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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CHEMICAL ENGINEERING

UNIT – I – DRUG AND PHARMACEUTICAL TECHNOLOGY – SCH1612

I. Introduction

Introduction to Pharmacology

A. Definitions:

1. Pharmacology: Pharmacology is the study of interaction of drugs with living organisms. It also includes history, source, physicochemical properties, dosage forms, methods of administration, absorption, distribution mechanism of action, biotransformation, excretion, clinical uses and adverse effects of drugs.

2. Clinical Pharmacology: It evaluate the pharmacological action of drug preferred route of administration and safe dosage range in human by clinical trails.

3. Drugs: Drugs are chemicals that alter functions of living organisms. Drugs are generally given for the diagnosis, prevention, control or cure of disease.

4. Pharmacy: It is the science of identification, selection, preservation, standardisation, compounding and dispensing of medical substances.

5. Pharmacodynamics: The study of the biological and therapeutic effects of drugs (i.e, “what the drug does to the body”).

6. Pharmacokinetics: Study of the absorption, distribution metabolism and excretion (ADME) of drugs (“i.e what the body does to the drug”).

7. Pharmacotherapeutics: It deals with the proper selection and use of drugs for the prevention and treatment of disease.

8. Toxicology: It’s the science of poisons. Many drugs in larger doses may act as poisons. Poisons are substances that cause harmful, dangerous or fatal symptoms in living substances.

9. Chemotherapy: It’s the effect of drugs upon microorganisms, parasites and neoplastic cells living and multiplying in living organisms.

10. Pharmacopoeia: An official code containing a selected list of the established drugs and medical preparations with descriptions of their physical properties and tests for their identity, purity and potency e.g. Indian Pharmacopoeia (I.P), British Pharmacopoeia (B.P).

B. Drugs are obtained from:

1. Minerals: Liquid paraffin, magnesium sulfate, magnesium trisilicate, kaolin, etc.

2. Animals: Insulin, thyroid extract, heparin and antitoxin sera, etc.

3. Plants: Morphine, digoxin, atropine, castor oil, etc.

4. Synthetic source: Aspirin, sulphonamides, paracetamol, zidovudine, etc.

5. Micro organisms: Penicillin, streptomycin and many other antibiotics.

6. Genetic engineering: Human insulin, human growth hormone etc.

Out of all the above sources, majority of the drugs currently used in therapeutics are from synthetic source.

II. Pharmacodynamics

Involves how the drugs act on target cells to alter cellular function.

A. Receptor and non-receptor mechanisms: Most of the drugs act by interacting with a cellular component called receptor. Some drugs act through simple physical or chemical reactions without interacting with any receptor.

• Receptors are protein molecules present either on the cell surface or with in the cell e.g. adrenergic receptors, cholinoceptors, insulin receptors, etc.

• The endogenous neurotransmitters, hormones, autacoids and most of the drugs produce their effects by binding with their specific receptors.

• Aluminium hydroxide and magnesium trisilicate, which are used in the treatment of peptic ulcer disease act by non-receptor mechanism by neutralizing the gastric acid.

Many drugs are similar to or have similar chemical groups to the naturally occurring chemical and have the ability to bind onto a receptor where one of two things can happen- either the receptor will respond or it will be blocked. A drug, which is able to fit onto a receptor, is said to have affinity for that receptor. Efficacy is the ability of a drug to produce an effect at a receptor. An agonist has both an affinity and efficacy whereas antagonist has affinity but not efficacy or intrinsic activity. When a drug is able to stimulate a receptor, it is known as an agonist and therefore mimics the endogenous transmitter. When the drug blocks a receptor, it is known as antagonist and therefore blocks the action of the endogenous transmitter (i.e. it will prevent the natural chemical from acting on the receptor). However, as most drug binding is reversible, there will be competition between the drug and the natural stimulus to the receptor. The forces that attract the drug to its receptor are termed chemical bonds and they are (a) hydrogen bond (b) ionic bond (c) covalent bond (d) Vander waals force. Covalent bond is the strongest bond and the drug-receptor complex is usually irreversible

B. Site of drug action:

- A drug may act:

(i) Extracellularly e.g: osmotic diuretics, plasma expanders.

(ii) On the cell surface e.g.: digitalis, penicillin, catecholamines

(iii) Inside the cell e.g.: anti-cancer drugs, steroid hormones.

C. Dose Response relationship

The exact relationship between the dose and the response depends on the biological object

under observation and the drug employed. When a logarithm of dose as abscissa and responses as ordinate are constructed graphically, the “S” shaped or sigmoid type curve is obtained. The lowest concentration of a drug that elicits a response is minimal dose, and the largest concentration after which further increase in concentration will not change the response is the maximal dose.

1**. Graded dose effect**: As the dose administered to a single subject or tissue increases, the

pharmacological response also increases in graded fashion up to ceiling effect. It is used for characterization of the action of drugs. The concentration that is required to produce 50 % of the maximum effect is termed as EC50 or ED50.

2. Quantal dose effect: It is all or none response, the sensitive objects give response to small doses of a drug while some will be resistant and need very large doses. The quantal dose effect curve is often characterized by stating the median effective dose and the median lethal dose.

Median lethal dose or LD50: This is the dose (mg/kg), which would be expected to kill one half of a population of the same species and strain.

Median effective dose or ED50: This is the dose (mg/kg), which produces a desired response in 50 per cent of test population.

Therapeutic index: It is an approximate assessment of the safety of the drug. It is the ratio of the median lethal dose and the median effective dose. Also called as therapeutic window or safety.

D. Structural activity relationship

The activity of a drug is intimately related to its chemical structure. Knowledge about the chemical structure of a drug is useful for:

(i) Synthesis of new compounds with more specific actions and fewer adverse reactions

(ii) Synthesis of competitive antagonist and

(iii) Understanding the mechanism of drug action.

Slight modification of structure of the compound can change the effect completely.

III. Pharmacokinetics

Pharmacokinetics deals with the absorption, distribution, metabolism and excretion drugs in the body.

A. Biotransport of drug: It is translocation of a solute from one side of the biological barrier to the other.

1. Structure of biological membrane: The outer surface of the cell covered by a very thin structure known as plasma membrane. It is composed of lipid and protein molecules. The membrane proteins have many functions like (a) contributing structure to the membrane (b)

acting as enzyme (c) acting as carrier for transport of substances (d) acting as receptors.

The plasma membrane is a semipermeable membrane allowing certain chemical substances to pass freely e.g. it allows water, glucose, etc. but it won't allow sucrose until it is converted into glucose and fructose.

2. Passage of drug across membrane.

Passive transfer

i) Simple diffusion

ii) Filtration.

Specialized transport

I) Facilitated diffusion

ii) Active transport

iii) Endocytosis.

i) Simple diffusion: Movement of a solute through a biological barrier from the phase of higher concentration to phase of lower concentration. No need of energy e.g. highly lipid soluble drugs.

ii) Filtration: Is the process by which water soluble drug of relatively low molecular weight crosses the plasma membrane through pores as a result of hydrodynamic pressure gradient across the membrane e.g. urea and ethylene glycol.

i) Facilitated diffusion: It means the passage of drug across the biological membrane along the concentration gradient by the protein carrier mediated system also called as carrier mediated diffusion. It depends on number of carrier e.g. tetracycline, pyrimidine.

ii) Active transport: The process by which drugs pass across the biological membrane most often against their concentration gradient with the help of carriers along with the expenditure of energy e.g. alpha methyl dopa, levodopa, 5-fluoro-uracil, 5 bromouracil.

iii) Endocytosis: It is the process by which the large molecules are engulfed by the cell

membrane and releases them intracellularly e.g. protein, toxins (botulinum, diphtheria)

B. Drug absorption: Absorption is the process by which the drug enters in to the systemic circulation from the site of administration through biological barrier. In case of intravenous or intra-arterial administration the drug bypasses absorption processes and it enters into the circulation directly.

1. Routes of drug administration:

a**) From the alimentary tract:**

(i) Buccal cavity: e.g. nitrates

(ii) Stomach: e.g. aspirin, alcohol

(iii) Intestine: e.g. most of non ionized and ionized drugs.

(iv) Rectum: e.g. rectal suppositories, bisacodyl laxatives.

Advantages of oral route: This route is safe, convenient and economical.

Disadvantages of oral route: Onset of drug action is slow, irritant drugs cannot be administered and it is not useful in vomiting and severe diarrhea, gastric acid and digestive enzymes may destroy some drugs, and water soluble drugs are absorbed poorly.

b) **From the parenteral route**:

(i) Intradermal: This is given into the layers of the skin e.g. B.C.G. vaccine

(ii) Subcutaneous: Non-irritant substances are given into subcutaneous tissue e.g. insulin

(iii) Intramuscular: Soluble substances, mild irritants, suspensions and colloids can be injected by this route. These injections can be given to deltoid or gluteal muscle. This route is one of the more common routes e.g. multivitamins, streptomycin, etc.

Advantages: rate of absorption is uniform, onset of action is faster than oral and it can be given in diarrhoea or vomiting.

Disadvantages: Pain at local site of injection, the volume of injection should not exceed 10 ml.

(iv) Intravenous: Drugs directly given into a vein, produce rapid action, no need of absorption as they enter directly into blood, can be given as bolus e.g. furosemide, morphine, dopamine or as continous infusion e.g. fluids during shock or dehydration.

Advantages: It can be given in large volumes, production of desired blood concentration can be obtained with a well designed dose.

Disadvantages: Drug effect cannot be halted if once the drug is injected, expertise is needed to give injection.

(v) Intrathecal: Injected into subarachnoid space of spinal cord e.g. spinal anaesthetics.

(vi) Intraperitonial: Injections given into the abdominal cavity e.g. infant saline, glucose.

(vii) Intra-articular: Injected directly into a joint e.g. hydrocortisone.

c) Transcutaneous route:

i) Iontophoresis: Galvanic current is used for bringing about the penetration of drugs into the deeper tissue e.g. salicylates.

ii) Inunctions: Absorbed when rubbed in to the skin e.g. nitroglycerin ointment in angina pectoris.

iii) Jet injection: With help of high velocity jet produced through a micro fine orifice; No need of needle and therefore painless. e.g. mass inoculation programmes.

iv) Adhesive units: A transdermal therapeutic system produce prolonged systemic effect e.g. scopolamine for motion sickness.

d) Topical/ local route: The absorption through skin is a passive process. The absorption occurs more easily through the cell lining e.g. dusting powder, paste, lotion, drops, ointment, suppository for vagina and rectum.

e) Inhalation: Drugs may be administered as dry powders, and nebulized particles when sprayed as fine droplets get deposited over the mucous membrane producing local effects and may be absorbed for systemic effects e.g. salbutamol spray used in bronchial asthma and volatile general anaesthetics.

2. Bioavailability:

It is the rate and amount of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given IV, the bioavailability is 100%. It is important to know the manner in which a drug is absorbed. The route of administration largely determines the latent period between administration and onset of action. Drugs given by mouth may be inactive for the following reasons:

a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, ACTH.

b) Poor absorption through gastrointestinal tract e.g. aminoglycoside antibiotic.

c) Inactivation by liver e.g. testosterone during first passage through the liver before it reaches systemic circulation.

3. Factors affecting drug absorption and bioavailability:

a) Physico-chemical properties of drug

b) Nature of the dosage form

c) Physiological factors

d) Pharmacogenetic factors

e) Disease states.

a) Physico-chemical properties of drug:

i) Physical state: Liquids are absorbed better than solids and crystalloids absorbed better

than colloids.

ii) Lipid or water solubility: Drugs in aqueous solution mix more readily than those in oily solution. However at the cell surface, the lipid soluble drugs penetrate into the cell more rapidly than the water soluble drugs.

iii) Ionization: Most of the drugs are organic compounds. Unlike inorganic compounds, the organic drugs are not completely ionized in the fluid. Unionized component is predominantly lipid soluble and is absorbed rapidly and an ionized is often water soluble component which is absorbed poorly. Most of the drugs are weak acids or weak bases. It may be assumed for all practical purposes, that the mucosal lining of the G.I.T is impermeable to the ionized form of a weak organic acid or a weak organic base. These drugs exist in two forms.

Acidic drugs: rapidly absorbed from the stomach e.g. salicylates and barbiturates.

Basic drugs: Not absorbed until they reach to the alkaline environment i.e. small intestine when administered orally e.g. pethidine and ephedrine.

b) Dosage forms:

i) Particle size: Small particle size is important for drug absorption. Drugs given in a dispersed or emulsified state are absorbed better e.g. vitamin D and vitamin A.

ii) Disintegration time and dissolution rate. Disintegration time: The rate of break up of the tablet or capsule into the drug granules. Dissolution rate: The rate at which the drug goes into solution.

iii) Formulation: Usually substances like lactose, sucrose, starch and calcium phosphate are used as inert diluents in formulating powders or tablets. Fillers may not be totally inert but may affect the absorption as well as stability of the medicament. Thus a faulty formulation can render a useful drug totally useless therapeutically.

c) Physiological factors: i) Gastrointestinal transit time: Rapid absorption occurs when the drug is given on empty stomach. However certain irritant drugs like salicylates and iron preparations are deliberately administred after food to minimize the gastrointestinal irritation. But some times the presence of food in the G.I tract aids the absorption of certain drugs e.g. griseofulvin, propranolol and riboflavin.

ii) Presence of other agents: Vitamin C enhances the absorption of iron from the G.I.T. Calcium present in milk and in antacids forms insoluble complexes with the tetracycline antibiotics and reduces their absorption.

iii) Area of the absorbing surface and local circulation: Drugs can be absorbed better from the small intestine than from the stomach because of the larger surface area of the former. Increased vascular supply can increase the absorption.

iv) Enterohepatic cycling: Some drugs move in between intestines and liver before they reach the site of action. This increases the bioavailability e.g. phenolphthalein.

v) Metabolism of drug/first pass effect: Rapid degradation of a drug by the liver during the first pass (propranolol) or by the gut wall (isoprenaline) also affects the bioavailability. Thus a drug though absorbed well when given orally may not be effective because of its extensive first pass metabolism.

d) Pharmacogenetic factors: Individual variations occur due to the genetically mediated reason in drug absorption and response.

e) Disease states: Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and liver cirrhosis.

4. Bioavailability curves

Single dose bioavailability test involves an analysis of plasma or serum concentration of the drug at various time intervals after its oral administration and plotting a serum concentration time curve.

C) Distribution of drugs

1. Definition: Penetration of a drug to the sites of action through the walls of blood vessels from the administered site after absorption is called drug distribution. Drugs distribute through various body fluid compartments such as (a) plasma (b) interstitial fluid compartment (c) trans-cellular compartment.

Apparent Volume of distribution (VD): The volume into which the total amount of a drug in the body would have to be uniformly distributed to provide the concentration of the drug actually measured in the plasma. It is an apparent rather than real volume.

Factors determining the rate of distribution of drugs:

1. Protein binding of drug: A variable and other significant portion of absorbed drug may become reversibly bound to plasma proteins. The active concentration of the drug is that part which is not bound, because it is only this fraction which is free to leave the plasma and site of action. (a) Free drug leave plasma to site of action (b) binding of drugs to plasma proteins assists absorption (c) protein binding acts as a temporary store of a drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids (d) protein binding reduces diffusion of drug into the cell and there by delays its metabolic degradation e.g. high protein bound drug like phenylbutazone is long acting. Low protein bound drug like thiopental sodium is short acting.

2. Plasma concentration of drug (PC): It represents the drug that is bound to the plasma proteins (albumins and globulins) and the drug in free form. It is the free form of drug that is distributed to the tissues and fluids and takes part in producing pharmacological effects. The concentration of free drug in plasma does not always remain in the same level e.g.

i) After I.V. administration plasma concentration falls sharply

ii) After oral administration plasma concentration rises and falls gradually.

iii) After sublingual administration plasma concentration rise sharply and falls gradually.

3. Clearance: Volume of plasma cleared off the drug by metabolism and excretion per unit time. Protein binding reduces the amount of drug available for filtration at the glomeruli and hence delays the excretion, thus the protein binding reduces the clearance.

4. Physiological barriers to distribution: There are some specialized barriers in the body due to which the drug will not be distributed uniformly in all the tissues. These barriers are:

a) Blood brain barrier (BBB) through which thiopental sodium is easily crossed but not dopamine.

b) Placental barrier: which allows non-ionized drugs with high lipid/water partition coefficient by a process of simple diffusion to the foetus e.g. alcohol, morphine.

5. Affinity of drugs to certain organs: The concentration of a drug in certain tissues after a single dose may persist even when its plasma concentration is reduced to low. Thus the hepatic concentration of mepacrine is more than 200 times that of plasma level. Their concentration may reach a very high level on chronic administration. Iodine is similarly concentrated in the thyroid tissue.

