PART-I
INTRODUCTION

The word drug is derived from the French word drogue, which means a dry herb. In a general way, a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animals. According to WHO, a drug may be defined as any substance or product which is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the recipient and it is presumed that this refers to total benefit-physical, mental as well as economical. An ideal drug should satisfy the following requirements:

i) When administrated to the ailing individual or host, its action should be localised at the site where it is desired to act. In actual practice, there is no drug, which behaves in this way. It generally tends to distribute itself any where in the tissues of the host.

ii) It should act on a system with efficiency and safety.

iii) It should not have any toxicity.

iv) It should have minimum side effects.

v) It should not injure host tissues or physiological processes.

vi) The cells should not acquire tolerance or resistance to the drug after some time. In actual practice, the cells which were originally susceptible to the action of a particular drug may after some time acquire tolerance or resistance to that drug.
Very few drugs satisfy all the above conditions. However, the search for ideal drug continues
To understand science, one has to know its history and development. Since the dawn of civilization, mankind has been concerned about their protection from the evils of diseases and sufferings. Conquering these afflictions often determined their survival but the current state of knowledge did not permit rational use of drugs, additional help was sought from supernatural powers. This was especially true of ancient Greeks and Indians who believed that the Gods dispensed prosperity or pestilence. There was a recognition that a regularity prevailed in the natural world that was independent of supernatural whim or will. This was a giant step in the making and formation of scientific medicine.

Human beings began to believe that nature alone could provide the means to remove pain and disease and thus they sought remedies in nature, i.e., in plants, minerals and animals. A variety of medicinal agents were collected on the basis of their symbolic qualities as well as their astrological signs and portents, e.g. Since the sword symbolized strength and power, the early Greek Physicians attempted to use iron therapy against weakness and anemia. The observation that the horn of rhinoceros is powerful, led Chinese physicians to prescribe it as a potent aphrodisiac.

One should keep in mind that these practitioners brought forth their explanations in good faith. Many of their drugs were added to the therapeutic
armamentarium only after considerable trial and error and application of clinical judgement. We should not automatically brand their explanations as silly and as having no basis for to-day's rational standards. These early drug users were just as intelligent as we are. In the light of the knowledge then available they had good reasons for what they said and did. The answer to the question, what did they consider good reasons, is not a simple one. It must take into consideration their entire intellectual, ethical and cultural background.

The earliest references about medicine preparations in writing come from India or Rigveda and from China in their Materia Medica 2500-3000 B.C. In India, later on, a large number of medicine preparations including Ayurveda were described by physicians such as Chark, Sushruta, Vaghbata and others. All the drugs used were of vegetable origin.

As a large number of drugs have been found to be listed on papyrus, and many clay tablets are discovered in Egypt, it is evident that the Western medicinal system comes from Egypt and from the kingdoms of Assyria and Babylonia.

It was the Greek physician, Hippocrates (450 B.C.) who laid the foundation of modern medicine. According to him, a disease is a pathological process and its treatment with drugs is not a magic. The medicine system introduced by Hippocrates had a scientific basis, i.e.; it was based on observation, analysis and deductions. However, on the whole upto
the nineteenth century it was believed that the treatment of diseases was mainly based on the combination of guess work and experience. This resulted quack doctors in many countries. These doctors used therapeutic preparations comprised of a limited number of substances extracted from herbs and animals or from the earth in the form of minerals. Some 500 years later the Roman, Galen of pergamon, besides conducting impressively detailed investigations of animal anatomy, was a convinced herbalist who also used certain metallic salts, copper and zinc ores, iron sulphate and cadmium oxide, and introduced the assaying of preparations in efforts to control the quantity and quality of his dosages. The next major advances were introduced by two Persians named Rhazes and Avrienna, who, in the tenth and eleventh century respectively, introduced opium pills for coughs and extracts of wild autumn crocus (colchicum) seeds to treat gout. Both of these remedies are still used in modern medicine. In Europe in the early sixteenth century theophrastus paracelsus extolled the virtues of antimony salts as cure-alls, and, for a period, metal therapy dominated herbal recipes.

