Water Determination (Karl Fischer Method)

Jarubol Chaichana
Bureau of Drug and Narcotic
Department of Medical Sciences
2 March 2012

<921> Water Determination USP34

Method 1 (Titrimetric)

Determine the water by Method Ia, unless otherwise specified in the individual monograph

Method 1a (Direct Titration)

- **Principle** –The titrimetric determination of water is based upon the quantitative reaction of water with an anh solution of sulfur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

Determination of Water
BP 2012

Use Method IA (Direct Titration) unless otherwise directed.

Method 1 *(Ph.Eur.method 2.5.12)*

- **Principle –** The semi-micro determination of water is based upon the qunatitative reaction of water with sulfur dioxide and iodine in a suitable anh medium in the presence of a base with sufficient buffering capacity.

Karl Fischer Titration

In the volumetric titration method, iodine required for reaction with water is previously dissolved in water determination, and water content is determined by measuring the amount of iodine consumed as a result of reaction with water in a sample.

Karl Fischer Titration

- This is a specific method. Only water will be determined. The method is rapid (a few minutes).

- With KF titration both free and bound water can be determined, e.g. surface water on crystals or the water contained inside them.

Karl Fischer Titration

- e.g. Cloxacillin sodium (BP2012).(2.5.12)
  Water : 3.0% to 4.5%, determined on 0.3 g

- It is indicated that when determined by accurately weighed about 0.3 g of the sample and performing KF Titration, the water content is NLT 3.0% and NMT 4.5% of the sample weight.

