Water determination in pharmaceuticals using an automated Karl Fischer Oven Technique

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Metrohm
Ion analysis

Karl Fischer

Summary

The Karl Fischer (KF) Oven Method permits the accurate, precise and straightforward determination of the water content of pharmaceuticals that are not amenable to direct KF titration because they either undergo detrimental side reactions with the KF reagent or release their water only slowly or at high temperatures.

Water determinations carried out with several pharmaceuticals demonstrate that the values obtained with the KF Oven Method all lie within the ranges specified in the European Pharmacopoeia. Moreover, the automated KF Oven Technique significantly enhances sample throughput and repeatability of the results.

Introduction

Quality and shelf life of active pharmaceutical ingredients depend primarily on the content of adsorbed (surface water) or bound water (water of crystallisation). Although the 4th Edition of the European Pharmacopeia (2002) describes the direct Karl Fischer (KF) Titration as the most important method for determining the water content, in some cases, where substances undergo side reactions with the KF reagents or where they release their water only at high temperatures, the European Pharmacopeia recommends the quantification via the loss on drying (LOD) in a drying cabinet or desiccator. However, besides the water to be determined, this method also includes all volatile compounds (e.g. impurities, degradation products) released at higher temperatures.

The KF Oven Method allows to resolve the above-mentioned problems. Depending on the water content of the sample, the KF titration can be performed either volumetrically for higher or coulometrically for lower water contents. Considering the relatively small amount of water in most pharmaceuticals, samples were analyzed coulometrically.

Instrumentation and Analytical Procedure

- 774 Oven Sample Processor
- 756 KF Coulometer, including KF cell without diaphragm
- 728 Magnetic Stirrer
- 6.5617.000 complementary equipment for automatic reagent exchange and 2.700.0020 Dosino (not shown)
- PC with VESUV 3.0 Metrodata software for data acquisition, storage and reprocessing (not shown)

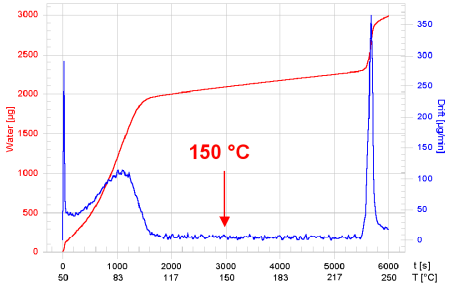
The calculation of the sample's water content involves also the determination of the humidity in the sample vessel and the moisture adhering to the vessel surface, vial cap and septum. Three empty but sealed sample vials are analyzed under the same conditions as the particular sample. The resulting mean value is stored as a blank value and automatically taken into account in the calculation.

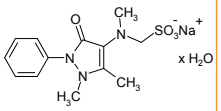
Subsequently a threefold determination for each compound is performed. Accuracy of the KF titrations is checked at regular intervals with a certified KF Oven standard.

Water release curve for metamizole sodium

The optimum oven temperature for driving off the water should ensure complete water extraction in a reasonable time excluding decomposition of the sample. This means that the oven temperature should be chosen as high as possible to ensure short determination times, but still be 20 to 30 °C below the decomposition temperature. The oven temperatures for unknown samples are determined on the basis of the water-release curves that were recorded for all investigated pharmaceuticals in the temperature range 50 to 250 °C.

By means of metamizole sodium, a pharmaceutical that is not accessible to direct KF titration, the determination of the adequate oven temperature is illustrated. The red curve represents the absolute water released as a function of total time while the blue curve corresponds to the associated drift as a function of oven temperature.



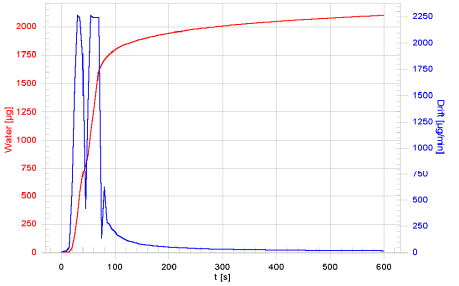


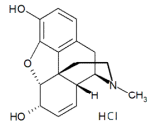
The water release curve was recorded using a heating rate of 2 °C/min.

- Both surface moisture and water of crystallisation are released within the first 1600 s (50…103 °C). Afterwards the drift (blue curve) drops to its original value of approximately 10 µg/min and remains almost constant for 3800 s, increasing again at 5400 s.
- At 5400 s (230 °C) both curves indicate by their increase that water is released by commencing decomposition

→ **For the rapid determination of the water content of metamizole sodium a temperature of 150 °C assures a fast water release without decomposition.**

Titration curve for morphine hydrochloride





The absolute amount of water and the drift are shown as a function of time.

- The three drift peaks point to the fact that morphine hydrochloride is present in the form of its trihydrate.
- After 180 s no more water is released. The slight increase of the red curve can be attributed to the background drift.

Comparison KF Oven Method/LOD

Substance	Empirical formula	Water content: Calcul. [%]	Water content: Loss on drying[1] (LOD) [%]	Water content: KF Oven Method [%]	Water content: KF Oven Method RSD[2] [%]	Recovery: LOD [%]	Recovery: KF [%]	Melting point [°C]	Temp. 774 Oven [°C]
Carbidopa	$C_{10}H_{14}N_2O_4 \times H_2O$	7.37	6.9-7.9	7.17	0.35	93.6-107.2	97.3	203 - 205	150
Cysteinehydrochloride monohydrate	$C_3H_8ClNO_2S \times H_2O$	10.25	8.0-12.0	10.33	0.30	78.0-117.1	100.8	≥ 170°	150
Ethacridine lactate monohydrate	$C_{13}H_{11}N_3O \times H_2O$	4.98	4.5-5.5	5.05	0.59	78.0-117.1	101.4	≥ 180°	180
Metamizole sodium	$C_{13}H_{16}N_3NaO_4S \times H_2O$	5.12	4.9-5.3	5.14	0.30	95.7-103.5	100.4	220 - 210°	150
Morphinehydrochloride	$C_{17}H_{20}ClNO_3 \times 3H_2O$	14.37	12.0-15.0	13.83	0.44	83.5-104.4	96.2	≥ 200°	180
Quinine sulfate	$C_{40}H_{48}N_4O_4S \times 2H_2O$	4.6	3.0-5.0	4.63	0.33	65.2-108.7	100.7	144 - 155	135

[2]= mean value of threefold determination, [1]= given in the European Pharmacopoeia, °= melting with decomposition

In contrast to the wide range of the recovery rates for the loss on drying (LOD) specified by the European Pharmacopoeia (60…120%), the KF oven method provides recovery rates between 90 and 110% (examples cited in the table between 96 and 101%). Additionally, the water content is determined with an excellent repeatability in less than 12 minutes.

Advantages of the KF Oven Method

- enables accurate and precise analysis of pharmaceuticals that formerly were not amenable to KF titration
- avoids contamination of the oven and titration cell; consequently there are no carryover and memory effects
- works nondestructively and requires only 15…30 mg of the potentially expensive pharmaceutical
- allows recording of water release curves providing information about the kinetics of the water release

The Oven Sample Processor

- significantly reduces manual sample preparation steps
- enhances sample throughput (high efficiency)
- analyzes all samples under identical und reproducible conditions, providing results of the highest precision

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