Theophrastus paracelsus, originally named Bombastus von Hohenheim, was ironically frustrated by unsuccessful attempts during his life time to introduce the useful laudanum (morphine tincture) for relief of pain and tartar emetic, still a useful antimonial, for the dread schistosomiasis.

One of the greatest herbal remedies of all was introduced into Europe in the seventeenth century by Jesuit missionaries who had accompanied the
Spanish conquistadors on their exploration of central and South America. This was an extract of the cinchona bark obtained from South America. Indians who had long used it as an against chills and malarias in Europe.

In eighteenth century in England, Withering introduced the use of an extract of the fox-glove plant for the treatment of dropsy, a heart condition characterised by excessive accumulation of liquid in the lower limbs of the afflicted. He used this extract on the personal recommendation of country folk who had been using the elixir for untold years, a fine example of an enquiring medical practitioner following up and developing a lead from folk culture. The active material digitals, is still used today for threatened heart failure and is even now obtained by extraction from the foxglove.

By the middle of the 19th century, modern medicine had brought to the fight against diseases only one effective weapon, i.e.; immunisation against smallpox. In quick succession came surgical anaesthesia and antisepsis. The last quarter of the 19th century marked the identification of the causative organisms of few diseases like malaria, plague, cholera, typhoid and dysentery so that areas of the globe till then mastered by them changed hands to man. Insect vectors were identified. Vigilant students of preventive medicine contributed more than their mite. Organic and biochemistry gave a tremendous fillip to the study of hormones and vitamins. During the last decade intensive work in chemotherapy has given us such valuable aids as the sulpha drugs and antibiotics.
In the subsequent years, the knowledge of the chemistry of natural substances particularly of enzymes increased. This was made possible with the help of new physical, chemical and biological techniques. It is widely accepted that the enzymes play some role in drug action.

In the last fifty years, there had occurred more spectacular advances in medicinal chemistry, particularly with the discovery of sulpha drugs and antibiotics. Recent years have seen the creation of new therapeutic agents by medicinal chemists working usually as part of interdisciplinary terms. All their names and contributions are too numerous to mention here.

The systematic research in pharmaceutical laboratories has led to the introduction of more and more synthetic drugs in the modern times. The synthetic work is carried out more or less along the following lines.

i) Compounds are synthesised whose structures are more or less similar to naturally occurring substances. This sometimes produces drug whose price is much less than the naturally occurring one.

ii) Attempts are made to prepare the compounds with simplified structure based on the structures of natural drugs. For example, the structure of a compound having specific physiological activity is varied systematically. This work sometimes leads to the discovery of new drug with simplified structure.
iii) Attempts are made to synthesize new drugs, which have the
properties of certain natural products but have no relation to
them in structure.

iv) Attempts are made to synthesize new drugs, which are unrelated
in structure and properties to natural products.

Sometimes it is found that a drug discovered poses certain serious
problems. For example, phthalidomide was at one time considered to be an
ideal hypnotic due to its low toxicity. Later on, this was found to be
responsible for the birth of thousands of deformed children. Thus, this is not
used at all. Certain drugs are known which are abused on the whole it is
found that the beneficial effects of drugs are much more than the problems
created. However, these problems could be overcome.
(B) SOURCES OF DRUGS

1. PLANTS

Medicinal plants have been used to treat various diseases from time immemorial. Crude medicinal preparations made from plants are called 'galenicals' because they were extensively used and popularized by Galen, the famous Greek physician. They owe their actions to biologically active ingredients contained in them. The important classes of active ingredients in plants and their characteristics are as follows.

(a) ALKALOIDS: These are plant bases containing nitrogen which form salts with acids. They are insoluble in water. Acid salts of alkaloids are freely soluble in water. Today hundreds of synthetic alkaloids are being produced. Examples are as follows:

Morphine (narcotic analgesic) from unripe capsule of papaver somniferum.
Ephedrine (bronchodilator) from plant Ephedra vulgaris.
Atropine (anticholinergic) from leaves of Atropa belladonna.
Quinine (antimalarial) from bark of cinchona.
Reserpine (antihypertensive) from root of Rauwolfia serpentina.

