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HIRANUMA APPLICATION DATA		Karl Fischer Titrator	Data No.	KF20	Apr. 13, 2022
Water contents	Drugs and Medicines – KF Volumetry Japanese Pharmacopoeia – Suitability test				

1. Abstract

Water contents of drugs and medicines could be determined by Karl Fischer volumetric titrator. In volumetric titration, the titrant have a factor which means the ability to react with how many milligrams of water per 1 mL of titrant. Factor is pre-determined before sample measurement and water content of sample is calculated from consumed titrant volume within sample measurement.

In the method of “Water determination (Karl Fischer method)” in Japanese Pharmacopoeia Eighteenth Edition, the suitability test is described as a verification procedure when modifying the test procedures. In this report, a case example of suitability test is introduced with using glycerin as a simulated measurement sample.

Reference

- 1) Japanese Pharmacopoeia Eighteenth Edition

2. Apparatus and Reagents

(1) Apparatus

Titration cell	: HIRANUMA Karl Fischer Volumetric titrator AQV-series or MOIVO-A19
Titration cell	: Standard cell
Sampler	: Syringe

(2) Reagents

KF Titrant	: AQUALYTE KF ₃ (HIRANUMA) An alternative if it is difficult to prepare, HYDRANAL Composit 5 (Honeywell)
Titration solvent	: HYDRANAL Methanol Dry (Honeywell)

(3) Sample

Measurement sample	: Glycerin (Guaranteed reagent)
Standard material	: AQUALYTE Water Standard 10 (Assay: 10.01 mg/g, HIRANUMA) An alternative if it is difficult to prepare, HYDRANAL Water Standard 10 (Honeywell)

3. Procedure

3.1. Factor determination of KF titrant

- (1) Fill 50 mL of titration solvent into the titration cell as shown in Fig.3.1.
- (2) Start blanking to attain stable background.
- (3) Draw DI water into syringe. And then weigh it and record its read (Size 1 [g]).
- (4) Inject a few drops of water from rubber septum of titration cell as shown in Fig.3.2. Approximate amount of addition is 20-40 mg. (40-60 mg when using Composite 5 for KF titrant)

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is set as sample size.

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The above sampling procedure is an example for a simulated sample. It should be performed according to the actual sample and the suitability test to be implemented.

