PHARMACY INDIA

PHARMACEUTICS

PHYSICAL PHARMACY | BIOPHARMACEUTICS | PHARMACEUTICAL JURISPRUDENCE | MICROBIOLOGY | HOSPITAL & CLINICAL PHARMACY | PHARMACEUTICAL ENGINEERING | BIOTECHNOLOGY

A Competitive Examination Book

Theory Book

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BIOPHARMACEUTICS

Chapter 1

TABLET

DEFINITION

- According to the Indian Pharmacopoeia: -Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents.

TYPES & CLASSES OF TABLET

1. Oral tablets for ingestion

(i) Compressed tablets or standard compressed tablets
(ii) Multiple compressed tablets
- Layered tablets
- Compression coated tablet

(iii) Chewable tablet
(iv) Sugar and chocolate coated tablet
(v) Film coated tablet
(vi) Repeat action tablet
(vii) Delayed action tablet & enteric coated tablet
(viii) Controlled release tablets

2. Tablets used in the oral cavity

(i) Buccal & sublingual tablets
(ii) Troches & lozenges
(iii) Dental cones

3. Tablets administered by other routes

(i) Implantation tablet
(ii) Vaginal tablet

4. Tablets used to prepare solutions

(i) Effervescent tablet
(ii) Dispensing tablet
(iii) Hypodermic tablet
(iv) Tablet triturates

ORAL TABLETS FOR INGESTION

COMPRESSED TABLET

- Uncoated tablet intended to provide rapid disintegration & drug release.

MULTIPLE COMPRESSED TABLET (Layered tablets & Compression coated tablet)

Two components or three-layer tablets

- Tablets with in a tablet
- To produce repeat action & Prolonged action products
- Complete physical separation is required for stability purpose in case of three-layer tablets

CHEWABLE TABLET

STA-Rx 1500:

- Directly compressible starch, free flowing.
- Used as diluent, binder and disintegrating agent.
- Self-lubricating: compressed alone→ When combined with 5-10% drug →Requires addition of lubricant & Flow promoter such as 0.25% colloidal SiO_2.

HYDROLYSED STARCHES (Emdex and Celutab)

- Directly compressible.
- 90-92% dextrose and 3-5% maltose.
- May be used in chewable tablets in place of mannitol.

DEXTROSE (Cerelose)

- For hydrous and anhydrous.

MANNITOL- widely used in chewable tablet:

- Negligible heat of solution
- Slow solubility
- Pleasant feeling in mouth
- Can also be used in vitamin formulation.

SORBITOL- optical isomer of mannitol

- Hygroscopic at humidifies above 65%
- Low cationic content
- They are non-carcinogenic

SUGAR BASED DILUENTS / Sucrose

- Trade name: - Sugar tab, Nutab, Dipac.
- SUGAR Tab: 90-93% sucrose + 7-10% invert sugar
- DIPAC: 97% sucrose + 3% dextrose modified
- NU-Tab: 95% sucrose +4% invert sugar with Small amount of corn starch, Magnesium Stearate.

MICROCRYSTALLINE CELLULOSE

- Available under the trade name of (Avicel, Aricel, Emocel)
- Also act as disintegrant agent
- Two tablet grades exist

(I) PH-101 (Powder)

(II) PH-102 (Granule)

Microcrystalline cellulose	Avicel, Aricel, Emcocel
Starch	Sta-Rx-1500
Sucrose (sucrose dextran ppt)	Di-Pac, Sugar tab. Nu- tab.
Anhyd. Lactose	DCL-30
Spray dried lactose	Fast flow Zeparox TM
Hydrolysed starch Dextrates	Celutab, Emdex
CaHP04	Encompasses
Microfine cellulose	Elcema

BINDERS AND ADHESIVES:

These materials are added either dry or in wet form to form granules or to form cohesive compacts for directly compressed tablet.

BINDER	PROPRIETERY NAME
Carboxymethylcellulose sodium	Nymcel
Cellulose, Microcrystalline	Avicel, Emcocel, Vivacel
Ethyl cellulose	Aqua coat
HPMC	Methocel, Pharma coat
Magnesium aluminium silicate	Pharmasorb, Veegum
Methylcellulose	Celacol, Methocel
Poly dextrose	Litesse

DISINTEGRANTS:

Added to a tablet formulation to facilitate its breaking or disintegration when it contacts in water in the GIT.

SUPERDISINTEGRANTS: Swells up to ten-fold within 30 seconds when contact water.