(b) GLYCOSIDES: They are ether-like combination of sugars and non-sugar moiety (cyclopentane-phenanthrene steroid nucleus). If a glycoside is boiled with mineral acid, it is hydrolysed and it splits off the sugar. The non-sugar residual part of the glycoside is called aglycone.
Examples of glycoside are digoxin, a cardiac stimulant obtained from the leaves of Digitalis Lanata.

(c). OILS: They are immiscible with water but dissolve readily in solvents like ether chloroform and alcohol. Oils of medicinal value can be divided into three classes.

i) Fixed oils: Chemically these are esters of fatty acids and glycerol. Most of them are edible oils e.g., ground nut oil, coconut oil, mustard oil, olive oil. Some have pharmacological actions e.g., castor oil (purging) and cod liver oil (rich source of vitamin A and D).

ii) Volatile oils: These are terpenes or their polymers. They are also called essential or flavouring oils. Most of them are liquids. For example, clove oil (anodyne-relieves pain when applied locally specially in toothache), eucalyptus oil, coriander oil, dill oil, ginger oil (carminative, for expulsion of gas from the stomach), methyl salicylate (oil of wintergreen) and terpentine oil (counter irritant, applied locally to relieve pain in arthralgia). Few volatile oils exist in a solid form and they are known as stearoptenes e.g. camphor and menthol.

iii) Mineral oils: They are hydrocarbon by chemical nature and are obtained from petroleum e.g. liquid paraffin (lubricant and laxative).
(d) RESINS: They are formed by oxidation or polymerization of volatile oils, e.g. podophyllum, colocynth, jalap. They are more of toxicological importance than pharmacological.

(e) GUMS: They are secretory products of plants chemically they are related to polysaccharides. They form thick mucilage when mixed with water. Some gums are pharmacologically inert and are mainly used as emulsifying agents e.g. gum acacia, gum tragacanth; while other gums are active e.g. agar (bulk purgative), gum guggul (hypolipidemic).

(f) TANNINS: They are non-nitrogenous compounds characterized by their astringent action on the mucous membrane, i.e. they precipitate proteins from the cells of the mucous membrane and have a protective action.

2. ANIMALS

Some drugs are obtained from animals. Examples are as follows: Insulin (hypoglycemic) from pancreas of sheep, oxen and pigs.

Thyroid extract (for hypothyroidism) from thyroid gland of oxen.

Gonadotropins (sex hormone) from serum of pregnant mares.

Pepsin (enzyme) from stomach of oxen and pigs.

3. HUMAN:

Some drugs are available from human source. Examples are as follows:

Immunoglobulins from blood.

Growth hormone from anterior pituitary.

Chorionic gonadotropin from urine of pregnant women.
4. MICROBES

They are mainly the source of antibiotics, i.e. chemical substances produced by one type of microorganism and lethal to others. Apart from antibiotics, certain other drugs have also been derived from microorganisms e.g. the enzyme streptokinase (fibrinolytic) as obtained from streptococcus. Examples of antibiotics are as follows:

Penicillin from the fungus penicillium chrysogenum. Streptomycin, neomycin and actinomycin from Actinomycetaceae. Griseofulvin from penicillium griseofulvum. Nystatin from streptomyces noursei.

5. MINERALS

Some elementary substances like iron, iodine and sulphur are used in the treatment of diseases. Some metallic compounds like antimony salts for kalaazar and bismuth salts for peptic ulcer are valuable drugs. Similarly magnesium and aluminium salts are widely used in antacid preparations. Some important examples are as follows:

Sulphur in sulphur ointment for scabies.

Iron in hematinic preparations for anaemia.

Magnesium sulphate (epsom salts) as a purgative.

Iodine in Lugol’s iodine for thyrotoxicosis and tincture iodine as antiseptic.

Aluminium hydroxide in antacid preparations.

