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

Johanna Saunier[1], Christian Marlière[2], Alexandre Dazzi[3], Ariane Deniset-Besseau[3], Najet Yagoubi[1]

[1] Université Paris-Saclay Matériaux et santé, 92296, Châtenay-Malabry, France.

[2] Université Paris-Saclay, CNRS, Laboratoire de Physique des Solides, 91405, Orsay, France.

[3] Université Paris-Saclay, CNRS, Institut de Chimie Physique, UMR 8000, 91405, Orsay, France.

Corresponding Author: J.Saunier

Email: johanna.saunier@universite-paris-saclay.fr

Abstract

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

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

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

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

Keywords

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

Introduction

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

suspected it to conduct to a particulate contamination of the infused solution. This particulate contamination is potentially harmful to the patient: depending on the particle's size and shape, on the patient's health and age, it may damage different organs; it may lead to a thrombo-embolization or to the formation of granulomas [2 3 4 5]. Moreover, during the infusion, mechanical stress on the tubing can occur because of the use of clamps. Pinch and slide clamps are used to stop the flow by pinching very locally the tubing (fig 1a). Roller clamps are equipped with a small roller which allows the tube to be more or less crushed in order to incrementally occlude it (fig. 1b). This allows a regulation of the flow rate by defining the size of the tubing lumen. Both kinds of clamps can be found on the same set (fig 1c). The aim of this paper was to characterize the effect of both kinds of clamp stresses on the layers found on the internai wall of PVC infusion tubes and the consequences of water injection into the tubing after this stress: we suspected it may lead to a potential higher and faster degradation of the layer with a higher risk of particulate contamination. Indeed, the effect of repeated compression of plastic tubing was studied in the case of hemodialysis circuit [6]; because of the high and complex stress exerted by the peristaltic pump, cracks were observed on the plastic surface and particles were then shed from these defects because of the shear stress exerted on the inner wall of the tubing [7 8 9 10]. These particles may then be injected into the bloodstream. This complication is well known in dialysis when using silicone tubing and is called spallation; it was studied by several authors mainly between 1980 and nowadays; it can be implicated in brain dysfunction, granulomatosis hepatitis, macrophage activation... long-term treated patients could show up to 250 mg of silicone particles lodged in organs because of the use of silicone tubing [11 12]. But, the PVC used to replace it produces particles too: they were mainly below 5 µm in diameter but they can reach 50 µm [13]. Moreover, in another publication, Madsen et al. [14] advised against the stripping of PVC infusion sets with a pair of scissors, by compressing the tubing between the thumb and a scissor blade, a clinical practice used to manage with flow malfunctions: because of this, an increased number of particles (5 to 100 µm) in the infused liquid were detected.

