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2.5.12. WATER: SEMI-MICRO DETERMINATION

The semi-micro determination of water is based upon the quantitative reaction of water with sulfur dioxide and iodine in a suitable anhydrous medium in the presence of a base with sufficient buffering capacity.

APPARATUS

The apparatus consists of a titration vessel with:

- 2 identical platinum electrodes;
- tight inlets for introduction of solvent and titrant;
- an inlet for introduction of air via a desiccant;
- a sample inlet fitted with a stopper or, for liquids, a septum.

Inlet systems for introduction of dry nitrogen or for aspiration of solvents may also be fitted.

The titration is carried out according to the instrument supplier's instructions. Care is taken throughout the determination to avoid exposure of reagents and solvents to atmospheric moisture. The end-point is determined using 2 identical indicator electrodes connected to an electrical source that maintains between the electrodes either a constant current (2.2.65. *Voltametric titration*) or a constant voltage (2.2.19. *Amperometric titration*). Where direct titration is used (method A), addition of titrant causes either a decrease in voltage where constant current is maintained or an increase in current where constant voltage is maintained, until the end-point is reached. Instruments with automatic end-point detection are commonly used. Instrument qualification is carried out according to established quality system procedures, for example using a suitable certified reference material (*sodium aminosalicylate dihydrate for equipment qualification CRS* may be used).

STANDARDISATION

To the titration vessel, add *methanol R*, dried if necessary, or the solvent recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce a suitable amount of water in an appropriate form (*water R* or a certified reference material) and carry out the titration, stirring for the necessary time. The water equivalent is not less than 80 per cent of that indicated by the supplier. Standardise the titrant before the first use and at suitable intervals thereafter.

Unless otherwise prescribed, use Method A.

METHOD A

Introduce into the titration vessel *methanol R*, or the solvent indicated in the monograph or recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce the substance to be examined rapidly and carry out the titration, stirring for the necessary extraction time.

METHOD B

Introduce into the titration vessel *methanol R*, or the solvent indicated in the monograph or recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell or carry out a pre-titration. Introduce the substance to be examined rapidly and in a suitable state of division. Add an accurately measured volume of the titrant, sufficient to give an excess of about 1 mL or the prescribed volume. Allow to stand protected from light for 1 min or the prescribed time, with

stirring. Titrate the excess of reagent using *methanol R* or the prescribed solvent, containing an accurately known quantity of water.

SUITABILITY

The accuracy of the determination with the chosen titrant must be verified for each combination of substance, titrant and solvent to be examined. The following procedure, given as an example, is suitable for samples containing 2.5–25 mg of water. The water content of the substance to be examined is determined using the reagent/solvent system chosen. Thereafter, in the same titration vessel, sequential known amounts of water, corresponding to about 50–100 per cent of the amount found in the substance to be examined, are added in an appropriate form (at least 5 additions) and the water content is determined after each addition. Calculate the percentage recovery (r) after each addition using the following expression:

$$r = 100 \frac{W_2}{W_1}$$

W_1 = amount of water added, in milligrams;

W_2 = amount of water found, in milligrams.

Calculate the mean percentage recovery (\bar{r}). The reagent/solvent system is considered to be acceptable if \bar{r} is between 97.5 per cent and 102.5 per cent.

Calculate the regression line. The x -axis represents the cumulative water added whereas the y -axis represents the sum of the initial water content determined for the substance (M) and the cumulative water determined after each addition. Calculate the slope (b), the intercept with the y -axis (a) and the intercept of the extrapolated calibration line with the x -axis (d).

Calculate the percentage errors (e_1 and e_2) using the following expressions:

$$e_1 = 100 \frac{a - M}{M}$$

$$e_2 = 100 \frac{|d| - M}{M}$$

a = the y -axis intercept, in milligrams of water;

d = the x -axis intercept, in milligrams of water;

M = water content of the substance, in milligrams of water.

The reagent/solvent system is considered to be acceptable if:

- $|e_1|$ and $|e_2|$ are not greater than 2.5 per cent;
- b is between 0.975 and 1.025.



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2.5.13. ALUMINIUM IN ADSORBED VACCINES

Homogenise the preparation to be examined and transfer a suitable quantity, presumed to contain 5 mg to 6 mg of aluminium, to a 50 mL combustion flask. Add 1 mL of *sulfuric acid R*, 0.1 mL of *nitric acid R* and some glass beads. Heat the solution until thick, white fumes are evolved. If there is charring at this stage add a few more drops of *nitric acid R* and continue boiling until the colour disappears. Allow to cool for a few minutes, carefully add 10 mL of *water R* and boil until a clear solution is obtained. Allow to cool, add 0.05 mL of *methyl orange solution R* and neutralise with