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Short Communication

Determination of quinine in some pharmaceutical preparations using a ring-coated piezoelectric sensor

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Introduction

Quinine is a highly active blood schizontocide and is still used in the treatment of *P. falciparum* malaria resistant to chloroquine or other antimalarial drugs. For its determination, most pharmacopoeias recommend non-aqueous titration [1–3] or an extraction-weighing method [1]. Other methods that have been proposed include spectrophotometry [4], fluorimetry [5], liquid chromatography [6] and ion-selective electrode potentiometry [7]. The conventional extraction-weighing method which is based on neutralization, extraction, evaporation and weighing the quinine base is time-consuming and rather inconvenient; in addition a relatively large sample is required. The piezoelectric quartz crystal is very sensitive for weight determination and is widely used as a quartz crystal microbalance (QCM) in both science and technology [8]. In the present paper, a new method is proposed for the determination of quinine based on the use of a specially designed ring-coated piezoelectric crystal sensor. The method is simple and sensitive and enables submicrogram amounts of quinine to be determined.

Materials and Methods

Apparatus

The piezoelectric quartz crystals used were 9 MHz AT-cut commercial crystals of JA-5 model (8 mm diameter) with silver electrodes (4 mm diameter) on each side (Tongtsei Factory No. 607, Gangsu, China). The crystals were coated by the following technique. A mixture of 0.5 g of sodium silicate with 2 ml of water was heated gently to boiling and, after cooling, blended with 0.1 g of finely powdered quartz (300 mesh) and 50 mg of sodium fluorosilicate. After standing for 5–10 min, the supernatant was applied in a circle on to the piezoelectric crystal along the electrode boundary. The coated crystal was held horizontally and dried at 80°C for 1 h. The resulting circular coating was 4.5 mm in o.d. and 2.5 mm in i.d.

The ring-coated quartz crystal was kept horizontally in the measuring cell which comprised a Plexiglass box (6 mm in length, 4 mm in width and height) with a rubber plug for sample injection on its top. The crystal holder was connected to an integrated circuit oscillator made in this laboratory [9] and supplied with a d.c. voltage regulator (JWY-30F model; Shijiazhong Electronic Factory No. 4). The crystal frequency was measured by a digital frequency counter (SS-3320 model; Shijiazhong Electronic Factory No. 4). A 1-μl microsyringe was calibrated and used for sample injection. Nitrogen flow from a nitrogen cylinder was regulated with a rotor flow-meter after passing the gas through a drying tower containing anhydrous calcium chloride and silica gel.

Chemicals and solutions

All chemicals used were of analytical-reagent grade. Chloroform which was used as extractant for quinine was saturated with water

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by repeated mixing. Double-distilled water was used throughout and was saturated with chloroform when used to prepare solutions for extraction. Quinine dihydrochloride was of pharmacopoeial quality [1]. A standard solution of 2 mg ml^{-1} of quinine dihydrochloride was prepared. Other standards were prepared from this solution by serial dilution.

Calibration graph

A 1.00 ml volume of the standard solution of quinine dihydrochloride was mixed with 1 ml of 0.1 M sodium hydroxide. The mixture was shaken for 1.5 min with 2.00 ml of chloroform. After phase separation and removal of the upper aqueous layer with a dropper, 1 μl of the organic layer was applied with a 1 μl microsyringe on to the ring-coated quartz crystal in the measuring cell, through which a stream of dried nitrogen was passed at a flow rate of 100 ml min^{-1}. After 2 min, the crystal frequency (F_1) was recorded and the frequency change calculated from the equation: $\Delta F = F_0 - F_1$, where F_0 is the frequency measured with the same ring-coated crystal with a blank under the same experimental conditions. A calibration graph of frequency changes against quinine dihydrochloride content was constructed. After each measurement chloroform (about 25 μl) was injected on to the coated-ring to remove the remaining free quinine. After soaking up the solvent with a filter-paper and leaving for 3 min, the crystal was ready for the next measurement.

Assay of quinine dihydrochloride injection

Ten ampoules of quinine dihydrochloride injection were mixed; 1.00 ml of the mixed solutions were diluted to volume in a 250-ml standard flask. The content of quinine dihydrochloride was determined as described above and calculated from the calibration graph.

