Water in Lyophilisates

Karl Fischer application

Product group

Pharmaceuticals

General Information concerning the product group

Pharmaceuticals

Pharmaceutical products are often characterized by complex formulations. Difficulties observed during Karl Fischer determination are often caused by the limited solubility. In some cases side reactions have to be considered. In dependance of composition and properties of the formulations, various measures are necessary for an undisturbed Karl Fischer determination.
In pharmaceutical guidelines (USP, Ph Eur, DAB) the Karl Fischer titration is described as common method for water determination. For some substances special procedures can be found. The determination of mass loss as method for water determination is not recommended.

Special Information concerning the sample and the methods

Freeze-dried substances have a very low water concentration (e.g. 100 µg / ampoule) but at the same time possess hygroscopic properties. Water determination thus requires careful sample handling. If possible, a glove box should be used.Water determination can be performed acc. to various methods.Which method is preferred, depends on the water content and on the available sample amount.Volumetric determination can be performed with one or two component reagents. Poor soluble samples are titrated in suspension. For very low water contents, the content of several ampoules has to be added to the titration cell.Coulometric analysis can only be carried out after external extraction of the sample. The titrated solution of the anode compartment in the coulometric cell serves as solvent or extraction agent. The advantage here is that there is no need to consider a blank value of the solvent, thus facilitating more accurate results. The solvent can be added directly to the sample vial, if the sample amount is known.Alternatively the Karl Fischer oven technique in combination with coulometry is recommended. For high requirements on the accuracy of results, samples should be weighed under a glove box, in order to exclude the influence of humidity of air.Suitable parameters for the KF oven are e.g. T = 130 °C, extraction time = 300 sec.

Titration one component system

Reagents

Titrant:	Aquastar - CombiTitrant 2	188002	
	One component reagent for volumetric Karl Fischer titration, 1 mL = approx. 2 mg water		
Solvent:	Aquastar - CombiMethanol	188009	50 mL
	Solvent for volumetric Karl Fischer titration with one component reagents, max. 0.01 % water		

Titration parameters
Extraction time: 120 sec.
Default titration settings, e.g.:
I(pol) = 20 - 50 µA, U(EP) = 100 - 250 mV
Stop criterion: drift < 20 µL/min

Sample size
0.1 - 1.0 g

Procedure
The titration medium is first placed into the titration cell and titrated dry by means of the titrant. Then the sample is added directly from the ampoule (exact sample weight determination by weighing of ampoule before and after addition) and the titration is started. For complete dissolution of the sample or rather full extraction of the water a stirring time of 120 seconds is recommended.

Titration two component system

Reagents

Titrant:	Aquastar - Titrant 2	188011	
	Titrant for volumetric titration with two component reagents, 1 mL = approx. 2 mg water		
Solvent:	Aquastar - Solvent	188015	50 mL
	Solvent for volumetric titration with two component reagents		

Titration parameters
Extraction time: 120 sec.
Default titration settings, e.g.:
I(pol) = 20 - 50 µA, U(EP) = 100 - 250 mV
Stop criterion: drift < 20 µL/min

Sample size
0.1 - 1.0 g

Procedure
The titration medium is first placed into the titration cell and titrated dry by means of the titrant. Then the sample is added directly from the ampoule (exact sample weight determination by weighing of ampoule before and after addition) and the titration is started. For complete dissolution of the sample or rather full extraction of the water a stirring time of 120 seconds is recommended.

Coulometry with diaphragm

Reagents

Catholyte:	Aquastar - CombiCoulomat frit	109255	5 mL
	Coulometric Karl Fischer reagent for cells with diaphragm		
Anolyte:	Aquastar - CombiCoulomat frit	109255	100 mL
	Coulometric Karl Fischer reagent for cells with diaphragm		

Titration parameters
Default coulometer settings for cell with diaphragm:
For end point indication, e.g.:
I(pol) = 5 - 10 µA, U(EP) = 50 - 100 mV
Stop criterion: drift < 20 µg/min

Sample size
1 ampoule

Procedure
The Karl-Fischer reagent is placed into the cathode and anode compartment of the titration cell with diaphragm. The coulometer is started and the solvent is titrated dry. After preliminary titration and stabilisation of drift titrated solvent is extracted from the anode compartment with a syringe and re-injected. Repeating this procedure several times will dry the syringe. If upon injection of the rinser solution into the coulometric cell the drift does not rise any further, titrated solvent from the anode compartment is again withdrawn and added to the material under investigation (mass M) via septum (sample + solvent = mass M + M1). The substance is dissolved through agitation (alternatively ultrasound bath). Extracted solution is withdrawn with the same syringe, injected into the titration cell (exact sample weight determination by weighing of syringe before and after addition)and the titration is started. The result of the determination corresponds to the water content of this partial sample (A). Calculation of the water concentration in the material to be analysed: Water [%] = A[%] x (M + M1)/M

Application

Coulometry without diaphragm

Reagents

Working medium:	Aquastar - CombiCoulomat fritless	109257	100 mL
	Coulometric Karl Fischer reagent for cells with or without diaphragm		

Titration parameters
Default coulometer settings for cell without diaphragm:
For end point indication, e.g.:
I(pol) = 5 - 10 µA, U(EP) = 50 - 100 mV
Stop criterion: drift < 20 µg/min

Sample size
1 ampule

Procedure
The Karl-Fischer reagent is placed into the cell without diaphrgm. The coulometer is started and the solvent is titrated dry. After preliminary titration and stabilisation of drift titrated solvent is extracted from the titration cell with a syringe and re-injected. Repeating this procedure several times will dry the syringe. If upon injection of the rinser solution into the coulometric cell the drift does not rise any further, titrated solvent from the anode compartment is again withdrawn and added to the material under investigation (mass M) via septum (sample + solvent = mass M + M1). The substance is dissolved through agitation (alternatively ultrasound bath). Extracted solution is withdrawn with the same syringe, injected into the titration cell (exact determination through weighing before and after addition) and the titration is started. The result of the determination corresponds to the water content of this partial sample (A). Calculation of the water concentration in the material to be analysed: Water [%] = A[%] x (M + M1)/M

Ordering Information

Product	Catalog No.
CombiCoulomat frit Karl Fischer reagent for the coulometric water determination for cells with diaphragm Aquastar®	109255
CombiCoulomat fritless Karl Fischer reagent for coulometric water determination for cells with and without diaphragm Aquastar®	109257
CombiTitrant 2 one component reagent for volumetric Karl Fischer titration 1 ml ca. 2 mg H2O Aquastar®	188002
CombiMethanol Solvent for volumetric Karl Fischer titration with one component reagents max. 0.01% H2O Aquastar®	188009
Titrant 2 titrant for volumetric Karl Fischer titration with two component reagents 1 ml □ ca. 2 mg H2O Aquastar®	188011
Solvent solvent for volumetric Karl Fischer titration with two component reagents Aquastar®	188015