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

Material and methods

Material

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

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

Table 1: dimensions of the tubes used

Mechanical stress

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

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

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

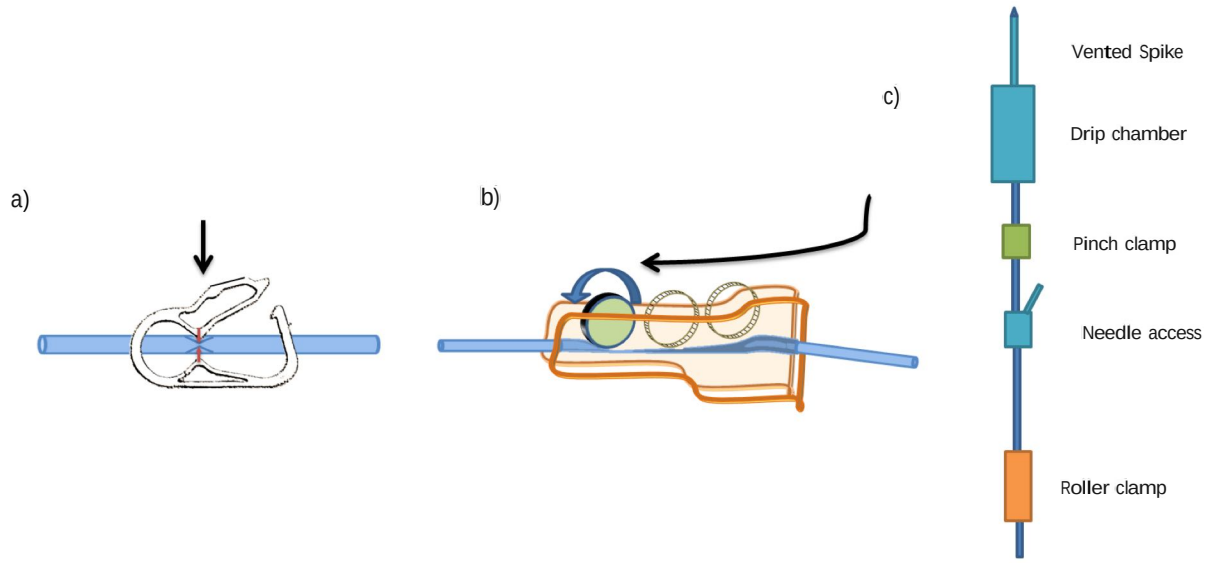

Figure 1: a) pinch clamp that allows stopping the flow by pinching the tube between two jaws b) roller clamp: the drawing shows the movement of the roller along the tube which it crushes progressively to regulate the flow rate c) example of placement of clamps on a standard primary set (Volumat®VLST22)

AFM

Tapping mode

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

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

Force imaging mode

The AFM used was a Nanowizard III (JPK Instruments AG, Berlin, Germany) using Quantitative Imaging® (QI) mode which is a force curve imaging mode. Force distance curve was realized for every pixel of the image. The probes were CSC 37 (Micromasch, stiffness around 0.35 N/m).The stiffness data were calculated from the slope of the force versus scanner elongation curves in the repulsive regime. For every point, the maximum applied force (set-up value) to the sample was 2nN. This analysis was used for studying the impact of water injection on stressed tubes because by using adhesion and stiffness measurements it is possible to easily identify the areas where the additive layer was removed. It was indeed showed in a precedent paper[1] that polymer surface was softer but has a higher interaction with the tip as compared to the bloomed additive layer.

FTIR-ATR

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

IR nanospectroscopy, AFM IR

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

The spectra were collected with 1 cm'' spectral resolution.

SEM

A FlexSEM 3000 (Hitachi) was used in back scattered electron mode (15 kEV) to image the internai lumen surface of the tube

Results and discussion

Initial texture of the layer

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

As we mentioned above, compared to the morphologies observed in a precedent publication[1], we observe similar but not identical structures. For the Intrafix® sample (fig 2.a.b) big ovoid and smooth nodules (20-30 nm high) were still present (mostly-around 3-6 µm in length and 2 µm in width), surrounded with thin protrusions (less than 0.2 to 1 µm wide and between 20-50 nm high) ; the rms roughness was equal to 9.5 ± 0.6 nm for Rq and 7 ± 0.5 nm for Ra (20*20 μm^2). For Volumat®, a kind of network of protrusions (5-10 nm high and less than 1 µm wide) was observed but the layer was less uniform and smooth than the samples previously analyzed from another batch (fig 2.c d): the roughness was 6.3 ± 1.4 nm for Rq and 4.6 ±1.1 nm for Ra (20*20 μm^2).

