I. INTRODUCTION

NOVEL DRUG DELIVERY SYSTEM

The aim of Novel Drug Delivery System is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The drug-delivery system should deliver drug at a rate controlled by the necessarily of the body over a specified term of treatment [Remington (2001)].

This idealized objective switch to the two aspects most important to drug delivery is as follows,

1. Spatial Drug Delivery
2. Temporal Drug Delivery

I. Spatial Drug Delivery:

Targeting drug to a particular organ or tissue.

II. Temporal Drug Delivery:

The drug delivery rate to the target tissue is controlled.

In India the prime areas of research and development for NDDS are:

1. Liposomes
2. Niosomes
3. Nanoparticles
4. Transdermal drug delivery
5. Implants
6. Oral system
7. Micro encapsulation/ Microcapsules
8. Polymer in drug delivery

Novel drug delivery system can be divided into classes.

1. Sustained release drug delivery system.

2. Controlled release drug delivery system.

**Sustained release drug delivery system**

It is a pharmaceutical dosage from formulated to retard the release of a therapeutic effect such that its look in the systemic circulation is delayed and/or prolonged and the plasma profile is sustained in duration. The onset of its pharmaceutical action is often slow, and the duration of its therapeutic effect is sustained. (for example: coated granules)

**Controlled release drug delivery system**

This system has a meaning that goes beyond the scope of sustained drug action. It manifests a predictability and reproducibility in the drug release kinetics. The release of drug substances from a controlled release drug delivery system gains at a rate profile that is not only predictable kinetically but also reproduced from one unit to another.

They are classified as follows [Y.W. Chein (1983)]

   I. Rate- preprogrammed drug delivery system
   II. Activation – Modulated drug delivery system
   III. Feed – Back Regulated drug delivery system
   IV. Site – Targeting drug delivery system

**I. Rate- Preprogrammed drug delivery system**

In this system the release of drug molecules from the drug delivery system has been preprogrammed at specific rate profiles. This was achieved by system designing which controls the molecular diffusion of drug molecule in and/or across the barrier medium in or surrounding the delivery system. e.g., Implants, Transdermal system [F.Tweenes (1983)].

**II. Activation- Modulated Drug Delivery System.**
The release of drug molecule from this delivery system is activated by some physical, chemical, biochemical process and/or facilitated by the energy supplied externally. Based on the nature of the process applied or the type of energy used, these activation modulated drug delivery system can be classified.


b. Chemical e.g., pH activated drug delivery system [H. Sezahi et al].

c. Bio Chemical e.g., Enzyme activated drug delivery system [T. A. Horbett (1984)].

III. Feed Back –Regulated Drug Delivery System.

The release of the drug molecule from the delivery system is activated by a triggering agent, such as biochemical substance in the body and regulated by its concentration via some feedback mechanisms. The rate of drug release is then controlled of the triggering agent detected by a sensor in the feedback regulated mechanism. e.g., Bioresponsive drug delivery system glucose triggered insulin delivery [Jantzen et al].

IV. Site –Targeting drug delivery system.

In this system the drug molecules are circulating the other tissues and moving towards the specific disease site and get released. This will enhance the therapeutic effectiveness and reduces the toxicity to other healthy tissues and improve the treatment spectrum, e.g., niosomes, microspheres.

Merits of drug delivery system:

1. Better treatment of many chronic illnesses e.g., Cancer, Asthma, Arthritis.

2. Increased Bio- availability.

3. Reduction in the occurrence and badness of untoward systemic side effects related to high blood plasma drug concentration.

4. Sustenance of the total amount of drug administered over the period dose periods.
5. Reduction in the total amount of drug administered over the period of drug treatment which reduce occurrence of systemic and local side effects.

6. Prevention from first pass metabolism and gastrointestinal tract degradation.

7. Better patient compliance effect from the reduction in the number and frequency of doses needed to maintain the want therapeutic responses.

8. Targeting the drug molecule towards the affected tissue or organ make smaller the toxicity to the normal tissues.

9. Versatile and pH dependent system release the drug whenever the body demands.


11. Fewer expenses are made from better disease management achieved with this system.

**Limitations:**

However there are many benefit in this system there are few factors that limit its usage.

1. Physiological factors such as gastrointestinal enzyme, activates pH/ gastric and intestinal transit rates, food and disease which often influence drug bioavailability from conventional dosage forms may interfere with the accuracy of control release and absorption of drug from the system.

2. The products which remain intact may become accommodates at some sites results slow release of drug from the dosage form may produce a high localized concentration of drug which produces local irritation.

3. Drugs with half-life of 1hr or less are difficult to be formulated as sustained release formulation. The high rate of elimination of such drugs from the body requires a highly large maintenance dose which provides 8-12 hrs of continuous release.

4. Since these products contain a large amount of drug. There is a chance of unsafe over dosage, if the product is improperly made and the total drug contained there is released at one time or over too short time of interval.
5. It is difficult to cease the therapy once after administration may be for reasons of toxicity or any other.

6. It may be not suitable to encompass potent drugs in such system.

**TARGETED DRUG DELIVERY SYSTEM (TDDS)**

1. Drug targeting is a phenomenon which perform the distribution of drug in the body in such a manner that the chief fraction of the drug interacts entirely with the target tissue at a cellular or sub cellular level [Welling, P. G. *et al* (1987)].

2. The aim of drug targeting is to achieve wish pharmacological response at a specific site without undesirable interactions at other sites.

3. This is particularly significant in cancer chemotherapy and enzyme substitute treatment. Drug targeting is the delivery of drugs to receptors or organs of the body to which one hopes to deliver the drug entirely [Gregoriadis. G, (1977)].

4. The targeted delivery of drugs is truly a very inviting aim because this supply one of the most potential ways to develop therapeutic index of the drugs.

Previous work done between late 1960s and the mid 1980s stressed the need for drugs carrier system originally to alter the pharmacokinetics of the before proven drugs whose efficacy might be improved by changing the rates of metabolism in liver or clearance by the kidneys. These approaches commonly were not focused to achieve site specific or targeted delivery such as getting a cytotoxic drug to cancerous tissue while sparing other normal, though equally sensitive tissue with the progress in the carrier technology the issue of delivering either single or the entire carrier to the specific site has been addressed during the last few decades.

- A number of scientific improve have since been made in the area of parenteral drugs delivery leading to the improvement of complicated systems that permits drug targeting and the sustained or controlled release of parenteral medicines.
• At present, drug targeting is achieved by one or two method. The first method entails chemical alteration of the parent compound to a derivative which is activated only at the target site.

• The second method utilizes carriers such as microspheres, liposomes, niosomes, nanoparticles, antibodies, cellular carriers (erythrocytes and lymphocytes) and micromolecules to direct drug to its site of action.

• Recent developments have led to the improvement of several novel drug deliveries system that could modernize the method of prescription and provides an integer of therapeutic benefits.

The objective of any drug delivery system is to offer a therapeutic quantity of drug to the appropriate site in the body to attain on time, and then maintain, the preferred drug content. The principle drug delivery systems delivers drug at a rate dictated by the requirement of the body over the episode of treatment and it channels the active entity only to the site of action. At present no existing drug delivery system can attain all these goals. The targeted drug delivery system attains the site- specific delivery but is incapable to control the release kinetics of drug in predictable manner.

Paul Ehrlich in 1906, initiated the era of progress for targeted delivery when he envisaged a drug delivery method that would target drugs directly to the disease to cells.

Numbers of carriers were used to carry drug to the target organ/ tissue which consist of serum proteins, immunoglobulins, synthetic polymers, lipid vesicles (liposomes), microspheres, erythrocytes, reverse micelles, surfactant vesicles (niosomes), and pharmacosomes etc [Gregoriadis. G et al (1982)].

Amongst the different carriers, few drug carriers reach the stage of clinical trials where phospholipids vesicle show tough potential for effective drug delivery to the site of action. This carries (magnetic microparticles) are biologically static in nature, devoid of any antigenic, pyrogenic or allergic reactions and their constituents can be utilized as the component of biological membrane. Drugs encapsulated in magnetic microparticles are not activated under physiological conditions and do not cause unfavorable side effects as well.
There are different techniques by which drug can be targeted consist of [D.M. Bramhankar et al (2011)].

1. Microspheres
2. Magnetic microparticles
3. Nanoparticles
4. Niosomes
5. Monoclonal antibodies
6. Resealed Erythrocytes
7. Liposomes

1. Microspheres:

Microspheres are free flowing powders composed of particles of size suitably less than 125 microns that can be suspended in an appropriate aqueous medium and injected. Each particle is essentially a matrix of drug scattered in polymer from which release take place by a first order process. The biocompatible polymers used are e.g., Polylactic acid, Poly lactidecoglycolide etc. Drug release is controlled by dissolution degradation of matrix. The system is preferably suitable for controlled release of peptide/protein drugs.

So as to overcome uptake of intravenously administered microparticles by the reticuloendothelial system and support drug targeting to tumors with desired perfusion, magnetic microparticles were development. There are prepared from albumin and magnetite and have size of 1 µg to allow intravascular injection.

2. Magnetic microparticles:

Magnetic microparticles are being of great concern due to their sole purposes. Magnetic microparticles have been lively examined as the next procreation of targeted drug delivery for more than three decade. The significance of targeted drug delivery and targeted drug therapy is to carry a drug directly to the centre of the disease under physiological conditions and thereby treat it intentionally, with neither effect on the body. Usage of microparticles depends largely on the preparation processes to select optimal conditions and election agents to modify their surface.

3. Nanoparticles:
Nanoparticles are one or numerous types of systems known together as colloidal drug delivery system. Examples are microcapsules, nanocapsules, macro molecular complexes, polymeric beads, microspheres, liposomes and niosomes.

A nanoparticle is a particle dispersed drug with a diameter of 200 to 500 nm. Materials used in the research of nanoparticles are sterilisable, biodegradable and non-toxic. They commonly are prepared by a manner similar to the coaceravation processes of micro encapsulation.

Nanospheres or nanocapsules depending upon whether the drug is in a polymer matrix or encapsulated in a cell. Nanoparticles can be stored for up to one year and it can be targeted via reticulo endothelial system to liver cells that are active phagocytically.

4. **Niosomes:**

Nonionic surfactant vesicles are employed as carriers to deliver drugs to target organs and transform drug disposition. Niosomes are found to increase therapeutic efficacy of drugs in cancer therapy, viral, microbial and parasitic diseases. Non-ionic surfactants like cetrimide, sodium dodecyl sulphate are used with cholesterol to entrap drugs in vesicles.

Livers serve as a depot for many drugs where they are broken down by lysosomal lipase slowly to release the free drug to the systemic circulation. Niosomes slowly degrades thereby providing a more sustained effect.

Niosomes are competent of releasing entrapped drug slowly. Niosomes establish selective drug delivery ability for cutaneous treatment of 5-α-dihydro testosterone triamcinolone acetamide and intravenous administration of otrexate for cancer treatment and sodium strilbogluconate in the treatment of leishmaniasis etc.

5. **Monoclonal antibodies:**

Monoclonal antibodies are especially high quality antibodies which consist of one molecular species and which might be obtained in an almost homogeneous state.
Kohler and Milstein in 1975 proved that somatic cell hybridization might be used to generate a continuous hybrid cell line yielding a single type of antibody. The basic principle was to remove b-lymphocyte from an antigen Primed mouse, having the secrete a specific antibody and to fuse this with a suitable mouse consequent plasmacytoma (frequently called myeloma) line. The result was hybrid cell line (hybridoma) which had the phenotypic properties of the parental cells, that is malignancy and specific antibody secretion indefinitely one b-lymphocytes or plasma cell is committed to one antibody specificity.

The breakthrough of hybridoma technology has been more remarkable than the advent of new scientific theory and has modernized immunology in a matter of few years.

6. Resealed Erythrocytes:

Erythrocytes suspended in a hypotonic medium, swell to about one and half times their normal size and the membrane ruptures resulting in the formation of pores with diameters of 200-500 Å. The pores allow equilibration of the intra and extra cellular solutions. If the ionic strength of the medium is made to isotonic and the erythrocytes are incubated at 37 °C, the pores will close and cause the erythrocytes and to use this system for targeted delivery by means of intravenous injection.

The advantage of this drug carrier that they are biodegradable, biocompatible and nonimmunogenic, exhibit flexibility in circulation time depending on their physiochemical properties, the entrapped drug is protected from immunologic detection and chemical alteration of drug is not necessary. Resealed erythrocytes can be targeted selectively to either the liver or spleen, depending on their membrane characteristics. The ability of resealed erythrocytes to delivery drugs to the liver or spleen can be viewed as a disadvantage in that other organs and tissues are inaccessible.

7. Liposomes:

Liposome is a spherical vesicle of lipid bilayers encircles an aqueous compartment typically range in diameter from 250Å to several nm. The lipid generally used is phospholipids, glycolipids, sphingolipids and sterols have also been used to prepare liposomes. Liposomes employed for drug delivery are usually suspended in a solution.
In recent years, liposomes have been broadly studied for their ability to serve as carriers for delivery of drugs, antigens, enzymes, hormones and other biologicals. Since liposomes are composed of naturally stirring substance they have the marked advantage of being nontoxic and biodegradable. Biological materials encapsulated within liposomes are protected to various extents from immediate degradations \textit{in vivo}. This property promotes the delivery of entrapped drugs to the target site through preventing a premature drug release after administration.

**Limitations of TDDS [Wirth M \textit{et al} (1998)]:**

- TDDS such as liposomes, released erythrocytes and platelets shows serious instability problems.
- Even though monoclonal antibodies show very high degree of site specificity the selection and isolation process are too difficult.
- If the particle size is high, they may be rapidly cleared by RES.
- Monoclonal antibodies may sometimes cause unwanted antigen-antibodies reaction which leads to severe consequences.
- Microspheres of particles size more than 50µg can lead to problem of thromboembolism in systemic circulation.
- Once administered the drug cannot be withdrawn if an undesirable action is precipitated or if the drug is no longer needed.
- Most of such system is administered by subcutaneous or intraperitoneal route. The carrier’s polymer in use should be sterile, nonirritating, hydrogen free, biocompatible and biodegradable in to nontoxic compounds within an appropriate time, preferably close to duration of action.
- The products which tend to remain intact may become accumulated at some sites. If this occurs slow release of drug from dosage form leads to a high localized concentration of drug which causes local toxicity.
• Drugs having $t_{1/2}$ 1hr or less is difficult to formulate as controlled release formulation. The high rates of elimination of such drugs from the body require an very large maintenance dose which offer 8-12 hrs of continuous therapy.

• As these products normally incorporate large amount of drug there is possibility of unsafe over dosage if the product is indecently made.

**Merits of TDDS:**

1. Targeting of the drug molecule towards the tissue or organ reduces the toxicity to the normal tissues.

2. Increased bioavailability.

3. Better treatment of many chronic illness where symptom break through occurs when the plasma level of the drug falls below the MEC.

4. The drug is protected from first pass metabolism and GI degradation.

5. Improved patient compliance can be achieved due to decrease in amount and frequency of dose administered.

6. Bio compatibility can be well achieved.

7. Maintenance of therapeutic action of the drug over night.

8. Systemic and local side effects are successfully reduced due to the reduction in the total amount of drug.

9. Magnetically controlled system can be used for targeting the drug towards superficial tissues.

10. Economic savings can be claimed due to reduction of total amount of drug used.

**Application of TDDS:**

- Red blood cells, leukocytes, lymphocytes and fibroblasts have also been used as potential delivery carriers for drugs. They have an advantage of inherent
biocompatibility, but they cannot cross barriers and cannot easily fuse with other cells. Erythrocytes have been identified as possible carriers for methotrexate and adriamycin.

- Many of the more biocompatible polymers can be used as small soluble molecular drug carriers or they can be assembled as both soluble and particulate drug vehicles. Large amount of drugs or agents can be incorporated through non-covalent forces into their assemble polymers. These particulate systems are best utilized as sustained release vehicles.

- Bovine albumin or bovine serum albumin and human serum albumin have been extensively investigated for target and sustained delivery of cancer chemotherapeutic agents.

- The intraperitoneal administration of microspheres sustained the drug release over a period of time.
SOLID DOSAGE FORMULATIONS [Metha, R. M. (2011)]

The solid dosage forms are available mostly in unit dosage forms, (consisting of doses which are taken by numbers), such as, tablets, capsules, pills, pastilles, lozenges, cachets or powders. When drugs are to be administered orally in dry state, tablets and capsules are the most convenient dosage form. They are effective and patients have no problem in their handling and administration. Some solids are packed and supplied in bulk powder. The bulk powders meant for external use are dusting powders, insufflations, snuffs and tooth powders. The bulk powders meant for internal use are supplied either as granules or fine powder.

POWDER

A pharmaceutical powder is a mixture of finely divided drugs and/or chemicals in dry form. These are solid dosage form of medicament which is meant for internal and external use. They are available in crystalline or amorphous form. The particle size of powder plays an important role in physical, chemical and biologic properties of dosage forms. There is a relationship between particle size of powder and dissolution, absorption and therapeutic efficacy of drugs.

Advantages of powders

1. Powders are one of the oldest dosage form and are used both internally and externally.

2. Powders are stable when compared to liquid dosage form.

3. It is easy for the physician to prescribe a specific amount of powdered/medicament depending upon the need of the patient.

4. The chances of incompatibility are less as compared to liquid dosage form.

5. The onset of action of powdered drug is rapid as compared to other solid dosage forms, e.g. tablets, capsules or pills. Due to smaller particle size of powder, it gets dissolved easily in body fluids. This rapid dissolution increases the blood concentration in the shorter time and hence the drug action is produced in a shortest period.
6. Powders are easier to carry than the liquid dosage forms.

7. Large quantity of powdered drugs can be easily administered to the patient orally by dissolving or mixing the powder in a suitable liquid.

8. Small children and elderly patients cannot swallow solid dosage forms, such as, tablets and capsules. They can easily take the powdered drug as such or dispersed in water or any other liquid.

9. Powders are more economical as compared to other solid dosage form, because these are prepared extemporaneously without involving any special machinery and techniques.

Disadvantages of powders

1. Drugs having bitter, nauseous and unpleasant taste cannot be dispensed in powdered form.

2. Deliquescent and hygroscopic drugs cannot be dispensed in powder form.

3. Drugs which get affected by atmospheric conditions are not suitable for dispensing in powder forms.

4. Quantity less than 100 mg or so, cannot be weighed conveniently on dispensing balance.

GENERAL METHOD OF PREPARATION OF POWDER

During powdering, weighing and mixing, there is a loss of powders, which cannot be avoided. Therefore, calculate the quantity for one extra powder than required. Sometimes a fraction of weight is the required quantity to be weighed and dispensed. In such cases a suitable number of extra powders may be calculated to produce directly weighable quantity.

The dispensing balance is not very sensitive. It is difficult to weigh the quantity less than 2 grain or 100 mg on the dispensing balance. Therefore, the quantities weighing less than 2 grain or 100 mg must be triturated with suitable diluents such as lactose, so that the quantities are made weighable on dispensing balance.
The crystalline substances are powdered separately and then weight the required quantity of each ingredient. Mix all the ingredients in the ascending order of their weights and mix thoroughly to obtain a homogeneous powder. Weight the required number of powders and wrap in the papers. The hygroscopic, deliquescent and volatile substances require to be double wrapped. The inner wrapper is usually made from wax paper, so as to prevent volatilization and absorption of moisture from the atmosphere.

MIXING OF POWDERS

The powers may be mixed by any one of the following methods:-

1. Spatulation
2. Trituration
3. Geometric dilution
4. Sifting
5. Trumbling

1. Spatulation: In this method, mixing of powders is done by the movement of a spatula throughout the powders on a sheet of a paper or on a porcelain tile. The method is very useful in mixing:-

   a) Small quantity of powder.

   b) Solld organic substances that covert into liquid or form eutectic powders, when in close and prolonged contact with one another since very little compression or compact results.

   The method is not suitable for large quantities of powders or for powders containing one or more potent substances because homogenous blending may not occur.

2. Trituration: it is used both to reduce particle size and mix powders. If particle size reduction is desired along with mixing of powders, a porcelain mortar with a rough inner surface is preferred to a glass mortar with a smooth working surface. A glass mortar may be preferred for chemicals that may stain a porcelain surface and for simple mixture cleans more readily after use.
3. **Geometric dilution:** The method is used when potent substances are too mixed with a large amount of diluents. The potent drug is placed upon an approximately equal volume of the diluents in a mortar and the substances are slightly mixed by trituration. A Second portion of diluents equal in volume to the powder mixture in the mortar is added and trituration is repeated. The process is continued, adding diluents equal in volume to the mixture in the mortar at each step, until all the diluents are incorporated.

4. **Sifting:** the powders are mixed by using sifters. This process produces a light fluffy product and is generally they are not employed for incorporation of potent drugs into a diluents base.

5. **Tumbling:** here mixing of powders takes place in a big container rotated by an electric motor. These blenders are widely employed in industry as large volume powder mixers.

**Packing of powers**

Powders may be wrapped in paper or dispensed in bulk powder in a wide mouth container.

**Wrapping of powders:** white glazed paper is generally used for wrapping. The wrapping should be done on a clean tile or large sheet of a glazed paper to protect the product. The powders are wrapped in the following manner.

1) Cut the required number of powder papers in a suitable size i.e. 120 mm x 100 mm.

2) Arrange the papers with their long edges and turn up the long edge of each paper to about one-seventh of its width.

3) Weight out the powder and place it in the centre of each paper.

4) Place the unfolded edge of paper under the folded edge so that it lies exactly in fold of the first fold. Then give another fold to the first fold bringing it in centre.

5) Finally bend ¼ th of each end sharply to bring the ends in the middle of the powder on a plain side.
6) Firm the creases using a clean flexible spatula but avoid excessive pressure which would cause caking of encloses powder.

7) The packets are arranged in pairs, flap to flap and restrained. With an elastic band.

8) The wrapped powders are send in an envelope if the numbers of powders are less than six. In case of large quantity, the boxed are preferred.

**Double wrapping** white glazed paper gives inadequate protection to volatile, hygroscopic and deliquescent substances unless it is lined with waxed paper. The lining is cut a few mm smaller each way than together. In exceptional cases, each packet may be wrapped externally in aluminium foil.

**Labeling** Patient should be instructed that individual powder should be dispersed in a little water or placed on the back of the tongue before swallowing.

**CLASSIFICATION OF POWDERS**

The powders are classified as

1. Bulk powder for internal use
2. Bulk powder for external use
3. Simple and compound powder for internal use
4. Powders packed in cachets and capsules
5. Compressed powders (tablets)

1. **Bulk powder for internal use**

   Powders are dispensed as such without dividing in large quantity, when dosage amount is not an important factor is not a important. They are dispensed in wide-mouthed bottless that permit easy removed of a spoonful of powder. e.g., are antacid and laxatives etc.

2. **Bulk Powders for External use**
Bulk powders meant for external use are non potent substances. These powders are supplied in cardboard, glass or plastic containers, which are often designed for the specific method of application. The dusting powders are preferably supplied in perforated or sifter top containers. The container should bear a label indicating that the powder is meant for external application.

The bulk powders which are commonly used for external applications are as follows:-

a) Dusting powders
b) Insufflations
c) Snuffs
d) Dentifrices

(a) Dusting powders:

These are meant for external application to the skin and are generally applied in a very fine state of subdivision to avoid local irritation. Hence, dusting powders should be passed through sieve no.85 to enhance their effectiveness.

Dusting powders are of two types:

(i) Medical
(ii) surgical

Medical dusting powders are used mainly for superficial skin treatments. Whereas surgical dusting powders are used in body cavities and also on major wounds as a result of burns and umbilical cords of infants. Surgical dusting powders must be sterilized before their use, whereas medical dusting powders must be free from pathogenic microorganisms.

Dusting powders are generally prepared by mixing two or more ingredients one of which must be starch, talc or kaolin as one of the ingredients of the formulation. Talc and kaolin are more commonly used because these are chemically inert. However, since such ingredients by dry heat method (160 °C for 2 hours) before their use.