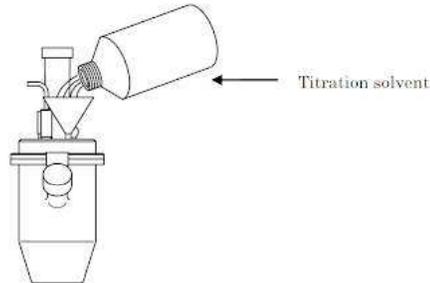


Fig.3.1 Preparation of the titration solvent

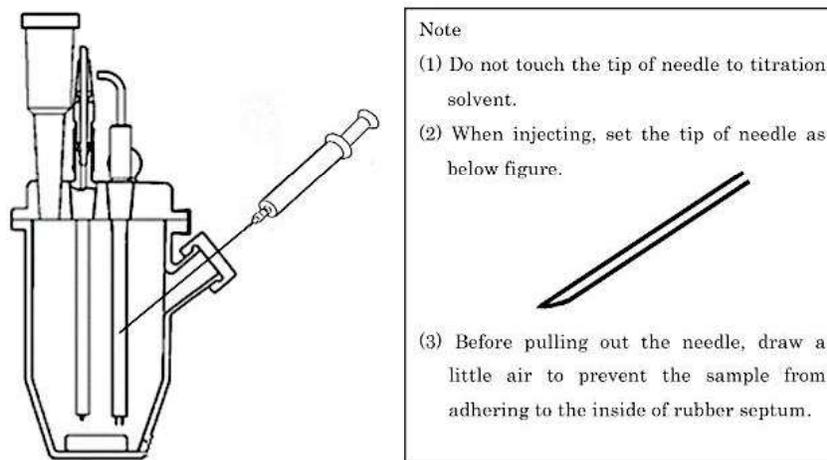


Fig.3.2 Injection of sample

3.2. Procedure for suitability test

- (1) Fill 50 mL of titration solvent into the titration cell as shown in Fig.3.1.
- (2) Start blanking to attain stable background.
- (3) Wash the syringe with the sample of glycerin and draw it into syringe. Then, weigh the syringe and record its read (Size 1 [g]).
- (4) Inject the sample from rubber septum of titration cell as shown in Fig.3.2. The injection amount is adjusted so that the detected water (mg) is within 5 to 30 mgH₂O.
- (5) Start titration. Measurement parameter is shown in Table 4.2.
- (6) Weigh the syringe again and record its read (Size 2 [g]). The difference of (Size 1-Size 2 [g]) is set as sample size.
- (7) After measurement of the sample is finished, the device, setting parameters, and reagents are used without change, and the water standard is measured subsequently. Wash the syringe with the water standard and draw it into syringe. Then, weigh the syringe and record its read (Size 1 [g]).
- (8) Inject the water standard from rubber septum of titration cell as shown in Fig.3.2. The injection amount is adjusted so that the detected water (mg) is 50 to 100 % of that of the sample measurement. Weigh the syringe again (Size 2 [g]). The difference of (Size 1-Size 2 [g]) is set as sample size.
- (9) Repeat the measurement of the water standard 5 times.

* The above sampling procedure is an example for a simulated sample. It should be performed according to the actual procedure of the suitability test to be implemented with actual sample.

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→ initial water content determined for sample of glycerin (mgH₂O)

M1-x :Amount of added water in the water standard measurement (mgH₂O),

“X” indicates the number of water standard measurement

⇒ Amount of added water (mgH₂O)

M2-x :Amount of found water in the water standard measurement result (mgH₂O),

“X” indicates the number of water standard measurement

⇒ Amount of found water (mgH₂O)

(2) Plot as follows using spreadsheet software.

x-axis	y-axis
M_{1-1}	$M + M_{2-1}$
$M_{1-1} + M_{1-2}$	$M + M_{2-1} + M_{2-2}$
$M_{1-1} + M_{1-2} + M_{1-3}$	$M + M_{2-1} + M_{2-2} + M_{2-3}$
$M_{1-1} + M_{1-2} + M_{1-3} + M_{1-4}$	$M + M_{2-1} + M_{2-2} + M_{2-3} + M_{2-4}$
$M_{1-1} + M_{1-2} + M_{1-3} + M_{1-4} + M_{1-5}$	$M + M_{2-1} + M_{2-2} + M_{2-3} + M_{2-4} + M_{2-5}$

(3) Create a regression line for the plots and find the following values.

b : Slope of regression line

a : y-axis intercept

d : x-axis intercept

(4) The percentage errors e1 (%) and e2 (%) are calculated from the following formulae.

$$e1 = \{(a - M) / M\} \times 100$$

$$e2 = \{(|d| - M) / M\} \times 100$$

(5) From the following formula, calculate the water recovery rate r (%) for each of the 5 measurements of the water standard, and calculate the average water recovery rate R (%).

$$r (\%) = (M2-X / M1-X) \times 100$$

4. Parameters and results

Table 4.1 Parameters for factor measurement of KF titrant

Item	Item
Cal Mode	7:KF Factor
	(By Pure water)
Interval Time	30 sec
Max Volume	20 mL
Min Feed Vol.	0.01 mL
S.Timer	0 min
KF Buret No.	1
	KF Speed(OUT) 24 mL/min
	KF Speed(IN) 24 mL/min
	Back Ground ON
	Sample Size Input Every Time
	Blank Value 0 mL
	E.P Detection uA
	Solvent S,O,CE
	C.P Level 150 uA
	E.P Level 200 uA
	Auto Interval 0 g
	Auto Input OFF

Table 4.2 Parameters for sample measurement

Item	Item
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			24 mL/min
	pages.		24 mL/min
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Min Feed Vol.	0.01 mL	Sample Size Input	Every Time
S.Timer	0 min	Blank Value	0 mL
KF Factor	3.3917 mg/mL	Unit Mode	AUTO mL
KF Buret No.	1	E.P Detection	uA
		Solvent	S,O,CE
		C.P Level	150 uA
		E.P Level	200 uA
		Auto Interval	0 g

* The above parameter settings are examples for a simulated sample. They should be set according to the parameters for suitability test to be implemented with actual sample.