DISINTEGRANT	PROPRIETERY NAME
Cellulose, microcrystalline	Avicel, Emcocel, Vivacel
Magnesium aluminium silicate	Veegum
Methyl cellulose	Celacol, Methocel
Sodium lauryl sulfate	Empicol
Polacrilin potassium	Amberlite
Sodium starch glycolate	Explotab, Primojel
Crospovidone	Kollidon CL, Polyplasdone XL
Croscarmellose sodium	Ac-di-sol, Solutab

LUBRICANTS

Lubricants are intended to prevent adhesion of the tablet materials to the surface of dies and punches, reduce inter particle friction and may improve the rate of flow of the tablet granulation.

LUBRICANT	PROPRIETERY NAME
Glyceryl palmitostearate	Precirol
Hydrogenated vegetable oil	Lubritab, Sterotex
PEG 4000 OR 6000	Macrogols, Carbowax
Sodium lauryl sulfate	Empicol, Steroweet

Example: Lubricants- Stearic acid, Stearic acid salt – Stearic acid, Magnesium stearate, Talc, PEG (Polyethylene glycols), Surfactants

GLIDANTS:

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.

GLIDANT	PROPRIETERY NAME
Cellulose	Elcema, Solka, Floc
Silicon dioxide, Colloidal	Aerosil, Cab-o-Sil, Syloid

- Corn Starch – 5-10% conc.
- Talc-5% conc.,
- Silica derivative - Colloidal silicas such as Cab-O-Sil, Syloid, Aerosil in 0.25-3% conc.

- Formulation of Acetyl Salicylic Acid tablets.
- Formulation of Vitamin B Complex.

C. Wet Granulation

Wet granulation or Moist granulation is the most conventional, versatile and widely used techniques for the manufacture of compressed tablets, as it imparts all the physical properties to the granules.
This technique differs from the other granulation methods as it involves the usage of liquids to form compact masses.

Ex. Of Formulations Prepared by Wet Granulation Method:

- Formulation of Acetaminophen tablets.
- Formulation of Aluminium Hydroxide Chewable tablets.

Wet Granulation procedure:

Drug
↓
Step -1 Grinding
↓
Step -2 Blending or Mixing
↓
Step -3 Shear mixer
↓
Step -4 Wet screening
↓
Step -5 Drying
↓
Step -6 Dry screening
↓
Step -7 Blending
↓
Step -8 Tablet press
↓
Tablet

INTRODUCTION

- ✓ An industrial pharmacist usually encounters number of problems during manufacturing.
- ✓ Majority of visual defects are due to inadequate fines or inadequate moisture in the granules ready for compression or due to faulty machine setting.
- ✓ Functional defects are due to faulty formulation.

TABLET DEFECTS

PROCESS RELATED	FORMULATION RELATED	MACHINE RELATED
• Capping • Lamination • Cracking • Chipping	• Sticking • Picking • Binding	• Double impression • Bridging

CAPPING

- The upper or lower segment of the tablet separates horizontally, either partially or completely from the main body and comes off as a cap, during ejection from the tablet press, or during subsequent handling.

Reason:

Due to the air–entrapment in a compact during compression, and subsequent expansion of tablet on ejection of a tablet from a die.

Causes and Remedies of Capping

SR. NO	CAUSES	REMEDIES
1	Poorly finished dies	Polish dies properly. Investigate other steels or other material
2	Deep concave punches	Use flat punches
3	Lower punch remains below the face of die during ejection	Make proper setting of lower punch during ejection
4	Incorrect adjustment of sweep – off blade	Adjust sweep- off blade correctly to facilitate proper ejection.
5	High turret speed	Reduce speed of turret (increase dwell time)

LAMINATION

- Separation of a tablet into two or more distinct horizontal layers.

Reason:

- Air–entrapment during compression and subsequent release on ejection.
- The condition is exaggerated by higher speed of turret.

Causes and Remedies of Lamination

Sr. No	CAUSES	REMEDIES
1	Large number of fines in the granulation	Remove some or all fines through 100 to 200 mesh screens
2	Too dry or very low moisture content.	Moisture the granules suitably. Add hygroscopic substance (leading to loss of proper binding e.g. – sorbitol, Methylcellulose or PEG-4000
3	Not thoroughly dried granules	Dry the granules properly
4	Insufficient amount of binder or improper binder	Increasing the amount of binder Add dry binder such as pre-gelatinized starch.
5	Insufficient or improper lubricant	Increase the amount of lubricant or change the type of lubricant

CHIPPING

- Breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

Reason:

- Incorrect machine settings, especially mis-set ejection take off.

