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Thermometry – enthalpimetry

THE DETERMINATION OF THE ORAL FORM OF 5-CHLORO-7-IODO-8-HYDROXYQUINOLINE (CLIOQUINOL)

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For the routine assay of tabletted dosage forms of clioquinol, as in quality control, the reproducibility of tablet manufacture makes it possible to omit any weighing procedure. The advantages of enthalpimetry allow assay without separation of the analyte from the matrix and colorants.

The method can be easily automated and gives an acceptable level of accuracy and precision.

5-Chloro-7-iodo-8-hydroxyquinoline has been employed for many years as an amoebicide. The generally accepted maximum single dose for oral purposes is 300 mg and the maximum daily dose suggested [1] is 1000 mg. Typical dosage forms are 250 mg of the analyte + approximately 150–200 mg of a suitable inert diluent to act as binder, taste modifier, colorant, etc. It is also available in ointments and creams. There are several methods available for the assay of the tablets used medicinally; the various Pharmacopoeia list those in general use. These vary from the determination of the halides, after oxygen flask combustion, with silver nitrate using a silver electrode and a mercuric sulphate/potassium sulphate reference electrode [1], and an assay for the total phenol content, by determination potentiometrically in a pyridine solvent using tetrabutylammonium hydroxide as titrant [2], to the determination of C_9H_5ClINO by g.l.c. by a comparison method involving derivatization of the phenol with bis(trimethyl silyl) acetamide. Spectrophotometrically the absorbance due to the colour of the 5-chloro-7-iodo-8-hydroxyquinoline dissolved in acetic acid is used in a comparative method. Using 1 cm cell path length cells it is found by the present authors that an absorbance of 1.00 unit is given by a solution containing approximately 10 ppm of the analyte. For most analytical instruments in routine laboratory use it is therefore necessary to crush the weighed tablet and then to use approximately 0.4%–0.5% of the total weight (viz. *ca.* 1.0–1,2 mg) dissolved in 10 ml of glacial acetic acid solution before the absorbance of the solution is determined against a blank of the acetic acid used. Whilst in general the colorants used do not significantly interfere with the spectroscopic determination, it is necessary to ascertain this before routine determinations are made. The sequence of counting, crushing, homogenization, weighing, dissolution, and then removal of an aliquot for measure-

ment does not readily allow the whole procedure to be automated. Thus the overall cost of the analysis, as a labour-intensive procedure, is high; the overall time for the analysis of a single dosage form is also relatively high.

With modern costing procedures in pharmaceutical analysis it is advantageous to have methods which are reliable, rapid, easily automated and relatively cheap, both from a point of view of capital expenditure and of day-to-day running costs. Thus any method, in which the time involved in weighing the dosage sample, using a portion of this sample, obtaining a result and relating this to the actual sample can be made a minimum, must have some advantage. If the method is also without the relatively high costs of computer interfaces necessary for automatic normalization of the electrical signals received from electronic balances and spectrophotometric recorders, which are necessary in order to automate such a process, then it must have further advantages.

Since the oral dosage form for 5-chloro-7-iodo-8-hydroxyquinoline is generally one tablet and the tolerance of the amount of analyte in the dosage form is about ±3%, it is not necessary to use a method which has, of necessity, a high precision. It is, however, desirable to use a method which does not require any separation steps, can readily be automated and which is cheap to operate. Automated enthalpimetry is such a method.

The use of thermometric and enthalpimetric methods for the determination of dosage forms of modern pharmaceutical products has been previously reported by various workers. These assays have included dosage forms in tablets [3], in syrups [4], and in creams [5]. In general, the enthalpimetric method is preferred since this is more readily automated, and for single or multiple tablet doses is more easily made comparative. (The advantage, etc., of enthalpimetric methods for dosage forms have been discussed in detail by previous workers [3, 4].)

There are several reactions available for the rapid reaction of the analyte with a reagent, in such a manner that the overall heat of the reaction is sufficient to be used for an enthalpimetric determination. Of those investigated, bromination of the analyte (using a solution of bromine in glacial acetic acid) was found to be the best.

In order to eliminate any effects of the heat of dilution of the reagent the sample was also dissolved in glacial acetic acid.

Experimental

Enthalpimetric determination of single tablets containing the required dosage amount of the analyte

(a) Enthalpimetric apparatus

The apparatus used was essentially that used for the enthalpimetric determination of Vitamin C tablets [3], being modified so that the output from the D. C. Wheatstone Bridge could be fed to either or both a digital voltmeter and a recording potentiometer. Th eoutput was amplified via a suitable FET-op amp so that the imbalance

of less than 1 mV from the bridge was amplified up to 100 times. By the use of a suitable variable shunt the output to the digital voltmeter could be adjusted to between 50 and 100 mV. This adjustment was made so that routine measurements could be compared directly to a previously determined standard sample, viz. if the shunt was adjusted so that the standard gave a signal equivalent to 100 mV, and if the reading obtained on a routine sample was, say, 95 then the routine sample was 95% of the standard value.

