

# A QUARTZ CRYSTAL MICROBALANCE-ASSISTED METHOD FOR THE ASSESSMENT OF IODINE CONTENT IN ORGANOIODINES

Iliyan Kolev<sup>1</sup>, Pavlina Koseva<sup>1</sup>, Mihail Marinov<sup>2</sup>, Gergana Alexieva<sup>3</sup>, Vesselin Strashilov<sup>3</sup>

<sup>1</sup>*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Medical University of Varna*

<sup>2</sup>*Freelance electronics engineer, Varna*

<sup>3</sup>*Department of Solid State Physics and Microelectronics, Faculty of Physics, Sofia University "St. Kl. Ohridski"*

## ABSTRACT

**INTRODUCTION:** A new experimental quantitative approach for evaluating iodine content in organoiodine compounds has been proposed, based on the quartz crystal microbalance (QCM) method. This approach relies on following the time behavior of the resonance frequency of the quartz plate under temperature activation of iodine-containing analyte deposited on its surface.

**MATERIALS AND METHODS:** We have applied the QCM method and the pharmacopoeial titrimetric method.

**RESULTS AND CONCLUSION:** From the mass variations observed, the quantity of emitted iodine is precisely obtained, which readily delivers its initial content in the studied sample. The obtained value corresponds exactly to the theoretical prediction, in contrast to the value obtained by applying the conventional pharmacopoeial metrics.

**Keywords:** iodine content, organoiodine compounds, QCM

## INTRODUCTION

Organoiodines are organic compounds, in the composition of which at least one carbon-iodine covalent center may be found. In the contents of the *European Pharmacopoeia*, on one hand, and the web-based science space, on the other, the references to this type of organohalides appear, however, rather

limited (1-3). This probably comes from the restricted distribution of these materials due to their photo- and thermosensitivity (structural instability), as well as thermodynamical lability in solutions or in the bulk (2,3).

In analogy with the other organohalides (organochlorides, bromides, and fluorides), the iodine-substituted organics should also be subject of quantitative (*sui generis* elemental) control with respect to their halogen content.

In this regard, many quantitative methods have been developed through the years, aiming to cover or overcome these analytical features (4).

In the present work we propose a new quantitative approach, targeting the evaluation of the iodine content in the compound, based on applying the quartz crystal microbalance (QCM) method.

---

### Address for correspondence:

Iliyan Kolev  
Faculty of Pharmacy  
Medical University of Varna  
84 Tzar Osvoboditel Blvd  
9002 Varna  
e-mail: [ilian.kolev@mu-varna.bg](mailto:ilian.kolev@mu-varna.bg)

**Received:** November 29, 2018

**Accepted:** December 20, 2018

## MATERIALS AND METHODS

For the aims of this study, KOH (ca. 85%, for analysis, Acros Organics), HCl (37%, PanReac), and KIO<sub>3</sub> (99.5%, for analysis, Acros Organics) were used without further purification. The solvents chloroform, toluene, and dichloromethane were received from Sigma-Aldrich and dried by standard protocols.

The QCM method is based on measuring the variation of the resonant frequency of a quartz plate under the change of the mass of a solid phase sample deposited on its surface (5-7).<sup>1</sup>

We used an AT-cut quartz plate with a thickness of 200µm and a diameter of 14.0mm. The two plate surfaces carried Au layers serving as electrodes for applying the exciting electric field. The use of this method in the present thermo-gravimetric study relied on employing an original experimental setup, schematically represented as following:

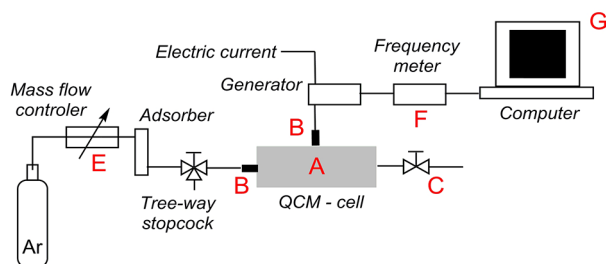


Fig. 1. Experimental QCM setup for the assessment of iodine content in organoiodines

The quartz resonator, which played the function of analyzer (B), was embedded in an isolated cell (A) fabricated from borosilicate glass.

The organoiodine compound synthesized by us<sup>2</sup> (~3.0 ÷ 4.0 µg) was deposited on the surface of

<sup>1</sup> The quartz crystal demonstrates piezoelectric properties. It becomes deformed under the action of an electric field applied across its crystal lattice or, conversely, acquires electric polarization when strained mechanically. Pieces in the form of thin plates cut from the single crystal along specific directions demonstrate pronounced mechanical resonant properties. The resonant frequency depends on the geometry and size of the plate. Precision quartz resonators are additionally tuned during fabrication by grinding the plate surface and controlling the thickness of deposited electrodes.

