Characterization of the heat behavior of amiodarone hydrochloride

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Abstract

Amiodarone hydrochloride, an antiarrhythmic and vasodilatory drug, was characterized from a thermodynamic point of view. Its XRPD profile was found to be in agreement with the single crystal structure previously reported. When the DSC heating rates are not high enough, the compound starts to degrade before melting. This phenomenon is emphasized during melting and also in the liquid state. The degradation products were identified by coupling TGA/FTIR experiments. When increasing the DSC scan rates, the onset of melting as well as the endothermic value of the signal increase to reach plateau values. This clearly indicates that the degradation processes have been pushed back to higher temperatures than the melting temperature. This allowed determining accurately the melting characteristics of the compound. The so-obtained melting temperature was then confirmed by Fast Scanning Calorimetry.

Keywords: amiodarone hydrochloride, melting degradation, thermal analyses, flash scanning calorimetry, X-ray powder diffraction, TGA-FTIR.

1. Introduction

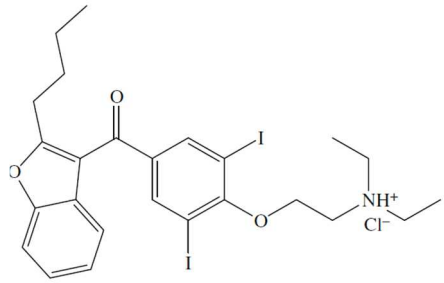
Amiodarone hydrochloride (2-butyl-3-benzofuranyl) [4-[2-(diethylamino)ethoxy]-3,5-diiodophenyl]methanone hydrochloride, $C_{25}H_{30}ClI_2NO_3$) is the hydrochloride salt of an iodine-rich benzofuran derivative known for its antiarrhythmic and vasodilatory activities. It is a class III antiarrhythmic agent that blocks myocardial calcium, potassium and sodium channels in heart tissue. In addition, this molecule is also known for its properties of inhibiting alpha and beta-adrenergic receptors (also called adrenoreceptors).

Regarding the solid state of amiodarone hydrochloride, its crystal structure was previously determined and showed that the related compound crystallizes in a monoclinic system, P21/c, with four molecules in the unit cell [1]. On the other hand, this substance is reported to degrade on melting. As far as the melting characteristics of this compound are concerned, some data are reported in the literature [2-7], but most of the melting temperatures are obtained at DSC scan rates not high enough to bypass the degradation of the compound.

The degradation pathway as well as the identification of the degradation products was performed by coupling thermogravimetric analysis (TGA) and FTIR experiments. We have previously shown that, when substance degrades on melting, the melting temperature as well as the melting enthalpy depend on the DSC scan rate [8,9]. Since degradation phenomena occurring during melting can be bypassed at high DSC heating rates, DSC studies at various scan rates are then carried out on this compound in order to get correct values of temperature and enthalpy of fusion. Flash Scanning Calorimetry (FSC) experiments were also performed in order to confirm the melting temperature and to try to push the degradation even further towards high temperatures.

2. Experimental

2.1. Chemicals Amiodarone hydrochloride (scheme 1) was purchased from SAFIC ALCAN, with a purity of 99.7 %. It is a white or almost white fine crystalline powder which needs to be protected from light and stored at a temperature not exceeding 30 °C. Its molecular weight was found to be 681.8 g/mol. The compound was used without further purification.



Scheme 1. Chemical structure of Amiodarone hydrochloride, $C_{25}H_{30}ClI_2NO_3$ (2-butyl-1-benzofuran-3-yl)-[4-[2-(diethylamino) ethoxy]-3,5-diiodophenyl] methanone).

2.2. Thermal analysis Differential scanning calorimetry and thermogravimetric analyses experiments were carried out using an 822e thermal analyzer, equipped with a FRS5 sensor, and a TGA 850 from Mettler-Toledo (Switzerland). The DSC and TGA experiments were achieved in the 25 – 250 °C temperature range under a constant dry air flow of 60 mL/min. Temperature and enthalpy of the DSC device were carried out using melting point of indium. An empty aluminum pan was used as a reference for all the DSC experiments. The onset of the corresponding endotherms was set as the melting temperature of the sample. Scan rates ranging from 1 to 100 K/min were used for the DSC experiments. Then, to avoid a calibration step for each heating rate, a tau lag calibration of the DSC device was performed beforehand [10]. This was made possible thanks to the multiple thermocouple sensor technology with which the device is equipped. The experiments were conducted using sample masses between 5 and 10 mg, weighed with a microbalance sensitive to 10 μg.

