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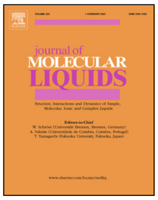

The behaviour of aluminium ions in artificial saliva and the impact of the chlorhexidine digluconate on its removal – A diffusion model

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ABSTRACT

Diffusion coefficients for aluminum chloride in artificial saliva or chlorhexidine digluconate solutions (pure and commercially, frequently used as a mouthwash), at tracer concentrations (D_T^0) at 298.15 K and at different pH, as well as ternary diffusion for aqueous $AlCl_3$ and chlorhexidine digluconate solutions, were measured by using the Taylor dispersion technique.

Notable coupled diffusion of $AlCl_3$ and chlorhexidine digluconate is observed by obtaining of the negative values of the cross-diffusion coefficients, D_{21}. These results show the occurrence of complex structures formed between Al^{3+} and gluconate anions. Support for these facts are given by molecular dynamics simulations (MDS).

1. Introduction

Titanium alloys have been used for decades in the manufacture of dental prostheses and implants due to their adequate mechanical properties, biocompatibility and good longevity. However, due to the fact that they are inserted in the oral cavity and surrounded by saliva, they can be subject to corrosion with the consequent release of undesirable species [1–3].

The presence of implanted biomaterials may lead to an increase in the concentration of trace metals in the body, in addition to those from foods and drinks [4].

The role of these ions released by the corrosion of prosthetic devices in the human body is a reason of concern [5–7]. So, the evaluation of the diffusion of such species, once they are released into the body, is of utmost importance to understand their toxicological potential. Particle debris released by orthopedic and dental implants is often related with failure of treatments [3,8,9].

In this study we gave special attention to the aluminum ions, because they are one of the components of the TiAlV alloys, used in several biomedical applications namely in the fabrication of dental implants, and other prosthetics components (abutments, healing components and supra-structures) as well as in orthopedics prosthesis, but show both low shear strength and wear resistance [10].

TiAlV alloys are characterized by their high resistance to corrosion, due to the passive layer of oxides that forms on their surface. Under certain circumstances the passive layer may be destroyed [5,11] and corrosion may occur.

Among these conditions, acidic pH or the presence of fluoride, which is part of the composition of most mouth rinses or tooth pastes used in the prevention of dental caries attack the superficial oxide layer of the titanium alloys leading to a decrease in its protective capacity [11–14].

Additionally, TiAlV alloys are very susceptible to the mechanical action caused by fretting and sliding wear [15,16].

In previous studies we have been able to quantify, by using atomic absorption spectroscopy, the ions released after subjecting TiAlV alloys to tribological tests [17].

Although not completely clear and predictable, the potential cytotoxicity of these ions is eventually susceptible to cause long-term health effects [3,18], as has been already demonstrated that TiAlV alloys may release aluminum ions even in short periods of time, which are capable of causing biological issues [3,12,17,19,20]. Aluminum has been related to bone fragility

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[21,22], Alzheimer's disease [22,23] and also Parkinson's disease [24], according to Willhite, high levels of Al^{3+}can originate cytotoxicity by oxidative damage [23], what is corroborated by Kermani *at al.* that relates Al_2O_3 nanoparticles with structural damage and cellular apoptosis [25]

Although in vivo Ti6Al-4 V implants may release low concentrations of ions, the systematic contact with *peri*-implant cells leads to a potentially hazardous condition displaying systemic and local effects [5,7]. At long term interactions between *peri*-implant tissues and ion release might lead to the release of inflammatory mediators from macrophages, that lead to bone resorption and may culminate with the implant failure [7,26,27].

For the above, it become relevant a better understanding the mass transport phenomenon of those ions, released by TiAlV prosthesis and by TiAlV supra-structures in *peri*-implant region.

An experimental model based on the Taylor dispersion technique to analyze the diffusion properties of the released ions and the influence of different media potentially present in the oral cavity has been developed.

Considering that the oral cavity undergoes several pH variations resulting from the diet and/or pathologies such as gastroesophageal reflux [1,7,28,29], a different pH range was considered in this work.

