CHAPTER

1

Introduction to Pharmaceutical Chemistry

INTRODUCTION

Pharmaceutical chemistry is the study of drugs used for treatment or prevention of diseases in human or animal, their analytical techniques, pharmacology, metabolism, quality assurance, drug absorption and delivery. It leads to careers in drug development, biotechnology, pharmaceutical companies and research facilities. It includes synthesis and isolation, identification using physical and chemical properties, spectroscopic studies, structural modification, structure–activity relationship (SAR) studies, the study of chemical characteristics, biochemical changes after drug administration and their pharmacological effects, etc.

Organic compounds are classified into two categories according to their origin: (i) *Natural compounds*–materials obtained from both plants and animals, e.g. vitamins, hormones, amino acids, antibiotics, alkaloids, glycosides, fatty acids and carbohydrates (ii) *Synthetic compounds*–either purely synthetic, e.g. aspirin or semi-synthesis of naturally occurring compounds (e.g. morphine, atropine, heroin, steroids and cocaine) to reduce their cost and side effects. Therefore, the natural intermediate of such drugs could be used for the synthesis of a desired product (e.g. semi-synthetic penicillins).

Inorganic chemistry is the study of all the elements and their compounds except carbon compounds (organic chemistry) which describes the characteristics of nonliving matters and minerals which are found on the earth. Inorganic pharmaceuticals are useful for their therapeutic purpose, e.g. astringents and antimicrobials; as pharmaceutical aids (bentonite and talc); as antacids, alkalis, mineral acids, for replacing or replenishing the normal content of body fluids (e.g. sodium, potassium, calcium, chloride and phosphate); as catalysts (platinum, nickel), oxidizing and reducing agents (lithium aluminium hydride); for pharmaceutical analysis (e.g. titrants such as potassium permanganate), for cleaning the teeth (e.g. dibasic calcium phosphate), as abrasives, absorbents used to absorb the toxins and bacteria in the GIT (e.g. calcium carbonate), acidifiers, adsorbents used to treat mild dysentery or diarrhoea (e.g. bismuth subcarbonate, bismuth subnitrate), alkalizers used to induce the alkaline condition in acidic condition of body (e.g. sodium citrate), anaesthetics, and analgesic (nitrous oxide), antacids (aluminium hydroxide gel, calcium carbonate, magnesium carbonate), anthelmintics (ammoniated mercury, sodium antimony tartarate), antibacterial and antiseptic (yellow mercuric oxide, iodine solution), anticonvulsants used for the treatment of epilepsy (potassium bromide), anti-coagulants (sodium citrate), antidepressants (lithium carbonate), antidotes (sodium nitrite, sodium thiosulphate), antifebriles (ammonium acetate), antifungal agents (zinc undecylenate topical use,

potassium iodide), anti-hypercalcemic agents (sodium acid phosphate), anti-infectives (potassium permanganate, silver nitrate, hydrogen peroxide, boric acid), anti-inflammatory agents used to relieve pain in rheumatoid arthritis (sodium aurothiomalate), anti-irritant agents (aluminium metal powder, anti-perspirants (aluminium sulphate), anti-protozoals (sodium antimony gluconate, anti-pruritics (topical, e.g. calamine), anti-thyroids (potassium perchlorate), anti-tumor agents (cisplatin for testicular and ovarian cancer), buffers, e.g. acetate buffer (pH-3.9) and sodium citrate buffer, as calcium supplements (calcium lactate, calcium gluconate), cathartics (calomel, magnesium sulphate), dentifrices (calcium carbonate, magnesium peroxide), depilatory agents used to remove hair (barium sulphide), diaphoretics used to promote sweating (potassium citrate), disinfectants (ammonium acetate), diuretics (ammonium chloride, ammonium iodide), dusting powders (talc, zinc stearate, light kaolin), electrolyte replenishers (sodium chloride, ringer lactate solution, potassium chloride), emetics (zinc sulphate, copper sulphate), expectorants (ammonium chloride, potassium iodide), fillers (gold and silver metals), germicides (chlorinated lime), haematinics (ferrous sulphate, ferric ammonium citrate) and inhalants (oxygen).

Radiopharmaceuticals are used both as diagnostic and therapeutic products. Inorganic compounds are also used as radiopaque contrast media, tabulating aids and suspending agents.

