Status: Currently Official on 12-Feb-2025
Official Date: Official as of 01-Aug-2024
Document Type: General Chapter
DocId: GUID-BCAF402E-9408-4F7C-BF53-B1F6E9DA6BA9_2_en-US
DOI: https://doi.org/10.31003/USPNF_M99300_02_01
DOI Ref: pm5r6



# ⟨541⟩ TITRIMETRY

***Change to read:***

## ▲INTRODUCTION

Titrimetry is a quantitative technique where a solution of known composition containing a reagent—the titrant—is quantitatively added to a defined quantity of a sample solution that contains an unknown amount of the analyte. The known reaction between titrant and analyte proceeds stoichiometrically until, ideally, the amount (volume) of titrant added is equivalent to the amount of analyte in the sample. In practice, the detection method(s) used in manual titrations indicate(s) endpoints, rather than equivalence points achieved by automatic titrations. The volume of the titrant consumed by the analyte present in the sample and the known reaction chemistry are used to calculate the amount of analyte.

## TYPES OF TITRATIONS

Several classification schemes are in use for titrations. These serve mainly for descriptive purposes enabling a better overview over the wide variety of methodologies currently employed. The classification schemes listed herein are not intended to be mutually exclusive, nor are they designed to be fully exhaustive.

### Reaction Type (Titration Type)

#### ACID−BASE TITRATIONS

Acids and bases are most simply defined as substances that furnish, when dissolved in water, hydrogen ions ($H^+$) and hydroxide ions ($OH^-$) respectively (Arrhenius). Newer, and more generally applicable definitions exist (Brønsted-Lowry, Lewis), which take into account that properties characteristic of acids and bases may apply in non-aqueous solvents as well.

The apparent strength of an acid or a base is determined by the extent of its reaction with a solvent. In mixtures of acids, the titration is always carried out in the sequence of the relative acid strengths. This means that the strongest acid is always titrated first, the weakest acid last. In aqueous solution, all strong acids appear equally strong because they react with water to undergo almost complete conversion to hydronium ion ($H_3O^+$) and the corresponding acid anion (leveling effect). A weak acid, e.g., acetic acid, reacts incompletely with water. Acid–base reactions usually occur very rapidly and are thus predestined for direct titrations.

Non-aqueous titrations are primarily carried out when:

- The substance is not soluble in water, e.g., fats and oils
- Single components of mixtures of acids or bases have to be determined separately by titration

Suitable solvent systems should:

- Dissolve the sample and not react with it,
- Permit the determination of components in a mixture, and
- Should address Environment, Health, and Safety (EHS) aspects as determined by the relevant authorities

#### PRECIPITATION TITRATIONS

In precipitation titration, the reaction between titrant and the analyte leads to the formation of an insoluble compound. A major difficulty for this type of titration is how to reliably identify the endpoint, because of turbidity due to formation of very fine precipitate particles, the co-precipitation of interfering species, or other contributing factors.

Examples of this form of titrimetry are the determinations of Halides [e.g., silver chloride (AgCl)] and Pseudo-Halides [e.g., silver thiocyanate (AgSCN)].

#### COMPLEXOMETRIC TITRATIONS

In complexometric titration the titrant generally forms a complex with the analyte (usually a metal ion).

The equilibrium constant for formation of the titrant–analyte complex must be sufficiently large that, at the endpoint, very close to 100% of the analyte has been determined by the use of complex-forming reactions.

In general, complexometric indicators are themselves complexing agents. The reaction between indicator and analyte must be rapid and reversible. The equilibrium constant for formation of the indicator–analyte complex should be large enough to produce a sharp color change but must be less than that for the titrant–analyte complex.

The pH of the complexation reaction needs to be taken into account to achieve completion of the reaction.

Potential interference of other ions present in the buffer or the sample may often be masked or "screened" via addition of another complexing agent. Moreover, the selection of a suitable pH allows for avoiding interference by other ions in the sample solution.

#### REDOX TITRATIONS

The redox reaction involves the transfer of electrons between two molecules. It is a combination of two reactions, oxidation and reduction where the oxidation reaction comprises an increase in the oxidation state or oxidation number, while the reduction involves a decrease of the oxidation number. Redox titrations may often be carried out conveniently by the use of a reagent that brings about oxidation or reduction of the analyte. Many redox titration curves are not symmetric about the equivalence point, and thus graphical determination of the endpoint is not possible.

### Indication of Equivalence Point or Endpoint

The distinction between chemical and physical methods is largely historical, as detection of the endpoint was initially performed by the unaided eye. Over the course of time advances in analytical science and technology have enabled methods of physical detection to gain prominence.

#### CHEMICAL OR VISUAL DETECTION

Chemical or visual detection employs chemical "indicators", i.e., chromophoric substances that change their color depending on conditions in the surrounding medium. Classically the progression of the reaction between analyte and titrant and the concomitant changes in indicator color are registered by the unaided "naked" eye as the "sensor".

#### PHYSICAL DETECTION

Physical detection employs any physical means of detecting changes in the amounts of species of interest in the reacting analyte or titrant system. This also includes spectrophotometric detection, e.g., UV-Vis.

Detection for many types of titrations is effected by virtue of the electrochemical properties of the analyte, titrant, or solvent, e.g., potentiometric method. While a multitude of electrodes exist, it is noted that every effort should be made to avoid the use of calomel- and mercury-containing electrodes.

