Ministry of Health of the Russian Federation

Volgograd State Medical University

Department of Pharmaceutical and Toxicological Chemistry

GENERAL PHARMACEUTICAL CHEMISTRY

Titrimetric methods of analysis.

Lesson 7

V term

Volgograd, 2022

QUESTIONS FOR THE LESSON

1. Terms and definitions in the titrimetric method of analysis.
2. Classification of titrimetric methods of analysis.
    A. Depending on the titration method.
    B. Depending on the approach of parallel determinations.
    C. Depending on the type of chemical reactions.
3. Methods for the preparation of standard solutions.
4. Titration curves. Equipment.

INTRODUCTION

Titration is a quantitative technique and methods based on titration provide high accuracy (99.5–100.5%) and precision (<0.5% relative standard deviation (RSD)). Titration is an official method in the European Pharmacopoeia (Ph. Eur.) and in the United States Pharmacopoeia (USP), State Pharmacopoeia of the Russian Federation.

In pharmaceutical analysis, titration is mainly used for quantitative analysis (assay) of active pharmaceutical ingredients (APIs) and excipients with the purpose of assessing the purity of a given substance (analyte).

Titrimetry, titrimetric analysis (titration) is a method of quantitative analysis that is based on measuring the volume of a reagent solution of exactly known concentration consumed in reaction with the determined substance.

More generally, a titration can be described by the following titration equation:

$$x(Analyte) + y(Titrant) \rightarrow Products$$

Here ***x*** and ***y*** are the number of mol of analyte (pharmaceutical compound) and titrant involved to complete the titration. The titration is completed when all the analyte has reacted and transformed to products. The titration has then reached the equivalence point.

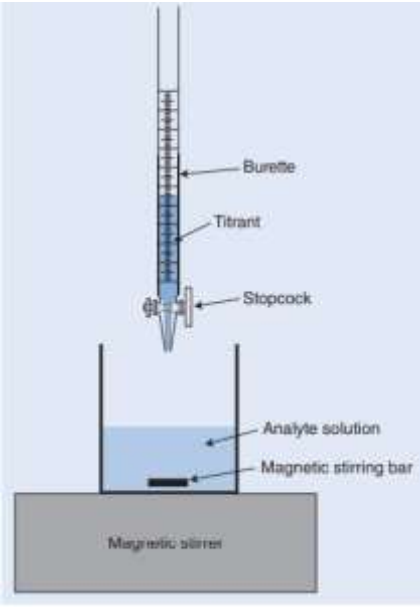


Figure 1. Schematic view of the burette used for titration

The titrant is added either manually from a burette or automatically from an automatic titration apparatus termed an automatic burette or titrator.

Detection of the equivalence point can be based on visual inspection of colour change (Indicator detection) or based on electrochemical measurements (Potentiometric endpoint detection). In the latter case,

the titration is often termed Potentiometric titration. The latter is preferred in the pharmaceutical industry because it can be automated.

The volume of titrant consumed is read from the burette/titrator and the quantity of analyte in the sample solution can be calculated on the basis of the underlying titration equation and the exact concentration of reagent in the titrant.

Control (blank) experiment

In many cases in titrimetry, regardless of the titration method, a control (blank) experiment is required. This is necessary to eliminate the influence of impurities, reagents used, inaccuracies associated with the use of measuring vessels, conditions of determination due to side reactions and other reasons. All reagents (titrated solutions, indicators, etc.) except the analysed substance, or reagents and the analysed substance without a characteristic reagent for the analysed substance, are involved in the control experiment.

The amount of titrated solution used for the control experiment is then taken from the total amount of titrated solution used for the titration of the test solution.

***A number of requireme*nts** should be fulfilled for a successful titration:

- ✓ The titration reaction must be well-defined and without any side reactions.
- ✓ The reaction must be virtually complete (≈100% of analyte must be converted to product).
- ✓ Other substances in the sample should not react with the titrant.
- ✓ The equivalence point should be clearly detected.
- ✓ The exact concentration of titrant must be known (standardized solution).

TERMS AND DEFINITIONS IN TITRIMETRIC ANALYSIS

Standardisation is the process of finding the concentration of an active reagent in a solution (most often by titrating it with a standard solution).

A standard or titrated solution is a reagent solution of exactly known concentration intended for titrimetric analysis.

Standard substances (reference substances) are used to prepare solutions of precisely known concentration used in titrimetric analysis.

A primary standard substance (primary standard) is a substance of high purity that is used to determine the concentration (standardisation) of a titrant, or can itself be used to prepare a titrant solution of exactly known concentration.

A primary standard solution is a standard solution prepared from a primary standard substance whose concentration is known.

Requirements for primary standard substances:

- ➢ high purity;

- stability in the air;
- absence of hygroscopic moisture (substances must be hygroscopic),
- higher molar mass equivalent (which reduces relative weighing error),
- availability,
- no toxicity.

Table 1 shows the most common primary standards for the titrimetric methods used.