The dusting powders are mainly used for their antiseptic, astringent, absorbent, antiperspirant and antipruritic action.
The dusting powders are dispensed in sifter-top containers or aerosol containers. The pressure aerosol containers are costlier than the sifter top containers but they help in the easy application of the preparation. Dusting powders may also apply with powder puff or sterilized gauze pad.

Dusting powders are generally considered to be nontoxic but the inhalation of its fine powdered ingredients by infants may lead to pulmonary inflammation. So proper care must be taken while handling these preparations.

(b) Insufflations:

These are medicated dusting powders meant for introduction into the body cavities such as nose, throat, ears and vagina with the help of an apparatus known as ‘insufflator’. It sprays the powder into a stream of finely divided particles all over the size of application. The following difficulties are however generally faced while using the insufflators.

(i) It is difficult to obtain a measured quantity of the drug as a uniform dose.
(ii) It gets blocked when it is slightly wet or the powder used is wet.

Insufflations should be in finely divided powders so that a stream of fine particles of medicaments gets applied to the site of application. Nowadays, the insufflations are available in the form of pressure aerosols. These are used for administration of potent drugs. This method has the advantage of excellent control of dose through metered valves. Moreover, it also protects the product from external environment.

Insufflations are used to produce a local effect, as in the treatment of ear, nose and throat infection with antiseptic or to produce a systemic effect from a drug that is destroyed in the gut.

(c) Snuffs:

These are finely divided solid dosage forms of medicament which are inhaled into nostrils for its antiseptic, bronchodilator and decongestion action.

Snuffs are dispensed in flat metal boxes with hinged lid.

(d) Dentifrices (tooth powders):
These are used for cleaning the surface of the teeth by using tooth brush. They contain a suitable detergent or soap, some abrasive substance and a suitable flavor. The abrasive substances for e.g., calcium sulphate, sodium carbonate magnesi um carbonate, and sodium chloride are used in fine powder. A strong abrasive substance should however not to be used as it may damage the tooth structure.

3. Simple and compound powders for internal use

In this form of powder, each individual dose is enclosed in paper. The number of ingredients may be one (simple powder) or more than one (compound powder). The minimum quantity of each powder should not be less than 100 mg so that it can be handled conveniently by patient and can be weighed accurately.

While dispensing simple and compound powders following rules should be observed.

1. Weigh out material for one power more than required.

2. If this produces quantities in fraction which is not directly weighable, calculate for sufficient extra powders to produce directly weighable quantity.

3. If the total weight of each powder includes a fraction of a gram, add the calculated amount of lactose to make each powder directly weighable.

4. If the powder contains a liquid, the weight of which is known, adjust the mixed material by the addition of lactose, so that each powder is directly weighable.

(a) Simple powder:

A simple powder contains only one ingredient either in crystalline or amorphous form. If they are in crystalline form, they are converted to fine powder, weighed the powder and divided into number of does and wrapped as individual doses.

(b) Compound powders:
Compound powders contain more than two different substances, they are added together and then they are divided into required number of individual doses which are dispensed into each powder paper.

4. **Powders enclosed in cachets**

Cachets are the solid unit dosage form of drugs. These are moulded from rice paper, which is made by pouring a mixture of rice flour and water between two hot, polished, revolving cylinders. The water evaporates and a sheet of wafer is formed. Cachets are used to enclose nauseous or disagreeable powders and are available in different sizes to hold drugs from 0.2 - 1.5 g of powder.

Cachets are also known as wafer capsule. They are quite hard to swallow as such but they are softened by dipping in water for a few seconds and then placed on the tongue and swallowed with a draught of water. After swallowing cached gets disintegrate and drug is released.

**Advantages of cachets**

1. They can be made easily because no complicated machinery is required.

2. They disintegrate quickly in the stomach.

3. The drug can be easily dispensed in cachets.

4. Large doses of drug can be swallowed by using caches, because once they get soften by immersion in water, even large sized cachets can be swallowed readily without any difficulty.

**Disadvantages of cachets**

1. They must be softened before swallowing.

2. They are easily damaged.
3. They cannot protect the enclosed drug from light and moisture.

4. They shell of cachets are fragile, so the drug contents cannot be compressed in cachets.

5. They are not suitable for filling the drug by large-scale machinery.

6. They occupy more space than the corresponding sizes of capsules and tablets.

**Cachets are of two types**

a) Wet seal cachets
b) Dry seal cachets

The B.P.C includes two cachets, sodium aminosalicylate and sodium aminosalicylate with isoniazid. These drugs have unpleasant taste. The daily dose of sodium aminosalicylate is up to 20 g which is normally taken in 1.5 g cachets.

**Packing and storage of cachets** the cachets are packed in boxes or tins in which they are placed on their edges or lying flat. The container containing cachets should be labeled with a direction for its use, “Immerse in water for a few seconds and then swallow with a draught of water.”

5. **Tablet triturates (Moulded Tablets)**

These are powders moulded into tablets. Moulded tablets are flat, circular disc and usually contain a potent substance which is mixed with lactose, dextrose or some other suitable diluents.

The apparatus used for the preparation of tablet triturates is made of stainless steel or plastic. It consists of an upper perforated plate which is having an exactly the same number of holes as that of number of pegs in a lower plate. The lower plate also has two large pegs which ensure correct fitting of the plates. The moulds are available in several sizes having a capacity ranging from 30 to 250 mg. Generally 50 to 250 tablet triturates can be prepared at a time from a tablet triturate mould.
The solid medicament and diluents are finely powdered and converted into a stiff paste with the help of alcohol 60%. The upper plate of the apparatus is placed on a clean tile and the paste is pressed into the holes with a spatula. While filling the holes of the upper plate, every care is placed over the lower plate. A little pressure is applied over the top plate which will force the plate move downward, leaving the mould tablets on the projected pegs. The ejected tablets are spread in a single layers on clean surface and dried and dried in a hot air oven or by keeping in warm place.

Nowadays automatic tablet triturate machines are available which can prepare 2500 tablet triturates per minute.

**Calibration of the mould:** The exact capacity of each mould must be determined before use. This is done by taking about 7.5 g of lactose in a mortar. Make into a stiff paste with 60 per cent alcohol. Fill the perforations and press out the tablets. Dry them for at least 24 hours, to ensure complete volatilization of the alcohol. Weigh only those tablets which are smooth and perfect. Calculate the weight for the whole number.

**Displacement value of medicaments:** it means find out the proportion of medicament which displaces one part of lactose. Normally, when the proportion of medicament in a tablet triturate is small, however, when the proportion is large and its density differs consider ably from that of lactose, a suitable correction is made in order to ensure the correct content of medicament must be present in each tablet triturate.

**Containers** The Tablet triturates are packed in an air-tight container to protect from moisture. It is better to pack it in a single row in a narrow tube sealed with plug type closure.

**Storage** The tablet triturates are stored in a cool place.

**DISPENSING OF POWDERS INVOLVING SPECIAL PROBLEMS**
A number of problems arise while dispensing a powder containing volatile substances, hygroscopic and deliquescent powders, eutectic mixtures, efflorescent powders, liquids, explosive substances and potent drugs. So special considerations are done while dispensing such powders.

**Volatile substances** certain vegetable powders contain volatile oils. To prevent the loss of volatile oils, these vegetable drugs must be powdered lightly in a mortar. Similarly the volatilization of substances like menthol, camphor and essential oils may take place on incorporation in powders. This is prevented or at least minimized by the use of double wrapping. The inner wrapper should be of wax paper and other wrapper may be of any thick paper.

**Hygroscopic and deliquescent powders** the powders which absorb moisture form the atmosphere are called hygroscopic powders. But certain powders absorb moisture to such a great extent that they go into solution and are called deliquescent powders. Examples of such substances include ammonium chloride, iron and ammonium citrate, pepsin, phenobarbitone, sodium bromide, sodium iodide, potassium citrate, zinc chloride etc.

Such substances are usually supplied in the form of granules in order to expose less surface area to the atmosphere. These powders should not be finely powdered. Such powders should be double wrapped, in humid weather or when dealing with every deliquescent substance, further wrapping in aluminium foil or plastic cover is advisable.

**Efflorescent powders** some crystalline substances liberate water of crystallization wholly or partly on exposure to humid atmosphere or during trituration and thus become wet or liquefy. Wet or liquefy. Example of such substances includes caffeine, citric acid, ferrous sulphate etc. This difficulty may be overcome by using either corresponding anhydrous salt or an inert substance may be mixed with efflorescent substance before incorporation with other ingredients.

**Eutectic mixtures** when two or more substances are mixed together they convert into liquid due to the formation of a new compound which has a lower melting point than room temperature. Such substances are called eutectic substances. Example of such substances includes menthol, thymol, camphor, phenol, salol, aspirin, phenacetin, chloral hydrate etc.
These substances can be dispensed by two methods:-

i. Dispense as separate set of powders with directions that one set of each kind shall be taken as a dose.

ii. An equal amount of any of insert absorbent like magnesium carbonate, light magnesium oxide, kaolin, starch, lactose, calcium phosphate etc. may be mixed with eutectic substance and then blended together lightly with a spatula on a sheet of paper. When in addition to liquefying substances, other ingredients are also present, the liquefiable substances should first be triturated together to form the eutectic mixture. Then the remaining ingredients of the prescription are incorporated and mixed together.

**Liquids** in certain prescriptions, the liquid medicaments are also incorporated in dispensing powders. If the quantity of the liquid is small, it may be triturated with an equal amount of powder, then the rest trituration. If the quantities of liquids are large than an absorbent must be added.

Liquid extracts and tinctures are evaporated to syrupy mass in a china dish. Lactose or some other suitable diluents is mixed and then continue the evaporation do dryness. Mix other in gradients. Another alternative is to substitute a liquid extract by a dry extract.

**Explosive substances** when an oxidizing substance, such as potassium chlorate is mixed with reducing substance, such as tannic acid, there are chances of violent explosion which may lead to serious consequences.

**Potent drugs:** the substances having a maximum dose of less than one gain (60mg) and poisonous substances are regarded as the potent drugs. Small quantities of potent drugs should not be weighed on dispensing balance. The potent drug is triturated with some diluents such as lactose in definite proportion to make a weighable quantity for each powder. Generally potent drug is reduced to fine powder and to this an equal quantity of diluent is mixed by thorough trituration in a mortar. Then the rest of diluent is incorporated in successive portions with thorough trituration each time. The whole of the diluent should never be added to the drug at one time otherwise the potent drug will not be mixed uniformly and thoroughly in the diluent.
Granular Powders  There are certain solid medicaments which are required to be administering orally in large doses. They cannot be prescribed in tablets and capsules because a large number of them will medicaments are difficult to dispense as such in powder form because of its bitter, nauseous and unpleasant taste. It is also difficult to convert it into liquid dosage form due to stability problem. The only alternative left is to convert these powdered medicaments into granular form.

The solid medicaments are mixed with sweetening, flavoring and colouring agent. A suitable granulating agent is added to moisten the powders so as to make a coherent mass. Pass the coherent mass through sieve number 10 to make granules. Dry the granules in an hot air oven at a temperature not exceeding 60 °C. The dry granules are passed through sieve number 20 and store in a dry

Nowadays, various antibiotics like erythromycin, phenoxyethyl penicillin, ampicillin etc., which are unstable in solution are prepared in the dry granular form in which dry ids mixed with suspending, sweetening, flavorings, colouring and granulating agents. The granules are prepared and packed in a special type of bottles with a specific direction on its label for the patient to add specified amount of freshly boiled and cooled water to dissolve it or shake well to from a homogenous solution. The label should also state the time limit within which the reconstituted preparation should be consumed.

Effervescent granules  Effervescent granules are the class of solid dosage containing medicament prepared by a special method, meant for internal use. They contain a medicament mixed with citric acid, tartaric acid and sodium bicarbonate. Sometimes saccharin or sucrose may be added as a sweetening agent. Before administration, the desired quantity is dissolved in water; the acid and bicarbonate react together producing effervescence. The carbonated water produced from the release of carbon dioxide serves to mask the bitter and saline taste of drugs. Moreover, carbon dioxides stimulate the flow of gastric juice and helps in the absorption of medicament.

Method of preparation: There are methods of preparation of effervescent granules:-

i. Heat method
ii. Wet method

i. **Heat method:** A Large porcelain or stainless steel evaporating dish is placed over the boiling water bath. The dish must be sufficiently hot before transferring the powder into it, to ensure liberation of the water of the crystallization from the citric acid. If heating of the dish is delayed, the powder which is added to it, will heat up slowly and the liberated water of crystallization will go on evaporating simultaneously. As a result, sufficient water will not be available to make a coherent mass.

The water needed for granulation is provided from two sources:-

(i) From water of crystallization of citric acid. The citric acid contains one molecule of water of crystallisation which is liberated during heating.

(ii) The water produced from the reactions of citric acid and tartaric acid with sodium bicarbonate.

\[ 3\text{NaHCO}_3 + \text{C}_6\text{H}_9\text{O}_7\cdot\text{H}_2\text{O} \xrightarrow{\Delta} \text{C}_6\text{H}_2\text{Na}_3\text{O}_7 + 3\text{CO}_2 + 3\text{H}_2\text{O} \]

\[ 2\text{NaHCO}_3 + \text{C}_4\text{H}_6\text{O}_6 \xrightarrow{\Delta} \text{C}_4\text{H}_4\text{Na}_2\text{O}_6 + 2\text{CO}_2 + 2\text{H}_2\text{O} \]

Generally, heating stage takes 1 to 5 minutes. The damp mass is then passed through a size. Dried in an oven at a temperature not exceeding 60 °C and the packed in an air tight container.

Loss of weight occurs during granulation as a result of:-

(i) Evaporation from the damp mixture

(ii) Loss of carbon dioxide

ii. **Wet method:** In this method, the mixed ingredients are moistened with a non-aqueous liquid to prepare a coherent mass which is then passed through a number 8 sieve and dried in an oven at a temperature not exceeding 60 °C. The dried granules are again passed through the sieve to break the lumps which may be formed during. Granules are packed in air tight containers.
PILLS

Pills are oral unit dosage form. These are small spherical or ovoid masses which are required to be made at the dispensing counter. These are rarely prepared extemporaneously nowadays. No formulae for pills are given in the latest edition of Indian pharmacopoeia these are also not prescribed by the physicians.

Essential requirements for a good pill

Following are the essential requirements for a good pill:-

Solubility: pill should readily disintegrate in the intestinal tract. The majority of freshly prepared pills fulfill this on condition, but once they become dry and hard with the passage of time, they are less soluble than become dry and hard with the passage of time; they are less soluble than freshly made pills. Sometimes they are less soluble than freshly made pills. Sometimes they pass through the intestinal tract without disintegration. In large-scale manufacture, Pills are usually coated with sugar and talc. The coating is possible only on dry and hard pills.

Uniformity in weight: The pills should be uniform in weight in order to ensure accurate dosage.

Homogeneity: the medicament should be thoroughly and evenly distributed thoroughly the pill mass in order to ensure accurate dosage.

Shape and size: pills should e round or oval in order to facilitate swallowing. Pills should not be too large or too mall for convenience in handling and swallowing. B.P.C gives a general recommendation hat pills should not be less than 3 mm in diameter for pills weighing up to 1 grain (60 mg) and not more than 8 mm for pills weighing an out 5 grains (300 mg).

Elegance and tastelessness: pills should be coated to mask taste and to improve elegance. Sugar coating or varnishing does not delay disintegration because these coatings are quickly washed off is the intestinal tract.

Formulation of Pills
Pills are made from pill masses which may contain three classes of substances:-

1) The medicinally active ingredients.

2) A diluent which is required in case the quantity of active ingredient is very small.

3) Excipients which are required to from a firm, plastic and adhesive pills mass. The commonly used excipients are:

   (i) **Binding agent:** which is used to bind the particles to assist adhesion e.g. acacia (5-10%), tragacanth (5%), compound to assist acacia (a mixture of equal parts of acacia and tragacanth), syrup of liquid glucose, beeswax, beeswax, lanolin and wool fat? Lanolin is used in combination with kaolin or oxidizing substances and for pills containing combination with kaolin for oxidizing substances and for pills containing oils whereas wool fat is used in combination with kaolin for hygroscopic substances.

   (ii) **Absorbing Agent:** This is necessary in pills containing oily ingredient e.g., kaolin, liquorices root powder, curd soap and hard soap.

   (iii) **Fluid or semi solid:** This is required to render the pill mass plastic e.g., syrup of liquid glucose.

**Preparation of pills**

The following steps are required to prepare good quality of pills.

1. Preparation of pill mass: pill mass is prepared as follows:-

   (i) Mix all the solid ingredients in ascending order of weight in a pill-mortar.

   (ii) Add any liquid ingredient and mix thoroughly by trituration.

   (iii) Add the fluid or semi-solid excipient, a little at a time with trituration until proper pill mass is formed. In general, the mass is completed when it tends to peel from the sides of the mortar. Remove the mass from the mortar and kneaded between the fingers.
2. Rolling, cutting sand rounding: the weighed quantity of pill mass is then rolled out on the flat board of the pill machine to the exact length for the number of pills required. The pill pipe thus formed should be perfectly cylindrical in order to prepare pills of equal side. The pill pipe is cut into equal part with the help of cutter. The cutter is usually dusted with powder to prevent adhesion of the pills. Liquorice powder is used from dark pills and kaolin for light pills. The cut part of pill pipe is made round with pill rounder. Talc is used to dust the pills to make them rotate easily and smoothly. The rounded pills are then placed one pill-rounder and gently rubbed with a powder paper to remove the talc. Dispense the pills in a pill ox or subjected to coasting if it is required.

3. **Coating:** coated pills are often more stable than the uncoated pills. They are more elegant. The following types of coating are generally done on pills:-

   (i) **Varnishing:** The varnish used is a sandarac varnish which is prepared from the following formula:-

   \[
   \begin{align*}
   \text{Sandarac} & \quad 1 \text{ part} \\
   \text{Absolute alcohol} & \quad 2 \text{ parts} \\
   \text{Ether} & \quad 2 \text{ parts}
   \end{align*}
   \]

   Dissolve sandarac 1 absolute alcohol and ether in a closed bottle by occasional shaking. Decant the clear liquid to remove debris.

   (ii) **Sugar – Coating:** This coating is not easily applied by hand. It is done by using a special apparatus on a large scale. Sugar is applied in the form of dilute syrup. The following material is required in small scale work:-

   \[
   \begin{align*}
   \text{Mixture A} & \quad \text{Syrup, Mucilage of acacia} \quad \text{Equal parts} \\
   \text{Mixture B} & \quad \text{Sugar in fine powder, Starch} \quad 7 \text{ parts, 1 part}
   \end{align*}
   \]
**Method:** spread sufficient quantity of mixture to be covering the bottom of a covered pot. Moisten the pills with mixture and dropped them into a pot ad rapidly rotated for about a minute. Transferred the pills into a clean pot and again rotated. This is done to detach any loosely held powder. The pills are then allowed to dry for about 10 minutes. This process is repeated 2-3 time to give a dense white finish to the pills. After drying the pills are finally polished by rotating them in a clean pot, containing a small ball of spermaceti.

(iii) **Enteric coating:** This coating is done to prevent the pills from disintegration in the stomach but to break up in the intestine. Such type of coating is done in following cases:-

a) The drug causes irritation of the mucous membrane of the stomach.

b) The drug get decomposed or destroyed by acidic medium of the stomach.

c) The action of medicament is required in the intestine e.g. anthelmintics and amoebicides are required to be absorbed from intestines to have the maximum effect at the site of parasitic worms and protozoa.

d) The drug absorption is better in the intestine.

The material communal used for enteric coating of pills are keratin, shellac, salol, and stearic and acid. Gelatin treated with formaldehyde has also been used. Nowadays cellulose acetate phthalate solution in acetone is commonly used for enteric coating of pills.

The solution of enteric coating material is prepared in volatile organic solvent and numbers of coatings are given as per requirements in the same manner as given in varnishing.

4. **Packing:** pills are finally packed in shallow circular pill boxes with flanged edges. A disc of wax paper of a thin circle of cotton wool should be placed on top and bottom. The box
should be sufficiently large to take all the pills in one layer to prevent them in lousing their shape.

**PASTILLES**

Pastilles are solid medicated preparations intended to dissolve slowly in the mouth. They are softer than lozenges. They consist of a base of glycogelatin containing a medicament in solution suspension. They are allowed to dissolve to dissolve slowly in the mouth to have a prolong local action of medicament.

Glycogelatin pastille base B.P.C is commonly used for preparing the pastilles. But the following improved formula is used to prepare pastilles of good qualities:

<table>
<thead>
<tr>
<th>Component</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelatin</td>
<td>1 part</td>
</tr>
<tr>
<td>Glycerin</td>
<td>2 ½ part</td>
</tr>
<tr>
<td>Water</td>
<td>2½ part</td>
</tr>
</tbody>
</table>

**Preparation of pastilles**

The pastilles are made by using following two types of moulds:

1. **Metal moulds:** These consist of a number of saucer-shaped pieces of metal fixed on a saucer-shaped pieces of metal fixed on a plate. The cavities are lubricated with liquid paraffin. The melted bases along with medicament are filled to the brim to ensure uniformity size.

2. **Starch moulds:** These are used in large-scale preparation. Trays measuring about 0.6 m x 0.9 m x 50 mm are fitted with dried are attached several rows of vulcanized rubber pastille shapes. Each tray is filled with dried starch starch corresponding to the rubber shapes. The lid is pressed down and then carefully raised. The depressions are formed in the starch corresponding to the rubber shapes. The melted pastille mass is then filled into these depressions and allowed to harden. The adherent starch is then removed from pastilles by rapid washing and then dried.
The capacity of the mold is determined by filling three or four depressions with the melted base, allow to set and then find the mean weight. After finding the capacity of the mould the pastilles are prepared.

**Containers** pastilles are dispensed in flat boxes with hinged lids which are made of metal. The box should be lined with the pastilles placed in layers. Each layer is being separated by a piece of waxed paper or metal foil.

**Storage** Pastilles should be placed in a cool and dry place.

**Uniformity of weight** Select 20 pastilles and find the average weight of a pastille. Weigh individual pastille. No pastille should deviate from the average weight by more than percent and not more than one of them by more 10 percent.

**LOZENGES**

These are solid preparations consisting of sugar and gum medicated with a substance usually having a local action in the mouth and throat. They are also used for the slow administration of indigestion and cough remedies. They are also called trouches. They are prepared either by moulding and cutting or by compression. But nowadays they are prepared by compression method of preparation of tablets.

**Moulded lozenges**

These are usually prepared by mixing the medicaments in powder or solution, with the following base:

- Sucrose, in fine powder \(100 \text{ g}\)
- Acacia, in fine powder \(7 \text{ g}\)
- Water \(\text{a sufficient quantity}\)

Powdered acacia is included in the entire lozenges official in B.P.C because it binds the ingredients to form a plastic mass which can be rolled and cut without crumbling. The quantity
of ingredients should be enough to produce about 15 per cent more lozenges than required i.e., in order to dispense 80-90 lozenges, sufficient mass should be prepared for 100 lozenges.

**Apparatus:** Moulded lozenges are prepared with the help of lozenge board. It consist of two slightly tapered bars fit into the sloping groove on each side of a thick board, above which they project to a height which is slightly altered by moving them along the grooves. On the underside of the bars are numerous saw cuts which fit over plates fixed across the ends of the grooves, thereby retaining the bars in the desired position.

The roller rides on the projecting edge of the bars and rolls out the lozenge mass to uniform thickness, which can be finely adjusted as stated above.

The lozenges are cut from the rolled cake by means of punches.

**Method**

1. Knead the ingredients of lozenges in a mortar to produce a mass of the required consistency. Weigh the mass. Divide it with number of lozenges to be prepared to find the average weight of each lozenge.

2. Roll out the mass on lozenge board previously dusted with powdered talc to uniform thickness. Cut a trial lozenge and record its weight. It should be similar to average weight of each lozenge. If it is above or below, the metal bars must be adjusted accordingly and the mass re-rolled until the weight of the trial lozenge is exactly the desired average weight.