Thereby, our aim is to assess the release of aluminium (Al) ions by using artificial saliva models; we also want to understand how chlorhexidine digluconate, a main constituent of mouthwashe formulations, can react with released free metal ions in order to address the following question: can digluconate be a proper carrier for the elimination of metal ions from the oral cavity?

2. Experimental section

2.1. Materials

All reagents were used without further purification and are described in the Table 1. The composition of Eludril Extra® with 0.2 % chlorhexidine digluconate is also showed in same table. The artificial saliva is prepared by using the following formulation: potassium chloride: 2.0×10^{-2} mol dm^{-3}; sodium bicarbonate: 1.79×10^{-2} mol dm^{-3}, sodium phosphate: 3.6×10^{-3} mol dm^{-3}, potassium thiocyanate: 5.1×10^{-3} mol dm^{-3} and lactic acid: 1.0×10^{-4} mol dm^{-3}.

All solutions were prepared by using Milli-Q (specific resistance = 1.82×10^5 Ω m, at 298.15 K).

2.2. Taylor dispersion method

The Taylor dispersion method is the most versatile technique for measuring interdiffusion coefficients in liquids, allowing the study of ionic and non-ionic species in binary and multicomponent systems. The Taylor technique is detailed elsewhere [30–36]. Briefly, the method consists on the dispersion of small amounts of solution injected into laminar carrier streams of water or solution of different composition, flowing through a long capillary tube with length and radius of 3.2799 (±0.0001) $\times 10^4$ mm and 0.5570 (±0.00003) mm, respectively [32,35,36]

Table 1
Reagents used in the experiments.

Chemical name	Source	CAS Number	Mass fraction Purity
$AlCl_3 \cdot 6H_2O$	Merck	7784-13-6	>0.99[a]
NaF	Sigma-Aldrich	7681-49-4	>0.99[a]
Lactic acid	Sigma-Aldrich	50-21-5	>0.85 wt%[a]
Chlorhexidine digluconate[b]	Sigma-Aldrich	18472-51-0	20% in water

[a] As declared by the supplier.

[b] In present work, a commercial formulation containing 0.2% (m/v) chlorhexidine digluconate was also used.

At the start of each run, a 6-port Teflon injection valve (Rheodyne, model 5020) is used to introduce 0.063 mL of solution into the laminar carrier stream of slightly different composition. Using a metering pump (Gilson model Minipuls 3), a flow rate of 0.17 mL min^{-1} is maintained to give retention times of about 1.1×10^4 s. The injection valve and the dispersion tube are kept at 298.15 K (±0.01 K) in an air thermostat.

Dispersion of the injected samples is followed by using a Waters (model 2410) differential refractometer. Detector voltages, $V(t)$, are measured at 5 s intervals with a Agilent 34401 A digital voltameter.

The present work describes the study on the diffusion behavior of the salts $AlCl_3$ at tracer concentrations in different aqueous systems: artificial saliva without and with other components (lactic acid, sodium fluoride and the mixture of both), and chlorhexidine digluconate pure or present in commercial mixture.

2.3. pH measurements

The pH of different solutions was measured by using a Radiometer PHM 240 coupled with an Ingold U457-K7 electrode. This was calibrated by using IUPAC-recommended pH buffers. The solutions at pH 2.3 and 7.9 were prepared by adding lactic acid.

2.4. Molecular dynamics simulations

The interpretation of the diffusion coefficients measured for the Al^{3+} was attempted by employing molecular dynamics simulations (MDS) to acquire further information on the interaction of this ion with gluconate in aqueous solution. The MDSs were carried out by using the 2019 version of the GROMACS package [37,38] and the OPLS-AA force field [39] to establish the interactions among the main species; the OPLS-AA parameters for Al^{3+} were taken from the work of Faro et al. [40].