Flash Scanning Calorimetry was performed using a Flash DSC1 (METTLER TOLEDO) connected with a TC45 Intracooler (Huber) and an UFS-1 sensor. The starting temperature was set at 20 °C and the measuring cell was continuously purged with nitrogen gas at a flow rate of 10 mL/min. Temperature calibration was done using melting of high purity indium. Since the sample was in powder form, a hair was used to place few grains on the surface of the sensor using the Leica microscope mounted on the Flash DSC. However, the contact between the sample and the sensor was therefore not optimal since the grains do not have a flat surface. To improve the contact, we applied a micro drop of silicone oil (Wacker AK 60 Pa.s) on both sides of the sensor. Then, to obtain a homogeneous oil film thickness, several heating ramps up to 300 °C were carried out before depositing one or more grains of the material. More details on the preparation of the sample and on the Flash DSC technique is reported in Ref. [11].

2.3. X-ray powder diffraction Powder X-ray diffraction measurements were carried out on a Brucker D8 Discover diffractometer, using Cu-Kα1 radiation (1.5405980 Å) selected with a primary Johansson-type focusing (101) quartz crystal monochromator, and equipped with the LynxEye XE-T detector (mode 1D). Data as collected on a spinner-type (15 rpm) zero-background sample holder from 4° to 65° in 2-θ with a step size of 0.015° and 5 seconds per step for a total collection time of 6 h 12 min 45 s. The white crystalline powder sample was used as received. Profile matching was performed with FullProf 2k (Version 7.40 - Jan2021-ILL JRC).

2.4. TGA/FTIR analysis Thermogravimetric analysis experiments were performed using a Hi-res TGA 2950 analyzer (TA Instruments, USA). The TGA experiments were carried out in the 15-500 °C temperature range under a constant nitrogen flow of 100 mL/min. The TGA experiments were conducted at a scan rate of 30 K/min for the analyses coupled with FTIR. Isatherm, Nickel and Trafoperm were used for temperature calibration of the TGA device. The infrared analysis were performed with a Nexus model 470 FTIR device (Thermo/Nicolet, USA) with a heating transfer line and a heating TGA Interface from Thermo/Nicolet. The operating temperature for the transfer line and the TGA Interface was 250 °C. FT-IR analyses of evolved gas from TGA device were performed with 32 scans, a mirror speed of 2.5317 cm/s and a resolution of 4 cm^{-1} in the scan range of 450–4000 cm^{-1}. The FTIR bench was permanently purged with dry air. The FTIR calibration is checked by using a polystyrene film for wave number accuracy and resolution performance. Sample masses between 3 and 35 mg were used for these experiments.

3. Results and discussion

X-ray powder diffraction confirms that the Amiodarone hydrochloride powder used in the present study is crystalline, as shown by the intense peaks observed at 5.2°, 7.3°, 10.3°, 11.6°, or 16.1°, corresponding to (100), (110), (020), (210), and (211) *hkl* planes, respectively (Fig. 1). An analysis of the experimental pattern with the ICDD and COD databases showed that the reference 00-045-1755 (PDF-2, ICDD), corresponding to the Amiodarone hydrochloride, was a close match, as displayed in Fig. S1 (in the Supporting Information), but some experimental low-intensity peaks were not indexed by the reference. The single crystal structure of the Amiodarone hydrochloride has already been reported [1], and the cell parameters and monoclinic space group were used as a starting point for a profile refinement.

The profile matching calculation of the XRD data, displayed on Fig. 1, confirms the analyzed crystalline powder is Amiodarone hydrochloride, in good agreement with the single crystal structure [1]. No crystalline impurity is evidenced by XRD. More information are given in the supporting information file.