<sup>2</sup> Synthesis of the analyzed compound (2,6-diiodoeduesmic acid) was achieved by the synthetic procedure described in (9). The identity and purity of the obtained product was also successfully proven by <sup>1</sup>H and <sup>13</sup>C NMR and FTIR

one of the Au electrodes of the quartz plate from a toluene solution using an automatic micropipette. Then the resonator was placed in the QCM cell. After evaporation of the toluene droplet (in dry flowing Ar) the remaining additive mass of the analyzed compound should not exceed the limit above which the QCM goes out of working regime (frequency should be kept in the interval 9.0÷10.0 MHz). For this purpose the sample was activated for an appropriate period of time (usually 30 min) in a flow of dry Ar at a rate of 100 cm<sup>3</sup>/min and temperature of 21°C until constant mass, i. e. stable frequency of the device, has been reached.

The connection between the setup elements and the cell unit was accomplished through a system of ground glass joints (B) and a one-way stopcock outlet (C).

After the establishment of a constant signal the cell was heated in a flow of warm air generated by a HotGun (Steinel HG 2310 LCD). The precise tuning of the velocity of the carrying gas was performed through a flow controller (E). The variation of the resonant frequency of the QCM sensor was monitored on a frequency counter BK precision 1823A (F). Separately, the change of the mass (frequency) was registered at each second using a personal computer provided with specific software (G). The registered data were then recalculated as changes of the mass of the analyzed organoiodine analyte using Sauerbrey's equation:

$$\Delta m = (\rho N A / f^2) \Delta f \quad (1)$$

where  $\Delta m$  is the mass change (g),  $f$  is the resonant frequency (Hz),  $\rho$  is the quartz density (2.648g/cm<sup>3</sup>),  $N$  is the frequency constant of quartz (1.668×10<sup>5</sup>Hz/cm),  $A$  is the active area of the resonator plate (cm<sup>2</sup>) and  $\Delta f$  is the frequency change (Hz).<sup>3</sup>

### Classical Pharmacopoeial Approach for Evaluation of Iodine Content (8)

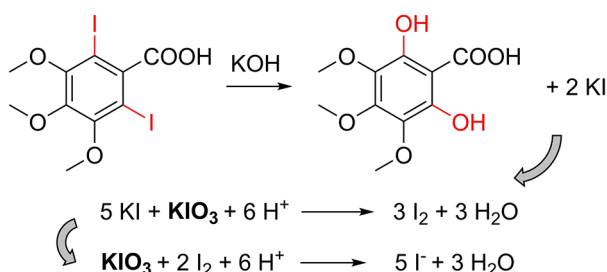
A 250 ml iodine flask was charged with 5.0 mL toluene solution of 2,6-diiodoeduesmic acid (24.5mg/mL), 10.0mL distilled water, and 0.5g KOH. The flask content was heated at 50°C for a period of 2 hours in a water bath. Then, 35.0mL conc. HCl and

spectroscopy (Kolev I, et al., unpublished results).

<sup>3</sup> This equation is valid under the conditions of constant thickness of the organic layer and constant temperature (basic and under heating).

5.0 mL chloroform were added to the obtained working solution. The final solution was titrated with 0.05 mol/L  $\text{KIO}_3$  under continuous agitation.

The equivalent point is reached at the moment when the chloroform layer is completely decolorized. According to the established conditions, 1.0 mL of the used titrant should be read as equivalent to 16.60 mg of KI. The results obtained from the analysis, done three consecutive times, are as follows:  $V_1=4.1\text{mL}$ ,  $V_2=4.2\text{mL}$ ,  $V_3=4.0\text{mL}$ .



*Scheme 1. Reaction equations illustrating the applied pharmacopoeial quantitative method for iodine content assessment*

The calculations show that the percent iodine content in 2,6-diiodo-3,4,5-trimethoxybenzoic acid should be equal to 42.3% - a value significantly different from the theoretically expected one of 54.31%.

## RESULTS AND DISCUSSION

### *Analysis of the Results for the Iodine Content in Organoiodine Compounds Obtained by Means of the QCM Method*

In this study we present the QCM technique as a new and unique method for determining the content of iodine in organoiodine compounds. This method seemingly resembles the other thermo-gravimetric methods for studying the mass variation of a sample in solid aggregate state as a function of temperature. However, apart from the mere  $\Delta m=f(T)$  dependence, this piezoelectric approach also covers, subject to appropriate spectral analysis, the phase variations occurring as a result of thermo-destructive reactions, such as those expected at aromatic deiodination.