D. Metabolism of drugs:

Drugs are chemical substances, which interact with living organisms and produce some pharmacological effects and then, they should be eliminated from the body unchanged or by changing to some easily excretable molecules. The process by which the body brings about changes in drug molecule is referred as drug metabolism or biotransformation.

Enzymes responsible for metabolism of drugs:

a) Microsomal enzymes: Present in the smooth endoplasmic reticulum of the liver, kidney and GIT e.g. glucuronyl transferase, dehydrogenase , hydroxylase and cytochrome P450

b) Non-microsomal enzymes: Present in the cytoplasm, mitochondria of different organs. e.g. esterases, amidase, hydrolase.

E. Excretion of drugs

Excretion of drugs means the transportation of unaltered or altered form of drug out of the body. The major processes of excretion include renal excretion, hepatobiliary excretion and pulmonary excretion. The minor routes of excretion are saliva, sweat, tears, breast milk, vaginal fluid, nails and hair. The rate of excretion influences the duration of action of drug. The drug that is excreted slowly, the concentration of drug in the body is maintained and the effects of the drug will continue for longer period.

Different routes of drug excretion

a) Renal excretion: A major part of excretion of chemicals is metabolically unchanged or changed. The excretion of drug by the kidney involves.

i) Glomerular filtration

ii) Active tubular secretion

iii) Passive tubular reabsorption.

The function of glomerular filtration and active tubular secretion is to remove drug out of the body, while tubular reabsorption tends to retain the drug.

i) Glomerular filtration: It is a process, which depends on (1) the concentration of drug in the plasma (2) molecular size, shape and charge of drug (3) glomerular filtration rate. Only the drug which is not bound with the plasma proteins can pass through glomerulus. All the drugs which have low molecular weight can pass through glomerulus e.g. digoxin, ethambutol, etc. congestive cardiac failure, the glomerular filtration rate is reduced due to decrease in renal blood flow.

ii) Active tubular secretion: The cells of the proximal convoluted tubule actively transport drugs from the plasma into the lumen of the tubule e.g. acetazolamide, benzyl penicillin, dopamine, pethidine, thiazides, histamine.

iii) Tubular reabsorption: The reabsorption of drug from the lumen of the distal convoluted tubules into plasma occurs either by simple diffusion or by active transport. When the urine is acidic, the degree of ionization of basic drug increase and their reabsorption decreases. Conversely, when the urine is more alkaline, the degree of ionization of acidic drug increases and the reabsorption decreases.

b) Hepatobiliary excretion: the conjugated drugs are excreted by hepatocytes in the bile. Molecular weight more than 300 daltons and polar drugs are excreted in the bile. Excretion of drugs through bile provides a back up pathway when renal function is impaired. After excretion of drug through bile into intestine, certain amount of drug is reabsorbed into portal vein leading to an enterohepatic cycling which can prolong the action of drug e.g. chloramphenicol, oral estrogen are secreted into bile and largely reabsorbed and have long duration of action. Tetracylines which are excreted by biliary tract can be used for treatment of biliary tract infection.

c) Gastrointestinal excretion: When a drug is administered orally, a part of the drug is not absorbed and excreted in the faeces. The drugs which do not undergo enterohepatic cycle after excretion into the bile are subsequently passed with stool e.g. aluminium hydroxide changes the stool into white colour, ferrous sulfate changes the stool into black and rifampicin into orange red.

d) Pulmonary excretion: Drugs that are readily vaporized, such as many inhalation anaesthetics and alcohols are excreted through lungs. The rate of drug excretion through lung depends on the volume of air exchange, depth of respiration, rate of pulmonary blood flow and the drug concentration gradient.

e) Sweat: A number of drugs are excreted into the sweat either by simple diffusion or active secretion e.g. rifampicin, metalloids like arsenic and other heavy metals.

f) Mammary excretion: Many drugs mostly weak basic drugs are accumulated into the milk. Therefore lactating mothers should be cautious about the intake of these drugs because they may enter into baby through breast milk and produce harmful effects in the baby e.g. ampicillin, aspirin, chlordiazepoxide, coffee, diazepam, furosemide, morphine, streptomycin

Clearance of a drug:

It is the volume of plasma cleared of the drug by metabolism (hepatic) and excretion (renal) and other organs.

Factors modifying the dosage and action of drugs :

The important factors which influence the effect of a drug are:

1. Drug intolerance: It is a quantitative deviation from the anticipated response to a given dose of a drug. Thus drug intolerance is inability of the individual to tolerate a drug. It is also called as hypersusceptibility.

2. Sex difference: Special care should be exercised when drugs are administrated during menstruation, pregnancy and lactation.

a) Menstruation: Drugs producing pelvic congestion should be avoided during menstruation e.g. drastic purgatives.

b) Pregnancy: During pregnancy, the use of all drugs except those essential to maintain pregnancy should be used with caution. Drugs which may stimulate the uterine smooth muscle, are contraindicated during pregnancy. Further, many drugs administered to mother are capable of crossing the placenta and affecting the foetus. Most of drugs can produce teratogenicity when they are used in pregnancy. Teratogenicity means congenital malformation i) Drugs known to produce teratogenicity e.g thalidomide, cyclophosphamide, methotexate, tetracyclines, phenytoin, carbamazepine and progestogens. ii) drugs may be teratogenic e.g Warfarin, lithium, quinine, primaquine, trimethoprim, rifampicin, anaesthetic agents.

c) Breast feeding: Nearly all agents received by mother are likely to be found in her milk and could theoretically harm the infant. Most of the lipid soluble drugs get into breast milk. Therefore the drugs, which are excreted in the milk and harm the infant health should be, avoided by breast-feeding mothers e.g. sulphonamides, tetracyclines, nalidixic acid, isoniazid, diazepam, lithium, Indomethacin, aspirin, etc.

3. Body Weight: The average dose is mentioned either in terms of mg per kg body weight or as the total single dose for an adult weighing between 50-100kg. However, dose expressed in this fashion may not apply in cases of excessively obese individuals or those suffering from edema, or dehydration nutritional factors can sometimes alter drug metabolizing capacity and this should be kept in mind in malnourished patients.

4. Age: The pharmacokinetics of many drugs changes with age. Thus gastric emptying is prolonged and the gastric pH fluctuates in neonates and infant, further the liver capacity to metabolize drugs is low, renal function is less developed and the proportion of body water is higher in the newborn and the neonates. Hence children may not react to all drugs in the same fashion as young adults. With a few exceptions, drugs are more active and more toxic in the new born than the adults.

Exercise

1) **What are different routes of drug administration and write about advantages and disadvantages of parenteral route of administration.**

2) **Define bio-availability and describe the factors affecting drug absorption.**
3) **Define the following:**
    a) **Half-life of a drug**
    b) **Steady state plasma concentration**
    c) **Adverse drug reactions**
4) **Write about the factors modifying drug action.**
5) **Write about different types of drug interactions.**

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UNIT – II – DRUG AND PHARMACEUTICAL TECHNOLOGY – SCH1612

1. INTRODUCTION

Development and evaluation of new drugs:

The ultimate aim of pharmacological studies in animals is to find out a therapeutic agent suitable for clinical evaluation in man. No doubt, animal studies provide analogies and serve as useful models. The administration of biologically active agent to human beings is associated with an element of risk, which cannot be predicted by even the most careful and exhaustive animal experiments. Scientists all over the world are in a continuous effort to develop new drugs although drug development is an extremely technical and enormously expensive operation. Among the contributors to new drug development, pharmacologists are more concerned in evaluating "new chemical entities" (NCE). Synthesis and evaluation of thousands of NCEs are usually necessary for new drugs to be introduced in the market. Research and development of new drugs have been done under strict government regulations which have greatly increased over the past couple of decades.

Drug development comprises of two steps.

a) Preclinical development and

b) Clinical development

A) Preclinical development: Synthesis of new chemical entities is done as per research policy

decision which is based on:

(i) Random synthesis

(ii) Structure activity relationship (SAR)

(iii) Biochemical and pharmacological insight and

(iv) Chance finding.

The aim of the preclinical development phase for a potential new medicine is to explore the drug's efficacy and safety before it is administrated to patients. In this preclinical phase, varying drug doses are tested on animals and/or in vitro systems. If active compounds are found, then studies on animals are done which include pharmacodynamics, pharmacokinetics, toxicology and special toxicological studies (mutagenicity and carcinogenicity) have to be done. In this study single dose is used for acute toxicity and repeated doses for sub chronic and

chronic toxicity studies. Most of the preclinical tests have to be conducted in accordance with the standards prescribed.

B) Clinical development: About one in 1000 NCEs reach this stage. The steps to be studied in this stage include:

a) Pharmaceutical study

b) Pharmacological study

c) Clinical trial.

a) Pharmaceutical study covers stability of formulation and compatibility of the NCEs with other tablet or infusion ingredients.

b) Pharmacological study includes further chronic toxicological study in animal, initially animal metabolic and pharmacokinetic study. When studies in animals predict that a NCE may be useful medicine i.e. effective and safe in relation to its benefits, then the time has come to put it to the test in man i.e. clinical trial.

c) Studies on human or Clinical Trial:

Clinical trial is a means by which the efficacy of drug is tested on human being. It may also give some idea about the risk involved. It is divided into 4 phases. With each phase, the safety and efficacy of the compound are tested progressively.

Phase - I: This is the first exposure of the new drug on man which is usually conducted in healthy volunteers and which is designed to test the tolerable dose, duration of action. This phase is usually carried out in only one centre on 20 to 50 subjects.

Phase - II: This phase comprises small scale trials on patients used to determine dose level and establish that the treatment offers some benefit. It usually involves 100-500 patients and is usually conducted in several centres.

Phase - III: Full scale evaluation of treatment comparing it with standard treatment is done in this phase. It involves randomised control trials on 250 to 2000 patients and is done in multiple centres. Information from all studies are received by the “Committee of safety of medicines” (CSM). If the drug is satisfied by the CSM, the product license is issued then the drug is marketed.

Phase - IV: It is also called as phase of post marketing surveillance. Reports about efficacy and

toxicity are received from the medical practitioners and reviewed by the committee of review of medicines. Renewal or cancellation of the product license depends on the comment of the review committee.

1. Drugs acting on the sympathetic nervous system

a) Sympathomimetics or adrenergic drugs: are drugs that mimic the effects of sympathetic nerve stimulation.

b) Sympatholytics: are drugs that inhibit the activity of sympathetic nerve or that of sympathomimetics.

2. Drugs acting on the parasympathetic nervous system

a) Parasympathomimetics or cholinergic drugs: are drugs which mimic acetylcholine or the effects of parasympathetic nerve stimulation.

b) Parasympatholytics: are drugs that inhibit parasympathetic nervous system activity or that of cholinergic drugs.

1. **Alkylation**:
Addition of alkyl radical (CH3) with side chain final product. This alkylation process is widely used in organic chemicals and petroleum industries. The reaction is given as,

C=C-C-C + C-C-C

2. **Amination by Ammonolysis**:

$Cl\text{-}CH_2CH_2Cl + 4NH_3 \text{ -------} > NH_2CH_2CH_2NH_2$
EDC Ethylene Diamine

This reaction is used in manufacture of dye stuffs, organic chemicals and synthetic fibres.

3. **Amination by Reduction**:

$CH_3CHNO_2CH_3 + 3H_2 \text{ ------} \circledcirc CH_3CHNH_2CH_3$
2 Nitro Paraffin Iso Propylamine

This unit process is also used in the manufacture of dye stuffs and organic chemicals.

4. **Amino Oxidation**:

$CH_3CH_2CH_3 + NH_3 + 1.5\ O_2 \text{ -----} \circledcirc CH_2{:}CHCN + H_20$
Propylene Acrylonitrile

This reaction is used in the manufacture of plastics and synthetic fibres.

5. **Calcination**:

$CaCO_3 \text{ ---}^{Heat}\text{---} \circledcirc CaO + CO_2$
Limestone Lime

This reaction is used in the cement industry.

6. **Carbonylation**:

$CH_3OH + CO$ -----✇ CH_3COOH
Methanol Acetic Acid
This is used in the manufacture of organic chemicals.

7. **Carboxylation**:
This reaction is used in the organic chemical industry.

8. **Combustion**:

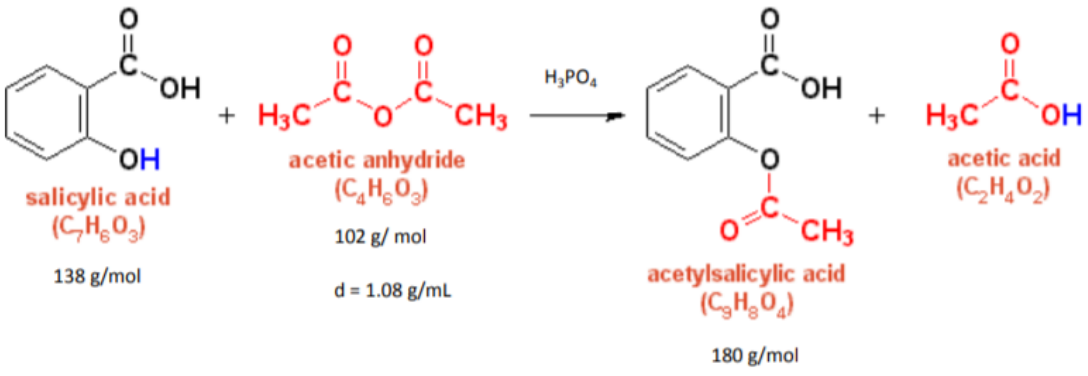
$CH_4 + O_2$ ------✇ $CO_2 + 2H_2O$ (Process Heating)

9. **Condensation**:

$C_6H_5CHO + CH_3CHO$ ------✇ $C_6H_5CH{:}CHCHO + H_2O$
Benzaldehyde+Acetaldehyde Cinnamaldehyde

Synthesis of Aspirin

Aspirin is the common name for the compound acetylsalicylic acid, widely used as a fever reducer and as a pain killer. Salicylic acid, whose name comes from Salix, the willow family of plants, was derived from willow bark extracts. In folk medicine, willow bark teas were used as headache remedies and other tonics. Nowadays, salicylic acid is administered in the form of aspirin which is less irritating to the stomach than salicylic acid. To prepare aspirin, salicylic acid is reacted with an excess of acetic anhydride. A small amount of a strong acid is used as a catalyst which speeds up the reaction. In this experiment, phosphoric acid will be used as the catalyst. The excess acetic acid will be quenched with the addition of water. The aspirin product is not very soluble in water so the aspirin product will precipitate when water is added. The synthesis reaction of aspirin is shown below:



Fermentation

Fermentation is a metabolic process that produces chemical changes in organic substrates through the action of enzymes. In biochemistry, it is narrowly defined as the extraction of energy from carbohydrates in the absence of oxygen.

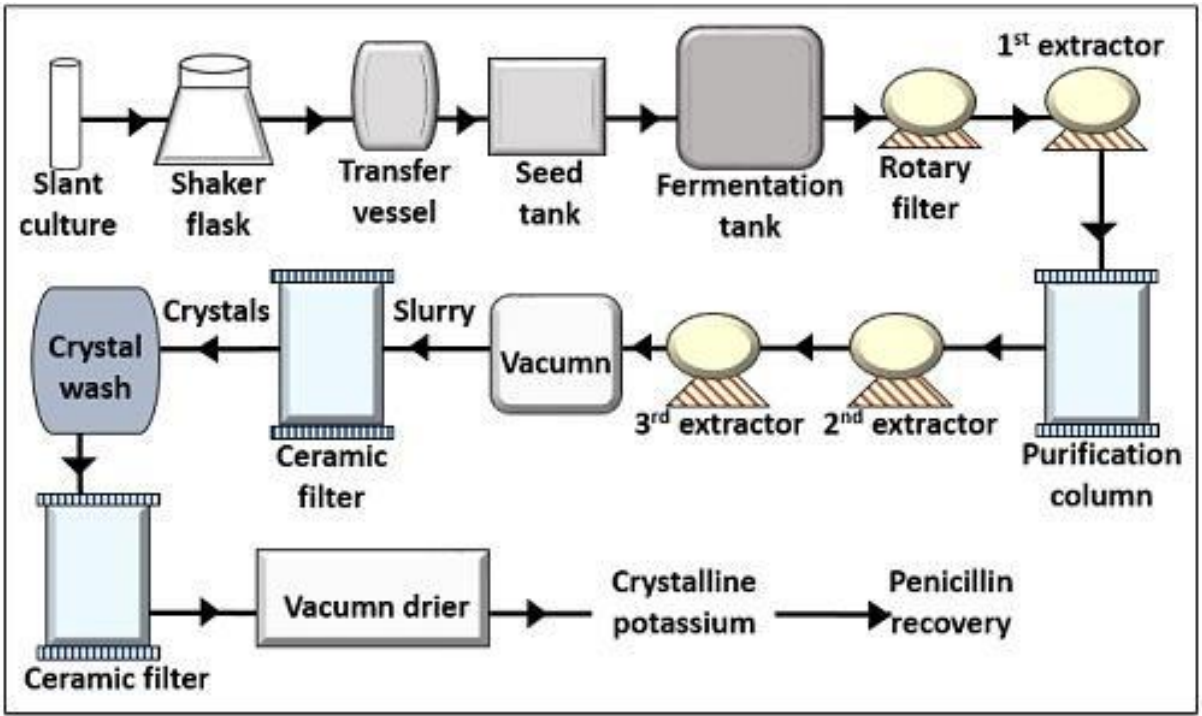
For many years, scientists knew that certain molds killed some bacteria. However, researchers needed to understand how to harness this antibacterial microbe and to manufacture enough of the substance before they could make a useful medicine.

