2.11 Micro determination of water by the Karl Fischer method

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*This text is based on the corresponding text in the*European Pharmacopoeia *with appropriate editorial modifications and changes agreed upon by the Expert Committee on Specifications on Pharmaceutical Preparations.*

Principle. The coulometric titration of water is based upon the quantitative reaction of water with sulfur dioxide and iodine in an anhydrous medium in the presence of a base with sufficient buffering capacity. In contrast to the volumetric method described in general chapter *2.8 Semi-micro determination of water by the Karl Fischer method*, iodine is produced electrochemically in the reaction cell by oxidation of iodide . The iodine produced at the anode reacts immediately with the water and the sulfur dioxide contained in the reaction cell. The quantity of water in the substance is directly proportional to the quantity of electricity (in coulombs), corresponding to electric current (in amperes) multiplied by time (in seconds), used for iodine generation up until the titration end-point. When all of the water in the reaction cell has been consumed, the end-point is reached and, thus, an excess of iodine appears. 1 mole of iodine corresponds to 1 mole of water, an amount of electricity of 10.71 C corresponds to 1 mg of water.

Moisture is eliminated from the reaction cell by pre-titration (i.e. the electrolyte reagent is titrated to dryness before starting the sample analysis). Individual determinations can be carried out successively in the same reagent solution, under the following conditions:

each component of the test mixture is compatible with the other components;

no other reactions take place; and

the volume and the water capacity of the electrolyte reagent are sufficient.

Coulometric titration is intended for the quantitative determination of small quantities of water (from 10 µg), however, a working range of 100 µg to 10 mg of water is recommended for reproducibility reasons.

Accuracy and precision of the method are predominantly governed by the sample preparation and the extent to which atmospheric moisture is excluded from the system. Control of the system must be monitored by measuring the amount of baseline drift.

Apparatus. The apparatus consists of a reaction cell, electrodes and a magnetic stirrer. The reaction cell consists of a large anode compartment and a smaller cathode compartment. Depending on the design of the electrode, both compartments can be separated by a diaphragm. Each compartment contains a platinum electrode. Liquid or solubilised samples are introduced through a septum using a syringe. Alternatively, an evaporation technique may be used in which the sample is heated in an oven and the water is evaporated and carried into the cell by means of a stream of dry inert gas. The introduction of solid samples into the cell should, in general, be avoided. However, if it has to be done, it is effected through a sealable port; appropriate precautions must be taken to avoid the introduction of moisture from air, such as working in a glove box in an atmosphere of dry inert gas. The analytical procedure is controlled by a suitable electronic device which also displays the results.

Instrument qualification should be carried out according to established quality system procedures, for example, using a suitable certified reference substance or a pharmacopoeial reference substance. A suitable sodium aminosalicylate dihydrate for equipment qualification reference substance may be used when proceeding by direct or liquid sample introduction, whereas a suitable amoxicillin trihydrate for performance verification reference substance may be used with the evaporation technique.

Method. Fill the compartments of the reaction cell with a suitable commercially available anhydrous reagent, or a combination of anhydrous reagents for the coulometric titration of water containing suitable organic bases, sulfur dioxide and iodide dissolved in a suitable solvent according to the manufacturer's instructions and perform the coulometric pre-titration to a stable endpoint. Introduce the prescribed quantity of the substance to be examined into the reaction cell and titrate again to a stable endpoint, stirring for at least 30 seconds, unless otherwise indicated in the monograph. If an oven is used, the prescribed quantity of sample is introduced into the oven and heated. After evaporation of the water from the sample into the reaction cell, the titration is started. Alternatively, the evaporated moisture is immediately titrated while heating the sample in the oven to avoid loss of evaporated water already collected in the reagent solution during prolonged heating. Read the value from the instrument's output and calculate, if necessary, the percentage or quantity of water that is present in the substance. When appropriate to the type of sample and the sample preparation, perform a blank titration.

Verification of accuracy. At appropriate intervals, such as at least at the beginning and the end of a series of sample titrations, introduce a defined quantity of water, in the same order of magnitude as the quantity of water in the sample, using a suitable certified reference substance and perform the coulometric titration. The recovery is within the range of 97.0 per cent to 103.0 per cent for the addition of 1000 µg of water and within the range of 90.0 per cent to 110.0 per cent for the addition of 100 µg of water. For apparatuses combined with ovens, the recovery is within the range of 95.0 percent to 105.0 percent cert for the addition of 1000 µg of water.