With the introduction of the endpoint detection by physical sensor-based techniques such as pH electrodes for acid–base titration, the sensitivity of endpoint detection has been greatly enhanced. In fact, the equivalence point can be now identified by continuously measuring the signal from a sensor during the titration without the need to wait for a color change of the indicator that can be detected by the "naked" eye.

### Procedural (Applies to All Titration Reactions)

#### DIRECT TITRATIONS

Direct titration is the determination of a soluble substance, contained in solution within a suitable vessel (the titrate), using an appropriate standardized solution (the titrant), the endpoint being determined instrumentally or visually with the aid of a suitable indicator.

To reduce uncertainty, it is considered good practice for the volume added to be 10%–90% of the rated capacity of the buret. This statement does not apply for blank determination. It is not advisable to refill the buret during titration; if necessary, it is preferred to reduce the sample amount or to increase the titrant concentration. The quantity of the analyte may be calculated from the volume and the concentration of the titrant and the equivalence factor for the substance given in the individual monograph.

#### INVERSE TITRATIONS

An inverse titration has the roles of the titrant and sample inverted, i.e., a measured amount of the titrant is titrated with a solution of the sample.

#### RESIDUAL TITRATIONS

In cases where a direct titration is not possible, or is difficult because the reaction rate is slow, a residual titration (back titration) is recommended. A residual titration is characterized by having two titrants.

A known excess of a titrant which reacts with the analyte is first added. The excess of the unreacted (first) titrant is subsequently titrated with a second titrant.

#### INDIRECT (SUBSTITUTION) TITRATIONS

The analyte first reacts with an intermediate reagent forming another reactive species. The newly formed reactive species is then determined by (direct) titration instead of the original analyte.

An example of this approach is the determination of copper ion (Cu(II)), which reacts with potassium iodide (KI) to form iodine ($I_2$). The iodine ($I_2$) formed is titrated with sodium thiosulfate ($Na_2S_2O_3$) and the amount of titrant is related with the amount of copper ion (Cu(II)) in the sample.

### Blank Corrections

Blank correction is employed, as appropriate, in titrimetric assays to enhance the reliability of the endpoint determination. A blank correction is usually obtained by means of a *blank titration*, wherein the required procedure is repeated in every detail except that the analyte being assayed is omitted. The actual volume of titrant equivalent to the analyte being assayed is the difference between the volume

consumed in the titration with the analyte present and the volume consumed in the blank titration. This corrected volume is used to calculate the quantity of the analyte.

## MATERIALS AND EQUIPMENT

### Electrodes

While a multitude of electrodes exist for various types of titrations, it is noted that wherever feasible, the use of calomel- and mercury-containing electrodes should be avoided. Silver/silver chloride (Ag/AgCl) or iodine/iodide ion ($I_2/I^-$) are recommended as reference electrodes.

### Automated Titration

In automated titration the dispensing of the titrant into the analyte as well as endpoint recognition, data acquisition, calculation, and output of results are performed by automated equipment. Automated titrators serve to improve the throughput capacity of the analytical lab, allowing the definition, customization, and automation of analysis sequences. Automated titrators mainly consist of a single integrated multifunctional processing unit that is able to automatically perform the steps of a titration. Such systems' performance requirements are evaluated over the entire automated system. See *Analytical Instrument Qualification* ⟨1058⟩.

### Standardization of Titrants

The real titrant concentration differs from the nominal concentration due to preparation, purity or stability of the titrant. Therefore, the real concentration has to be determined by performing a standardization of the titrant with a reference standard, i.e., a titration of a substance of known concentration—usually a primary standard. This is applicable to methods with endpoint as well as to methods with equivalent point detection.

A primary standard needs to be chosen with care so that the accurate determination of the titrant can be performed. It is highly recommended that the primary standard:

- React with the titrant in a known ratio
- Be available in high purity, very stable, and non-hygroscopic
- Have a high molecular weight

From the actual titrant concentration, $C_{actual}$, and the nominal titrant concentration value, $C_{nominal}$, the correction factor is calculated. The correction factor is defined as the ratio between the actual concentration of the titrant and its nominal concentration:

$$\text{Correction factor} = C_{actual} / C_{nominal}$$

According to this definition, the correction factor is a dimensionless number. The correction factor is commonly referred to as the titer when working with automatic titrators.

In general, the correction factor has a value of approximately 1 for pure, high quality, and freshly prepared titrants. The actual concentration $C_{actual}$ is then equal to the product of the correction factor times the nominal concentration $C_{nominal}$ of the titrant:

$$C_{actual} = C_{nominal} \times \text{Correction factor}$$

An example using hydrochloric acid (HCl) is given below:

Nominal concentration of hydrochloric acid: $C_{nominal}$ (HCl) = 0.1 mol/L

Actual concentration after titrant standardization: $C_{actual}$ (HCl) = 0.09678 mol/L

Correction factor of hydrochloric acid: Correction factor = 0.9678

▲ (USP 1-Aug-2024)



**Auxiliary Information** - Please check for your question in the FAQs before contacting USP.

| Topic/Question | Contact | Expert Committee |
|---|---|---|
| <541> TITRIMETRY | Yang Liu<br>Manager, Product Quality and Analytical Methods | GCCA2020 General Chapters - Chemical Analysis 2020 |

**Most Recently Appeared In:**
Pharmacopeial Forum: Volume No. 48(5)

**Current DocID: GUID-BCAF402E-9408-4F7C-BF53-B1F6E9DA6BA9_2_en-US**
**DOI: https://doi.org/10.31003/USPNF_M99300_02_01**
**DOI ref: pm5r6**