Effective inhibition of the early copper ion burst release by purine adsorption in simulated uterine fluids

Concepción Alonso[a,*], Elena Casero[b], Elisa Román[c], Sara F.-P. Campos[a],
Mónica Fernández Lorenzo de Mele[d,e]

[a] Departamento de Química Física Aplicada, Facultad de Ciencias, c/Francisco Tomás y Valiente, N°7, Campus de Excelencia de la Universidad Autónoma de Madrid, 28049 Madrid, Spain
[b] Departamento de Química Analítica y Análisis Instrumental, Facultad de Ciencias. c/Francisco Tomás y Valiente, N°7, Campus de Excelencia de la Universidad Autónoma de Madrid, 28049 Madrid, Spain
[c] Instituto de Ciencia de Materiales de Madrid (CSIC), c/Sor Juana Inés de la Cruz N°3, Campus de Excelencia de la Universidad Autónoma de Madrid, 28049 Madrid, Spain
[d] Instituto de Investigaciones Fisicoquímicas Teóricas y Aplicadas (INIFTA, CCT-CONICET La Plata), Departamento de Química, Facultad de Ciencias Exactas, Universidad Nacional de La Plata, CC 16, Suc. 4 (1900), La Plata, Argentina
[e] Facultad de Ingeniería, Universidad Nacional de La Plata, Calle 47 y 1, (1900), La Plata, Argentina

ABSTRACT

Burst release of ions from copper-based intrauterine devices (IUD) occurs during the first day after the insertion in uterus and may induce side effects in the users. In the present work, we investigate the mechanism of the inhibitory action of ex-situ pretreatment of copper samples with purine (10^{-2}-10^{-4} M PU) in simulated uterine fluids (SUF) with and without urea (UR). Quartz crystal microbalance measurements showed that the PU inhibition effect depends on the concentration and adsorption time increasing in presence of chloride. In particular, PU pretreatment (10^{-2} M-10^{-3} M) leads to an inhibition of copper ions release over 24 h immersion time in SUF, without and with UR. UR may act for a few hours as a weak corrosion inhibitor leading to temporary control of corrosion, but the protection decreases quickly due to formation of soluble Cu-UR complexes, being the total amount of released copper higher when UR is present.

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1. Introduction

Copper-based intrauterine device (IUD) is the most common form of reversible contraception [1]. IUD is effective for concentrations as low as 2 μg/day. However, it was reported that higher corrosion rates of these devices were obtained during the first one-three days (burst release) after immersion in simulated uterine fluid (SUF). Since the overexposure to copper ions may induce side effects in the users [2,3], it is neccesary to reduce the initial burst release effect by an ex-situ tratment with an inhibitor.

There are several interesting and detailed reports about the use of biocompatible inhibitors of metallic corrosion such as purine, adenine [4–8], some non-toxic polypirrole and imidazole derivatives [9,10], and some amino acids [11,12], including cysteine

[13,14]. In the latter case, the molecule contains the amino group besides the -SH group, which has a high affinity for copper, leading to the formation of a Cu (I)-cys film on the electrode surface resulting in better corrosion protection.

The effect of purine on copper corrosion was investigated profusely in different media as chloride [15], nitrate [8] and neutral and acidic sulfate media [6,7] as well as in alkaline sulfate solutions [5]. The results show that the inhibition efficiency increases as the purine concentration increases and PU is adsorbed on copper surface according to the Langmuir adsorption isotherm irrespective of the medium used. This research had as priority to produce "green" or environmentally "friendly" inhibitors for industrial purposes. The results obtained cannot be extrapolated for medical applications since the corrosion protection is maintained with an inhibitor-containing solution and in the absence of other biological components that may interfere with the inhibitory action.

In recent years has been investigated [16,17] the effectiveness of biocompatible organic inhibitors to reduce the initial burst release effect of copper ions in simulated uterine fluid for biomedical applications. Among these inhibitors, purine (PU), tiourea (TU),

pterin (PT) and 6-mercaptopurine (6-MP) were assayed and adequate inhibitory action was found with the exception of TU. Inhibitory efficiency values higher than 98% for pretreatments with 10^{-3} M PU were obtained. However, the mechanism that governs copper dissolution in SUF and its inhibition by the action of PU has not been elucidated and is probably complex since components of SUF such as chlorides, urea, carbonates and phosphates may interfere with the corrosion process on PU-treated copper surface.

The aim of this work is to investigate the mechanism by which copper ions release is inhibited in PU-treated copper immersed in SUF. With this purpose, quartz crystal microbalance (QCM), a fundamental tool able to sense PU adsorption and the mass change of copper during the immersion in SUF, was used. Measurements of electrochemical parameters such as polarization resistance (R_p), open circuit potential (OCP), reduction charges (Q) and XPS analysis were also employed to investigate in detail the effect of treatments with different PU concentrations on copper immersed in SUF.

2. Materials and Methods

2.1. Reagents and solutions

Synthetic uterine fluid (SUF), originally formulated by Zhang [18], has been widely used to test UID wires. SUF composition is as follows [19–21]: $NaHCO_3$ (0.25 g L^{-1}), NaH_2PO_4 2 H_2O (0.072 g L^{-1}), $CaCl_2$ (0.167 g L^{-1}), KCl (0.224 g L^{-1}), NaCl (4.97 g L^{-1}) and glucose (0.5 g L^{-1}). SUF + UR has the same composition, but it also contains urea (0.48 g L^{-1}). They were prepared with analytical grade chemicals and ultrapure water by means of a Millipore Milli-Q system (18.2 MΩ^{-1}). Assays with SUF and SUF+ urea (UR) were made. All measurements were made at 37.0 ± 0.1 °C, pH = 6.0.

PU (98% from Sigma Aldrich) was dissolved at concentrations in the range of 10^{-4}-10^{-2} M in 4.97 g L^{-1} NaCl solutions (pH = 6.8). PU treatments were performed in solutions at 25 °C ± 0.1°C.

2.2. Voltamperometric tests

Voltamperometric tests were performed using a potentiostat Autolab PGSTAT 30 EcoChemie with GPES 4.9 software.

The electrochemical cell with a three-electrode setup was used [22]. A platinum wire (99.99% purity) served as the auxiliary electrode. All the potentials were quoted with respect to Ag/AgCl reference electrode. Copper electrodes (99.99% electrolytic metal copper; Merck, area of 2.25 cm^2) were employed as working electrodes. They were polished with emery paper grade 1200 and rinsed with ultrapure water and dried with N$_2$.

Polarization curves were carried out with copper samples at v = 1 mV s^{-1} from the open circuit potential (OCP) in the cathodic direction up to -1.4 V in SUF (T = 37 °C and pH = 6.0). I/E curves were recorded after immersion in ultrapure water, NaCl solution (4.97 g L^{-1}), SUF or SUF + UR at 37 °C, for 24 h.

Copper samples were treated by immersion in a PU (10^{-4} M, 10^{-3} M or 10^{-2} M) NaCl solution (4.97 g L^{-1}) for 1 h and 3 h at 25 °C; samples without treatment were used as controls. OCP measurements were made during these treatments. Thereafter, cathodic polarization curves were performed in SUF (T = 37 °C and pH = 6.0) to determine whether corrosion occurred during the adsorption time of inhibitor. R_p values were calculated from the slope of polarization curves ($\Delta E/\Delta I$) obtained in SUF at 37 °C for a potential range around OCP ± 20 mV before and after PU treatment.

Additionally, cathodic polarization curves were performed after 24 h immersion in SUF and SUF + UR of copper samples, without and with PU pretreatment, to determine the inhibitory effect of the PU treatment after 24 h after immersion in SUF.