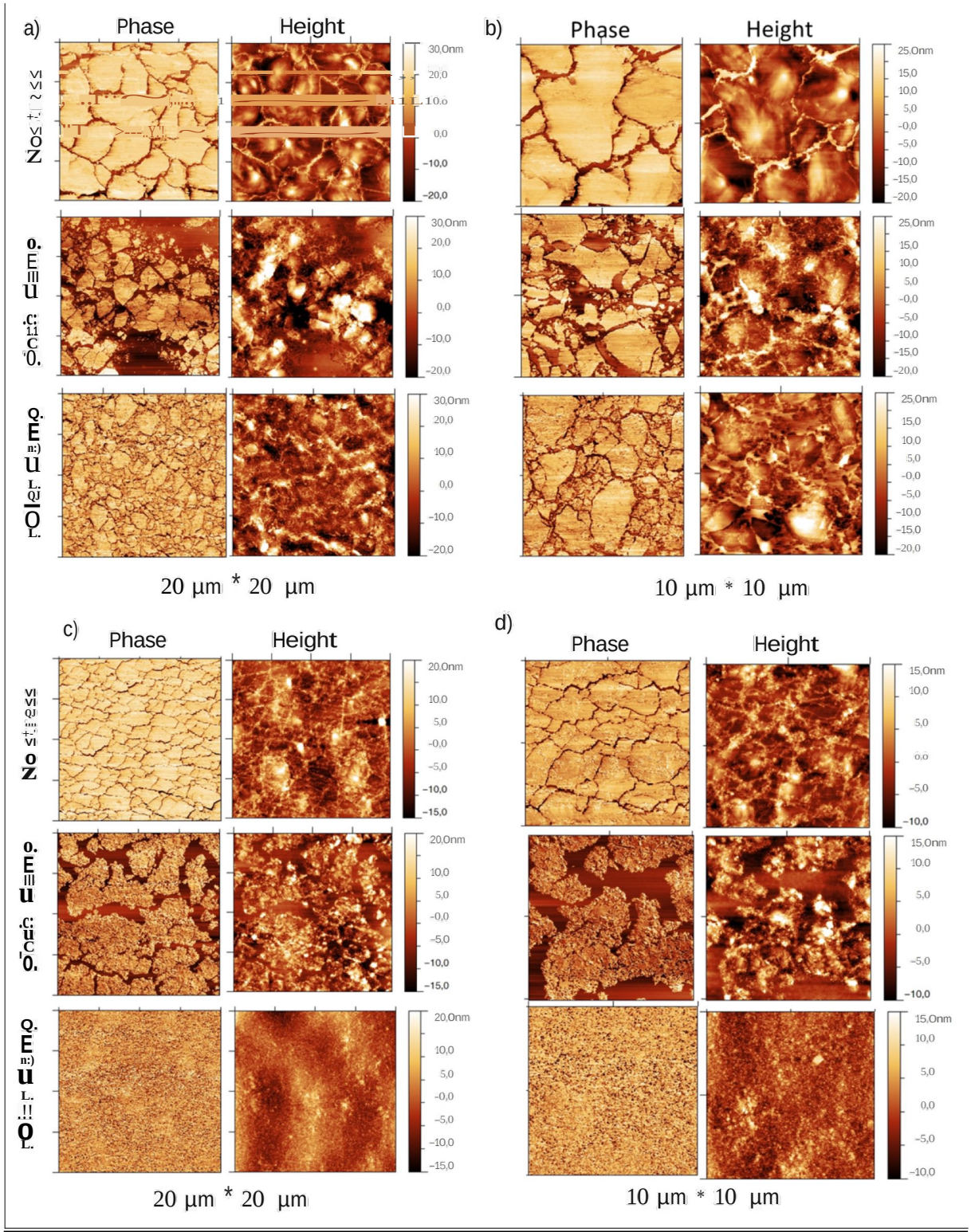

Figure 2: **AFM** images (height and phase) in tapping mode of the internal layer a) of the Intrafix® tube 20*20 µm^2. b) of the Intrafix® tube 10*10 µm^2 c) of the Volumat® tube 20*20 µm^2 d) of the Volumat® tube 10*10 µm^2

For Infusomat® the layer shows the same kind of needle- like structure previously observed but with a lower density of these needles (fig 3). The rms roughness of the surface was 7.1 ± 1 nm for Rq and 5.3 ±0.9 nm for Ra (10*10 µm^2).

