

PHARMACEUTICAL ANALYSIS

Fundamentals of Volumetric Analysis

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Keywords

Fundamentals of Volumetric Analysis, Calibration, Primary standard, secondary standard

Fundamental Concepts

Some concepts are considered as fundamental with regard to the principles of quantitative analysis. These include ideas such as solution concentration, chemical equilibrium etc. The main purpose in this chapter is to discuss some of these concepts.

Solution Concentration

In all the techniques of quantitative analysis the use of solutions require some basis for the expression of solution concentration. All the systems of concentration expression have a fundamentally similar basis with respect to weight relationships of solute and solvent, but actual method of expression of concentration should take on some convenient and specific form.

Normality: The normality 'N' of a solution is, given by the number of equivalents of solute per litre of solution

$$N = \frac{\text{No. of equivalents of Solute}}{\text{Volume of solution in litre}}$$

OR

$$N = \frac{W / EW}{V}$$

Where,

N	=	Normality
W	=	Weight of solute
EW	=	Equivalent weight of solute
V	=	Volume of solution in litre

Normality varies according to the reaction; as the equivalent weight of a substance may vary according to the reaction, which the solute participates. The equivalent weight is generally calculated after determining the specific changes in chemical reaction of the solute.

Percent Concentration: Concentration is many-a-times expressed in terms of percent (parts per hundred). Percent composition of a solution can be expressed as :

$$1. \quad \text{Per cent w/w} = \frac{\text{mass of solute}}{\text{mass of solution}} \times 100$$

$$2. \quad \text{Per cent v/v} = \frac{\text{volume of solute}}{\text{volume of solution}} \times 100$$

$$3. \quad \text{Per cent w/v} = \frac{\text{mass of solute}}{\text{volume of solution}} \times 100$$

Percent w/w is frequently employed to express the concentration of commercial aqueous reagents, per cent v/v is used to specify the concentration of a solution prepared by dilution a pure liquid with another liquid and percent w/v is employed to indicate the composition of dilute aqueous solutions of solid reagents.

Molality : Number of moles of solute dissolved in 1 kg (1000 g) of solvent

$$\text{Molality (or Molal Concentration)} = \frac{\text{moles of solute}}{\text{kg of solvent}}$$

In units of ***molal*** = ***m***

One of the most commonly used concentration units among chemists is the Molarity concentration term. Molarity is defined as the moles of solute divided by the volume of the solution in liter units. An alternative definition is the number of millimoles of solute divided by the volume of the solution in milliliters. The symbol that we use is the capital letter M. For example, if we have a 3 M HCl solution, then we have 3 moles of HCl in every liter of that solution. Alternatively, we can say that we have 3 millimoles of HCl in every milliliter of solution. A shortened term for this concentration term is the word "molar".

Application of the Molarity Term: Example

Problem: A sample of NaNO_3 weighing 8.5 grams is placed in a 500 ml volumetric flask and distilled water was added to the the mark on the neck of the flask. Calculate the Molarity of the resulting solution.

Solution:

1. Convert the given grams of solute to moles of solute by dividing by the molecular weight of NaNO_3 :
2. 1 mole NaNO_3 = Molecular mass of NaNO_3 expressed in grams = $23 + 14 + 3(16) = 85$ grams
 $8.5 \text{ grams NaNO}_3 \times 1 \text{ mole NaNO}_3 / 85 \text{ grams NaNO}_3 = 0.1 \text{ mole NaNO}_3$
3. Convert given ml of solution to liters by dividing by 1000:
 1 liter = 1000 ml
 $500 \text{ ml} \times 1 \text{ liter} / 1000 \text{ ml} = 0.500 \text{ liters}$
4. Apply the definition for Molarity:
 Molarity = moles NaNO_3 / volume of the solution in liters
 $M = 0.1 \text{ mole} / .500 \text{ liters} = 0.200 \text{ Molar NaNO}_3$

Since molarity involves a basis of solution volume, it is apparent that the molarity of a solution will change as volume changes which is associated with changes in temperature.

Formal Concentration: Some substances do not exist in molecular form, whether in solid or solution form, they remain in ionic form in solid state as well as in solution. In such cases instead of molecular weight, formula weight is used in preparation of solution and its concentration is

expressed in terms of formality, for example Concentration of NaCl and FeCl₃ can be defined very simply as number of formula weight of a solute per litre of solution. It is represented by 'F'.

$$F = \frac{\text{Weight of solute in g / Formula weight}}{\text{Volume of solution in litre}}$$

Formal solutions generally show changes in formality where volume changes associated with temperature.

