1.6 Methods of Weighing

The samples for analysis work can be weighed by two types of weighing procedures namely; (a) weighing by difference and (b) weighing by addition.

(a) *Weighing by difference*: Weigh accurately the weighing bottle. Place more than the specified amount of sample in the weighing bottle. Weigh the bottle and the contents accurately. Tip out the contents of the bottle into the receiving vessel. When most of the sample has been transferred, replace the stopper carefully to prevent the sample from being blown out of the bottle. Reweigh the bottle and contents. The difference between the two Weighings gives the weight of the sample. If the sample is hygroscopic in nature, exposure to atmosphere should be minimised.

(b) *Weighing by Addition*: In case of a solid sample, weigh the empty watch glass or weighing bottle or the vessel accurately and introduce the sample in small amounts until the correct weight has been added. Weigh the vessel along with the material accurately. Transfer the contents into a receiver slowly and wash the weighing vessel thoroughly with a jet of distilled water, collecting all the washings.

For a water-miscible liquid sample a similar procedure as described above is followed. The liquid sample is added into the weighing vessel by means of a test pipette without touching the rim of the vessel. After correct weight is added the sample is poured gently down into a receiving vessel in the above manner. Weighing vessel is washed down with a jet of distilled water.

In case of a water immiscible liquid sample, the liquid may be weighed directly into the vessel after the vessel is weighed empty. Care is taken that the liquid does not touch the rim of the vessel.

For volumetric work in general, the sample weighings should be within ± 0.0001 g and for gravimetric work, all weighings should be within ± 0.0002 g.

Care of the Balance: the Following rules should be observed in the handling of the analytical balances:

1. Test the adjustment of the balance before weighing and call an instructor if it requires an adjustment.
2. Brush the pan and surroundings of the balance before starting to weigh any substances.
3. No sample should be ever placed directly upon the balance pan.
4. Hot objects must never be placed inside the balance case.
5. After completion of a weighing the balance pan and surroundings should be cleaned.
6. All levers and knobs should be turned carefully and slowly.
7. Personal responsibility for the condition of the balance should be adopted.

1.7 Various Methods Of Drug Analysis

Every analytical determination is based on the measurement of some physical or structural property which is related directly or indirectly to the amount of the desired constituent present in the sample. Consequently various analytical methods available for drug analysis can be classified on the type of physical quantity which is measured. Thus we can identify four major common procedures namely; (a) volumetric (b) gravimetric (c) electrical (d) optical

The volumetric methods involves the measurement of volume. The various categories of volumetric procedures used for analysis are acid-base methods, oxidation — reduction methods, complexo-metric methods etc.

The gravimetric methods involves the measurement of weight. The method consists in the separation of the desired constituent in a form that is of known percentage composition and which can be weighed accurately. The various categories of gravimetric methods are precipitation methods, electrodeposition methods and volatilisation methods depending upon how the desired constituent is separated into a weighable form before its measurement.

Precipited in the presence of mineral acid	Precipited in the presence of a weak acid	Precipited by NH_3 and H_2S	
		KCN absent	KCN present
Ag,Hg,Pb, Bi,Cu,As, Sb,Sn,(Cd)	Zn,Ni,Co	All the metals in the preceding Columns,	A large group of Metals form complex salts with KCN from except AS, which they are not Sb(Sn) PPtd. as sulphides by H_2S. The following give ppts with KCN. Pb(black), Zn(white), Cd(Yellow).

(ii) Alkaline Earth Metals : As barium salts are usually used in the removal of large amounts of sulphate ions, they become a common impurity. They are tested by the addition of dilute H_2SO_4. Calcium sulphate does not get precipitated unless present in large quantity because it is soluble. Strontium is not generally found as impurity but will precipitate along with Ba if present. Calcium can be precipited with ammonium oxalate in presence of NH_3. Magnesium is precipited along with calcium as phosphate in the presence of NH_3.

(iii) Alkali Metals: Although no specific tests are applied but the common method to limit them is to boil the sample with water, filter, evaporate the filtrate to dryness and weighed.

(iv) Acid radical Impurities: Simple procedures are available to detect and limit the presence of nitrate, oxalate, phosphate, fluoride, and silicate. Pharmacopoeias should be consulted for their specific tests.

2.11 Impurities In Organic Medicinal Substances :

So far we have discussed the contamination among the inorganic substances and how to control them by limit tests. It is to be understood that organic medicinal substances get contaminated in exactly the same manner during their manufacturing processes.

Since the organic drug substances belong to a very wide range of chemical groups and at the same time the contaminating impurities being of varied nature the task of detecting impurities becomes a difficult job. Therefore, the contaminating impurities for organic medicinal compounds can be classified into (a) inorganic impurities (b) organic impurities and (c) contamination by chemical intermediates.

(a) Inorganic Impurities: The control of inorganic impurities has already been dealt upon in some detail. However for organic medicinals there are some special specific test to detect ammonium salts, heavy metals, acid radicals as well as free halogen and halide ions. These tests can be found in pharmacopoeias.

