CHAPTER 1

A CRITICAL REVIEW ON THE ANALYTICAL RESULTS OF PHARMACEUTICAL COMPOUNDS
Definition of Drug

A substance, which is used as a cure for an ailment or for alleviation of symptom, is known as drug. Drug may be a single chemical substance or combination of two or more different substances. Each drug has optimum dosage, below which it has no action and it becomes a poison after a certain concentration limit.

Paul Ehrlich discovered and described the drugs as magic bullets. The sulpha drugs are derivatives of sulphanilamide and these were the first synthetic compounds found to be effective against pathogenic organisms.

Origin of drugs

The history of the use of medicinal plants for diseases is as old as the history of mankind itself. The medicinal properties of plants are described in Indian Scriptures. Ayurveda is developed from Rigveda and Adharvanaveda (3500-1500 BC). The Charak samhita dealing mostly with plants and Sisrut samhita dealing with surgery are the well known ancient treatises in Ayurveda. The antileprotic action of the Chaulmoogra fruit, the efficiency of amla fruit as tonic, the bark of Saraca indica (Ashoka) as uterine tonic, the dried roots and stems of Withania somnifere (Aswagandha) as sedative were known to Indians.

Many new drugs of botanical and mineral origin came into use and several pharmacopeias were compiled in the 16th century in various countries. The active components of herbal drugs were extracted, purified and physiological actions of these pure drugs were quantitatively estimated. Thus, classification of drugs derived
from plants on the basis of their biological functions made its beginning in the 18th century itself. Terms like antispasmotic, antiseptic, emetic etc. found their use in the field of modern medicines. Efforts were therefore indicated by the organic chemistry to unravel the structures of organic compounds derived from these medicinal plants and to synthesize them in the laboratory during the later part of the 19th century.

The first use of synthetic organic chemicals for useful interference with life processes was probably, when ether and chloroform were introduced for anaesthesia during the first half of the 19th century. Aspirin was introduced later in 1899 with an attempt to reduce the nausea caused by the salicylates used as antipyretics. The next period for the history of use of chemicals in the treatment of diseases relates to the use of synthetic anaesthetics and antipyretics. The use of chemical substances for such treatments is known as chemotherapy. The chemotherapy and the use of primarily, the synthetic organic chemicals registered a rapid growth in the subsequent years and many kinds of drugs were synthesized and used. The discovery of the antibacterial activity of sulphonamides in the early 1930s marked the beginning of the present era of chemotherapy. The use of chemical compounds in the treatment of infectious diseases so as to destroy the infective parasites on the organisms without damaging the host tissues. Woods DD observed in 1940 that the bateriostatic action of sulfonamide drugs is antagonized completely by p-aminobenzoic acid. This led to the idea that a drug should interfere with the biological synthesis or utilisation of a recognised cell metabolite.

The approach to the practice of medicinal chemistry is developed from an emperical activity involving the synthesis of new organic compounds, based largely
on modification of structures of compounds of known activity as stated by Manfred Wolff. Drugs are classified (a) on the basis of their chemical structure (b) on the basis of their activity and (c) on the basis of diseases against which the drugs are used. The drugs used today in medicine are obtained both from the nature as well as through synthesis in a laboratory. The first category namely the natural compounds are obtained from the plants, animals or minerals. The drugs obtained from the microorganisms known as antibiotics, are the latest additions.

Classification of drugs

The classification of natural drugs on the basis of their biological functions made its beginning in the 18th century. The systematic studies in pharmacology have made available the mode of action of drugs on the various physiological mechanisms in the body, the mechanism of their therapeutic action, their acute and chronic toxicity and their biological fate and elimination. The pharmacological activity of a drug allows a rational basis of classification. Thus, the drugs are classified as analgesics, hypnotics, sedatives, tranquilizers, antimalarials, antibacterials, antibiotics, antidiabetics, antidysentry agents, antiallergic agents, cardiovascular and central nervous system stimulants, antileprotic agents, antihelmintics, harmones and vitamins.

The pharmacological activity of drugs

Pharmacology deals with a study of the preparation of various drugs and their application in diagnosis, prevention and cure of disease. Pharmacological study deals with the scientific aspects of drugs and its relation to the curative aspects of diseases.
The characteristic action of a drug is related to its chemical structure and this relationship is helpful in the synthesis of many valuable drugs. The adverse effect of drug is called toxicity. It is an important aspect in drug chemistry. The toxic effect of pharmacological agents employed in therapy is studied in the general principles applicable to the presentation, recognition and treatment of drug poisoning. When drug formulations are developed, many of these adverse effects are rectified. The drug formulations are effective as antacids, fever reducers, antibiotics, central nervous system stimulators etc. The drug formulations not only contain the drug, but also the binding material associated with it. Because of the fact that newly developed drugs are often more physiologically active, they are administered in small doses.