Equivalent weight: Equivalent weight of the substance is defined as the weight of the substance that contains or reacts with 1.0078 g of hydrogen or 8 g of oxygen, or 35.45 g of chlorine. This generalized definition is used for the calculation of equivalent weight. But depending upon the reaction involved, equivalent weight can be simplified as below.

Equivalent weight in Neutralization Reactions: Equivalent weight of an acid is that weight of it which contains one g atom of replaceable hydrogen e.g. 1.0078 g of hydrogen. Equivalent weight of monobasic acids is equal to its molecular weight

$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Basicity}}$$

Equivalent weight of a dibasic or a tribasic acid is $\frac{1}{2}$ and $\frac{1}{3}$ respectively of its molecular weight. Similarly, equivalent weight of a base is the weight of the substance, which contains one replaceable hydroxyl group.

$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Acidity}}$$

$$\text{Ex. (a) HCl} \quad \text{EW} = \frac{\text{Molecular weight}}{1} = 36.5$$

$$\text{(b) H}_2\text{SO}_4 \quad \text{EW} = \frac{\text{Molecular weight}}{\text{Basicity}}$$

$$= \frac{98}{2} = 49$$

$$\text{(c) NaOH} \quad \text{EW} = \frac{\text{Molecular Weight}}{\text{Acidity}}$$

$$= \frac{40}{1} = 40$$

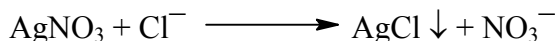
$$\begin{aligned}
 \text{(d) Ca(OH)}_2 \quad \text{EW} &= \frac{\text{Molecular weight}}{\text{Acidity}} \\
 &= \frac{74}{2} = 37
 \end{aligned}$$

Equivalent weight in Complexation Reactions: The equivalent weight is the weight of the substance, which contains or reacts with 1 g atom of an univalent cation M^+ (equivalent to 1.0078 g of hydrogen), $\frac{1}{2}$ g atom of a bivalent cation M^{+2} , $\frac{1}{3}$ g atom of a trivalent cation M^{+3} etc. Equivalent weight of complexing agent is calculated on the basis of above definition.

For cations, equivalent weight is the atomic weight divided by the valency of atom.

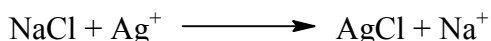
Equivalent weight in Precipitation Reactions: Equivalent weight of a salt in a precipitation reaction is the gram molecular weight of the salt divided by the valency of the reacting ions.

1. AgNO_3



$$\begin{aligned}
 \text{E.W.} &= \frac{\text{Molecular Weight}}{\text{Valency of reacting ions}} \\
 &= \frac{\text{Mol. Wt.}}{1}
 \end{aligned}$$

2. NaCl



$$\begin{aligned}
 \text{E.W.} &= \frac{\text{Molecular weight}}{1}
 \end{aligned}$$

Equivalent weight in Oxidation-Reduction Reactions: Equivalent weight of an oxidant or reductant can be defined as that weight of the substance, which reacts or contains 1.0078 g of available hydrogen or 8.0 g of available oxygen. Equivalent weight can be calculated by:

- Ion-electron balance method.
- Oxidation number method.

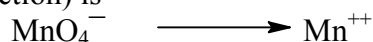
a) Ion-electron balance Method: Ion electron balance method is based on following steps:

- Ascertain the reactants and products of the reaction.

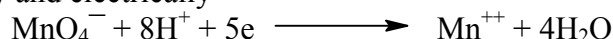
2. Determine oxidizing agent. Write down partial equation for oxidizing agent.
3. Determine reducing agent. Write down partial equation for reducing agent.
4. Add both partial equations and cancel out common substances after multiplying both partial equations by suitable coefficient.

Example: Reduction of potassium permanganate by ferrous sulphate in presence of dilute sulphuric acid.