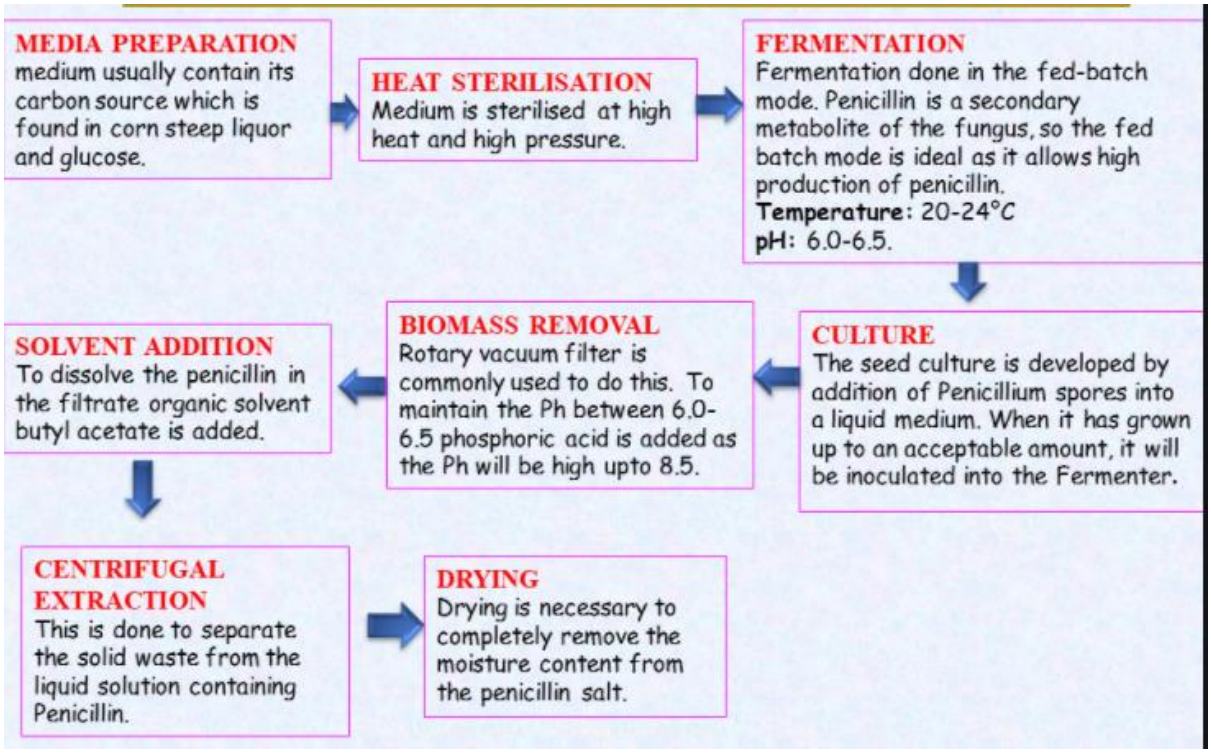
1. Penicillium mold naturally produces the antibiotic penicillin.

2. Scientists learned to grow Penicillium mold in deep fermentation tanks by adding a kind of sugar and other ingredients. This process increased the growth of Penicillium.

3. Then, scientists separated the penicillin product from the mold.

4. Finally, penicillin is purified for use as an antibiotic medicine.





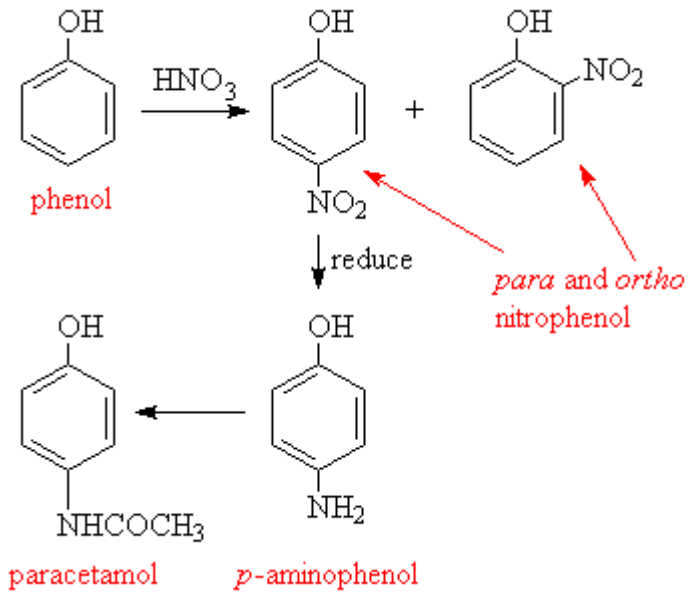
Placebo: It is a Latin word meaning" I shall please" and it is a tablet looking exactly like the active treatment but containing no active component. It refers originally to substances merely to please the patient when no specific treatment was available.

Therapeutic class

- Analgesics - Aspirin
- Antibiotic - Pencillin
- Anticoagulant
- Antidepressant
- Anticancer
- Antiepileptic
- Antipsychotic
- Antiviral
- Sedative
- Antidiabetic
- Cardiovascular

Synthesis of paracetamol by acetylation

Synthesis and crystallization



It is an effective antipyretic and analgesic. Activity of the drug on the hypothalamic heat-regulating centre is the mechanism behind the antipyretic effect, whereas analgesia is shown due to elevation of the pain-threshold. It is also found to be useful in diseases accompanied by pain, discomfort, and fever, for instance the common cold and other viral infections.[2] It is also active against arthritic and rheumatic disorders involving musculoskeletal pain as well as the pain occurred due to headache, myalgia, dysmenorrhea and neuralgia.

Anesthesia Drugs

Anesthesia drugs are also known as “anesthetics” used to induce anesthesia to avoid pain and discomfort during and after surgery. Benzodiazepines, Diazepam, Lorazepam, Midazolam, Etomidate, Ketamine, Propofol. These drugs can be administered intravenously. We have different class of anesthetics in practice such as general anesthetic, local anesthetic, regional anesthetic. Lidocaine, propaine, cocaine, desflurane, xenon are few anesthetics used to induce anesthesia to avoid pain and discomfort.

Chloroform

Chloroform, or trichloromethane, is an organic compound with formula $CHCl_3$

In industry production, chloroform is produced by heating a mixture of chlorine and either chloromethane (CH_3Cl) or methane (CH_4). At 400–500 °C, a free radical halogenation occurs, converting these precursors to progressively more chlorinated compounds:

$CH_4 + Cl_2 \rightarrow CH_3Cl + HCl$

$CH_3Cl + Cl_2 \rightarrow CH2Cl_2 + HCl$

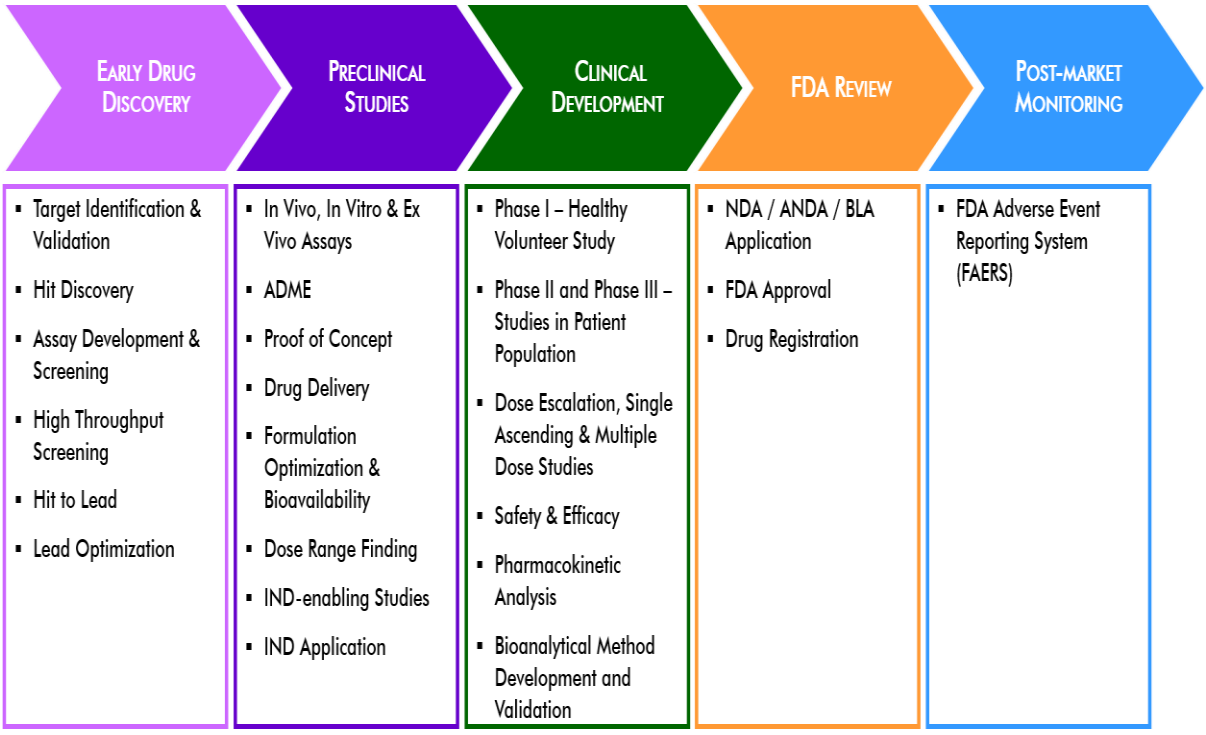
$CH_2Cl_2 + Cl_2 \rightarrow CHCl_3 + HCl$

Chloroform undergoes further chlorination to yield carbon tetrachloride (CCl4):

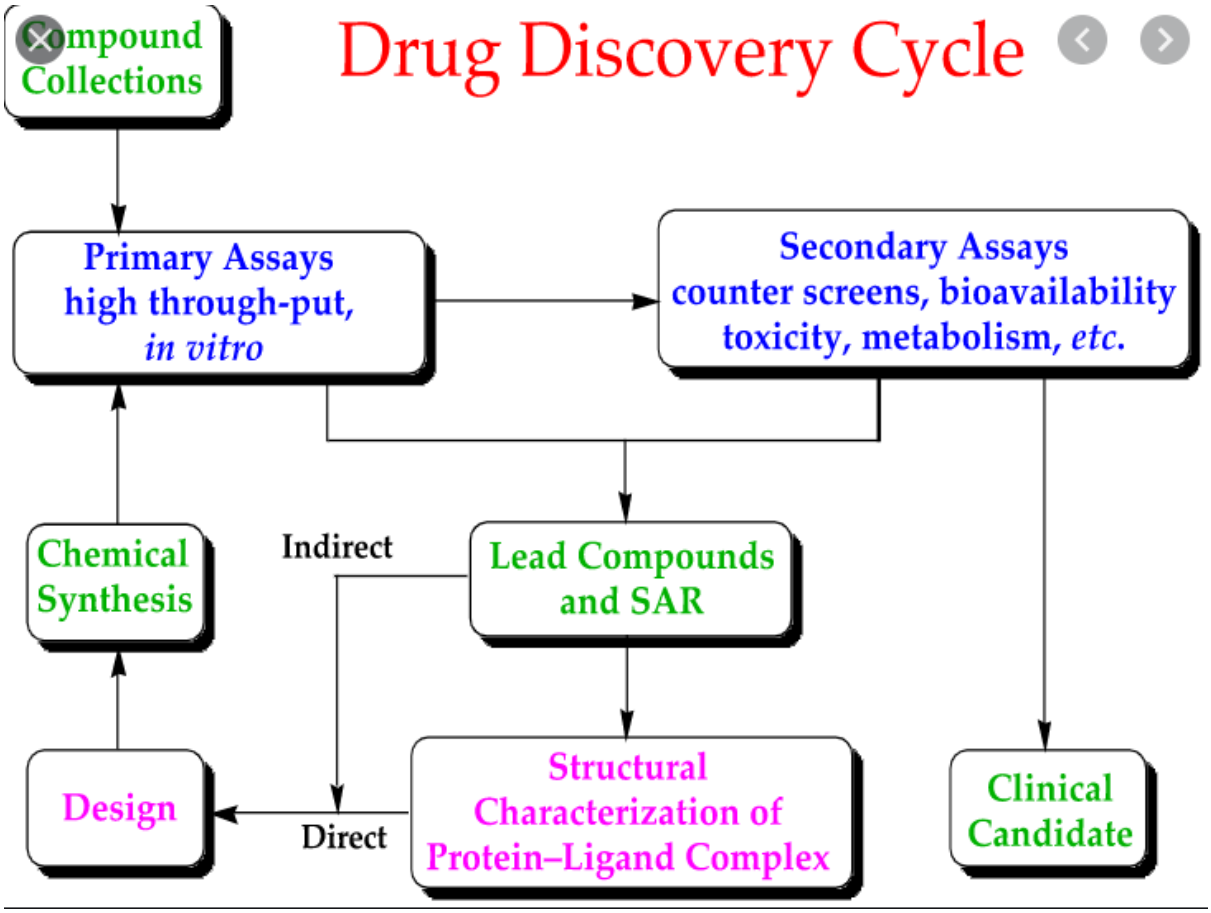
$CHCl_3 + Cl_2 \rightarrow CCl_4 + HCl$

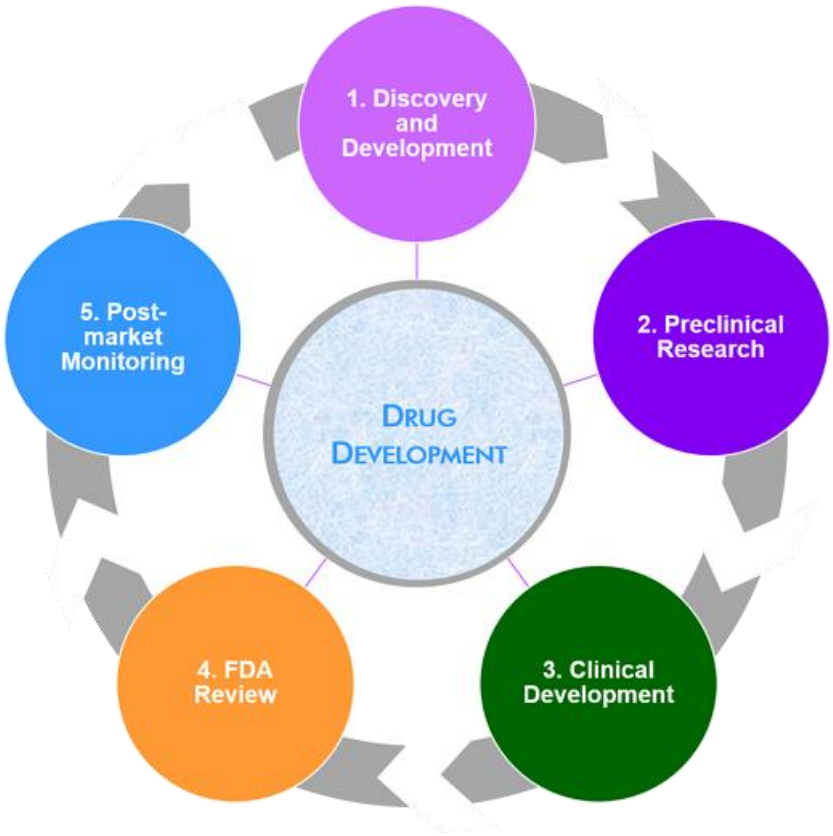
The output of this process is a mixture of the four chloromethanes (chloromethane, dichloromethane, chloroform, and carbon tetrachloride), which can then be separated by distillation.

