Residual Moisture / Water Content

Determination of water content according to Karl Fischer in free dried products and stoppers

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introduction & basics

of Karl-Fischer-Titration

differentiation

residual moisture	water content according to KF
moisture analyzers using infrared-, halogen-, microwave-heating	titrator, using electrode for indication
loss on drying under given conditions	water content
gravimetric method	chemical reaction with water
all volatile constituents, not only water	specific for water
chemically bound water not found completely	be aware of side reactions

properties of freeze dried products

- small sample sizes
- small water content
- packed in glass vials of different sizes
- closed with various stoppers and caps
- not equilibrated with laboratory conditions / humidity
- packed under vacuum
- containing hazardous APIs (active pharmaceutical ingredients)

Karl Fischer reaction

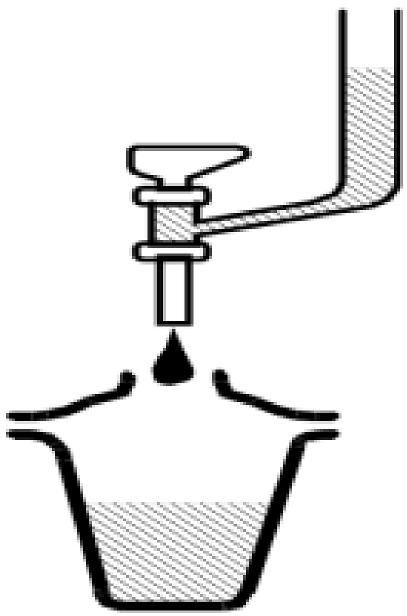
$$CH_3OH + SO_2 + RN \rightleftharpoons (RNH)SO_3CH_3$$

$$H_2O + I_2 + (RNH)SO_3CH_3 + 2\ RN \rightleftharpoons (RNH)SO_4CH_3 + 2\ (RNH)I$$

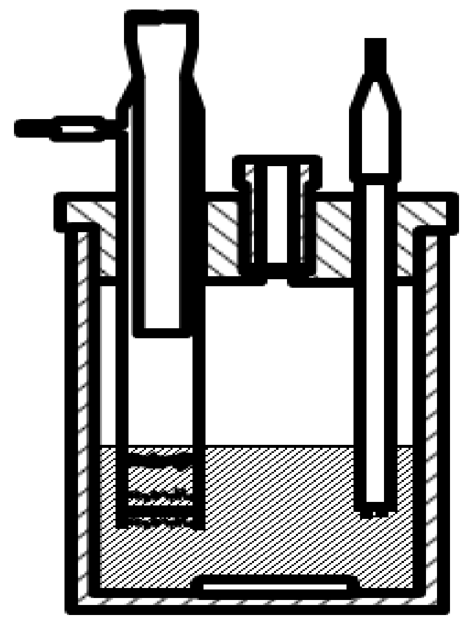
volumetric and coulometric KFT

2 possibilities to add iodine to the reaction

- volumetric titration



- coulometric titration



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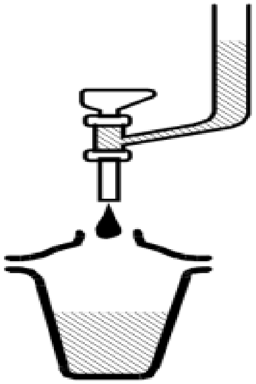
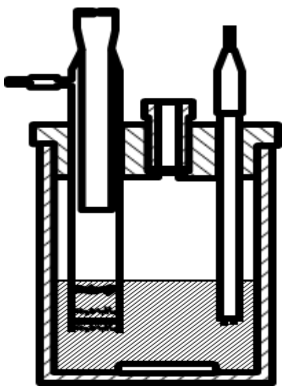
volumetric KFT



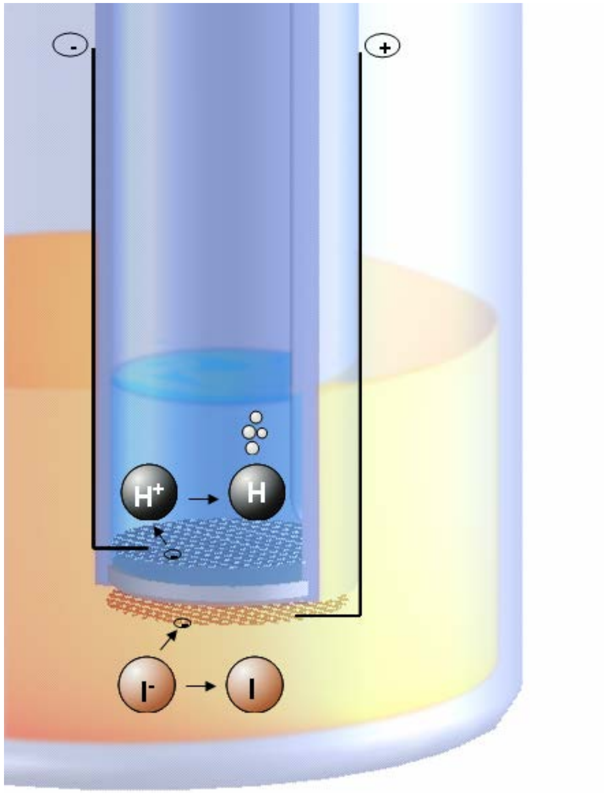
- dosage of a volume
- analytical method
- iodine is added as a standard solution / titrant
- the consumption of titrant is used to calculate the water content
- titer determination is required
- measuring range: approx. 100 mg/kg - 100 %

coulometric KFT



- dosage of electric current
- absolute method
- iodine is generated by oxidation of iodide at the anode of the generator electrode
- the applied amount of electrical charge is used to calculate the water content
- titer determination is not required
- measuring range: approx. 1 mg/kg - 5 %

coulometric KFT



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volumetric and coulometric KFT

volumetric KFT

Measuring range:

100 mg/kg - 100 %

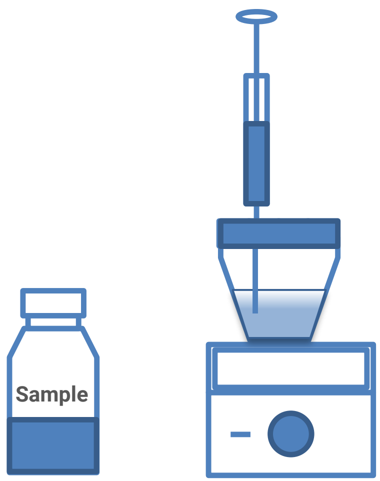
coulometric KFT

Measuring range:

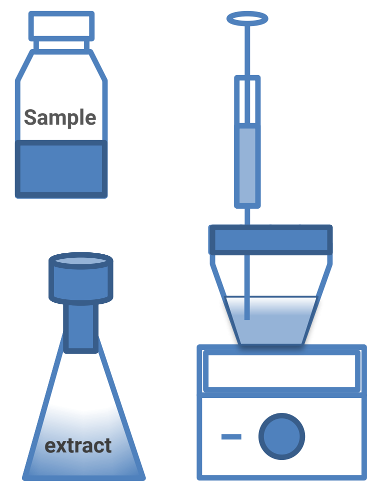
1 mg/kg - 5 %

techniques of application

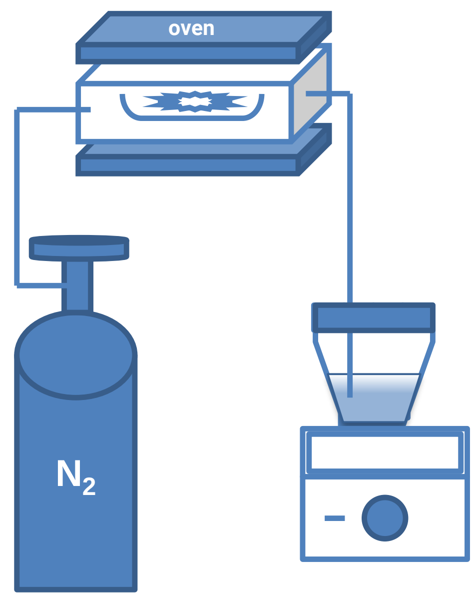
direct titration



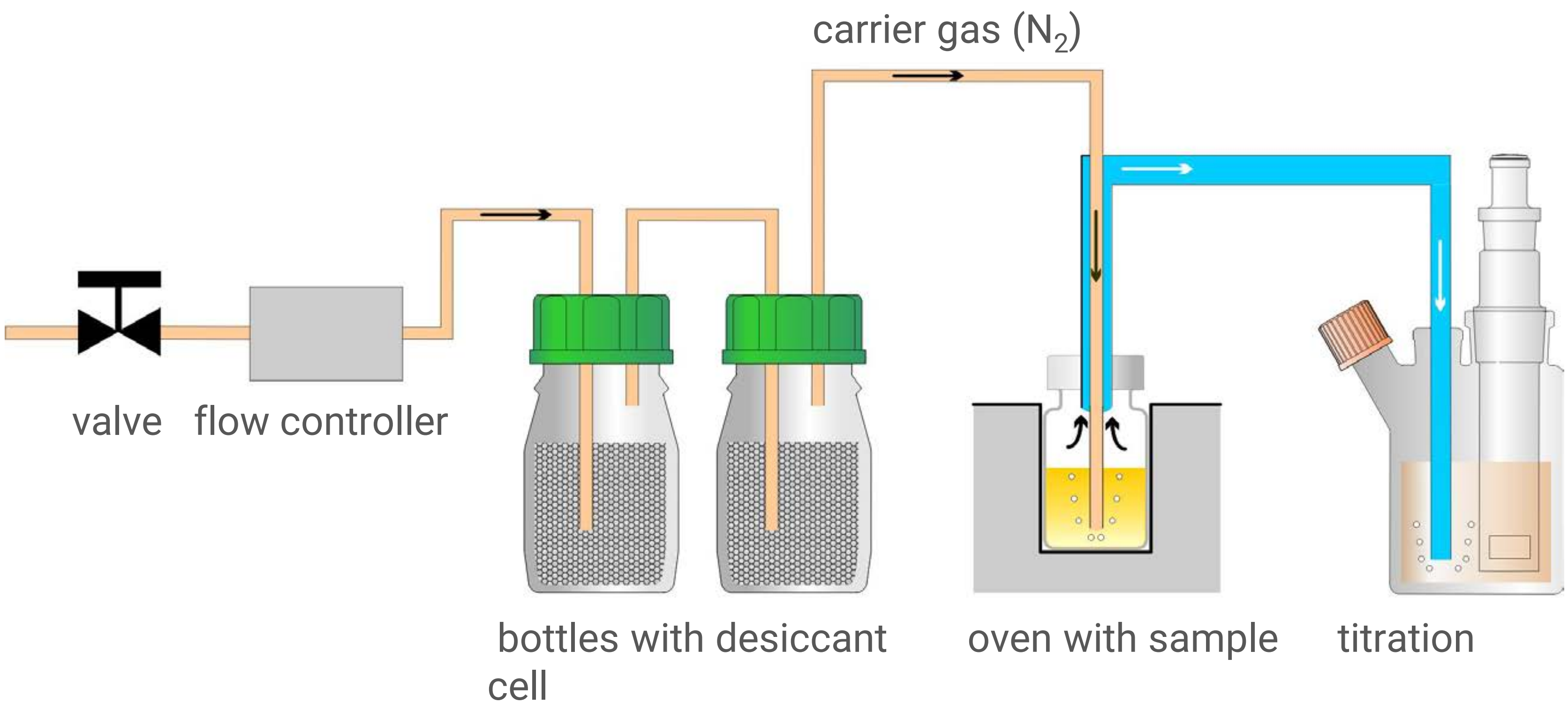
extraction



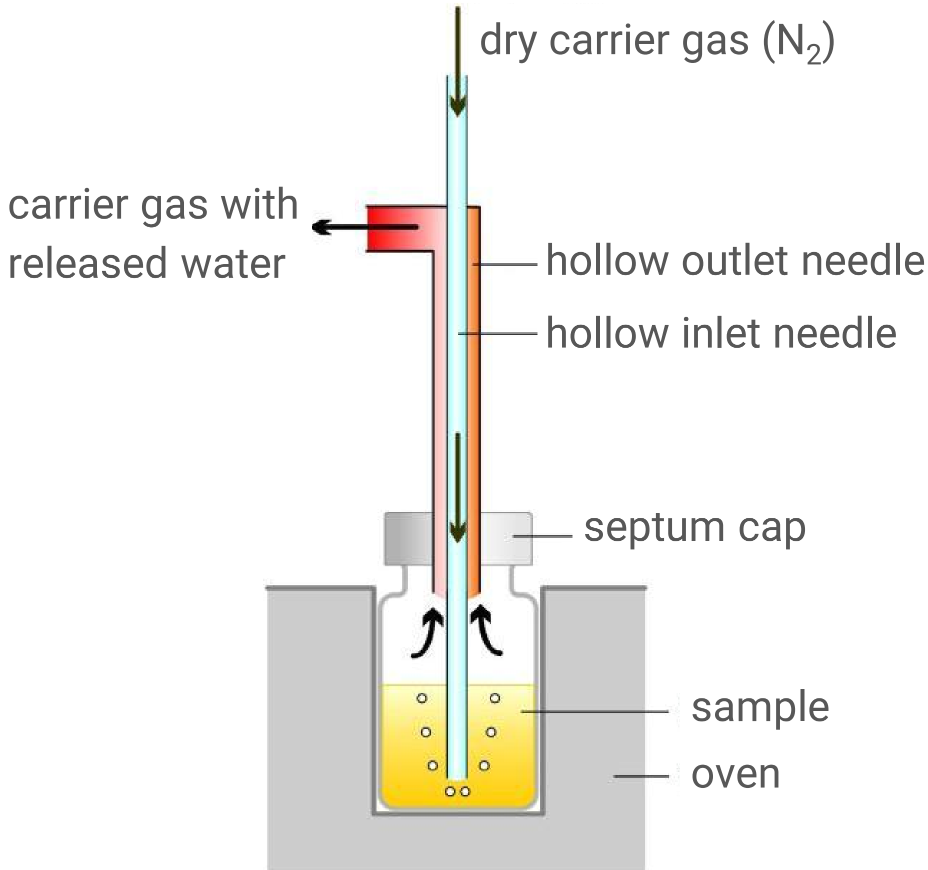
evaporation technique



principle of evaporation technique



principle of evaporation technique