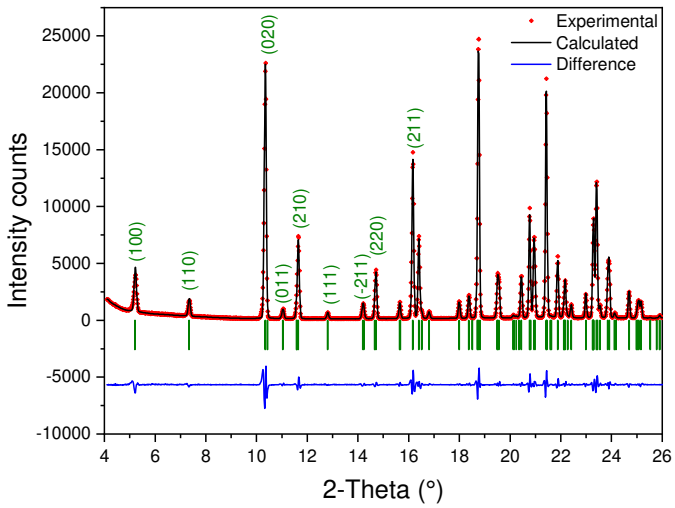


Fig. 1. XRD pattern for Amiodarone hydrochloride (red dots), its calculated profile (black line) and the difference between the experimental (red crosses) and calculated patterns (blue line). The *hkl* indexes of selected Bragg peaks are given in brackets (green dashes). More information is provided in the Supporting Information.

When Amiodarone hydrochloride is heated at different scan rates from 1 to 100 K/min, the resulting DSC thermograms undergo significant shifts through high temperatures (Fig. 2) indicating that the compound degrades on melting. Moreover, this hypothesis is confirmed when observing the sample itself. Indeed, samples turned from a white powder before analysis to a black viscous liquid.

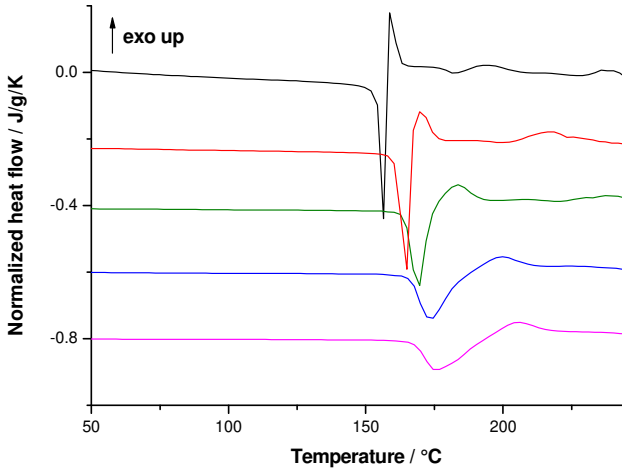


Fig. 2. Selected DSC thermograms of amiodarone hydrochloride as a function of the heating rate. From top to bottom: 1, 5, 20, 60 and 80 K/min. (The curves were shifted for clarity).

As a consequence, the onset of the ‘‘apparent’’ melting temperature increases with the scan rate to reach a plateau from v = 80 K/min, with a value equal to 165.9 ± 0.8 °C (Fig. 3A, Table 1). From Fig. 3A, it can be seen that the value of 156 °C, reported in Ref. 2 (Table 1), is obtained at very low scan rate (1 K/min).

We can also observe on the DSC thermograms an exothermic signal corresponding to degradation of amiodarone hydrochloride. It is interesting to note that at 1 K/min, the return to the baseline of the melting peak seems “ballistic”, which could mean that the departure of the degradation compounds occurs concomitantly with fusion, probably linked to the fact that the heating rate is low. This phenomenon of rapid return to the baseline is less and less abrupt as the heating rate increases.