Drug Concept to Market



Drug Discovery Cycle


Drug Discovery Cycle
Compound Collections
Primary Assays high through-put, in vitro
Secondary Assays counter screens, bioavailability toxicity, metabolism, etc.
Chemical Synthesis
Indirect
Lead Compounds and SAR
Design
Direct
Structural Characterization of Protein–Ligand Complex
Clinical Candidate


1. Discovery and Development
2. Preclinical Research
3. Clinical Development
4. FDA Review
5. Post-market Monitoring
DRUG DEVELOPMENT

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CHEMICAL ENGINEERING

UNIT – III – DRUG AND PHARMACEUTICAL TECHNOLOGY – SCH1612

I. Introduction

Tablet formulation

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. Tablets remain popular as a dosage form because of the advantages, afforded both to the manufacturer [e.g.: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g.: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration. Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

Properties of Tablets :

The attributes of an acceptable tablet are as follows:

1) The tablet must be sufficiently strong and resistance to shock and abrasion and to with stand handling during manufacturing, packing, shipping, and use. Hardness and friability tests measure this property.

2) Tablet must be uniform in weight and in drug content of the individual tablet. This is me assured by the weight variation and content uniformity tests.

3) The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels of the drug after its administration.

4) Tablets must be elegant in appearance and must have characteristic shape, color, and other markings necessary to identify the product.

5) Tablets must retain all these functional attributes, which include drug stability and efficacy.

Advantages of Tablet :

1) It is easy to be administered.

2 It is a unit dosage form, and they offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.

3) Cost is lowest of all oral dosage forms.

4) It is the lightest and most compact of all oral dosage forms.

5) Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.

Disadvantages of Tablets:

1) Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

2) Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

3) Bitter drugs, drugs with objectionable odor or drugs that are sensitive to oxygen or atmosphere moisture may require encapsulation or a special type of coating which may increase the stability of the finished tablets.

Types of Tablets:2-3

Tablets are classified according to their route of administration or function. The following are the 5 main classification groups.

1. **Tablets ingested orally**

- Compressed tablets
- Multiple compressed tablets
- Multilayered tablets
- Inlay tablets
- 1.3. Sustained action tablets
- 1.4. Enteric coated tablets
- 1.5. Sugar coated tablets
- 1.6. Film coated tablets

- 1.7. Chewable tablets

2. Tablets used in the oral cavity
    - Buccal tablets
    - Sublingual tablets
    - Lozenge tablets and torches
    - Dental cones
3. Tablets administered by other routes
    - 3.1. Implantation tablets
    - 3.2. Vaginal tablets
4. Tablets used to prepare solutions
    - 4.1. Effervescent tablets
5. Molded tablets or tablet triturates (TT)
    - Dispensing tablets (DT)
    - Hypodermic tablets (HT)

TABLET COMPONENTS/ FORMULATION

A tablet contains active ingredients as well as other substances known as excipients, which have specific functions. Ingredients used in tablet formulation are:

1. Active Ingredient/Drug/API

a. Insoluble drug- exert local effect

b. Soluble drug- exert systemic effect

2. Excipients/Additives/Inactive Pharmaceutical ingredients/Nonactive ingredients

a. Diluents/Fillers

b. Binders/Adhesive

c. Disintegrants

d. Antifrictional agent

I. Lubricants

II. Glidants

III. Antiadherants

e. Organoleptic additives

I. Colors

II. Flavoring agent

III. Sweetener

f. Co-processed Excipients

Additives/Excipients:

A pharmaceutical excipient is defined as an inactive ingredient or any component other than the active ingredient added intentionally to the medicinal formulation or everything in the formulation except the active drug. Pharmaceutical excipients are also called additives, pharmaceutical ingredients, or inactive pharmaceutical ingredients.

DILUENTS/FILLERS

Diluents are the inert substance added to increase the bulk of the tablet.

Objectives of incorporating diluents:

 In order to produce tablets of reasonable size (i.e. minimum diameter of 3mm), it is necessary to add an inert material known as Diluent/ Filler.

 Diluent increase the bulk in order to make the tablet a practical size for compression.

 The dose of some drugs is sufficiently high that no filler is required (e.g. aspirin and certain antibiotics).

 Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties that will help in disintegration of the tablet in the mouth by chewing. Such tablets are commonly called chewable tablets.

 Diluents used for direct compression formulas give the powder mixture necessary flowability and compressibility.

 To delay or control the rate of release of drug from the tablet.

Characteristics of ideal diluents:

 They must be nontoxic and acceptable to the drug-regulatory agencies in all countries where the product is to be marketed.

 They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.

 They must be cheap compared to the active ingredients.

 They must be physiologically inert.

 They must be chemically stable alone and/or in combination with the drug(s) and/or other tablet components.

 They must be free of any unacceptable microbiologic “load”.

 They must be color-compatible.

 They must have no negative effects on the bioavailability of the drug(s) in the product.

CLASSIFICATION OF DILUENTS:

Sugars	Polysaccharides	Inorganic compounds	Miscellaneous compounds
Dextrose Lactose Sucrose Amylose Mannitol Sorbitol Inositol	Starches Modified starch e.g. Sta-RX 1500, Celutab etc. Cellulose Cellulose derivatives Microcrystalline cellulose (MCC)	Calcium phosphate dihydrate Calcium sulfate dihydrate Calcium lactate trihydrate Calcium carbonate Magnesium carbonate Magnesium oxide	Bentonite Polyvinyl Pyrrolidone (PVP) Kaolin Silicone derivatives

Commonly Used Granulating (Binding) Agents

Granulating Agent	Normal Concentration (%)
Starch Paste	5 – 25
Pregelatinized starch	0.1-0.5
Acacia	1-5
Polyvinylpyrrolidone (PVP)	2-8
Hydroxypropyl methylcellulose (HPMC)	2-8
Methylcellulose (MC)	1-5
Gelatin	10-20

Lubricants are included to reduce the friction during tablet ejection between the walls of the tablet and the wall of the die in which the tablet was formed.

Antiadherents are used for the purpose of reducing the sticking or adhesion of any of the tablet ingredients or powder to the faces of the punches or to the die wall.

Glidants are intended to promote flow of the tablet granulation or powder materials by reducing the friction between the particles. An ingredient used for lubrication purpose may possess other two properties as well.

COLOURING AGENT

Objectives of using colors

i. Agent impart colour to the tablets

ii. It makes the tablet more esthetic in appearance.

iii. Colour helps the manufacturer to identify the product during its preparation.

Flavours are usually limited to chewable & effervescent tablets or other tablets intended to dissolve in the mouth.

Sweeteners: - Mainly used in chewable, effervescent & mouth dissolving tablets for improvement of taste.

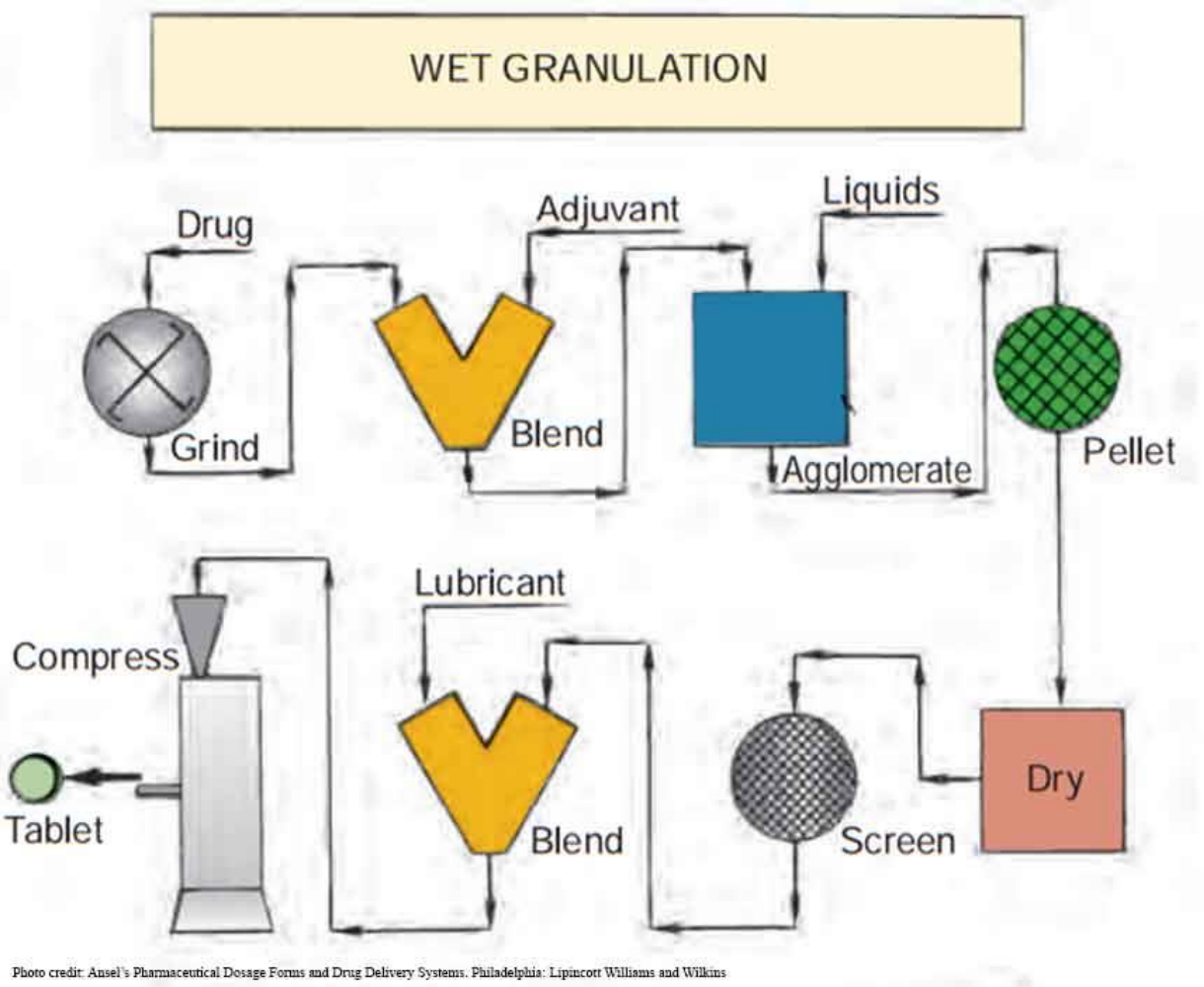
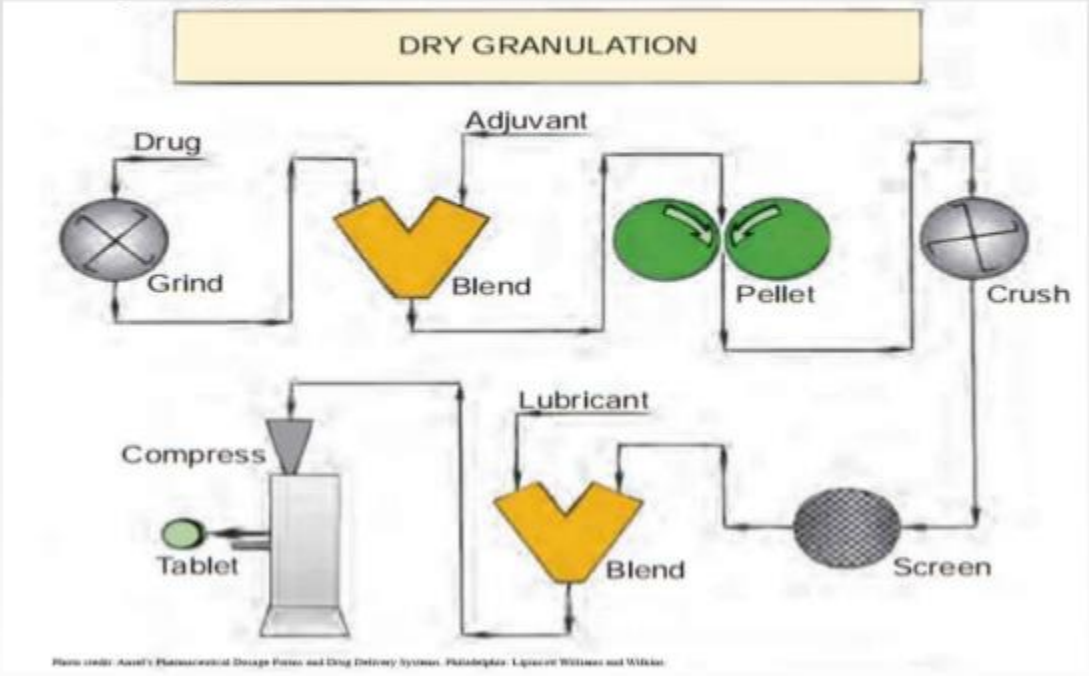
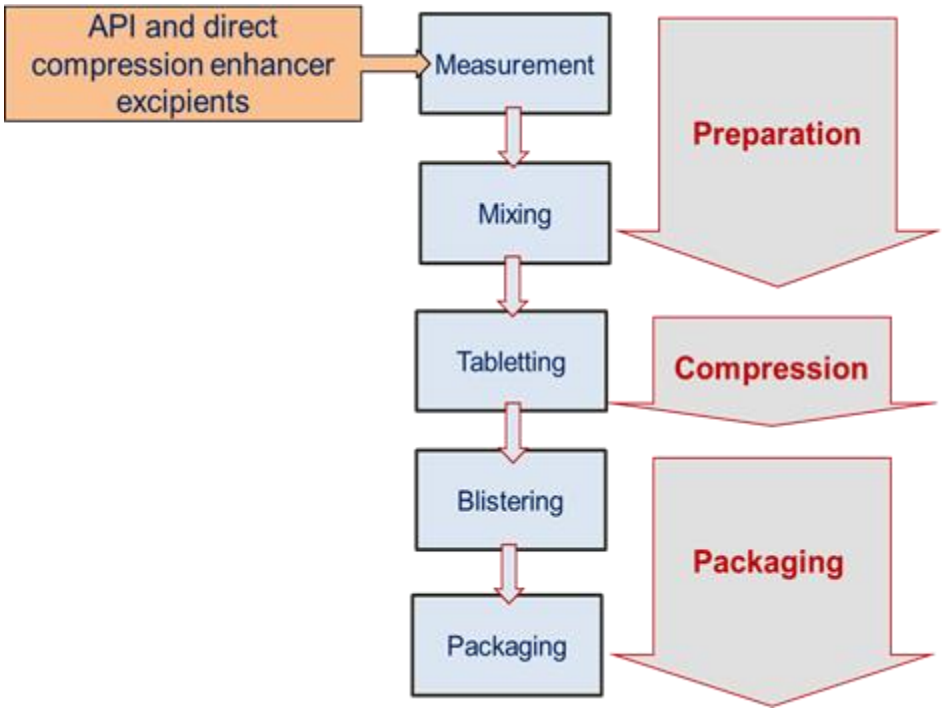


Photo credit: Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lipincott Williams and Wilkins

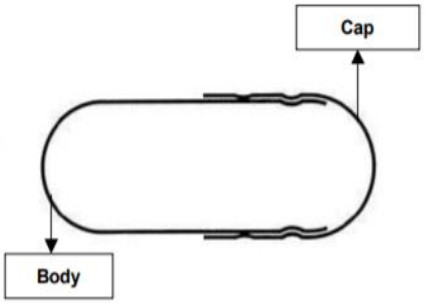
❖The roller compaction method is often preferred to slugging. Excessive pressures that may be required to obtain cohesion of certain materials may result in a prolonged dissolution rate.