The preparation of the system for the simulations has followed a set of well-established steps: (i) the OpenBabel program [41] was employed to obtain a 3D structure of the gluconate ion, which was optimized at the RHF/6-31G* level with the GAMESS package[42]; (ii) for the optimized geometry, the partial charges (see Figure S1 and Table S1 of the Supplementary Information) were obtained by using the RESP method, which is implemented in the RED code [43]; (iii) the topology of gluconate to be used in GROMACS was generated through the LigParGen server [44]; (iv) one Al^{3+} and three gluconate ions (GLU1, GLU2 and GLU3) were placed, far apart, in a cubic simulation box (whereas the gluconate concentration was set at 0.008 mol dm^{-3}) and, then, solvated with TIP4P-2005 water molecules [45]; (v) finally, the system was subjected to energy minimization in order to reduce repulsions and, then, equilibrated at a T = 298.15 K and P = 1 bar by performing two consecutive simulations of 250 ps, respectively, within the *NVT* and *NPT* ensembles. The average values of temperature and pressure were kept constant by employing the velocity-rescaling thermostat [46] (with a coupling time of 0.1 ps) and the Parrinello-Rahman barostat [47] (with a coupling time of 2 ps), respectively.

By departing from the equilibrated configuration, we have carried out a 100 ns MDS within the *NVT* ensemble to investigate the possibility of forming an Al^{3+}-gluconate complex. The equations of motion were numerically integrated by employing the standard leapfrog algorithm and a time step of 2 fs. In addition, bond constrains were imposed by applying the linear constraint solver (LINKS) scheme [48]. In turn, the particle-mesh Ewald method [49,50] was applied to calculate the long-range electrostatic energy; periodic boundary conditions were employed in all simulations and cut-offs of 1.2 nm were used for Coulomb and van der Waals interactions.

3. Results

Table 2 shows our results of diffusion coefficients for $AlCl_3$ at tracer concentrations in different media, that is, artificial saliva (for the sake of simplicity, henceforward referred as saliva) without and with other components (lactic acid, sodium fluoride and the mixture of both), by injecting saliva with $AlCl_3$ 0.001 mol dm^{-3} into carrier streams of saliva (or in chlorhexidine digluconate). Having in mind the previous studies about the corrosion of the dental alloys in these media [17], it was only measured these transport coefficients of these salts at tracer concentrations.

Concerning our experimental diffusion coefficients obtained for $AlCl_3$ at tracer concentrations in chlorhexidine digluconate (CLO) pure 0.2% at pH 5.3 (that is, D^0_{1T} = 1.105 ± 0.010 × 10^{-9} m^2 s^{-1}), and in the commercial mixture containing 0.2% at pH 5.6 (that is, D^0_{1T} = 0.629 ± 0.014 × 10^{-9} m^2 s^{-1}), it can been see that, in both situations, these data (D^0_{1T}) are lower than those obtained in saliva, regardless of the pH of the medium, although a more accentuated difference is observed when using the chlorhexidine digluconate in commercial mixture flux as carrier.

Table 3 shows the average values for ternary diffusion coefficients (D_{11}, D_{12}, D_{21}, D_{22}) for the {$AlCl_3$ (C_1) + CLO pure (C_2)} aqueous solutions. Main diffusion coefficients D_{11} and D_{22} provide molar fluxes for $AlCl_3$ (1) and CLO (2) components, respectively, driven by their own concentration gradients, whilst cross-diffusion coefficients D_{12} and D_{21}, describe the coupled diffusion of $AlCl_3$ and CLO.

4. Discussion

4.1. Tracer diffusion of $AlCl_3$ in artificial saliva at different pH

Table 2 shows that in saliva and in water, tracer diffusion coefficients of $AlCl_3$ are similar. The exception is at pH 2.3 where the diffusion coefficient decreases ca. 49%, when compared with that obtained in water. Despite the possible occurrence of complexes as, for example, $[Al(OH)_2Cl_2]^-$ or $[Al(OH)Cl_3]^-$ [51], this behaviour may be rationalized by an electrostatic mechanism. It is known that in acidic solutions, H_3O^+ is a predominant species; this ion is characterized by a fast mobility in comparison with others. Thus, a strong electric field will be generated by a concentration gradient in H_3O^+, slowing down these ions and driving large counter-current fluxes of $Al^{3\,+}$ in aqueous solutions. This is supported by negative diffusion coefficients (i.e., a salting-in effect is occurring). Regarding the presence of sodium fluoride, it can be observed that this component is responsible for a significant increasing of the diffusion coefficients of this salt in saliva (pH 2.3).