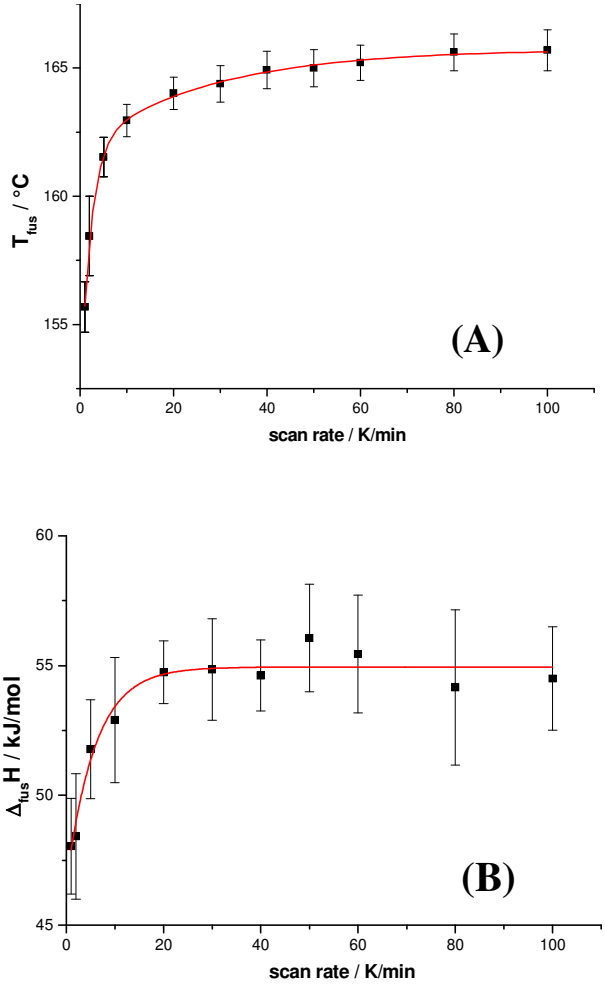


Fig. 3. ‘‘Apparent’’ melting temperature (A) and enthalpy (B) of amiodarone hydrochloride as a function of the DSC scan rate.

As for the melting temperature, the “apparent” melting enthalpy increases with the scan rate to reach a plateau from v = 20 K/min, with a value equal to 54.9 ± 0.2 kJ/mol (Fig. 3B, Table 1).

Table 1 gathers the thermal data resulting from this study as well as the values found in the literature. As can be seen, discrepancies are observed both for temperatures and enthalpies of fusion. It should be noted that in reference 3, two sets of data are reported. One set is obtained from TG/DTG/HF experiments and another set from by DSC analysis. Both experiments were carried out at 10 K/min. The enthalpy of fusion obtained by DSC agrees well with our value found for higher heating rates. Surprisingly, their value obtained by TG/DTG/HF is very different. The other experiments reported in the literature were carried out at heating rates of 10 or even 20 K/min. On reading the thermograms, it can be observed that degradation takes

place during melting. It is therefore surprising that some values may coincide with the values we have found pushing back the degradation at temperatures above the melting temperature. In ref. [7], TGA experiments are carried also out on amiodarone hydrochloride. The authors report two thermal decomposition stages, the first one being between 250 and 415 °C with a mass loss of 61.94 %. But no more details are given about this decompostion.

Table 1

Experimental melting properties of amiodarone hydrochloride compared to literature data.

T_{fus} (°C)	$\Delta_{fus}H$ (kJ/mol)	DSC scan rate (K/min)	Ref
165.9 ± 0.8	54.9 ± 0.2	> 80	This work
156			2
149-157	44.6	10 (TG/DTG/HF)	3
157	54.95	10 (DSC)	3
169.1	49.159	20	4
159	60.1	10	5
166		10	6
164		10	7

The degradation was demonstrated by simultaneously coupling DSC and ATG analyses, for a given scan rate. The experiments were carried out at different heating rates between 2 and 80 K/min. The experiments at 10 and 60 K/min are presented in Fig. 4 to illustrate the following statement. The melting temperature is located on the graphs in order to observe the temperature shift between melting and the beginning of degradation (indicated by an asterisk on the figure). Then, it is unquestionable that at low heating rate the product begins to degrade before melting (Fig. 4A). This is no longer the case when the heating rate increases where it can be observed that degradation takes place just after melting (Fig. 4B).

This therefore favorably argues the fact that the product degrades on melting but that this degradation is bypassed when we increase the heating rate to be displaced at higher temperatures.