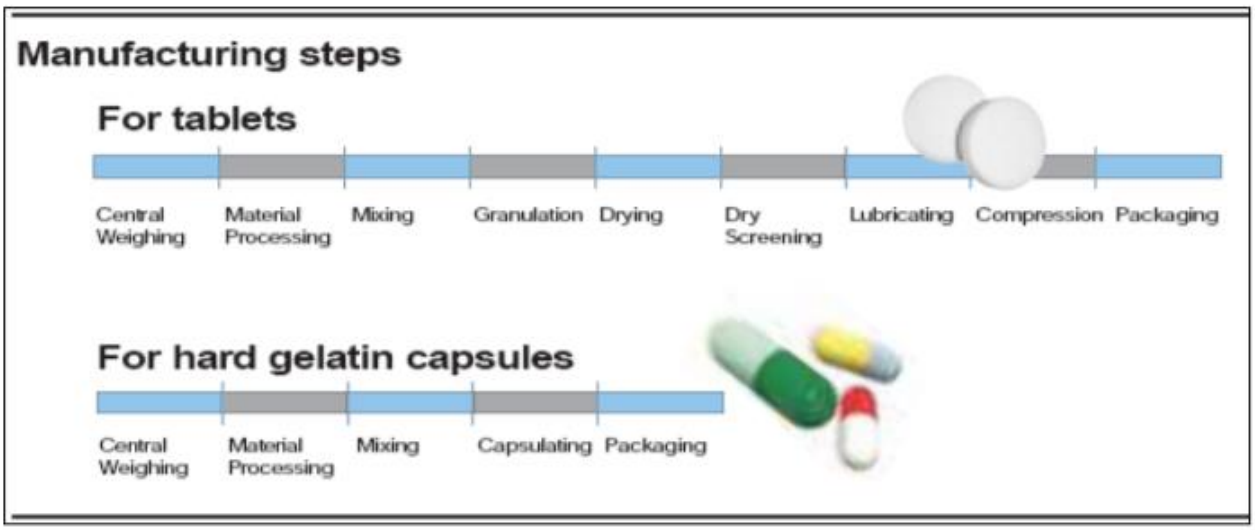


Capsule Formulation

1. Hard Gelatin Capsule
2. Soft Gelatin Capsule



Capsules offer many advantages. 1. Capsules, because of their elongated shape, are easy to swallow, which is one reason for the number of capsule-shaped tablets manufactured today. 2. Flexibility of formulation is another advantage of the capsule dosage form. However the biggest formulation advantage of capsules is that there is less need for additional excipients. 3. Since capsules are tasteless, they effectively mask any unpleasant taste or odor of their contents. 4. They offer rapid release characteristics, due to the rapid dissolution rate of the capsules. 5. The use of hard capsules is also a common feature in clinical trials, as the filling of tablets or even capsules themselves will blind the dosage forms studied 6. The manufacture of capsules as illustrated in figure 2-5 also involves a much shorter process compared to that for other modern dosage forms (e.g. tablet). 7. Controlled release can be achieved using capsules. Dry powder mixtures, granules, pellets and tablets can be filled into hard capsules. Moreover combination of two or three types (i.e. dry powder mixtures, tablets or pellets) also can be put into capsules.



Advantages of capsule dosage forms

1. They obscure the taste and odour of unpleasant drugs.

2. They are attractive in appearance.

3. They are slippery when moist and, hence, easy to swallow with a draught of water.

4. If properly stored, the shells contain 12-15% of moisture which gives flexibility and, consequently very considerable resistance to mechanical stresses (cf. cachets).

5. Less adjuncts are necessary than tablets.

6. The contents are usually in fine powder which combined with adjuncts, provides rapid and uniform release of medicament in the GIT.

7. The shells can be opacified with TiO_2 or coloured to give protection from light.

8. The shells are physiologically inert and easily and quickly digested in the GIT.

9. Presentation of a drug in capsules, rather than in tablets, allows quicker submission of anew drug for clinical trials, because fewer development problems are involved. Also it is easier to vary the dose.

Disadvantages of capsule dosage forms

1. Capsules are not used for administering extremely soluble materials such as potassium chloride, potassium bromide, or ammonium chloride since sudden release of such compounds in the stomach could result in irritation.

2. Capsules should not be used for highly efflorescent or deliquescent materials.

Efflorescent materials may cause the capsules to soften.

Deliquescent materials may dry the capsule shell to excessive brittleness.

MATERIALS

Capsules are made principally of gelatin blends and may contain small amounts of certified dyes, opaquing agents, plasticizers and preservatives.

To modify the solubility of the capsules (e.g. to impart enteric property) methyl cellulose, polyvinyl alcohols and denatured gelatin are used.

GELATIN

Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen (obtained from animal skin and bone).

Common sources of collagen are animal bones, hide portions, and frozen pork skin.

There are mainly two types of gelatin commercially available:

Type A: Gelatin is derived mainly from pork skin by acid treatment. This gelatin has an isoelectric point in the region of pH 9.

Type B: Gelatin is derived from bones and animal skins by alkaline processing (pH 4 - 5).

SOFT GELATIN CAPSULES

Advantages of soft gelatin capsules:

(i) Soft gelatin capsules are useful when it is desirable to seal the medication within the capsule.

(ii) The capsules are especially important to contain liquid drugs or drug solutions.

(iii) Also, volatile drug substances or drug materials especially susceptible to deterioration in the presence of air may be better suited to a soft gelatin capsule than hard gelatin capsules.

(iv) Soft gelatin capsules are elegant and are easily swallowed by the patients.

Shape	Diagram	Size range (number represents the nominal capacity in minims (1 cc = 16.23 minim)
Round		1,2,3,4,5,6,7,9,28,40,90, 40T,80T
Oval		1,2,3,4,5,6,7.5,10,.12,16,20,30,40,60 ,80,85,110.
Oblong		3,4,5,6,8,9.5,11,14,16,20,90,360
Tube		55,65,90,160,250,320,480

CAPSULE MANUFACTURING

Plate process: It is the oldest process, contains sets of plates containing die packets.

Rotary die process

Reciprocating die process

Accogel machine is unique in that it is the only equipment that accurately fills powdered dry solids into soft gelatin capsules.

PROCESS

Gelatin preparation department

(i) Weighing of gelatin and other liquids

(ii) The resultant fluffy mixture transferred to melting tanks and melted under vacuum at 930C

(iii) A sample of the resulting fluid mass is visually compared with a color standard, and additional colorants are added if required.

(iv) The mass is then maintained at 57 to 600C before and during capsulation process.

Suspension Formulation

DEFINITION:

A Pharmaceutical suspension is a biphasic coarse dispersion in which internal phase (therapeutically active ingredient) is dispersed uniformly throughout the external phase.

Internal phase: The internal phase consisting of insoluble solid particles having a range of size(0.5 to 5 microns) which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent.

External phase: The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non oral use.

Classification:

Based On General Classes:

- Oral suspension: ex: antibiotic, paracetamol suspension, antacids.
- Externally applied suspension: ex :Calamine lotion.
- Parenteral suspension: ex: Procaine penicillin G ,Insulin Zinc Suspension

Based on Proportion of Solid Particles:

- Dilute suspension (2 to10%w/v solid): Ex: cortisone acetate, predinisolone acetate.
- Concentrated suspension (50%w/v solid): Ex: zinc oxide suspension.

Based on Size of Solid Particles:

- Colloidal suspensions(0.1-0.2microns): Suspensions having particle sizes of suspended solid less than about 0.2 micron in size are called as colloidal suspensions.
- Coarse suspensions (>0.2microns): Suspensions having particle sizes of greater than about 0.2 micron in diameter are called as coarse suspensions.
- Molecular dispersion (<1.0 nm):Suspensions are the biphasic colloidal dispersions of nanosized drug particles stabilized by surfactants.

FORMULATION OF SUSPENSIONS:

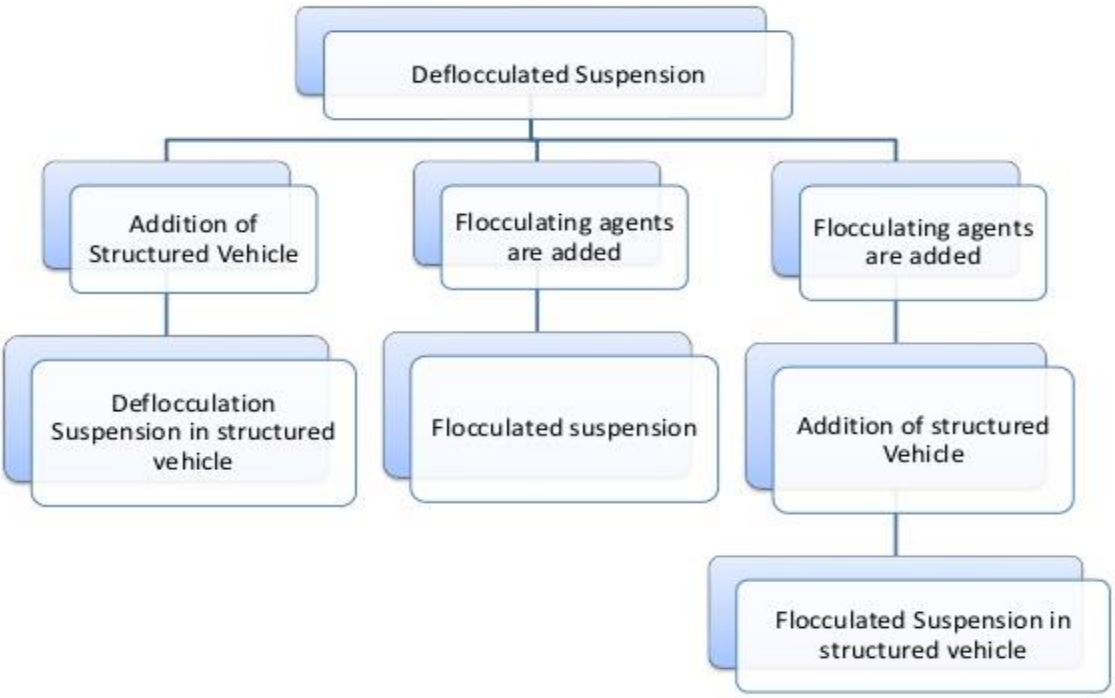
- Wetting agents: They are added to disperse solids in continuous liquid phase . ex: polysorbate 80,20, span etc
- Suspending agents: They are added to flocs the drug particles.
- Thickeners: They are added to increase the viscosity of suspension. ex: gaur gum , xanthan gum.
- Buffers and pH adjusting agents: They are added to stabilize the suspension to a desired pH range.
- Coloring agents: They are added to impart desired color to suspension and improve elegance.
- Preservatives: They are added to prevent microbial growth.

Step 1: Suspensions are prepared by grinding the insoluble materials in the mortar To a smooth paste with a vehicle containing the wetting agent.

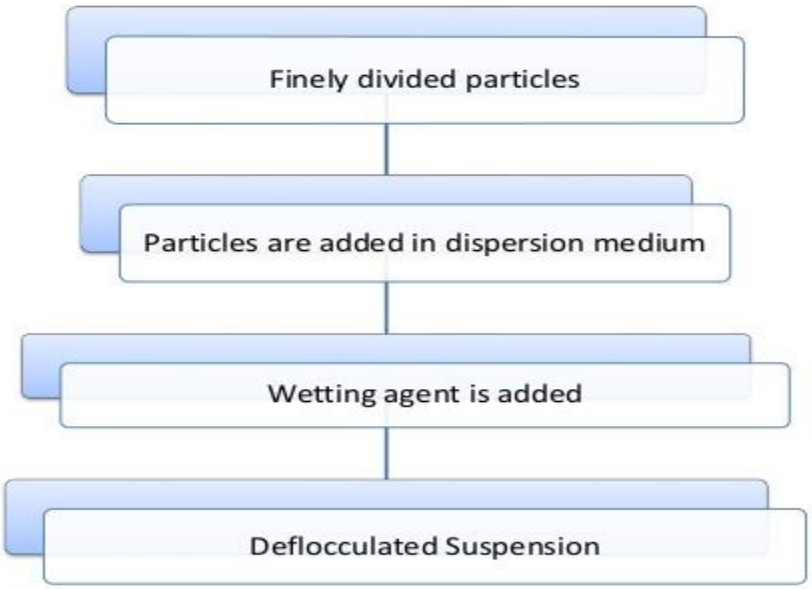
Step 2: All soluble ingredients are dissolved in same portion of the vehicle and added to the smooth paste to step1 to get slurry.

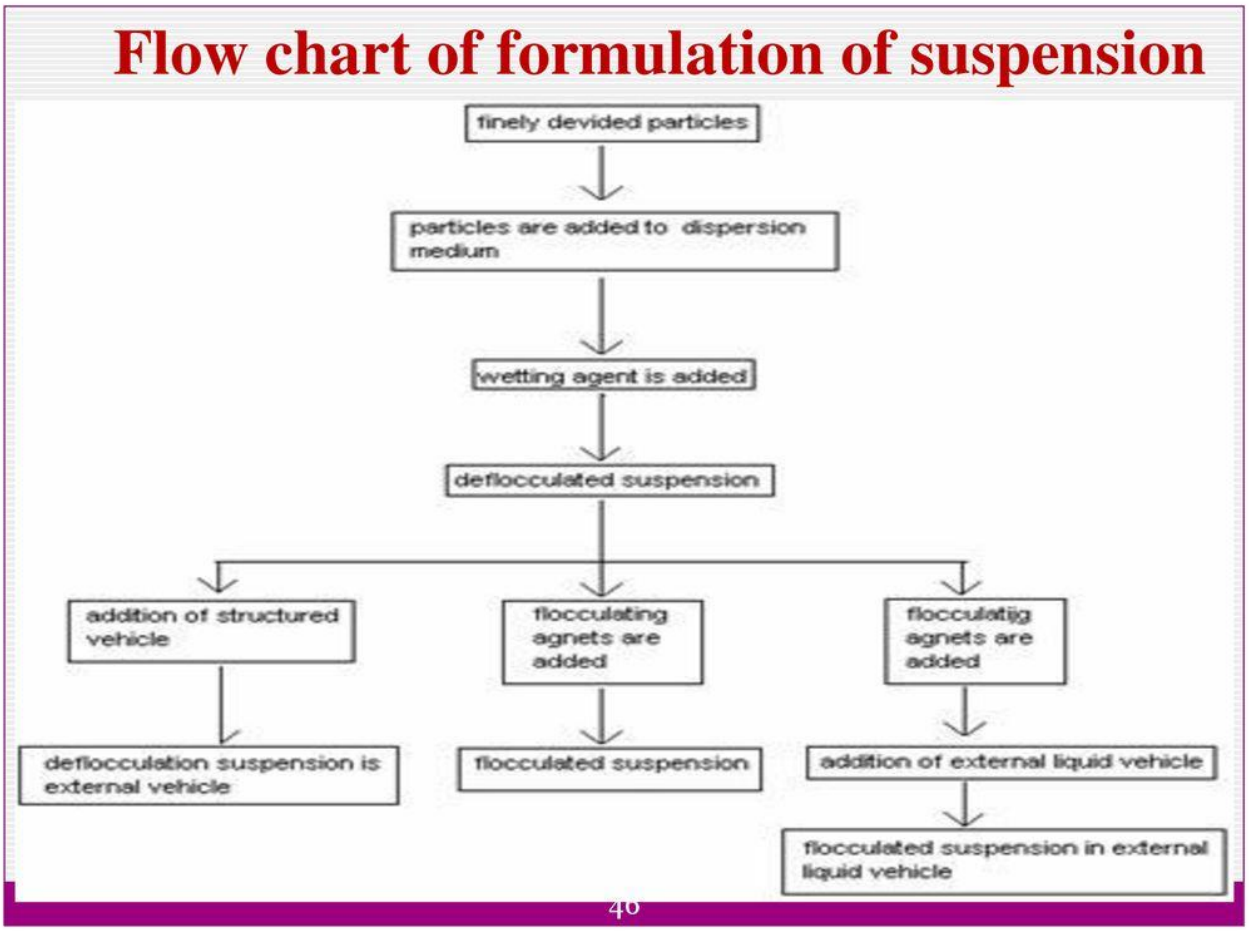
Step 3: The slurry is transformed to a graduated cylinder, the mortar is rinsed with successive portion of the vehicle.

Flow Chart for formulation of Suspension



Flow Chart for formulation of Suspension





Oinment Formulation

Ointments and creams are the semisolid dosage forms and intended for topical application to the skin, placed on the surface of eye, or used nasally, vaginally or rectally for therapeutic or protective action or cosmetic function. These preparations are used for the localized effects produced at the site of their application by drug penetration in to the underlying layer of skin or mucous membrane. These products are designed to deliver drug into the skin in treating dermal disorders, with the skin as the target organ.

Types of Ointments

The various types of ointments are: Unmedicated ointments Medicated ointments **UNMEDICATED OINTMENTS** These ointments do not contain any drugs. They are useful as emollients, protectants . Example: Petroleum jelly.

MEDICATED OINTMENTS These ointments contain drugs which show local or systemic effects. These are of several sub-types: Dermatologic ointments Opthalmic ointments Rectal ointments Vaginal ointments Nasal ointments

DERMATOLOGIC OINTMENTS These ointments are applied topically on the external skin. The ointment is applied to the affected area as a thin layer and spread evenly using gentle pressure with the fingertips. These are of three types: (1) Epidermic ointments: The drugs present in these type of ointments exert their action on the epidermis of the skin. Example: Ketoconazole ointment. (2) Endodermic ointments: The drugs present in these types of ointments exert their action on the deeper layers of cutaneous tissue. Example: Demodex ointment. (3) Diadermic ointments: The drugs present in these types of ointments enter into the deeper layers of skin and finally in the systemic circulation and exert systemic effects. Example: Nitroglycerine ointment.