4.2. Diffusion coefficients of $AlCl_3$ in chlorhexidine digluconate

Concerning the pseudo diffusion coefficients of aluminium chloride in chlorhexidine digluconate solutions (present in commercial mixture, and prepared from of the pure sample), they are lower than values obtained in water. From these facts, it can be concluded that this salt also suffers more resistance to its motion which can be related to its ionic character in these mixtures.

Ternary diffusion coefficients measured at tracer concentration for both components (chlorhexidine digluconate and $AlCl_3$) are summarized in Table 3.

In the first situation, $C_2/C_1 \rightarrow 0$ (chlorhexidine digluconate - free solutions), it is observed that the limiting value of D_{22} tends to approach the diffusion coefficient value at infinitesimal concentration, D^0_{CLO}, in aqueous solutions (i.e., D^0 = 0.762 × 10^{-9} m^2 s^{-1}). Under these conditions, the salt concentration gradient does not lead to a coupled flow of chlorhexidine and, consequently, cross-coefficients D_{21} should be zero. In fact, it can be seen in Table 3 that D_{21} value is approximately zero within the precision of the measurements. However, D_{12} value is negative, suggesting a remarkable coupled diffusion. In the other words, the presence of chlorhexidine digluconate at trace concentration affects the behaviour of diffusion of this salt by the presence of the $AlCl_3$ counter-current transport, ranging from low to high CLO concentrations. In addition, despite the D_{22} is close to the binary diffusion coefficients of chlorhexidine digluconate at infinitesimal concentration (D^0_2 = 0.635 × 10^{-9} m^2 s^{-1}) [52], D_{11} are not similar to those previously obtained for binary $AlCl_3$ (0.001 mol dm^{-3}) system (that is, D_1 = 1.144 × 10^{-9} m^2 s^{-1}) [53]. This observed significant deviation (10%) reveals the presence of strong interactions between these components. Indeed, the values of the ratio D_{12}/D_{22} show that a mole of diffusing chlorhexidine digluconate can counter-transports 0.4 mol of this salt (or Al^{3+} ions).

In second case, $C_1/C_2 \rightarrow 0$ ($AlCl_3$ free solutions), whereas D_{12} is almost zero and D_{11} approaches to the binary diffusion coefficient of this component at infinitesimal concentration (D^0_1 = 1.225 × 10 $^{-9}$ m^2 s^{-1}), D_{21} value is negative and significant. Since $D_{21} < 0$, it is expected D_{22} value to be considerably larger than the binary D_2 value at 0.004 mol dm^{-3} (that is, D_2 = 0.602 × 10^{-9} m^2 s^{-1}). The ratio D_{21}/D_{11} show that a mole of $AlCl_3$ can counter-transports 0.6 mol of the chlorhexidine digluconate

From these observations, it can be concluded that a relevant interaction between aluminium chloride and chlorhexidine digluconate is apparent. This assumes special importance because free cations have greater probability of combining with biomolecules, and become toxic. Due to their strong interaction with chlorhexidine digluconate [4] is possible to reduce potential toxicity.

Support for this effect of chlorhexidine digluconate was also found by other authors [54–57], considering there are mononuclear complexes between Al^{3+} and gluconate, where the metal ion-binding takes place via the deprotonated carboxyl groups in acidic to mild basic media.

In order to get insight on interactions between Al^{3+} and gluconate ions, in aqueous solution, molecular dynamics simulations have been performed; details about these simulations were described in Section 2.4.

Table 2

Tracer diffusion coefficients, $D^0_{1T}/(10^{-9}m^2\ s^{-1})$, of $AlCl_3$ in water and saliva at different pH values, at 298.15 K.