Analysis of drugs

Sensitive analytical methods are needed for monitoring the physiological activity of these drugs. A rapid analysis is necessary at the production stage because large number of samples are to be analysed in a given time. Many techniques employed for drug analysis such as electroanalytical methods, TLC, GLC, HPLC, colorimetry, spectrofluorimetry, spectrophotometry proved to be extremely useful in the field of pharmaceutical analysis.

The electrochemical methods are almost similar to biological reactions taking place inside the body. In electrochemical reactions, the electron transfer takes place at the electrode solution interface. In biological reactions, it occurs at an enzyme solution interface. Both types of reactions take place at similar pH and in presence of similar inert electrolytes. Both types of reactions can occur effectively under non-aqueous conditions and at similar temperatures. In both the processes, the substrate
molecule has to be oriented in a specific fashion before the electron transfer takes place.

General TLC procedures were described for a number of common pharmaceuticals including benzodiazepines and local anaesthetics. Combined TLC densitometry has been used in the analysis of aminoacrine hydrochloride, clotiazepam and oxyphenbutazone. HPLC method was used to assay asplatin and related derivatives, methyl nicotinate, lanatoside C, aspirin, phenacetin, mebeverine hydrochloride and caffeine. Reverse phase conditions were employed in two of these procedures. Phenacetin and caffeine were determined in combination with phenazine using HPTLC. Thin layer plates with a bonded chiral phase were used to determine the optical purity of DOPA. Several barbiturates were separated on silica gel plates impregnated with various copper salts and alkyl amines. HPLC technique was employed in the analysis of salicylic acid and tetracyclines.

Spectral methods provide useful information in the study of pharmaceuticals, their metabolites and degradation products. Colorimetric methods are prescribed for the assay of many drugs in British Pharmacopia. For example, in the assay of glyceryl trinitrate tablets, the ester nitrates are quantitatively hydrolysed by phenol-2,4-disulphonic acid to an yellow coloured solution in ammonical medium. The intensity of yellow colour is measured colorimetrically. The assay of ergometrine maleate and other alkaloids has been carried out by converting them into blue coloured solution by paradimethyl amino benzaldehyde and a trace of ferric chloride in sulphuric acid. The intensity of the blue coloured solution is measured at 520 nm.
Many limit tests are carried out spectrophotometrically on number of pharmaceutical compounds such as the test for iron and chloraniline in progianil, free amino acid in acetarsol, salicylic acid in acetyl salicylic acid, thiourea in methyl thiouracil, dimethyl aniline in dextromethorphan hydrobromide. Chlopromazine and its sulphoxide impurity in dosage forms are characterised by UV spectroscopy. Vakulskya et al. employed EPR and polarography for the determination of nitrazoles and nitroimidazoles. Gamot et al. used Raman spectroscopy in the toxicological investigations of crystalline and aqueous solutions of cocaine. Turozan et al. used NMR spectroscopy for the determination of bisulphan in tablets. Hofmann et al. employed Mass and IR spectral methods associated with chromatographic techniques for the determination of benzimidazoles. Hydrazine products are identified by IR and Mass spectra. Using PMR spectroscopy, Ashmaur et al. determined ascorbic acid.

A variety of colorimetric methods have been reported for the analysis of antibiotics, antiinflammatories and analgesics. Abdel Khalek employed spectrophotometry for the determination of penicillin using ammonium vanadate. Sastry developed an indirect spectrophotometric method for the determination of antibiotics. Different co-workers have studied the spectrophotometric assay of paracetamol and phenacetin. Singhai developed a colorimetric method for determining ibuprofen in presence of paracetamol. A spectrophotometric method for the simultaneous determination of paracetamol and diclofenac sodium is also reported by Huang et al., Zhao et al. used ferroin for the colorimetric estimation of ascorbic acid. Subrahmanyam et al. proposed simultaneous determination of trimetoprim
and sulpha diazine in combined dosage forms. Abounasiff et al.\textsuperscript{43} used derivative spectrophotometry to determine sulphametrole and trimethoprim mixture in tablets. Derivative spectrophotometry was employed by Barary, Magdal et al.\textsuperscript{44} for the determination of cephalosporins from their alkali induced degradation products. Extraction spectrophotometric method\textsuperscript{45} for determining ascorbic acid in pharmaceutical preparations are also reported.

Extensive spectrophotometric studies are being carried out in our laboratories in the analytical studies of metal complexes. In the course of our studies on the kinetic spectrophotometric investigations of Ag(I) - ferrocyanide - hydrazone systems\textsuperscript{46}, it is observed that in alkaline medium, silver reacts with riboflavin and folic acid producing intense red and yellow colourations respectively. Detailed spectrophotometric studies are carried out on these coloured solutions and the results obtained are presented in the following chapters.
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