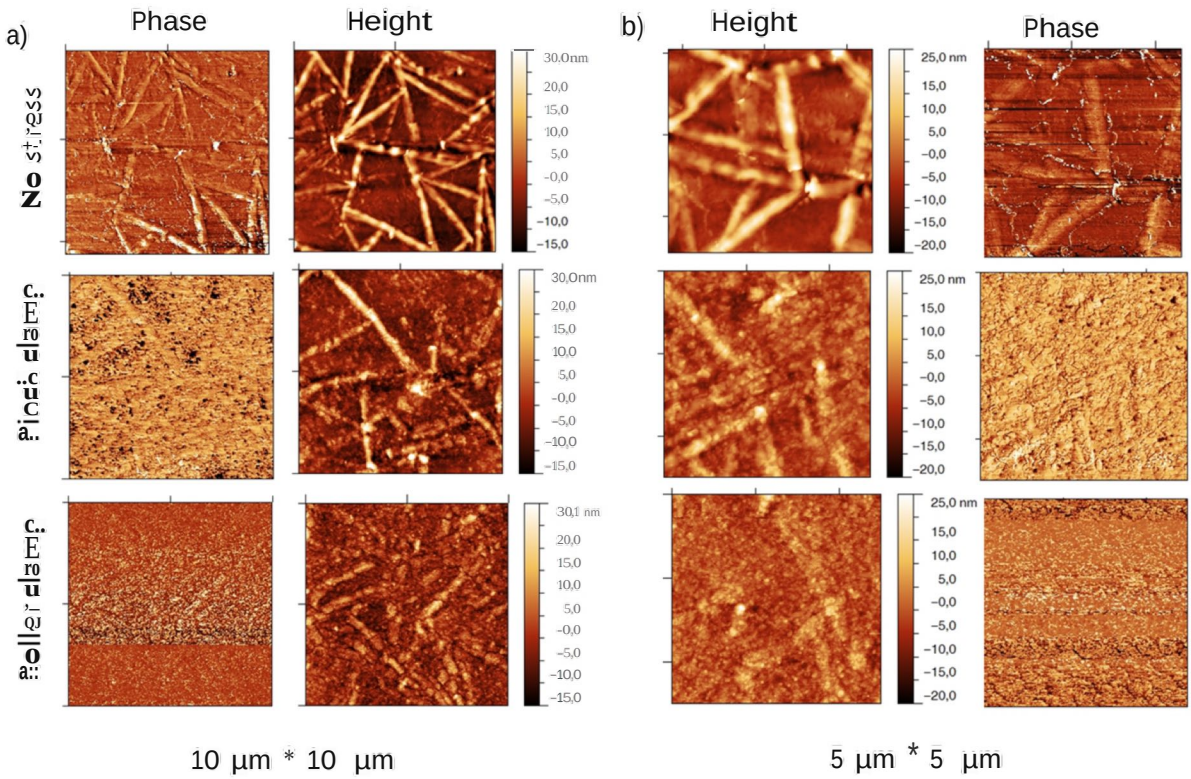

Figure 3: AFM images in tapping mode (height and phase) of the internal layer of the Infusomat® tube. Scan sizes are either a) 10*10 µm^2 or b) 5*5 µm^2