OPTHALMIC OINTMENTS These are sterile preparations which are applied inside the lower eye lid. Only anhydrous bases are used in their preparation. The ointment is applied as a narrow band of approximately 0.25 - 0.5 inch. Example: Sulfacetamide sodium ointment. RECTAL OINTMENTS These are the ointments to be applied to the peri- anal or within the anal canal. The bases used are combinations of PEG 300 and PEG 3350, cetyl alcohol and cetyl esters, wax, liquid paraffin and white paraffin. Example: Benzocaine ointment.

Ointments are used topically for several purposes, e.g., as protectants, antiseptics, emollients, antipruritics, kerotolytics, and astringents. In the case of a protective ointment, it serves to protect the skin against moisture, air, sun rays and other external factors. It is necessary that the ointment neither penetrates the human skin barriers nor facilitates the absorption of substances through this barrier.

An antiseptic ointment is used to destroy or inhibit the growth of bacteria. Frequently bacterial infections are deeply seated; a base which has the capacity to either penetrate or dissolve and release the medication effectively is therefore desired. Ointments used for their emollient effect should be easy to apply, be non-greasy and effectively penetrate the skin.

ADVANTAGES

 Handling of ointments is easier than bulky liquid dosage forms. They are chemically more stable than liquid dosage forms. They facilitate application of the directly to the effected body part and avoid exposure of other parts to the drug. They are suitable for patients who find it difficult to take the drugs by parenteral and oral routes. They prolong the contact time between the drug and effected area. The bioavailability of drugs administered as ointments is more since it prevents passage through liver.

DISADVANTAGES

They are bulkier than solid dosage forms. When applications of an exact quantity of ointment to the affected area is required, it is difficult to ascertain the same. They are less stable than solid dosage forms.

Ointment bases

There are five (5) classes or types of ointment bases which are differentiated on the basis of their physical composition. These are: 1. Oleaginous bases. 2. Absorption bases. 3. Water in oil emulsion bases. 4. Oil in water emulsion bases. 5. Water soluble or water miscible bases.

These bases are fats, fixed oils, hydrocarbon or silicones. They are anhydrous, greasy, non-washable does not absorb water and occlusive (form a film on skin so it increases the skin hydration by reducing the rate of loss of surface water. They should not be applied to infected skin. they are used as protectants, emollients , vehicles for hydrolysable drugs.

Selection of the Appropriate Base Based on: 1. Desired release rate. 2. Desirability for enhancement of per-cutaneous absorption. 3. Advisability of occlusion. 4. Short-term or long-term stability. 5. Influence of drug on consistency or other features of ointment base. 6. Patient factor - dry or weeping (oozing) skin. Choice of the O.B.Choice of the O.B.

Among the properties which an Ideal ointment base should possess are: 1. Does not retard wound healing. 2. Low sensitization index. 3. Pharmaceutical elegance. 4. A low index of irritation. 5. Non dehydrating. 6. Non greasy. 7. Neutral in reaction. 8. Good keeping qualities. 9. Compatible with common medicaments. 10. Efficient release of medicament at site of application. 11. Washable (easily removed with water). 12. Minimum number of ingredients. 13. Ease of compounding.

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CHEMICAL ENGINEERING

UNIT – IV – DRUG AND PHARMACEUTICAL TECHNOLOGY – SCH1612

I. Introduction

VITAMINS

Vitamins are a group of chemically diverse organic compounds that an organism requires for normal metabolism. Apart from a few exceptions, the human body cannot synthesize vitamins on its own in sufficient amounts and must, therefore, ensure a steady supply through the diet. Vitamins are micronutrients that do not provide energy (like macronutrients) but instead have very specific biochemical roles. They can be coenzymes in various reactions (B vitamins, vitamins A and K) and/or antioxidants that protect the cell and its membrane from (vitamins C and E).

The vitamins are natural and essential nutrients, required in small quantities and play a major role in growth and development, repair and healing wounds, maintaining healthy bones and tissues, for the proper functioning of an immune system, and other biological functions. These essential organic compounds have diverse biochemical functions.

Types of Vitamins

Based on the solubility, Vitamins have been classified into two different groups:

Fat-Soluble Vitamins.

Water-Soluble Vitamins.

Fat-soluble vitamin

Fat-soluble vitamins are stored in the fat cells and as the name suggests, these vitamins require fat in order to be absorbed. Vitamin A, D, E and K are fat-soluble vitamins.

Water-soluble vitamin

Water-soluble vitamins are not stored in our body as its excess gets excrete through the urine. Therefore, these vitamins need to be replenished constantly. Vitamin B and C are water-soluble vitamins.

Sources of Vitamins

The best sources of fat-soluble vitamins include:

Vitamin A: Found in potato, carrots, pumpkins, spinach, beef and eggs.

Vitamin D: Found in fortified milk and other dairy products.

Vitamin E: Found in fortified cereals, leafy green vegetables, seeds, and nuts.

Vitamin K: Found in dark green leafy vegetables and in turnip or beet green.

Vitamin B1 or Thiamin: Found in pork chops, ham, enriched grains and seeds.

Vitamin B2 or Riboflavin: Found in whole grains, enriched grains and dairy products.

Vitamin B3 or Niacin: Found in mushrooms, fish, poultry, and whole grains.

Vitamin B5 or Pantothenic Acid: Found in chicken, broccoli, legumes and whole grains.

Vitamin B6 or Pyridoxine: Found in fortified cereals and soy products.

Vitamin B7 or Biotin: Found in many fruits like fruits and meats.

Vitamin B9 or Folic Acid: Found in leafy vegetables.

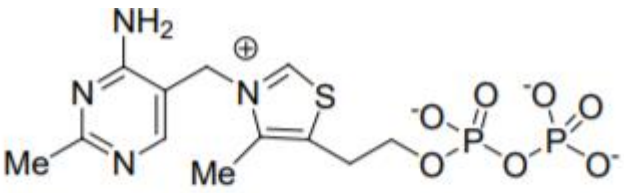
Vitamin B12: Found in fish, poultry, meat and dairy products.

Vitamin C: Found in citrus fruits and juices, such as oranges and grapefruits.

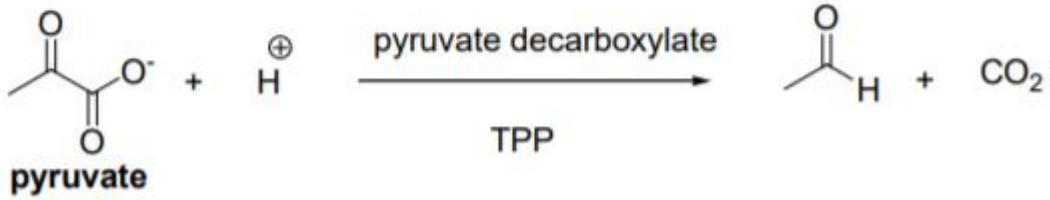
Name	Solubility	Food Sources	Deficiency Diseases
Vitamin A	Fat	Green leafy vegetables, ripe yellow fruits, guava, milk, liver, nuts, tomatoes, oranges, carrots, broccoli, watermelon etc.	Hyperkeratosis, night blindness, and keratomalacia
Vitamin B1 (Thiamine)	Water	Fresh fruits, potatoes, sweet potatoes, peas, corn, cashew nuts, wheat, milk, black beans, dates etc.	Beriberi
Vitamin B2 (Riboflavin)	Water	Banana, dates, mushrooms, grapes, mangoes, peas, pumpkin, popcorn etc.	Slow growth, sore eyes
Vitamin B3 (Niacin)	Water	Meat, fish, eggs, milk products, cereals, mushroom, guava etc.	Pellagra
Vitamin C	Water	Fresh fruits, black currant, broccoli, goat milk and chestnuts.	Scurvy
Vitamin D	Fat	Fish, egg, liver, beef, cod, chicken breast etc.	Rickets and Osteomalacia
Vitamin E	Fat	Potatoes, pumpkin, guava, mango, milk, nuts, seeds etc.	Heart problems, Haemolysis and sterility
Vitamin K	Fat	Tomatoes, broccoli, chestnuts, cashew nuts, beef, lamb, mangoes, grapes etc.	Haemorrhage

Vitamin B1 Synthesis

Thiamine is known as vitamin B1. It is required to form the coenzyme thiamine pyrophosphate (TPP). TPP is required by enzymes that catalyze the transfer of a two carbon fragment from one species to another. For example, pyruvate decarboxylase enzyme requires TPP for the decarboxylation of pyruvate and transfer the remaining twocarbon fragment to a proton to afford acetaldehyde.

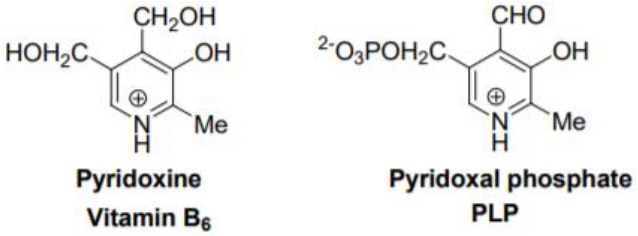


Thiamine pyrophosphate (TPP)



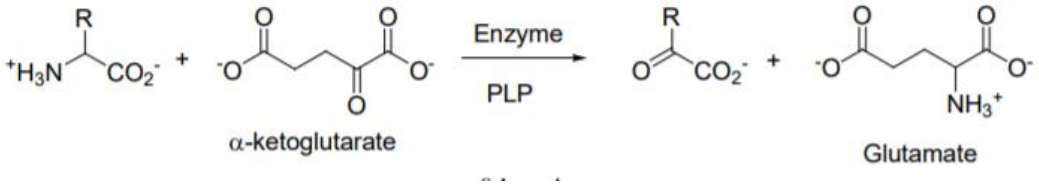
Vitamin B6

The coenzyme pyridoxal phosphate (PLP) is derived vitamin B6. The deficiency of vitamin B6 causes anemia. Enzymes that catalyze the reactions of amino acids require PLP. One of the common examples is the transamination using enzyme aminotransferases.



Pyridoxine
Vitamin B_6

Pyridoxal phosphate
PLP



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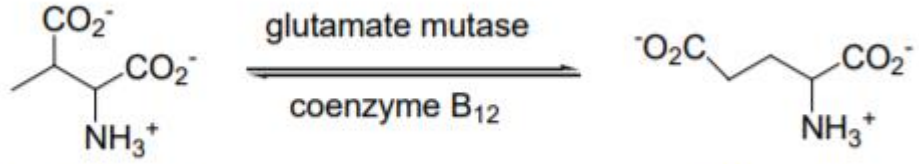


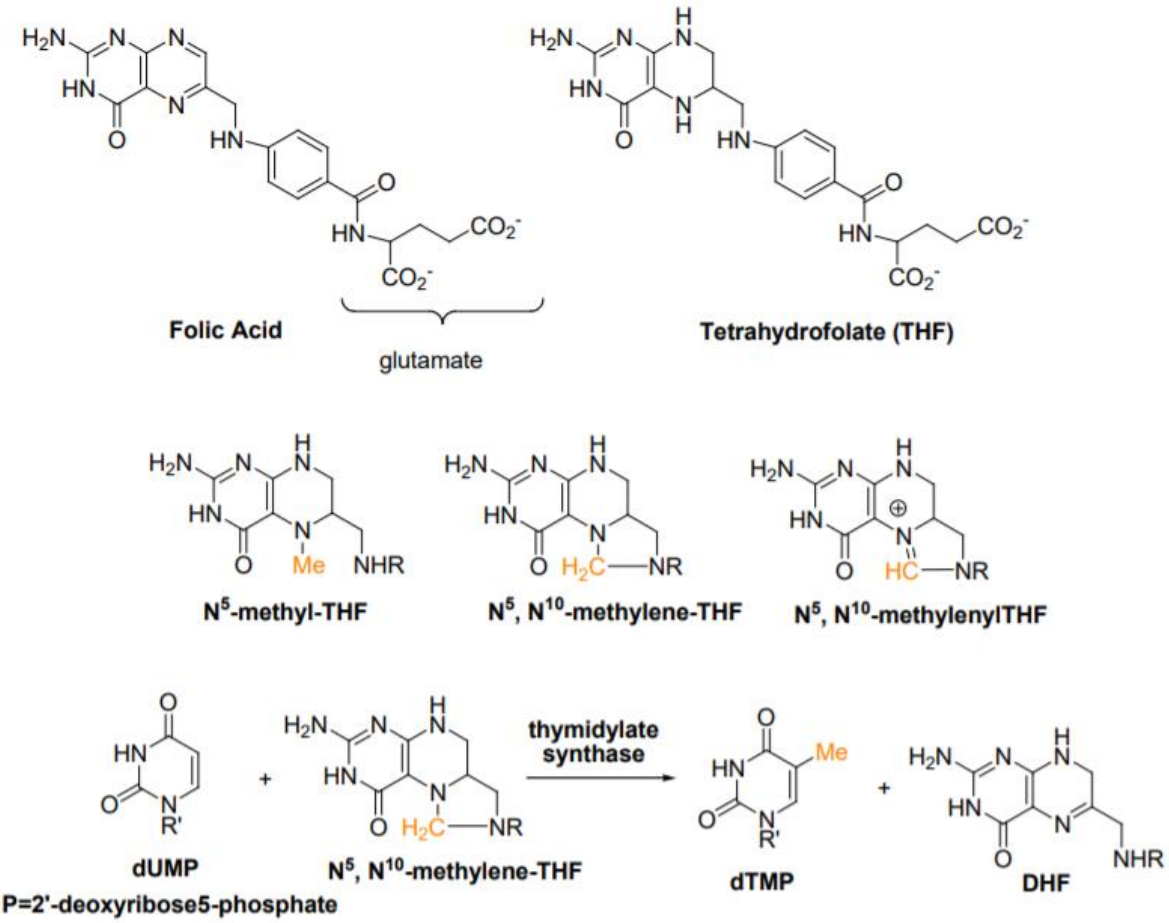
β-methylaspartate

Glutamate

Folic Acid

Tetrahydrofolate (THF) is the coenzyme required by enzymes which catalyze the transfer of a group having a single carbon to their substrates. The one carbon may be methyl (CH3), methylene (CH2) or formyl (CH) group. The coenzyme THF is required for the synthesis of bases in RNA and DNA and synthesis of some aromatic amino acids. Folic acid is the vitamin used for the synthesis of the

coenzyme THF. For example, thymidylate synthase is the enzyme that catalyzes the synthesis of T's from U's. This transformation requires N5 ,N10-methylene-THF as a coenzyme



Vitamin K

• Vitamin K is synthesized by intestinal bacteria.

• Vitamin K is required for proper clotting of blood. In order for blood to clot, blood-clotting proteins must bind to Ca2+.

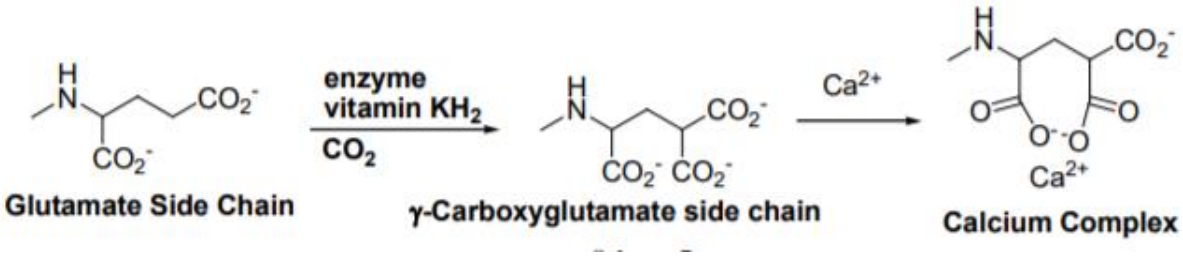
• Vitamin K is synthesized by intestinal bacteria. Thus, deficiency of vitamin K is rare.

• Vitamin KH2 is the coenzyme that is derived from vitamin K.

• The coenzyme vitamin KH2 is required by enzyme that catalyzes the carboxylation of the γ-carbon of glutamate side chains in proteins, forming γcarboxyglutamates.

• The process uses CO2 for the carboxyl group that is introduced in to the glutamate chains.

• The protein involved in the blood clotting contains several glutamates near the Nterminal ends.