workflow of evaporation technique

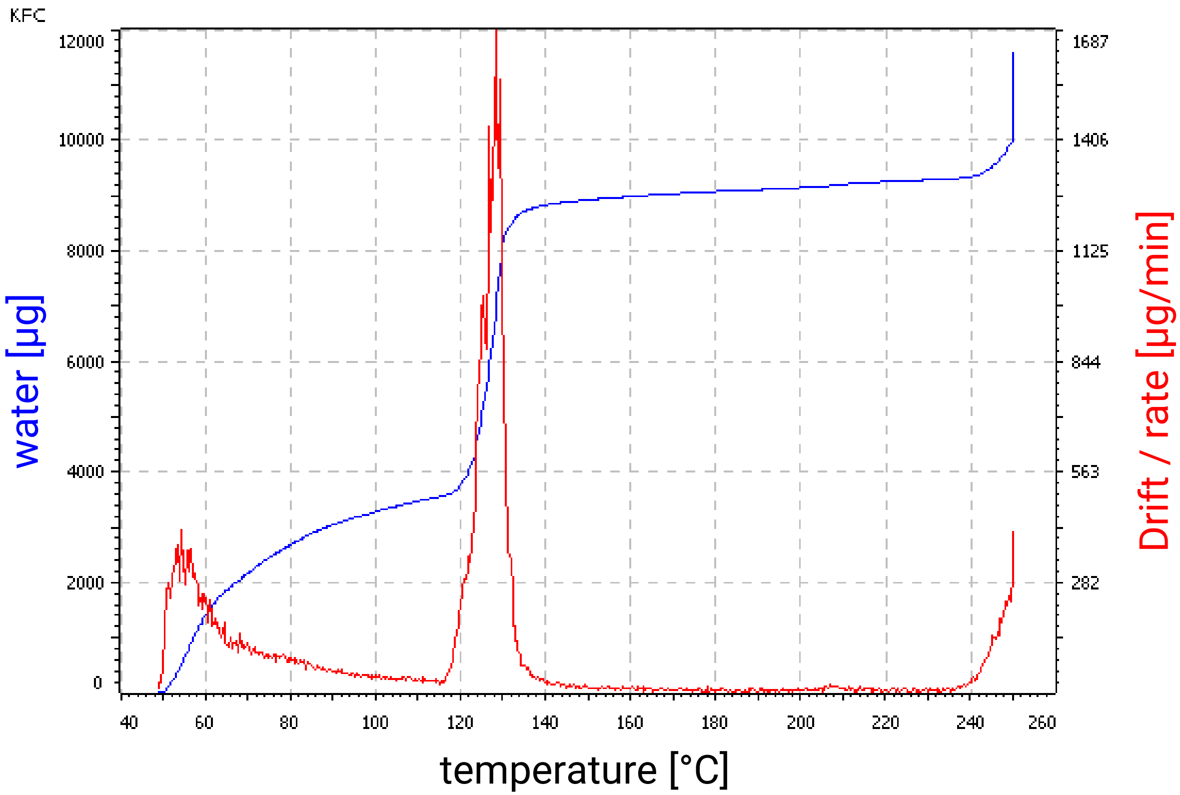
typical ovens for evaporation technique

typical ovens for evaporation technique

feature: customized oven inserts

typical ovens for evaporation technique

feature: temperature ramp



sample: standard sodium tartrate dihydrate

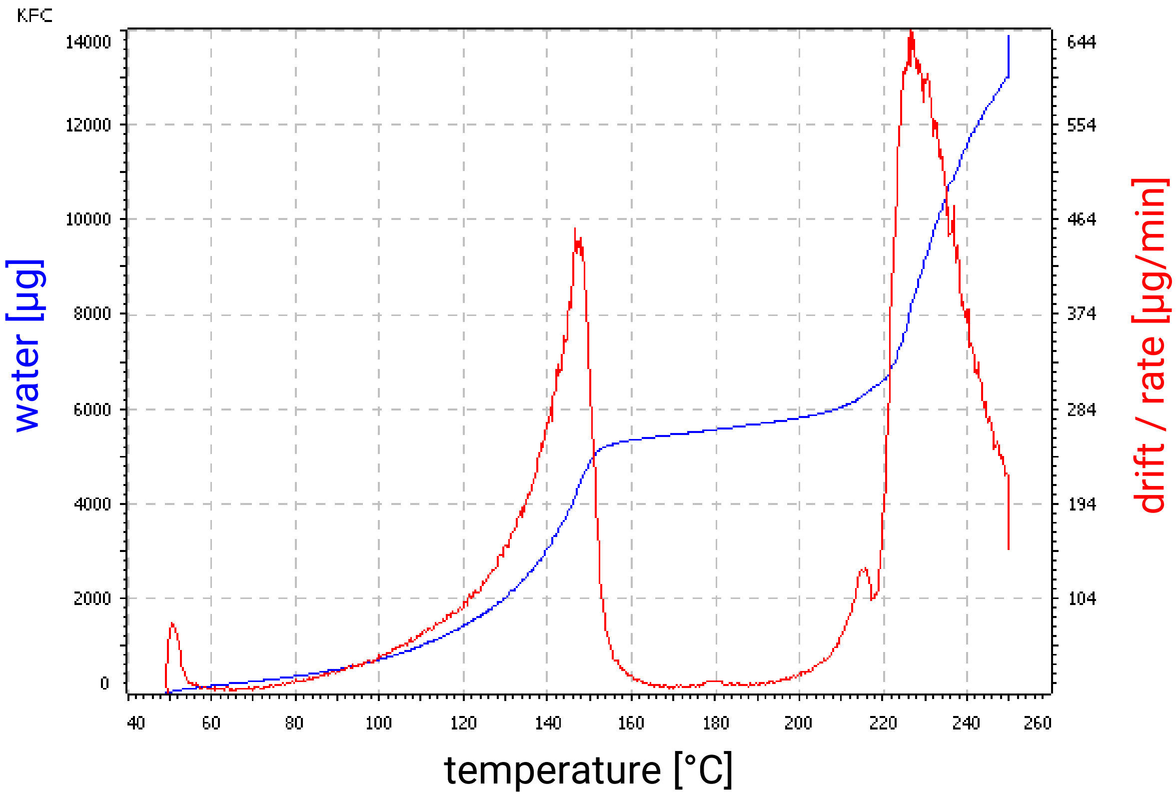
temperature gradient: 0,5°C/min

temperature range: 50 – 250°C

carrier gas: air