Assay of quinine dihydrochloride tablets

A sample of 20 tablets was weighed and finely powdered. A portion of the powder was weighed out accurately (about 100 mg) and saturated with water. The mixture was transferred to a 100-ml standard flask and diluted to volume with water; the solution was filtered through a dry filter and the first 20 ml of filtrate was discarded. A 5.00 ml volume of the filtrate was analysed as described above.

Results and Discussion

It has been found that when a droplet of organic solution is applied on to the surface of a conventional piezoelectric quartz crystal, the liquid, in contrast to the aqueous solution, diffuses and spreads over the crystal surface before the solvent wholly evaporates. According to Sauerbrey's equation, $\Delta f = -f^2 \Delta M/N\rho S$ [10], if the applied mass ΔM is homogeneously applied over a definite area S, the frequency change Δf is proportional to ΔM, while N, the frequency constant of the quartz crystal, f, the oscillation frequency of the crystal, and ρ, the density of quartz, are constants. The spread-over effect of the organic solution makes the frequency determination practically unfeasible owing to unstability in frequency and poor reproducibility of the result. Therefore, it is necessary to confine the surface area of the quartz crystal so as to eliminate such effects on the determination of quinine; the piezoelectric quartz crystal microbalance can then be applied to 'weigh' microamounts of free quinine base deposited on the crystal surface after evaporation of the extracting solvent.

More than 50 inorganic and organic substances and their mixtures have been tested. It has been found that the best way to solve the aforementioned problem is to coat the quartz crystal surface in a circle with a ring as described in the experimental section, in this way the determination of the extracted quinine is made possible. Submicrogram amounts of quinine can be determined with such a ring-coated crystal sensor.

Factors affecting the frequency measurement were investigated in order to select the optimum conditions for the quinine determination with the ring-coated crystal sensor. The most favourable formulation for the crystal coating is 10 parts of sodium silicate, 2 parts of powdered quartz and 1 part of sodium fluorosilicate (by wt). For the ring-coated crystal prepared with this coating material, the oscillation frequency of the quartz crystal decreases by approximately 0.15%. The sensitivity in quinine determination reaches down to 10^9 Hz g^{-1}. In order to avoid adsorption of moisture from the surrounding air, all measurements were carried out in a nitrogen stream, previously dried with anhydrous calcium chloride and silica gel, at a flow rate of 100 ml min^{-1}. Study of the effect

of temperature on the determination of quinine showed that no significant influence was caused by temperature within the tested range 5–50°C. Volatilization of the extracting agent from the quinine analyte is complete within 0.5 min at 15°C. Even at lower temperatures, volatilization is still fast, e.g. 1 min at 8°C. Hence, the determination of quinine by this method can be achieved at room temperature without any need for heating to evaporate the extracting solvent; in contrast, heating is required in the conventional extraction–weighing method for the determination of quinine.

Factors affecting the determination of quinine

In the proposed method, quinine dihydrochloride was first neutralized with a basic reagent to form the free alkaloid which was then extracted into an appropriate organic solvent; measurement was made of the frequency change of the ring-coated quartz crystal caused by the deposition of quinine base after evaporation of the solvent. Factors affecting the determination were investigated so as to find out the most appropriate conditions. From a study on the effect of extracting solvents, it was found that chloroform gives the highest extraction of quinine and also better reproducibility (Table 1). The pH of the aqueous phase may affect the determination of quinine. Results showed that the frequency change becomes constant when the solution pH is not less than 8; at lower pH values, it decreases with decreasing pH. No significant differences in the frequency change were found between the different basic reagents tested, such as ammonia (1 + 1 or 1 + 3), 20% NaOH, 10% Na_2CO_3 and 5% $NaHCO_3$. The influence of extraction time was examined. The result showed that extraction proceeds very fast; equilibrium is established within 0.5 min. Investigation of the effect of organic to aqueous phase-volume ratio demonstrated that there was no significant influence for phase-volume ratios of 2:1–1:4.5. The organic extract was stable and the frequency change was constant even after 48 h. Since different crystals give different sensitivities in frequency measurement, it is necessary for the measurement to be carried out with the same ring-coated quartz crystal so as to obtain comparable results.

Calibration graph and reproducibility

The frequency change of the proposed ring-coated piezoelectric quartz crystal sensor was directly proportional to the content of quinine (recalculated as its dihydrochloride salt) in the range 0.015–1.0 μg; the regression equation was $\Delta F = 705.2\ W + 0.4$ with a regression coefficient of 0.998, where ΔF is measured in Hz and W in μg. The standard deviation was 8.0 Hz (relative standard deviation = 2.3%) for six determinations of 0.5 μg of quinine dihydrochloride.