2.3. Quartz crystal microbalance (QCM)

QCM measurements were performed with a QCM200, Stanford Research Systems (SRS) quartz crystal microbalance. Commercial QCM Cu-crystals (Cu-QCM) of 25 mm diameter and 300 nm thicknesses (Maxtek Inc., Santa Fe Springs, CA) were used as the test specimens. The Cu-crystals were cleaned by rinsing with ultrapure water and drying with nitrogen. The Crystal Holder was connected to the QCM25Crystal Oscillator. The QCM probe was stabilized in air obtaining a frequency value close to 5 MHz. Subsequently, it was immersed in the working solution to measure the change of frequency (related to mass change) corresponding to:

a The copper corrosion during the immersion in pure water, NaCl solutions or SUF (without and with urea) for 24 h (T = 37 °C, pH = 6.0).
b PU adsorption on Cu during 1 h or 3 h periods at different concentrations (10^{-2}, 10^{-3} and 10^{-4} M in 4.97 g L^{-1} NaCl solutions (T = 25 °C, pH = 6.8).
c PU adsorption on Cu during 1 h or 3 h periods at different concentrations followed by 24 h of Cu immersion in SUF or SUF + UR (T = 37 °C pH = 6.0).

2.4. X-ray photoelectronic spectroscopy (XPS)

The XPS measurements were performed in an ultra-high vacuum (UHV) chamber with a base pressure of 1×10^{-10} mbar. The angle between the hemispherical analyzer (Specs-PHOIBOS100) and the plane of the surface was kept at 60° and the X-ray radiation was the Mg Kα line (1253.6 eV). The survey spectra were recorded with pass energy of 40 eV and an energy step of 0.25 eV. Narrow scans of C1s and Cu2p core levels and X-ray excited Cu LVV, were recorded using pass energy of 15 eV with an energy step of 0.1 eV. The binding energy (BE) scale was calibrated with respect to the C1s at 285 eV. The analysis of the XPS results was carried out with the Casa XPS software, using Gaussian with 30% Lorentzian for the fitting procedure. Before the XPS data were analyzed, the contribution of Mg Kα satellite lines was subtracted. XPS measurements were performed with the aim of studying the composition and chemical state of the copper surface:

1. Without any treatment.
2. After immersion in SUF for 24 h (T = 37 °C, pH = 6.0).
3. After immersion in SUF + UR for 24 h (T = 37 °C, pH = 6.0).
4. After immersion for 1 and 3 h in 4.97 g L^{-1} NaCl solutions containing different PU concentrations (10^{-2} M, 10^{-3} M and 10^{-4} M; T = 25 °C, pH = 6.8).
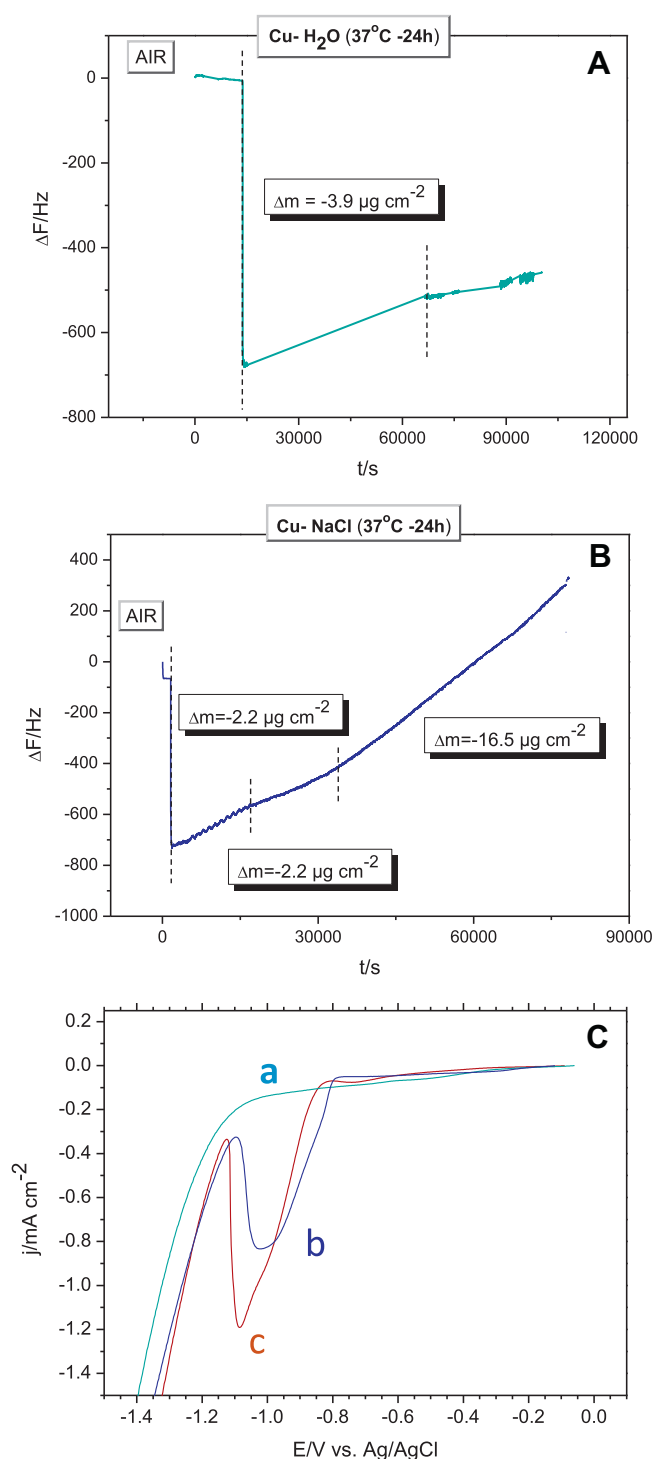
3. Results

3.1. Burst release of copper ions from copper surface

3.1.1. QCM and voltamperometric measurements

In order to follow the change of copper mass after immersion in SUF, it is interesting to make firstly a comparative study in water and NaCl solution [Fig. 1(A, B)]. QCM measurements were performed over a period of 24 h in these media. The change of mass over a period of 24 hours immersion in each medium was calculated using Sauerbrey equation [23].

Fig. 1A shows the variation of the oscillation frequency of a Cu-QCM crystal with immersion time in ultrapure water (T = 37°C, pH = 6). The typical decrease of frequency (ΔF = -776 Hz) associated with the immersion of a Cu-QCM crystal

A Cu- H$_2$O (37°C -24h)

AIR

Δm = -3.9 μg cm^{-2}

ΔF/Hz — t/s

B Cu- NaCl (37°C -24h)

AIR

Δm=-2.2 μg cm^{-2}

Δm=-16.5 μg cm^{-2}

Δm=-2.2 μg cm^{-2}

ΔF/Hz — t/s

C

a

b

c

j/mA cm^{-2} — E/V vs. Ag/AgCl

Fig. 1. Variation of the oscillation frequency of a Cu-QCM crystal with immersion time (24 h) in: (A) water and (B) NaCl 4.97 g L^{-1} (T = 37°C, pH = 6). (C) Cathodic polarization curves made at v = 1 mV s^{-1} in SUF at 37 °C after 24 h immersion in water (a) NaCl 4.97 g L^{-1} (b) and SUF (c).

in a liquid environment was observed. This value is similar to that obtained by Kanazawa and Gordon [24]. Subsequently, a progressive increase of frequency, resulted in a mass decrease (-3.9 μg cm^{-2}) after 24 h immersion period with an average corrosion rate v = 0.4 10^{-4} μg s^{-1} cm^{-2}.