3. Cut out from the cake as many lozenges as possible. Re-Mass and re-roller the remaining mass left to make more lozenges.

4. Place the lozenges on a slab dusted over with starch and dry skin a hot air oven at 40 °C for 24 hours in order to obtain uniform hardness.

**Compressed lozenges**
These are prepared by the method used in the preparation of tablets by compression. Heavy compression is necessary in order to ensure slow disintegration in the mouth. These generally contain a sweetening agent, a flavoring agent and a substance which produces a cooling effect along with medicaments.

**Uniformity of weight** Select 20 lozenges at random and find the average weight of lozenges. No lozenge should deviate from the average weight by more than 15 per cent and not less than 10 per cent.

**Containers** Lozenges should be packed in an air tight containers or strip packed.

**Storage** Lozenges may soften on storage and become mouldy in damp conditions. Lozenges should be kept in a cool dry place.

**CAPSULES**

Capsules are a solid unit dosage form intended orally in which the drug substance is enclosed in a water soluble shell or an envelope. A capsule shell is made from gelatin. The capsules are available both as hard capsule and soft capsule.

**Advantages of capsules**

A capsule is a very popular dosage form these days due to the following advantages:

1. The drugs having unpleasant odour and taste can be administered by enclosing them in a tasteless shell.
2. They are smooth, become very slippery when moist and can be easily swallowed.
3. They are economical.
4. They are easy to handle and carry.
5. The capsules release the medicament as and when desired in gastro-intestinal tract.
6. Capsules are made from gelatin and hence they are therapeutically inert.
They are attractive in appearance.

Capsules are available in various sizes and therefore suitable for all types of medicaments and for administering the desired quantity of medicament in a single dose.

Micro-capsulation provides the sustained released dosage form.

**Disadvantages of capsules**

1. The hygroscopic drugs cannot be filled in capsules. They absorb water present in the capsule shell and hence make it very brittle.

2. The concentrated preparations which need previous dilution are unsuitable for capsules because it may lead to irritation in stomach if administered as such.

**TYPES OF CAPSULES**

Capsules are available in two types

1. Hard gelatin capsules
2. Soft gelatin capsules

**1. Hard Gelatin capsules**

These are used for administration of solid medicaments. The capsule shell is prepared from gelatin, colour and titanium dioxide to make it opaque. It consists of two parts i.e., body and cap. The powdered material is filled into the cylindrical body of the capsule and then the cap is placed over it. The empty capsules are available in various sizes. They are numbered according to the capacity of the capsules. The number starts from 100 and goes up to 5. The approximate capacity of a capsule with respect to its number is given in the following table

**Capsule number and its approximate capacity**
<table>
<thead>
<tr>
<th>Capsule number</th>
<th>Approximate capacity in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>000</td>
<td>950</td>
</tr>
<tr>
<td>00</td>
<td>650</td>
</tr>
<tr>
<td>0</td>
<td>450</td>
</tr>
<tr>
<td>1</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>250</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>

**Excipients used in the filling of capsules** while filling solid medicaments in powder form into the body of a hard gelatin capsule, the following additives, too, are included in the formulation:

1. **Diluents**: The diluents are needed in certain cases where the quantity of the medicament is too small in bulk to get it filled in the smallest available capsule size. In such cases, diluents are added to bring the medicament up to the desired bulk. The commonly used diluents are lactose, mannitol, sorbitol, starch etc. The quantity of the diluents to be incorporated depends on the dose of the medicament and the capsule size.

2. **Absorbents**: Sometimes the medicaments are physically incompatible with each other e.g., eutectic substances or hygroscopic substances. In such cases absorbents, such as oxides and carbonates of magnesium and calcium and kaolin are added to the powdered drug. These inert materials act as a protective sorbent.

3. **Glidants**: To ensure a regular flow of powder into the automatic capsule machine glidants are mixed with the medicaments. The various glidants used for this purpose are talc, magnesium stearate and calcium stearate.

4. **Antidusting compounds**: During the filling of capsules by an automatic filling machine, a lot of dust comes out of the machine. The dust is inhaled by the operator of the machine. It can pose a serious health hazard if allowed to be unchecked, especially, when the dust of the potent drugs is inhaled by the workers. To avoid this, some antidusting components, like insert edible oils, are added to the formulation.
Methods of filling the hard gelatin capsules

The capsules can be filled either by hand or by a semi-automatic device or by an automatic filling machine.

It is not easy to fill the capsules by hand because of their small size. For dispensing purpose one of the following procedures can be adopted:-

(1) Calculate the quantity of each ingredient and mix them in a mortar in ascending order of their weight. The powder is then placed on a glazed paper or glazed tile and spread it with a powder spatula so that the layer of the powder is not more than one third of the length of the capsule. The paper is held in the left hand, and body of the capsule, held in the right hand is pressed repeatedly into the powder until the empty capsule shell in the other pan of the balance as tare. The method is not suitable of granular powders that do not bed well and therefore, fall out when the inverted capsule is lifted.

(2) Place a heap of powder on glazed paper or a clean glazed tile. Hold the capsule on its side and push powder into the shell with the aid of a spatula until required weight has been enclosed.

(3) In order to fill the capsules more hygienic, a simple apparatus as shown in fig 7.5 can be used. It consists of a plastic block (A) with rows of cavities which hold the capsules and allow them to project slightly. Each row is designed to hold a different size of capsule. A plastic bridge (B) contains a row of holes corresponding in position to the cavities in any row of the block. This is used to support a long stemmed funnel so that the end of the stem of the funnel can pass into the mouth of the capsule below.

The capsule bodies are placed in the cavities in the block and a funnel of appropriate size is passes through the hole in the bridge and down into the neck of the capsule. A weighed quantity of powder is or plastic rod or piece of wire is used to break any blockage and also as a plunger to loosely compress the material inside the capsule. Place the cap on the capsule and then weigh in before sealing.
(4) A capsule filling machine (hand operated) is used for filling of large number of capsules. With a 200 hole machine, about 500 capsules can be filled in one hour. Whereas in a machine having 300 holes, about 7500 capsules can be filled in one hour.

By using above methods of filling of capsules, a small amount of the powder sticks to the sides of the capsule. Moreover the whole process involves much handling of the capsules which leaves finger prints on the capsules. Hence it is necessary to clean the capsules after filling. The filled capsules are rolled in dry towel and very lightly sprinkle liquid paraffin. By doing so the sticking material will be removed and it will impart shine to the capsules.

2. Soft Gelatin capsules

These are used for administration of liquid medicaments. Soft gelatin capsules are available in round, oval and tube like shapes. They are made from gelatin. The gelatin is plasticized by the addition of glycerin and sorbitol etc. The soft gelatin shell may contain a preservative to prevent the growth of fungi. They are used to enclose liquid medicaments-oils, suspensions, food concentrates and ophthalmic products.

Method of filling of soft gelatin capsules soft gelatin capsules are generally filled mechanically. The manufacturing of the capsule shell and the filling of the medicament take place simultaneously. Nowadays a rotary machine is used for this purpose.

**Differentiation between hard gelatin capsules and soft gelatin capsules**

<table>
<thead>
<tr>
<th>Hard gelatin capsules</th>
<th>Soft gelatin capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 The hard gelatin capsule shell consists of two parts:-</td>
<td>1 The soft gelatin capsule shell becomes a single unit after sealing the two halves of the capsules.</td>
</tr>
<tr>
<td>Body, Cap</td>
<td></td>
</tr>
<tr>
<td>2 They are cylindrical in shape.</td>
<td>2 They are available in round, oval and</td>
</tr>
<tr>
<td></td>
<td>tube like shapes.</td>
</tr>
</tbody>
</table>
3 The contents of a hard gelatin capsule usually consist of the medicament or mixture of medicaments in the form of powder, beads or granules.

4 These are prepared from gelatin, titanium dioxide, colouring agent and plasticizer.

5 Capsules are sealed after they are filled to ensure that the medicaments may not come out of the capsule due to rough handling.

3 The contents of soft gelatin capsules usually consist of liquids or solids dissolved or dispersed in suitable excipients to give a paste-like consistency.

4 These are prepared from gelatin, plasticizer (glycerin or sorbitol) and a preservative.

5 Filing and sealing of soft gelatin capsules are done in a combined operation on machines.

**Containers** capsules should be dispensed in tightly closed glass or plastic containers protected from dust and from extremes of humidity and temperature.

**Storage** capsules should be stored at a temperature not exceeding 30 °C. The capsules contain 12 to 16 % water, varying with storage condition. When humidity is low, capsules become brittle and when humidity is high, capsules become flaccid and shapeless. The storage of capsules in high temperature can also affects the quality of hard capsule.

**MARKETED SOLID DOSAGE FORMS**

(A) Powders
1. Prequest powder sached (Parke-Davis (India)): contains sodium chloride 0.365%, sodium acid phosphate 0.975%, sodium citrate 1.839%, potassium chloride 2.330%, magnesium sulphate 0.736%, Calcium lactose 0.545% and Dextrose anhydrous 89.900%.

2. Acidin (East India Pharmaceutical works): contains magnesium carbonate 165 mg, calcium carbonate 165mg, sodium bicarbonate 82mg, light kaolin 105 mg, belladonna herb 0.03mg.

3. Electrobion(E. Merck (India) Ltd.): Each sachet of 28.5 g contains sodium chloride 12.3%, potassium chloride 5.3%, sodium citrate 10.2% dextrose anhydrous 70.21

4. Oral rehydration salts (NEPC Pharmachem): Each sachet of 27.5 g contains sodium chloride 3.5 g, potassium chloride 1.5 g, sodium citrate 2.9 g, anhydrous dextrose 20 g.

(B) Dusting powders

1. Cibazol dusting powder (Hindustan Geigy): contains 20 % sulphathiazole.

2. Neosporin dusting powder (Burrows Wellcome (India)): Each gm contains Polymyxin-B sulphate 5000 units, Zinc bacitracin 400 units, Neomycin sulphate 3400 units.

3. Nebasulf dusting powder (Pfizer: Neomycin sulphate 5mg, Bacitracin 250 units, Sulphacetamide 60 mg,

4. Alsporin dusting powder (Alpine Industries): Each gm contains Polymyxin-B sulphate 5000 units, Zinc bacitracin 400 units, Neomycin sulphate 3400 units.

5. Mycoderm dusting powder (FDC): contains Salicylic acid 3% w/w, Benzoic acid 6%w/w.

(C) Dentifrices

1. Steradent denture cleansing powder (Reckitt and Colman)

2. Clinsco-dent (ICPA Health Products)
3. Sensoform tooth-paste with formalin (Warren Pharmaceuticals’): contains potassium nitrate B.P. 5% in a flavoured base.


5. Thermoseal (IPCA Laboratories): Contains Strontium chloride 10% w/w in favoured base.


(D) Granules

1. Protinex granules (Pfizer): it is a multi-vitamin preparation.

2. Antepar granules [Burroughs Wellcome (I)]: Each sachet contains Piperazine citrate equivalent to 4.5 g of Piperzine hexahydrate and Calcium sennoside equivalent to 12 mg of Sennoside A&B.


4. Protinules granules (Alembic Chemical Works Co) contain partially predigested milk proteins and multivitamins.

5. Calcirol granules (Cadila Pharmaceuticals): 1 g sachet contains vitamin D₃ 60,000 IU.

6. Electral granules (FDC): each 35 g sachet contains Sodium chloride 1.25 g, Potassium chloride 1.5 g, Sodium citrate 2.9 g, Anhydrous dextrose 27 g.

**BIOAVALIBILITY OF DRUGS** [Sampathkumar, K.; (2008)]
A drug can exert a pharmacological effect when it reaches the site of action in active form. Bioavailability may be defined as the rate at which the drug reaches the systemic circulation in the active form. The rate at which the drug enters the circulation controls the onset, intensity and sometimes the duration of pharmacological effect. Other definitions are the extent to which the active ingredient in the drug product is taken up by the body in the form in which it is physiologically active.

The basic equation is to assess what the physiologically active species is. This is known only for a few drugs. Most of drugs acting on CNS are difficult to assess with reference to their physiologically active molecular species.

The FDA in US (1973) defined bioavailability as “the degree to which a drug is absorbed from the drug product into the body or site of action”. It is, however, difficult to measure the availability at the site of action. Indirectly, it is measured by its pharmacological effect.

The Committee of Academy of pharmaceutical Sciences (1972) defined bioavailability as “a term used to indicate a measurement of both the relative amount of administered drug that reaches the general circulation and the rate at which this occurs”. This definition is acceptable since it is possible to measure and compare the amount absorbed and rate of absorption of the drug.

However, the above definition does not address itself to the question of bio-equivalence of the products from the stand point of their therapeutic effectiveness.

It may so happen that the same drug may show difference in bioavailability when administered from different dosage forms or also when administered from the same dosage form, but from different manufactures.

It may be noted that those drug which show good bioavailability in vitro actually may not do so in vivo.

The concentration of drug at the receptor sites and circulation depends upon the absorption, distribution, metabolism and excretion of the drug.
Absorption is the movement of solute into the circulation from the site of administration. Distribution is movement of solute from the blood into the tissue. Metabolism is the process by which chemical reactions carried out by the body convert a drug into a compound different from that originally administered. Excretion is the process by which the drug and its metabolites are removed from the body mainly through kidney or liver.

Relative bioavailability is the availability of the drug from dosage form as compared to a reference standard.

Absolute bioavailability is the availability of the drug after intravenous administration.

Bioequivalence: A product is considered bioequivalent if its rate and extent of systemic absorption does not show a significant difference from the pioneer drug product when administered at the same dose of the therapeutic ingredient, by the same route and under the same experimental conditions.

Factors Affecting Bioavailability:

The rate and extent of availability of drug from a dosage form is affected by various factors as under.

1. Physical Properties of Drug
   i. pKa: Drugs which are weak electrolytes exist in ionized as well as non ionised form. The extent of ionization depends on pKa of the drug and pH of the surrounding fluid. The drugs are more water soluble in ionized or salt form. But ionized from is not readily absorbed e.g. Organic acids which have pKa values between 3-7 remain unionised in gastric (pH 1) fluid. Thus it gets well absorbed from stomach.

   ii. Partition coefficient: Partition coefficient of a drug is the ratio of its solubility at equilibrium in an aqueous solvent to its solubility in a nonaqueous solvent. Hydrophilic drugs have higher water solubility and dissolution rate than lipophilic drugs. Nonionised form of drug is more lipophillic than ionized form. Nonionised form is better absorbed as the biological membrane is absorbed.
iii. **Particle size:** As particle size of the drug is reduced, the surface area increases. Increase in surface area increases dissolution rate and in turn availability of drug. E.g. decrease in particle size increased the absorption of griseofulvin.

2. **Pharmaceutical Factors**
   i. **Dosage form:** For drug to reach the circulation from dosage form drug has to undergo the steps as shown

![Diagram of drug dosage form process](image)

The availability of drug from dosage forms in general can be of following order: Solution > Suspension > Power > Capsule > Plain Tablet > Coated Tablet.

**Solutions:** They are absorbed most rapidly from the GI tract. Aqueous solutions are absorbed faster than the non-aqueous emulsions may show a faster rate. The absorption of solution is affected by viscosity, reversible complexation, solubilization, and chemical stability.
**Suspensions:** In suspensions, the particles must dissolve before their absorption. Therefore, they rank next to solution in terms of its bioavailability. However as compared to other dosage forms like capsules and tablets, they show a higher rate of absorption because they provide a large surface area. Antacids are better presented as suspensions. Chemically unstable drugs like antibiotics, Gastric irritating agents are better presented as suspensions. Bioavailability of suspensions is affected by particle size, formation of non-absorbable complexes, crystalline form and viscosity.

**Capsules:** The absorption problem in respect of capsule is associated with the diluents present along with the drugs in the capsule; which itself may absorb the drug. For example, the absorption of tetracycline in capsules will be retarded by the presence of calcium phosphate used as a diluents, and form insoluble complexes. As fine particles are not subjected to compression the surface area is not reduced. On wetting with biological fluids, a larger effective surface area is available for dissolution. The facilitator for this is the surfactants. Fine particle though good for fastness in absorption, they are not advisable for drugs like nitrofurantoin (NFT) which causes gastric irritation. The shell of the capsule may also affect its absorption. The factors that govern the absorption form capsules include particle size, crystalline form, interaction of drugs and fillers, selection of diluents and fillers.

**Compressed Tablets:** Moist granulation is a common method for compressing tablets. Binding agents are used for formation of surface area for absorption is also smaller till disintegration of the tablet. The process of breakdown of a tablet depends on the concentration of the binder, disintegrant, lubricant, compression force etc. Thus there is appreciable variation in the bioavailability of the different tablets.

**Coated Tables:** The time taken for the coating materials to dissolve affects its bioavailability. Coating is used to make disagreeable drugs palatable or to protect the drug during storage. The coatings like sugar-coating film-coating and enteric coating show variations in bioavailability.

ii. **Manufacturing variables:** The addition of various excipients in the process like compression force, rate and order of addition of ingredients may affect bioavailability
from a given dosage form e.g. addition of lubricants which are generally hydrophobic in nature reduce wetting of the drug particles. This reduces rate of dissolution and in turn rate of availability of drug to the body. Excipients may interact with the drug and may affect bioavailability from a given dosage form e.g., addition of lubricants which are generally hydrophobic in nature reduce wetting of the drug particulars. This reduces rate of rate of dissolution and in turn rate of availability of drug to the body. Excipients may interact with the drug and may affect bioavailability of the drug.

iii. **Dissolution Rate:** For drug which are poorly water soluble dissolution rate of the solid drug often the rate-limiting step in the bioavailability of the drug. Dissolution rate is determined by Noyes and Whitney equation.

\[
\text{Rate of dissolution} = \frac{DAK}{h} (C_s - C_b)
\]

Where D = diffusion coefficient, A = surface area of the drug, K = Partition coefficient, h = thickness of the stagnant layer, C_s = Conc. of drug in a saturated stagnant layer around the drug particle and C_b = Conc. of drug in the bulk phase of the solvent.

Hence dissolution rate is being prescribed for more formulations (dosage forms) in the pharmacopoeias.

3. **Physiological Factors**

i. **Effect of GIT fluid:** Mucin forms a thin layer over the gastric and intestinal epithelium. Mucus may form complexes with various drugs decreasing their absorption and reduce their bioavailability. Hypotensive and anticholinergic drugs form complexes hence are poorly absorbed. Various proteinaceous materials reduce the activity of aluminium antacids by a complex interaction. Bile salts enhance the dissolution rate of poorly soluble drugs and promote absorption of various drugs. Bile salts inactivate many antibacterial and antifungal agents such as nystatin, polymyxin and vancimycin. Benzylpenicillin is deactivated at stomach pH.
ii. **G.I. Transit time:** The motility of the stomach is important to the rate at which orally administered drug is passed into the intestine. Food also affects gastric emptying time. Absorption of amoxicillin, ampicillin and cephalexin is reduced in presence of food. This is due to enhanced gastric emptying.

iii. **First pass effect:** Orally administered drugs go to the systemic circulation via hepatic portal system which first presents the drug to the liver. Thus entire absorbed dose of drug is exposed to the liver during first pass through the body. The drug if it is rapidly metabolized in the liver, a small fraction will only reach the systemic circulation. This is known as first pass-effect and may cause significant reduction in bioavailability. Route of administration highly affect first pass effect. Bioavailability of propranalol, oxyphenbutazone, chlorpromazine, and aspirin undergo first pass effect.

iv. **Diseases state:** In various disease states such as thyrotoxicosis the metabolism of the drug is highly affected which changes the bioavailability of that drug.

**ADVERSE DRUG REACTIONS**

With the wide spectrum of increasingly potent and high cost therapeutic agents now at our disposal the process of deciding on and implementing a drug therapy is much more complex risky and more costly than in the past. In most cases drugs are used exclusively and indiscriminately in combination with another giving rise to new kinds of toxicity and adverse drug reaction. This added dimension in the causation of disease is termed as iatrogenesis.

**Definition:** Adverse drug reaction is a reaction that is noxious, unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological functions. It includes the documented and accepted adverse drug effects e.g., toxic side effects of the cytotoxic drugs; but excludes important drug related problems resulting and dispensing errors and intentional overdose (attempted and successful suicide or homicide).

Adverse drug reactions are more frequent in patients taking large number of drugs and in patients taking treatment from more than one physician simultaneously perhaps for different
ailments. About 25 to 30 percent of the people undergoing treatment experience some sort of adverse reactions temporary or permanent. Of this about four percent get themselves into hospital for treatment.

**Reasons for Adverse Reactions**

1. Medication administration error.
   
   (a) Over prescribing of potent drugs to patients.
   
   (b) Self medication by patients leading to overuse or misuse of drugs leading to excess therapeutic effect or complication respectively.

2. Failure to set therapeutic end point
   
   With drugs like corticosteroids digitalis, diuretics certain antibiotics etc. Continuing the administration beyond the therapeutic endpoint may result in adverse reaction. This may be due to failure of the physician to monitor the patient taking the prescribed drugs without reporting to the doctor regularly for follow up of treatment and change in does regimen.

3. Sudden withdrawal of drugs
   
   Treatment with drugs like corticosteroids and hormones cannot be stopped abruptly in certain cases .They are to be withdrawn by gradually decreasing the does otherwise it may lead to adverse reactions or secondary side effects.

4. Bioavailability difference
   
   Difference in the bioavailability of same drug from different brands may also cause the adverse reactions same Case with different formulations of same drug due to the pharmaceutical processes used. Studies have been made with oxtetracycline, phenytoin and digoxin confirming different levels of bioavailability.

5. Patient factors
   
   (a) Idiosyncrasy of individuals
   
   (b) Young and old patients are more susceptible to adverse reactions as compared to the adults .This is due to marked difference in the metabolism and excretion pattern at this age.
(c) Physiological and disease conditions of patients may produce adverse drug reaction. Patients with renal and hepatic damage or dysfunctions are prone to adverse reaction due to disturbed metabolism and excretion absence or deficiency of certain specific enzymes.

(d) Stoppage of treatment in the middle by patients due to

i. Ignorance

ii. High cost of medicines

iii. Unpleasant nature of medicines

iv. Complex therapeutic regimen and

v. Lack of faith on the prescriber or medicine.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

1. Predictable

   1.1. Excessive pharmacological activity

   1.2. Secondary pharmacological effect

   1.3. Rebound response on discontinuation

2. Unpredictable

   2.1. Allergic reactions and anaphylaxis

   2.2. Idiosyncrasy

   2.3. Genetically determined effects

Role of Pharmacist in Adverse Drug Reactions
No drug is absolutely safe. Adverse effect due to overdose of drugs are available before the introduction of drugs in the market from the clinical trials carried out by the parent company. Unpredictable adverse effects will be known after actual usage of the drugs. Drug monitoring, being one of the functions of the clinical pharmacist (refer earlier chapters) is in a better position to advise the Patients in consultation with the drug therapy physician. He assists the doctors in making the drug therapy safe, as his better knowledge of the pharmacological actions. Adverse reactions and the pathophysiology of disease. He has aloes with him, the detailed in formations on drug s collected from various literatures, reviews, clinical trials etc and patient’s medication history book.

Reduction of Adverse Drug Reaction

The risk of adverse drug reactions can be reduced by taking into consideration the following points.

1. Always take a detailed drug history as a part of clinical history.

2. Drug treatment should be used when there is a clear indication for it and is no non-pharmacological alternative.

3. Multiple drug regimens should be avoided as far as possible.

4. Particular attention must be paid to drug does and response in neonates and attention must be paid to drug dose and response in neonates and geriatric patients and those with renal hepatic and cardiac disease.

5. The need for continuing treatment should be regularly reviewed and increase or decrease of dosage or stoppage of drug carried out.

DRUG INDUCED DISEASES

Drugs may induce disease conditions in various body systems. Few important and common ones are discussed below.
1. **Drug induced liver disease**

As liver is a major site of metabolism and excretion of drugs, it is commonly affected by drugs very much. Drugs are responsible for 2 to 10 percent of cases of jaundice and acute hepatitis. The hepatotoxic drugs may be classified into two types

a) Drugs causing direct liver damage e.g. Isoniazid, Tetracycline.

b) Drugs causing liver damage through host hypersensitivity e.g. Sulphonamides, Erythromycin estolate.