KF Titration

Volumetric KF Titration

KF Titration

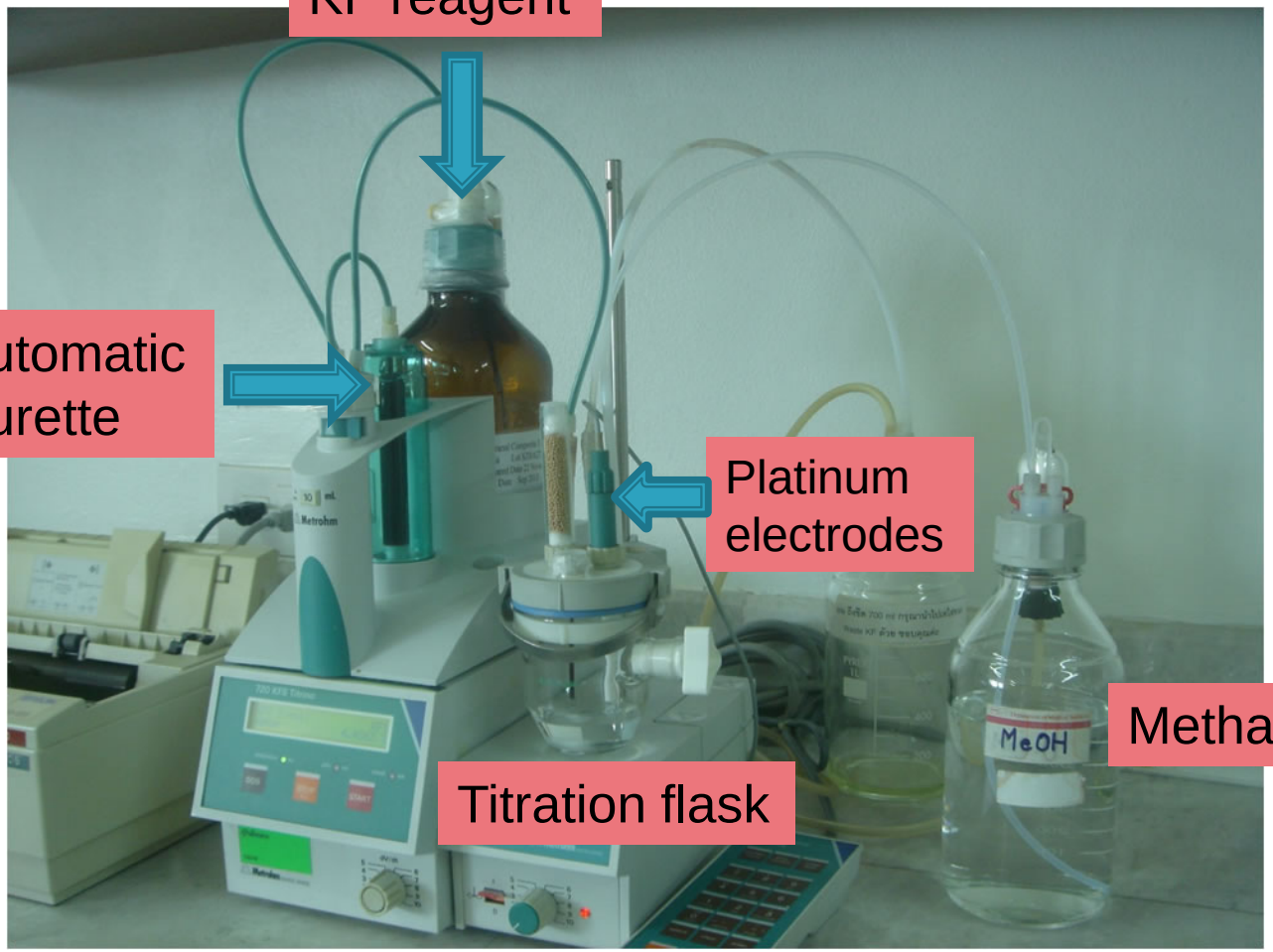
Accessories and reagent required

- Analytical balance (min resolution 0.1 mg)
- Syringe with long, thin needle
- Karl Fischer reagents for volumetric water determination

Requirements

KF instrument should not be set up in areas that are subject to large temp fluctuations, high humidity. They must not be placed in the proximity of heating, cooling devices.

Apparatus



The titration apparatus should be protected from atmospheric moisture.

The close system

Basic ingredients of KF reagents

- **Iodine** I_2
- **Sulfur dioxide** SO_2
- **Buffer** Imidazol
- **Solvent** Methanol

KF reagents

- **HYDRANAL® Karl Fischer Reagents**

Advantage……

The HYDRANAL® reagents uses imidazole or diethanolamine as a base, rather than noxious pyridine. Imidazole and diethanolamine are both safe and effective and guarantee reliable analyses.

Replacement of noxious pyridine with bases that are both safer and more effective.

Method for Karl Fischer Titration

2 Steps

1. Standardization of the reagent (Titer determination)

2. Water determination

Step 1. Standardization

Standardization USP34

Place enough methanol or other suitable solvent in the titration vessel to cover the electrodes, and applied 100±50 µA at about 200 mV.

Purified Water, sodium tartrate dihydrate, a USP Reference Standard, or commercial standards with certificate of analysis traceable to a national standard may be used to standardize the *Reagent.*

For *Purified Water* or water standards, quickly add the equivalent of between 2 and 250 mg of water.

Step 1. Standardization

Standardization [BP2012]

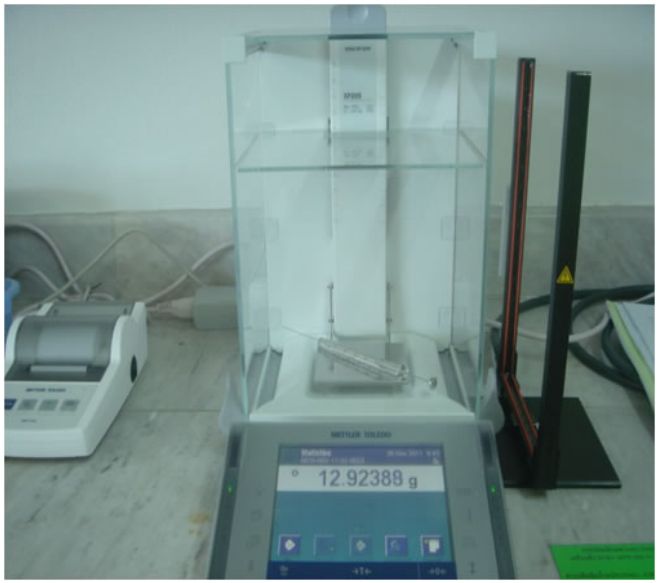
To the titration vessel, add MeOH, dried if necessary, or the solvent recommended by the supplier of the titrant. Where applicable for the apparatus used, eliminate residual water from the measurement cell of carry out a pre-titration.

Introduce a suitable amount of water in an appropriate form (*water R* or a certified reference material) and carry out the titration, stirring.

Step 1. Standardization

Substance	Remarks	Water content
Purified water	Ideal if technician knows how to proceed	100.00%
Certified water standards	Not hygroscopic Balance essential with test certificate	10 mg/g & 1 mg/g

Step 1. Standardization



Fill MeOH in the titration flask to cover the electrodes.
Condition system to conditioning drift OK (<20 µL/min).
Quickly add the water standard, accurately weighed containing 20 to 25 mg of water into the titration flask, stir and titrate until the endpoint.

Step 1. Standardization

Calculate the water equivalency factor, F, in mg of water per mL of reagent, by the formula:

$$F = W/V$$

W = the weight, in mg, of water contained in aliquot of standard use.

