HIRANUMA APPLICATION DATA	Karl Fischer Titrator	Data No.	KF11	Apr. 13, 2022
Water contents	**Drugs and Medicines – KF Volumetry Back-Titration Dextromethorphan Hydrobromide Monohydrate**			

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.

There are two methods in KF volumetric titration, forward-titration and back-titration. Forward-titration is used in general. However, some of the sample should be measured by back-titration method according to Pharmacopeias. In back-titration method, firstly excess amount of KF titrant is added to the water contained in the sample, and then the remaining unreacted of KF titrant is titrated with water-in-methanol solution. Therefore, it is necessary to measure the factor not only KF titrant but also the water-in-methanol before the sample measurement.

An example for water contents measurements of dextromethorphan hydrobromide monohydrate performed by back-titration method is introduced here. The measurement method was determined with the reference to Japanese Pharmacopeia. Please refer to Application Data No. 22 for the suitability test of Japanese Pharmacopoeia eighteenth edition by the back titration method.

Reference

1) Japanese Pharmacopoeia Eighteenth Edition

2. Apparatus and Reagents

(1) Apparatus

Titrator	:	Karl Fischer Volumetric titrator AQV-series
Additional Buret	:	1 unit
Titration cell	:	Standard cell without drain valve
Sampler	:	Syringe
		Powder funnel (Outer diameter of leg less than 12 mm)

(2) Reagents

KF Titrant	:	AQUALYTE KF3 (HIRANUMA)
		An alternative if it is difficult to prepare
		HYDRANAL Composit 5 (Honeywell)
Water-in-methanol solution	:	2 mg/mL, prepared from reagent grade methanol and DI water
Titration solvent	:	HYDRANAL Methanol Dry (Honeywell)

(3) Sample

Dextromethorphan Hydrobromide Monohydrate (Guaranteed reagent)

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. Then, weigh the syringe 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)

(5) Start titration. Measurement parameter is shown in Table 4.1.

(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) Repeat the measurement 3 times and obtain an average value for factor of KF titrant.

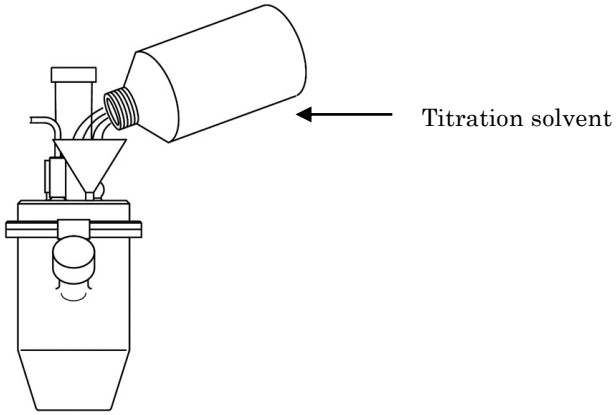
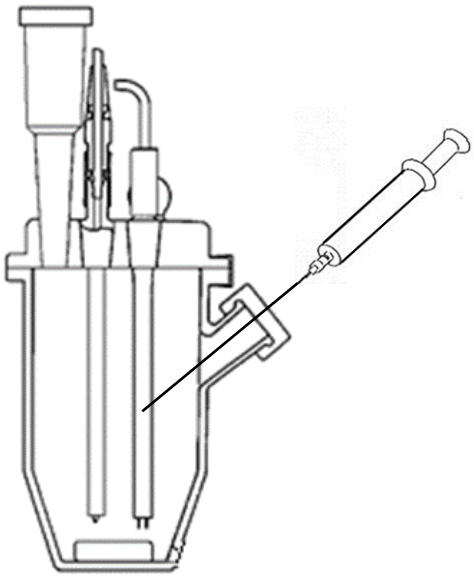


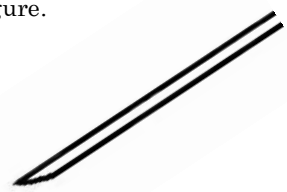
Fig.3.1 Preparation of the reagents



Note

(1) Do not touch the tip of needle to titration solvent.