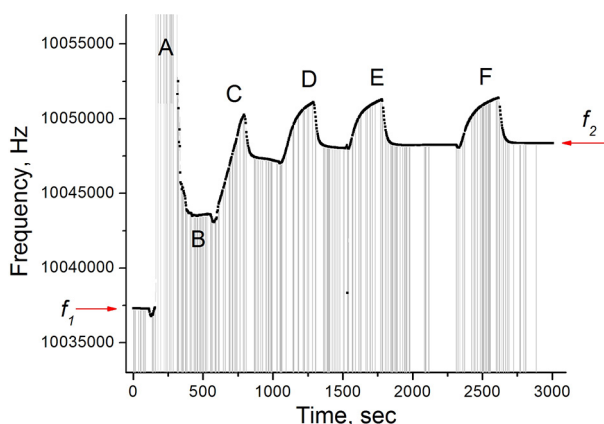
We present experiments which: 1. allow monitoring the frequency variation in a repetitive mode; 2. analyze the thermo-gravimetric profile at each activation step of heating or cooling; 3. register sharp

dynamic deviations in the visco-elastic properties of the sample.

We succeeded in forming a homogeneous layer of 2,6-diiodo-3,4,5-trimethoxybenzoic acid on the Au electrode obtained by gentle evaporation of a droplet of the toluene solution of the examined analyte. Previous attempts including powdering of the surface with tiny crystal dust of the explored material did not allow obtaining a stable output signal ( $f_1$ ) as with other kinds of materials (10).

After reaching a constant frequency signal the sample was exposed to thermal activation through hot air stream flashing the pyrex cuvette where the quartz plate was positioned.

The impact of heating was sensed immediately – the resonant frequency sharply increased until a moment where the oscillator went down (stage A, Fig. 2).



*Fig. 2. Time-frequency variation of the QCM loaded with the studied organoiodine compound resulting from thermo-programmed processing*

The observed effect probably comes from additive changes due to phase transitions (solid-solid and solid-liquid) and thermo-associated mass losses related to destruction of unstable C-I bonds with further emission of molecular iodine.

Upon continuous exposure still within this stage the resonant frequency came back to working regime (the 10 MHz range). After discontinuing the thermal activation – stage B – the frequency stabilized at a new value, much higher than the basic one  $f_1$  preceding the thermal activation. As commented before, we relate the frequency variations in this

working range to mass variations in the composition of the studied organoiodine sample only.

Subsequently, the analyte has been subjected to further thermal processing under analogous conditions – temperature 150°C and flow of dry Ar fed at a rate of 100mL/min. These are stages C, D, E, and F, respectively (Fig. 2). The number of activation cycles was fixed by the necessity of reaching stable frequency, i. e. interruption of the variations in the mass of the sample.

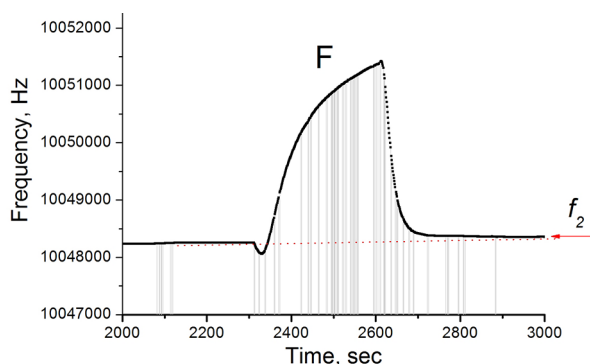


Fig. 3. Frequency change in the last stage F of the thermo-programmed processing of the sample

This condition has been reached at stage F where the observed minimum frequency deviation (before/after thermal processing) was about 80 Hz, built up for 30 min (Fig. 3) and reducing to the so-called *drift effect*, inherent to all spectral analytical methods.

Table 1 summarizes the obtained numerical results at the ends of stages A-B, C, D, E, and F, obtained under the discussed experimental conditions of the thermal study.

The following two observations are indicative of the presence of a residual sample at the end of the measurements:

Table 1. Variations in the resonance frequency of the quartz plate resulting from the manipulations carried out

Starting frequency $f_0$ (Hz)	Basic frequency of the loaded plate $f_1$ (Hz)	Stationary frequency after heating the sample $f_2$ (Hz)
10057650	10037280	B 10043600
		C 10047100
		D 10048019
		E 10048310
		F 10048430

- ◆ the final frequency  $f_2$  differs from the starting one  $f_0$  with much more than the drift;
- ◆ a photograph of the resonator shows traces of a material left on the surface, Fig. 4.