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

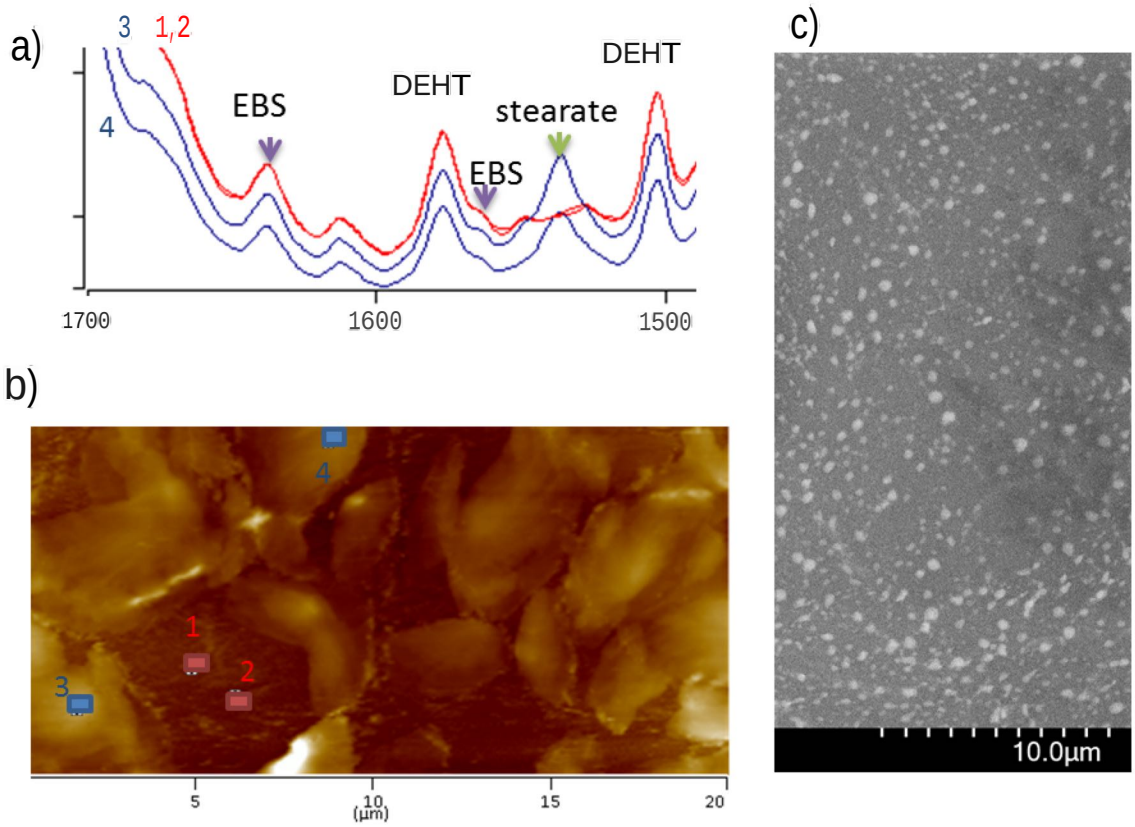

Figure 4: a) Local IR spectra obtained on the surface of Intrafix using IR nanospectroscopy, AFMIR b) AFM height image of the surface with dots corresponding to the spectra c) backscattered electrons SEM image of Intrafix intern lumen. Three contrasted zones appear in the images; the brighter correspond 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)

Impact of pinch and roller clamps

The topography (roughness and texture) was impacted by the mechanical stress but it may differ depending on the initial layer topography and on the nature of the clamp used. For example, the pinch clamp has a trend to increase the roughness (fig 5.a.b) and to locally dislocate the layer with significant parts of it that were clearly detached from the PVC surface (this can be seen by analyzing conjointly phase and height images on the fig 2; the area of lower height are not in the same color in the phase image