Conversely, due to the well-known corrosive effect of chloride-containing media, when NaCl (4.97 g L^{-1}) is employed instead of water (Fig. 1B), a higher mass loss is obtained over the same period

(Δm = -20.9 μg cm^{-2}). It is important to highlight that results obtained from QCM inform about the total mass variation that it is taking place over the copper surface. This mass variation represents a balance between several processes: i) the initial formation of chloride-containing cuprous compounds [Cu(Cl)$_{ad}$, CuCl] that, after hydration, gives rise to the corresponding cuprous oxide/hydroxide [Cu$_2$O, Cu(OH)$_{ad}$] [25]; ii) possible precipitation of products from the solution [26]; iii) release of copper ions to the solution that is oxidized to Cu(II) in oxygen-containing solutions; These processes involve an increase and a decrease of mass, respectively. Then, a Δm value of -20.9 μg cm^{-2} indicates that the process related to the release of copper ions is the main one. As can also be observed in Fig. 1B, the evolution of the frequency with time shows three different regimes. The first one, going from 0 to 4 h, is characterized by an average corrosion rate v$_1$ = 1.6 10^{-4} μg s^{-1} cm^{-2}. After this period, from 4 to 8 hours, a small slope decrease is observed, corresponding to a corrosion rate v$_2$ = 1.5 10^{-4} μg s^{-1} cm^{-2}. Finally, after 8 hours, the corrosion rate increases reaching v$_3$ = 2.9 10^{-4} μg s^{-1} cm^{-2}. As expected, in all cases the corrosion rate was markedly higher than that obtained in water (v = 0.4 10^{-4} μg s^{-1} cm^{-2}).

In order to determine the reduction charge associated to the oxidized species formed on the electrode during 24 hours immersion period in water and NaCl solution, cathodic polarization curves from OCP to -1.4 V were made (Fig. 1C, curves a, b). A cathodic peak at -1.1 V could be distinguished in NaCl solution after 24 h immersion (curve b), but it was absent in pure water (curve a). This peak has been attributed to the reduction of Cu$_2$O that was obtained by hydrolysis of CuCl previously formed on Cu surface [25]. Considering that cathodic contributions were not evident when the immersion was made in pure water, it may be inferred that chlorides were directly involved in the formation of oxidized species, such as Cu(I), formed on Cu surface in chloride-containing solutions. On the other hand, the limiting current corresponding to oxygen reduction in aerated solutions decreased when corrosion products were formed on the surface.

After immersion of Cu-QCM in SUF (Fig. 2A), an initial decrease in frequency related to the environmental change from air to the liquid medium was detected, subsequently the frequency increased drastically during 4 hours, corresponding to a high mass loss (-42.8 μg cm^{-2} with a dissolution rate v = 29.7 10^{-4} μg s^{-1} cm^{-2}), which can be associated to the "burst release" effect. Afterwards, the corrosion rate diminished to 6.1 10^{-4} μg s^{-1} cm^{-2} and a maximum frequency value was reached after 8.5 h. Subsequently, frequency diminished, giving rise to a slight mass increase Δm = 1.1 μg cm^{-2}. After 24 hours immersion, a total mass loss of Δm$_T$ = -51.9 μg s^{-1} cm^{-2} was obtained.

The comparison between the behavior of Cu-QCM in NaCl (Fig. 1B) and SUF (Fig. 2A) leads to interesting conclusions. As mentioned above, the initial corrosion rate obtained in NaCl solution is lower than that obtained in SUF. Taking into account that pH and NaCl concentration are the same for both solutions, it is clear that the presence of other salts in SUF, such as NaHCO$_3$, NaH$_2$PO$_4$.2H$_2$O, KCl, CaCl$_2$, are responsible of this fact (see discussion). Notwithstanding that, after 4 hours of immersion, the corrosion rate diminishes in both cases (NaCl solution and SUF), for longer times important differences were observed. While the slope in NaCl solution has a positive value, indicating the progressive corrosion of copper, it takes a zero or even a negative value in SUF, indicating that a gain of mass due in part to the formation of copper oxidation products may be involved. This has been corroborated by cathodic polarization curves made after 24 h exposure in NaCl and SUF. As can be observed in Fig. 1C, reduction charge of copper oxidation products is higher in SUF (curve c) than in NaCl solution (curve b).
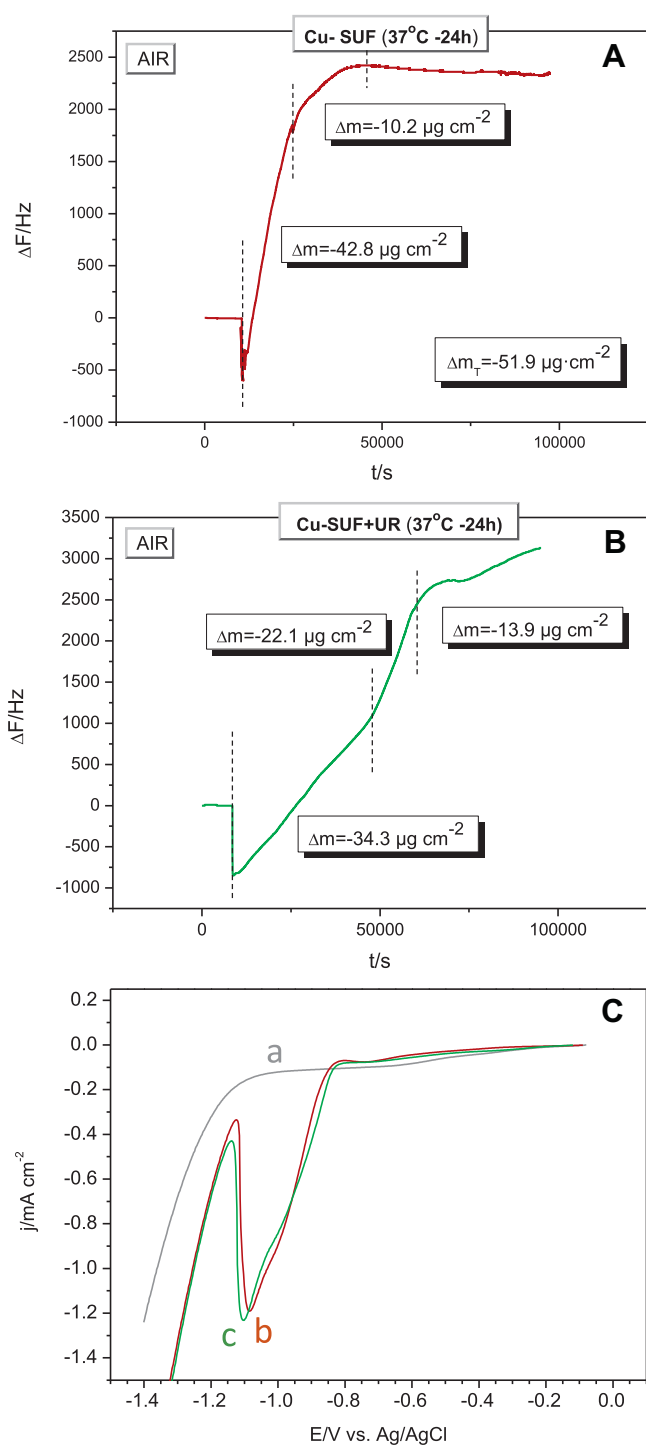
Fig. 2. Variation of the oscillation frequency of a Cu-QCM crystal with immersion time (24 h) in: (A) SUF and (B) SUF+UR (T = 37 °C, pH = 6). (C) Cathodic polarization curves made at v = 1 mV s^{-1} in SUF at 37 °C of a copper sample without previous immersion (a) and after 24 h immersion in: SUF (b), SUF+UR (c).

Marked differences in QCM measurements can be noticed if curves in the presence and in the absence of UR are compared. When UR was added to SUF (Fig. 2B), the curve shows that during the first 11 h the rate of mass loss (v = 8.6 10^{-4} µg s^{-1} cm^{-2}) was significantly lower than in SUF without UR (29.7 10^{-4} µg s^{-1} cm^{-2}). However, the inhibitory effect is temporary since during the next 4 hours the corrosion rate increased (v = 19.7 10^{-4} µg s^{-1} cm^{-2}) and finally decreased again (v = 8.1 10^{-4} µg s^{-1} cm^{-2}). This variable behavior resulted in a higher total mass loss after 24 h immersion

in UR-containing SUF (-70.3 µg s^{-1} cm^{-2}) than in the absence of UR (-51.9 µg cm^{-2}). This result seems to be in disagreement with that obtained from cathodic polarization curves (Fig. 2C, curves b, c) since a higher mass loss is produced after 24 hours immersion in SUF+UR, although the reduction charge is very similar in both media. Thus, the presence of UR seems to modify the rate of copper ions release with less significant changes in the formation of copper oxidation products.