(2) When injecting, set the tip of needle as below figure.



(3) Before pulling out the needle, draw a little air to prevent the sample from adhering to the inside of rubber septum.

Fig.3.2 Injection of sample

3.2. Factor determination of water-in-methanol solution

(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) Start titration. Measurement parameter is shown in Table 4.2.
10 mL of KF titrant is dispensed and then titrated by water-in-methanol solution.

(4) Repeat the measurement 3 times and obtain an average value for factor of water-in-methanol solution.

3.3. Sample measurement by back-titration

(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) Put a sample container, powder funnel and spoon on the balance. Record its read (Size 1 [g]).

(4) Open the glass stopper of titration cell lid to introduce the sample with powder funnel as shown in Fig.3.3.

(5) Start titration. First, 10 mL of KF titrant is dispensed into the cell and then titrated with water-in-methanol solution. Measurement parameter is shown in Table 4.3. Set the factors measured in section 3.1 and 3.2 for the KF reagent and the water-in-methanol solution.

(6) Weigh the sample container, powder funnel and spoon again and record its read (Size 2 [g]). The difference of (Size 1-Size 2 [g]) is set as sample size.

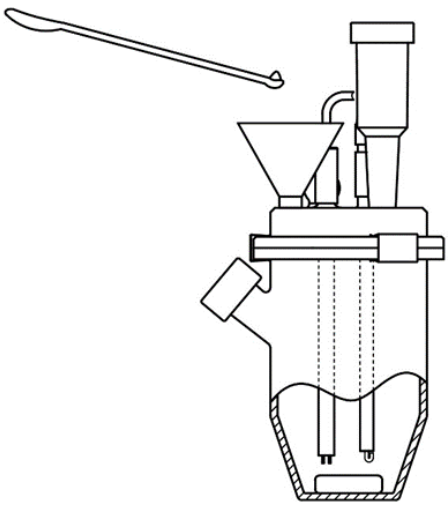


Fig.3.3 Introduction of sample with powder funnel

3.4. Blank test measurement by forward-titration

(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) Open the glass stopper of titration cell lid and introduce the funnel. Without adding the sample, leave to stand for the same amount of time as it takes to add the sample in section 3.3, then attach the stopper.

(4) Start titration. Blank test is performed with forward-titration. Measurement parameter is shown in Table 4.4.

(5) Set the result of titrant volume obtained in the blank test as the blank value for the measurement conditions of the sample.

4. Parameters and results

Table 4.1 Parameters for factor measurement of KF titrant

Item		Item	
Cal Mode		KF Speed(OUT)	24 mL/min
7:KF Factor(By Pure water)		KF Speed(IN)	24 mL/min
Interval Time	30 sec	Back Ground	OFF
Max Volume	20 mL	Sample Size Input	Every Time
Min Feed Vol.	0.01 mL	Blank Value	0 mL
S.Timer	0 min	E.P Detection	uA
KF Buret No.	1	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 factor measurement of water-in-methanol solution

Item		Item	
Cal Mode		KF Speed(OUT)	24 mL/min
10:MeOH Factor(Back tit.MeOH)		KF Speed(IN)	24 mL/min
Interval Time	30 sec	MeOH Speed(OUT	24 mL/min
Max Volume	20 mL	MeOH Speed(IN)	24 mL/min
Min Feed Vol.	0.01 mL	Back Ground	OFF
S.Timer	0 min	Blank Value	0 mL
KF Factor	2.9263 mg/mL	E.P Detection	uA
KF Buret No.	1	C.P Level	150 uA
KF Disp.Vol.	10 mL	E.P Level	200 uA
MeOH Buret No.	2	Fact Meas.	1
MeOH Disp.Vol.	10 mL	Auto Input	OFF
MeOH Timer	1 min		