Some important drug induced liver diseases are as follows:

<table>
<thead>
<tr>
<th>Liver Disease</th>
<th>Responsible drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Acute Hepatotoxicity</td>
<td>Cimetidine, Rifampicin, Phenylbutazone, Methylldopa, INH, PAS, Erythromycin, Halogenated Anesthetics.</td>
</tr>
<tr>
<td>ii. Chronic Drug-Induced Diseases</td>
<td></td>
</tr>
<tr>
<td>a) Cirrhosis</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>b) Phospholipidosis</td>
<td>Antiarrhythmic drugs.</td>
</tr>
<tr>
<td>c) Vascular injuries</td>
<td>Anabolic steroide, Alcohol, Anticancer drugs.</td>
</tr>
<tr>
<td>d) Hepatic granuloma</td>
<td>Sulphonamides, Penicillin, Allopurinol</td>
</tr>
<tr>
<td>e) Hepatoportal Sclerosis</td>
<td>Arsenicals, Vinyl chloride, Vitamin A.</td>
</tr>
<tr>
<td>f) Hepatic neoplasms</td>
<td>Oral contraceptives, Anabolic steroids</td>
</tr>
</tbody>
</table>

2. **Drug induced renal disease:**

Kidney is highly sensitive to the effects of drugs as compared to other organs. This is mainly because of the following reasons:

1) Kidney is a highly perfused organ which receives around 25% of the cardiac output and gets exposed to high concentration of toxins.
2) Drug when bound to protein is non-toxic. This drug carrier complex breaks at the tubule liberating free toxic drug.

3) Precipitation of some drugs occurs due to change in urinary pH.

4) Due to large endothelial surface of kidney it is prone to deposition of antigen-antibody complexes which may cause hypersensitivity reactions.

Some nephrotoxic conditions and the drugs that may be responsible for them are as follows.

<table>
<thead>
<tr>
<th>Nephrotoxicity</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Direct glomerular or tubular damage</td>
<td>Cephalosporins, Polymyxins, Aminoglycosides.</td>
</tr>
<tr>
<td>2. Nephrogenic Diabetes insipidus.</td>
<td>Lithium, sulfonylureas, Methoxyflurane</td>
</tr>
<tr>
<td>3. Acute interstitial nephritis</td>
<td>Methicillin, ampicillin, Nafcillin, phenytoin, Thiazides.</td>
</tr>
<tr>
<td>4. Kidney stone, crystals</td>
<td>Sulphonamides</td>
</tr>
<tr>
<td>5. Uric acid crystallization</td>
<td>Probenecid methotrexate, Sulfinpyrazone, allopurinol.</td>
</tr>
<tr>
<td>6. Renal ischemia</td>
<td>Methysergide</td>
</tr>
</tbody>
</table>

3. **Drug induced hematologic disorders:**

Drugs may affect the haemopoietic system and cause abnormalities in cell components or cell numbers. Some drugs may affect the functioning of bone marrow, thereby disturbing all components of blood, whereas some may affect only a particular component of blood. Common drug induced haemotologic disorders are anaemias, leukopenia and thrombocytopenia, produced by the following drugs.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Drugs responsible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aplastic anaemia  Chloramphenicol, butazones, continued exposure to insecticides
Megaloblastic anaemia  Isoniazid, phenytoin, purine, Pyrimidine analogues.
Heamolytic anaemia  Antimalarials, antibacterials, Antirheumatics, analgesics
Leukopenia  Phenylbutazone, sulphonamides, Antithyroid drugs, oncologic drugs.
Thrombocytopenia  Aspirin, butazones, ibuprofen, penicillin, alcohol, colfibrate, cycotoxic agents, dextran, heparin.

4. Drug induced gastrointestinal disorders:

The common ones are constipation, diarrhea, vomiting, ulceration and pancreatitis. The drugs responsible for these includes haematinics, antibiotics, salicylates, steroidal drugs, ephedrine, methotrexate, frusemide, cimetidine, methyldopa etc., All these depends upon the nature of diet had, along with the drug and the timing of administration.

5. Drug induced dermatologic reactions:

This is mainly due to photosensitive reactions and occurs due to interaction between the drug and its metabolite and ultra-violet rays. The reaction may be phototoxic or photoallergic.

The phototoxic reaction is a dose related effect occurring after first drug exposure. These reactions do not show cross-sensitivity and are characterized by skin conditions similar to exaggerated sunburn. Common phototoxic agents are tetracyclines, hexachlorophene.

The photoallergic reaction is caused by antigens formed by the action of light on drug and skin proteins. Photoallergy is dose independent and need previous exposure to drug. It is characterized by papulae, eczematous eruption & urticaria. Photoallergic agents are cinnamates, antihistamines, estrogens, coaltar, thiazides etc.

TERATOGENICITY
Teratogenicity means the process of abnormal growth. Certain chemical agents can affect the somatic cells of a developing embryo in such a way that defects are produced in one or another organ system; malformation or abnormal growth. Drugs or other factors that effects deviations or abnormalities in the development of the embryo that are compatible with pre-natal life and are observable post-natally are called “teratogens”. True teratogens cause abnormalities at lower doses than are necessary to cause a toxic effect on the mother. The period of first ten to twelve weeks of gestation is quite vulnerable to foetus with teratogens. Foetus is more susceptible to drugs than mother as foetal hepatic enzymes function is minimum. So far known teratogens are thalidomide, androgens, methotrexate, tetracyclines, diethylstibesterol etc.

In view of the health care with respect to teratogenicity, pharmacist should obtain the important information from the patient; who includes the details of drugs taken with exact does and dates, last menstruation period so as to determine the development stage of foetus at the time of exposure of the drug (teratogens).

Thus the pharmacist can play an important role in the safe use of drug by maintaining the medical history, studying in detail all the facts that are available and by efficient monitoring of adverse drug reactions as also drug induced diseases.

**CLINICAL TOXICITY**

**INTRODUCTION**

Clinical toxicity is the poisonous effects produced clinically in human being by drugs and chemicals. The happening of poisoning may be for suicidal, homicidal, or by accident. The substances involved commonly are – oxalic acid, carbolic acid, potassium cyanide, barbiturates, aconite, datura, arsenic and antimony compounds, chloral hydrate, methyl alcohol, insecticides etc.

**Classification of poisons:** Poisons are classified into three main categories according to their mode of action.
1. **Corrosives:** A corrosive poison is simply a high active irritant and produces inflammation and acute ulceration of tissues. The symptoms are odour of acid, pain in throat and stomach. Examples –

   1.1 Strong acids like sulphuric acid, nitric acid, hydrochloric acid

   1.2 Organic acids like oxalic acid, carbolic acid

   1.3 Concentrated alkalies like caustic soda, caustic potash, and carbonates of sodium, potassium and calcium

2. **Irritants:** Irritant poisons produce symptoms of intense pain, vomiting, usually purging and finally collapse. Examples –

   2.1 Inorganic metallic compounds of arsenic, antimony, mercury, lead, copper, iron, silver and bismuth.

   2.2 Inorganic non-metallic compounds of phosphorous, chlorine, bromine, iodine and boron.

   2.3 Organic vegetable poisons like castor seeds, ergot, aloes, cannabis indica and marking nut.

   2.4 Organic animal poisons like cantharides, scorpion venom, poisonous insects and snake venom.

3. **Neurotics:** These poisons act primarily on the central nervous system. The common symptoms are headache, giddiness, drowsiness, delirium, stupor, coma, sometimes convulsion and paralysis. Death usually comes from failure of respiration. Examples -

   3.1 Poisons acting on cerebrum – alcohol, ether, chloroform, sedatives, hypnotic chloral hydrate and barbiturates, opium alkaloids, insecticides and coal-tar derivatives.

   3.2 Poisons acting on spinal chord-nux-vomica and its alkaloids, gelsemium

   3.3 Poisons acting peripherally – conium and curare
Gravity of poisoning – this can be divided into two types

a) Acute poisoning: symptoms appear suddenly soon after consumption of poison. The symptoms rapidly increase in severity and are followed by death or recovery. Poison can be detected in the ingested food, medicine or fluid, or vomit, urine or stool of the victim.

b) Chronic poisoning: symptoms develop gradually like malaise. There is remission or even complete disappearance of symptoms on the removal of suspected food, medicine or fluid poisons.

GENERAL TREATMENT OF POISONING

The main aim of treatment is to help the patient to stay alive, relieve the pain and restore normalcy. The various steps involved in the treatment of poison cases are-

1. First aid treatment – the cardinal rule is to remove the unabsorbed poison from contact with the patient (unless such removed is contraindicated) and to obtain definite medical care at the earliest.

2. Use of antidotes

3. Elimination of the absorbed poison

4. Treatment of general symptoms

5. Maintenance of the patients general condition

Removal of unabsorbed poison

The prime step with the ingested poison is its removal from stomach. This can be brought about by vomiting and/ or by washing the stomach (gastric lavage). Emetics can be used to bring about vomiting. The usual emetics are:

a) Copious draught of warm water

b) Warm solution of common salt- two tablespoon full in 500 ml of water
c) Warm solution of mustard powder

d) Warm solution of zinc sulphate ammonium carbonate, ipecac powder – 1-2 g in 200 ml of water

e) Tincture ipecac – 15 to 30 ml. if the patient has not vomited within 15 to 20 minutes, repeat the dose of ipecac and give more water

f) Warm solution of copper sulphate (dilute)

g) Apomorphine injection – 6 mg subcutaneously

Ticking the back of the throat with fingers, a spoon or a spatula is not very effective. Collect the vomitus for chemical examination, if needed. Do not induce vomiting, if the patient is unconscious or having convulsions (fits) or has swallowed strong caustics/ corrosives, since it may rupture the stomach and possibility of poison entering the lungs.

**Antidotes** falls under four categories – Mechanical, chemical, systematic and Universal.

a) Mechanical antidotes are substances which prevent further absorption of poisons. These act by forming a coat over mucus membranes of the stomach. e.g., oils, fats and egg albumin. Charcoal is especially useful in adsorbing alkaloidal poisons.

b) Chemical antidotes are substances which react with poisons and neutralize their toxic effect. e.g., magnesium oxide, calcium oxide and tannins.

c) Systematic antidotes are substances which produce the opposite actions to that of poisons. e.g., chloroform for strychnine, caffeine for morphine etc., one must be cautious complete. The remedy may itself produce undesirable effects and complicate the situation. Complexes with heavy metals and prevent the poisonous effect further. e.g., dimercoprol, EDTA salts sodium and calcium.

d) Universal antidote is used in cases where the nature of poison is not known. This is a mixture of three ingredients and administered in does of a tablespoonful, repeated twice or thrice. It has formula as follows.-
Powdered charcoal - 2 parts (absorbs alkaloids-good adsorbent)

Magnesium oxide - 1 part (neutralizes acids)

Tannic acid - 1 part (precipitates alkaloids)

**Elimination of absorbed poison**- forced diuresis using intravenous chlorthiazide or mannitol solution is useful in aspirin and barbiturate poisoning. Peritoneal dialysis is useful in salicylate poisoning. Haemodialysis is carried out in cases of barbiturates, boric acid, bromides, salicylates etc poisoning.

**Treatment of general symptoms**- look into victim’s mouth and remove all tablets, powders, plants or any other material that is found. Wipe out mouth with a cloth and wash thoroughly with water. If the victim is not breathing, start artificial respiration immediately. Use oxygen if available. Morphine may be given to reduce pain. If caustic poison has been swallowed, dilute it by giving 1 or 2 glasses of milk or water.

**Maintenance of patients general condition** – the patient should be kept warm and comfortable. Loosen all tight fitting clothing and shift the victim into fresh air. Avoid giving substances like hot coffee, alcohol or stimulants.

**POISONING BY INSECTICIDES**

Most of the insecticides contain organophosphorous compounds in petroleum distillate base e.g., hexaethyl tetra phosphate, tetraethyl pyrophosphate, octamethyl pyrophosphate, octamethyl pyrophosphramide and malathion. Other chemicals are DDT, Endrin, Deltamethrin, Allethrin, metallic arsenates etc., (for complete list of insecticides, please refer the “Schedule” under the insecticides Act 1968)

**Symptoms**: irritation of eyes, nose and throat. Headache, blurring of vision, cough, malaise, followed by nausea, abdominal pain, vomiting. In severe cases, nervousness, anxiety, salivation tremor and convulsions occur. If not attended in time, may terminate in respiratory failure and death.
**Treatment:** vomiting to be induced if the poison is ingested. Gastric lavage and saline cathartics to be carried out in severe cases. Gently open. Eyes with plenty of water for 10 to 15 minutes with eyelids open. Do not allow victims to rub their eyes. Wash poisons off the skin with large amounts of plain water. Wash with soap if possible. Remove and discard all contaminated cloths. Remove the victim into fresh air area. Start artificial respiration if needed without any delay.

**Antidotes**

<table>
<thead>
<tr>
<th>Insecticide</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Organophosphorous compound</td>
<td>Atropine, mercurial diuretic</td>
</tr>
<tr>
<td>b. DDT</td>
<td>Phenobarbitone</td>
</tr>
<tr>
<td>c. Endrin</td>
<td>Calcium lactate</td>
</tr>
<tr>
<td>d. Deltamethrin, Allethrin</td>
<td>Diazepam or atropine</td>
</tr>
</tbody>
</table>

**HEAVY METAL POISONING**

The metals that are responsible for poisoning effect in our life are lead, copper, arsenic and mercury. With these, the poisonous effect may be acute or chronic. The symptoms and treatment are dealt under.

1. **Arsenic symptoms:** in acute poisoning nausea, faintness, heat and constriction in the throat and burning pain in the stomach. Vomit initially consists of stomach contents, later becomes blackish or greenish due to bile, followed by mucus and at last serum with blood. Severe purging sometimes bloody, legs and joints painful due to dehydration. Urine greatly diminished and painful urination.

   Chronic poisoning results in loss of appetite, nausea, impairment of vision, repeated headache, drowsiness, and patchy brown pigmentation of skin.
**Treatment:** if there is not already free emesis, empty the stomach hydrated (ferric oxide) is an antidote and given at once in large dose. Dimercaprol in oily solution administered intramuscularly.

2. **Lead symptoms:** in acute poisoning manifestation are metallic taste and offensive breath. Vomited matters often milk white. Burning pain in abdomen stools black. Sometimes nervous symptoms will be most marked.

Chronic poisoning will result in blue or black lines on gums, stiff joints, constipation and anemia,

**Treatment:** gastric lavage with zinc sulphate followed by large draughts of milk and eggs. Administer magnesium or sodium sulphate to ensure purgation of any poison that has passes into intestine.

**BARBITURATE POISONING**

**Symptoms:** there is prolonged coma, with respiratory depression, low blood pressure and Liguria. There may be mental confusion, in coordination and muscular weakness. It is followed by stupor. Face becomes cyanotic. Death is due to respiratory failure.

**Treatment:** artificial respiration must be given by a mixture of 95 % oxygen and 5 % carbondioxide. Gastric lavage must be performed by potassium permanganate. If coma is there, 5 % glucose solution must be given to the patient. Recently, forced osmotic diereses (Urea) with large amounts of fluid and alkalinisation, (Sodium Lactate) has been used to treat severe cases of barbiturate poisoning.

**NARCOTIC DRUG POISONING**

1. **Opium poisoning:**

   Symptoms: the symptoms of poisoning can be divided into 3 stages i.e., (i) excitement (ii) stupor and (iii) narcosis.
i. **State of excitement:** Initially there is pleasurable mental excitement, usually of very short duration. Laughter, hallucinations and rapid heart rate occur.

ii. **State of stupor:** in this there is weariness, headache, giddiness, a sense of weight in the limbs, diminution of sensibility and a strong tendency to sleep from which the patient can be roused by external stimuli. The pupils are contracted and face turns morbid blue.

iii. **State of narcosis:** the patient passes into deep coma. Pupils are contracted, to pin point. There is a full in blood pressure. The breathing is slow, the rate being 2 – 4 per minute, labored and stertorous, and then gradually fails. The muscles are relaxed and reflexes abolished.

**Treatment:** the stomach must be washed immediately with tepid water and then with potassium permanganate solution of strength of 1:1000. Potassium permanganate oxidizes morphine to least toxic substances. The intestines must be cleared out by an enema or by purgatives like magnesium sulphate 15 ml orally.

The patient must be kept awake i.e. he must not be passed not comatose state. An injection of atropine dose 1.5 mg is useful. Injection of warm saline and glucose may be of value. Adrenaline exhibits an antitoxic effect. Artificial respiration may be given.

2. **Cannabis poisoning:**

**Symptoms:** symptoms are similar to those of alcohol causing excitement first and then narcosis. The excitement is followed by hallucinations of sexual character. The man may see beautiful women nude, dancing in front of him. In stage of narcosis there is confusion, drowsiness and dilated pupils. There may be generalized anaesthesia.

Chronic poisoning is characterized by anorexia, anorexia, loss of weight, weakness, tremors, importance and moral deterioration. The patient suffers from hallucinations and delicious of a persecuting nature.
Treatment: This is on same lines as that of other narcotics. The stomach is washed with warm water. Hypodermic injection of strychnine is useful. Saline purgatives are useful. Artificial respiration may be necessary.

3. Cocaine poisoning:

Symptoms: it initially acts as stimulant and then depressant of the CNS. At first, the higher cerebral functions of intellect, attention and judgment are increased. Sense of fatigue is abolished. Restlessness, excitement and delirium may appear. The face is flushed, the pupils are dilated, the vision blurred, the heart beats faster and there is an increase in rate of respiration. There may be an increase in body temperature. It is followed by muscular twitching and convulsions.

Depressions then follow excitement, ending in death due to cardiac or respiratory failure.

Treatment: if the drug is injected absorption of drug from site of injection should be limited by tourniquet or by application of ice. If swallowed, the stomach should be washed with a dilute solution of potassium permanganate or tannic acid. Medicinal charcoal can also be employed. Excitement can be controlled by barbiturates. Cardiorespiratory stimulants and artificial respiration may be required.

ROLE OF PHARMACIST IN CLINICAL TOXICITY

There is much that the pharmacist can do to help prevent poisoning and to improve the treatment there of. While he may not become involved in the therapy of poisoning except for necessary first-aid, he plays a key role in ensuring that adequate equipment and information are available.

He also plays an important role with regard to non-prescription items. The pharmacist should explain and amplify directions for proper use of potentially toxic materials, bearing in mind all the members in the household. He should warn the buyer about the hazards of leaving the material within the reach of children.
QUALITY CONTROL OF DRUGS AND PHARMACEUTICALS

IMPORTANCE OF QUALITY CONTROL [Rajasekaran, V. N. (1994)]

The drugs and pharmaceuticals used in the prevention and treatment of diseases are derived from plant, animal or mineral origin or made synthetically. Usually they are not available in a state of purity since many other substances known as impurities are also present along with them. Therefore it is necessary not only to identify these impurities but also to precisely estimate their amount so that we can decide whether they are within the permitted limits. Similarly the drug should be present in the sample in the quantity prescribed. We will be in the dark about not only its efficacy but also its stability, safety and purity. So the quality control of drugs and pharmaceutical formulations is very important and enable us to achieve this objective.

ERRORS IN QUALITY CONTROL

In any analysis errors may be present to make the results obtained in the analysis unreliable. Therefore it is necessary to have full knowledge of the sources of these errors so that they may be eliminated or reduced ensuring that the results of the analysis will be reliable. The errors are of two types:

1. Indeterminate or accidental errors.
2. Determinate or constant errors.

**Indeterminate errors:** are not easily observable and their elimination also is impossible, since indeterminate errors are caused by differences in judgment and also skill of the analysts. It means that two analysts analyzing the sample of a drug may not get identical results, if they do not have the same skill in performing the analysis and also if their awareness of the intricacies of the analysis is different.

**Determinate errors:** are those which occur again and again in a series of determinations in the analysis of a drug. These errors may be caused because the analyst commits some errors
unwittingly such as that he is not taking a representative sample of the drug or that his selection of the indicator for the analysis is wrong or that he overshoots the end point properly. If the apparatus used in the balance used for weighing the drug suffers from some defect such as inequality in the length of the arms or if incorrect weights are used, it will also contribute to the determinate errors. However these errors can be easily identified and rectified if proper care is taken.

**Signification errors:** In the number 145, the digits 1, 4 and 5 are known as significant numbers. In the number 10.6, the zero is also a significant figure. In the number 1.000, all the zeros are significant figures. In the number 10.6 the zero lies to the left of the decimal and together with the other numbers gives the value of the number. In the other example, the zeros lie to the right of the decimal. Though normally they do no seem to have any value because 1.000 is equal to 1 only, yet if it is considered to be the weight of a substance, it means that the weight has been determined to an accuracy of 1 mg. in this sense the zeros are considered to be significant figures.

In an analysis all measurements can be carried out only with a certain amount of accuracy which means that some errors are always there. For example let us assume that we are doing a titration using a burette calibrated to 0.01 ml. The titer value obtained is 22.5 ml. it means that the correct titer value lies somewhere between 22.45 and 22.55 ml. Therefore it is better to do a series of titrations and obtain the average of the titer values. Suppose five titrations are done and the titer values obtained are 22.45, 22.46, 22.48, 22.52 and 22.53 ml. the mean or average of these five titer values is 22.488. However if it is taken as 22.488, it would be a mistake of taking too many figures if it is taken as 22.488, it would be a mistake of taking too many figures than necessary since it extends it to a third decimal, thereby indicating that the error of measurement is 0.0005 ml. So it should be rounded off to 22.49 and the error on account of this eliminated.

**METHODS OF QUALITY CONTROL**

As per the pharmacopoeia, the official drug or pharmaceutical formulation has to comply with the following standards:
**Description of the drug:** A brief description of the drug including odour and taste. Example: A white, crystalline solid with a bitter taste and a characteristic odour.

**Tests for identity:** by doing these tests for identity, we can prove that the sample is nothing but the particular drug.

**Physical constants:** physical constants are the characteristic properties of the particular drugs. If the drugs comply with the physical constants, it means the drugs are pure. In addition, physical constants also serve as additional tests for identity. The following are the important physical constants, some of which may be prescribed for particular drugs:

- **Melting point:** if the drug melts sharply at the stated melting point, it means that the drug is pure. Additionally melting points is also test for identity.

- **Solubility:** Solubility in particular solvents serves as a test for identity.

The other physical constants prescribed are-

1. Weight per ml (for liquids) or specific gravity.
2. Refractive index.
3. Optical rotation.
4. Viscosity.
5. Light absorption in the visible and ultraviolet ranges.
6. Infrared absorption etc.

**Limit tests:** Limit tests are done to ensure that impurities, if present in the drug, are within the permitted limits.

**Assay:** Assay is done to estimate precisely the amount of the drug in the sample or the active ingredients in any formulation. The following assay methods are used:

a. Volumetric methods such as acid- base titrations, oxidation reduction titrations, precipitation titrations, complex metric titration, non-aqueous titrations etc.
b. Gravimetric analysis in which a drug or a derivative of the drug is finally weighed.

c. Instrumental methods of analysis such as colorimetry, spectrophotometry, flame photometry etc.

IMPURITIES AND LIMIT TESTS

IMPURITIES IN PHARMACOPOEIAL SUBSTANCES

Chemical purity means freedom from all foreign materials. It is not possible to obtain and absolutely pure compound and even analytically pure samples contains minute trace of other substances which are called as impurities. Purification of chemicals is expensive and therefore purifying a substance to a much higher degree than is necessary for the purpose for which it is intended to be used will increase its cost too much.

However it is possible at a comparatively less cost to mass produce certain substances in a high state of purity. Refined sugar contains more than 99.9 per cent of sucrose. Similarly vacuum salt contains more than 99.9 per cent of sodium chloride. It is made by purifying rock salt.

The different types of impurities commonly occurring in drugs

1. Impurities which are produce unpleasant reactions in the body when present beyond certain limits, e.g. lead and arsenic.