V = the volume, in mL, of the Reagent used in the titration.

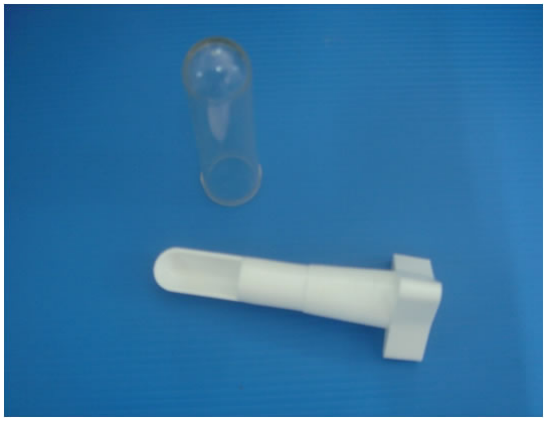
Step 1. Standardization

Titer of KF reagent = mg H_2O/ mL

Hydranal composite-5® : One mL of KF solution when freshly prepared is equivalent to approx. 5 mg of water, but it deteriorates gradually; therefore, Standardize the titrant before the first use and at suitable intervals thereafter. Protect from light while in use.

The water equivalent is NLT 80% of that indicated by the supplier. BP2012

Step 2. Water determination



- **Test Preparation**[USP34]**-** Unless otherwise specified in the individual monograph, use an accurately weighed or measured amount of the specimen under test estimated to contain 2 to 250 mg of water.

Step 2. Water determination

- **Test Preparation**[USP34] - The minimum amount of specimen, in mg, can be estimated using the formula:

$$FCV/KF$$

F = the water equivalency factor of the Reagent, in mg/mL

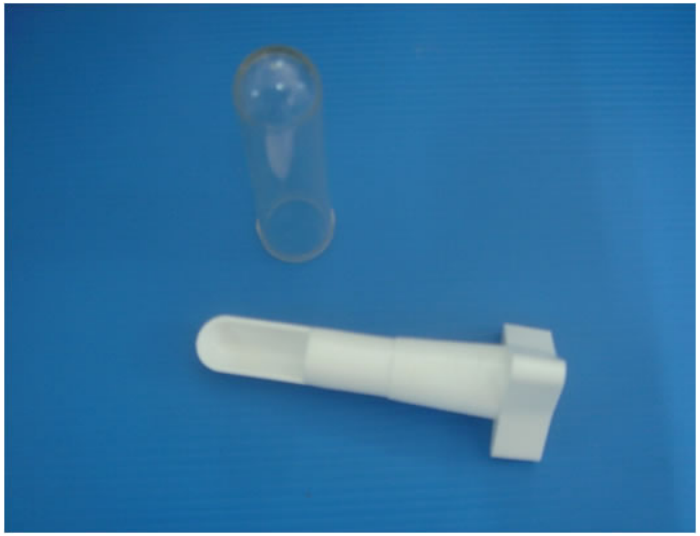
C = the used volume, in %, of the capacity of the buret

V = the buret volume, in mL

KF = the limit or reasonable expected water content in sample, in%

C is generally between 10%-100% for the instrument method endpoint.

Step 2. Water determination



- Quickly transfer the Test Preparation into the titration flask, stirring. And again titrate the solution with KF reagent to the end point under vigorous stirring.

Step 2. Water determination

Calculate the water content of the specimen, in mg, taken by the formula:

$$SF$$

S = the volume, in mL, of the Reagent consumed in the second titration.

F = the water equivalence factor of the Reagent.

Step 2. Water determination

Water content (%)

$$= \frac{SF \times 100}{\text{mg of Test Preparation}}$$

S = the volume, in mL, of the Reagent consumed in the second titration.

F = the water equivalence factor of the Reagent.