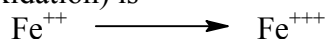
The first partial (reduction) is



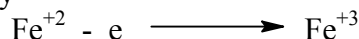
To balance atomically and electrically



The second partial (oxidation) is



To balance electrically



Molecular weight

$$\text{Equivalent weight} = \frac{\text{Molecular weight}}{\text{Number of electrons transferred}}$$

$$\text{E.W. KmnO}_4 = \frac{\text{M W}}{5} = \frac{158}{5} = 31.6$$

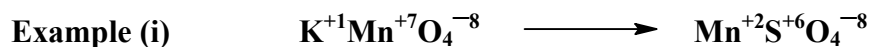
$$\text{E.W. FeSO}_4 = \frac{\text{M W}}{1} = 278$$

(b) Oxidation number method: Oxidation and reduction are the processes involving the changes in the valency. Oxidation number (O.N.) indicates the amount of oxidation or reduction, which is required to convert one atom of the element from free state to that in the compound. If oxidation is taking place the oxidation number is positive and if reduction is necessary oxidation number is negative.

Following general rules apply in determination of O.N.

- a) O.N. of free or uncombined element is zero.
- b) O.N. of hydrogen (except hydrides) is + 1.
- c) O.N. of oxygen except peroxides is -2.
- d) O.N. of metal in combination is generally positive.
- e) O.N. of radical or ion is equal to its electrovalency with correct sign.

f) O.N. of compound is zero and is determined by sum of O.N. of individual atoms.

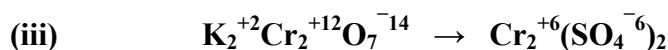


Change in oxidation number of manganese is from + 7 to + 2.

$$\begin{aligned}\text{Equivalent weight} &= \frac{\text{Molecular weight}}{\text{Change in O.N.}} \\ &= \frac{\text{Mol. weight}}{5} \\ &= \frac{158}{5} = 31.6\end{aligned}$$



Change in O.N. per atom of iron is from +2 to +3 i.e. by 1 unit. Hence equivalent weight of ferrous sulphate is equal to its molecular weight.



The change in oxidation number is from +12 to +6 i.e. by 6 units and hence equivalent is $\frac{1}{6}$ the molecular weight of potassium dichromate.

Titer: Solution concentration is expressed in the form of titer in quantitative analysis involving volumetric methods particularly. The titer gives the weight of some particular substances with which the solute in 1 ml of solution will react.

When the normality of solution is known in relation to a specific reaction titer of the solution can be calculated as

$$\text{Titer} = \text{Normality} \times \text{equivalent weight}$$

The titer of the solution changes with volume changes associated with temperature.

Parts per Million and parts per billion: Parts per Million is frequently used to express the concentration of very dilute solutions and is expressed as 'ppm'.

$$C_{\text{ppm}} = \frac{\text{Mass of solute}}{\text{Mass of solution}} \times 10^6 \text{ ppm}$$

For every dilute solution the concentration is expressed in parts per billion (ppb).

These terms are also employed to express the concentration of impurities in pharmaceuticals.

Volumetric Methods

Definitions of Terms:

Volumetric or titrimetric analysis: It consists of determination of the volume of solution of accurately known concentration required to react completely with the solution of substance to be determined.

Standard solution: The solution of accurately known concentration is called as the *Standard Solution*.

Titrand: The substance that is analyzed in a titration procedure.

Titrant: A solution of known concentration, which is added (titrated) to another solution, to determine its concentration of a second chemical species.

Equivalence point of stoichiometric end point: The point at which the reaction between titrant and titrate is just complete.

Indicator: It is an auxiliary substance, which shows clear visual, changes after the reaction between titrate and titrant is practically complete.

Titration error: In practice, very small difference between theoretical end point and actual end point usually occurs. This is called as titration error.

Requirements for Volumetric Methods:

In volumetric methods, the volume of solution of the known concentration (titrant) that reacts completely with the substance to be determined (titrate).

For use of chemical reaction in volumetric methods, the reaction should fulfill some of the requirements. These are as follows:

1. The reaction should be simple and expressed by a well-defined chemical equation. There should not be any side reactions, so that from the reaction stoichiometry, calculation of amount of the reacting substance can be estimated.
2. The reaction should be rapid; i.e. should be instantaneous or should proceed with great speed. Sometimes addition of catalyst increases the speed of reaction. Slower reaction rates make the reaction unsuitable with respect to time consumed in the reaction.
3. The reaction must proceed to completion when an equivalent amount of standard solution has been added. This gives satisfactory end point detection. The criterion for reaction completion may vary somewhat depending on the quantity determined.
4. There must be some sharp change in either physical or chemical properties of the solution at the equivalence point.
5. Reaction should have some simple method for the detection of end point or equivalence point of the titration. The equivalence point is that point in the titration where an equivalent amount of standard solution is added to the solution

of the substance under determination. Usually, indicator technique will signal the end point of the titration.