2. Impurities which, though otherwise harmless, are present in such proportions that is not desirable. The presence of sodium bromide in the more expensive potassium bromide is not likely to cause harm to the patient. However medicinal quality potassium bromide should contain only potassium bromide and not contain large quantities of sodium bromide.
3. Impurities which bring down the keeping properties of the substances. For example a small amount of moisture may cause many substances to be easily oxidized or to undergo hydrolysis.

4. Impurities which render the medicament incompatible with other substances.

5. Impurities which cause what are known as technical difficulties in the use of the substance, for example presence of potassium iodate in a sample of potassium iodide. Such a sample will liberate iodine on being mixed with a mineral acid due to the interaction of both the substances.

6. Impurities which contribute a different odour or colour to the main substance and so are not desirable. Sodium salicylate in often discolored due to phenolic impurities. Sodium chloride becomes damp due to the presence of traces of deliquescent magnesium salts.

Generally medical compounds should not only be free from undue amounts of toxic and undesirable substances but should also be of a reasonably pure quality. Those impurities, such as lead and arsenic which have deleterious effects, should not be present in amounts likely to be harmful. Very low limits are fixed for such impurities. Similarly very low limits are fixed for the other types of impurities also stated and is at the same time difficult to remove, the limits may be fixed every as high as 5-10%.

**Sources of impurities in pharmacopoeial substances:**

Impurities in pharmacopoeial may be due to the following sources:

a) **Raw material used in manufacture**

A good example is the presence of tin, lead, silver, copper, cobalt and gold in bismuth salts. These metals occur along with bismuth ores. Rock salt contains small amounts of calcium and magnesium salts so that sodium chloride prepared from rock salt may contain traces of calcium and magnesium salts.

b) **The method of manufacture**
Contamination by reagents and solvents at various stages of the manufacturing process may give rise to impurities as given below.

i. Reagents employed in the process. Lead as an impurity may result from the sulphuric acid used as reagent, especially if it has been prepared by the lead chamber process. Soluble alkali may be an impurity in calcium carbonate if the calcium carbonate is made by reacting calcium chloride and sodium carbonate and not properly washed.

ii. Solvents. Water is the solvent easily available and cheap and is used in the manufacture of inorganic chemicals. This can give rise to trace impurities such as sodium, calcium, magnesium, carbonate, chloride and sulphate ions. These difficulties do not arise in the use of purified water (distilled or demineralised water).

iii. The reaction vessels. The vessels used in the manufacturing process are made of metals like copper, iron, aluminium, zinc, nickel and tin though these days may of these metals are replaced by stainless due to the solvent action of the raw materials on the material of the plant. Glass vessels may give rise to traces of alkali, though this is unlikely if the vessels are made of neutral glass.

c) Atmospheric contaminants

Atmospheric contamination may take place through dust, sulphur dioxide, hydrogen sulphide etc. Carbon dioxide and water vapour also contaminate substances which are affected by their action.

d) Decomposition of the product during storage

Many chemical substances undergo changes due to careless storage. Ferrous sulphate is slowly changed into insoluble ferric oxide by air and moisture. Solution of potassium hydroxide absorbs carbon dioxide on exposure to air and exerts a solvent action on lead glass. Therefore it should be stored in well-stopper bottles of green glass which is lead-free. There are certain precautions regarding storages and if they are observed, decomposition and deterioration of substances could be brought down if not totally eliminated. All chemicals should be stored in
tightly closed containers made of dark glass and extremes of temperatures should be avoided. Sunlight affects many chemicals. For example bismuth carbonate turns black on exposure to sunlight for a long period. Such chemicals should be stored in a dark preferably.

e) Deliberate adulteration with spurious of useless materials

This is a still common occurrence in some parts of the country where the drug and cosmetics Act has not yet been properly enforce therefore one has to be vigilant and purchase drugs only from repeat manufacturers.

LIMIT TESTS [Rajasekaran, V. N. (1994)]

Limit tests are quantitative or semi-quantitative tests which and designed to detect and limit small quantities of impurities which likely to be present in the substance. They may to of three types:

a) Tests which show no visible reaction

It may be stated that on testing as prescribed there shall be colour, opalescence or precipitate, whichever is relevant. Such negative tests only indicate the absence of an undesirably large amount of the impurity.

b) Methods of comparison

These tests need a standard containing a certain quantity on impurity and a test to be set up at the same time and under the same conditions. In this way, it is possible to compare the amount of the impurity in the substance with a standard of known concentration and find out whether the impurity is within or excess of the limit prescribed this is the basis of the official limit tests for chloride, sulphate, iron etc.

c) Quantitative determinations

Here the amount of the impurity present is actually determined and compared with the numerical limit given in the pharmacopoeia.
Examples are:

1. Limits of soluble matter
2. Limits of insoluble matter
3. Limits of non-volatile matter
4. Limits of moisture and volatile matter
5. Limits of residue on ignition
6. Loss on ignition
7. Ash values

However we will limit our discussion to the comparison methods. These limit tests involve simple comparisons of opalescence, turbidity or colour with the standards prescribed in the pharmacopoeias. The variations in the permissible limits for the various substances are obtained by taking varying quantities of the substance under test. In these limit tests the extent of opalescence, turbidity or colour produced influenced by the presence of other impurities present in the substance and also by variations in time and method of performance of tests and hence the pharmacopoeias do not prescribe values for these tests.

RADIO PHARMACEUTICALS AND CONTRAST MEDIA [Rajasekaran, V. N. (1994)]

ATOMIC STRUCTURE

Matter is made up of atoms. An atom is composed of a very small, very dense, positively charged nucleus surrounded by sufficient number of negatively charged electrons in different orbits so that the atom is electrically neutral. Practically all the mass of the atom is in the nucleus.

The nucleus contains positively charged protons and neutrons. The neutrons have no charge. The number of protons in the nucleus is known as the atomic number (Z). It is equal to the number of electrons revolving around the nucleus. The mass number (A) is the number of
protons and neutrons in the nucleus. The mass number represents the weight of the atom (atomic weight), since the weight of the electrons is negligible.

The hydrogen atom is the lightest of the atomic species. It contains only one proton in the nucleus which is surrounded by one electron. The heaviest naturally occurring element is uranium. It contains in its nucleus 92 protons and 146 neutrons. To represent an atom with all the above details, its symbol is written as below;

\[ A \text{ } X \]

\[ Z \text{ } \]

\[ X \text{ } \]

\[ Z \text{ } \]

\[ X \text{ } \]

Examples:

1. Hydrogen  \[ \frac{1}{1} H \]
2. Lithium  \[ \frac{7}{3} Li \]
3. Nitrogen  \[ \frac{14}{7} N \]
4. Oxygen  \[ \frac{16}{8} O \]
5. Sodium  \[ \frac{23}{11} Na \]
6. Chlorine  \[ \frac{35}{17} Cl \]

ISOTOPES

Sometimes an atom of an element (known as a nuclide) may have the same number of protons on the nucleus but the number of neutrons may be different. Therefore its mass number is different while the atomic number is the same. This is called an isotope of the element.

Isotopes occur in nature and an element may be considered to be a mixture of isotopes. However the isotopes occur mixed in the same proportions always. Thus the atomic weight is always the same because it is the average weight of all the atoms in the isotopic mixture.
Examples of Isotopes

1. Isotopes of hydrogen

   (Hydrogen, deuterium and tritium)

   \( ^1\text{H} \), \( ^2\text{H} \) and \( ^3\text{H} \)

2. Isotopes of carbon

   \( ^{12}\text{C} \) and \( ^{13}\text{C} \)

3. Isotopes of oxygen

   \( ^{16}\text{O} \), \( ^{17}\text{O} \) and \( ^{18}\text{O} \)

4. Isotopes of Chlorine

   \( ^{35}\text{Cl} \), \( ^{37}\text{Cl} \) and \( ^{38}\text{Cl} \)

5. Isotopes of iron

   \( ^{54}\text{Fe} \) and \( ^{56}\text{Fe} \)

6. Isotopes of bromine

   \( ^{79}\text{Br} \) and \( ^{81}\text{Br} \)

All the isotopes of an element follow the same chemical reactions. Therefore isotopes are chemically identical.

RADIOACTIVITY

The atoms of heavy elements such as uranium are unstable. In their nucleus the neutrons to proton ration is high. Only nuclei which have almost the same number of neutrons and protons are stable. So the nucleus of elements like uranium-235 throw out or emit some particles such as the alpha particles or beta particles and also give out some radiation like the x-rays in order to attain stability. This is known as radioactivity.

Types of Radiations: The radiations emitted due to radioactivity are of three types. They can be easily separated by passing them between oppositely charged plates.

The radiation which bends towards the negatively charged plate must itself be positively charged and is known as alpha rays. That which bends towards the positively charged plate is obviously negatively charged itself and is known as beta rays. The third one which does not bend towards either the positively charged plate or the negatively charged plate but passes straight through is uncharged and is known as gamma rays.
**Alpha Rays:** Alpha rays consist of streams of alpha particles. They have two positive charges and a mass of 4 amu (atomic mass units). So they are helium nuclei and may be represented as $^4_2 \alpha$ or $^4_2 \text{He}$.

They have very high velocity equal to about one-tenth (1/10) of that of light. However their penetrating power through matter is very low. They can be stopped even by a sheet of paper. They have the capacity to cause intense ionization in the molecules of gases through which they pass. This means that alpha rays, because of their positive charge and relatively high velocity, break off electrons in the gas molecules and produce ion-pairs (that is, electrons and positively charged irons).

**Beta rays:** Beta rays consist of streams of electrons. They have very small mass and a negative charge of one. A beta particle may be represented as $^0_{-1} \beta$ or $^0_{-1} \text{e}$. They move with a velocity equal to that of light. They are very much more penetrating than alpha rays. They can be stopped only by a 1 cm thick aluminium sheet. This is because of their small mass.

**Gamma rays:** Gamma rays do not consist of particles. They are radiation of wave form shorter than x-rays. They are usually emitted along with alpha rays or beta rays. They have neither mass nor charge and may be represented as $^0_{0} \gamma$. Gamma rays also move with the velocity of light and have the height penetrating power. They can be stopped only by a 5 cm thick sheet of lead or concrete of many meters thickness. However they are very weak ionizers.

**DETECTION AND MEASUREMENT OF RADIO ACTIVITY**

There are several methods for detecting and measuring radioactive radiation these are:

1. Cloud chamber method.
2. Ionisation chamber method.
4. Scintillation counter method.

The most widely used methods are.
GEIGER – MULLER COUNTER

This consists of a cylindrical metal tube serving as the cathode and a central wire inside the tube serving as the anode. Argon gas is filled in the tube at a reduced pressure of 0.1 atmosphere.

A potential difference of about 1000 volts is applied across the two electrodes. The argon gas is ionized whenever any alpha or beta particle enters the tube through the mica window. The positively charged argon ions, formed due to the ionization of the gas, are attracted to the cathode and the negatively charged electrons to the anode. Thus an electrical pulse flows between the electrodes whenever one alpha or beta particle enters the tube. The electrical pulses are counted in an automatic counter. The intensity of the radioactivity of any radioactive material can be found out by finding the number of pulses per minute.

SCINTILLATION COUNTER

Scintillation means a flash of light. In this counter the radioactive substance mounted on a wire emits alpha particles. Each alpha particle strikes a zinc sulphide screen and gives a flash. The flashes produced per second can be counted to find out the intensity of radiation.

In the well-type scintillation counter, instead of the zinc sulphide screen a crystal of sodium iodide mixed with a little thallium iodide is used. The sample of the radioactive substance is kept in a well cut in the crystal wall and produces flashes. There scintillations fall on a photoelectric cell which converts the light energy into electrical energy for each flash. There are counted in a counter, even up to one million scintillations per second. The counter can be used for counting either alpha or beta particles.

BIOLOGICAL EFFECTS OF RADIATION

Humans may at times be exposed to radiation from various sources such as cosmic rays, x-rays (in diagnostic procedures), monazite sands of Kerala containing radioactive thorium etc. abnormally we may be exposed to the intense radiation due to the testing and explosion (as in Hiroshima and Nagasaki in 1945) of fission bombs (atom bombs) and radiation due to leakage
form nuclear reactors such as the Chernobyl nuclear disaster in Russia in which the radiation was carried to many parts of Europe from Russia as a fallout.

Therefore in this context there is need to study the biological effects of radiation. The radiations that can produce damage are alpha particles, beta particles, protons, neutrons, gamma rays and x-rays. They do so by ionization and excitement of molecules in cells. One theory says that they ionize the water present in the cells to the extent of 80% and produce free radicals. These free radicals are highly unstable and very active. They react with each other and also with organic molecules in the cells producing a variety of secondary chemical substance such as peroxides which are very injurious to the cell. The DNA in the cell is particularly sensitive and is damaged, destroying the cell. There is also inhibition of mitosis or cell division.

The damage caused by radiation may be divided into two types.

1. Somatic effects, affecting the various parts of the body.
2. Genetic effects, affecting the reproduction and heredity.

The initial symptoms in humans are severe nausea, vomiting and prostration. After a few hours diarrhea comes on due to ulceration of the gut with bleeding. Red cells, lymphocytes, blood platelets and granulocytes are found to be reduced in number, leading to anaemia etc. antibody production is decreased and the body resistance comes down promoting infection. Death will follow after 2 to 3 weeks after heavy does of radiation.

**Delayed Effect of Radiation**

Continuous exposure to low level radiation can give rise to delayed effects of radiation. The hair grays quickly and other degenerative changes take place leading to premature ageing. Several types of cancer are induced. These include cancer of skin, lung cancer, leukemia, Hodgkin’s disease etc. Large doses of radiation may inactive the gonads leading to sterility. Radiation exposure also produces chromosomal damage giving rise to mutations and consequent decreased fertility.

**ARTIFICIAL RADIO ACTIVITY**
Artificial radio activity can be brought about by bombarding a suitable element with neutrons (slow neutrons are very effective). This disturbs the nucleus which becomes unstable. To regain stability it starts disintegrating and emitting some rays and thus has become radioactive.

The radio active isotopes of certain elements have been used as tracers in various types of investigations. The stable element and a little of its radioactive isotope are mixed and converted to the required compounds. The compounds are now said to be labeled. The stable and the radioactive isotopes go through all physical and chemical changes in the same ratio. Thus the compound can be estimated by simply measuring the radioactivity of the active isotope. Biochemical and physiological properties of certain compounds can be studied like this. For this mixture of stable and radioisotopes is fed to an animal. It may be distributed to different parts of the body or concentrated in one particular part of body. Thus sodium radioiodide is absorbed mainly by the thyroid gland.

Important artificial radio nuclides used in medicine are cobalt-60 (used, like radium, for the treatment of cancer), phosphorus-32 (used in blood studies) and iodine-131 (used in the diagnosis and treatment of thyroid disease).

**MEDICAL USES OF RADIO ISOTOPES**

1. **Radiation sterilization:**
   Thermo-labile drugs such as penicillin may be sterilized by radiation from radio nuclides. All microorganisms and their spores are killed within seconds and the drug becomes sterile. Gamma rays from radio-isotopes are used for this purpose in addition to high speed electrons.

2. **Radio Therapy:**
   Here the aim is to destroy diseased tissue without destroying healthy tissue. Gamma radiation, being the most penetrating, is used for destroying deep-seated tumours. Both external and internal therapy is used. X-radiation can only be used for external therapy. In internal therapy the radio nuclide is placed in a natural or surgical cavity of the body or injected into the tissue. Sometime, there is selective uptake by a diseased organ. Gamma-
emitter iodine-131 is given orally and is taken up by the thyroid. Sources with a short half-life such as iodine-131 and gold-198 can be left in the body permanently but sources such as radium-226 with a long half-life must be removed after the treatment is over.

3. **Radio Diagnosis:**

   Many materials which are opaque to visible light are transparent to x-rays and gamma rays.

   The function of a particular organ may be studied by following or tracing the manner in which it secretes or removes a particular radio-isotope e.g., Iodine (given in the form of sodium radioiodide) is taken up by the thyroid gland. This can be easily followed by a radiation detector. Another use of iodine-131 is in the form of diiodofluorescein used to map out a brain tumour before surgery.

**Storage of Radio Isotopes:**

   It is necessary to protect people from the harmful radiations emitted by the radioisotopes since we earlier studied about the harmful biological effects caused by the radiations. For this purpose the radioisotopes should be kept in remote places in the general store where people should be allowed to go. The radioisotopes emitting gamma rays should be kept in lead containers of suitable thickness, as gamma rays are most penetrating. Alpha and beta rays are not as penetrating as gamma rays. The area where the radioactive materials are kept should be monitored regularly for radioactivity and any untoward increase in radiation should be detected in time and remedial measures taken.

**Precautions in the use of radioisotopes:** The following precautions should be observed while handling the radio isotopes:

1. Glass apparatus and other equipment should be tested for radioactivity before use.
2. Rubber gloves should be used while handling radioactive materials.
3. Absorbent paper should be used while handling radioactive liquids so that any liquids so that any liquid spilled may be absorbed by the paper and paper thrown out.
4. Pipettes should not be used for withdrawing or transferring radioactive liquids.

**Half-life Period:**
The rate of disintegration of a radio active element is independent of temperature, pressure or its state of chemical combination. The time required for the disappearance of one half of the original amount of the radio active substance is called its Half-life Period.

**UNITS OF RADIO ACTIVITY**

The unit of radio activity is the Curie (Ci). It is the weight of any radio active substance undergoing the same number of disintegrations per second as 1g of radium, which are \(3.7 \times 10^{10}\) disintegrations per second. Each disintegration is also known as a Becquerel (Bq). Therefore 1curie is equal to \(3.7 \times 10^{10}\) Becquerel’s. Curie is a large unit; so in its place smaller units such as millicuries and microcuries are used frequently. One millicurie is one-thousandth (1/1000) of a curie and therefore represents \(3.7 \times 10^7\) disintegrations per second or becquerels. Likewise one microcurie is one – thousandth (1/1000) of a millicurie and so represents \(3.7 \times 10^4\) disintegrations per second or becquerels. It is stressed that the weight of any radioactive substance with a radioactivity of one curie needs not be 1 g in the case of radium but may be different.

**RADIO PHARMACEUTICALS IN MEDICAL PRACTICE**

The following are some of the radio pharamaceuticals official in B.P.

**FERRIC CITRATE (\(^{59}\)Fe) INJECTION**

This is a sterile solution containing \(^{59}\)Fe iron in the ferric state. It also contains 1 per cent of sodium citrate and also enough sodium chloride to make the solution isotonic with blood serum. Neutron irradiation of iron-58 produced the radio-active isotope, iron-59. Its half-life is 44.6 days only. The rion-58 selected for radiation should be sufficiently low in the content of iron-54 others wise the radioactive isotope; iron-55 may also be produced. Since it has a half-life of 2.87 years, its presence in this injection is not desirable. Therefore a limit of 2 per cent is prescribed on the content of iron-55 in the total activity. Iron-54 present along with iron-58 is irradiated to get radioactive iron-59; any irion-54 present along with iron-58 is electromagnetically separated so that the product will be able to comply with this provision of the content of iron-55 not to exceed 2 per cent of total activity. Radioactive isotope \(^{59}\)Fe is
capable of emitting both beta particles and gamma rays. It is sterilized by heating in an Autoclave. The Following are the official standards that then injection is required to comply with:

**Description:**

A clear, colour less or faintly orange-brown solution.

**Tests for Identity**

(a) It has already been indicated that it emits gamma rays. Therefore the gamma ray spectrum of the injection should be compared with the gamma ray spectrum of an already standardized iron-59 solution. The two must be identical. Further the principal energies of the gamma rays should be 1.10 and 1.29 MeV (million electron volts). The activity of the injection also decays with a half-life of 44.6 days.

(b) When the injection is boiled with mercuric sulphate solution and potassium permanganate is added, the potassium permanganate is decolorised and a white precipitate is produced. This is a general test for citrates.

**pH:** 6 to 8.

**Radionuclidic purity:**

The gamma ray spectrum of the injection is compared with the gamma ray spectrum of a standardized iron-59 solution. These should be no significant difference indicating that the injection contains only the required iron-59 isotope. In short this is a test for isotopic purity (refer also the first test for identity). If any iron-55 is present in may be detected by this test.

**Total iron:**

The amount of iron present is limited by this test. In this test a volume of the substance equivalent to 10 micro curies is subjected to the limit test for iron and required to comply with it.

**Sterility:**
Since this a parenteral preparation, it must comply with the test for sterility. However the B.P. State that the preparation may be released for use before completion of the test. Because of the radioactive nature of the preparation, it is not always possible to wait for final results of the test for sterility for use of the batch.

**Standard:**

The content of iron-59 should be between 90 and 110 per cent of what is stated on the label on the particular date stated on the label. The specific activity is not less than 1 microcurie per mg of iron (37 megabecquerels) on the date stated on the label.

**Assay:**

It is assayed for its activity by detection of its gamma radiation in a scintillation counter and comparing it with the activity of a standardized iron-59 solution.

**Use:**

In the investigation of blood disorders.

**SODIUM IODIDE (\(^{131}\text{I}\)) SOLUTION**

This solution is suitable for oral administration and it contains iodine-131 in the form of sodium iodide. Sodium thiosulphate or other suitable reducing agent is also present. By irradiating tellurium with neutrons, we can obtain the radioactive isotope of iodine-131 which is converted to sodium radio iodide.

**Description:**

It is a clear, colour less solution. It has a half-life of 8.06 days and emits both beta particles and gamma rays.

**Test for identity:**
The gamma ray spectrum of this solution is compared with the gamma ray spectrum of standardized iodine-131 solutions. There should be no significant difference. Further the principal gamma-photon has energy of 0.36 MeV.

**pH:** 7 to 10.

**Radionuclidic purity:**

The gamma ray spectrum measured in a suitable instrument is compared with the gamma ray spectrum of a standardized iodine-131 solution. There should be no significant difference.

This test is meant to ensure the absence of isotopes other than sodium (\(^{131}\)I) iodide.

**Radiochemical purity:**

This test is meant to ensure that the entire radioactivity is present only in the iodide ion and not because of the presence of some other iodine-containing compound such as the iodate.

It is done by paper chromatography. In this it should be proved that the radioactive part of the paper chromatogram coincides with the position of the iodide ion. It should also be proved that the position corresponding to the iodate ion has no radioactivity.

**Standard:**

The content of iodine-131 activity should be between 90 and 100 per cent of that stated on the label at the time and hour stated on the label. The specific activity is not less than 5 mCi per microgram or 185 MBq (megabecquerels) per microgram of iodine at the date and hour stated on the label.

**Assay:**

By using a suitable counter, the activity is compared with the activity of a standardized iodine-131 solution. It should have the iodine-131 activity and specific activity as prescribed.

**Use:** used for the diagnosis and treatment of disorders of the thyroid gland.

**SODIUM PHOSPHATE (\(^{32}\)P) INJECTION**
This is a sterile solution of disodium and monosodium orthophosphates in isotonic saline. Phosphoius-32 is produced by the neutron irradiation of sulphur and is a radioactive isotope of phosphorus. It emits only beta particles with energy of 1.71 MeV. It general requirements for all injections and in addition should comply with the following also:

**Tests for identity:**

The beta ray spectrum or the beta ray absorption curve of the injection is measured and compared with that of a phosphorus-32 solution obtained under the same conditions. There should be no significant difference. The beta radiation has also an energy of 1.7 MeV.

**pH:** between 6 and 8

**Radionuclidic purity:**

This is to prove that the radio activity in the solution comes only from the radioisotope phosphorous-32 and not from any other radioisotope. For this purpose the beta-ray spectrum or the beta-ray absorption curve is measured and compared with that of a standardized phosphorus-32 solution obtained under the same conditions. There should be no significant difference.

**Radiochemical Purity:**

This test is designed to prove that the entire radioactivity resides in the phosphate ion and not in any other ion such as the phosphate. For this purpose the solution is first diluted to a subjected to paper chromatography separately along with inactive orthophosphoric acid. The position of the inactive phosphoric acid is determined by spraying perchloric acid and ammonium molybdate solution and then exposing to hydrogen sulphide when a blue colour develops. The radioactive spot is then located by suitable instrument and measured. Not less than 95 per cent of the total radioactivity should be present in the spot corresponding to the orthophosphoric acid.