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

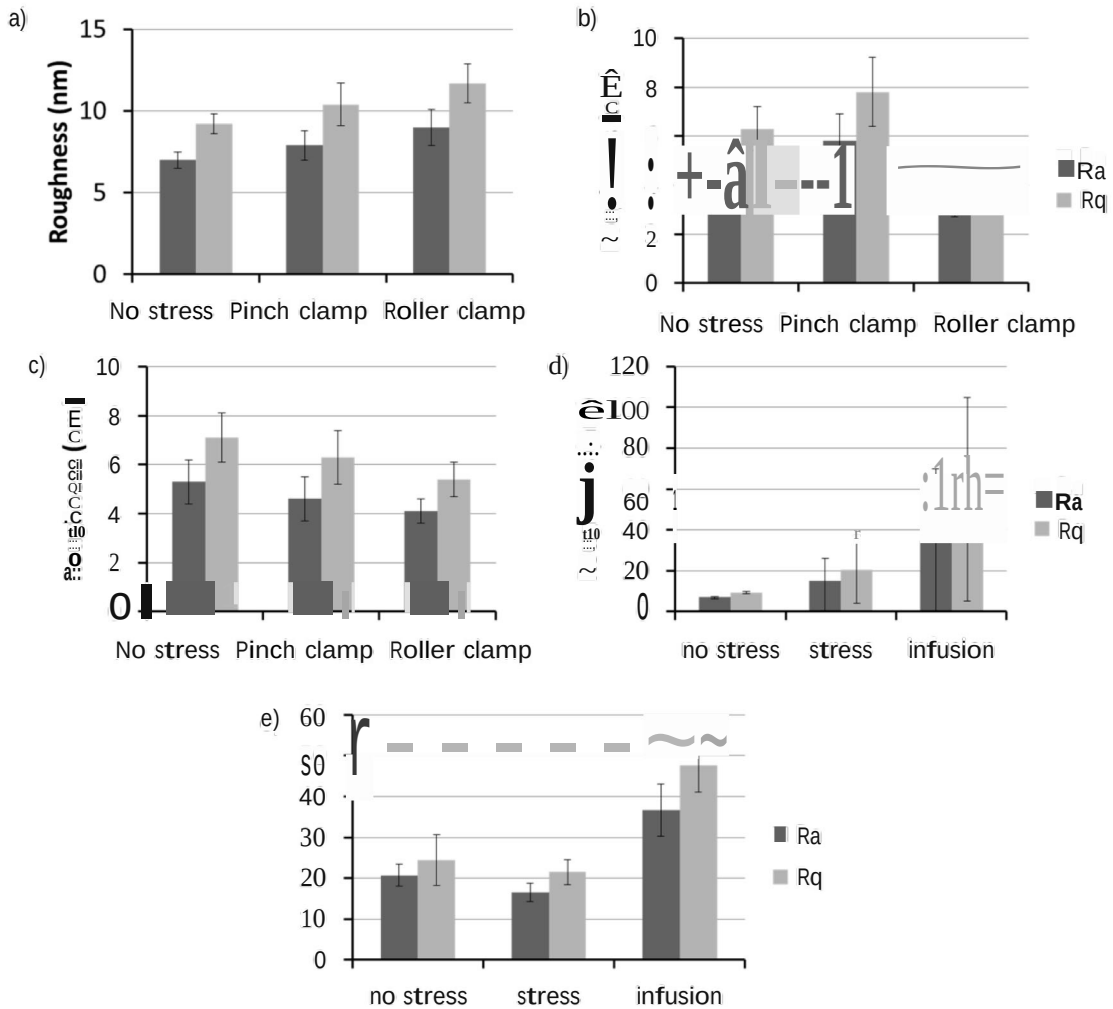

Figure 5: Roughness Ra and Rq of the inner surface a) for stressed and not stressed Intrafix® 20*20 µm^2 b) for stressed and not stressed Volumat® 20*20 µm^2 c) for stressed and not stressed Infusomat® 10*10 µm^2 d) for stressed Intrafix® before and after infusion 20*20 µm^2 e) for stressed Infusomat®before and after infusion 10*10 µm^2