3.1.2. XPS analysis

To gain a better understanding on the surface composition of Cu sample before and after immersion in SUF and SUF+UR, the Cu samples were examined by XPS spectroscopy. The Cu2 p regions of the spectra are shown in Fig. 3. Cu2 p displayed the characteristic Cu2p$_{3/2}$-Cu2p$_{1/2}$ spin-orbit splitting, whose peak-to-peak separation was around 20 eV. For better comparison straight line background was used. Before the immersion (Fig. 3A), the binding energy of the Cu2p$_{3/2}$ peak corresponds to 932.4 eV, and may be attributed to Cu°/Cu$^+$ value [27], but should be assigned mainly to Cu° due to the absence of the reduction peak under this condition. Additionally, Auger Cu LVV spectrum (Fig. 3D) shown the contribution due to Cu^0 (peak at 918.8 eV) which enable us to conclude that the mayor fraction of the copper surface was metallic.

Fig. 3B shows the spectrum obtained after the immersion of Cu in SUF. In this case, considering the presence of copper oxidation products formed because of immersion in SUF (Fig. 2C curve b), the Cu2p$_{3/2}$ peak (E$_B$ = 932.4 eV) can be attributed to Cu$^+$. Additionally, in Auger analysis (Fig. 3E), the Cu LVV peak shift to the values corresponding to Cu$_2$O, but leaving a contribution due to metallic copper on the surface. Moreover, the presence of satellite peaks (Fig. 3B) demonstrates the existence of thin layer of Cu^{2+} on the surface. XPS spectrum obtained after the immersion of Cu in SUF+UR (Fig. 3C) is similar to that obtained in SUF. Only Cu 2 p peaks broaden and the satellite peak intensity increases. The intensity of the satellites peak relative to that of the Cu 2p$_{3/2}$ peak can be considering as rough indication of the extent of oxidation to CuO. Besides, the attenuation of Cu^0 signal in the Cu LVV peak (Fig. 3F) indicates a thicker layer on top of the surface.

### 3.2. Inhibition of copper release by Purine

3.2.1. QCM measusments during PU treatments

As mentioned above, our main goal is to reduce the initial corrosion rate after the immersion of a copper surface in SUF. In this sense, in order to diminish the burst release of copper ions to the solution during the first 24 hours of immersion, we have treated the copper surface with an organic inhibitor, purine.

QCM measurements corresponding to immersion of a Cu-QCM in NaCl solution containing different PU concentrations (0, 10^{-2} M, 10^{-3} M and 10^{-4} M) at 25 °C for 1 h and 3 h were assayed. In order to discern the role of chlorides during the treatment, a similar measurement employing a 10^{-2} M PU dissolved in pure water was also carried out. The results are displayed in Fig. 4 and summarized in Table 1.

In the absence of PU, the decrease of frequency (increase in mass) measured after the immersion in NaCl solution for 3 h is very small (ΔF = -8 Hz, Δm = 0.1 µg cm^{-2}) and should be associated to the presence of corrosion products on the surface. However, this change is smaller than expected because frequency increases slightly for long immersion times due to the tendency of copper to be corroded in chloride medium.

Surprisingly, in the presence of PU (10^{-2} M) in NaCl, an extremely high frequency decrease is observed (ΔF = -488 Hz), which corresponds to a high mass gain (Δm = 8.6 µg cm^{-2}). Moreover, as the concentration of PU diminishes (10^{-3} M and
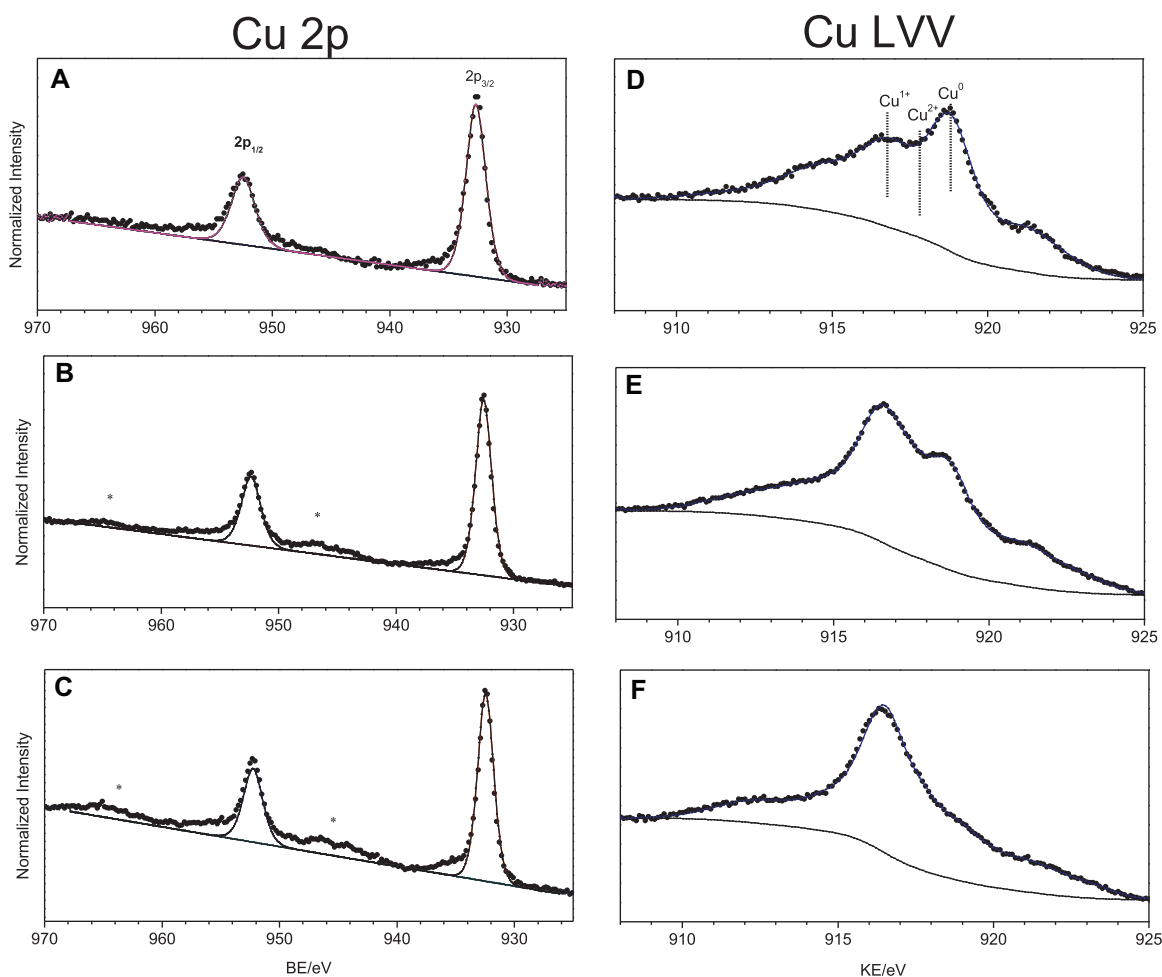
Cu 2p

Cu LVV

Fig. 3. XPS spectra of the Cu2 p and Auger Cu LVV region of copper sample, before (a, d) and after the immersion in SUF (b, e) and in SUF + UR (c, f). Asterisks indicate satellite bands.

10^{-4} M), Δm values increase as can be observed in Table 1. However, when PU adsorption was carried out in water, instead of NaCl solution, the frequency decrease and the mass gain were significantly smaller (ΔF = -101 Hz; Δm = 1.8 μg cm^{-2}).

