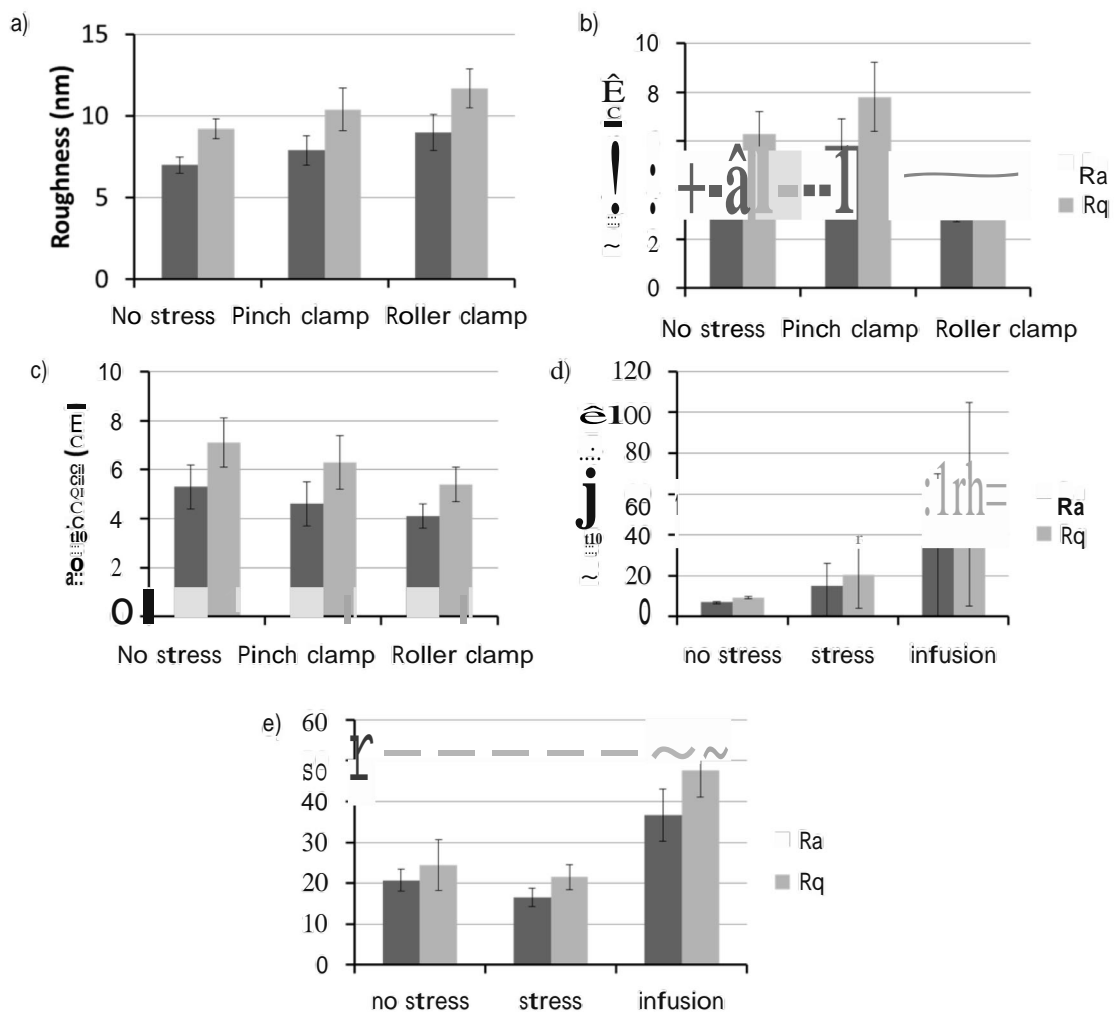
198

the PVC surface (this can be seen by analyzing conjointly phase and height images on

199

the fig 2; the area of lower height are not in the same color in the phase image

200 suggesting it is only bare PVC surface and no more a bloomed additive layer). This was
 201 true for Intrafix® and Volumat® layers. However, this was not the case for the Infusomat®
 202 layer: the kind of needle-like structure seems to be crushed, flattened and it seems that
 203 no part of the layer was removed (fig 3). As a consequence, in this case, the roughness
 204 was slightly decreased (fig 5c). In a general way, the crushing of the tubing by roller
 205 clamp has a trend to reduce the roughness by crushing, flattening and smoothing
 206 efficiently the layer (fig 2-3). This was very significant for Infusomat® and Volumat®
 207 tubing: the layer was much more homogenous and uniform after crushing (fig 2c.d-5)
 208 and the roughness decreased from 25%-30% for R_q (fig 5 b.c). This decrease in
 209 roughness was not observed for Intrafix®, because, by crushing the surface, the very
 210 smooth initial surface of nodules was lost because of their fragmentation by the stress
 211 (see phase and height images of the fig.2.a.b).