Table 1

Titrant	**Primary standard**
Acid-base titration	
HCl, H_2SO_4	Sodium carbonate Na_2CO_3
	Sodium tetraborate $Na_2B_4O_7 \cdot 10H_2O$
NaOH, KOH	Potassium biphthalate $KHC_8H_4O_4$
	Oxalic acid $H_2C_2O_4 \cdot 2H_2O$
	Benzoic acid C_6H_5COOH
Precipitation titration	
$AgNO_3$	not need
Redox titration	
$KMnO_4$	Sodium oxalate $Na_2C_2O_4$
$Na_2S_2O_3 \cdot 5H_2O$	Potassium bichromate $K_2Cr_2O_7$
Complexometric titration	
$Na_2C_{10}H_{14}N_2O_8$ (Trilon B, disodium salt ethylenediaminetetetraacetic acid)	not need

A secondary standard solution is a solution whose concentration has been determined by standardisation or prepared from a known mass of a secondary standard substance.

A secondary standard substance (secondary standard) is a substance used for standardisation; the content of the active ingredient is found using the primary standard.

Titration is the process of adding a titrated solution to a test solution of a determined substance until the equivalence point is reached.

The equivalence point is the state of the system when the quantity of the titrated solution added is equivalent to the quantity of the determined substance.

The titration end-point is the point at which the titration ends, which is determined using indicators or physical parameters of instrumental methods.

CLASSIFICATION OF TITRIMETRIC METHODS OF ANALYSIS

Titrametric methods are divided into:

1. Depending on the method of titration.
2. Depending on the approach to making parallel determinations.
3. Depending on the type of chemical reaction occurring between the substances of the test solution and the titrated solution.

1. Depending on the titration method:

- direct titration,
- reverse titration,
- indirect (substitution) titration.

In ***direct titration***, the solution containing the test substance is titrated with the standard (titrated) solution until the equivalence point.

$$A + T(titrant) = product$$

Direct titration is carried out in the following cases:

1. the reaction of the interaction of the test substance with the reagent must be specific;
2. the interaction between the substance and the titrant must be stoichiometric, with the titration end-point clearly fixed;
3. the reaction must take place at a sufficient speed and be practically irreversible;
4. the reaction must go through to the end;
5. there must be no substances in the solution that could interfere with the main reaction or the fixation of the titration endpoint.

In ***reverse titration***, a test solution and two standard (titrated) solutions are used. One standard solution is an auxiliary solution and the second (main) solution is used directly for the titration.

In the test, to the precisely measured volume of the test solution, add a knowingly excess, but precisely measured volume of the first titrated solution. As a result of the chemical reaction, the detectable substance (A) present in the test solution is completely consumed, interacting with the first titrated solution (T_1). The second (basic) titrated solution (T_2) then titrates an excess of the first auxiliary titrated solution which has not reacted with the detectable substance:

$$A + T_1 \text{ (excess)} = \text{product 1} + T_1\text{(residue)}$$

$$T_1\text{(residue)} + T_2 = \text{product 2}$$

The quantity of the determining substance shall be calculated from the difference in volume of the titrated solutions, corrected for the control experiment taking into account the molarity of the solutions and the titer of the determining substance as specified in the pharmacopoeia and/or the regulatory documentation.

Reverse titration is usually used in the following cases:

1. the speed of the direct reaction is slow;
2. there is no suitable indicator;
3. the determined substance may be lost due to its volatility.

In ***indirect or substitution titration***, a test solution and two titrated solutions are also used.

During the test, an excess of the first (auxiliary) titrated solution (B) is added to a precisely measured volume of the test solution containing the substance (A). As a result of the reaction, the substance of the test solution is completely consumed to form an equivalent amount of the corresponding reaction product (A1), which is then titrated with a second (basic) titrated solution until the equivalence point is reached.

$$A + B \text{ (reagent)} = A_1\text{(substitute)}$$

$$A_1\text{(substitute)} + T = \text{product}$$

Indirect titration is usually used in the following cases:

1. the determined substance does not interact with the titrant in question;
2. the interaction of the determined substance and the titrant leads to the formation of a mixture of several products, the quantitative ratio of which is not constant;
3. the titration reaction is non-stoichiometric;
4. the suitable indicator is not available;
5. the substance to be determined is unstable.

2. Depending on the approach to making parallel determinations:

- Single-sample method
- Pipetting method

Single-sample method

1. A sample weight of the substance to be analysed is calculated.
2. The individual, closely related samples are weighed on the analytical scales. and then weighed on an analytical balance.
3. Dissolve it in a suitable volume of solvent and and titrated with a standard solution.

Pipetting method

1. Calculate a sample weight of the analysed substance.
2. Weigh the sample on an analytical balance.
3. The quantity is transferred to a volumetric flask, dissolved in solvent and the volume of the solution is adjusted to the mark with the same solvent.
4. Pipette an aliquot of the prepared solution into a conical flask and titrate with a standard solution.

3. Depending on the type of chemical reaction occurring between the substances of the test solution and the titrated solution.

- acid-base,
- redox,
- complexometric,
- precipitation.