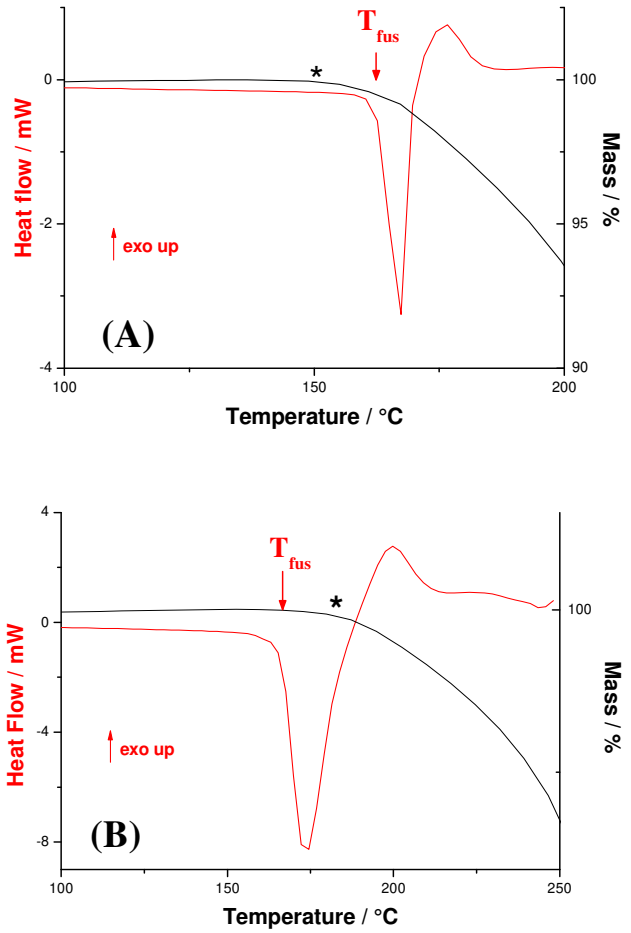


Fig. 4. Superposition of TGA and DSC curves for amiodarone hydrochloride at two different scanning rates (in K/min): (A): 10, (B): 60. The asterisk indicates the beginning of mass loss.

In order to identify the evolved gas from amiodarone hydrochloride degradation, TGA experiments, carried out at 30 K/min, were coupled with FTIR analysis. Then, upon heating, one can observe that amiodarone hydrochloride starts to degrade before melting since between 135 and 159 °C, the departure of water and 2-fluoroethanol is observed on the FTIR spectrum (0.2 % mass loss, Fig. S3, Table S1). This corroborates the result we have found from DSC and TGA experiments carried out at 10 K/min (Figure 4A). From the FTIR analysis, triethylamine was identified as the following degradation product the departure of which is comprised between 159 and 190 °C, *i.e.* during and after melting (2.0 % mass loss, Fig. S3, Table S1). Regarding the departure of hydrogen chloride, it is not observed at the very beginning of the thermal decomposition but rather after 229 °C. This compound is not

subject to a resolved event on the TGA thermogram since the departure of other degradation compounds such as hydrogen fluoride or hydrogen iodide is also observed in the same time (Fig. S3).

In figure S4 are shown the FTIR spectra of the main evolved gas obtained during TGA experiment carried out at 30 K/min.

With regard to the thermogram obtained for the highest heating rate by conventional DSC (80 K/min), although the degradation process is pushed back to higher temperatures, the exothermic signal remains. We therefore undertook thermal analysis measurements using the flash DSC technique in order to obtain much higher heating rates and thus ensure that the degradation process could be pushed towards higher temperatures. In order to facilitate the departure of the degradation compounds, a first series of measurements was made by directly depositing a small crystal of amiodarone hydrochloride on the sensor without silicone oil (Fig. 5). A first FSC experiment was carried out at the heating rate of 60 K/min (curve A on Fig. 5), for comparison with the conventional DSC. One can observe that the behavior is the same. However, for higher heating rates, the exothermic signal related to the departure of the degradation compounds is no longer visible at all (curves B and C on Fig. 5).

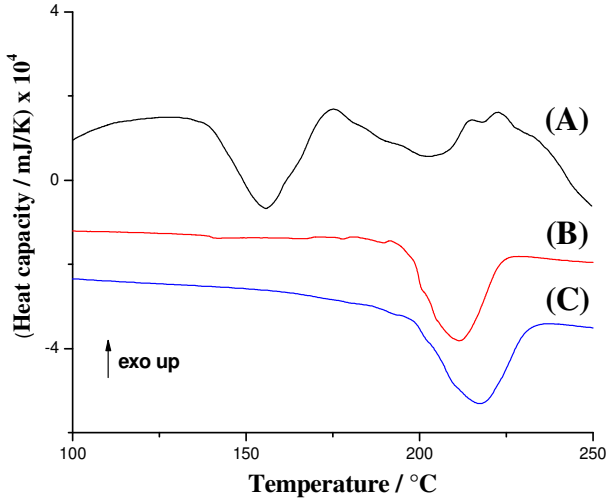


Fig. 5. FSC thermograms of amiodarone hydrochloride obtained without oil silicone as a function of the heating rate (in K/s): (A): 1; (B): 1000 and (C): 2000. The curves were shifted for clarity.