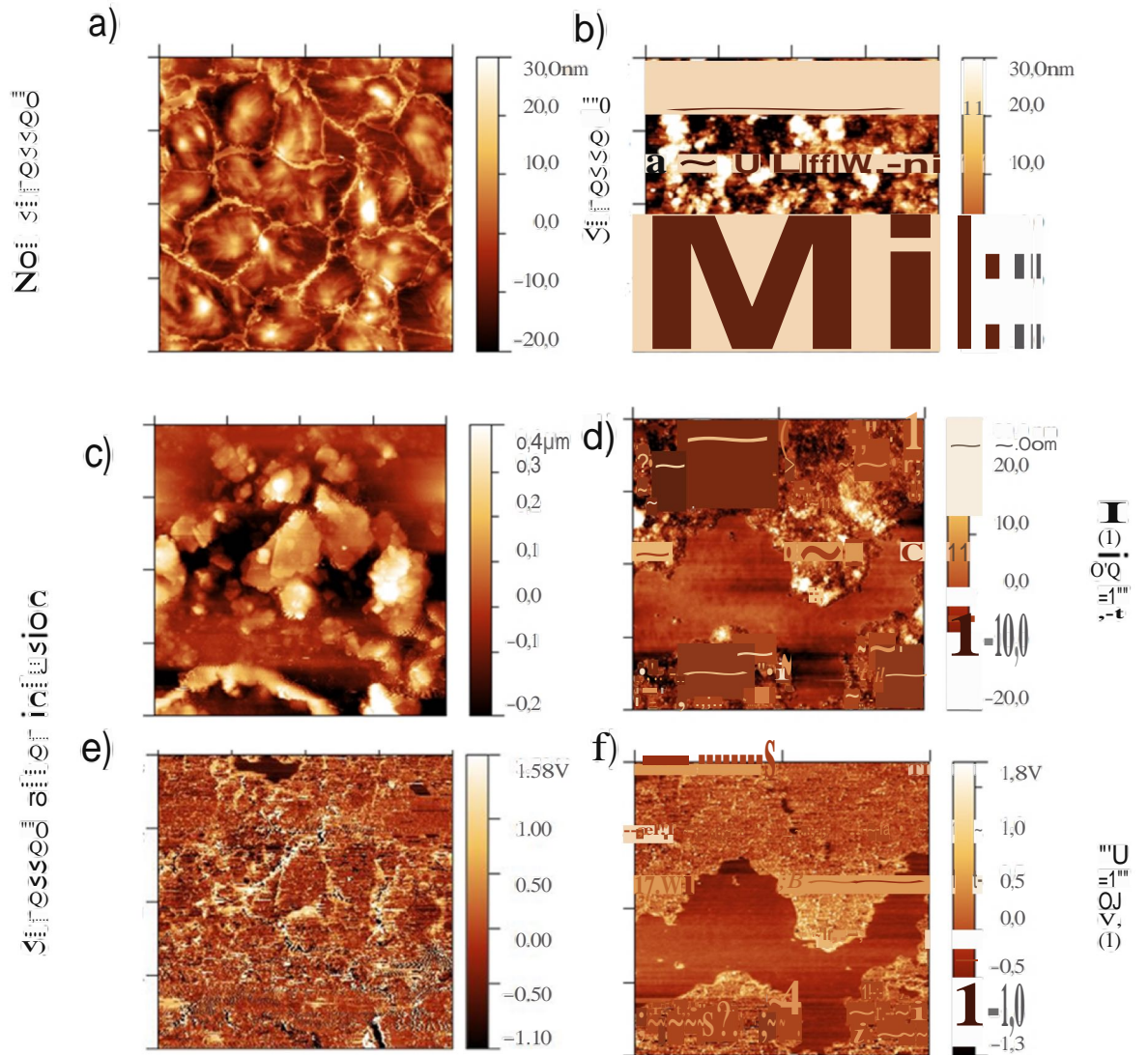


213 Figure 5: Roughness Ra and Rq of the inner surface a) for stressed and not stressed Intrafix®
214 20*20 μm² b) for stressed and not stressed Volumat® 20*20 μm² c) for stressed and not
215 stressed Infusomat® 10*10 μm² d) for stressed Intrafix® before and after infusion 20*20 μm²
216 e) for stressed Infusomat® before and after infusion 10*10 μm²