Causes and Remedies of Chipping related to 'Formulation'

Sr. No	CAUSES	REMEDIES
1	Sticking on punch faces	Dry the granules properly or increase lubrication
2	Too dry granules	Moisten the granules to plasticize. Add hygroscopic substance

Chapter 2

CAPSULES

INTRODUCTION

- The term capsule is derived from the Latin word capsule, meaning a small container.
- The first capsule prepared from gelatin was a one- piece capsule patented in France by Mothes and Du Blanc in 1834.
- Capsules are solid dosage forms in which the drug substance is enclosed within either a hard or soft soluble shell, usually formed from gelatin.

TYPES OF CAPSULES

- **Hard gelatin capsule: -**
  - Disintegration time is 30 minutes
  - Made up from **gelatin +sugar + water**
  - Dry filled capsules
- **Soft gelatin capsule: -**
  - Disintegration time is **60** minutes
  - Made up from **gelatin +plasticizer + water**
  - Soluble elastic and soft elastic caps
  - Liquid filling capsule

GELATIN

Gelatin derived from hydrolytic extraction of animal collagen. Common source of gelatin is skin, bones, white connective tissue frozen, pork skin.

TYPES OF GELATIN

TYPE A	TYPE B
Pharma gel A (cationic)	Pharmagel B (anionic)
By acid treatment	By alkali treatment
Isoelectric point (pH-9)	Isoelectric (pH-4.7)
Processing of an acid bone gelatin, isoelectric point pH – 5.5 -6	From green bones

PROCESS & MANUFACTURING OF GELATIN

- Dry bone →5 %HCl 10-15 days→ Lime 10% 4-8 weeks → Lime removal → Ph adjustment
- Calf skin→ Lime 10 % 6-12 weeks → Water wash 10-30 hours →
- Pork skin → Acid 1-5 % HCl 10 – 30 hours → Acid removal →

Hot water extraction → Filter → Vaccum concentration → Cool to solid → Air-dry → Mill to size

BLOOM/GEL STRENGTH

- Measure cohesive strength of cross linking between gelatin molecules
- Bloom strength α molecular wt. of gelatin (directly proportional)

Sugar (sucrose)	Upto 5 %	To produce chewable shell and taste
Fumaric acid	Upto 1 %	Aids solubility: reduces aldehydic tanning of gelatin

POINTS TO BE REMEMBER

- Formalin treatment: - decrease solubility of gelatin and cross linking of gelatin molecules takes place
- 40% of formaldehyde →formalin
- Roto fill (Eli lily company) designed for filling of pellets
- Roto sort →for removing the loose powder
- Turett → to hold upper and lower punch
- Cam track →guide the movement f punches
- Fette machine →used to provide cool temperature
- Emptying capsule moisture content →12- 16%
- Humidity range → 30 - 40%

HARD GELATIN CAPSULE

HARD GELATIN CAPSULE

The hard gelatin capsule consists of a base or body and a shorter cap, which fits firmly over the base of the capsule

- Capsules should not be used for highly efflorescent or deliquescent materials.
- Efflorescent material may cause the capsule to soften whereas deliquescent powders may dry the capsule shell to excessive brittleness.

METHOD OF MANUFACTURING OF EMPTY GELATIN CAPSULE

Dipping →Spinning →drying → Stripping → Trimming → Joining → Polishing

STEPS	DESCRIPTION
Dipping	One hundred and fifty pairs of these pins are dipped in a gelatin solution to form bodies and caps simultaneously • Temperature of pins=22°C • Solution temperature=50°C • Time=12seconds
Spinning	Pins are rotated to distribute the gelatin uniformly around the pins during which time the gelatin may be set or gelled by a blast of cool air.
Drying	By use of dry air and dehumidification
Stripping	By bronze jaws
Trimming	By stationary knives
Joining	Cap and body are joined
Polishing	Polishing by the polymer

POINTS TO BE REMEMBER

Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and speed and time of dipping.

MOISTURE CONTENT

- Optimum moisture content of capsule shell ranged between 12-15%.
- Below 10 % moisture content they become brittle and suffer dimensional changes.
- Moisture content above 16% may cause problem in the filling and in loss of mechanical strength.