Life-span and restoration of the ring-coated crystal sensor

The life-span of the ring-coated quartz crystal sensor was not less than 6 months. When not in use, it should be kept in a desiccator over silica gel. No deterioration was caused by the extracting solvent used in this work.

For the crystal to be restored after the quinine determination, about 25 μl of chloroform was used to completely remove the free quinine base left within the coated ring. The piezoelectric crystal is ready for the next measurement after the restoring solvent has been soaked up by a filter paper and evaporated within 2–3 min. An increased flow rate of nitrogen may be used to accelerate solvent evaporation.

Table 1
Effect of extracting solvent on the determination of quinine*

Extracting solvent	Frequency change† (Hz)	Standard deviation (Hz)
Chloroform	283	4
Carbon tetrachloride	165	4
1,2-Dichloroethane	218	6
Benzene	227	4
Xylene	148	11
Di-i-propyl ether	216	7
Diethyl ether	182	12

*0.4 μg of quinine dihydrochloride was tested.
†Values given here are means from four to five measurements.

Table 2
Effect of foreign substances on the determination of 0.3 μg of quinine dihydrochloride

Foreign substance*	Analyte found (μg)	Foreign substance*	Analyte found (μg)
Glycine	0.300	Magnesium chloride	0.291
Alanine	0.305	Ammonium ferric sulphate†	0.303
dl-Aspartic acid	0.300	Nickel sulphate†	0.314
Glucose	0.308	Manganous sulphate†	0.294
Sulphamic acid	0.296	Sodium fluoride	0.303
Urea	0.312	Potassium monohydrogen phosphate	0.303
Thiourea	0.308	Potassium iodide	0.314
Glutamic acid	0.305	Lead nitrate†	0.299
Sucrose	0.298	Cadmium sulphate†	0.306
EDTA	0.310	Ammonium acetate	0.308
Calcium chloride	0.295	Sodium bromide	0.308
Zinc sulphate†	0.310	Ethylenediamine	0.400
Copper sulphate†	0.310	Mercuric nitrate‡	0.118

*Other substances were added as 0.05 M solution.
†Added as 0.01 M solution.
‡Added as 5 mM solution.

Interference

The interfering effect of a number of inorganic and organic substances on the determination of quinine has been investigated by adding 1 ml of a solution of the substance under test to an aqueous sample solution containing 0.3 mg of quinine dihydrochloride and following the standard procedure. The results are given in Table 2. Ethylenediamine and mercury (II) demonstrate severe interference. Calcium (II), magnesium (II), copper (II) and iron (III) give precipitates with sodium hydroxide. These precipitates remain in the aqueous phase and therefore cause no interference with the determination of quinine. Alkaloids such as cinchonine, ephedrine, carbetapentane and chlorpheniramine can also be extracted by chloroform and cause interference. No significant interference was caused by other substances listed in Table 2.

Quinine dihydrochloride assay

The results obtained for the piezoelectric assay of quinine dihydrochloride using a ring-coated crystal sensor and the calibration graph are given in Table 3. The mean recovery was 100.3% and the relative standard deviation was 1.4%.

Pharmaceutical preparations of quinine dihydrochloride can also be analysed by the proposed piezoelectric method with a ring-coated crystal sensor. The result for quinine dihydrochloride tablets with a nominal amount of 0.3 g in each tablet was 298.3 mg per tablet, and the standard deviation for 12 determinations was 4.0 mg per tablet. The result for quinine dihydrochloride injection with a nominal content of 250 mg ml^{-1} was 244.3 mg ml^{-1}, the standard deviation being 4.6 mg ml^{-1} (12 determinations). The corresponding results for preparations determined by non-aqueous titration [1] were 296 ± 3 mg per tablet and 246 ± 3 mg ml^{-1}.

Table 3
Assay of quinine dihydrochloride*

Test no.	Taken (μg)	Found (μg)	Recovery (%)
1	0.0500	0.0493	98.6
2	0.100	0.102	102.0
3	0.200	0.203	101.5
4	0.300	0.296	98.7
5	0.400	0.400	100.0
6	0.500	0.504	100.8

*Values given here are means from three to five measurements.

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