typical ovens for evaporation technique

feature: temperature ramp



sample: standard lactose monohydrate

temperature gradient: 0,5°C/min

temperature range: 50 – 250°C

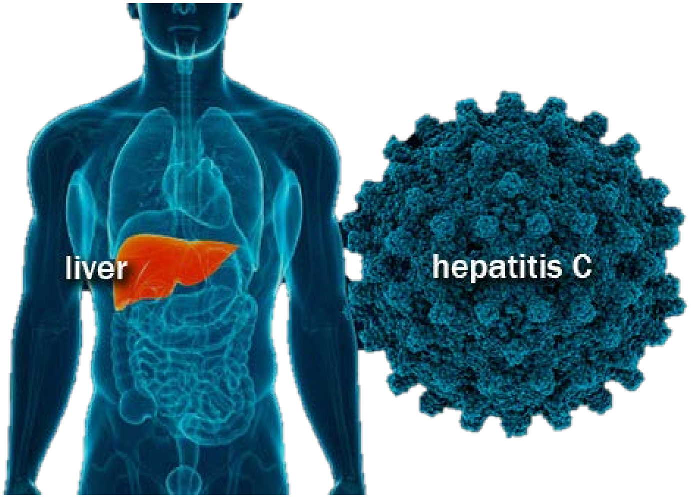
carrier gas: nitrogen

customer sample

as an example for KF water determination

sample: Elecsys Anti-HCV

- antibody test
- reagent to diagnose hepatitis C virus infection through the antibody Anti-HCV