**Total phosphate:**

The amount of phosphate is limited by diluting the solution with water and treating with ammonium metavanadate, ammonium molybdate and perchloric acid solutions. The color
produced after diluting to the specified volume is compared with the colour produced in a standard solution prepared at the same time and under the same conditions and containing a definite amount of orthophosphate. The colour in the test solution should not be more intense than the colour in the standard solution.

**Sterility:**

The test for sterility is done. However the preparation may be released for use before the completion of the test.

**Standard:**

The content of phosphorus-32 activity is between 90 and 110 percent of that stated on the label at the date and hour stated on the label. The specific activity is not less then 0.3 mCi (11.1MBq) per mg of orthophosphate ion.

**Assay:**

The activity is determined by comparing with a standardized phosphorus-32 solution by using a suitable instrument.

**Use:** Used in the treatment of polycythaemia vera.

**X-RAY CONTRACT MEDIA**

Most of the body tissues are transparent to x-rays which means x-rays are able to pass through them. However some chemicals such as barium sulphate are opaque to x-rays that is they block the passage of x-rays. These substances are known as radio-opaque media or x-ray contrast media. They are used for diagnostic purposes. For example in the case of barium sulphate, it is made into a suspension with water and administered either orally or rectally by injection. The barium sulphate coats the mucosa of the gut and when x-rays are allowed to pass through and fall on an x-ray film, diseases such as ulcers etc are mapped out.
**SOLUBILITY DESCRIPTIONS** [Alfred Martin, (2011a)]

<table>
<thead>
<tr>
<th>Description</th>
<th>Approximate volume of solvent required to dissolve 1 part of solute by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>Less then 1 part</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1 to 10 parts</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30 parts</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 10 parts</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1,000 parts</td>
</tr>
<tr>
<td>Very Slightly soluble</td>
<td>From 1,000 to 10,000 parts</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>More than 10,000 parts</td>
</tr>
</tbody>
</table>

**MEDICATION HISTORY** [Sampathkumar, K.; (2008)]

The pharmacist should guide and assist the people in the maintenance of “medication history” of each patient. This shall be in the form of a booklet. They should advice the people to maintain this, right from the beginning of the birth of a child. The following information shall be entered in the history book,

1. Name and sex
2. Date of birth
3. Primary immunization dates
4. Booster dose administration
5. Blood group
6. Diseases infected (chronic illness), period and therapy details.
7. Hereditary diseases if any on both mother and father sides.

8. Allergic details to any food items.

9. Allergic details to any specific group of drugs.

10. Details of over the counter drugs (OTC), which are normally taken as self-medication.

11. Details of any side effects had with the drugs, permanent and temporary (i.e., which disappeared on withdrawal/ discontinuing of the drug).

12. Habits like late to bed and late to rise, type and time of food eating, smoking, tobacco, alcohol drinks etc.

13. Periodicity of getting affected by headaches, loose motion, vomiting due to hyperbilirubinemia, sleeplessness, diarrhea and constipation.

The medication history contains all vital information about the individual. Previous background of drug therapy because drugs are also one of the cause of disease. Withdrawal of drugs can cause certain disease. Drugs now being taken for disease may conceal another disease of the body by false results in clinical chemical tests. One drug can interact with another drug taken and may neutralize each other without producing any therapeutic in the body or they may produce a toxic effect due to synergism.

Medication history can assist the choice of drugs in the future. The pharmacist should assist the patients in preparing the past information by suitable questions and from the old prescriptions if available. People should be advised to carry the medication history booklet, with them, whenever they visit physicians, especially when they consult new doctors.

**PATIENT COUNSELLING** [Sampathkumar, K.; (2008)]

Patient counselling is of two types- one for the prescription drugs and the other for the OTC drugs. In case of prescription drugs, this will be easier, as the prescribes instructs orally or writes most of the instructions in the prescription itself like dose, administration, diet restrictions
etc. The patient has to only comply with them. World Health Organization defines “Compliance as a faithful adherence by the patient to the prescribers instructions”. ‘Compliance’ or ‘Adherence’ can also be described as the extent to which a patient takes their medication, in accordance with the prescriber.

“Patient non-compliance” is a term which refers to the fault of the patient inappropriate use of medication. Non-compliance is not restricted to drug therapy, but also includes failure to obey instructions on other aspects of health care such as dieting, exercise, and drinking or smoking habits.

For counseling to be successful, communication, the main form used should be good and effective. For this the communication should be simple, clear and understandable by receiver. There should not be any scope for doubt or ambiguity. Compliance can never be assumed in patients.

Some of the counselling advises which a pharmacist can perform are given under. These may appear as simple, but are relevant and important for general public.

1. How to remove the drugs from the pack and use – blister, strip, pack etc.
2. How to fit in the dropper assembly and use.
3. To specify whether the drug is for internal or external use.
4. To tell the route of administration.
5. To close and store the opened the drug pack properly.
6. Diet restrictions and recommendations.
7. Side effects, drug interactions, allergies that can occur.
8. As far as possible give the reasons for following certain instructions like “Do not take with milk”, “Take after meals” and “not on empty stomach” etc.

**Other specific instructions that can be given are:**
1. Do not break an enteric coated tablet for easy swallowing.

2. Chew and masticate well the chewable tablets.

3. Lozenges and troches to be sucked slowly in the tongue.

4. Aluminium hydroxide plain may cause constipation with some patients.

5. Liquid paraffin shall not be used for long period as laxative.

6. Vitamin B2 (Riboflavine) may produce yellow urine.

7. Phenolphthalein tablets may colour urine and faeces pink.

8. Diabetic patients should avoid alcoholic beverages.

9. Milk or antacids should not be taken with tetracyclines.

10. Butazzone tablets not to be taken on empty stomach.

11. Silica gel bags kept in some of the bottle packs (moisture absorbent) should not be consumed.

12. Shake the bottle before use instruction has to be followed every time before administration.

13. Keep all medicines away from the reach of children.

The pharmacists know the common factors responsible for medication errors, so that he can prevent some of them and counsel the patient effectively. They are:

1. Misinterpretation of the prescription due to:

   (a) bad handwriting, (b) poor design of the prescription sheet, (c) incomplete or insufficient instructions, (d) overwriting by which doubts or double meaning are created.

2. Failure to follow uniform metric system in the prescription.
3. Duplication of drug prescribing

4. Absence of prescription from the patient and absence of case history on the bed side in the ward.

5. Non-available drugs being prescribed.

6. Prescribing incompatible drugs.

7. Using old container without removing the old label.

8. Transfer of drugs from one container to another in the ward.

9. Large number of less essential drugs being prescribed simultaneously.

10. Increase mobility of patients within the ward and within the hospital.

11. Mobility of visitors indiscriminately within the hospital and wards.

12. The number of nurses involved in the administration of drugs, as a result of shorter span of duty, part time and shift working.

13. Setting out the doses in advance, especially when the nurses change their duty.

14. Not sticking to the time schedule.

**DRUG INTERACTIONS** [Sampathkumar, K.; (2008)]

The development of many new therapeutically effective drugs in recent years has resulted in considerable progress in the treatment of numerous disease states. However, accompanying the therapeutic benefits derived from use of these agents has been an increased incidence of drug-related problems.

Although many drug-related problems develop unexpectedly and are impossible to predict, others are related to known pharmacologic actions of the drugs and can reasonably be anticipated. Many individuals are being treated with a number of drugs during the same period of time, the drug therapy becomes more complex and the ability to predict the magnitude of a
specific action of any given drug diminishes. This requires the maintenance of complete (past and present) medication records of patients. Also monitoring and supervision of drug therapy enables the physician to prevent the complication at the early stage itself. The Pharmacist is in a unique involvement in and contribution to provision of drug therapy that is both efficacious and safe.

Definition: A drug interaction may be defined as a situation in which the effects of one drug are altered by prior or concurrent administration of another drug. Apart from drug – drug interaction, it also includes

1. Interaction with food (drug – food interaction)
2. Interaction due to disease status (Drug – disease interaction)

Drug interactions become clinically more significant in patients with alcoholics, smokers, impaired renal function and abnormal metabolic activity. Certain group of drugs like oral hypoglycemic agents, antihypertensive agents, anticoagulants, digitalis and monoamine oxidase inhibitors show large number of drug interactions. Drug interactions are harmful to the patients by increasing efficacy or toxicity or by decreasing the therapeutic effect of a coadministered drug. Sometimes interactions may be beneficial when it allows reduction in dose by enhanced efficacy without increased toxicity (Synergistic effect).

Drug interactions may be due to other factors like

i. Concurrent use of prescription and non-prescription use of drugs,
ii. Patient’s non-compliance of instructions,
iii. Abuse of drugs,
iv. Environmental factors, etc.

Mechanism of drug interaction

The Mechanism of drug interaction is categorized as being pharmacokinetic or pharmacodynamic types. Pharmakokinetic interactions are those in which the absorption, distribution, metabolism or excretion (ADME) of a drug is altered. Pharmacodynamic
interactions are those that involve the actions or effects of drugs and include situations such as the concurrent administration of drugs having similar or opposing pharmacological effects and situations in which the sensitivity or responsiveness of the tissues to one drug is altered by another. Pharmacodynamic interactions are more frequently encountered than Pharmacokinetic interactions.

I. Pharmacokinetic Interactions

1. Gastrointestinal Absorption interferences reduce the therapeutic effect of the drug. Sometimes there is delay of absorption process and onset of action is prolonged. One oral drug may interfere with absorption of another in the GIT by altering number of variables.

   a. Alteration of pH – Non-ionised from of drug is more lipid soluble; hence it is rapidly absorbed than the ionized form. Acidic drugs (e.g., aspirin) remains unionized at the stomach pH and get rapidly absorbed from stomach. Similarly, basic drugs are better absorbed from the intestine where they are in unionized state.

      Antacids may reduce the absorption of acidic drugs and enhance the absorption of basic drugs. Antacids delay the absorption of Phenobarbital. If enteric coated tablets like Biscodyl tablets are given a short period after an antacid, these tablets will disintegrate in stomach instead of intestine.

   b. Complexation and adsorption – certain substances can bind with other drugs thereby preventing absorption, e.g., Tetracyclines combines with metal ions such as calcium, magnesium, aluminium and iron in GIT to form complexes that are poorly absorbed. Therefore tetracycline should not be given with dietary items like milk (containing calcium), antacid, and iron preparations.

      Adsorbents like kaolin are given in diarrhea so as to adsorb substances causing diarrhea. These adsorbents may adsorb certain drugs like digoxin, tetracycline, and phenothiazines.

   c. Alteration of Motility/Rate of Gastric Emptying – A drug like cathartic increases the gastric motility, thereby shortens gastric emptying time. This could result in a decreased absorption of drugs in the stomach/
Anticholinergics reduce the gastric motility. This increases the absorption of certain drugs like digoxin and prednisone. In some cases, it may decrease absorption of active substance, due to reduced peristalsis resulting in retardation of dissolution.

d. Surfactants- some surfactants can influence the rate and / or the extent of absorption of certain drugs. Some may favour drug absorption. On prolonged administration of deoctyl sodium sulfosuccinate concurrently with mineral oil increases the absorption of mineral oil.

e. Inhibition of Gastrointestinal Enzymes – folic acid is present in the form of polyglutamates in the food sources is absorbed poorly. But by the intestinal conjugase enzyme, this is converted into monoglutamate which is absorbed easily in the body.

2. Alteration of Distribution

Displacement from Protein Binding Sites – drugs binds to proteins in different sites in our system. When two drugs are administered concurrently and are capable of binding to proteins, competitive binding takes place. The drug that has the greater affinity will displace the other from plasma or tissue proteins. Some examples are as follows.

<table>
<thead>
<tr>
<th>Bound drug</th>
<th>Displacing drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) warfarin</td>
<td>Phenylbutazone, Chloral hydrate</td>
<td>Haemorrhage</td>
</tr>
<tr>
<td>(ii) Methotrexate</td>
<td>Sulphonamides, Salicylates</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>(iii) Thiopentone</td>
<td>Sulphonamides</td>
<td>Prolonged anesthesia</td>
</tr>
<tr>
<td>(iv) Tolbutamide</td>
<td>Salicylates, Phenylbutazone</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>(v) Bilirubin</td>
<td>Sulphonamides, Salicylates</td>
<td>Kernicterus</td>
</tr>
</tbody>
</table>

3. Stimulation of metabolism (Enzyme induction)
A drug may stimulate metabolism of another drug mainly by increasing the activity of hepatic enzymes, which are involved in the metabolism of the therapeutic agents. This increase in enzyme inducing drug may cause faster biotransformation and a decrease in the pharmacologic action of the subsequent drug. Alcohol, chloral hydrate, phenytion, testosterone, prednisone are enzyme inducing drugs.

4. Inhibition of metabolism

One drug inhibits the metabolism of another drug, resulting in prolonged and intensified activity of the latter. Isoniazid, oral hypoglycemic, anabolic agents, metronidazole, cimitidine, chloramphenicol and oral anticoagulants are some inhibitor agents.

5. Alteration of Excretion

a. Alteration of urinary pH- Non – ionized drugs diffuse from urine, back into the blood, whereas ionized form of drugs is excreted easily. Thus any drug that will change urinary pH will alter he excretion of weak acid or weak base.

b. Interference with Urinary excreting – competition for tubular transport between concurrently administered drugs commonly interferes with urinary excretion. This can block or lower down excretion of the competing drugs.

II. Pharmacodynamic interactions

1. Drugs having opposing pharmacological effects- At times two drugs having opposite pharmacological effects (antagonistic) may be administered to the patient, by different doctors for different may be administered to the patient, by different doctors for different ophthalmologist may prescribe a also cholinergic drug such as pilocarpine for a patient who is also taking an anticholinergic preparation by another for a gastrointestinal problems.

2. Thiazides increase the blood glucose levels. Thus if it is administered in a diabetic patient who is treatment with insulin or tolbutamide, hypoglycemic action of these drugs will be counter acted. This needs increase in dose of antidiabetics.
3. Drugs having similar pharmacological effects- drugs acting at the same site or influencing same physiological effects, causes synergistic effect. It will be difficult to predict the response in such cases. Example- Administration of CNS depressants when the patient has alcoholic beverage; Antiparkinsonism agent trihexyphenidyl with chlorpromazine and amitriptyline resulting in excessive anticholinergic action; salicylates, propranol with oral hypoglycemic agents, Diuretic thiazide with diazoxide; Diuretics with aminoglycoside antibiotic like streptomycin, kanamycin, neomycin, gentamicin etc.,

4. Drugs interactions at receptor sites – This may occur at the same receptor site or at different receptor sites with same target organ. The effect site or at different receptor sites with same target organ. The effect occurs as a result of binding to specialized areas on depends upon amount of drug in the body, accessibility of drugs to the receptor and affinity of drug for the receptor.

To sum-up, more than one Mechanism will be responsible for certain drug interactions. These Mechanisms may work in concert or in opposition as determinants of the resulting effect.

**DRUG-DRUG INTERACTION [Sampathkumar, K.; (2008)]**

**A. Analgesic Drug Interactions:**

1. **Combination:** Salicylates - Urine alkaliser

   **Mechanism:** Urine becomes alkaline. Renal tubular reabsorption of salicylates is reduced from urine. Enteric coated aspirin tablets may break prematurely in stomach.

   **Clinical significance:** Salicylates serum levels are reduced. Therefore patients on large dose of salicylates should take care if antacids are started or stopped.

2. **Combination:** Salicylates – acidifiers (Ascorbic acid, ammonium chloride)

   **Mechanism:** Urine becomes acidic. Renal tubular reabsorption of salicylates is increased.
Clinical significance: Salicylates serum levels are increased. Prolonged activity leading to adverse effects.

3. Combination: Salicylates – Indomethacin

Mechanism: Aspirin inhibits gastrointestinal absorption of indomethacin

Clinical significance: Serum level of indomethacin decreases. Fecal excretion increases.

4. Combination: Salicylates – Heparin

Mechanism: Aspirin inhibits platelet function. This disturbs haemostatic mechanism necessary to prevent bleeding in heparin treated patients.

Clinical significance: Chances of bleeding are very high. Substitute aspirin with acetoaminophen or non-acetylated salicylate like sodium salicylate.

5. Combination: Salicylates – phenylbutozone

Mechanism: Salicylate compete with phenylbutazone

Clinical significance: Phenylbutazone inhibits uricosuric effects of salicylates. Thus a patient with gout will be adversely affected.

6. Combination: Salicylates – probenecid

Mechanism: Salicylates and probenecid compete for same binding site on plasma albumuinch molecule

Clinical significance: Uricosuric activity of probenecid is decreased.

7. Combination: Phenylbutozone - oral anticoagulants

Mechanism: Phenylbutazone displaces warfarin from plasma protein binding. It inhibit metabolism of more potent isomer of warfarin. It may also cause GIT ulceration and impairs platelet function.
**Clinical significance:** Avoid phenylbutazone in patients receiving oral anticoagulants

8. **Combination:** Phenylbutazone and antidiabetic

**Mechanism:** Carboxylation of tolbutamide is inhibited by phenylbutazone. This increases serum tolbutamide level. It displaces tolbutamide from plasma protein binding.

**Clinical significance:** Increased hypoglycemic response to antidiabetics. Phenylbutazone should be avoided in patients receiving antidiabetics.

**B. Diuretic Drug Interactions**

1. **Combination:** Diuretics (Frusemide, thiazides, ethacrynic acid) - Antidiabetic

**Mechanism:** Thiazides and chlorthiazides antagonize the action of sulfonyl ureas. They cause depression of islets of Langerhans. Potassium loss due to diuretics may also be responsible for this effect.

**Clinical significance:** Patient should be given potassium supplement with less diabetogenic diuretic.

2. **Combination:** Diuretics (thiazides) – Antihypertensives.

**Mechanism:** Thiazides increase the effect of hypotensive effect of antihypertensives like methyl dopa, guanethidine, reuwolfia alkaloids.

**Clinical significance:** Patients should be watched for excessive hypotension.

3. **Combination:** Diuretics (frusemide, thiazides, ethacrynic acid) – Cardiac glycoside

**Mechanism:** Hypoekelemia due to potassium loss by these diuretics may enhance digitalis effects and toxicity.

**Clinical significance:** Potassium replacement therapy should be followed.

4. **Combination:** Ethacrynic acid – Aminoglycoside antibiotics. (gentamicin, neomycin)
**Mechanism:** Ethacrynic acid and aminoglycoside antibiotics both are ototoxic. Similarly ethacrynic acid increases renal toxicity of aminoglycoside antibiotics.

**Clinical significance:** Substitute ethacrynic acid by other diuretic.

5. **Combination:** Frusemide - Phenytoin

**Mechanism:** After chronic therapy with phenytoin, there is increase in sod. absorption. This decreases absorption of frusemide by around 50%. Thus in these patients response to frusemide is very low.

**Clinical significance:** As absorption is decreased increase the dose of frusemide to get desired diuresis.

6. **Combination:** Acetozolamides and thiazides – Quinidine

**Mechanism:** Acetozolamides and thiazides make the urine alkaline; hence ionization of quinidine is suppressed. This increases renal tubular reabsorption of quinidine and in turn its serum level. Thiazides show additive hypotensive effect with parenteral quinidine.

**Clinical significance:** Care should be taken on urine alkalinization on patients on quinidine treatment.

7. **Combination:** Spironolactone, amiloride and triamterine – Potassium chloride

**Mechanism:** Spironolactone is a potassium sparing diuretic (i.e., it conserves potassium), thus if potassium supplement is given along with it, hyperkalemia may occur. It is more dangerous in patients having renal damage.

**Clinical significance:** Potassium supplement should be discontinued.

C. **Cardiovascular Drug Interactions:**
C–1. Cardiac glycoside interactions

1. **Combination**: Digitalis glycosides – Antacids (MgCO$_3$, CaCO$_3$, Mg(OH)$_2$, Al(OH)$_3$, Mg trisilicate)

   **Mechanism**: Gastrointestinal absorption of digoxin is impaired. Absorption is reduced by Mg – trisilicate by 99.5%

   **Clinical significance**: As digoxin has a very narrow therapeutic range; with antacid administration on it may go in sub-therapeutic level. If antacid is to be given the interval between two medicaments should be long enough.

2. **Combination**: Digitalis glycosides – Cimetidine

   **Mechanism**: Cimetidine inhibits metabolism of digoxin. This causes cardiotoxicity.

   **Clinical significance**: Antacids may be substituted for cimetidine if required.

3. **Combination**: Digitoxin - Barbiturates

   **Mechanism**: Barbiturates induce hepatic microsomal enzymes and promote metabolism of digitoxin to digoxin. Half life of digoxin is less than digitoxin. Thus it causes ‘underdigitalization.’

   **Clinical significance**: Digitoxine dose should be increased.

C–2. Antiarrhythmic drug interactions

1. **Combination**: Quinidine digitalis – Glycoside.

   **Mechanism**: Quinidine decreases renal and non renal clearance of digoxin. It also displaces digoxin from binding sites. It increases GIT absorption of digoxin. This increases serum digoxin level and chances of digoxin toxicity.

   **Clinical significance**: Reduce the dose of digoxin or substitute quinidine by lidocaine.

2. **Combination**: Amiodarone - Oral anticoagulants
Mechanism: Amiodarone reduces metabolism of oral anticoagulants. It displaces warfarin from protein binding site. On chronic treatment it may lead to hypoprothrombinemia.

Clinical significance: Avoid this Combination, if possible.

3. Combination: β – blockers (propranolol, atenolol etc.) – Antidiabetic agents

Mechanism: Propranolol inhibits release of glucose from liver glycogen. The various effects seen are:

(i) Increase in insulin induced hypoglycemia.

(ii) Hypertension and bradycardia during hypoglycemia.

(iii) Inhibition of insulin in response to glucose or sulfonylureas.

(iv) Peripheral circulation is impaired.

Clinical significance: Reduce dose of antidiabetic.

C–3 . Antihypertensive drug interactions

1. Combination: Guanethidine (Bethanidine) – Tricyclic antidepressants

Mechanism: Tricyclic antidepressants inhibit the uptake of guanethidine or bethanidine into its site of action in the adrenergic neuron. Thus antihypertensive action of guanethidine or bethanidine is antagonized.

Clinical significance: Avoid tricyclic antidepressants.

2. Combination: Methyldopa - Amphetamine

Mechanism: Amphetamine displaces norepineprine to the site of action. It will cause increase in sympathetic action and antihypertensive action of methyldopa.
Clinical significance: Amphetamine should be given cautiously to the patients on methyldopa.

3. Combination: Captopril - Salicylates

Mechanism: Salicylates inhibit the synthesis of prostaglandins which are responsible for inhibition of antihypertensive action of captopril. Thus hypotensive effect of captopril is reduced.

Clinical significance: Avoid salicylates. Substitute it with acetaminophen.

D. Antidiabetic (hypoglycemic) agent interaction:
1. Combination: Antidiabetic agent - alcohol

Mechanism: Alcohol has hypoglycemic action. Thus when alcohol is given with antidiabetic agent severe hypoglycemia occurs. Biguanides (metformin and penformin) – Alcohol interact causing lactic acidosis. Chlorpropamide alcohol interaction causes facial flush.

Clinical significance: Alcohol should be completely avoided


Mechanism: Glucose tolerance is impaired.

Clinical significance: Diabetic patients may use contraceptives other than oral.

3. Combination: Protamine zinc insulin and insulin injection (soluble insulin)

Mechanism: These two insulins if mixed in the same syringe due to excess Protamine in Protamine zinc insulin injection, insulin will be converted to long active protamine zinc insulin. Thus onset of soluble insulin is delayed.

Clinical significance: Do not mix these two insulins. If required administered them at different sites.

E. Vitamins interactions:
1. Combination: Vitamin - B\textsubscript{12} - Chloramphenicol

   Mechanism: Patients with pernicious anaemia respond poorly to vit. B\textsubscript{12} if chloramphenicol is also given, as chloramphenicol interferes with erythrocyte maturity.