FORMULATION COMPONENTS

DILUENTS: -determination of amounts of diluents to be used is based on

- Total amount of material that can possibly be put in the capsule in relation to the amount of active ingredients
- The amount of lubricant and oil that can be used

GLIDANTS /LUBRICANTS

- Materials that may be considered for improvement of flow characteristics may include the following: - glycol esters, silicones dioxide, metallic stearate, stearic acid and talc

ANTI DUSTING

- Oils that may be considered for use in assisting in the control of dusting, as well as in providing additional cohesiveness to a powder mix, may include any inert, edible FDA approved material.

FINISHING

- Finished capsules from all filling equipment require some sort of dusting or polishing operation before the remaining operation of inspection, bottling and labelling are completed.

1.Pan polishing

- Because of its unique design (primarily in the area of air flow) the Accela Cota tablet coating pan may be used to dust or polish capsules
- Polyurethane or cheese cloth liner is placed in the pan and the liner is used to trap the removed dust as well as impart a gloss to the capsule.

2. Cloth dusting

- In this method the bulk filled capsules are rubbed with a cloth that may or may not be impregnated with an inert oil.
- This method is a hand operation

CAPSULE SIZE WITH THEIR QUANTITIES

CAPSULE SIZE	BP (ML)	IP (ML)
0	0.75	0.68
1	0.55	0.51
2	0.45	0.37
3	0.30	0.30
4	0.25	0.21
5	0.15	0.13

TRICK = to learn the BP (ml) quantity go to decreasing order which is highlighted like 7,5,4,3,2,1 and after these digits 5 is common in every number.

CLASSIFICATION:

SMALL VOLUME PARENTERALS
LARGE VOLUME PARENTERALS

- **Small Volume Parenterals (SVP)**

USP: -An injection that is packed in containers labeled as containing 100 ml or less.

- **Large Volume Parenterals (LVP)**

LVP are Parenterals designed to provide:

- Electrolytes - Volume 101- 1000 ml
- Fluid Calories - dextrose solution

PARAMETER	SMALL VOLUME PARENTERAL	LARGEB VOLUME PARENTERAL
Volume	100 ml or less	101-1000 ml
Routes	IV, IM & SC	IV
Dosage unit	Single or multiple S	Single
Preservative	Used	Not used
Buffers	Used	Not used
Formulation	Solution, emulsion, suspension	Solution & o/w nutrient emulsion
Isotonicity	Not essential	must
Pyrogenicity	Not essential	must
Use	Therapeutic & diagnostic	Nutrition, detoxification, And during surgery

FORMULATION OF PARENTERALS

- Active drug
- Antioxidants
- Vehicles
- Adjuvants

FORMULATION OF PARENTERAL PRODUCTS

In the preparation of parenteral products, the following substances are added to make a stable preparation:

- The active drug
- Vehicles
  - Aqueous vehicle (e.g., water for injection, water for injection free from CO_2)
  - Water miscible vehicles (ethyl alcohol, liquid glycol & propylene glycol)
  - Non-aqueous vehicle (corn oil, cottonseed oil, peanut oil & sesame oil
- Adjuvants
  - Solubilizing agents (e.g., Tweens & polysorbates)
  - Stabilizers & antioxidants (e.g., thiourea, ascorbic acid, tocopherol)
  - Buffering agents (e.g., citric acid, sodium citrate
  - Antibacterial agents (e.g., benzyl alcohol, metacresol, phenol)
  - Chelating agents (e.g., EDTA)
  - Suspending, emulsifying & wetting agents (e.g., MC, CMC)
  - Tonicity factor (e.g., sodium chloride, dextrose)

VEHICLES

1. Aqueous vehicle

- Water for injection (WFI) USP-
  - Highly purified water used as a vehicle for injective preparations which will be subsequently sterilized.

- USP requirement include not more than 10 parts per million of total solids.
- pH of 5.0 – 7.0.
- WFI may be prepared by either distillation or reverse osmosis.
- Stored in chemically resistant tank.

- Bacteriostatic water for injection
  - This type of water used for making parenteral solutions prepared under aseptic conditions and not terminally sterilized.
  - Need to meet USP sterility test.
  - It can contain an added bacteriostatic agent when in containers of 30 ml or less.

✓ Sterile water for injection
- SWFI containing one or more suitable bacteriostatic agent.
- Multiple – dose containers not exceeding 30 ml.
- They are permitted to contain higher levels of solid than WFI because of possible leaching.
- Used for washing wounds, surgical incisions, or body tissues.