The obtained results can be explained by the initial presence of cuprous chloride-containing compounds and the subsequent formation of Cu(I)-PU complex. Previous studies related to voltammetric measurements of aminopurines in the presence of copper ions support this idea [28]. Accordingly [28], copper ions Cu (I) and PU molecules form a complex in solution for subsequent adsorption. In contrast, here we propose a displacement reaction where the adsorbed chlorides are replaced by PU, which directly bonds to the Cu(I) ions of the surface, according to (1).

$$(CuCl)_{ads} + PUH \rightarrow [Cu(I)\text{-}PU]_{ads} + H^+ + Cl^- \qquad (1)$$
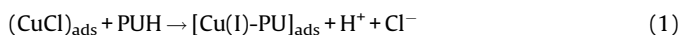
However, for high inhibitor concentrations, an excess of PU blocks the copper surface initially according to (2):

$$Cu + PUH \rightarrow (Cu\text{-}PU)_{ads} + H^+ + 1e^- \qquad (2)$$
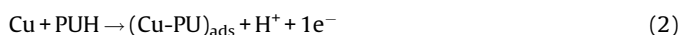
hindering the formation of Cu(I) ions, which are the precursor of Cu(I)-PU complex. Accordingly, a decrease of mass gain is observed for high PU concentration.

For a same PU concentration (10^{-2} M), but in the absence of chlorides (PU-water treatment), a significantly lower frequency decrease was observed (Fig. 4E). Previous QCM results (see Fig. 1A,

B) indicate that the copper corrosion rate in water was lower than in chloride media. Therefore the chloride presence, that induces copper oxidation, is a necessary requirement to form chloride compounds (CuCl)$_{ads}$ as precursor of PU complex. So the possibility of Cu (I)-PU complex formation in water diminishes, being the mass gain markedly lower.

3.2.2. XPS analysis

We analyzed the surface composition of copper after 3 h immersion in NaCl solution containing different PU concentrations by XPS.

For high PU concentrations (10^{-2} M and 10^{-3} M), N1s spectra are very similar (data not shown). A peak centered at 399.2 eV, resolved into one single component, is observed. This peak was associated to N of PU directly adsorbed on Cu surface. Since PU presents N atoms with different environments, it could be expected that N1s peak could be resolved in different components. But this was not the case; the existence of different resonant structures of PU may be a possible explanation.

In the case of the sample with 10^{-4} M PU treatment, the spectrum (data not shown) is different from the previous since the N1s peak broaden towards higher energy, indicating the presence of not only (Cu(0)-PU)$_{ads}$ but also [Cu(I)-PU]$_{ads}$ compounds. Besides, the higher percentage of chlorine signal (2.2%) indicates
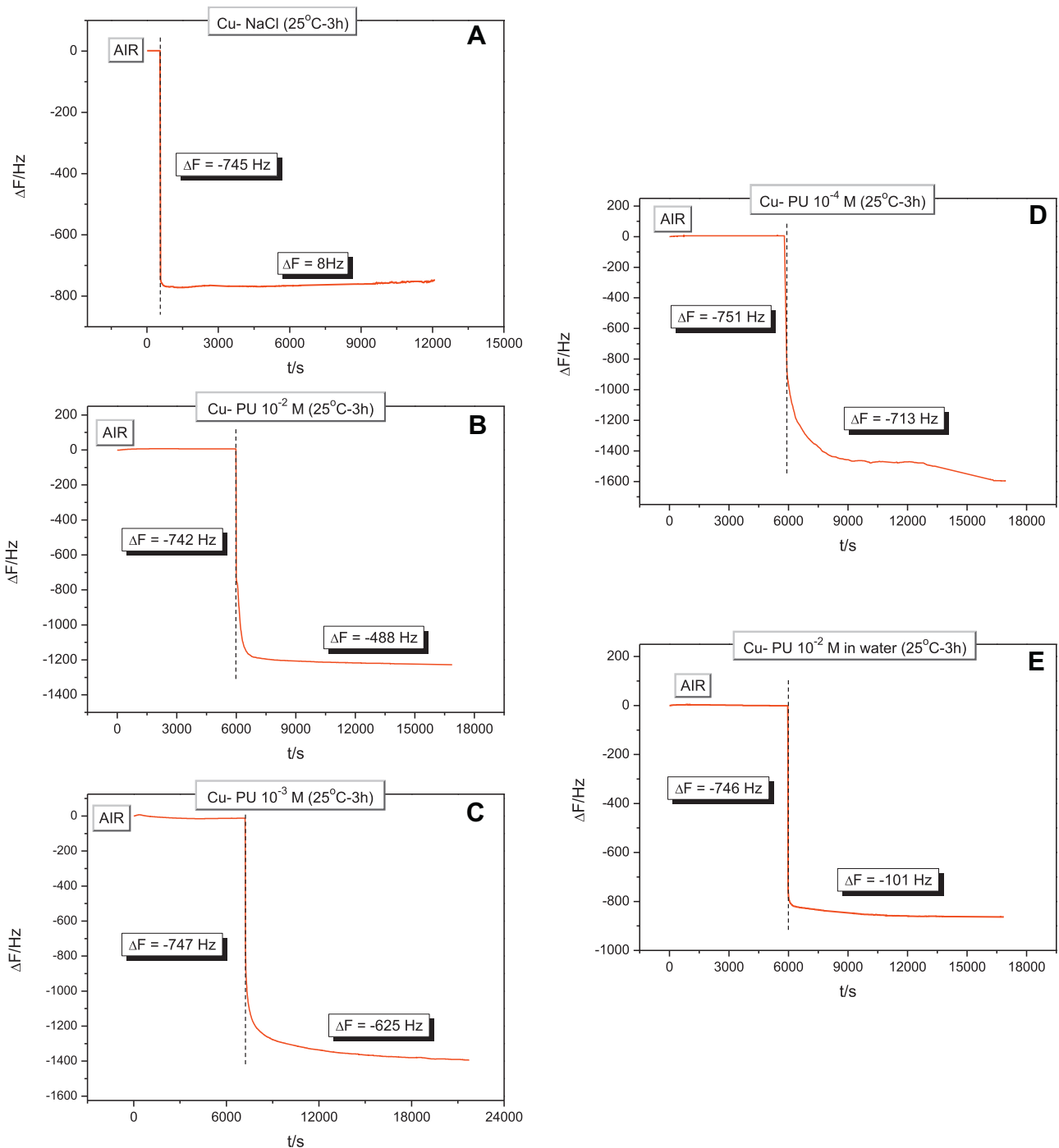
Fig. 4. Variation of the oscillation frequency of a Cu-QCM crystal during 3 h treatments in: NaCl solution (4.97 g L^{-1}) (A), PU 10^{-2} M in NaCl solution (B), PU 10^{-3} M in NaCl solution (C), PU 10^{-4} M in NaCl solution (D) and PU 10^{-2} M in water (E). (T = 25 °C).

that more copper chloride remains on the surface under low PU concentration, contributing to the mass gain.

3.2.3. Open circuit potential measurements

To follow the electrochemical behavior of the samples during the adsorption time we studied the evolution of copper open circuit potential (OCP) at different PU concentrations in chloride medium (Fig. 5). During the 3 h treatment a passive behavior was shown in case of 10^{-2} M and 10^{-3} M solutions, i.e. OCP increased to more anodic potentials reaching a nearly stable value (Fig. 5 a,b). This behavior is consistent with the corrosion inhibition by PU adsorption as was previously reported in case of other inhibitors
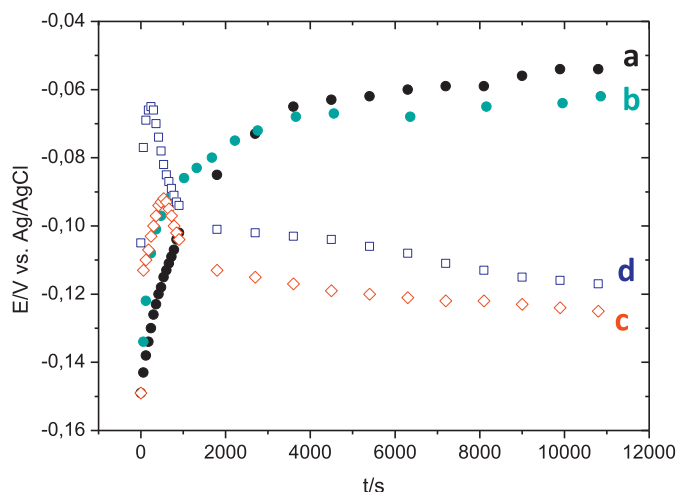
Table 1
ΔF and Δm values obtained during immersion of a Cu-QCM in NaCl solution containing different PU concentrations at 25 °C for 1 h and 3 h.