Reactants

Bromine solution. A solution (nominally 2*M* w.r.t. bromine) was prepared by dissolving the appropriate weight of liquid bromine in glacial acetic acid.

Standard solutions of 5-chloro-7-iodo-8-hydroxyquinoline

This was prepared from a pure sample of the analyte (supplied by Ciba-Geigy U.K. Ltd.) and glacial acetic acid. A stock solution containing 30.0 g l^{-1} was prepared.

Calibration curve

The calibration curve was established by injecting aliquots (1 ml) of the 2*M* bromine solution into a series of solutions of the analyte. (1, 2.5, 5, 10, 15, 20 ml of the stock solution made to 20 ml with glacial acetic acid).

The signals, corresponding to the temperature pulses, were plotted against the amount of the analyte. A linear plot was obtained.

Determination of the precision of the general method

The precision of the determination was obtained from eleven determinations of aliquots of the 5-chloro-7-iodo-8-hydroxyquinoline dissolved in glacial acetic acid (30 mg in 20 ml). The results are presented:

Run	1	2	3	4	5	6	7	8	9	10	11
Amount, mg	30.0	30.5	30.3	30.5	30.3	30.3	29.9	30.4	30.0	30.0	29.9

Average value = 30.19.
Standard deviation = 0.215.
Relative standard deviation = 0.71%.

Determination of single oral dosage forms

(i) The single dosage form used was 1 tablet of the commercial product "Enteroviform" (Ciba-Geigy Ltd.).

(ii) *Matrix effects*

In order to ascertain the possible effects of the matrix, weighed amounts (from 10 tablets) equivalent to 1 tablet were dissolved in glacial acetic acid. To each of 6 randomly chosen samples was added a known amount of the stock solution of the analyte. The volumes of all solutions were adjusted to 20 ml

with glacial acetic acid. Each solution was assayed. The results indicated that there was no significant effect on the matrix.

(iii) *Determination of the precision of assay of single tablets*

The dosage level is approximately 10 times that used in the previous experiment.

The circuit was made less sensitive by decreasing the sensitivity of the recorder by a factor of 10, or by decreasing the sensitivity of the bridge using the FET-op amp transducer.

The procedure used was as follows: a weighed single tablet was crushed in a 25 ml beaker and the powder was quantitatively transferred, using glacial acetic acid, to the polypropylene titration vessel. The volume was adjusted to 20 ml with glacial acetic acid. The titrant, in the appropriate pipette, was placed in the suspension, which was stirred. When thermal equilibrium had been obtained (usually within 60 sec) the titrant was injected into the analyte solution. The signals were recorded, and the amount of analyte was determined directly from a prepared calibration graph, using solutions of a pure sample of 7-iodo-5-chloro-oxine dissolved in glacial acetic acid. Twenty tablets were taken and individually weighed. The weights (nominally 0.4 g) varied from 0.400 to 0.404 g with an average of 0.402 g. The average amount of analyte was 25.2 mg, from a range 25.10–25.32 mg. The maximum divergence was thus 0.84%. The relative standard deviation was 0.78%.

A similar series of 20 tablets were assayed by dissolving each tablet in glacial acetic acid, and making to a known volume (50 ml) to contain approximately 7–10 ppm. The absorbance at 326 nm was measured. The analyte concentration was determined from a previously prepared calibration curve.

The error was approximately 1.8%.

Proposed method

Crush a tablet of the dosage form in the reaction vessel in glacial acetic acid. Adjust volume to 20 ml. Place titrant, in an appropriate dispenser, in the vessel. Allow thermal equilibrium to be attained.

Inject the titrant, record the heat pulse. Determine the amount of analyte from an appropriate calibration curve.

References

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Zusammenfassung – Für die Routineuntersuchung von Clioquinol in Tabletten, beispielsweise zur Qualitätskontrolle, ist ein Wägeverfahren infolge der Reproduzierbarkeit der Tablettenherstellung überflüssig. Die Vorteile der Enthalpimetrie erlauben ein Verfahren ohne Trennung der zu bestimmenden Verbindung von der Matrix und den farbgebenden Substanzen. Die Methode kann leicht automatisiert werden und ist ausreichend genau.

Резюме – Для рутинного анализа таблетированных форм клиохинола, как качественного контроля, воспроизводимость получения таблеток дает возможность избежать процесса взвешивания. Преимущества энтальпиметрии позволяют проводить анализ пробы без отделения ее от матрицы и окрашивающих веществ. Метод можно легко автоматизировать и дает приемлемую степень точности.