Hormones

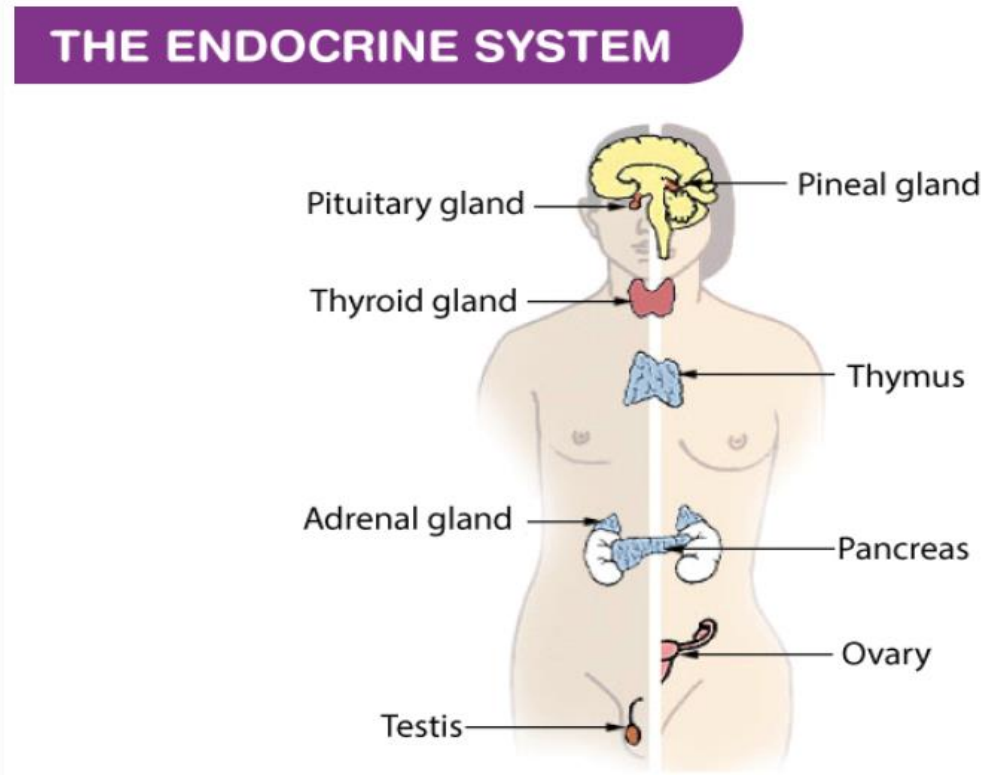
A hormone is a chemical that acts as a messenger transmitting a signal from one cell to another. When it binds to another cell which is the target of the message, the hormone can alter several aspects of cell function, including cell growth, metabolism, or other function. Hormones can be classified according to chemical composition, solubility properties, location of receptors, and the nature of the signal used to mediate hormonal action within the cell. Hormones that bind to the surfaces of cells communicate with intracellular metabolic processes through intermediary molecules called second messengers (the hormone itself is the first messenger), which are generated as a consequence of the ligand receptor interaction

Classification of Hormones

- Autocrine: An autocrine hormone is one that acts on the same cell that released it.
- Paracrine: A paracrine hormone is one that acts on cells which are nearby relative to the cell which released it. An example of paracrine hormones includes growth factors, which are proteins that stimulate cellular proliferation and differentiation. Specifically, consider the binding of white blood cells to T cells. When the white blood cell binds to a T cell, it releases a protein growth factor called interleukin-1. This causes the T cell to proliferate and differentiate.
- Endocrine: An endocrine hormone is one that is released into the bloodstream by endocrine glands. The receptor cells are distant from the source. An example of an endocrine hormone is insulin, which is released by the pancreas into the bloodstream where it regulates glucose uptake by liver and muscle cells.

There are three major classifications one should be aware of:

- Steroids: Steroid hormones are for the most part derivatives of cholesterol.
- Amino acid derivatives: Several hormones (and neurotransmitters) are derived from amino acids.
- Polypeptides: Many hormones are chains of amino acids



- **Hypothalamus:** It controls the body temperature, regulates emotions, hunger, thirst, sleep, moods and allow the production of hormones.
- **Pineal**: Pineal is also known as the thalamus. It produces serotonin derivatives of melatonin, which affects sleep patterns.
- **Parathyroid**: This gland helps in controlling the amount of calcium present in the body.
- **Thymus**: It helps in the production of T-cells, functioning of the adaptive immune system and maturity of the thymus.
- **Thyroid:** It produces hormones that affect the heart rate and how calories are burnt.
- **Adrenal**: This gland produces the hormones that control the sex drive, cortisol and stress hormone.
- **Pituitary**: It is also termed as the “master control gland,”. This is because the pituitary gland helps in controlling other glands. Moreover, it develops the hormones that trigger growth and development.
- **Pancreas**: This gland is involved in the production of insulin hormones, which plays a crucial role in maintaining blood sugar levels.
- **Testes:** In men, the testes secrete the male sex hormone, testosterone. It also produces sperm.
- **Ovaries**: In the female reproductive system, the ovaries release estrogen, progesterone, testosterone and other female sex hormones.

List of Important Hormones

1. **Cortisol** – It has been named as the “stress hormone” as it helps the body in responding to stress. This is done by increasing the heart rate, elevating blood sugar levels etc.

2. **Estrogen**-This is the main sex hormone present in women which bring about puberty, prepares the uterus and body for pregnancy and even regulates the menstrual cycle. Estrogen level changes during menopause because of which women experience many uncomfortable symptoms.
3. **Melatonin** – It primarily controls the circadian rhythm or sleep cycles.
4. **Progesterone** – It is a female sex hormone also responsible for menstrual cycle, pregnancy and embryogenesis.
5. **Testosterone** – This is the most important sex hormone synthesized in men, which cause puberty, muscle mass growth, and strengthen the bones and muscles, increase bone density and controls facial hair growth.

Functions of Hormones

Following are some important functions of hormones:

- Food metabolism.
- Growth and development.
- Controlling thirst and hunger.
- Maintaining body temperature.
- Regulating mood and cognitive functions.
- Initiating and maintaining sexual development and reproduction.

ANTACID

An antacid is a substance which neutralizes stomach acidity and is used to relieve heartburn, indigestion or an upset stomach. Some antacids have been used in the treatment of constipation and diarrhea. Currently marketed antacids contain salts of aluminum, calcium, magnesium, or sodium. Examples of antacids include:

- Aluminum hydroxide gel (Alternagel, Amphojel)
- Calcium carbonate (Alka-Seltzer, Tums)
- Magnesium hydroxide (Milk of Magnesia)
- Gaviscon, Gelusil, Maalox, Mylanta, Rolaids.
- Pepto-Bismol.

ANTISEPTIC

An antiseptic is a substance that stops or slows down the growth of microorganisms. They're frequently used in hospitals and other medical settings to reduce the risk of infection during surgery and other procedures. An antiseptic is applied to the body, while disinfectants are applied to nonliving surfaces, such as countertops and handrails. In a surgical setting, for example, a doctor will apply an antiseptic to the surgical site on a person's body and use a disinfectant to sterilize the operating table. Both antiseptics and disinfectants contain chemical agents that are sometimes called biocides. Hydrogen peroxide is an example of a common ingredient in both antiseptics and disinfectants. Antiseptics have a variety of uses both in and out of medical settings. In both settings, they're applied to either the skin or mucous membranes.

Specific antiseptic uses include:

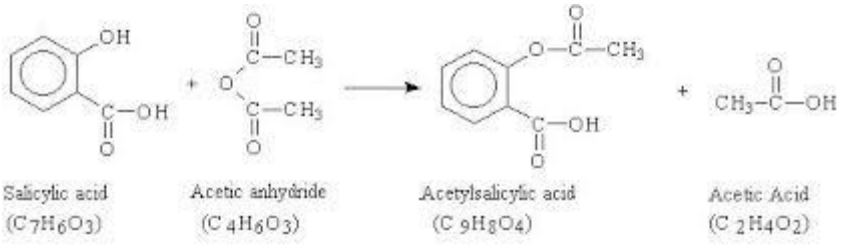
- Hand washing. Medical professionals use antiseptics for hand scrubs and rubs in hospitals.
- Disinfecting mucous membranes. Antiseptics can be applied to the urethra, bladder, or vagina to clean the area before inserting a catheter. They can also help to treat an infection in these areas.
- Cleaning skin before an operation. Antiseptics are applied to the skin before any kind of surgery to protect against any harmful microorganisms that might be on the skin.
- Treating skin infections. You can buy OTC antiseptics to reduce the risk of infection in minor cuts, burns, and wounds. Examples include hydrogen peroxide and rubbing alcohol.
- Treating throat and mouth infections. Some throat lozenges contain antiseptics to help with sore throats due to a bacterial infection.

Antiseptics are usually categorized by their chemical structure. All types disinfect skin, but some have additional uses. Common types with varied uses include:

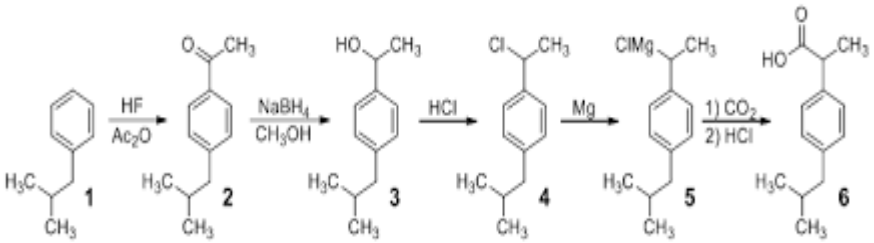
- **Chlorhexidine and other biguanides.** These are used on open wounds and for bladder irrigation.
- **Antibacterial dye.** These help to treat wounds and burns.
- **Peroxide and permanganate.** These are often used in antiseptic mouthwashes and on open wounds.
- **Halogenated phenol derivative.** This is used in medical-grade soaps and cleaning solutions.

ANTIPYRETIC

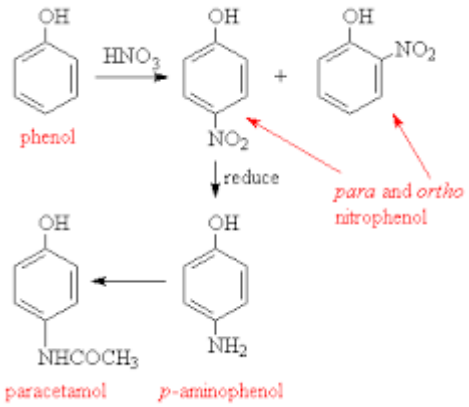
An antipyretic is a substance that reduces fever. Antipyretics cause the hypothalamus to override a prostaglandin-induced increase in temperature. The body then works to lower the temperature, which results in a reduction in fever. Antipyretic is medication used to lower body temperature when a fever is present. Examples: Aspirin, acetaminophen/paracetamol (Tylenol), ibuprofen.



Scheme 1 Synthesis of Aspirin



Scheme 2. Synthesis of ibuprofen



Scheme 3 Synthesis of Paracetamol

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SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF CHEMICAL ENGINEERING

UNIT – V – DRUG AND PHARMACEUTICAL TECHNOLOGY – SCH1612

I. Introduction

GMP – Good Manufacturing Practices

Related to process

1. QA (Quality Assurance) is to be done before send the drug for packing
2. Maintaining batch details.
3. Controlling the environmental condition (HVAC)
4. Personal hygiene wear gloves, aprons, safety shoes
5. SOP
6. Discard the rejected batch drug or unused materials
7. Inspection of site
8. QMS (Quality Management System) Monitor, Asses, Evaluate and Improve
9. Standards for References
10. License of the drug
11. pre operational and operational sanitation procedure to prevent direct product contamination or adulteration
12. Identify Opportunities To Improve Process ,Products And Services To Enhance Customer Satisfaction
13. appropriate education, training and experience should be given to personnels
14. equipment must be properly identified cleaned and maintained to prevent cross contamination
15. Any deviation in the process should be reported and recorded
16. Conduct regular Audit
17. instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided
18. manufacturing processes must be clearly defined, validated and controlled to ensure consistency and compliance with specifications

Related to packing

- Store one drug at one packaging location
- Use code no, Batch no, Lot no. during the process.
- Controlling the environmental condition (HVAC)
- Personal hygiene wear gloves, aprons, safety shoes
- Mention the Expiry date in drug packing.
- SOP
- Excess packing materials should be return to warehouse.
- Inspection of site
- QMS (Quality Management System) Monitor, Asses, Evaluate and Improve
- Standards for References
- fill the various log books accurately and regularly to keep a detailed record of packing operation
- Use eco-friendly packing materials

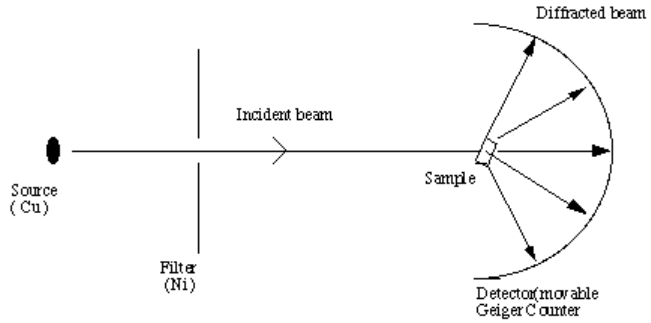
- Trackability of Records
- Packing materials should be non-reactive, non-additive, non absorbtive
- License of the drug
- Labelling of the drug/product
- Non hazardous materials should be used for packing
- Customer complaints should be evaluated, investigated and remediation.
- Use recyclable packing materials
- segregate the products and packing components in the packing area by physical barrier or adequate special separation to minimize mix ups.

X-RAY DIFFRACTION:

X-ray diffraction analysis (XRD) is a **technique** used in **materials** science to determine the crystallographic structure of a **material**. XRD works by irradiating a **material** with incident X-rays and then measuring the intensities and scattering angles of the X-rays that leave the **material**

PRINCIPLE GOVERNING XRD:

- X-ray diffraction is based on constructive interference of monochromatic X-rays and a crystalline sample. These X-rays are generated by a cathode ray tube, filtered to produce monochromatic radiation, collimated to concentrate, and directed toward the sample.
- The interaction of the incident rays with the sample produces constructive interference (and a diffracted ray) when conditions satisfy Bragg's Law ($n\lambda=2d\sin\theta$). This law relates the wavelength of electromagnetic radiation to the diffraction angle and the lattice spacing in a crystalline sample.
- These diffracted X-rays are then detected, processed and counted.
- All diffraction methods are based on generation of X-rays in an X-ray tube. These X-rays are directed at the sample, and the diffracted rays are collected. A key component of all diffraction is the angle between the incident and diffracted rays.



- X-ray diffractometers consist of three basic elements: an X-ray tube, a sample holder, and an X-ray detector.
- X-rays are generated in a cathode ray tube by heating a filament to produce electrons, accelerating the electrons toward a target by applying a voltage, and bombarding the target material with electrons. When electrons have sufficient energy to dislodge inner shell electrons of the target material, characteristic X-ray spectra are produced. These spectra consist of several components, the most common being K_α and K_β

- The specific wavelengths are characteristic of the target material (Cu, Fe, Mo, Cr). Filtering, by foils or crystal monochrometers, is required to produce monochromatic X-rays needed for diffraction.

These X-rays are collimated and directed onto the sample. As the sample and detector are rotated, the intensity of the reflected X-rays is recorded. When the geometry of the incident X-rays impinging the sample satisfies the Bragg Equation, constructive interference occurs and a peak in intensity occurs. A detector records and processes this X-ray signal and converts the signal to a count rate which is then output to a device such as a printer or computer monitor

APPLICATION OF THE TECHNIQUE

- X-ray diffraction is commonly used to determine the cutting agents used in illegal drugs because it is non-destructive, can be performed on the crystalline form of the drug, and requires no sample preparation.
- Tooth enamel and dentine have been examined by XRD
- XRD is certainly is helpful to the development chemist as it provides valuable details on degree of crystallinity and amorphous content of synthetic mixtures. Crystalline impurities present can be quantified down to 0.05% levels.
- The elucidation of structure of penicillin by XRD paved the way for later synthesis of penicillin

Infrared Spectroscopy

A. Regions: -- near IR (800-2500 nm — quartz optics/W-I lamp, diode or thermal detect)

anharmonic vib, overtone and combination bands. Return to this later, specific use

-- mid IR (2500-25000 nm, 2.5-25, 4000-400 cm-1

FTIR Fourier Transform Infrared Spectrophotometry is a sensitive technique particularly for identifying organic chemicals in a whole range of situations including solid, liquid and gas samples. FTIR can also be used to characterise some inorganic compounds. It may be used to identify both pure compounds and simple mixtures.