|	Immersion time (1 h)		Immersion time (3 h)	
Concentration	ΔF (Hz)	Δm (μg cm^{-2})	ΔF (Hz)	Δm (μg cm^{-2})
10^{-2} PU + NaCl	- 473	8.4	- 488	8.6
10^{-3} PU + NaCl	- 558	9.9	- 625	11.0
10^{-4} PU + NaCl	- 711	12.6	- 713	12.8
10^{-2} PU + H$_2$O	- 83	1.5	- 101	1.8
NaCl	-24	0.4	- 8	0.1

Fig. 5. Variation of copper open circuit potential (OCP) with the immersion time in PU solutions: (a) 10^{-2} M, (b) 10^{-3} M, (c) 10^{-4} M. (d) control without PU.

[29]. However for 10^{-4} M PU (Fig. 5c), OCP increased in anodic direction reaching a maximum value after 9 minutes due to the formation of CuCl, $(Cu-PU)_{ads}$ and Cu(I)-PU complex, but subsequently decreases to more cathodic potentials indicating that Cu(I)-PU was not an insulting layer and allows the diffusion of oxygen that control the corrosion process.

For NaCl solutions without PU (Fig. 5d) the change in OCP is similar to that of 10^{-4} M PU solution but occurs after a shorter immersion period (4′), indicating the formation of soluble complexes $(CuCl_2^-)$ from CuCl compounds [30].

Therefore, both QCM and OCP measurements indicate that high PU concentrations (10^{-2} M and 10^{-3} M) present a similar inhibitor effect for the copper corrosion. However, the behavior for low PU concentration (10^{-4} M) is similar to that of NaCl solution without PU.

Accordingly, cathodic polarization curves (Fig. 6) show a cathodic peak at -0.96 V in absence of treatment (NaCl solution) or when copper was treated with PU 10^{-4} M, although in the latter case, oxides reduction charge is lower. This result demonstrates that for low inhibitor concentrations, copper is corroded during the treatment time (3 h). The reduction peak appears also after 1 h of pretreatment (data not shown). This result corroborates OCP measurements since, as mentioned above, for low PU
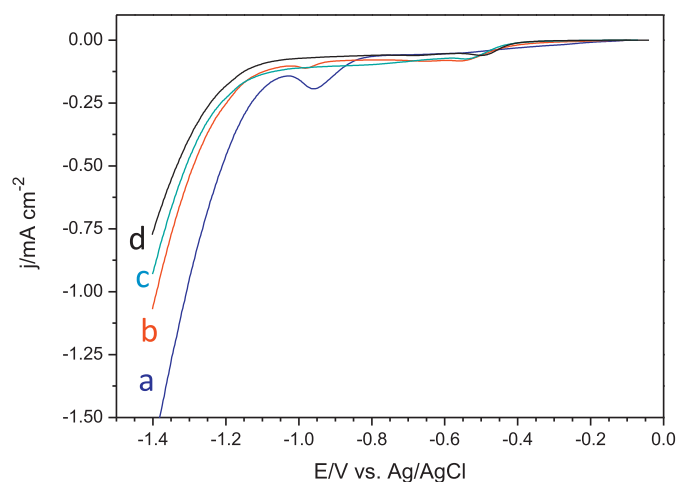
concentrations, OCP is moving towards cathodic potential values with immersion time (Fig. 5c).

Conversely, after treatments with higher PU concentration, the reduction peak is absent, indicating the inhibitory effect of adsorbed PU (Fig. 6). This result is in good agreement with the OCP shift towards anodic values with immersion time observed in Fig. 5 (a,b).

3.2.4. Polarization resistance

Polarization resistance (Rp) was calculated from the slope of polarization curves (Rp = $\Delta E/\Delta I$), measured in SUF, at a scan rate of 1 mV s^{-1}, for a potential range corresponding to OCP ± 20 mV. With this purpose Cu samples were pretreated with PU at different concentrations (0, 10^{-2} M, 10^{-3} M and 10^{-4} M) in NaCl solution during 1 and 3 hours. Subsequently, inhibitory effect (IE) was calculated [17].

As can be concluded from results presented in Table 2, polarization resistance increases after PU treatment, showing for 1 h and 3 h treatments concentration dependent relationships that increases with increasing PU concentration. Besides, for a given PU concentration, R_p increases as adsorption time increases.

Accordingly, for PU 10^{-2} M and 3 hours of adsorption time, maximum values are reached. In particular, an inhibitory effect of 85% is obtained. This value is between the 76% IE value given by Scendo [15] for copper corrosion in NaCl 1.0 M solution at pH 6.8 with the inhibitor in solution and the 99% IE value obtained by Alvarez [17] from anodic polarization curves with an adsorbed inhibitor.

For high PU concentration, an adherent protective layer is formed by chemisorption of the inhibitor on active sites of the copper surface, according to a Langmuir isotherm [15]. In contrast, for low PU concentration, a displacement reaction of chloride ions by purine molecules occurs, as previously mentioned.

3.3. Copper release during immersion in SUF with urea after PU treatment
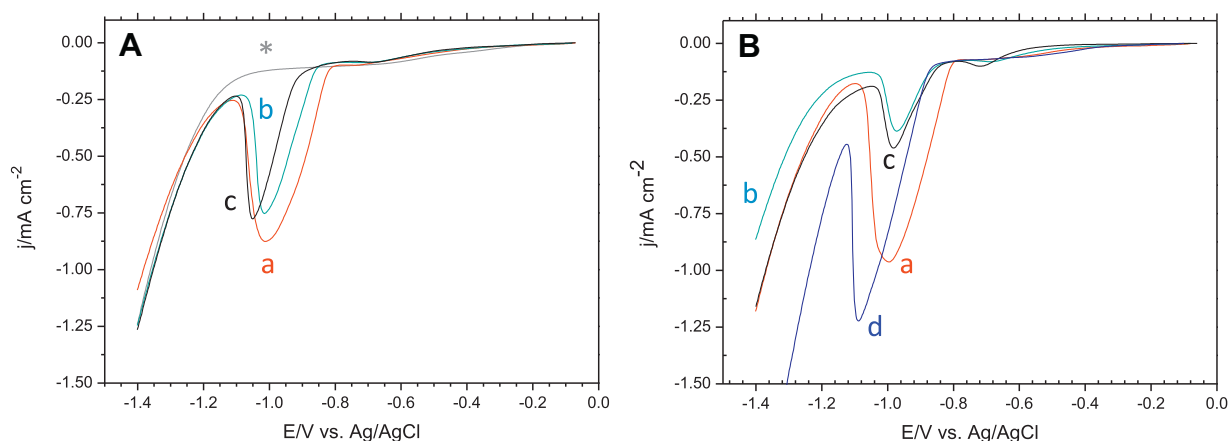
3.3.1. Cathodic polarization curves

In order to assess the reduction of oxidized species formed during the PU treatment, cathodic polarization curves were recorded for copper in SUF after 1 h (Fig. 7A) and 3 h (Fig. 7B) treatments with different PU concentrations (10^{-4} M, 10^{-3} M and 10^{-2} M) in NaCl solution, followed by 24 h of immersion in SUF + UR.