Table 4.3 Parameters for sample measurement by back-titration method

Item		Item	
Cal Mode		KF Speed(OUT)	24 mL/min
11:Back tit1(Fixed KFreagent disp)		KF Speed(IN)	24 mL/min
Interval Time	30 sec	MeOH Speed(OUT	24 mL/min
Max Volume	20 mL	MeOH Speed(IN)	24 mL/min
Min Feed Vol.	0.01 mL	Back Ground	OFF
S.Timer	1 min	Sample Size Input	Every Time
KF Factor	2.9263 mg/mL	Blank Value	0.01 mL
KF Buret No.	1	Unit Mode	AUTO
KF Disp.Vol.	10 mL	E.P Detection	uA
KF Timer	1 min	C.P Level	150 uA
MeOH Factor	2.0279 mg/mL	E.P Level	200 uA
MeOH Buret No.	2	Auto Interval	0 g
MeOH Disp.Vol.	0 mL		
MeOH Timer	0 min		

Table 4.4 Parameters for blank test by forward-titration method

Item		Item	
Cal Mode		KF Buret No.	1
13:Auto input blank value mode		KF Speed(OUT)	24 mL/min
Interval Time	30 sec	KF Speed(IN)	24 mL/min
Max Volume	20 mL	Back Ground	OFF
Min Feed Vol.	0.01 mL	E.P Detection	uA
S.Timer	0 min	C.P Level	150 uA
		E.P Level	200 uA
		Auto Input	OFF

Table 4.5 Results of factor measurement of KF titrant

Sample	Meas. No.	Meas. Time	Sample size (g)	Titrant volume (mL)	KF factor (mg/mL)	Statistic result	
Water	1	0:04:25	0.0490	16.74	2.9271	Avg.	2.9263 mg/mL
	2	0:04:09	0.0520	17.78	2.9246	SD	0.0014 mg/mL
	3	0:03:28	0.0454	15.51	2.9271	RSD	0.05 %

Table 4.6 Results of factor measurement of water-in-methanol solution

Sample	Meas. No.	Meas. Time	Sample size (g)	Titrant volume (mL)	KF factor (mg/mL)	Statistic result	
KF titrant	1	0:05:25	0	14.44	2.0265	Avg.	2.0279 mg/mL
10 mL	2	0:08:03	0	14.44	2.0265	SD	0.0024 mg/mL
	3	0:10:18	0	14.41	2.0307	RSD	0.12 %

Table 4.7 Results of sample measurement

Sample	Meas. No.	Meas. Time	Sample size (g)	Titrant volume (mL)	Water (mg)	Water content (%)	Statistic result	
Blank test	1	0:00:40	-	0.01	-	-	Avg.	0.01 mL
	2	0:00:36	-	0.01	-	-		
Dextromethorphan	1	0:07:02	0.2000	9.62	9.725	4.8625	Avg.	4.9106 %
Hydrobromide	2	0:09:12	0.1968	9.64	9.685	4.9212	SD	0.0438 %
Monohydrate	3	0:12:57	0.1990	9.56	9.847	4.9482	RSD	0.89 %

5. Note

(1) Sampling tools should be dried up well before use.

(2) Purge and fill the titrant homogeneously into the buret.

(3) Organic solvents which have relatively high volume expansion coefficient are used as a constituent of titrant. For accurate measurement, factor titration and sample measurement should be performed at the same room temperature as much as possible.

(4) When adding a solid sample to the cell by opening the stopper of the cell lid, blank test should be performed separately to measure the water incorporated during the procedure of sample addition. Perform the blank test by forward-titration method instead of back-titration, and set the obtained titration volume in the blank value of the measurement condition of the sample.

(5) Compared to forward-titration, back-titration tends to take longer time to measure. If the titration volume of the water-in-methanol solution can be predicted in advance, set a value 3 to 5 mL smaller than the expected titration volume in the parameter "MeOH Disp. Vol.", and also set the parameter "MeOH Timer" to 1 minute. As a result, the measurement time is shortened by dispensing the water-in-methanol solution with the set value immediately after the start of titration with the water-in-methanol solution.

Keywords : Karl Fischer, Volumetric titration, Back titration, Pharmacopeia, Dextromethorphan hydrobromide monohydrate