   Clinical significance: Substitute chloramphenicol with other antibiotic.

2. Combination: Vitamin A – Mineral oil.

   Mechanism: Mineral oil may impair gastrointestinal absorption of vitamin A.

   Clinical significance: Separate the doses of vitamin A and mineral oil to avoid mixing in GIT.

3. Combination: Pyridoxine (vit. B\textsubscript{6}) - Levodopa

   Mechanism: Pyridoxine increases metabolism of levodopa and decreases the amount of levodopa at the site of action in brain.

   Clinical significance: Avoid this Combination.

4. Combination: Vit. D – Phenyntoin and Phenobarbitone

   Mechanism: Use of anticonvulsants like phenyntoin and phenobarbitone stimulate vit. D metabolism. This results in low calcium serum level and development of rickets.

   Clinical significance: Expose patient to sunlight. Increased calcium diet is suggested.

5. Combination: Vitamins – Oral contraceptives

   Mechanism: Oral contraceptives cause deficiency of vit.B\textsubscript{12}, vit. C, vit. B\textsubscript{6}, folic acid. This is due to inhibition of gastric enzyme required for absorption of these vitamins.

   Clinical significance: Vitamin supplement is suggested.

F. Gastrointestinal agent interaction:

15. Antacid interactions:
a. **Combination:** Aspirin – Antacids

**Mechanism:** Antacid reduces GIT irritation.

**Clinical significance:** Better aspirin absorption and less irritation

b. **Combination:** Bisacodyl – Antacids

**Mechanism:** Enteric coated Bisacodyl tablet may disintegrate prematurely.

**Clinical significance:** May result in irritation and vomiting.

c. **Combination:** Isoniazid – Antacid (Alu-hydroxide gel)

**Mechanism:** Alu-hydroxide adsorbs INH.

**Clinical significance:** Decreased isoniazid absorption.

16. **Antidiarrhoeal interactions:**

a. **Combination:** Digoxin – Kaolin and pectin mixture.

**Mechanism:** Adsorption of digoxin by kaolin

**Clinical significance:** Poor availability of digoxin

17. **Cathartics**

a. **Combination:** Slowly absorbed drugs

**Mechanism:** Cathartics increases GIT motility and increases rate at which drug passes through the GIT.

**Clinical significance:** Decreased absorption of slowly absorbed drug.

**DRUG - FOOD INTERACTION**

Food may affect the absorption of the drug. It may be attributed to (i) dilution of the drug (ii) adsorption or complexation of drug or (iii) the alteration of gastric emptying.
The effect of food on different drugs is discussed below:

a) Food reduces the absorption of aspirin, isoniazid, tetracyclines, benzylpencillin, amozycillin, ampicillin, levodopa and rifampicin.

Iron absorption is reduced if food has been taken within the previous two hours. On the other hand nausea is more likely if iron is taken on empty stomach and for this reason iron tablets are often given with food.

b) Absorption of hydraliazine, nitrofurantoin, lithium citrate, riboflavin, carbamazepine, metoprolol, propranolol, spironolactone is increased in presence of food. This may be due to alterations in tablet disintegration and dissolution along with effect of different types of meals on gastric emptying.

c) Nitrofurantoin is given with food to avoid GIT irritation; this also causes increase in drug absorption because more drug dissolves in stomach before it passes into the optimum environment for absorption in the small intestine.

Meals containing that absorption fat content increases absorption of fat soluble drug griseofulvin.

d) It is observed that absorption of nitrazepam, glibenclamide, metronidazole, oxazepam, theophylline is unchanged by food.

e) Monoamine oxidase (MAO) is an enzyme which breakdown catacholamines such as norepinephrine. When the enzyme is inhibited, increased levels of norepinephrine within adrenergic Tyramine is metabolised by MAO. Patients being treated with MAO inhibitors also take tyramine containing food (cheeses, chocolate, alcoholic beverage, liver, yeast extract), tyramine reaches the systemic circulation causing severe hypertension.

THERAPEUTIC DRUG MONITERING [Sampathkumar, K.; (2008)]

Any substance or chemical to be used for therapeutic purpose has to meet the following condition before it is being declared as a drug.
1. Chemical properties and purity of the substances has to be established. Analytical method to be fixed.

2. The intended pharmacological effect to be studied.

3. Unavoidable impurities in the substances has to be identified and their limits to be fixed. Their pharmacological effects to be minimum and negligible.

4. Studies on animals to be carried out wherever possible Animal toxicology studies.

5. After obtaining permission from the relevant authorities, chemical studies have to be undertaken. Schedule Y of the drugs and Cosmetics Rules 1945 gives details for this.

6. Phase I, II and III studies are to be conducted.

7. Safe dose of the substance to be arrived at.

8. Absorption and fate of the drug to be studied.

9. Adverse effects and treatment for it to be determined.

10. Indications and contraindication are arrived at.

Submitting all the above information, permission to be sought from the Drugs Controller General of India for the use of the substance as a new drug.

The new drug introduced should cure the infection / disease in shortest possible time with the minimum side effects. The therapeutic objective is achieved only after extensive trials of the drug in various dose levels and either various types of groups of people. In- vitro and in-vivo studies either bioavailability are studied.

Even after the introduction of the new drug for treatment, its therapeutic effect is to be monitored constantly. A drug which is the first choice now for a particular treatment may loose its place in due course of time, due to never drugs, having still lower side effects, replacing it or pushes back in priority. It may also loose its use due to finding of some new adverse reactions that has not been noticed earlier in the clinical trial and double blind studies.
For this the WHO as well as our Central Government has constituted the “Therapeutic Monitoring Committee”. This committee collects information from all over the country, critically studies them, debates among its members, calls for expert opinions and comes to certain conclusions, based purely on scientific and medical grounds. This committee may provide the following:

1. The level of dose that can provide the full therapeutic effect and control on the infective state.

2. The toxic dose level and its manifestations.

3. If it is found at any time that the use of the drug is unsafe, to declare it so and recommend for its withdrawal from use.

4. If the drug is used in combination with other drugs and found unsafe and useless for the purposes the combination claims, then to declare the combination as irrational and prohibit them for use.

On the recommendations of the Therapeutic Drug Monitoring Committee, the Drugs Controller General of India issues notifications for will be an offence to produce or market such banner drugs and lists the irrational combination of drugs. It will be an offence to produce or market such banner drugs. The Drugs Controller of India permits some combinations of drugs with certain conditions.

Similarly the Drug Monitoring Committee may advise to incorporate certain warning/cautionary notes on the labels and packing inserts of some drugs. Example (i) “Not to be used in newly born or premature infants” on the labels of injectables containing benzyl alcohol as preservative. (ii) Carcinogenic warnings (iii) warning note on tooth pastes containing fluoride, (iv) cautionary note on the Hexachlorophene not to be used on babies” etc.

The drug monitoring committee may appoint sub-committee to assist or to go into specific cases and ask it to submit the report in specified time limit.
The pharmacist must keep himself known up to date of the directions regarding the banned drugs/combinations and the various warnings on the use of permitted drugs. He assists the physicians and nurses as well with this information.

The Medical Wing of the Pharmaceutical Industry and the Pharmacy Therapeutic Committee of the Hospitals monitors constantly the therapeutic effect of the drugs in use also, apart from their other activities. They coordinate with the Drugs Control Authority.

PARENTERAL PRODUCTS [Jain, N. K. (1994)]

The term parenteral is derived from Greek word ‘Para’ meaning beside and ‘enteron’ meaning the intestine. This parenteral administration should include the administration of drugs by any route other than intestine. In pharmaceutical practice however parenteral products are considered to be those sterile drugs, solutions, suspensions or emulsions that are administered by hypodermic injection either in the form in which they are supplied or after the addition of suitable solvent or suspending agent etc.

Historically, Sir Christopher Wren in about 1657 injected drugs into the veins of living animals. In 1855 Dr Alexander Wood of Edinburgh described the first subcutaneous injection of drugs for therapeutic purposes using a true hypodermic syringe. The importance of sterilizing both the syringe and the solutions was realized by the 1890s. Injections were not official upto1962 when for the first time 6 injections were included in NF V under the name ‘Ampoules’. Subsequently injections became official in many pharmacopoeias. IP ’85 has more then monographs on injections.

Routes of administration

Various routes of parenteral administration are follows.

1. Intradermal (ID) Route – It is also known as intracutaneous. The drug is injected between the epidermis and the dermis. Absorption by this route is slow. Volume of such injections is usually between 0.1 to 0.2 ml.
2. **Subcutaneous (SC) Route** – The drug is injected into the muscular tissue under the skin, generally into the outer surface of the arm or thigh. Volume of such infections rarely exceeds 1ml.

3. **Intramuscular (IM) Route** – The drug is injected into the muscular tissue, a common site being the deltoid muscle in the upper arm. Usually up to 2 ml of such an injection is administered. Absorption is more rapid than that by subcutaneous route.

4. **Intravenous (IV) Route** – The drug is injected directly into a vein for rapid absorption. The volume of such injections may vary from 5 to 50 ml even more.

5. **Intra-arterial Route** – The drug is injected directly into an artery terminating in a target area. It is used in place of the IV route when immediate action is desired in peripheral areas of the body.

6. **Intracardiac** – Injection into the heart chamber.

7. **Intrathecal** – Injection into the subarachnoid space surrounding spinal cord which contains cerebrospinal fluid.

8. **Intracisternal** – Injection into the cistern containing cerebrospinal fluid.

9. **Peridural** – Injection between the duramater and inner aspects of the vertebrae.

10. **Intra-articular** – Injection into a joint.

11. **Intrasynovial** – Injection into a joint fluid area.

12. **Intrapерitoneal** – Injection into the peritoneum.

13. **Intrapleural** – Injection into the pleural cavity of the lung.

**Advantages and Disadvantages of parenteral administration**

As compared to other dosage forms, parenteral administration offers some selective advantages. Injections provide a direct route for achieving the drug effect within the body. Modification of the formulation can however slow down the onset and prolong the action. This
may also be achieved by the change in the route of injection. An immediate physiological response is usually provided by an intravenous injection of an aqueous solution. Another significant advantage is the successful administration of the drugs sensitive to the digestive system. The drugs which are degraded or erratically or unreliably absorbed when administered orally can be given by injection. The parenteral route is also suitable when administration by gastrointestinal or dermatomucosal routes is not desirable.

The main disadvantages of parenteral products include the necessity of aseptic technique in production, compounding and administration, the requirement of trained personnel for administration, the real or psychological pain associated with the injection and its higher cost as compared to oral dosage forms.

General requirements of parenteral products are (1) sterility (2) freedom from physically and chemical contaminants, (3) freedom from microbial products such as toxins, pyrogens etc., (4) isotonicity, and (5) matching of specific gravity with body fluid(s).

Considerations in development of formulae

The general requirements of parenteral products as described above lead to a difficult problem of selection of the vehicle, additives, stabilizers, buffers, preservatives, containers and closures, a reliable method of sterilization and the measures to check the sterility, physical and chemical contamination, pyrogenicity etc., for the product. However as a rule, one should always endeavour to use minimum number of essential additives in smallest possible quantities.

1. **Vehicle-** Water for injection (WFI) is the vehicle of first choice. It should be free from ions and pyrogens. Medicaments like barbiturates and sulphonamides need water free form carbon dioxide. Oxygen-sensitive drugs call for oxygen free water. Water of suitable quality must be prepared drugs call for oxygen free water. Water of suitable quality must be prepared by distillation/reverse osmosis. It can also be rendered free from ions by passing through an ion exchanger. Sterile water for injection (SWIF) is water for injection sterilized and suitable packaged in single-dose container not exceeding 100ml capacity and contains no bacteriostatic agent.
Bacteriostatic Water for Injection (BWFI) is sterile water for injection containing one or more suitable bacteriostatic agents. Boiling of water makes it free from atmospheric gases and such water should be stored suitably so that the readorption of oxygen and carbon dioxide is not possible.

In addition to water, some cosolvents are sometime used to replace a portion of water in certain formulations. Thus cosolvents may be used either to increase the stability of the drug or to reduce its hydrolytic degradation. Commonly used water-miscible cosolvents include ethyl alcohol, glycerin, propylene glycol, polyethylene glycol and dimethyl-acetamide. Limited solubility and poor stability of some drugs either in water or in aqueous solvents may necessitate the use of nonaqueous hydrophobic solvents like fixed oils. Such vehicles must meet the requirements of degree of saturation, saponification value, iodine number, free fatty acids and unsaponification, saponification value, iodine number, free fatty acids and unsaponifiable matter. Most commonly used oils include peanut, sesame, corn and cottonseed. These oils are prepared by expression and hence may contain fragmentary cellulose matter and bacteria. They must therefore be clarified by repeated filtration. No aqueous vehicles should be disposable by the body and should be non-irritant to the tissues. Mineral oils are rarely used body and should be non-irritant to the tissues. Mineral oils are rarely vehicles for parenteral preparations because the same are not metabolizable. Primary considerations involved in the selection of the vehicle are solubility, stability and safety.

2. Additives – A part form the vehicle, parenteral products contain many solutes as stabilizers or additive substances. All the solutes employed in the preparation of parenterals should be of highest purity. In addition, solutes should be free from microbial contamination and pyrogens. They should also conform to the solubility characteristics as desired by the physical form of the compound and should be free from gross dirt.

(a) Stabilizers- Stabilizers ensure the stability for the drug compound in the preparation. Drugs in the form of their solution are more liable to degradation through oxidation and hydrolysis and hence the stability of parenteral products against such degradation should be ensured. Oxidative degradation can be minimized by the use of antioxidants and when this course is not feasible, the products may be sealed in an inert atmosphere of nitrogen
or carbon dioxide. Hydrolytic degradation can be minimized by adjustment of pH or by replacing water with other vehicles partially or wholly. Some degradations are catalyzed by stray metallic ions and such a problem can be overcome by the use of sequestering or chelating agents like EDTA.

(b) Buffering Agents – Formulations must maintain the intended pH. Changes in the pH of a product may occur during storage because of degradative reactions taking place in the product, interaction of the product with the components of the containers and loss or dissolution of gases and vapours. Such problems are avoided by the use of buffering agents to suppress the changes in pH. Commonly used buffering systems include acetates, citrates, phosphates and the like.

(c) Antioxidants – Antioxidants are needed in the parenteral products containing oxygen-sensitive drugs so as to avoid oxidative degradation. Sodium bisulfate (0.1 %) is the most commonly used antioxidant. Other antioxidants include acetone, sodium formaldehyde sulfoxylate and thiourea. Activity of certain antioxidants may be enhanced by the sodium salt of EDTA because it can chelate the metallic ions which otherwise catalyze the oxidative degradation reactions.

(d) Antimicrobial Agents – These agents are to be essentially included in multiple – dose packagings, to prevent multiplication of any accidentally introduced microbes in the products during the withdrawal of doses. Such agents should always be used with full recognition of their potential toxicity. Frequently used antimicrobial agents include phenol or creson (0.5 %), chlorocresol (0.2 %), phenlmercuric nitrate (0.002 %), chlorbutanol (0.5 %), benzethonium chloride and benzalkonium chloride (0.001 %).

(e) Tonicity Contributors – Some parenteral solutions are required to be isotonic with blood serum or other body fluids. The overall tonicity of a solution can be calculated by computing the molecular concentration of the solute or by determining the freezing point of the solution. Tonicity of a solution is a function of the quality and quantity of sum total of the solutes present. If necessary, the tonicity of a solution may be increased by the addition of calculated amounts of substances like sodium chloride, borax etc. The
materials used for tonicity adjustment must be compatible with other ingredients of the solution.

(f) Wetting, Suspending & Emulsifying Agents – Wetting agents are used in injectable suspensions to maintain the particle size and to counteract caking. Commonly used wetting agents include tween-80, sorbitan trioleate, Pluronic F-68 etc. Commonly used suspending agents in parenteral suspensions are sodium CMC, methylcellulose, acacia, gelatin, polyvinyl-pyrrolidone etc. Sodium citrate may be included to prevent flocculation of suspended particles. Lecithin is the most commonly employed emulsifying agent for parenteral emulsions.

3. Containers and Closures – Any container for parenteral product should maintain the integrity of the product as a sterile, pyrogen free, high purity preparation till it is used. It should also be attractive, allow the withdrawal of the contents and be strong enough to withstand processing and shipping; and finally it should not interact with the product.

Glass seems to be the material of choice for container for parenteral products. Glass containers may either be sealed or closed with rubber stoppers. Containers of Type I glass are best for aqueous preparations. Siliconization i.e. the application of a thin film of silicone to coat the inside surface of the vials and ampoules; has been employed to prevent interaction of the product with the glass surface. The process also minimizes adsorption of active ingredients from homogeneous solutions, prevents adsorption of solids from suspensions and prevents aggregation at the glass surface in colloidal preparations.

Plastics used in the packaging of parenteral products are based on polyethylene or polypropylene. Plastic containers are much less used as compared to glass but the former are becoming increasingly popular for intravenous fluids. Only polypropylene containers can withstand sterilization by autoclaving. Many plastics contain additives like plasticizers, antioxidants, antistatic agents and lubricants. These additives may be leached from the plastic into the product. Most plastics selectively permit passage of chemical molecules and are permeable to gases. Plastics are extensively used for containers of administration sets particularly disposable type.
As compared to glass, plastics are light weight, less fragile and easy to handle but most of them are not as clear as glass.

Rubber is the material of choice for closures for multiple-dose vials, intravenous fluids bottles, plugs for disposable syringes and bulbs for ophthalmic pipettes. Rubber closures permit the introduction of a needle from a hypodermic syringe into a multiple-dose vial and provide for resealing of the vial after the needle is withdrawn. Rubber closure is held in place by an aluminum band. Such closures are composed of several ingredients, basic structural unit being a linear unsaturated hydrocarbon, isoprene. All or part of the natural polymer is sometimes replaced by a variety of synthetic rubber polymers. In addition, a vulcanizing agent usually sulfur; an accelerator e.g. 2-mercaptobenzothiazione; an activator, usually zinc oxide; fillers such as carbon black or limestone; antioxidants and lubricants etc., may also be present in rubber closures. These substances may be leached into the product or may cause chemical interaction. Lacquer or plastic coating applied to the surface of the rubber closures in contact with the product may partially reduce leaching and also permeation. Another most commonly encountered problem with rubber closures is that of coring i.e. the generation of rubber particles cut from the closures when needles are inserted; the particles are known as cores. Selection of the proper gauge needle and its proper use may minimize the problem of coring.

Rubber closures must be resistant to ageing changes, to sterilization procedures, and to permeation to moisture and vapors. They must be elastic but hard enough to permit the insertion of a hypodermic needle with menial cutting of fragments, and resalable upon withdrawal of the needle. Compatibility of the rubber compounds should always be determined with each preparation with which it is to be used. Physical tests of elasticity, hardness, fragmentation and vapor transmission should be performed and the rubber closures should also be exposed to the product for prolonged periods of time at designated temperature and humidity conditions, biological toxicity tests are also performed to ensure freedom from toxicity.

Contamination in parenteral Products
Parenteral products may be contaminated with chemical, physical and biological contaminants.

Chemical contamination may be due to the presence of undesirable impurities in compounds or due to cross contamination with other chemicals. As mentioned earlier, the solutes etc. employed in the preparation of parenteral products must be of highest purity. Some drugs are available in specific parenteral grades whereas others may necessitate further purification.

Particulate matter may often be present in parenteral products constituting physical contamination. It can be contributed by various sources such as the solution itself or the chemicals comprising it; the process of manufacturing, environment, equipment and personnel; the packaging components in which it is packed; the sets and devices used in administering the products; and the manipulations involved in the preparation of the product. Particulate matter may consist of cellulose and cotton fibers, glass, rubber, metal and plastic particles; undisclosed chemicals; rust; diatoms; dandruff etc. Particles of 50µ or larger can be detected by visual inspection whereas the detection of smaller particles is possible only by special instruments and techniques. One simple technique consists of pouring a solution through a membrane filter followed by microscopic examination of the particles retained on the membrane. Rapid measurement and counting of particles obtained by the membrane method can be performed by the automatic image analyzer systems. Coulter counter is another device. Light blockade is employed for the counting and sizing of particles in the HIAC Particle Counter (High Accuracy Products Corporation, USA). Royco Liquid Counter (Royco Instruments, USA) is based on the light scattering principle.

The key for avoiding the particulate matter in parenteral products lies in observing Good Manufacturing Practices (GMP) as laid down in Schedule M of the Drugs & Cosmetics Rules. As it is difficult to detect particulate matter with certainly, one should endeavour to prevent the same.

By definition parenteral preparations are sterile and hence they are expected to be completely free from microbial contamination. However our present day methods of sterility testing do not afford a guarantee that the tested product is really free from microbial contamination. As such, sterility packaged unit can not be subjected to such testing.
Microbial contamination may be contributed by air, breath, skin, hair clothing, working surfaces, raw materials, equipment etc. either during the processing of parenterals or during their use. Generally speaking everything involved in the processing of parenterals and their administration may contribute microbial contamination to the product. As they are meant for injection, the microbial contamination in these products may lead to serious hazards including death. Once the possible sources of contamination have been identified it is simple to devise methods which will minimize the risk arising from them.

Adjustment of Tonicity and Specific Gravity

When red blood cells are introduced into water or sodium chloride solution containing less than 0.9 % of the solute, they swell and often burst due to the diffusion of water into the cell and the fact that the cell wall is not strong enough to resist the pressure. This phenomenon is called hemolytic. Parenteral products are made isotonic with the body fluids otherwise they may penetrate the red blood cells and cause hemolytic. Additives present in parenteral solution contribute to the overall hemolytic character of the solution. If the solutions are hypotonic, the osmotic pressure of the solutions can be increased by the addition of either sodium chloride or dextrose. Compounds which contribute to the isotonicity of a product also reduce pain at the site of injection in areas with nerve endings. A 0.9 % solution of sodium chloride is isotonic with blood. Iso-osmotic solutions need not necessarily be isotonic e.g. a 1.8% solution of urea has the same osmotic pressure as 0.9 % sodium chloride solution of urea has the same osmotic pressure as 0.9 % sodium chloride solution but the urea solution produces hemolysis. Hence a product should not be considered isotonic until it has been tested in the biological system.

Administration of hypertonic solutions into the blood stream may cause crenulation of cells which may return to normal with equalization of osmotic pressures. In such cases a slow injection into a vein in which circulation is rapid is indicated as the solution is hereby rapidly diluted and swept away.

Parenteral products are sometime required to possess specific gravity matching with that of the body fluids and hence such adjustments may also be called for. The intraspinal injections should have predetermined specific gravity as compared to body fluid into which it is to be injected. This is of particular importance in spinal anesthesia. In case the upper part of the
patient’s body is raised by slopping the operating table, the solution of lower specific gravity than the spinal fluid will tend to rise on injection and that or higher specific gravity will tend to sink. For operation on the lower part of the body where the patient is tilted head downwards the opposite effects will occur. Hence a careful choice must be made of the specific gravity of the solution and the position of the patient. The average specific gravity of spinal fluid at 37 °C may be taken as 1.0059. The specific gravity of injection solution with respect to that of spinal fluid is expressed as isobaric (i.e. of equal), hypobaric (i.e. lower) and hyperbaric (i.e. higher). A 1 in 5000 solution of cinehocaíne hydrochloride in 0.5% saline is a hypobaric solution having a specific gravity of 1.0036 at 37 °C A 1 in 200 solution of cinchocaine hydrochloride in 6% dextrose gives a hyperbaric solution having specific gravity of 1.02.

**Processing of Parenteral Products**

The use of superior quality materials alone in the preparation of parenteral products is not sufficient because parenteral products are subject to a variety of stringent requirements. If the manufacturing process is not carried out properly then the purpose of selecting best quality components is automatically defeated.

**Layout of Sterile Products Area**

This should be worked out in meticulous details. Area should be free particulate and microbial contamination; Particle count should not exceed a total of 100 particles/ft³, of 0.5 and larger. Entire area can be conveniently divided into clean-up area, preparation area aseptic area, quarantine area and the finishing and packaging area. The design and construction of these areas should provide effective case of cleaning, operation, attraction and comfort of personnel. A hypothetical floor plan of a sterile products area is given in and flow of materials is illustrated in by the process flow scheme.