$D^0_{1T} \pm S_D$	$D^0_{1T} \pm S_D$	$D^0_{1T} \pm S_D$	$D^0_{1T} \pm S_D$	$D^0_{1T} \pm S_D$
water, pH = 6.5	pH = 7.5	NaF, pH = 7.9	pH = 2.3	NaF, pH = 2.3
1.208 ± 0.005	1.216 ± 0.021	1.199 ± 0.010	0.683 ± 0.011	1.184 ± 0.017

S_D: standard deviation; $u_r(c)$ = 0.03 and $u(T)$ = 0.01 K.

Table 3
Ternary interdiffusion coefficients (D_{11}, D_{12}, D_{21}, D_{22}) of $AlCl_3$ (C_1) + CLO (C_2) aqueous solutions, at 298.15 K.

C_1[a]	C_2[a]	$D_{11} \pm S_D$[b]	$D_{12} \pm S_D$[b]	$D_{21} \pm S_D$[b]	$D_{22} \pm S_D$[b]	D_{12}/D_{22}	D_{21}/D_{11}
0.001	0.000	1.260 ± 0.002	−0.250 ± 0.005	0.008 ± 0.003	0.640 ± 0.003	−0.390	0.006
0.000	0.004[c]	1.236 ± 0.010	−0.036 ± 0.030	−0.448 ± 0.01	0.679 ± 0.010	−0.053	−0.563

[a] C_1 and C_2 in units of mol dm^{-3}.
[b] Values of physical parameters are divided by 10^{-9} m^2 s^{-1}.
[c] C_2 = 0.004 mol dm^{-3} is approximately 0.2 % in chlorhexidine digluconate (CLO) m/v.

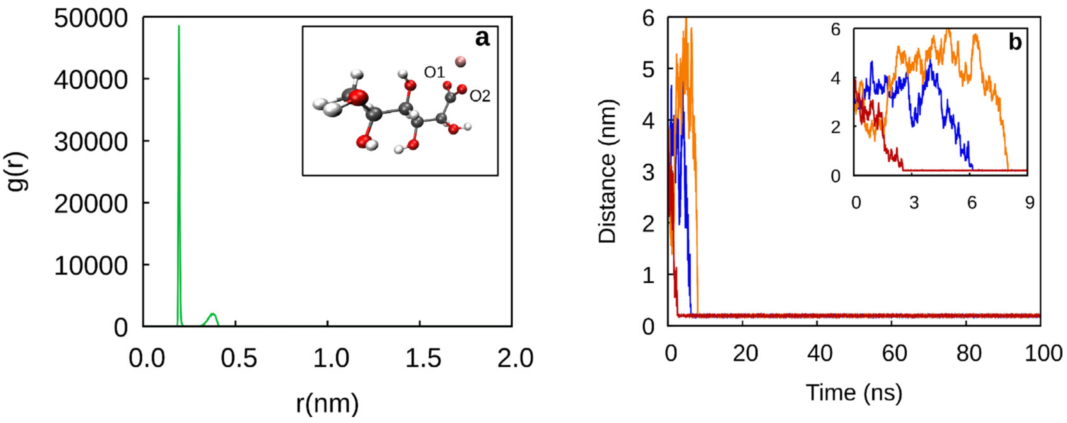

Fig. 1. (a) Radial Distribution Function of Al^{3+} around the O1 and O2 of the three gluconate ions, and (b) average distance between aluminium ion and O1 and O2 of GLU1 (red), GLU2 (blue), GLU3 (orange). The insert in panel **a** labels the O1 and O2 of the gluconate ion, while the insert in panel **b** is a zoom of the plotted curves for the first 9 ns. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 1 shows the average radial distribution function (RDF) between the aluminium ion and the O1 and O2 oxygen atoms of the three gluconate ions (panel a).

The prominent peak of the RDF observed in Fig. 1a at approximately 0.2 nm is clear evidence of the formation of a stable Al^{3+}-gluconate complex. As shown in Fig. 1b, the complex begins to be formed at about 2.5 ns, when the O1 and O2 atoms of GLU1 approaches close to Al^{3+}; a snapshot illustrating the geometry of the complex is displayed in Fig. 2a and a video of the simulation is presented as Supplementary Material. Then, after 6.5 ns of simulation time, a second gluconate ion (GLU2) joins the Al^{3+}-GLU1 complex (cf. structure in Fig. 2b). Finally, the third gluconate ion (GLU3) also approaches de aluminum at about 8 ns of simulation, and a complex with three gluconate ions is formed (cf. structure in Fig. 2c). Moreover, it is apparent from Fig. 1b that such complex does not dissociates during the remaining of the simulation that lasts for 100 ns.

