

Determination of the water content in tablets by automated Karl Fischer titration

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Karl Fischer

Summary

The water content of tablets determines the release of their active ingredients as well as their chemical, physical, microbial and shelf-life properties. Accordingly, the water content is of crucial importance and has to be accurately determined. This paper describes the straightforward determination of the water content using automated volumetric Karl Fischer titration (KFT). Tedious sample preparation steps are eliminated by using a high-frequency homogenizer that additionally serves as a stirrer. Prior to titration, the homogenizer comminutes the tablets directly in the KF solution. As the comminution process takes place directly in the hermetically sealed titration vessels, interferences from atmospheric humidity do not occur. Even after 24 h in the vessels, the moisture content of four different tablet type samples was within 93...108% of the initially determined values. With a coefficient of determination of 0.99993 the KF method is highly linear for water amounts between 4 and 215 mg. For all investigated tablet types, KFT provides results that lie in the range expected by the manufacturer.

Introduction

The quality, hardness, compaction and shelf life of pharmaceuticals depend to a large extent on their water content, which means that its determination is very important. Most pharmacopoeias stipulate thermogravimetry and Karl Fischer titration (KFT) for water quantification. While the former method suffers from laborious sample preparation steps and insufficient accuracy, KFT had to face the problem of the limited solubility of tablets in Karl Fischer working media.

This problem was successfully overcome by using a high-frequency homogenizer that also serves as a stirrer during the titration. This poster describes the analytical procedure and discusses the results obtained for different tablet types.

System setup

The system for the automated determination of the water content by volumetric Karl Fischer titration consists of the

- 841 Titrand (volumetric KF Titrator)
- 815 Robotic USB Sample Processor XL with two towers
- Polytron with comminution aggregate (high-frequency homogenizer).

The Polytron homogenizer is mounted on the robotic titration head of the sample processor tower and is adjusted to the correct working height. The second tower is used for emptying the sample beakers after the determinations, reducing reagent handling to a minimum. All instruments are controlled by the Metrodata *tiamo*TM software.

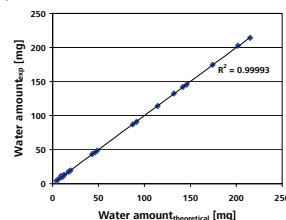


The procedure in detail

- initially, the Dosinos are pre-flushed to displace air bubbles and moisture
- four «blank determinations» (working solution without sample) are carried out; the first one is the system preparation value, the latter three provide the **mean blank value**
- the titer of a commercially available water standard is determined (n = 3)
- a defined amount of tablets is directly weighed out into the sample vessel
- samples are placed on the sample processor rack and all relevant data (sample weight, sample identification) is entered into the *tiamo*TM software
- all sample vessels are sealed with aluminum foil and a sleeve
- the working medium is transferred to the sample vessel
- the Polytron comminutes the tablets; comminution speed and time depend on tablet size and hardness and were determined in preliminary experiments
- the released water is titrated with KF reagent at a stirring speed of 7500 rpm
- after each determination a cleaning step with methanol is performed to avoid sample material carry-over; in order to prevent cross-contamination, the methanolic cleaning solution is titrated to dryness

Linearity test

A linearity test in the range of 4...215 mg was performed with the sodium tartrate dihydrate standard.

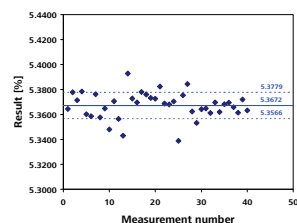


	Water amount [mg]	
	Experimental	Theoretical
1	4.05	4.09
2	4.97	4.75
...
18	91.26	90.72
...
24	201.79	202.79
25	215.18	214.36

The experimentally determined amount of water agreed very well with the theoretical amount, resulting in an outstanding coefficient of determination.

Seal integrity

Prior to titration, 200 µL distilled water were added to the working medium.



Mean value [%]	5.3672
Number of determinations	40
Standard deviation	0.0106
Relative standard deviation [%]	0.1975

The obtained relative standard deviation (RSD) of approximately 0.2% is ten times better than the maximum allowed RSD of the customer.

Water content in tablets

For each of the four analyzed tablet types – in addition to determining the system preparation value, the blank and the titer – ten determinations were carried out.

Sample	Tablet type 1 ^a methanol dry (60%) formamide (39%) octanol (1%)	Tablet type 2 ^b methanol dry (60%) formamide (39%) octanol (1%)	Tablet type 3 ^b methanol dry (60%) formamide (39%) octanol (1%)	Tablet type 4 ^a methanol dry (100%)
Number of analyzed tablets	5	1	3 or 5	5
1. System preparation [mL]	1.160	2.028	2.8920	1.0360
1	1.1420	1.402	1.5120	0.7020
2	1.1140	1.448	1.5420	0.6980
3	1.1200	1.380	1.4700	0.7100
Mean value [mL]	1.1253	1.4100	1.508	0.7033
Standard deviation	0.0120	0.0283	0.0295	0.0050
Relative standard deviation [%]	1.0696	2.0093	1.9582	0.7093
1	5.2851	5.2966	5.3540	5.3898
2	5.3104	5.2576	5.3431	5.3523
3	5.2851	5.2604	5.3300	5.3667
Mean value [mg/mL]	5.2935	5.2715	5.3424	5.3696
Standard deviation	0.0119	0.0178	0.0098	0.0154
Relative standard deviation [%]	0.2253	0.3369	0.1837	0.2877
1	0.87	10.81	3.24	3.80
2	0.87	10.79	3.25	3.86
3	0.88	10.68	3.21	3.83
4	0.87	10.67	3.30	3.84
5	0.88	10.68	3.43	3.88
6	0.87	10.63	3.39	3.86
7	0.88	10.59	3.34	3.88
8	0.87	10.85	3.31	3.83
9	0.88	10.61	3.36	3.82
10	0.87	10.54	3.39	3.79
Mean value [%]	0.874	10.685	3.322	3.839
Expected water content [%]	-1	-12	-3	-3
Standard deviation	0.005	0.096	0.069	0.029
Relative standard deviation [%]	0.560	0.902	2.080	0.768

The determined water contents were all within the range expected by the manufacturer and corresponded to the values previously validated by using a different system.

Recovery rates after 24 h

Working medium	Tablet type 1		Tablet type 2		Tablet type 3		Tablet type 4		
	0 h	24 h Recovery	0 h	24 h Recovery	0 h	24 h Recovery	0 h	24 h Recovery	
Blank	1.6447	1.6813	-	1.6447	1.6813	-	1.6447	1.6813	-
Standard deviation	0.0252	0.0560	-	0.0252	0.0560	-	0.0252	0.0560	-
Relative standard deviation [%]	1.5322	3.3308	-	1.5322	3.3308	-	1.5322	3.3308	-
Titer [mg/mL]	5.4134	5.4134	-	5.4134	5.4134	-	5.4134	5.4134	-
Standard deviation	0.0297	0.0297	-	0.0297	0.0297	-	0.0297	0.0297	-
Relative standard deviation [%]	0.5486	0.5486	-	0.5486	0.5486	-	0.5486	0.5486	-
Water content [%]	0.88	0.95	107.95	10.97	11.03	100.55	3.35	3.13	93.43
Standard deviation	0.012	0.001	-	0.041	0.012	-	0.040	0.056	-
Relative standard deviation [%]	1.364	0.105	-	0.374	0.109	-	1.194	1.789	-

In normal operation, the mean residence time of the sample in the titration vessel is much less than 24 h.