217

218 Impact of both mechanical stresses followed by water injection into the tubing on the
219 surface morphology

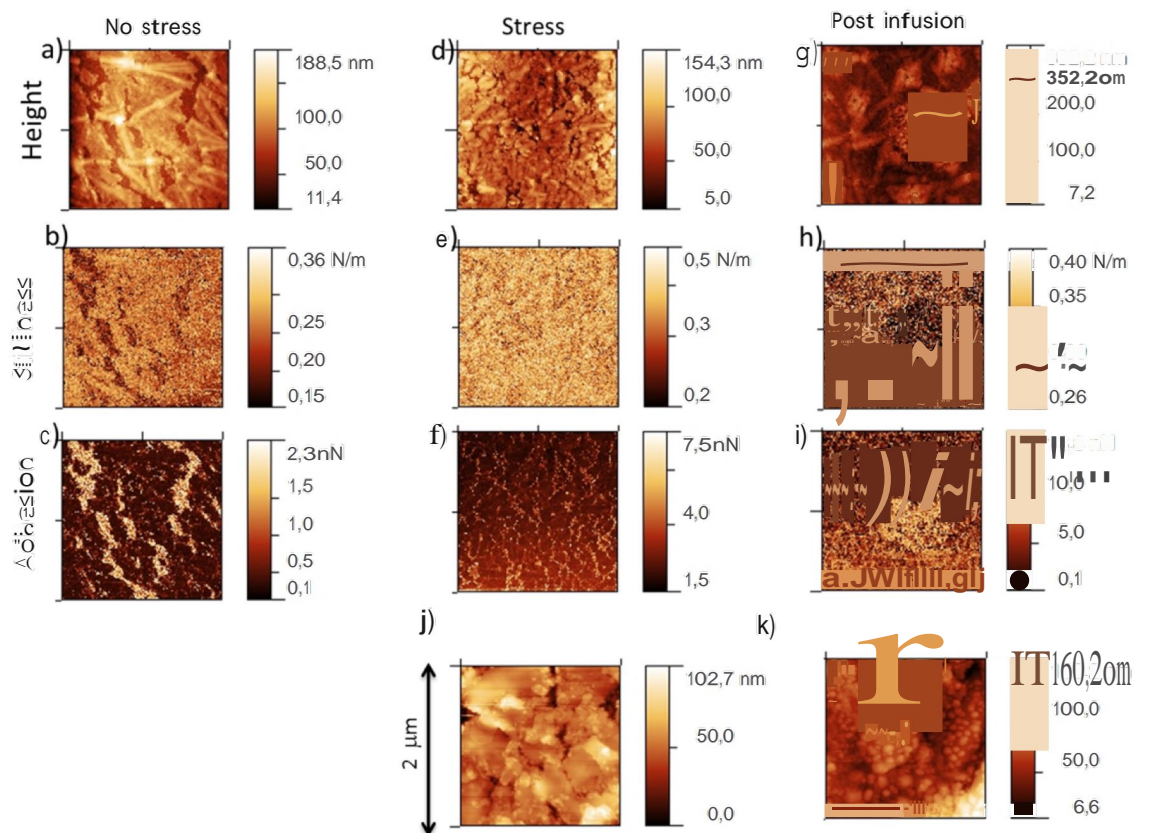
220 Intrafix®, for which both stresses conduct to a higher roughness and
221 Infusomat® for which the opposite trend was observed, were subjected successively
222 to both clamp stresses and then water was injected into the tubing. The appliance of
223 the mechanical stresses led to the same trend as before: the stress on the smooth
224 nodules of the Intrafix® layer led to a rougher and more heterogeneous surface (fig 5d
225 and 6b). On the contrary, the Infusomat® layer was flattened and smoothed (fig 5e
226 and 7d). this flattening was very clear on the force images (fig.7), because initially
227 there were some kinds of crazes (fig 7a) in the layer of the studied tube; we observed
228 on fig 7b and 7c that these crazes correspond to areas that were less rigid and have
229 a higher interaction with the tip and thus may be characteristic of bare PVC surface.
230 After mechanical stress, the crazes tend to disappear (fig 7 d-f).



