Application Note

Quantitation of chlorpromazine hydrochloride by titration with acetic acid/acetic anhydride as the solvent

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

1. Scope

Chlorpromazine hydrochloride is one of the pharmaceuticals listed in the Japanese Pharmacopoeia. This Application Note describes an example of the quantitation of this compound based on the Japanese Pharmacopoeia.

2. Precautions

• Desiccate the sample prior to use. The desiccation conditions are as follows.
(Desiccation conditions: Introduce 1 g of the sample. Heat it for 2 hours at 105 °C. Then cool it to room temperature in a desiccator.)
• The sample is not easily dissolved in the solvent, so stir it thoroughly, and start the measurements after the sample is completely dissolved.
• The sample gradually deteriorates when exposed to light, so refrigerate and shade it from light during storage.
• In this titration, if water is mixed in, it will lead to errors. To avoid water contamination, use one of the following for the electrolyte in the reference electrode.

1) 1 mol/L Lithium chloride acetic acid solution
2) Saturated sodium perchlorate acetic acid solution

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

To prevent leakage of the electrolyte, when the combined glass electrode is not in use, seal the electrolyte filling port with a rubber stopper.
The performance of the electrodes quickly deteriorates if they are stored while dry. The following storage methods are recommended.

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

4. Apparatus

Main unit	Automatic potentiometric titrator (preamplifier: STD)
Electrode	Combined glass electrode double junction type

5. Reagents

Titration liquid: 0.1 mol/L perchloric acid acetic acid solution*
Solvent: Solution combining acetic anhydride and acetic acid in a 7:3 volume ratio

* Refer to the Japanese Pharmacopoeia for details on the preparation procedures.

6. Procedure

-Pretreatment-
1) Desiccate the sample. (Desiccation conditions: 1 g, 105 °C, 2 hours)

-Measurement-
1) Introduce approximately 0.7 g of the sample into a beaker, and weigh it.
2) Add 50 mL of the solvent, and stir until the sample is completely dissolved.
3) Titrate using a 0.1 mol/L perchloric acid acetic acid solution, with the inflection point in the titration curve as the end point.
4) In addition, perform a blank test separately to correct the titration volume when measuring the sample.

7. Calculation

Purity of chlorpromazine hydrochloride (%) = (EP1 - BL1) × TF × C1 × K1/S

EP1	Titration volume (mL)
BL1	Titration volume during a blank test = 0.0662 mL
TF	Titration liquid factor = 1.0469*
C1	Concentration conversion coefficient = 35.53 mg/mL
K1	Unit conversion coefficient = 0.1
S	Amount of sample introduced (g)

* This factor is calculated by using potassium hydrogen phthalate, the standard substance for volumetric analysis, as the standard.
Refer to the Japanese Pharmacopoeia for details on standardization procedures.

8. Example

— Parameter —

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

<Titr. Para.>

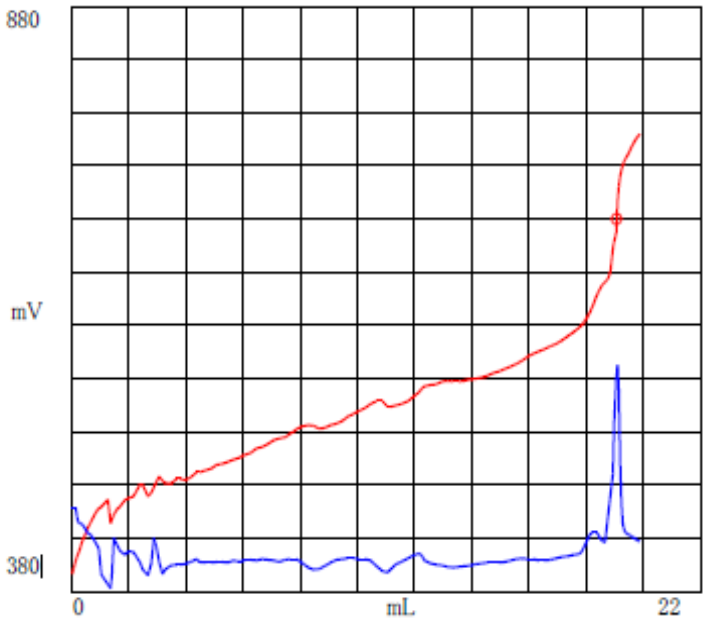
Bullet No.	1
Max Volume	30 (mL)
Channel/Unit (Ctrl.)	Ch1, mV
Channel/Unit (Ref.)	Off
pH Polarity	Standard
Titr. Type Check	None
Direction	Auto
Wait Time	0 (s)
Dose Mode	None

<Ctrl. Para.>

End Point No.	1
Gain	1
End Sense (dE/dmL)	Auto
Data Sampling	Auto
Ctrl. Speed	Standard
Other Control	Standard
Stirrer Speed	4

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

— Example of Titration curve —



— Measurement results —

Table 1 Measurement results of Chlorpromazine hydrochloride

	Sample (g)	Titration (mL)	Time (h:m:s)	Purity (%)
1	0.7072	19.1955	0:11:23	100.62
2	0.7064	19.0974	0:09:54	100.21
3	0.7039	19.0472	0:09:51	100.30
Mean				100.38
SD				0.21
RSD (%)				0.21

9. Summary

Quantitation of chlorpromazine hydrochloride satisfying the standards in the Japanese Pharmacopoeia (99.0 to 101.0 %) is possible using a KEM automatic potentiometric titrator.

10. Reference

Quantitation is difficult in the case of very weak bases with a base dissociation constant pKb of 7 or more because no inflection occurs with titration in aqueous solutions. In addition, many pharmaceuticals do not dissolve easily in water. In such cases, aqueous solution titration cannot be applied. This issue is 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 apparent, thus enabling quantitation. For this reason, non-aqueous titration with acetic acid as the solvent is specified as a quantitation method for many pharmaceuticals listed in the Japanese Pharmacopoeia.