Medicinal substances and pharmaceutical aids are included in monographs of the pharmacopoeia of each country and are considered as official records. An official substance is required to compile with certain standards of purity specified in the pharmacopoeia and may often contain some other substances for specific reasons. For example, all oxidants generally contain preservatives that reduce their oxidising action. Official chloroform contains 1–2% of ethyl alcohol to retard formation and to inactivate phosgene gas which is formed in contact with the air during storage.

Scope and objectives: Study of pharmaceutical chemistry provides various job opportunities in the field of drug industry. It includes the development and formulation of drugs to treat various diseases and research areas on how these chemicals affect different biological systems. In this field, new drugs and products with low cost and least negative side effects can be developed. Methods of chemical analysis can be designed and applied to a product to ensure the purity of a drug. One can develop his own academic carrier in research fields of pharmaceutical chemistry. It helps to adjust a person in research organizations and academic institutes as a scientist, research officer, research executive, professor, quality control and quality assurance analyst, scientific data entry specialist, Patent analyst, Pharmaceutical patent analyst and assistant manager. Some sectors for recruitment in pharmaceutical chemistry are pharmaceutical industry, academic institutes and universities, biotechnological, chemical or biomedical industries, scientific industries, hospitals and defence services.

ERRORS

An error is the difference between real standard result and measured result. The errors are caused by faults in the analytical procedure or the instruments used for the analysis. If an error in an experiment or analysis is large, unpleasant effects may result. In analytical chemistry, reliability, reproducibility and accuracy are very important. On the basis of an analytical error due to an incorrect laboratory report, a patient may undergo expensive and even difficult and dangerous medical treatment. The difference between the experimental value and true value is known as an *absolute error*. This error may be negative or positive.

Types of errors: In analysis, there are two main types of error: (i) Determinate or systematic error (ii) Indeterminate or random error. A determinate error is a systemic error, i.e. it is not random. The cause of this type of error may be determined and then it can be avoided or corrected. A particular determinate error may cause the analytical results too high or very low. It can be additive or multiplicative. It depends on the error and how it enters into the calculation of the final result. This type of error could be the result of incorrectly calibrated balance.

1. **Systematic error:** It is the mean that would result from an infinite number of measurements of the same measure and carried out under repeatability conditions, minus a true value of the measurement. A systematic error is caused by a defect in the analytical method or by an improperly functioning instrument or analyst. A procedure that suffers from a systematic error is always going to give a mean value that is different from the true value. A systematic error can be estimated, but it cannot be known with certainty because the true value cannot be known. Systematic errors can therefore be avoided, i.e. they are determinate. Sources of systematic errors include spectral interferences, chemical standards, volumetric ware, and analytical balances where improper calibration or use will result in a systematic error.
2. **Random error:** It is the result of a measurement minus the mean that would result from an infinite number of measurements of the same measurand carried out under repeatability conditions. Random errors are unavoidable as every physical measurement has a limitation, i.e. some uncertainty. The analyst can only obtain a weight to the uncertainty of the balance or deliver a volume to the uncertainty of the glass pipette. If the balance is set so that the zero point is actually 0.5 mg too high, all masses determined with this balance will be 0.5 mg too high. If this balance is used to weigh any standard solution in the laboratory, the standard concentration will be erroneously high, and all of the results obtained using this standard solution will be erroneously high.
3. **Determinate error:** It may arise from some faulty steps in the analytical process. The faulty step is repeated every time the determination is performed. Whether a sample is analyzed 5 times or 50 times, the results may agree with each other but differ widely from the true answer.

   The absolute value is the difference between the true and measured value and is calculated as:

   Measured mean value – true value = Absolute error

   Systemic error is under the control of the analyst. This error is determined and corrected by analysis of a sample with a different analytical procedure that is known to involve no systematic errors. Such method is called *standard method*. If the results from two analytical methods agree, it is reasonable to assume that both analytical procedures are free of determinate errors. The second method is to run several samples of reference material of known, accepted concentration of analyte. The difference between the known concentration and that measured by analysis should reveal the error. If the results of analysis of a known standard are consistently high or low, then a determinate error is involved in the method. This error can arise from uncalibrated balance, improperly calibrated volumetric flasks or pipettes, malfunctioning instruments, impure chemicals, incorrect analytical procedures or techniques and analyst error.
4. **Analyst error:** Analyst error is resulted due to inexperience and insufficient training. An analyst may use the instrument incorrectly, place the sample in the instrument

incorrectly each time, set the instrument in wrong directions for analysis and improper reading in the volumetric flask as high or low.