MD results clearly point out the formation of a stable Al^{3+}-gluconate complex. This may explain the decrease of the diffusion coefficient of $AlCl_3$ in the presence of gluconate ions observed in the experimental measurements reported in Section 3.

By the data obtained, we can assume that it may be very useful to advise rinsing with mouthwashes with chlorhexidine gluconate after meals when the prosthetic devices are subject to tribocorrosion and when the oral cavity is subject to a very acidic pH, such as in patients with gastroesophageal reflux or after acidic food intake.

5. Conclusions

The effect of chlorhexidine digluconate, in different saliva media, on aluminum chloride has been studied by using the Taylor dispersion method and molecular dynamics simulations. It has been found from binary *D* that aluminum ions suffer less frictional resistance to motion through the saliva pH 7.5 and 7.9, and chlorhexidine digluconate, when compared to water. As a result, their diffusion coefficients become higher in all systems, with the exception of saliva at pH 2.3. In the latter, the diffusion coefficients decrease significantly.

For the particular aqueous system {$AlCl_3$(component 1) + Chlorhexidine digluconate (component 2)}, the limiting values of cross-coefficients D_{12} are negative, and there is significant

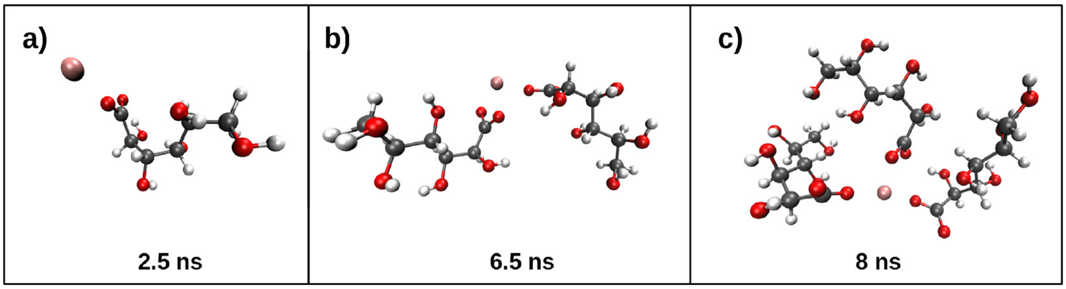

Fig. 2. Three snapshots of the MD simulation showing the formation of the complex between Al^{3+} and the gluconate ions. Colors for atoms: hydrogen (white); carbon (grey); oxygen (red); aluminium (pink). Snapshots have been obtained with the VMD (Visual Molecular Dynamics) program [58]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

difference between D_{11} and D_1. Consequently, we conclude that $AlCl_3$ and chlorhexidine digluconate can interact. This conclusion is fully supported by the present MDS, which clearly indicate a strong interaction between gluconate ions and Al^{3+}. This can also explain the decrease of the diffusion coefficient of $AlCl_3$ in the presence of gluconate ions. Hence, we can consider that chlorhexidine digluconate can be an important therapeutic agent acting as a carrier in the elimination of aluminum ions from the oral cavity.

CRediT authorship contribution statement

Sónia I.G. Fangaia: Conceptualization, Methodology, Validation, Investigation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Pedro M.G. Nicolau:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration. **Fernando A.D.R.A. Guerra:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration. **M. Melia Rodrigo:** Conceptualization, Methodology, Validation, Investigation, Formal analysis, Resources. **Ana C.F. Ribeiro:** Conceptualization, Methodology, Validation, Investigation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration. **A.J.M. Valente:** Conceptualization, Validation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Joana R.C. Santos:** Investigation, Writing – original draft. **Jorge M.C. Marques:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision. **Miguel A. Esteso:** Conceptualization, Validation, Resources, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.molliq.2022.118749.

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