Radioactive isotopes (I$^{131}$) in diagnosis and treatment of thyroid disorders and (P$^{32}$) in polycythemia vera.
NEED FOR STUDY
(C) NEED FOR STUDY

Drugs and pharmaceuticals play a very significant role in the present days for the reason that these drugs find important application in the prevention, control and curing of different kinds of human diseases. It is a common observation and the practical truth that a single drug of a particular composition is marketed in various brand names by different manufactures. The possibility of minor changes in the chemical composition and standard of the drug will have a profound effect on the physiological and biological activities of the patient. It is very much painful for the present day scientist in general and to the analytical pharmaceutical chemist in particular to note in the various dailies about the entry of the spurious and substandard drugs into market, which definitely will have an adverse effect on the human beings at large.

It is with this challenge in mind, the author has taken up his thorough investigations to know and evaluate the purity of the various drugs released into the market. The author has made an extensive survey of the chemical and biochemical literature to know whether the reports involving simple experimental techniques such as the spectrophotometric techniques are available for ascertaining the assay and purity of the drugs. It is the observation of the author that not much attention has been paid to such simple and rapid spectrophotometric methods for the assay of drugs is available in literature. Among the several instrumental techniques (HPLC,
GC, Fluorimetry, NMR, IR, UV and Visible regions) available for the assay of drugs. These methods are either expensive or do not give reproducible results are found reported in literature. Usually spectrophotometric technique is simple and less expensive. The selectivity and sensitivity of the spectrophotometric methods depends only on the nature of chemical reactions involved in colour development and not on the sophistications of the experiment.

UV and Visible spectrophotometric methods are highly versatile, sensitive and reproducible. In an attempt to develop new UV and Visible spectrophotometric techniques for the evaluation of purity of the pharmaceutical preparations, the author has selected sixteen drugs and established new methods. The drugs selected are

1. MOSAPRIDE 2. CISAPRIDE 3. DAPSONE 4. SULFAMOXOLE
5. RITODRINE HYDROCHLORIDE 6. SPARFLOXACIN.
7. FRUSEMIDE 8. SPIRONOLACTONE 9. OFLOXACIN
10. METRONIDAZOLE 11. PARACETAMOL 12. NIMUSULIDE
13. DILOXAMIDE FUROATE 14. RIFAMPICIN 15. ISONIAZIDE
16. ORNIDAZOLE.
PRINCIPLES OF SPECTROPHOTOMETRY
Spectrophotometrically is one of the most widely used physico-chemical techniques, which is remarkable for its sensitivity and precision. Visible spectrophotometry is more often called Colorimetry, and even at present such definitions as colorimetric, photometric or absorptiometric methods are some times used in the literature besides the term spectrophotometric method. This is a convenient and direct technique, which does not effect changes in composition and properties of the experimental solutions.

The origin of absorption spectrophotometry can be traced to the work of Bouguer and Lambert in the eighteenth century but it was not until one century that a general law for the absorption of radiation was well established by Beer and Bernard. This law which provided the bases for visual colorimetric analysis, a method well accepted as a useful adjunct to classical method of analysis by the end of the last century.

Visible light represents a very small part of the electro-magnetic spectrum and generally considered to extend from 380 nm 780 nm. A solution or object appears coloured when it transmits or absorbs only part of the radiation in the visible spectrum. The optical characteristic of the substance is its absorption spectrum. Description of a colour by name is a very rough means of characterization.

There is a close relation between the colour of a substance and its electronic structure. The production or change of a colour is connected with deformation of the normal electronic structure of the molecule. Irradiation
causes variations in the electronic energy of molecules containing one or more chromophoric groups atomic groups with unsaturated linkages. Presence of colour bearing groups in an organic molecule often depends the colour by displacing the absorption maximum towards longer wavelengths. This is called a bathochromic shift. The displacement of the absorption maximum from the red towards the UV is known as a hypsochromic shift. The colour of a molecule may be intensified by substitents called auxochromic groups. These groups may also effect bathochromic shifts.

