Application Note

Determination of Cimetidine by Titration with Acetic Acid as the Solvent

Industry	:	Pharmaceutical
Instrument	:	Automatic potentiometric titrator
Measurement method	:	Potentiometric titration / Neutralization titration
Standards	:	Japanese Pharmacopoeia

1. Scope

Cimetidine is one of the pharmaceuticals listed in the Japanese Pharmacopoeia. This application introduces an example of determination of cimetidine based on the Japanese Pharmacopoeia.

2. Precautions

In this titration, acetic acid is used as the solvent. If water is mixed into the sample solution, inflections in the titration curve become unclear, leading to errors. To avoid water contamination, use one of the following electrolytes for the reference electrode.

(1) 1 mol / L lithium chloride in acetic acid
(2) Saturated sodium perchlorate solution in acetic acid

Electrolyte (1) is available from KEM, so contact us if you would like to order it. Electrolyte (2) must be prepared by the operator. When preparing this solution, saturate acetic acid with anhydrous sodium perchlorate, and use the supernatant liquid.

3. Post-measurement procedure

Seal the refill port for electrolyte of reference electrode by rubber septum so that electrolyte is prevented from leaking out or concentrating, and store the electrode.
The performance of the electrodes quickly degrades if it is stored while dry. The following storage methods are recommended.

- Short-term storage (less than one month): Store it immersed in pure water.
- Long-term storage (one month or longer): Store it immersed in a 1:1 volume ratio mixture of a standard solution of pH4 and a 3.3 mol/L KCl solution.

4. Apparatus

- Automatic potentiometric titrator (preamplifier : STD)
- pH glass electrode
- Reference electrode (Double junction type)
  (Electrolyte: 1 mol / L lithium chloride in acetic acid)

5. Reagents

- 0.1mol/L Perchloric acid in acetic acid
- Acetic acid

6. Procedure

1) Collect about 0.24 g of sample into a beaker and measure the mass of sample.
2) Add 75 mL of acetic acid, and dissolve the sample completely.
3) Titrate the mixture with 0.1 mol/L perchloric acid solution.
4) Using the same procedure, perform a blank test, and correct the titration volume.

7. Calculation

Cimetidine (%) = (EP1-BL1)×TF×C1×K1 / S

EP1	･･･Titration amount of sample (mL)	
BL1	･･･Titration amount of blank titration	＝0.0126
TF	･･･Factor of titrant	＝0.9763
C1	･･･Concentration conversion coefficient	＝25.23mg/mL
K1	･･･Unit conversion coefficient	＝0.1
S	･･･Quantity of sample (g)	

8. Example

-Titration parameter-

＜Titr. Mode＞ : Auto Intermit
＜Titr. Form＞ : EP Stop

＜Titr. Para.＞

Max. Volume	: 20 (mL)
Channel/Unit(Ctrl.)	: Ch1, mV
Channel/Unit(Ref.)	: Off
pH Polarity	: Standard
Titr. Type Check	: No Check
Dose Mode	: None

＜Ctrl. Para.＞

Number of EP	: 1
End Sense	: Auto
Gain	: 1
Data Sampling	: Auto
Ctrl. Speed	: Standard
Other Ctrl.	: Standard
Auto Int. Mode	: Standard
Stirrer Speed	: 4

(The above condition is an example. The setting condition depends on the model.)

—Titration curve—

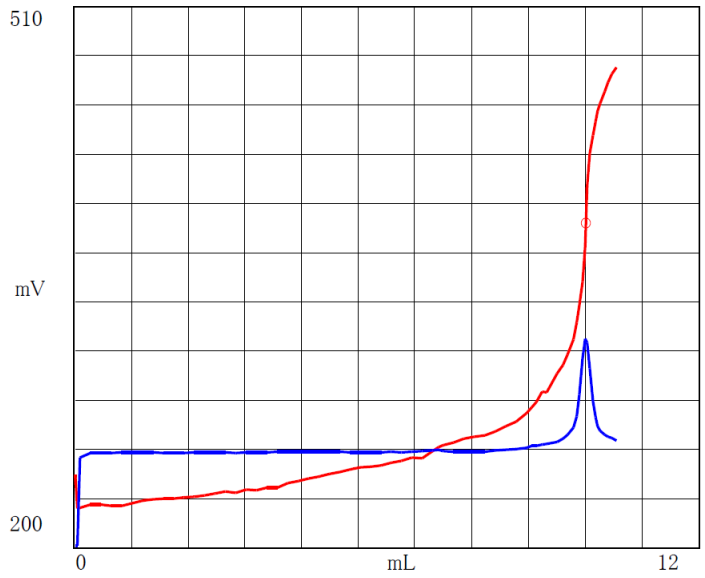

Table1 Measurement result

	Sample (g)	Titration volume (mL)	Cimetidine (%)
1	0.2442	9.9331	100.07
2	0.2420	9.8440	100.07
3	0.2438	9.9052	99.95
Mean	-	-	100.03
SD	-	-	0.07
RSD(%)	-	-	0.07

9. Summary

Excellent accuracy was obtained with a relative standard deviation (RSD) of less than 0.1 %.
In addition, the results obtained satisfied the requirements (99.0 to 101.0 %) specified in the Japanese Pharmacopoeia.

10. For your information

With very weak bases with a base dissociation constant pK_b of 7 or more, inflections do not occur with titration in aqueous solutions, so determination is difficult. In addition, many pharmaceuticals are hard to dissolve in water. If a pharmaceutical is hard to dissolve in water, aqueous solution titration cannot be applied. These issues are resolved by non-aqueous titration with acetic acid as the solvent. Acetic acid, which is an acidic solvent, is a strong proton donor, so chemicals that are weak bases in an aqueous solution behave like strong bases in acetic acid. As a result, when acetic acid is used as the solvent, inflections near the end point become clear, enabling determination. For this reason, non-aqueous titration with acetic acid as the solvent is stipulated as a determination method for many chemicals listed in the Japanese Pharmacopoeia.