HIRANUMA APPLICATION DATA	Karl Fischer Titrator	Data No.	KF13	Apr. 19, 2018
Water contents	**Drugs and Medicines – KF Volumetry, Powder Sample Lactose hydrate and L-Histidine hydrochloride hydrate**			

1. Abstract

Water contents of drugs and medicines are usually determined by Karl Fischer volumetric titrator. In volumetric titration, titrant have a factor which means the capacity to react with 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.

This application introduces an example for the water determination in lactose hydrate and L-histidine hydrochloride hydrate with reference to *Japanese Pharmacopeia*. Sample is measured by direct injection into the cell. When the solubility of the sample in methanol is not sufficient, use a mixed solvent of methanol and formamide as the titration solvent.

Reference

1) Japanese Pharmacopoeia Seventeenth Edition

2. Apparatus and Reagents

(1) Apparatus

Titrator	:	Hiranuma Karl Fischer Volumetric titrator	AQV-series
Titration cell	:	Standard Cell, without drain valve	P/N D327511-1
Powder funnel	:	Less than 13 mm outer diameter of leg	

(2) Reagents

Titrant	:	HYDRANAL Composite 5 (Honeywell)
Methanol	:	HYDRANAL Methanol (Honeywell)
Formamide	:	HYDRANAL Formamide dry (Honeywell)
Titration solvent	:	Mixed solvent of methanol and formamide at a volume ratio of 2: 1

3. Procedure

(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 (S_1 [g]).
(4) Open the glass stopper of titration cell lid to introduce the sample with powder funnel as shown in Fig.3.2.
(5) Start titration. Measurement parameter is shown in Table 4.1.
(6) Weigh the sample container, powder funnel and spoon again and record its read (S_2 [g]). The difference of (S_1-S_2 [g]) is set as sample size.

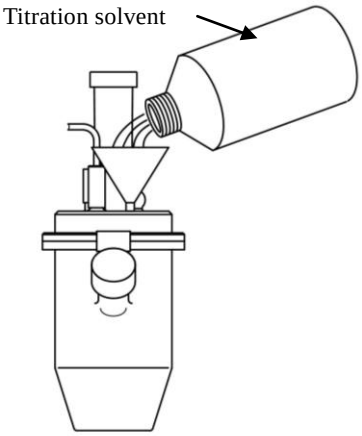

Fig.3.1 Preparation of the reagents

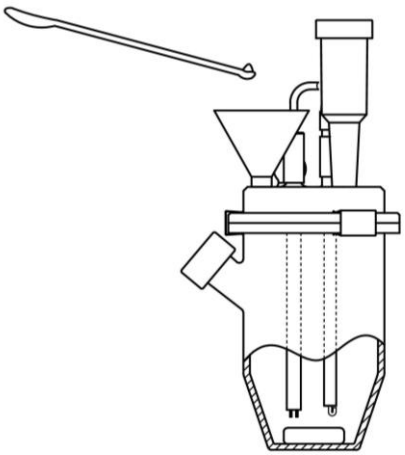

Fig.3.2 Introduction of sample with powder funnel

4. Parameters and results

Table 4.1 Parameters

Condition File		
Cal Mode	0:Sample weight (net)	
Interval Time	30	sec
Max Volume	20	mL
Min Feed Vol.	0.01	mL
S.Timer	5	min
KF Factor	5.7246	mg/mL
KF Buret No.	1	
KF Speed(OUT)	12	mL/min
KF Speed(IN)	24	mL/min
Back Ground	OFF	
Sample Size Input	Every Time	
Blank Value	0	mL
Unit Mode	AUTO	
E.P Detection	mV	
C.P Level	150	mV
E.P Level	2	
Auto Interval	0	g

Table 4.2 Results of water content measurement in drugs and medicines

Sample	Sample size (g)	Titrant volume (mL)	Water (mg)	Water content (%)	Statistics result		
Lactose hydrate	0.9933	8.74	50.033	5.0370	Avg.	5.0202	%
	1.0074	8.81	50.434	5.0064	SD	0.0155	%
	1.0212	8.95	51.235	5.0171	RSD	0.31	%
L-Histidine hydrochloride hydrate	0.1227	1.84	10.533	8.5844	Avg.	8.5406	%
	0.1230	1.84	10.533	8.5634	SD	0.0586	%
	0.1270	1.88	10.762	8.4740	RSD	0.69	%

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) The blanking might become unstable when time has passed since the solvents of methanol and formamide were mixed. The cause could be due to the ammonia generated by mixing solvent. Adding 3 g of benzoic acid to 50 mL of titration solvent improves the unstable state of blanking.

Keywords：Karl Fischer, Volumetric titration, Pharmacopeia