The applicability of the spectrophotometric technique to the determination of traces of metal, non-metals and organic substances is one of the main reasons for the wide spread utilization of this opticometric method of analysis.
In spectrophotometric analysis, a measure is made of the light transmitted by an absorbing medium placed between a light source and spectroscope. The plot of light absorbed or transmitted as ordinate versus wavelength is characteristic for an absorbing component and gives a clue to the nature of the component, there by providing the basis for qualitative analysis. The height of the ordinate due to the component under investigation at any particular wavelength affords a measure of the concentration of the component and provides the necessary basis for quantitative work.
Laws of Photometry:

When electro-magnetic radiation interacts with matter, absorption occurs if the frequency of the radiation corresponds precisely to the energy required to raise the system to a higher allowed energy level. When light of intensity $I_0$ falls on a homogeneous medium, a part of this light is reflected ($I_r$), a part is absorbed ($I_a$) within the medium and the remainder is transmitted ($I_t$). This can be mathematically expressed by the following equation:

$$I_0 = I_r + I_a + I_t \quad \text{(1)}$$

since the measurements are always made with respect to a reference solution in a similar cell, $I_r$ is usually regarded as constant and hence can be neglected. Then the equation (1) becomes:

$$I_0 = I_a + I_t \quad \text{(2)}$$

Quantitative measurements of light absorption are based on two fundamental laws concerned with the intensity of the light incident upon a layer of an absorbing solution and the intensity of the light transmitted by this solution. These laws relate the intensity of a beam of monochromatic electro-magnetic radiation to the path length of the beam in an absorbing medium and the concentration of the absorbing species. In the practical application of these laws, the light referred to is to be regarded as monochromatic and the solvent is to be considered non-absorbing.
**Lambert’s Law:**

Lambert observed that, when a parallel beam of monochromatic radiation passes through a transparent medium of thickness \( db \), some radiant energy is absorbed. The fraction absorbed increases exponentially with linear increase in the thickness of the medium. This can be written as

\[
-\frac{dI}{I} = K' \, db..........................(3)
\]

Where \( dI \) is the change in the intensity, \( K' \) is a proportionality constant and the negative sign denotes that \( I \) becomes smaller as \( b \) increases. Equation (3) can be written as

\[
I = I_0 e^{-K' \, b} ..................................(4)
\]

Where \( I_0 \) is the intensity of the incident radiation when \( B = 0 \). The ratio \((I/I_0)\) is the fraction of the incident light transmitted by the medium and is called the transmission or transmittance. Its reciprocal \((I/I_0)\) is called opacity.

**Beer’s Law:**

Beer noticed that when a radiation passes through a solution, there is reduction in the intensity provided the radiation does not react with the solution. The fractional loss of intensity is proportional to the infinitesimal increase in the concentration of the absorbing species. This is mathematically represented as
where \( K'' \) is a proportionality constant. The combined Lambert-Beer’s law can be stated that the fraction of the radiation absorbed increases exponentially with the linear increase in thickness and concentration. This can be expressed mathematically as:

\[
I = I_0 e^{-K'C} \tag{5}
\]

Where \( K \) is a new proportionality constant. Equation (5) can be expressed in the logarithmic form as

\[
\log (I_0/I) = abc \tag{6}
\]

Where \( a = K/2.303 \). The ratio \((I_0/I)\), which is referred to as transmittance, is dimensionless. Since \( abc \) is a logarithmic quantity, it is a pure number. \( a \) is called the absorptivity or absorbancy index, or specific absorption coefficient and its units are liters per gram-centimeter, when the thickness is expressed in centimeters and the concentration in grams per litre. When the concentration is expressed in moles per litre, the proportionality constant \( a \) is changed to \( \varepsilon \) and is called the molar absorptivity, or molar extinction coefficient or molar absobancy index.

\[
\log (I_0/I) = \varepsilon bc \tag{7}
\]

or \( A = \log (I_0/I) \) is referred to as the absorbance or optical density or extinction.
When there are more than one absorbing species present in the solution, the absorbance is usually equal to the sum of the individual absorbance of the components. This law of additivity generally holds good and can be expressed as

$$A = (\epsilon_1 C_1 + \epsilon_2 C_2 + \ldots + \epsilon_n C_n)b \quad (8)$$

$$= b \sum_{i}^{n} \epsilon_1 C_1 \quad (9)$$

When the path length is kept constant.