The Clean-up area should be constructed to withstand moisture, steam and detergents. Accumulation of dust ad microbes should be prevented by avoiding inward air leaks and dirt collecting crevices, corners, and projections. Ceiling and walls can be coated with epoxy and vinyl polymeric continuous film coating materials.
The Preparation area is meant for compounding the formula and making preparation for the filling operations such as assembling equipment. This area necessitates stricter controls than desired for clean-up area. Cabinets and counters should be of stainless steel and fitted in such a manner that they do not leave any catch area for dirt to accumulate. Adequate sink and counter space should be provided. Ceiling, walls and floor should be sealed.

Construction of aseptic area must ensure maximum security as it is the heart of processing the sterile products. The environment in this area must be ultra clean. The ceiling, walls and floor may be painted with germicidal paint such as Fungi Check. Glass panels built into the walls permit greater visibility and facilitate supervision from a non-sterile area. All fixtures should be recessed in the walls or ceiling to eliminate ledges, joints and other locations where the dust and dirt may accumulate. Similarly all counters should be hung from wall and constructed of stainless steel. Operating parts of all mechanical equipment should be preferably sealed in by having them as completely as possible within a stainless steel cabinet. For small scale operation an aseptic hood may be sufficient. Entry of personnel into the aseptic area should be through an air lock. The personnel must use sterile dresses, masks, caps and footcovers etc. As a rule there should be minimum movement in the aseptic area. The air in the aseptic area should be free from fibers, dust and microbes. This can be conveniently achieved by the use of High Efficiency Particulate Air (HEPA) filters which can remove particles up to 0.3 with an efficiency of 99.97% or more. HEPA filters are made use of in Laminar Air Flow in which air moves with uniform velocity along parallel lines with minimum of eddies. The air flow can be either horizontal or vertical and 100 10ft/min. is considered to be the minimum effective air velocity. Such laminar flow stations and work beneches are commercially available.

The air in the sterile products area should be adequately clean as it is one of the greatest sources of contamination. Preferably it should be passed through a prefilter usually of glass wool, cloth or shredded plastics to get rid of large particles. Next it may be passed through an electrostatic precipitator which induces an electrical charge on particles in the air which are removed by attraction to oppositely charges plates. This treated air is finally passed through HEPA filters. Ultraviolet lamps may also be installed for producing a disinfectant action on directly irradiated surfaces between the UV rays having an antibacterial action.
It is needless to mention that the aseptic area should be carefully maintained and the total viable count of bacterial should be determined in sterile products area on a routing basis so as to ensure freedom from microbial contamination.

Personnel working in the sterile products area may also be a potential source of particulate and microbial contamination to the products under process. Therefore the personnel must be neat, orderly and reliable. They ought to wear special clothing including hoods and gloves and footcovers. Garments should be made of materials like Dacron, nylon, terylene etc. which shed minimum of particles.

Suitable environmental control tests should also be performed on a routine basis in the sterile products area. Most of such tests are based on the exposure of nutrient media plates to the environment so as to allow the microbes if any, to settle on the media and subsequently inculcating the plates and examining them. This can also be done by taking the sample of air from the environment through the filters which are then exam index microscopically for particulate matter such as lint and dust or placed on culture media and incubated for the determination of microbes. Several instrumental methods have also been developed to obtain particle count from a volume of air based on light scattering by the particles.

**Precautions for Aseptic Work**

The prime object of aseptic work is to keep the products being processed free from microbial contamination. The following precautions should always be observed in aseptic work.

1. Whenever possible, a non-touch technique should be used.
2. Air disturbance should be minimum.
3. Interruption should be minimum.
4. There should be a program for maintenance of the area and the personnel.
5. Only trained personnel should perform aseptic work.
6. Frequent tests should be performed in the aseptic area to check the level of contamination.

7. Whenever contamination is detected, the sources should be identified and dealt with accordingly.

8. After the aseptic work is over, the product should be removed to quarantine and aseptic area should be adequately cleaned, disinfected and kept ready for next operation.

**Filling, Sealing and Sterilization**

Mixing, clarification, filling, sealing and sterilization are the common techniques involved in the preparation of parenteral products. The mixing tanks or containers should preclude any chemical or phylogenic contamination. Clarification may be achieved by passing the solutions under differential pressure through filters made up of materials such as sintered glass, asbestos, unglazed porcelain, stainless steel, silver, cellulose esters etc. Asbestos pad filters are however most reactive. The filters must be able to remove particles as small as approximately 0.2. Membrane filters are disposable and hence are used most commonly for the filtration of parenteral solutions. They are effective and reliable as they are manufacture to have uniform and controlled pore size. They are inert and have little or no adverse effect on solutions passed through them. Membrane filters can be sterilized either by means of steam under pressure or by ethylene oxide. Sintered glass and asbestos filters are available in the form of discs whereas unglazed porcelain and kiesclghur filters are available in the form of dises as well as candles.

Filling – Solution sterilized by filtration are to be filled under aseptic conditions. The containers and closures must be properly cleaned, sterilized and made available for use at this point in the process. Initially filling operations ere carried out manually by employing hypodermic needles, burettes, flasks etc. This practice has been replaced by sophisticated automated filling machines. Filling consists of transferring a quantity of the unit container. The transferring derive should not contribute any contamination and the product at this stage should
be adequately protected so that it does not pick up any particulate or microbial contamination from the environment. Modern day automatic high speed filling machines can fill up to 300 or more containers per minute. A filling machine suitable for laboratory and small scale operation is as a safeguard against the entry of particulate matter in a product during filling, a final filter is often inserted in the system between the filter and the delivery tube.

As compared to liquids, filling of solids is rather troublesome. On a small scale, solids like antibiotics are divided by weighting and then filled into the individual containers. Alternately, an approximate quantity is filled in the container and finally weighted on a balance. Large scale filling devices for solids involve the measurement and delivery of a volume of granular material which has been calibrated in terms of the weight desired. Another type of machine utilizes an auger which rotates in the stem of a funnel containing the powder. The amount of powder dispenses is regulated by the size and rotation of the auger.

For mobile liquids an excess of 20 % for a volume of 0.5 ml to 2 % for a volume of 50ml is recommended. Whereas for viscous liquids of the same volume the variation may be from 24 to 30 %. Allowable tolerances in case of solids may be as high as 10 % calculated from the average labeled net weight of contents.

Sealing – Sealing of the filled container should be done as soon as possible to prevent the contents from being contaminated. Sealing represents the final aseptic procedure. Ampoules are sealed by melting a portion of the glass neck with a fine jet of flame. For rapid sealing, a high temperature gas-oxygen flame is most suitable. A variety of automated sealing devices are available today. For making ‘pull – seals’ the neck of the ampoule is heated below the tip leaving most of the tip for grasping with forceps or from a single burner to soften the glass and then the tip is grasped firmly and pulled quickly away from the body of the ampoule which still continues to rotate. A small capillary tube is formed which is closed by twisting. Although pull sealing is slow yet the seals are more perfect than tip sealing.

Vials and bottles are sealed by closing the opening with a rubber closure which is held in position by means of aluminum caps. An intact aluminum cap is the proof that the closure has not been removed. Single layered aluminum caps may be applied by means of a hand crimper while double or triple layered caps are crimped by means of heavy duty mechanical crimpers.
Sterilization – it is process of complete destruction or removal of all forms of life. Except in case of them labile substances, parenteral products are commonly sterilized after filling and sealing in the final containers and the process is called terminal sterilization.

Thermo labile products should be sterilized by non-thermal methods. Thermo labile solutions are mostly sterilized by filtration through bacteria proof filters. Other thermo labile preparations like colloids, oleaginous solutions, suspensions and emulsions may require a process of sterilizing each component separately and the product is formulated and processed under aseptic conditions. Sterilization by radiation is another non-thermal method. Dry solids such as penicillin, sterilized by ionized radiations, Gaseous sterilization is no good when a glass container or other impervious barrier prevents the gas from permeation to the material.

Dry heat sterilization is also of limited application because the materials being sterilized by this method should not be adversely affected by the elevated temperatures. Another approach for preparing sterile solids is lyophilization.

Most useful sterilization method is autoclaving which employs steam under pressure. It is probably the most effective method for sterilization of aqueous liquids or substances that can be reached or penetrated by steam. This method is ineffective under anhydrous conditions like a sealed ampoule containing a dry solid or an anhydrous oil. To prevent subsequent contamination after sterilization, the materials subjected to autoclaving must be wrapped or covered but this is not necessary in case of parenteral solutions as they are already sealed. The effectiveness of any sterilization method should be verified from time to time. Biological indicators are a useful tool for ascertaining the effectiveness of this method.

**Evaluation of Parenteral Products**

Parenteral Products are subjected to most strict quality control tests as they are to be injected into the body. To ensure the desirable characteristics, these products are evaluated for sterility and pyrogens. Other tests are also performed in a manner common to all pharmaceutical products.

**Sterility Testing**
Tests for sterility are intended for detecting the presence of aerobic and anaerobic viable forms of bacteria, fungi and yeasts in pharmaceutical preparations. For procedural details the Drugs & Cosmetics Act and Rules as well as the Indian Pharmacopoeia should be consulted. It should be remembered that sterility test is not meant to prove that a product is sterile but to estimate the probable sterility of a batch of articles. To be sure that a product is sterile, each unit has to be tested individually which is impossible. The principles of sterility testing are being discussed here briefly.

A suitable amount of the material under test is transferred aseptically into sterile nutrient media and incubated for suitable period of time at optimum temperature. Living microbes present if any, are expected to grow under favorable conditions like nutrient media are examined for the presence or absence of any microbe which might have grown, if at all one was present. The entire procedure is carried out under aseptic conditions so as to prevent entry of any microorganism during the test. False negative tests are likely to be observed when the product contains bacteriostatic agent. In such cases the bacteriostatic agent is suitably diluted or neutralized so that it becomes ineffective as bacteriostatic. For example, preparations containing 0.5 % phenol are diluted with such amounts of media that the phenol content would be diluted by about 50 times thus rendering antimicrobial drugs like penicillin and sulfa drugs etc, have to be tested in presence of adequate amount of antagonistic materials. For example, penicillin can be counteracted by penicillinase and sulfa drugs can be countered by small amounts of p-amino benzoic acid. When the preparations contain solid or oily materials, normal tests have to be modified because such materials may themselves produce turbidity in the media. In such cases further subculturing is done by transferring small quantity of the medium under test to fresh sterile medium to ensure that the indicated turbidity is not due to the material itself but due to the growth of contaminating micro-organisms.

Suitable controls should also be run simultaneously to check the sterility of the test medium as well as its ability to support microbial growth.

If the test for sterility gives negative result i.e. no growth of microbes, then the product is considered to be sterile. But to make sure, the test is repeated once or twice. Similarly when a positive test indicates non-sterility, the test is repeated a second and a third time to account for
any accidental contamination. When the test fails for second and third time also then the product is declared to be non-sterile. Once again it is emphasized that sterility tests should be performed under strict aseptic conditions following aseptic techniques.

**Pyrogen Testing**

Pyrogens are the metabolic products of living or the dead microbes which cause a pyretic reaction upon injection. Pyretic reaction includes malaise, headache and increased body temperature. In man the pyrogenic reaction is manifested by fever and chills. Chemically pyrogens are lip polysaccharides soluble in water but insoluble in organic solvents. As they are soluble in water they are not eliminated either by autoclaving or by filtration. All parenteral products must be tested for freedom from pyrogens. Recommended test employs rabbit as the test animal because it is highly sensitive to pyrogens. Samples to be tested are injected into the ear vein of three rabbits to determine whether the sample causes an increase in the body temperature of the test animal. The sample passes the test if at no time during a three hour period following injection, the temperature of any rabbit rises by more than 0.6 °C or the sum of the rise for the three rabbits exceeds 1.4 °C. Earlier, the body temperature of the test animals was measured by inserting thermometer into rabbits anus and manually recording the temperature. Nowadays the temperature is measured by employing automatic temperature recording devices. The pyrogen test should preferably be run separately on the vehicle as well as the finished products.

Limulus Amebocyte Lysate (LAL) test is another method for the determination of pyrogenic endotoxins. In this method the test solution is combined with a cell lysate from the amebocytes (blood cells) of the horseshoe crab. Any endotoxin that might be present will be coagulated with protein fraction of the amebocytes and result in the formation of a gel. This test is considered to be simple, rapid and of greater sensitivity than the rabbit test.

**Clarity Testing**

Clarity test are performed to prevent the distribution and use of parenteral Products which contain particulate matter. Clarity is a critical consideration in the injectable preparations. The basic and traditional method of clarity testing consists of human visual inspection with the aid of
good direct lighting on the containers with the product against a black and a white background. Thus transparent particles would be visible against black background and the white background would reveal coloured particles. This method is employed even today as a routine in all manufacturing houses. However, visual inspection has its own limitations. Particulate matter can also be detected by passing the solution through a filter and examining the filter microscopically. Many automatic image analysis devices like the Quanitimat 720 system have been developed. Such devices focus the image of particles on a TV screen and a permanent record is prepared simultaneously. Other devices for detecting particulate contamination are based on light absorption, light scattering or change in electrical resistance. Coulter counter is also useful in detecting particulate matter.

**Leaker Testing**

Leaker test is performed by dipping the sealed containers in coloured solution and producing negative pressure. A 1% methylene blue solution is most commonly employed. Release of vacuum is accompanied by the entry of the coloured solution into the imperfectly sealed ampoule. In another frequently employed test the ampoules are autoclaved in a dye bath. In modification of this test the hot ampoules are removed from the autoclave and quickly dipped into a cool path of dye solution. A leaking ampoule is called a leaker and all leakers are to be discarded. Vials and bottles are not subjected to a leaker test.

In addition to the above tests, routine safety tests should also be performed on all parenteral products.

**COMPUTER** [Sampathkumar, K.; (2008)]

Being computer age, the computers play a positive role and are a companion to pharmacist. They are widely used in all form of activities involving drug – in analytical, manufacturing, marketing, inventory control, research & development etc. they find use in hospital and clinical pharmacy also.

**Definition**
The computer can be defined as an electronic machine which can accept data (about events and activities) in a prescribed form, process this data in a specified manner and supply the result in a predefined form. The personal computer (PC) consists of a central processing unit, monitor (screen), keyboard and printer.

**Application**

In hospital pharmacy, the computers are used for planning and control purposes by health care professionals, in the maintenance of hospitals. They are used for the treatment, planning and monitoring patients, maintenance of records. Drug information retrieval, etc. by this, past medication record and current treatment can be maintained. personal files can be created for those who register with the hospital, giving all details about them like the treatment, immunization given right from birth their drug allergic details, sickness and treatment given with dates, report details of various check ups – ups carried in their life time etc. the computer stores all these datum in floppy disks and called a “file” occupying negligible place and one can have these details immediately, whenever required for interpretation and for further treatment. The computers can be used for accounting, invoicing, stock control and for ordering of drugs, medical devices etc., details of drugs issued to each patient in the wards, making bills at the time of discharge of patients – in short A patient management.

The data fed into the computers are continuously updated to reflect the current status, by additions and deletions. The use of files saves time and energy. We can maintain any type of files and each may have several sub files under them.e.g. files can be disease wise of patients admitted in the hospital with sub-files of sex wise and age group wise. From these files we can know how many patients came in same month previous year and the break up of details which will throw same light on the disease. The preventive measures can be taken to avoid recurrence in further. In clinical trial of drugs, computers are used to decide further dosing of drugs based on the profile already had, to keep the drug, level in the therapeutic range. Thus the pharmacists clinical service standards are enhanced by using computers, it saves valuable man-hours. The integrity of the software is pre - established.

In purchases and inventory control, the computer can be used for
1. To detect the items which have reached minimum order level.

2. To prepare list of items to be purchased and their quantities.

3. To prepare purchase orders for vendors and avoid duplicate order.

4. To make staggered orders.

5. To detect infrequently purchased items for possible return or elevation from the pharmacy’s drug supply.

6. To produce periodic summary of purchasing and inventory control statistics.

Characteristics of a Computer

1. **Speed:**

   Computers can perform arithmetic calculations and logical comparisons at an incredible speed with remarkable accuracy. The processing speed of a computer is generally measured in nano seconds (one nano second = one billionth of a second). Equivalently one could say that, computers can add thousands of numbers in a second.

2. **Storage:**

   Computers have a larger storage capacity. We could store say the contents of around two hundred sheets of paper on a medium which is not even half of one sheet of paper. What would typically take larger storage cabinets can be comfortable stored in a storage device of the size of a lunch box. However the storage capacity is useless if it is not matched by an easy retrieval mechanism. Computers excel in this aspect by providing quick and easy access.

3. **Accuracy:**

   The accuracy of computer is consistently high. Errors in computing are generally due to human negligence (inaccurate data, improper procedure, poor design), rather than technological faults.
4. **Diligence:**

   Computers being machines do not suffer from fatigue and lack of concentration. If five million calculations have to be performed, a computer would perform the five millionth calculations with the same accuracy and speed as the first.

5. **Versatility:**

   A major strength of computers is that they can do a very wide range of jobs – both related and unrelated – with speed, accuracy and diligence. In a large organization, it is quite likely that the same computer is being used for preparing bills, generating pay slips, printing reports on sales and patients keep track of Doctor’s appointments, help the assistant/staff to manage their correspondence.

6. **Analysis:**

   Computers can generate Trend Analysis for user defined critical parameters. The results can be obtained in several ways of graphical representation.

**Drug Information retrieval:**

A Complete search of the drug information is necessary for the clinical pharmacist, as he needs to know about pharmacology, drug interactions, adverse drug reactions, toxicology, etc., of them. Some Libraries, Associations and universities keep all these information stored in computers. Few of them are:

(a) National Library – U.K.

(b) American Society of Hospital Pharmacists

(c) British Medical Society

(d) Bioscience Information Service.

Each have their own coding system and one should know it for retrieving i.e., to search for and fetch, information from it. Then we have to give the commands of what we want and it
will be produced in no time. If the information asked for is not available, that also will be provided on the screen.

How computer is useful in the manufacturing management and in the quality assurance of a drug manufacturing unit is detailed below.

BENEFITS (Manufacturing)

- Reduced paperwork and lower clerical costs
- Reduced disruption of production
- Controlled stock levels
- Shorter and more reliable product delivery time
- Increased ability to supply customers with required product specifications.

TANGIBLE BENEFITS (Quality Assurance)

- Improved utilization of chemist time
- Reduction in analysis lead time
- Instrument calibration / service planning

INTANGIBLE BENEFITS

- Maintain records for quality Management system requirements
- Standardization of Reporting Pattern
- Improvement of company image in market
- Operating staff is motivated
Information system helps even middle and senior management for fast and accurate analysis.

The data entry work is reduced to minimum, still to cover present and many additional reports.

The reduction in duplicate data entry reduces manual mistakes.

The system will help to enhance scope of documentation for ISO 9000 system

On line information about supplier evaluation is possible.

DATA PROCESSING EQUIPMENTS

Location:

The computer shall be installed and used in a dust free atmosphere (use of air-conditioned room and leaving foot-wear outside before entering the room is recommended).

General Instructions:

At the end of day’s work, computers shall be dedusted and closed properly with a suitable cover. All parts of it shall be handled gently and carefully. Operators shall be well versed with the PC application like commanding, feeding and to read properly what is coming on the screen. They should proceed by step as the computer command, since the packages are menu driven. Orders shall be given sequentially.

As and when the data are fed into the computer, they shall be stored suitably. All the dates can be recalled as per one’s requirement, to know the latest position like stocks, for analysis and interpretation, as also for financial implication.

Starting of computers:

Few important steps in the starting are Powering on a PC is not as simple as switching on a light bulb. Several hardware components need to be initialized. Every PC has a set of ROM (Read Only Memory) chips that contain the instructions necessary to achieve this. Some of these
instructions perform a Power On self Test (POST) whenever the PC is switched on. This test includes a reliability check of memory, initialization of various chips etc. When all tests are complete, another set of instructions called Boot Strap Loader loads the Operating System into memory—it expects the Operating System to be present at a particular location on the disk called the Boot record. If found, the Operating System is loaded into memory, otherwise an error message is displayed. This process of loading OS or DOS (Disk Operating System) since the OS is assumed to be on a disk into memory is called Booting.

The two ways of booting a PC are Cold boot and Warm boot. A cold boot is the process by which the computer is started from the Power Off state. A warm boot is the process where the PC is already powered on and user desires to reinitialize the RAM (Random Access Memory) with DOS. This becomes necessary when an executing program develops a fault and the user loses control. The difference between the two kinds of booting procedure is that a cold boot initiates the ROM POST procedure, while a warm boot does not. Once the operating system is into RAM, the PC is fully functional and is ready to execute commands. At this stage the screen will display the A > which is known as a Prompt. The prompt indicates that DOS is ready to accept a command. This prompt is called the System prompt or the DOS prompt.

**Internal and External Commands**

Certain DOS commands, which are frequently used, are loaded in the RAM during the process of booting (they are part of COMMAND.COM). Such commands are called internal commands, as they are available in DOS itself. External commands reside outside the RAM in a secondary storage media in form of a file and should be loaded into the RAM and executed as and when required. In other words an external and command could be defined as a command file which is read from the disk into RAM, executed from RAM and then erased from RAM at the end of execution. Few commonly used external commands are of execution. Few commonly used external commands are FORMAT, F DISK, LABEL, CHKDSK, DISKCOPY, TREE, TREEMORE and SORT.

**Other steps involved in a computer operation are:**

1. Loading and creating a Document.
2. Saving the Document.


4. Erasing, Retrieving.

5. Closing or Quitting.

A program is a sequence of instructions which direct the computer to perform specific actions. Data are collections of characters or numbers manipulated by programs and are assigned different file names.
Loading and Creating a Document

Loading refers to entering the data, so that one can start working on a computer creating a document or file. It is essential when one start working on a particular topic for the time, which will be stored. For subsequent working on the same file, one has just to retrieve the document only.

Saving or Storing a Document

Once a file has been created and used, it has to be stored or “Saved” in such a way that it can be easily retrieved whenever it has to be used or required the next time. For this one has to give the respective command, which is stored in a secondary storage device. Generally files are stored under a ‘Directory’ and have a logically relating name. Usually a file name consists up to eight Characters.

Similar files are stored in a common Directory. For example the various containing details of dosage forms like ‘TABS’, ‘CAPS’, ‘LOTNS’, ‘OINTS’, etc can be stored in a Directory “DOSE FORM”

Printing a file

A file with all its contents can be safely stored in the Hard Disk of the computer or on a Floppy Disk. Whenever information is required in the form of a ‘report’, it can be taken out as a ‘Print-out’ or ‘Hard Copy’ using the peripheral called Printer. Even after the hard copy or print copy is taken out, the file remains as such in the hard disk/floppy as it was before, for subsequent retrieval.

Erasing & Retrieving

Once a file is created and saved, it can be reused, corrected & altered (amended) as many times as required. For this has to be activated and this process is referred to as retrieving of the file.
If a particular file is no more required, it will be unnecessarily occupying the ‘Disk-Space’. Hence the unwanted files can be “Deleted or Erased” by giving suitable command. Files once erased cannot be retrieved.

### Closing or Quitting

As mentioned earlier, information in a computer is stored in files which are in turn put under logical heads called Directories. When the work on a particular file is over, the file is “closed” and kept aside for future use.

### Virus in Computers

Virus contamination in a computer means that a computer program has entered into the computer without the knowledge of the user and without anybody programmed it. The computer virus possesses a quality that makes it easy for it to propagate from one computer to another via floppies that are to transport data and also through networks. In a virus infected computer, the virus remains in a corner of the memory and waits for an opportunity to replicate (copy itself) on to the storage media.

The entry of virus can be prevented by loading special programs into the commuter’s memory. This is called inoculation. Virus can be removed by using anti-virus software that kills the virus.

The computer virus is nothing to do with the virus of Bacteriology and is entirely different, except the name.