231
 232 **Figure 6:** AFM images in tapping mode of the internal layer of the Intrafix® tube 20*20
 233 μm^2 . a) Height image of the initial state b) height image after stress and before
 234 infusion c-d) height images of different areas after stress and infusion e-f) Phase
 235 image corresponding to the height images after stress and infusion

236
 237 However, after the water injection, an increase in roughness was clearly
 238 observed for the both tubes (fig 5 d,e). Their surfaces become much more chaotic,
 239 with the presence of big deposits (fig 6 c and 7g). Surface state may change a lot
 240 between two areas and it explained the great dispersity of the roughness in particular
 241 for Intrafix® tubing. Moreover in the case of Intrafix®, we observed several areas for

242 which the additive layer was in part detached after the infusion (fig 6 d-f); this was
 243 suggested by the comparison of height image 6d to its phase image 6f: lower height
 244 and smoother area on the height image appear darker on the phase image, showing
 245 the nature of the surface has changed and may correspond to a bare PVC surface
 246 (unfortunately it was not possible to properly image Intrafix® in the force imaging
 247 mode because of disruptive interactions between the tip and surface); by using 6d
 248 image, the additive layer thickness can be estimated to only a few dozen of
 249 nanometers. For Infusomat®, big deposits observed had different properties than the
 250 layer before infusion: they were less stiff and had higher interactions with the AFM tip
 251 (fig 7 h.i), certainly because of a lower hydrophobicity. Moreover, at a small scan size,
 252 we observed that the residual layer of Infusomat® became very different in texture
 253 with small nodules on its surface (fig 7.j,k). However, no bare PVC surface was put
 254 into evidence on the Infusomat® sample.

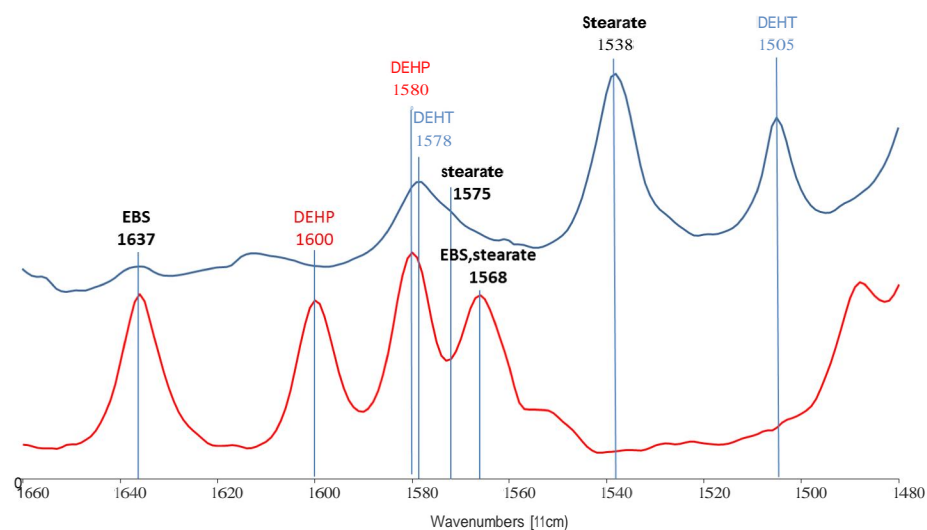


255

256 **Figure 7:** Infusomat® tube a-k) AFM images in force imaging mode of the internal layer of the
257 tubing. a-c) Initial state d-f)) after both stresses pre infusion g-i)k) after both stresses post
258 infusion.; a, d, g, j, k are height images ; b, e, h are stiffness images and c,f, i are adhesion
259 images. Scan size is 10*10 μm^2 except for j) and k) ($2*2 \mu\text{m}^2$)