In Fig. 7A a cathodic peak, associated to the reduction of copper oxidation products, is observed for all the samples pretreated with PU. In accordance with the results of Fig. 6, during treatment with PU in chloride media only for the lowest PU concentration (10^{-4} M) significant corrosion products were formed on the surface. However, after 24 h immersion in SUF +UR, copper corrosion products are formed independently of the PU concentration used in the treatment. The reduction charge after 1 h treatment is higher for PU 10^{-4} M than for 10^{-2} M and 10^{-3} M (Table 3). This difference is more significant for 3 h adsorption treatment (Fig. 7B). Therefore, it is expected that the release of copper ions during

Fig. 6. Cathodic polarization curves made at v = 1 mV s^{-1} in SUF at 37 °C after 3 h treatments with NaCl solution (4.97 g L^{-1}) in the absence of PU (a) and with PU 10^{-4} M (b), 10^{-3} M (c) and 10^{-2} M (d).

Table 2
Polarization resistance obtained for Cu samples pretreated during 1 and 3 hours with PU at different concentrations in NaCl solution.

Sample	1 h treatment Rp Ω cm^2	3 h treatment Rp Ω cm^2
1 10^{-2} M PU	19786	10401
1·10^{-3} M PU	15543	8588
1 10^{-4} M PU	3603	3436
NaCl	1703	1068

Fig. 7. Cathodic polarization curves made in SUF at 37 °C ($v = 1$ mV s^{-1}) of a copper sample before any treatment (*) and after (A) 1 h treatment and (B) 3 h treatment in NaCl containing PU 10^{-4} M (a), 10^{-3} M (b), 10^{-2} M (c) and without any treatment (d), followed by 24 h immersion in SUF + UR (37 °C).

Table 3
Reduction charge for copper oxidation products.

1 h Treatment	Q_{red} mC cm^{-2}	3 h Treatment	Q_{red} mC cm^{-2}
10^{-2} PU 1 h + 24 h SUF + UR	47	10^{-2} PU 3 h + 24 h SUF + UR	24
10^{-3} PU 1 h + 24 h SUF + UR	56	10^{-3} PU 3 h + 24 h SUF + UR	23
10^{-4} PU 1 h + 24 h SUF + UR	105	10^{-4} PU 3 h + 24 h SUF + UR	119
24 h SUF + UR	127	24 h SUF + UR	127

24 h in SUF +UR was lower for samples treated with high PU concentration during 3 hours.

It should be noted that for 10^{-4} M PU, a similar reduction charge was obtained after PU 1 h and 3 h treatments (data not shown). However, as can be observed in Table 3, the protective effect for this low PU concentration diminishes with adsorption time since $Q_{red} = 119$ mC cm^{-2} and $Q_{red} = 105$ mC cm^{-2} were obtained for 3 h and 1h, respectively. Thus, copper samples are less protected after 3 h of treatment, which is in accordance with the decrease of OCP towards more cathodic values for longer adsorption times (see Fig. 5).

3.3.2. QCM measurements

Finally, in order to assess the effect of the PU treatment on copper dissolution and the influence of UR, QCM measurements of PU pretreated copper samples during 24 h of immersion in SUF and SUF + UR were performed. PU 10^{-3} M was selected to carry out the treatment since its inhibitory effect is similar to 10^{-2} M.

Results obtained for 1 h treatment followed by 24 h immersion in SUF are displayed in Fig. 8A . This figure shows a frequency decrease (mass increase) during the first 4 hours after immersion in SUF which is opposite to the behavior observed in the absence of inhibitor (see Fig. 2A). In that case, the release of copper to the solution was the predominant process. However, in the presence of inhibitor, a gain of mass is produced during the first 4 hours. Afterwards, frequency was stable during a long period (15 h) and finally diminished again. The total mass gain for 24 h immersion period, was 13.5 µg cm^{-2}.

For a higher adsorption time (3 h) (Fig. 8B), a similar tendency was observed but the mass gain during 24 h immersion period was lower (8.4 µg cm^{-2}). This can be explained taking into account that for high PU concentration, PU molecules adsorb directly onto the copper surface, giving rise to higher coverage for higher adsorption time and therefore leaving less free surface for both copper oxides formation (Table 3) and carbonates precipitation. Then, the amount of compounds formed onto the surface (and therefore, the mass gain) diminishes with adsorption time.

Fig. 8C shows Δf vs t for a Cu-QCM crystal during 3 h immersion in 10^{-3} M PU followed by the immersion in SUF + UR for 24h. In this case, the mass gain is slightly lower (6.2 µg cm^{-2}) compared with that obtained in SUF. In this sense, urea seems to act as a weak corrosion inhibitor [31] at short times, even at small concentrations.

4. Discussion

With the aim of elucidating the mechanism by which PU adsorption in saline solutions is effective to inhibit copper "burst release" in case of IUD, the electrochemical behavior of copper in water and in chloride-containing solutions was first investigated. The QCM results showed that due to the well-known corrosive effect of chloride-containing media, when NaCl solution was employed instead of water, a higher mass loss was obtained. It is important to highlight that this mass variation represents a balance between the formation of cuprous/cupric chloride-containing products [Cu(Cl)$_{ad}$, CuCl] that subsequently may be hydrated forming hydroxides and oxides [Cu(OH)$_{ad}$, Cu$_2$O, Cu$_2$(OH)$_3$Cl] (gain of mass) and a release of copper ions to the solution (loss of mass) being the latter the main one.

When the electrochemical response of copper in NaCl solutions and SUF are compared (Fig. 1C), it can be observed that the action of chlorides is affected by the presence of the other inorganic components of SUF (carbonates, phosphates) that can modify the corrosion behavior of copper. In agreement, QCM measurements showed important differences in the change of frequency between NaCl and SUF solutions during the 24 h immersion (-20.9 µg cm^{-2} and -51.9 µg cm^{-2}, respectively). Thus, copper dissolution is initially higher in SUF (release rates $v = 29.3 \ 10^{-4}$ µg s^{-1} cm^{-2} and $v = 1.6 \ 10^{-4}$ µg s^{-1} cm^{-2} in SUF and in the plain NaCl solution, respectively). The total soluble copper may consist in:

$$Cu_{soluble} = [Cu^{2+}] + [CuCl_x{}^{x-2}]^-] + [Cu(CO_3)_x{}^{x-2})^-] \text{ at pH} < 8 \text{ [26,32]}$$
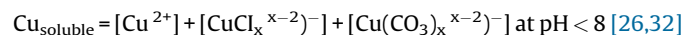
Soluble carbonates compounds may react with Cu(I) compounds (Cu$_2$O or CuCl) to form these complexes [26,33]. This may
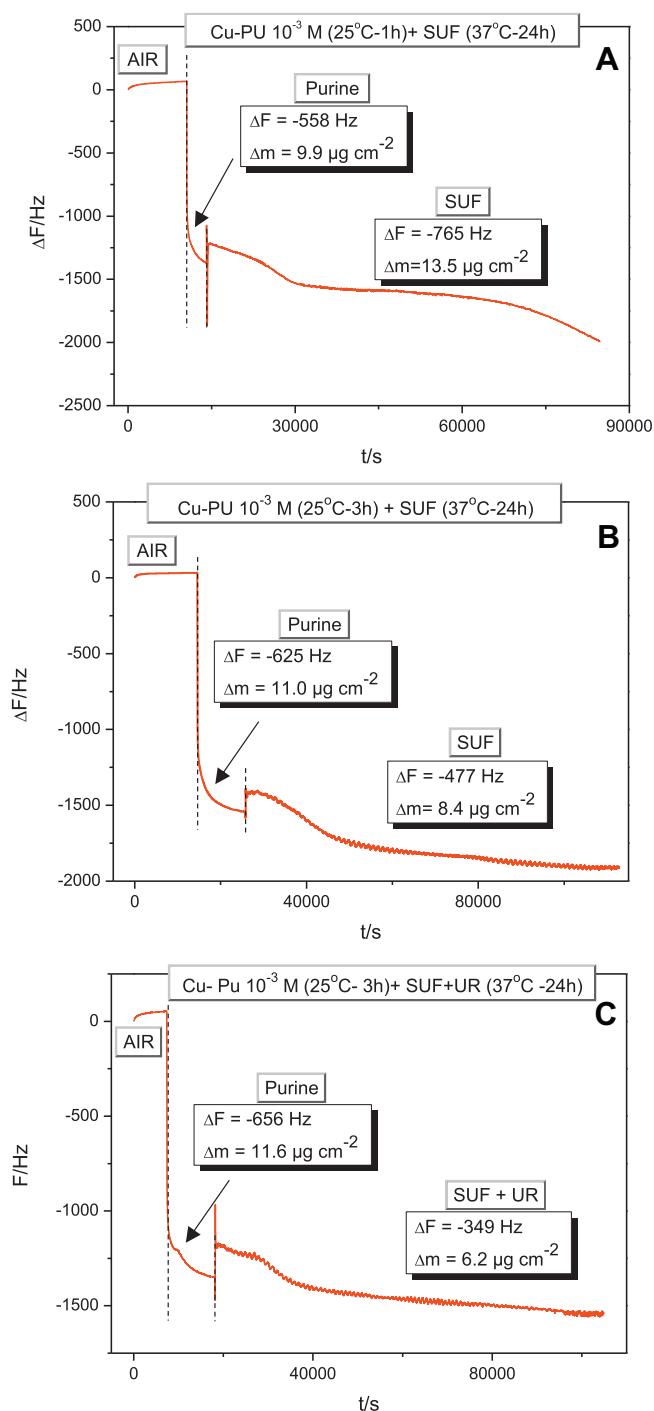
Fig. 8. Variation of the oscillation frequency of a Cu-QCM crystal during 1 h (A) or 3 h (B, C) of treatment in PU 10^{-3} M (T = 25 °C), and then tested in SUF (A, B) or SUF + UR (C) for 24 h (T = 3 °C, pH = 6).