Table 4.3 Results of factor measurement of KF titrant

Sample	Meas. No.	Sample size (g)	Titrant volume (mL)	KF factor (mg/mL)	Statistics result	
Water	1	0.0269	7.92	3.3995	Avg.	3.3917 mg/mL
	2	0.0297	8.81	3.3735	SD	0.0158 mg/mL
	3	0.0321	9.44	3.4022	RSD	0.47 %

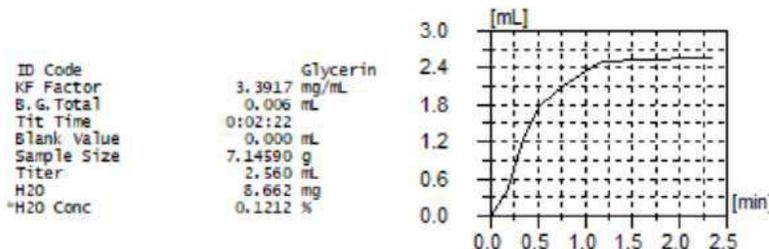


Fig.4.1 Measurement result of the sample

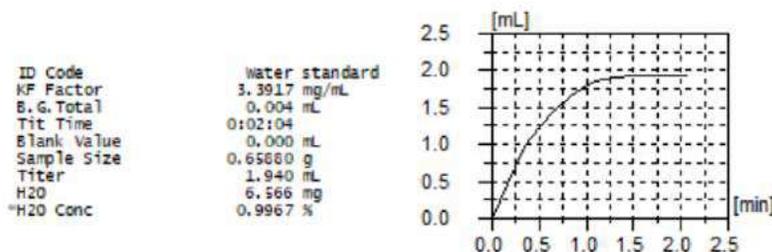


Fig.4.2 Example of measurement results of the water standard

Table 4.4 Values used for regression line of suitability test

Sample	Meas. No.	Sample size (g)	Added water	Found water	x-axis Cumulative	y-axis M +	percentage recovery
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Sample	1	2	3	4	5	6	7	8
Water	1	0.6588	6.595	6.566	6.595	15.228	99.57	
Standard	2	0.7001	7.008	6.994	13.603	22.222	99.80	
	3	0.6728	6.735	6.651	20.337	28.873	98.76	
	4	0.6680	6.687	6.624	27.024	35.497	99.06	
	5	0.7204	7.211	7.136	34.235	42.633	98.96	

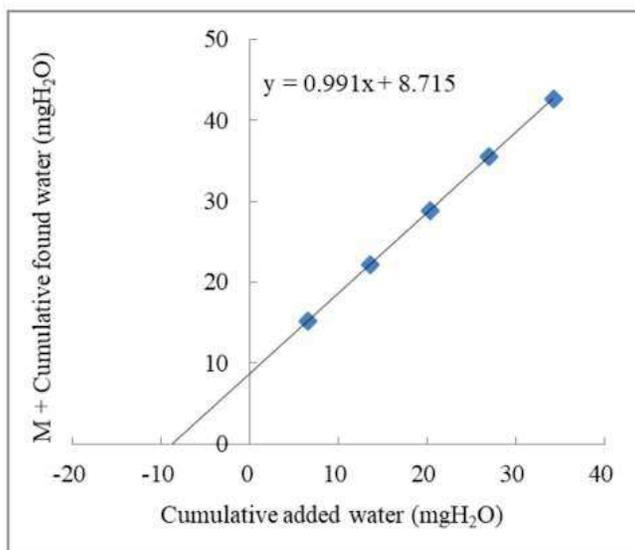


Fig.4.3 Result of calculated regression line

Table 4.5 Result of suitability test for Japanese Pharmacopoeia

Item	Result	Standard	Compliant
Found water of sample M (mgH2O)	8.662	5 ~ 30 mgH2O	OK
Average percent recovery R (%)	99.23	97.5 ~ 102.5 %	OK
y-axis intercept a (mgH2O)	8.715	-	-
Slope of regression line b	0.991	0.975 ~ 1.025	OK
x-axis intercept d (mgH2O)	-8.794	-	-
Percentage error e1 (%)	0.61	2.5 % or less	OK
Percentage error e2 (%)	1.52	2.5 % or less	OK

5. Note

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Adapt these to the actual sample to be verified by the suitability test.

Even if the sample, parameters, and sample addition method are different, the analysis procedure of suitability test can be performed in the same way.

In addition, from the Eighteenth Edition of Japanese Pharmacopoeia, the suitability test was adopted and the specific description on the preparation of Karl Fischer reagent was deleted. The purpose of this is as follows; as premises for complying the suitability test, it is possible to select and use the appropriate KF reagent from commercially available products, considering the solubility and interfering reaction according to the properties of the measurement sample.

Keywords: Karl Fischer, Volumetric titration, Japanese Pharmacopoeia, Suitability test



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