5. **Operational and personal errors:** These errors are due to factors for which the individual analyst is responsible and are not connected with the procedure they form part of the personal equation of an observer. For example, mechanical loss of materials in various steps of analysis, improper washing of precipitates and ignition of precipitates at incorrect temperatures. Some analysts are unable to judge colour changes sharply in visual titrations, which may result in slight overstepping of the endpoint and writing wrong information into a laboratory notebook. Proper training, experience, and attention to detail on the part of the analyst can correct these types of errors.
6. **Reagents and instrumentation errors:** Contaminated or decomposed reagents can cause determinate errors. Sometimes reagents may also be improperly labeled. Impurities in the reagents may interfere with the determination of the analyte, especially at the ppm level or below. Numerous errors involving instrumentation are possible, including faulty operation of balance, incorrect instrument alignment, incorrect wavelength settings, and use of uncalibrated or improperly calibrated weights. These problems can be eliminated by a systematic procedure to check the instrument settings and operation before use. Such methods are called standard operating procedures (SOPs). There should be a written SOP for each instrument and each analytical method used in the laboratory. In instrumental analysis, electrical line voltage fluctuations are an important problem. This is especially true for automated instruments running unattended overnight. Instruments are often calibrated during the day when electrical power is in high demand. At night, when power demand is low, there is a variation of relationship between concentrated analyte and measured signal.
7. **Analytical method:** The most serious errors are those in the method itself, e.g. incorrect sampling, incomplete reaction for chemical methods, unexpected interferences from the sample itself or reagents used, and the loss of analyte during sample preparation by volatilization or precipitation. In titrimetric analysis, errors may occur due to failure of reactions to proceed to completion. In gravimetric analysis, there may be decomposition, co-precipitation and post-precipitation and precipitation of constituents other than the desired ones.

   Reproducibility (of results of measurement) is the closeness of the agreement between the results of measurements of the same measure and carried out under changed conditions of measurement.
8. **Mean and true values:** The definition of mean is, "an average of n numbers computed by adding some function of the numbers and dividing by some function of n." The central tendency of a set of measurement results is typically found by calculating the arithmetic mean ($\overline{x}$) and less commonly the median or geometric mean. The mean is an estimate of the true value as long as there is no systematic error. In the absence of systematic error, the mean approaches the true value (μ) as the number of measurements (n) increases.

CONTAMINATION

Contamination of a sample by external sources can be a serious source of error and may be a variable. Aluminium levels in the dust in a normal laboratory are so high that dust prohibits the determination of low levels of aluminium in samples.

Indeterminate errors: These errors cannot be any specific well defined reasons. They are random in nature and take place in several successive measurements performed by the

same analyst under the same conditions and identical experimental parameters. Sources of random error include the limitations of reading balances, electrical noise in instruments and vibrations caused to the building by heavy vehicular trafficking. A balance that is capable of measuring only to 0.001 g cannot distinguish between two samples with masses of 1.0151 and 1.0149 g. In one case, the measured mass is low, and in other case, it is high.

ACCURACY

Accuracy is a measure of how close a measurement is to the correct or accepted value of the quantity being measured. In analytical chemistry, the term 'accuracy' is used in relation to a chemical measurement. In accuracy, an accurate result is very close with the true value of a measured amount. Accuracy is inversely proportional to the error, i.e. the greater the accuracy, smaller the error.

PRECISION

Precision is a measure of how close a series of measurements are to one another. Precise measurements are highly reproducible, even if the measurements are not near the correct value. Measurements that are both precise and accurate are repeatable and very close to true values. Precision is a measure of how close a series of measurements are to one another. Precise measurements are highly reproducible, even if the measurements are not near the correct value. Measurements that are both precise and accurate are repeatable and very close to true values. Precision is usually expressed in terms of the deviation of a set of results from the arithmetic mean of the set (mean and standard deviation to be discussed later in this section). Precision designates reproducibility of a measurement, whereas accuracy is the correctness of a measurement.

Quantitative methods are used to measure the concentrations of target analytes in biological specimens for accuracy and limits of quantification. While dissolving powdered materials, calibrated analytical balances should be used and corrections should be made to the resulting concentration for accuracy and precision of the balance as well as starting material purity. When diluting a stock solution, volumetric flasks should be used to obtain a high degree of accuracy. Calibration curves should then be analyzed over the course of at least seven runs spanning multiple days and the accuracy, precision, and coefficient of determination should be calculated for the specific batch of calibrators. For the lowest calibrator, accuracy should be within 30% and the coefficient of variation is usually within 20%.