https://www.webmd.com/hepatitis/ss/slideshow-hepatitis-c-overview

feasibility: water determination of sample

direct titration

contamination of the sample and KF-cell with humidity

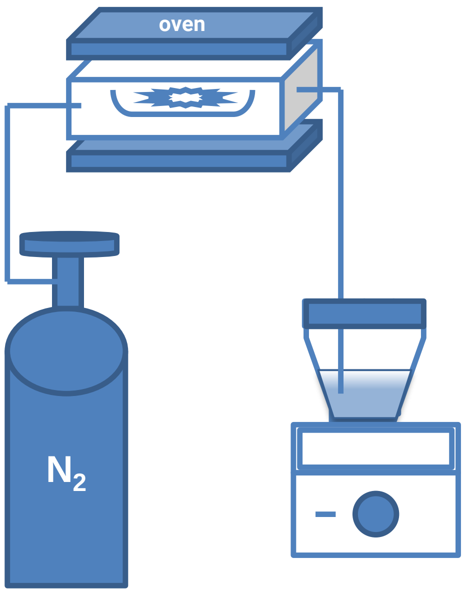
handling in glove box neccessary

sample should be soluble

extraction

sample must be soluble, otherwise a different technique must be applied

evaporation technique



feasibility: solubility of sample

- Coulometric titration cell after sample was added to the cell and titrated

→sample did not dissolve completely and thus clogs the anode of the generator electrode

feasibility: sample vials

specification:

- vial diameter: 10.0 … 32.0 mm
- immersion depths of vial: 20.0 … 45.0 mm
- vial sizes: 2R … 25R or 2H … 25H

feasibility: sample vials

- Maximum vial diameter: 22.2 mm
- immersion depths of vial: 30 mm
- vial sizes: 6R

→ label must be removed

feasibility: sample stoppers and caps

stoppers:

caps:

feasibility: sample stopper and cap

- type of cap: screw cap GL14 / closed center / polymer
- type of stopper: rubber / cruciform
- height of stopper: 13 mm / no thin center for injection

→ exchange screw cap → use temperature stable cap with hole

→ use long needle

feasibility: sample

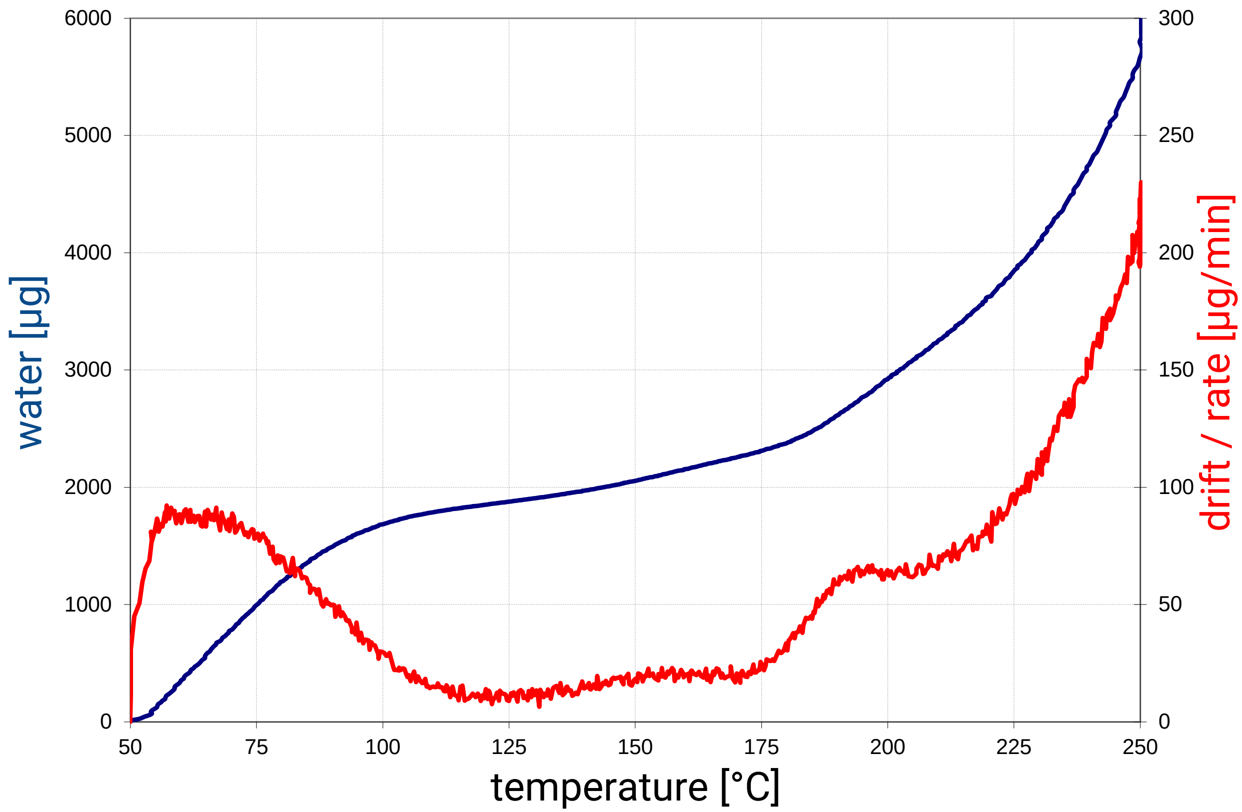
It needs to be clarified:

- which temperature has to be applied to make the sample release the water?
- Up to which temperature are the rubber stoppers heat-resistant?
- Up to which temperature are the screw caps heat-resistant?

→ the feasibility is given,
if the temperature of the sample is lower than the decomposition temperatures of the screw caps and stoppers

feasibility: sample

temperature ramp



sample:
Elecsys Anti-HCV

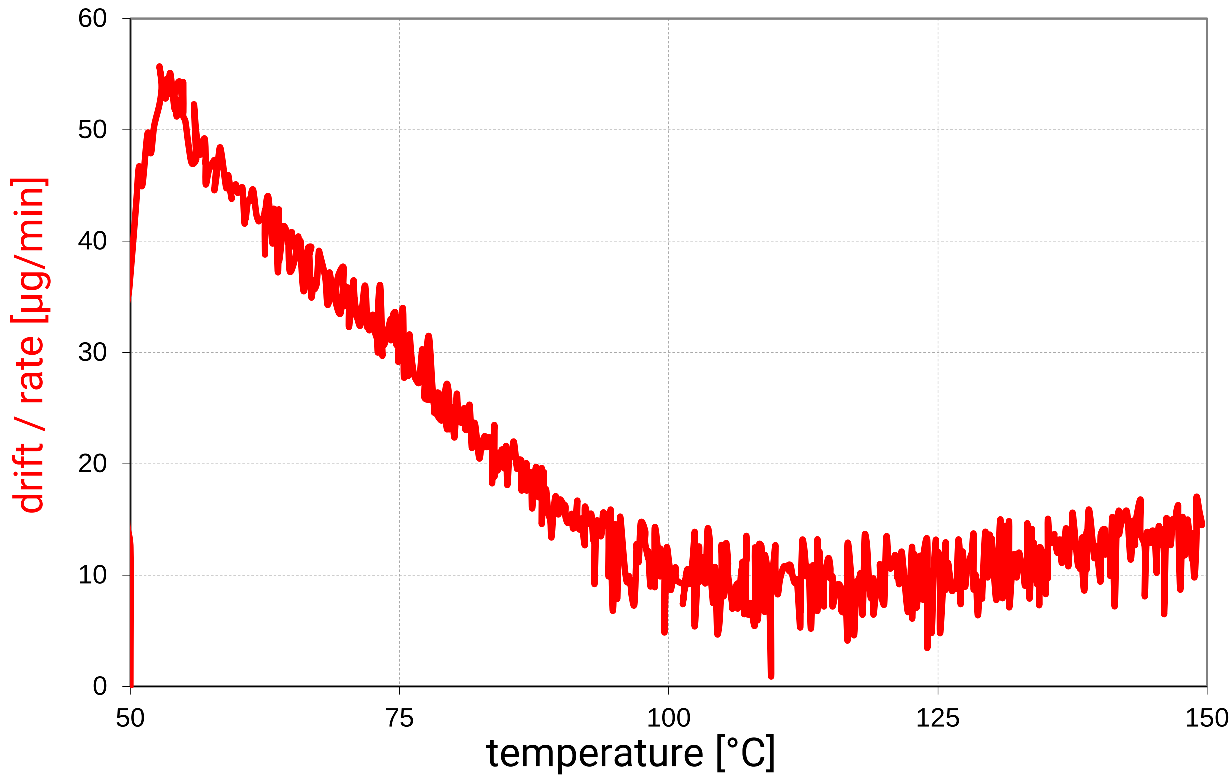
temperature gradient:
2°C/min

temperature range:
50 – 250°C

carrier gas:
nitrogen

feasibility: sample

temperature ramp



sample:
Elecsys Anti-HCV

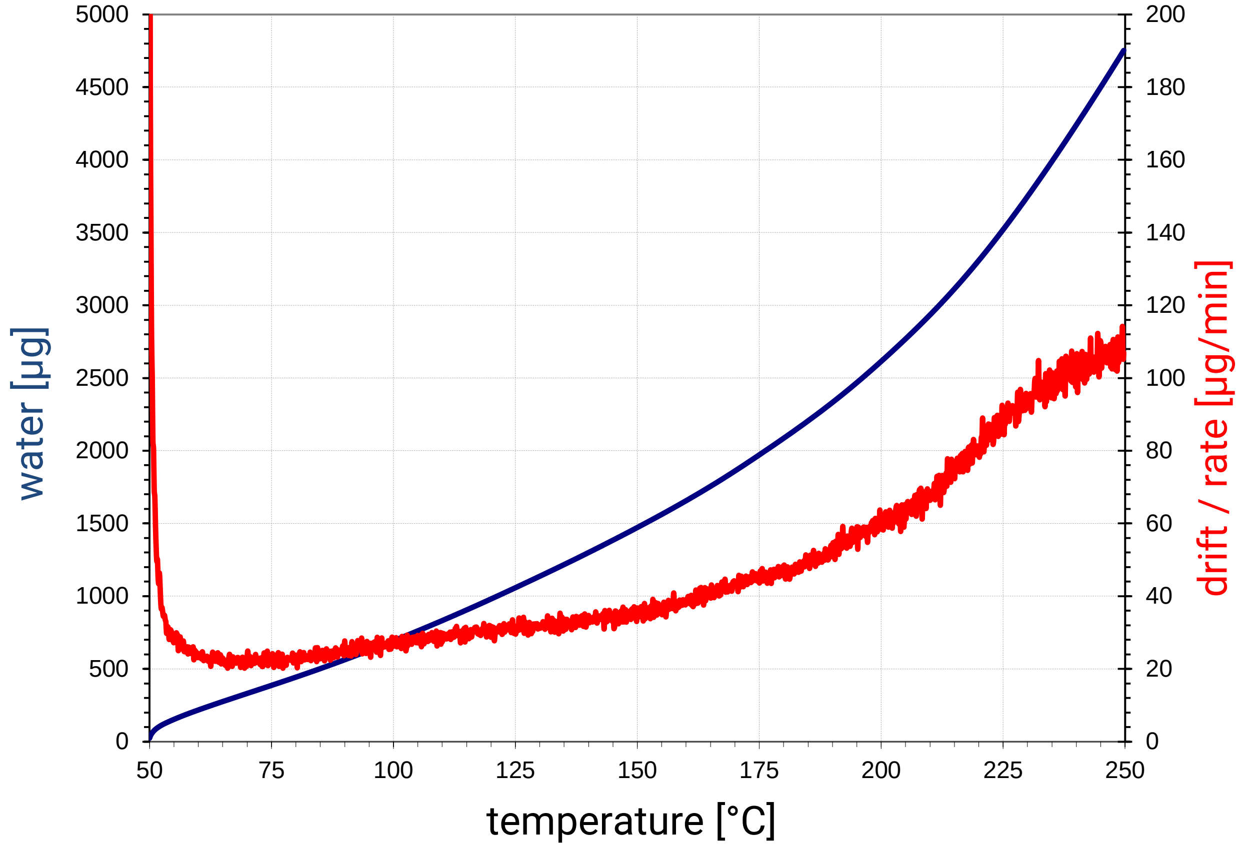
temperature gradient:
1°C/min

temperature range:
50 – 150°C

carrier gas:
nitrogen

feasibility: sample

temperature ramp



sample:
stopper

temperature gradient:
2°C/min

temperature range:
50 – 250°C

carrier gas:
nitrogen

results: sample

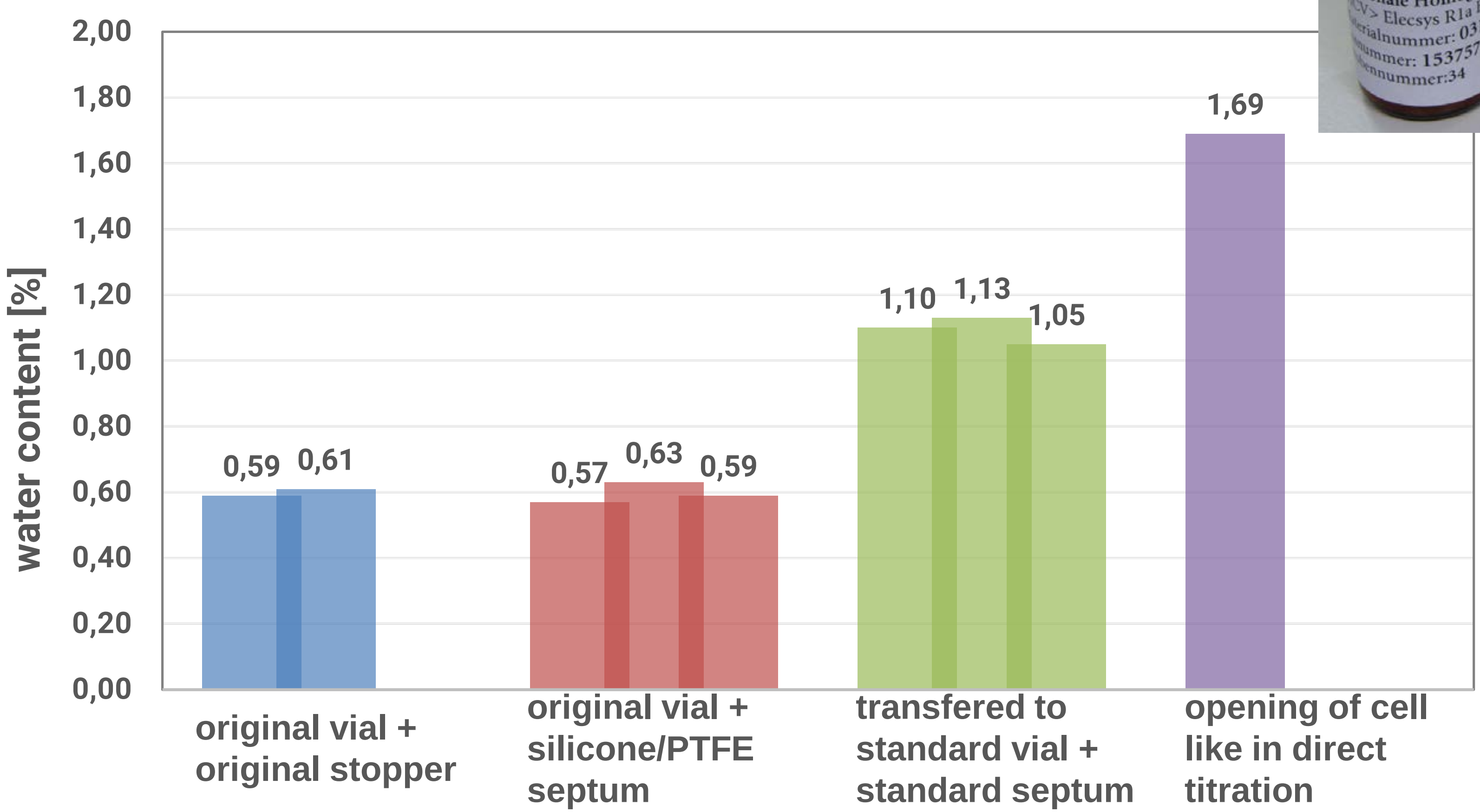
Parameter:

- temperature: 110 °C
- flow: nitrogen 50 mL/min
- determination time: approx. 6 – 8 min
- sample size: 85 mg

Sample: Elecsys Anti-HCV parameter	n	water [µg]	water content [%]	RSD [%]
original vial + original stopper	2	509	0,60	3,25
original vial + silicone/PTFE septum	3	507	0,60	5,13
transfered to standard vial + septum	3	928	1,09	3,70
direct titration in coulometric cell *	1	1435	1,69	
opening of cell like in direct titration	1	254	0,30	

* sample is not completely dissolved in reagent

results: sample



water determination of freeze drying closures

according to DIN ISO 8362-5 appendix A

water determination in closures according to DIN ISO 8362-5 appendix A

<u>Procedure:</u> preparation of apparatus

- heat oven to a temperature of (140±2) °C
- purge the oven with dry nitrogen at a suitable rate
- wait for low blank drift
- constant slope of the cumulative graph water/time when running a blank
- correct determination of water of a control solution
- correct determination of water of sodium tartrate
- daily checks are recommended

water determination in closures according to DIN ISO 8362-5 appendix A

<u>Procedure:</u> sample preparation

- use tweezers or wear gloves when handling the closures
- keep in original packing or in airtight containers
- handle under standard laboratory conditions (T= (23±2)°C; RH=(50±5)%
- take 10 closures and cut 1 segment from each
- Weigh to an accuracy of 0,1 mg

water determination in closures closures according to DIN ISO 8362-5 appendix A

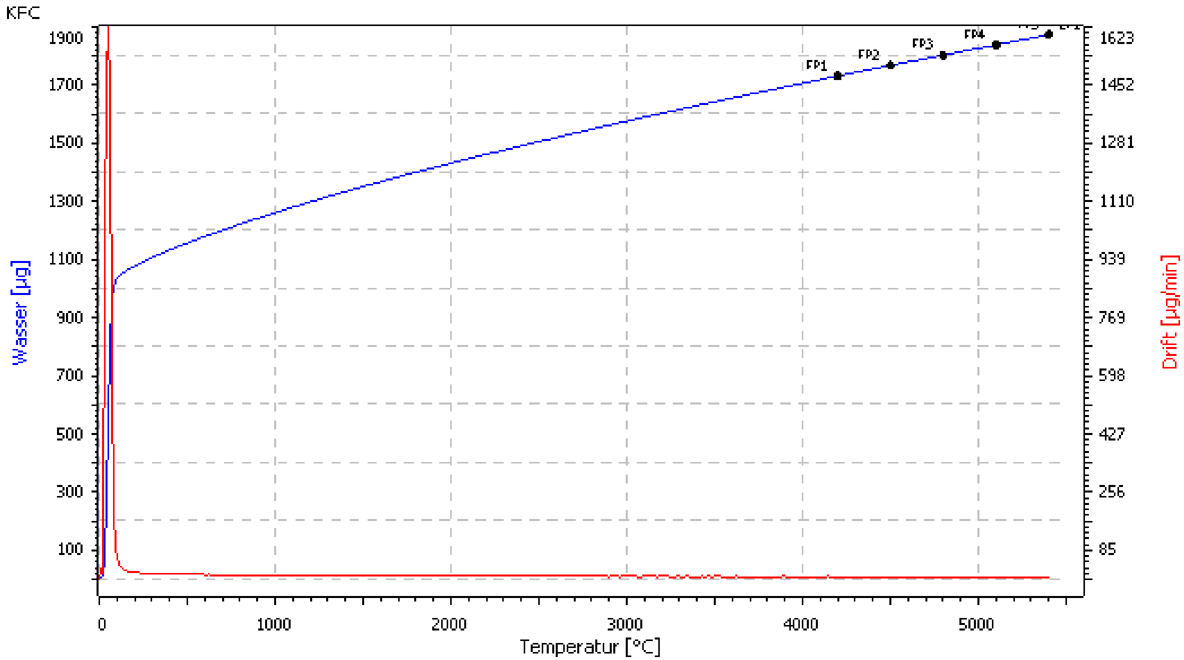
determination:

- start the determination
- record the curve of water content versus time for at least 90 min
- run the test in duplicate

water determination in closures according to DIN ISO 8362-5 appendix A

extrapolation & calculation:

- for extrapolation use the line drawn through the values at 70,75,80,85,90 min
- calculate the water content by using the amount of water of the intercept



Thank you for your attention.

Questions?

I am also happy to answer questions that arise later.

Please contact me:

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