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

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

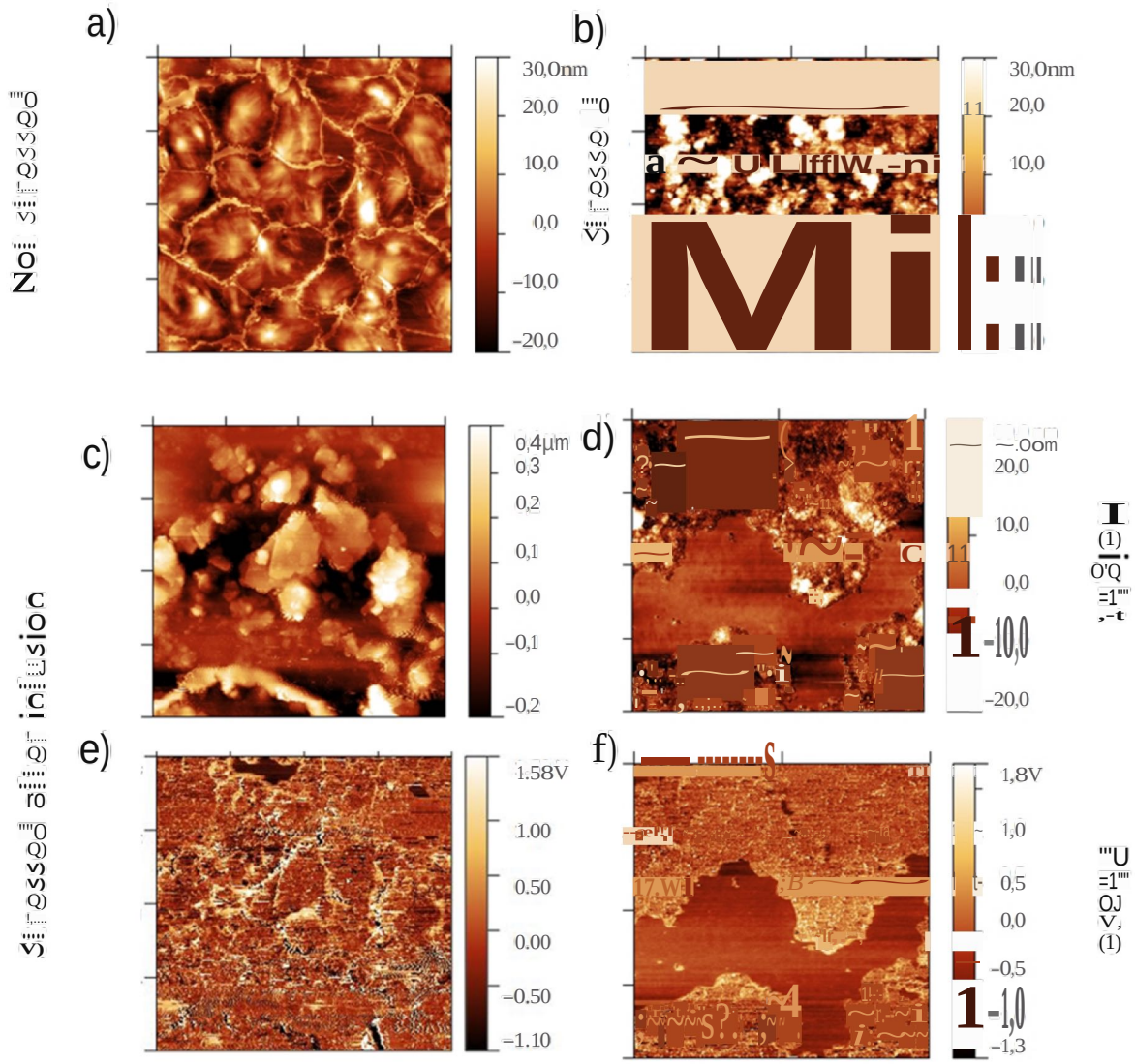

Figure 6: AFM images in tapping mode of the internal layer of the Intrafix® tube 20*20 µm^2. a) Height image of the initial state b) height image after stress and before infusion c-d) height images of different areas after stress and infusion e-f) Phase image corresponding to the height images after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