Typical Applications of FTIR and FTIR Microscopy

- Routine qualitative and quantitative FTIR analysis.
- Low volume Quality Control and Pharmacopeia testing.
- Identification of polymers and polymer blends.
- Assessment of changes of polymers and rubbers due to both ageing and environment like oxidation and hydrolysis.
- Indirect identification of trace organic contaminants on surfaces.
- Thin film analysis of organic coatings and oxide thicknesses on metals such as aluminium.
- Analysis of adhesives, coatings and adhesion promoters or coupling agents.
- Small visible and Microscopic particle chemical analysis by FTIR microscopy.
- Analysis of stains and surface blemishes remnant from cleaning and degreasing processes combined with optical microscopy, SEM/EDX, XPS, SIMS and FTIR microscopy techniques.
- Analysis of resins, composite materials and release films.

- Solvent extractions of leachables or contaminants, plasticisers, mould release agents and weak boundary layers coupled with XPS surface chemical analysis techniques.
- FTIR identification of rubbers and filled rubbers coupled with pyrolysis GCMS.
- Determination of degrees of crystallinity in polymers like LDPE and HDPE.
- Comparative chain lengths in organics.
- Extent of thermal, UV or other degradation or depolymerisation of polymers and paint coatings.
- Analysis of a gaseous samples using a gas cell for headspace analysis or environmental monitoring.
- FTIR analysis of unknown solvents, cleaning agents and detergents combined with GCMS.
- Temperature dependent study of materials using the heated stage accessory.
- Small visible and microscopic particle chemical analysis by FTIR microscopy.
- Contaminants in pharmaceutical API's, WFI water for injection and blood products.
- Identifying specific fibres and particles in inhalable dust by FTIR microscopy and SEM/EDX.
- FTIR microscopy of microplastics in freshwater, sea water, soil and wastewater with pyrolysis GCMS.
- Checks for localised antiseptic chemical products and wipes attack of rubbers and plastics in hospitals and the medical device industry.
- Cross-sectional analysis and imaging of different primer, top coat and clearcoat paint layers looking for missing layers, interface contaminants combined with SEM/EDX of filler materials.
- FTIR analysis and reverse engineering of unknown compounds and formulations particularly when combined with GCMS.

PACKING OF PHARMACEUTICAL INGREDIENTS

Packing: Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This operation is mostly done by hand and machine.

Pharmaceutical Packaging: Pharmaceutical packaging means the combination of components necessary to contain, preserve, protect & deliver a safe, efficacious drug product, such that at any time point before expiration date of the drug product, a safe & efficacious dosage form is available.

Types of Packaging Systems:

o Primary package system: Made up of those package components & subcomponents that come into direct contact with the product, or those that may have a direct effect on the product shelf life.

o Secondary or tertiary package system: Includes cartons, corrugated shippers & pallets.

Packaging must meet the following Requirements: [ideal requirements]

 Protect the preparation from environmental conditions.

 Non-reactive with the product and so does not alter the identity of the product

 Does not impart tastes or odors to the product

 Nontoxic

 FDA approved

 Protect the dosage form from damage or breakage

 Meet tamper-resistance requirements, wherever applicable.

 Adaptable to commonly employed high-speed packaging equipments.

Criteria for the Selection of package type and package material:

 Stability

 Compatibility with the contents

 Strength of container and the degree of protection required

 Moisture-proofness

 Resistance to corrosion by Acids or Alkalis

 Resistance to grease

 Protection against salt

 Resistance to microorganisms

 Resistance to insects and rodents

 Resistance to differences in temperature

 Protection against light, fire and pilferage

 Odor retention and transmission

 Aesthetic effect

 Cost

 Machine suitability of packaging and the filling method

Possible Interactions between primary packaging materials and the included pharmaceutical product:

 The release of chemicals from components of the packaging materials

 The release of visible and/or sub visible particles

 The absorption or adsorption of pharmaceutical components by the packaging materials

 Chemical reactions between pharmaceutical product & the packaging materials

 The degradation of packaging components in contact with the pharmaceutical products

 The influence of the manufacturing process (e.g. sterilization) on the container.

Presentation & information

 Packaging is essential source of information on medicinal product.

 Information provided to patient may include:

- Identification no. for dispensing records.

- Name, strength & quantity

- Storage instructions.

- Direction for use.

- Name and address of dispensers.

Packaging materials & closures:

 Glass

 Plastic

 Metals

 Paper and Board

 Rubber

 Cotton

 Adhesives and Inks

 Closures

GLASS CONTAINERS:

Advantages:

1. Superior protective qualities

2. Economical

3. Readily available in a wide variety of sizes & shapes

4. Essentially chemically inert, impermeable, strong and rigid

5. Has FDA clearance

6. Does not deteriorate with age

Disadvantages:

1. Fragility

2. Heavy Weight.

Composition of glass

 Mainly made up of

1. Sand – pure silica

2. Soda-ash – sodium carbonate

3. Limestone – calcium carbonate

4. Cullet – broken glass that is mixed with the batch & acts as a fusion agent for the entire mixture.

The most common cations found in pharmaceutical glassware are silicone, aluminum, boron, sodium, potassium, calcium, magnesium, zinc & barium. The only anion of consequence is oxygen.

TYPES OF GLASS

Type I – Borosilicate Glass

Type II – Treated Soda-Lime Glass

Type III – Regular Soda-Lime Glass

Type NP – General Purpose Soda-Lime Glass

Type I: Borosilicate Glass

 Highly resistant glass

 A substantial part of the alkali & earth cations are replaced by boron and/or aluminum & zinc.

 It is more chemically inert than the soda-lime glass (which contains either none or an insignificant amount of these cations).

 It is used to contain strong acids & alkalies as well as all types of solvents.

 The addition of approx 6% boron to form type I glass reduces the leaching action.

Type II: Treated Soda-Lime Glass

 When glassware is stored for several months, especially in a damp atmosphere or with extreme temperature variations, the wetting of the surface by condensed moisture (condensation) results in salts being dissolved out of the glass. This is called “blooming” or “weathering” & it gives the appearance of fine crystals on the glass.

 Type II containers are made of commercial soda-lime glass that has been de-alkalized or treated to remove surface alkali.

 The de-alkalizing process is known as “sulfur treatment” and virtually prevents “weathering” of empty bottles.

 Some manufactures expose the glass to an atmosphere containing water vapor & acidic gases. This results in a reaction between gases & surface alkali, which makes it resistant to attack by water.

 The alkali removed from the glass appears on the surface as a sulfate bloom, which is removed when the containers are washed before filling.

 Thus sulfur treatment neutralizes the alkaline oxides on the surface & thus rendering the

glass more chemically resistant.

Type III – Regular Soda-Lime Glass

 Containers are untreated & made up of commercial soda-lime glass of average or betterthan-average chemical resistance.

Type NP – General Purpose Soda-Lime Glass

 Containers made up of soda-lime glass are supplied for non-parenteral products, those

intended for oral or topical use

PLASTIC CONTAINERS:

Advantages:

1. Ease of manufacturing

2. Available in various types of quality

3. Freedom of design to which they lend themselves

4. Extremely resistant to breakage

METAL CONTAINERS:

 Aluminum & stainless steel are the metals of choice for both primary & secondary pharmaceutical packaging.

 Form excellent tamper-evident containers.

 Metals are strong, impermeable to gases & shatterproof, so they are ideal packaging material for pressurized containers.

FILMS, FOILS & LAMINATES:

 Regenerated cellulose film based on viscose (chemical used for manufacturing of rayon) & laminating two or more types of films, cellulose coatings, foil and paper play diff roles such as supportive, barrier, heat seal & decorative.

 For Example:

 Aluminum foil even in the thinnest gauges offers the best barrier properties, which are not approached even by the most impermeable plastics.

 „Metallization": A relatively new process whereby particles of metal are laid down onto a surface under vacuum, can significantly improve the barrier properties of a material but these do not approach the properties of a pure foil.

 In the newer technology „Co-Extrusion", a number of plastic plies are extruded in combination to produce cheaper laminations.

Uses of films, foils, laminations:

 Strip packs

 Blister packs

 Sachets

 Diaphragm seals for bottles

 Liners for boxes either attached or loose bag-in-box systems & bags.

Foil blisters:

 When sealed with a metal foil-cover, the blister can provide a hermetic pack i.e. an isolated system, which excludes any exchange of gases between the product & surrounding atmosphere.

PAPER & BOARD:

 The paper-based materials are the important part of pharmaceutical packaging.

 Paper-based materials include: Labels, Cartons, Bags, Outers, Trays For Shrink Wraps, Layer Boards On Pallets, etc.

 The Applications as well as Advantages of Cartons include:

- Increases display area

- Provides better stacking for display of stock items

- Assembles leaflets

- Provides physical protection especially to items like metal collapsible tubes.

 Fiberboard outers either as solid or corrugated board also find substantial application for bulk shipments.

 Regenerated cellulose film, trade names Cellophane & Rayophane, is used for either individual cartons or to assemble a no. of cartons.

RUBBER

Mostly used to make stoppers and bulbs for dropper assemblies.

 Examples of rubber for pharmaceutical products include:

1. Natural rubber

2. Neoprene rubber

3. Nitrile rubber

4. Butyl rubber

5. Chlorobutyl rubber

6. Bromobutyl rubber

7. Silicone rubber

ADHESIVES and INKS:

Some substances, such as cements and lacquers used as label adhesives, are not waterbased emulsions. They are usually dissolved in toluene, alcohol, naphtha, methyl ethyl ketone, or other organic solvents. ⇒ When an adhesive of this type is used on plastics or elastomers, the solvent may allow migration of adhesive components into the formulation. Therefore, appropriate testing should

be performed to determine whether adhesive and ink components migrate through the container. If they do, adequate information to justify the use of the container system in combination with the drug product should be submitted. ⇒ For all containers, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions (e.g., temperature and humidity). ⇒ If direct label imprinting is used on containers, such as on containers of injectable drug products, it is necessary that resistant ink be used so that the imprint having the required information resists the normal handling of the containers during their customary conditions of purchase and use.

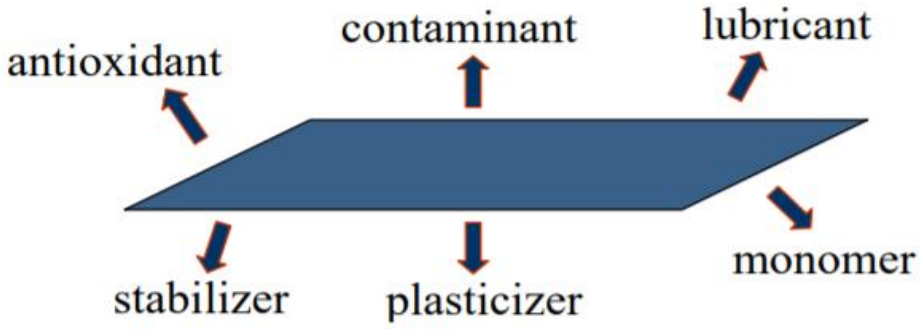
CLOSURES

¬ Depending upon the type of container, closures may have different shapes & sizes. ¬ Special design of stopper may also be required for some pharmaceutical production processes such as lyophilization. ¬ Closures, which form a part of the primary packaging system, are very important & should be therefore carefully selected. They form essential component of the container & an integral part of the drug preparation.

Packaging Evaluation:

Package evaluation is performed to investigate the physicochemical interactions that might occur between the product & package. The ideal package would be completely inert relative to the product & would provide maximum shelf-life. Therefore, evaluation is designed to identify, characterize & monitor these interactions to achieve a safe, unadulterated, stable & efficacious product.

- ❑ An important step -- characterizing the materials and the chemicals that can migrate or extract from packaging components to the drug product.
- ❑ Figure shows the various types of chemicals that can migrate from polymeric materials. The identities and abundance of these chemicals determine a material's suitability.



- ✓ A number of tests can be used to establish *initial qualification* of the container closure system, and a *quality control plan* can help ensure compatibility and safety.
- ✓ To establish suitability , evaluation of four attributes is required : protection, compatibility, safety, and performance/ drug delivery .
- ✓ Suitability refers to the tests used for the initial qualification of the container closure system with regard to its intended use.

DOSAGE FORM	CONDITION	ROUTE OF DELIVERY	POSSIBLE PACKAGE FORM
Solids (Tablets, Capsules, Powders)	Non-Sterile	Oral	- Glass Or Plastic Bottle And Cap - Blister And Strip Packaging - Sachet, Pouches - Drums And Jars
Solids	Non-Sterile	Rectal (Suppository)	- Foil Pouch Or Blister
Solids	Aseptic	Inhalation	- Dry-Powder Inhaler
Liquids	Non-Sterile	Oral	- Glass Or Plastic Bottle And Cap - Bottle With Spray Pump - Bottle With Dropper Assembly - Sachet, Pouches - Drums And Jars
Liquids	Non-Sterile	Topical	- Glass Or Plastic Bottle And Cap Over Dropper Tip - Collapsible Tube - Aerosol Sprays - Drums And Jars
Liquids	Sterile	Parenteral, Ophthalmic	- Glass Ampoules - Glass Or Plastic Vial With Stopper - Glass Or Plastic Vials With Applicators

Packaging of MEDICAL / SURGICAL DEVICES

¬ The medical device packages are usually evaluated to meet the following requirements: ¬ They must be capable of being sterilized economically. ¬ They must withstand the shipping and handling environment. ¬ They must be compatible with the procedures set up by the hospitals. ¬ Sterility ¬ Environmental ¬ Product resistance: oils, water, chemicals, gas, etc. ¬ Physical: Dimensional stability (rigidity or flexibility, resists puncture, tearing, abrasion, impact and pressure, provides cushioning and structural support.

Evaluation of Medical Device Packages:

¬ The Medical Device Packages Testing Laboratory is set up with the following principle goals: ¬ To evaluate the component materials of container and the inner protective cushioning materials ¬ To develop (through research) improved methods or concepts and improved package testing techniques. **The types of tests carried out** for Medical Device Packages are as follows:

¬ Sterility Testing ¬ Manual handling ¬ Vehicle stacking ¬ Loose-load vibration ¬ Vehicle vibration ¬ Drop test ¬ Compression ¬ Package seal strength testing

Classifications of child-resistant packages

Type I: Reclosable packaging - continuous thread closure

Type II: Reclosable packaging - lug finish closure

Type III: Reclosable packaging - snap closure

Type IV: Unit non-reclosable - flexible (strip/pouch)

Type V: Unit non-reclosable - rigid

Type VI: Unit reclosable packages

Type VII: Aerosol packages

Type VIII: Non-reclosable packages - semi-rigid (blister)

Type IX: Dispensers (not intended to be removed)

Type X: Box or tray package

Type XI: Reclosable packaging - flexible

Type XII: Dispenser (may be removed)

Type XIII: Reclosable packaging - semi-rigid (blister)

TESTING PROTOCOL FOR CHILD RESISTANT PACKAGING

REQUIREMENTS:

 On full scale production batch

 Adult test must be carried out initially

 A new package must be used for every test

 Test panel may involve upto 200 children in the ages between 20 and 42 months,

 100 normal adults between 18 and 65

TAMPER PROOF CONTAINERS

• Film Wrappers

• Blister or Strip Packs

• Bubble Packs

• Heat Shrink Bands or Wrappers

• Foil, Paper, or Plastic Pouches

• Bottle Mouth Inner Seals

• Tape Seals

• Breakable Caps

• Sealed Metal Tubes or

• Plastic Blind-end Heat Sealed Tubes

• Cans

• In-Built Tamper-Evident Controls

REGULATIONS

It includes various offices from CDER, CBER and CVM.

 CDER - Centre For Drug Evaluation And Research

a. Office Of New Drug Chemistry
b. Office Of Generic Drug
c. Office Of Compliance
d. Office Of Testing And Research
e. Quality Implementation Staff

 CBER- Centre For Biological Evaluation And Research

a. Office Of Compliance And Biologics Quality

 CVM – Centre For Veterinary Medicine

a. Office Of New Animal Drug Evaluation

PACKGING GUIDANCE COMMITTEE

 Disentwining the packaging information to CDER, CBER, and CVM.

 Reviewing pharmacopoeial forum packaging proposal

 Internal guidance and comment to

- Reviewer
- CMC CC committee
- CTDQ document

 External guidance via CMC CC PACKAGING equivalency test

 Drafting revision to packaging guidance bulk container , Q and A format

Quality control

The term quality control refers to the sum of all procedures undertaken to ensure the identity and purity of a particular pharmaceutical. Such procedures may range from the performance of simple chemical experiments which determine the identity and screening for the presence of particular pharmaceutical substance (thin layer chromatography, infrared spectroscopy, etc.), to more complicated requirements of pharmacopoeial monographs. Activities extend to the area of quality

control laboratories (good laboratory management practices, models, e.g. for certificate of analysis and lists of laboratory equipment, and an external assessment scheme.