Fig. 4. Photograph illustrating the presence of a residual organic sample on the plate surface at the end of stage F

In Table 1, the difference  $f_0-f_1$  is indicative of the quantity of sample deposited on the resonator surface, and the difference  $f_2-f_1$  – to that of the contained iodine. Specifically, we use these data to calculate the change in the mass of the organoiodine sample and its iodine content (IC). The calculations are carried out using the following equation:

$$IC = \frac{\Delta m_{12}}{\Delta m_{01}} 100, \quad (2)$$

where  $\Delta m_{01}=m_0-m_1=4.454\mu\text{g}$  is the mass of 2,6-diiodoeudesmic acid, calculated from the difference  $f_0-f_1$ , and  $\Delta m_{12}=m_1-m_2=2.453\mu\text{g}$  is the mass of emitted iodine, calculated from the difference  $f_2-f_1$ .

So, for the IC in the synthesized 2,6-diiodoeudesmic acid we have received, using the applied acoustic method, the value of 55.07 wt.%, which is practically equivalent to the theoretically expected one of 54.31 wt.%.

As commented earlier, the percentage of iodine in the studied analyte has also been determined using the classical pharmacopoeial quantitative approach, resulting in the value of 42.3 wt.%. The serious deviation observed should be related to the expected systematic errors typical for the iodometric analysis (3).

In conclusion, the applied QCM approach for determining iodine content in organoiodine compounds proves to exhibit high accuracy and sensitivity in working with small ( $\mu\text{g}$ ) sample quantities, leading to experimental results very close to the theoretical values.

## CONCLUSION

A new assay, based on the QCM technique, for evaluating the quantitative content of iodine in a newly synthesized iodo-substituted analyte, has been proposed. This quantitative method differs from the existing ones by being completely defined by a set of analytical positives, namely: capability for directly analyzing organoiodine analytes without the necessity of their complicated chemical conversions; accessibility to microgram quantities of studied samples; capability for real time registration of mass variations in the samples; experimental easiness giving access to less experienced researchers; lower expected systematical and methodical errors.

In that capacity, the present method is also convenient to the purposes of the quantitative pharmacopoeial analysis. This method's suitability should be assessed in detail, along with presenting its potential for studying various analytes of the pharmacopoeial group.

## REFERENCES

1. European Pharmacopoeia, Strasbourg: Council of Europe. 8th ed. Vol. 1 and 2;2013.
2. Lyday PA. Iodine and Iodine Compounds. In: Ullmann's Encyclopedia of Industrial Chemistry, Weinheim: Wiley-VCH;2005. doi:10.1002/14356007.a14\_381.
3. Kaiho T (ed.). Iodine Chemistry and Applications. Hoboken: John Wiley & Sons;2014. ISBN 1118466292, 9781118466292.
4. Cheng FW. Simple and specific microdetermination of organoiodine via oxygen flask combustion. *Microchem J.* 1980;25(1):86-92. doi:10.1016/0026-265X(80)90247-7.
5. Kolev I, Mavrodinova, V, Alexieva G, Strashilov V. Pore volume probing of boron-modified MCM-22 zeolite by quartz crystal microbalance assisted study of o- and p-xylene adsorption. *Sens Actuators B-Chem.* 2010;149(2):389-94. doi:10.1016/j.snb.2010.06.044.
6. Youssef IB, Sarry F, Nysten B, Alexieva G, Strashilov V, Kolev I, Alem H. Growth and toxic gas sensing properties of poly(urethaneimide) thin films. *Talanta.* 2016;153:145-51. doi:10.1016/j.talanta.2016.03.021.
7. Kolev I, Alexieva G, Strashilov V, Youssef IB, Sarry F, Alem H. Layer thickness impact on the capacity of poly(urethaneimide) for sorbing toxic gases. *J Appl Polym Sci.* 2016;133(48):44214. doi: 10.1002/app.44214.
8. The Japanese Pharmacopoeia, Tokyo: Society of Japanese Pharmac. 15th ed.;2006.
9. Kolev IN, Petrova SP, Nikolova RP, Dimowa LT, Shivachev BL. Synthesis, characterization, and crystal structure of 2-iodo-3,4,5-trimethoxybenzoic acid. *J Mol Struct.* 2013;1034:318-24. doi:10.1016/j.molstruc.2012.10.039.
10. Kolev IN, Ivanova NA, Alexieva GE, Tsutsumanova GG, Strashilov VL. Diltiazem-loaded Eudragit RS 100 microparticles for drug delivery: the challenge of viscosity. *Scr Sci Pharm.* 2018;5(1): 20-4. doi: 10.14748/ssp.v1i1.5004.