explain the initial increase of copper release when carbonates are present in the solution. After attaining the solubility limit, carbonate-containing complexes may precipitate as $Cu_2(OH)_2CO_3$. Precipitation of $Cu_2(OH)_2CO_3$ could explain the drastic reduction of the release of copper after the first 4h. However, the presence of carbonates on the surface could not be verified, due to the interference of C signals from the environment.

The effect of the presence of UR in SUF was also evaluated. Results show that the presence of UR markedly affects the corrosion behavior of untreated copper in SUF. In case of chloride-containing solutions, it seems that UR initially adsorbs on Cu(I)

species (CuCl or Cu_2O) hindering the formation of soluble carbonate-containing species at these sites and reducing the corrosion rate with respect to SUF without UR ($v = 8.6\ 10^{-4}\ \mu g\ s^{-1}\ cm^{-2}$). However, the dissolution rate in SUF + UR increased thereafter ($v = 19.7\ 10^{-4}\ \mu g\ s^{-1}\ cm^{-2}$). Thus, after 24 h immersion, the total mass decrease was -70.3 $\mu g\ cm^{-2}$, higher than in the absence of UR (-51.9 $\mu g\ cm^{-2}$). However, the amount of copper oxidation products on the surface was not significantly modified when UR is presence since the cathodic charge recorded during polarization curves was not markedly changed. Accordingly, XPS spectrum obtained after the immersion of Cu in SUF + UR (displayed in Fig. 3C) is similar to that obtained in SUF showing Cu(I) and Cu(II) contributions. UR ΔG°_{ads} value found in the literature is consistent with physisorption, for UR coverage below 0.25 [31]. However, this process is probably followed by the formation of soluble Cu-UR complexes such as $CuCl_2.2UR\ 4H_2O$ and $Cu(UR)_2Cl_2$ [34] that may lead to a higher release of Cu and to the formation of carbonate complexes at the vacant sites of the Cu(I) compounds. This could explain that after few hours a higher Cu dissolution is detected when UR is present.

Most of previous assays to evaluate the PU inhibitory action were performed maintaining the inhibitor (PU) in solution during measurements. Since, obviously, this condition is not suitable for IUD applications, in this work, we have treated copper samples with PU *ex-situ* and subsequently we have tested the ions release in uterine fluid without PU.

The results show that the inhibitory action of PU is concentration dependent and only effective at concentrations $\geq 10^{-3}$ M after 3 h treatment. In agreement, different parameters such as Rp and reduction charge value reveal higher protection at concentrations $\geq 10^{-3}$ M. Shorter treatments (1 h) or lower concentrations are not efficient to prevent burst release due to chloride action.

In order to assess the copper release during immersion in SUF without and with urea after PU treatment, we performed QCM measurements. QCM measurements showed that the mass gain after the immersion of PU treated copper is slightly lower after the 24 h immersion in SUF with UR than in SUF (6.2 vs 8.4 $\mu g\ cm^{-2}$). Considering that the mass gain measured by QCM is the balance between the formation/precipitation of corrosion products, this may indicate that the amount of released copper is higher when UR is present. As previously discussed it seems that UR acts as a weak corrosion inhibitor. It may be hypothesized that UR adsorbs on the sites that are released during PU desorption [35]. Thus, the mechanism is similar to that observed without PU-treatment and the formation of soluble Cu-UR complexes seems to be possible leading to a higher release of Cu in presence of UR. Nevertheless, the formation of carbonate complexes at the vacant sites of the Cu (I) compounds and its subsequent precipitation give rise to a partial inhibition of copper ions release.

Overall, 3 h treatment with 10^{-2} or 10^{-3} M PU is a temporary inhibitory treatment based in the direct adsorption of PU on Cu(0), suitable for applications in IUD due to the reduction of copper release and corrosion products formation during the first days after insertion. After longer exposures (several days) the release of copper ions decreases due to the deposition of corrosion products on the surface. Thus, the conjoint inhibitory action of PU and precipitates is enough to reduce the burst release effect and to guarantee the contraception effect verified by atomic absorption spectrometry [17].

5. Conclusions

The mechanism by which PU adsorption in chloride containing solution is effective to inhibit copper "burst release" in case of copper based IUD was investigated by QCM, electrochemical

measurements (Rp, OCP, reduction charge value), and XPS analysis. Results revealed that:

In the absence of PU treatment, the initial copper corrosion rate is higher in SUF than in chloride media due to the formation of phosphate and carbonate soluble complexes. Precipitation leads to inhibition of copper ions release for long times.

- PU Inhibitory action is enhanced if PU adsorption is made in chloride-containing solution.
- The better Inhibition efficiency to reduce copper burst release and corrosion products formation was obtained after 3 h treatment with high PU concentrations (10^{-2} and 10^{-3} M) in NaCl solutions. Inhibition mechanism depends on PU concentration: for 10^{-2} M and 10^{-3} M PU treatment a narrow N1s peak assigned to PU directly adsorbed on copper (Cu(0)N) was found by XPS while for 10^{-4} M PU the N1s peak broaden, indicating also the presence of PU molecules forming Cu(I)-PU complexes. Poor protection was found for PU 10^{-4} M, due to the presence of both CuCl (precursor of copper oxides/hydroxides) and Cu(I)-PU complex, which probably allow oxygen diffusion leading to copper corrosion during the pretreatment and the subsequently immersion in SUF.
- PU pretreatment leads to an inhibition of copper ions release over 24 h immersion time in SUF without and with UR, being lower in presence of UR. During the immersion of PU-treated Cu samples in SUF + UR, PU may be partially desorbed and UR may act for a few hours as a weak corrosion inhibitor. UR probably adsorbs on the vacant sites leading to temporary control of corrosion, but the protection decreases quickly due to formation of soluble Cu-UR complexes. Therefore, the total amount of released copper is higher when UR is present. Nevertheless, the formation of carbonate complexes at the vacant sites of the Cu(I) compounds and its subsequent precipitation give rise to a partial inhibition of copper ions release.
- PU inhibitory action is temporary in case of IUD because PU is absent in the corrosive SUF + UR solution. Thus, the PU pretreatment, as desired, is able to reduce copper ions burst release into SUF + UR, ensuring contraception action of IUD and avoiding side effects associated to the high copper release in users.

Acknowledgments

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