Endpoint indication

Bivoltametry $I_{pol} = 50\ \mu A$

Current applied to a double Pt electrode

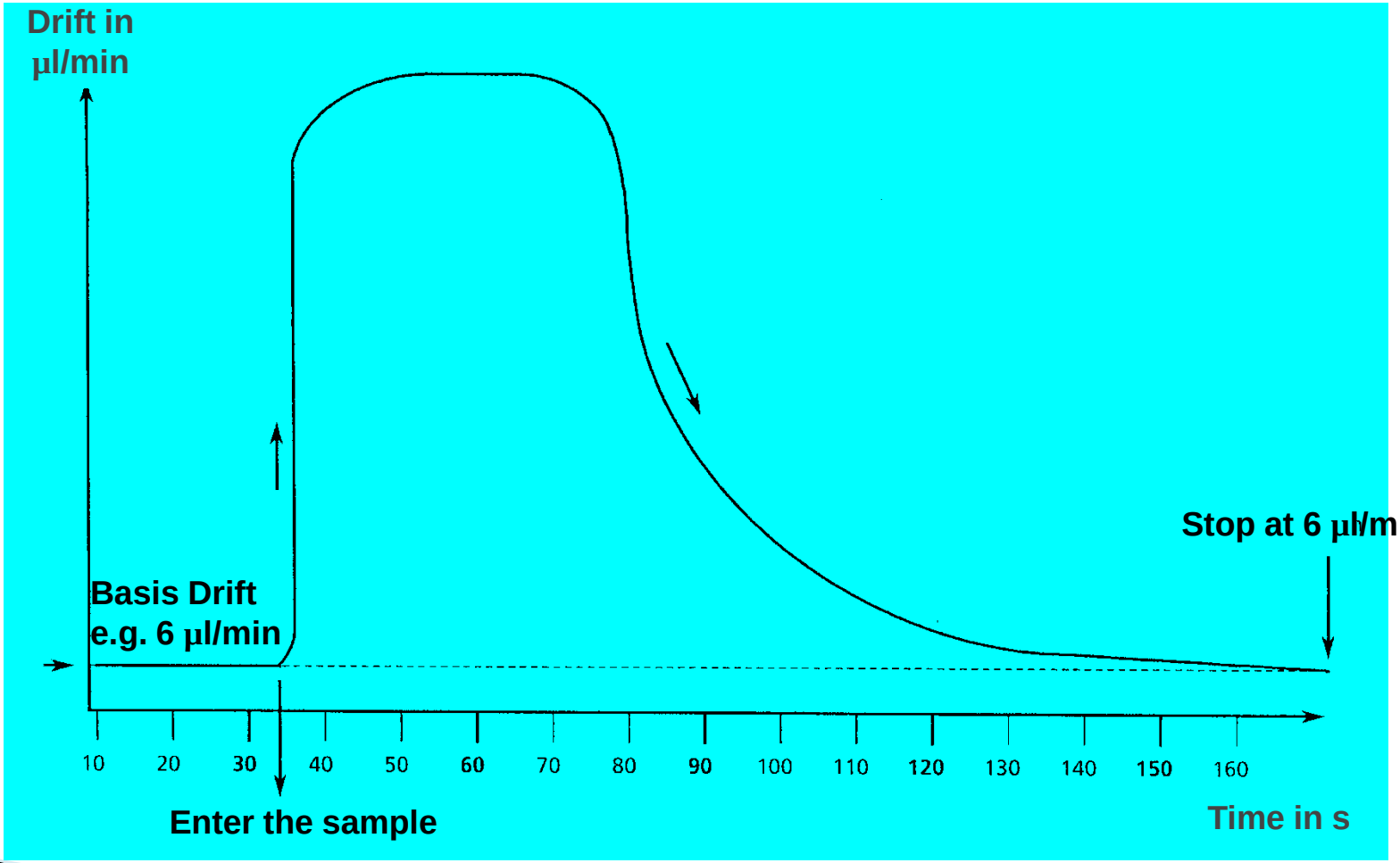
During titration: Excess H_2O

→ High voltage between the Pt wires

At the end of titration: Small excess of free iodine

→ Voltage decreases sharply

"Drift"- criteria



Acceptance criteria

Water content of sample (absolute content in µg)		Maximal permitted RSD%
< 500	(< 0.5 mg)	Not reported
500–1000	(0.5–1.0mg)	5.0%
1000–2000	(1.0–2.0mg)	3.0%
2000–5000	(2.0–5.0mg)	2.0%
5000–15000	(5.0–15.0mg)	1.50%

Example

- 0.0244 g of Standard water is equivalence to KFR 5.249 mL

$$\text{Titer} = \frac{0.0244 \times 1000}{5.249} = 4.6485 \text{ mg/mL}$$

- 0.1564 g of Lidocaine HCl is eq. to KFR 2.094 mL

$$\text{water content(\%)} = \frac{2.094 \times 4.6485 \times 100}{156.4} = 6.22\%$$

Limit USP34 (Lidocaine HCl) : between 5.0% and 7.0%

Conclusion: ☑ Pass

Reference

1.1 General Chapter: <921> WATER DETERMINATION. The United States Pharmacopoeia 34. The National Formulary 29. The United States Pharmacopoeial Convention, Inc.

1.2 Appendix IX C. Determination of Water. British Pharmacopoeia 2012.

1.3 Validation of Metrohm KF Titrators according to GLP/ ISO9001. Application Bulletin 255/3 e. Page 1-8.