It should be noted that the temperatures reported in Fig. 5 have no physical significance insofar as the contact between the measuring cell and the amiodarone sample is not optimal.

However, these experiments clearly show that the departure of the degradation compounds can be pushed to temperatures well above the melting point. No exothermic signal is no more detected on the thermograms, probably due to the quick departure of the products of degradation given the very high heating rates. The only exothermic signal which is observed on the thermograms is therefore necessarily linked to the melting of amiodarone.

Another set of experiments were carried by FDSC but using, this time, silicone oil in order to have a better contact between the sample and the measuring cell and then to get a better precision on the measurement of the melting temperatures.

Based on the value of the melting enthalpy found previously (54.9 kJ/mol or 80.4 J/g), we were then able to determine the mass of the amiodarone hydrochloride samples subjected to the different temperature ramps. They were estimated at 183, 54 and 36 ng for the speeds of 100, 200 and 500 K/s respectively. Then, normalized curves could then be drawn taking into account the heating rate and the sample mass (Fig. 6) The melting temperatures thus measured confirm the one obtained by conventional DSC for high scanning rates (165.9 ± 0.8 °C). As for experiments realized without silicone oil, the departure of the degradation products seem to be pushed to higher temperatures but with better definition of the thermograms and better accuracy about melting temperatures.

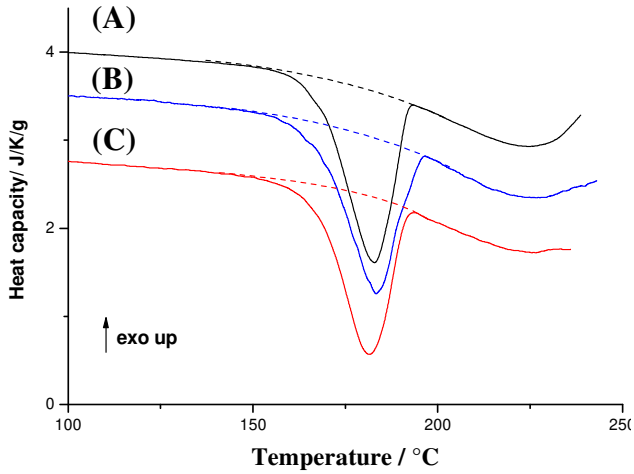


Fig. 6. FSC thermograms of amiodarone hydrochloride obtained with oil silicone as a function of the heating rate (in K/s): (A): 100; (B): 200 and (C): 500. (The curves were shifted for clarity).

4. Conclusion

As a first approach, the X-ray diffraction analysis confirmed that the product used in a pharmaceutical context was indeed of the same nature as that already published. In a second step, the accurate melting data of amiodarone hydrochloride were obtained by using high DSC scan rates, allowed separating melting and degradation. The use of FSC made it possible not only to confirm the melting temperature obtained by the "plateau method" but also to obtain a melting signal independent of the degradation, thus confirming our hypothesis that the disturbance of the melting signal was due to the loss of degradation compounds, as corroborated by TGA-FTIR experiments.

The knowledge of the thermal behavior of amiodarone hydrochloride is of importance from the point of view of the formulation of amiodarone hydrochloride as a drug. Indeed, the degradation of amiodarone hydrochloride on melting indicates that this active ingredient must not be heated alone to be formulated as a drug. In the case where this active ingredient is formulated as a solid dispersion to increase its aqueous solubility and its absorption, for example, a strategy would be to use ingredients with lower melting point and a sophisticated technology (like Hot Melt Extrusion with proper process conditions) to bypass degradation effect potentially observed.

CRediT authorship contribution statement

Mohamed Elkhashab and Atourya Mhoumadi: DSC and TGA experiments. **Franck Collas**: FSC experiments and writing. **Nicolas Louvain and Bernard Fraisse**: XRPD experiments, profile matching and writing. **Sylvain Prillieux and Jean-Bernard Dumas**: supervision. **Philippe Espeau**: conception and design of the study, writing.

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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Graphical abstract