260 FTIR-ATR analysis

261 We focused on the analysis on the 1660-1500 cm^{-1} range because there are
262 characteristic bands of the lubricant (1637 cm^{-1}) and of the metallic stearates (Ca:
263 1535+1574 cm^{-1} , Zn: 1535 cm^{-1}) in this range. The band positions for stearates are
264 however very dependent on the crystalline state and the formation of complexes^{15 16}
265¹⁷. As the analysis was performed in ATR mode, it focused on an area close to the
266 surface and was useful to put into evidence the additive blooming. For the tubing
267 batches studied in this paper, the FTIR spectra are given on figure 8. For Intrafix®, we
268 observed a small band for EBS at 1637 cm^{-1} and two bands at 1574 and 1538 cm^{-1}
269 that can be attributed to metallic stearates. For Infusomat®, a band was clearly
270 observed for the lubricant at 1537 cm^{-1} ; moreover some bands were observed at
271 1568 and 1555 cm^{-1} which can be attributed to EBS or mix of stearates complexes
272 and EBS. The bands were normalized by using a plasticizer band (DEHP band at
273 1580 cm^{-1} for Infusomat® and DEHT band at 1578 cm^{-1} for Intrafix®) and we compared
274 the band ratio A_{1537}/A_{1574} for Intrafix® and the band ratio A_{1537}/A_{1568} for Infusomat®.



275

276 *Figure 8: FTIR-A TR spectra of Intrafix® (top blue spectrum) and Iniusomet®*
277 *(bottom red spectrum) in the 1660-1480 cm⁻¹ range.*

278 By working on different parts of a same tube and on different tubes, we
279 observed variations in the precedent band ratios; it should be noticed that the
280 absorbances of the plasticizer band were quite similar on a same sample: for
281 example, the variation coefficient (standard deviation, divided by the absolute value of
282 the arithmetic mean) for the DEHT band absorbance was below 6% for each sample
283 (before and after stress, before and after infusion); moreover we do not correlate an
284 evolution of this band absorbance with the treatment of the tube (infusion, stress...):
285 the coefficient for all the values of this band absorbance observed on the different
286 parts of a same tube were below 6% too. The band ratio variations can be mostly
287 correlated to the significant variations of the stearate and EBS band absorbance even
288 before infusion for the not stressed samples: the variation coefficient was between 10
289 to 64 % for the stearate depending on the sample and between 5 and 117% for EBS.
290 These variations occur certainly because of thickness variations of the bloomed
291 additive layer along the tube. As a consequence, it was not possible to put into
292 evidence significant variations of the mean absorbance of the bands of the bloomed
293 species after stress, infusion or stress and infusion. In some cases, for the stressed
294 Intrafix® tube after infusion, some areas without bloomed additive layer were
295 analyzed, but in most cases, the layer was always present on the sample. Moreover
296 the surface analyzed was much bigger than for AFM (crystal size=2000*2000
297 microns, that is to say 10 000 times higher than our bigger images in AFM): so it is
298 possible that small fragments (only several micrometers wide and several dozen of
299 nanometers thick) detached from the layer that we observed by AFM does not impact
300 in a significant way the band absorbance of the bloomed additives.

301

302 **Conclusion**

303 This study proves that the internal layer of infusion tubing made of bloomed lubricant
304 and stearates is quite fragile and can be damaged by the stress exerted by the clamps
305 during the infusion act. It must be kept in mind that this stress is not only applied once on the
306 tubing, because readjusting the flow rate is necessary during infusion for several reasons:
307 bent or kinked tubing, venous pressure change, decreasing fluid volume in the bottle, and
308 change in arm position... Flow rate has to be checked hourly and adjusted if necessary.
309 Moreover, as the rate is readjusted, the clamp should be repositioned along the tubing on a
310 new part of it, because of the cold creep of the plastic that can have a pinched section ¹⁸.
311 This means that, during one infusion, the internal layer will be damaged in several parts of
312 the tubing, increasing the risk of leaching solid particles into the solution. It was indeed
313 shown in this paper that injecting water into the damaged tubing may increase the risk of
314 detaching parts of the internal layer and increase the level of particulate contamination.
315 However, several points have to be further studied, such as the impact of water contact time
316 and flow inside the tubing; moreover this contamination can be difficult to be put into
317 evidence by classical methods recommended by pharmacopeia, due to the potential very
318 small size of detached layer part. Further studies must be conducted to try to evaluate if the
319 particle leaching is significant compared to other sources of contamination.

320

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324

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