(b) Organic Impurities : One of the most common method of limiting the organic impurity is the determination of melting points for active ingredients. In some of the medicinals a melting point range is allowed e.g. phenobarbitone (m.p. 174-77°) atropine (m.p. 115-18°) etc. to give an allowance for storage effect. Along with melting point other physical constants like refractive index, optical rotation and weight/ml etc. wherever applicable can also be measured as a criteria for purity.

$$\therefore \quad k_a \cdot k_b = [H^+] \cdot [\overline{O}H]$$

$$\therefore \quad k_a \cdot k_b = k_w$$

From the above it can be implied that the stronger thc acid the weaker is its conugate base and vice-versa.

Since the dissociation constant of weak acids and weak bases are numerically small, therefore logarithmic notation is used.

The dissociation constant exponent, pk is obtained from the dissociation constant in a manner similar to the derivation of pH from hydrogen ion concentration, i.e.

$$pk_a = -\log_{10} k_a$$

Thus higher the value of k_a, the smaller will be the value of pk_a which means that stronger the acid the smaller the pk_a value.

3.2 Autoprotolysis of Water

It is well known that pure water is slightly ionized because it is capable of accepting a proton from a second molecule of water as shown by the reaction.

$$H_2O + H_2O \rightleftharpoons H_3O^+ + \overline{O}H$$

The above described equilibrium reaction is called "autoprotolysis". This equilibrium expression can be written in terms of "activities" or effective concentrations, as :

$$K = \frac{(H_3O^+)\ (\overline{O}H)}{(H_2O)^2} \text{ or } K = \frac{a_{H_3O^+} - a_{O^-H}}{a^2H_2O}$$

However, the expression is simplified by following the thermodynamic convention that pure liquid has unit activity and this convention is assumed to be also applicable for relatively dilute solutions. Hence, the activity for each species equals the actual equilibrium concentration. Accordingly, we can rewrite the above equation by the ion-product expression by water :

$$K_w = [H^+]\ [\overline{O}H]$$

The term $[H_2O]^2$ remains constant since it is present in large excess and the term $[H^+]$ is written instead of $[H_3O^+]$. The constant K_w is called "dissociation Constant" or ion-product constant or ionization constant of water. Its value is temperature dependent, ranging from 1.14×10^{-15} at 0°C through 1.01×10^{-14} at 25° and 5.47×10^{-14} at 50°C to 5.4×10^{-13} at 100°C. The value at 22°C is $1.00 \times 1\ 0^{-14}$ which is used in all calculations involving K_w.

The main purpose of acid and base titrations is the determination of acid which is required to exactly neutralize a given amount of a base. The point at which this is obtained is known as the "end point" or equivalence point or "stoichiometric point". Thus neutralization involves reaction between acid and alkali such that at the end point the solution consists of salt and water only. However, the correct end point is characterised by a definite value of the hydrogen ion concentration of the solution.

3.3 pH

The concept of hydrogen ion concentration (pH) has a great importance in pharmaceutical analysis because many analytical methods require optimum pH condition for reactions to complete. Also, in the

$$\log [H_3O^+] = \frac{1}{2} \log k_w + \frac{1}{2} \log k_a \frac{1}{2} \log c$$

$$-\log [H_3O^+] = -\frac{1}{2} \log k_w - \frac{1}{2} \log k_a - \frac{1}{2} \log C$$

$$pH = \frac{1}{2} pk_w = \frac{1}{2} pK_a + \frac{1}{2} \log c$$

$$= \frac{1}{2} (14.00 + 7.42 - 4.00)$$

$$= \frac{1}{2} \times 17.42 = 8.71$$

3.5 Salts

A salt is defined as a chemical substance other than water which is produced by the neutralization of an equivalent amount of (i) a strong acid and a strong base (ii) a weak base and a strong acid, (iii) a strong base and a weak acid and (iv) a weak acid and a weak base. Further it should be noted that (a) the pH of a salt solution obtained by the dissolution of the crystalline form of a salt is the same as that obtained during the neutralization reaction of chemically equivalent quantities of acid and base and (b) that salts exist in solution as ions.

3.5.1 Salt Solution of a Strong Acid and a Strong Base

In salt solutions of this type the equilibrium reaction of water is not seriously affected and the pH will remain constant as that of water i.e. 7.00.

The examples of these salts are sodium chloride, sodium nitrite, potassium sulphate.

3.5.2 Salt Solution of a Weak Base and a Strong Acid

In salt solution of this kind the cationic portion is considered the weak acid and reacts with water to produce hydronium ions. The pH equation is represented by $pH = (pk_w - pk_b - \log c)$. The examples of these salts are ammonium chloride, ephedrine sulphate, atropine hydrochloride, chlorpromazine hydrochloride.

3.5.3 Salt Solution of Weak Acid and a Strong Base

In salts of this nature, the anionic portion is considered the weak base and reacts with water to produce hydroxyl ions. The derivation of the pH equation is $pH = (pk_w + pk_a + \log c)$

3.5.4 Salt Solution of a Weak Acid and a Weak Base

Ammonium acetate may be considered such a case and it undergoes hydrobysis in aqueous solution as shown belows:

$$N^+H_4 \rightleftharpoons H^+ + NH_3$$

$$CH_3COO^- + H_2O \rightleftharpoons CH_3COOH + \overline{O}H$$

$$N^+H_4 + CH_3COO^- + H_2O \rightleftharpoons NH_3 + CH_3COOH + H^+ + OH$$