The requirements mentioned above are not always realized for every volumetric method. Many volumetric methods can also be applied where one or more of the above requirements are not ideally met.

Classification of Volumetric Methods:

Volumetric methods involve the chemical reactions. Depending upon the type of reaction involved, volumetric methods have been classified as:

1. **Neutralization (Aqueous acid-base) titrations:** It involves neutralization reaction in presence of water as solvent.
2. **Non-aqueous titrations:** It involves the reaction between acid and base in presence of non-aqueous medium i.e. organic solvents.
3. **Precipitation titrations:** It involves the reaction leading to precipitate formation. It includes the methods where the reacting substance and standard solution react to yield a precipitate or a slightly soluble salt as the primary reaction product.
4. **Complexometric titrations:** It includes all the methods where in the reacting substance and the standard solution react to form a soluble but very slightly dissociated complex substance. In other words, it is based on complex formation reaction mainly EDTA titrations.
5. **Redox titrations:** These titrations involve simultaneous oxidation-reduction reactions. It includes all the methods where in reacting substance is oxidized or reduced by the standard solution.

Steps involved in Quantitative analysis

1. Selection of method of analysis.
2. Sampling.
3. Preparation of sample solution.
4. Elimination of interferences.
5. Calibration and measurement.
6. Calculation of results.
7. Evaluating results and their reliability.

1. **Selection of method of analysis:** Selecting the method of analysis is vital in quantitative analysis. The choice of method requires experience as well as scientific knowledge. Accuracy required is the first and foremost consideration in the selection. Another consideration is simplicity, economy of time and money.
2. **Sampling:** This is important step and is aimed to get the representative sample from the large mass of material available. The methods differ according to the nature of the

sample. It can satisfy the sample provided the material is reasonably pure and is homogeneous.

3. **Preparation of sample Solution:** After sampling, the solid samples are ground to decrease particle size and mixed to ensure homogeneity and are stored. A known amount of sample is weighed and dissolved in a suitable solvent. The condition of dissolution should be kept in mind.
4. **Elimination of interferences:** The reaction used and properties measured are characteristic of a group of compounds. The analyst should devise a scheme that effectively isolates the species of interest from all others in the sample that can influence the measurement. Substances that can prevent the direct measurement of the analyte concentrations are called as *interfering substances*.
5. **Calibration and measurement:** All analytical results depend on a final measurement of a physical property of the analyte. The physical property measured is often directly proportional to the concentration. K is proportionality constant. The process of determining K is an important step and is termed as calibration.

Whenever possible, standards for calibration should be made up in the same matrix as the samples are to be analyzed. Only gravimetric and coulometer methods do not require calibration.

6. **Calculation of results:** The analysis is not complete until the results have been expressed in such a way that the person can understand the significance of it. Computation of analyte from experimental data is ordinarily simple and easy task with modern calculators or computers.
7. **Evaluating results and their reliability:** Analytical results are incomplete without an estimate of their reliability. In recent years much attention is given for statistical techniques to confirm the reliability and accuracy of the results.

Accuracy of Volumetric Analysis

Volumetric methods of analysis are very susceptible to high accuracy and possess several advantages. Accuracy of volumetric analysis is mainly affected by following three factors.

1. Substance of known purity for preparation of standard solution.
2. Careful end point detection.
3. Use of calibrated volumetric glassware.

1. **Standardization Process:** It is the process of finding out the concentration of the solution by using primary standard. In this process, standard solution is prepared by dissolving a fixed weight of primary standard substance in solvent to prepare known volume of solution. The concentration of this solution is calculated theoretically.

- a) Reasonable volume of titrant should be used during standardization.
- b) Reasonable weight of primary standard substance should be used.
- c) Standardization process should involve at least triplicate observations.

The above observations made in relation to the standardization procedure are equally applied to any of the titration procedure

Primary Standard Substances: Primary standard substance should satisfy the following requirements:

1. It must be easy to obtain, to purify, to dry and to preserve in pure state.
2. It should be 100.00 % pure although 0.01 to 0.02 % impurities is tolerable if accurately known.
3. It should be stable to atmospheric conditions. It should not decompose or be hygroscopic, or deliquescent.
4. It should show a high equivalent weight in order to reduce the effect of weighing errors. In weighing a greater amount of substance, the relative error will be smaller for a small amount.
5. The reaction with standard solution should be stoichiometric and practically instantaneous.
6. The reaction to be amenable to use simple indicator to determine the end point of the titration.
7. There should not be any difference between end point and theoretical equivalence point i.e. titration error should not be there.
8. It should be readily soluble under the conditions in which it is to be employed.
9. It should not have water of hydration, so that the composition of the solid does not change with variation in relative humidity.