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

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

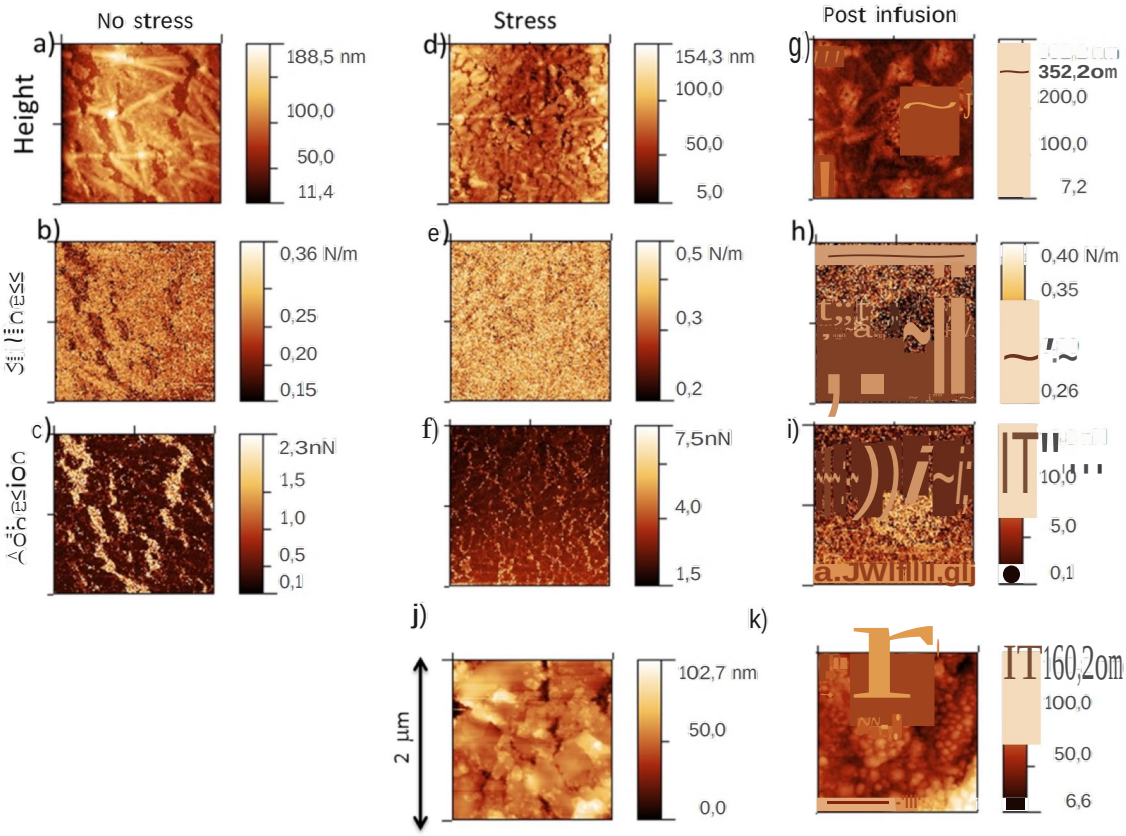

Figure 7: Infusomat® tube a-k) AFM images in force imaging mode of the internal layer of the tubing. a-c) Initial state d-f)j) after both stresses pre infusion g-i)k) after both stresses post infusion.; a, d, g, j, k are height images ; b, e, h are stiffness images and c,f, i are adhesion images. Scan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

FTIR-ATR analysis

We focused on the analysis on the 1660-1500 crn' range because there are characteristic bands of the lubricant (1637 cm') and of the metallic stearates (Ca: 1535+1574 crn', Zn: 1535 cm') in this range. The band positions for stearates are however very dependent on the crystalline state and the formation of complexes [15 16 17]. As the analysis was performed in ATR mode, it focused on an area close to the surface and was useful to put into evidence the additive blooming. For the tubing batches studied in this paper, the FTIR spectra are given on figure 8. For Intrafix®, we observed a small band for EBS at 1637 crn' and two bands at 1574 and 1538 crn' that can be attributed to metallic stearates. For Infusomat®, a band was clearly observed for the lubricant at 1537 crn'; moreover some bands were observed at 1568 and 1555 cm'' which can be attributed to EBS or mix of stearates complexes and EBS. The bands were normalized by using a plasticizer band (DEHP band at 1580 crn' for Infusomat® and DEHT band at 1578 crn' for Intrafix®) and we compared the band ratio A1537/A157a for Intrafix® and the band ratio A1537/A15a0 for Infusomat®.

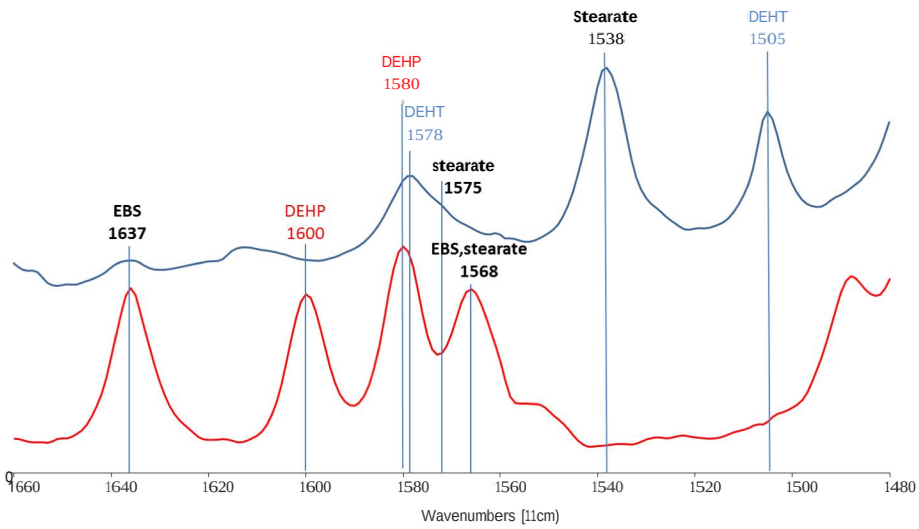

Figure 8: FTIR-ATR spectra of intrafix® (top blue spectrum) and tnîusomet® (bottom red spectrum) in the 1660-1480 cm⁻¹ range.

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

Conclusion

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

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