WAYS OF PREPARING STANDARD SOLUTIONS

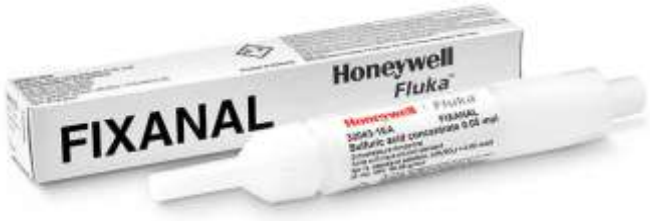
1. From an accurate weighing of the starting substance (primary standard solution).

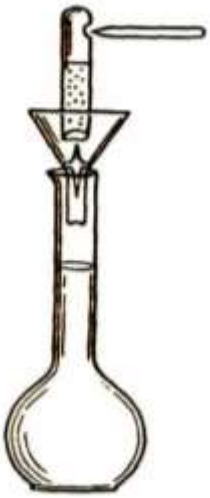
The main steps of the work:

1. calculate the required weighing weight to the nearest 0,0001 г;
2. weigh the exact sample on an analytical balance;
3. the weighed sample is transferred quantitatively to a volumetric flask of the same volume as the solution, the substance is dissolved, topped up to the mark with purified water and stirred;
4. if the sample taken differs from the theoretical calculation, then the concentration of the solution is recalculated.

2. With the help of fixanals.

Fixanals (standard-titres, primary standards) are substances in strictly defined amounts contained in ampoules.





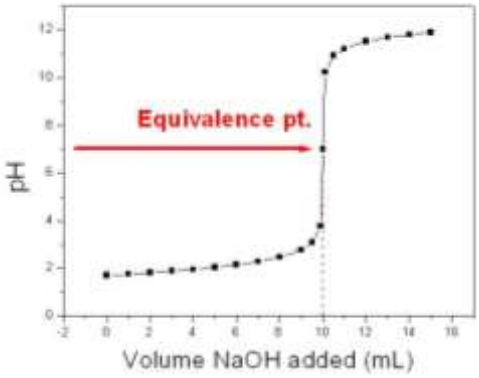
1. The ampoule is broken with a special striker in the funnel.
2. The contents are transferred quantitatively to a volumetric flask and diluted to the required volume.

The resulting solution is often used in titrimetry as a titrant. As a fixanal that can be used as a fixanal are $KMnO_4$, $K_2Cr_2O_7$, HCl, $AgNO_3$, etc.

The compounds used as f fixanals must be extremely pure, stable at room temperature and must not adsorb H_2O and CO_2 from the air.

TITRATION CURVES

A titration curve is a graphical illustration of the relationship between the value determined in the titration (concentration of the titrated substance) and the volume of the added standard solution of titrant.



There are four sections of the titration curve:

1. The starting point;
2. The section before the titration jump;
3. The titration jump including the equivalence point;
4. The section after the titration jump.

A titration jump is a section of the titration curve that corresponds to an extreme change in the properties of the system near the equivalence point. For example, in acid-base titration, an extreme change in pH.

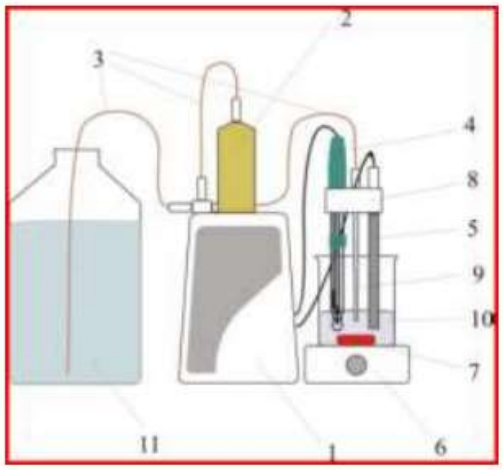
EQUIPMENT FOR TITRIMETRIC METHODS

Burettes, pipettes and other utensils are used for ***manual titrimetric analysis***. In addition to traditional glass pipettes, modern dispensing devices such as pipettes and electronic pipettes can be used to accurately measure solution volumes.

For ***automated titrimetric analysis***, various automatic titrators (autotitrators) are used, which have an electronic control system that allows any type of titration and automatic processing of the results obtained.

Titrators are instruments designed for partially or fully automated automated measurements.

The software supplied with the titrator allows the titration curve to be drawn automatically from the data obtained, the titration end-point to be determined and the concentration of the solution tested to be calculated.



The titrator consists of a titration block (1), burette (2), liquid tract (3), combined electrode for pH-metry (4), resistance thermometer (5), magnetic stir bar (6), magnetic stir bar armature (7), and stand (8). Electrode, thermometer and spout of the liquid path (9) is submerged in the beaker sample (10). The titrant is in a bottle (11).

Depending on the type of titrimetric analysis used, different ***instrumental methods*** are used to record the titration endpoint:

- potentiometric;
- photometric;
- conductometric;
- amperometric;
- coulometric