It is not always possible to satisfy all the requirements of a primary standard but the requirements mentioned above should be met at all times as closely as possible.

If any compound does not fulfill the above mentioned criterion, is called as **secondary standard**. In practice ideal primary standard is difficult to obtain and hence, a compromise between above requirements is usually necessary.

The commonly used primary standard substances are:

Acid-base Titrations: Sodium carbonate, potassium hydrogen phthalate, succinic acid, benzoic acid, oxalic acid and adipic acid.

Redox, titrations: Potassium dichromate, potassium bromate, potassium iodate, sodium oxalate, arsenious oxide.

Precipitation titrations: Sodium chloride, potassium chloride, potassium bromide, silver nitrate.

Complexometric titration: Various pure metals such as zinc, magnesium, manganese and salts such as lead nitrate, calcium carbonate etc.

2. **End point Detection:** The main object of end point detection is to find out the volume of standard solution, which reacts with the analyte completely. If the end point is not detected accurately, the quantitative estimation will not be accurate. In volumetric methods, the end point is usually detected by use of some external substance, which shows sharp change in its

colour at the end point of the reactions. This external substance, which detects the end point, is called as visual indicator. This detection of end point is affected by various factors such as:

- (a) **Indicator selection:** Indicator should be selected depending upon the properties of the substance to be analyzed. For example, in neutralization titrations transition interval of the indicator should be close to and around the equivalence point of titration.
 - (b) **Colour change detection:** Colour change in the titration by using visual indicator is nothing but the first deviation from the original colour, which can be clearly detected. For visual detection of the colour the chemist must rely on its own ability to detect the colour and hence, it is quite possible that differences of either more or less extent from one individual to another are possible. In many individuals who are suffering from poor or outright colour blindness, detection of colour change is difficult.
 - (c) **Quantity of indicators:** Generally, indicators are added in a very small quantity approximately 0.0001-0.0004% of the solution being titrated. If large quantity of indicator is added then appreciable large quantity of titrant will be needed to show the colour change of indicator. But it is to be noted that high colour intensity is necessary in the process.
 - (d) **Presence of colloidal substances:** Colloidal particles are having property to adsorb ions on their surface and this property leads to the problems in detection of end point. Possibility of either premature or delayed indicator colour change and hence, the errors in detection of end point.
 - (e) **Effect of temperature:** Change in temperature has many-folded effect on the end point detection in the titration. Change in temperature leads to dissociation of substances to be analyzed and in addition it will also affect the degree of dissociation of indicator leading to change in colour of indicator.
3. **Calibration of volumetric Glass Wares:** Volumetric glasswares generally used are burettes, volumetric flasks for measurement of accurate volume. Reliability of these volumetric glasswares depends upon the volume actually contained/delivered by that glassware.

The Indian Standards Institution has specified 27°C as the temperature at which glassware is calibrated. Since laboratory temperature is usually not exactly 27°C glassware must be calibrated when used at other temperature. This is because of errors due to expansion (or contraction) of both glass vessel itself and solution contained there in. The coefficient of expansion of glass is sufficiently small and the correction required for this factor is negligible. The change in the volume of the solution itself is also important but it can still be ignored in many cases if working temperature is reasonably constant and is around 27°C .

It may be noted that, the volumetric glassware should meet the standards laid down by the Indian Standards Institution (ISI) and such glassware's should be purchased in analytical laboratory.

However, because of the high cost the certified glassware of ISI specifications less expensive glassware's are used after calibration.

Since most analytical work involves dilute aqueous solutions, distilled water is generally used as the reference material in the calibration of volumetric glassware. The general principle is to determine the weight of water contained or delivered by particular glassware and converting weight of water into volume via the density.

Suggested Readings:

1. K A Connors, A Text Book of Pharmaceutical Analysis, Wiley-Intersciences, New York.
2. A H Backett and J B Stenlake, Practical Pharmaceutical Chemistry, Vol.I and II, The Athlone Press of The University of London.
3. Pharmacopoeia of India, Govt.of India, Ministry of Health, Delhi.
4. J Bassett, R C Denney, G H Jeffery, J Mendham, Vogel's Textbook of Quantitative Inorganic Analysis, The ELBS and Longman, London.