Minimizing Systematic Errors

Instruments commonly used in a laboratory, such as spectrophotometers, electrical balance pipettes, burettes, volumetric flasks and thermometers must be calibrated. The response of most of the instruments changes with time because of wear corrosion or mishandling. The determinate personal errors may be eliminated by care, practice and self-discipline.

Analysis of Standard Samples

The errors of method can be checked by carrying out the analysis of a standard sample prepared in such a way that its composition is exactly the same as that of material to be analyzed. For this purpose, standard materials containing carefully analyzed constituents are available from National Bureau of Standards.

Independent method of analysis: It is carried out to maintain accuracy of the result, e.g. Iron (III) is first determined gravimetrically by precipitation method as iron (III) hydroxide and then determined titrimetrically by reduction to the iron (II) state. For performing a parallel control determination, a separate estimation under almost identical experimental parameters with a quantity of a standard substance is performed that consists of exactly the same weight of the components as is present in the unknown sample. It can be calculated by following expression:

Weight of component in standard substance =

Result obtained for standard substance × result obtained for unknown sample.

[where x = weight of the component present in the unknown sample.]

A blank determination is performed to determine the effect of impurities present in the reagents and vessels used and where it is necessary to locate the exact endpoint. It may be accomplished by performing a separate parallel estimation, without using the sample. In certain specific cases, the accuracy of a result may be cross-linked by performing another analysis of the same substance by another method. For example, hydrochloric acid (HCl) solution may be assayed either by titration with a standard solution of sodium hydroxide (NaOH) or by precipitation and weighing as silver chloride (AgCl).

SIGNIFICANT FIGURES

The number of digits used to express a measured or calculated quantity. The number of digits in a value, also a ratio, that contributes to the degree of accuracy of the value are significant figures. Significant figures (also known as significant numbers) are an integral aspect of statistical and mathematical calculations, which deal with numerical accuracy and precision.

By using significant figures, we can show how precise a number is. If we express a number beyond the place to which we have actually measured, we compromise the integrity of what this number is representing. It is important after learning and understanding significant figures to use them properly throughout one's scientific career.

In pharmaceutical chemistry, significant figures are the digits of value which carry meaning towards the resolution of the measurement. All the experimental measurements have some kind of uncertainty associated with them. In order to ensure precision and accuracy in measurements and to get real data, a fixed method to compensate for these uncertainties was required and this led to the significant figures. In number 4.0321, 0.03 is the first significant, 0.002 is the second significant, and 0.001 is the third significant.

An appropriate number of significant data is important in order to have a meaningful level of power resolution when reporting analytical concentrations. Various methods or parameters can be used to determine how many significant figures are required. In most cases, three key figures are sufficient. In the coefficient of expression in the scientific notation, "significant figures" refers to the number of important single digits (0 to 9 inclusive). The number of significant figures in the expression indicates the confidence or precision with which an engineer or scientist indicates a quantity.

There are certain rules to be followed to measure the significant figures of a calculated measurement. For example,

1. All nonzero digits are significant.
2. Zeroes between nonzero digits are significant.
3. A trailing zero or final zero in the decimal portion only is significant.

Following are the significant rules that govern the determination of significant figures.

Digits which are nonzero are significant. For example, in 6575 cm, there are four significant figures and in 0.543, three significant figures. The number 14.3 is included with three significant digits. All the time, significant digits are known as the nonzero digits. The value of 6.14134 possesses 6 significant digits. Here, all the numbers offer useful information. Also, 59 have two significant digits, and 78.3 have three significant digits.

Number 1000 has only one significant digit as 1 is remarkable; we do not recognize anything certainly about the units, tens, and hundreds of places, but the place holders are the zeroes in that number. It is also the same with the number having a decimal given as 0.00028, which contains 2 significant digits, i.e. only the digits 2 and 8 tell us something. The total availability of zeros is only the place holders and help to aid the information about approximate size.

Two thousand five (2005) has 4 significant digits, i.e. two and five are significant and we need to sum the zeroes as they are between the two significant digits. If any zero precedes the nonzero digit then it is not significant, and preceding zero indicates the location of the decimal point, in 0.005 there is only one and the number 0.00232 has 3 figures.

If there is a zero between two nonzero digits then it is also a significant figure.

For example:

1. 4.5006 have five significant figures. Zeroes at the end or on the right side of the number are also significant.
2. 0.500 has three significant figures. Counting the number of objects, for example, 10 bananas and 15 oranges, have infinite figures as these are inexact numbers.