2. Water miscible vehicles

- The number of solvents that are miscible with water has been used as a portion of a vehicle.
- Primarily to affect solubility of drugs and to reduce hydrolysis.
- Example: Ethyl alcohol, Liquid propylene glycol Glycerin Ethyl alcohol used in the case of cardiac glycoside

3. Non aqueous vehicle

Fixed oils (vegetable origin, liquid, and rancid resistance, unsaturated, free fatty acid content)

Peanut oil	Sesame oil
Corn oil	Soyabean oil
Cotton seed oil (depo-testosterone)	Ethyl oleate, Isopropyl myristate

ADJUVANTS

Solubilizing agents

- Solubilise the active ingredient.
- Polyoxythylene sorbitan monooleate & Sorbitan monooleate.

Antioxidants

- To protect the formulation from oxidation.

Reducing agents	Synergistics	Blocking agent	Chelating agent
Ascorbic acid Sodium bisulfite 0.01% Sodium metabisulfite Thiourea	Ascorbic acid Citric acid Tartaric acid	Tocopherol BHT Ascorbic acid esters	EDTA

Buffering agents

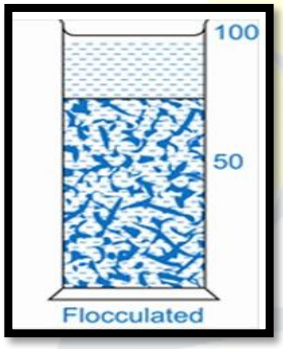
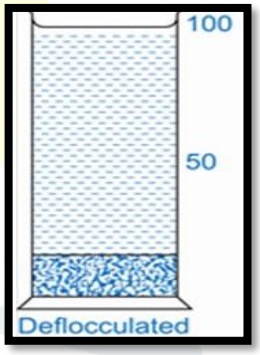
- Added to maintain pH.
- To stabilize a solution from chemical degradation.
- Citrate and acetate buffer,Sodium benzoate ,benzoic acid , Sodium tartarate , tartaric acid & Phosphate buffer.

Antibacterial agents

- These are added in multiple dose containers.
- To prevent microorganism growth.
- Limited concentration of agents are used. Phenyl mercuric nitrate and thiomersal 0.01%.
- Benzethonium chloride & benzalkonium chloride 0.01%. Phenol & cresol 0.05%, Chlorobutanol 0.05%.

a. Oral suspension (Example is Paracetamol suspension)
b. Topical suspension (Dispersed phase is in high concentration often exceeds 20% w/v. Example is Calamine Lotion)
c. Parenteral suspension (Solid Contents is between 0.5-5% w/v. Example includes Procaine penicillin G suspension.

DIFFERENCE BETWEEN FLOCCULATED AND DEFLOCCULATED SUSPENSION

FLOCCULATED SUSPENSION	DEFLOCCULATED SUSPENSION
Slightly sediment and clear supernatant layer.	Pleasant appearance, because of uniform dispersion of particles.
Supernatant is clear.	Supernatant remains cloudy
Particles experiences attractive forces.	Particles experience repulsive force.
Particles forms loose aggregates.	Particles exist as separate entities.
Rate of sedimentation is high , as flocs are the smaller particles (higher size).	Rate of sedimentation is slow as the size of the particles are small.
Sediment is loosely packed network and hard cake cannot form.	The sediment is closely packed and form hard cake.
Easy to redisperse	Cannot be redispersed
In the potential energy curve, it represents the secondry minimum.	In the potential energy curves, it represents the primary minimum.
Bioavailability is comparatively less	Bioavailability is relatively high
	

Physical stability

- Physical stability is defined as the condition in which the particles remain uniformly distributed throughout the dispersion without any sign of sedimentation.
- Flocculated suspension –
  - Initial state, F = 1.0
  - State of suspension on storage after some time F =0.6
  - Deflocculated suspension
- The extent of sedimentation is quantitatively expressed by two parameters:
- **Sedimentation volume (F)**

$$\mathbf{F} = \frac{Vu}{Vo} = \frac{\text{Final volume of sediment}}{\text{Initial volume of sediment}}$$

  - F is denoted as sedimentation volume.it is a dimension less number.
  - If sedimentation volume measuresd in measuring cylinder then the equation can be written as Hu/Ho where H represents height of sediment.
  - F = 1, when there is no sedimentation which is a desirable property of an ideal suspension.
  - F = 0 to 1 → higher the sedimentation volume better the physical stability.
  - F = 0, → complete sedimentation

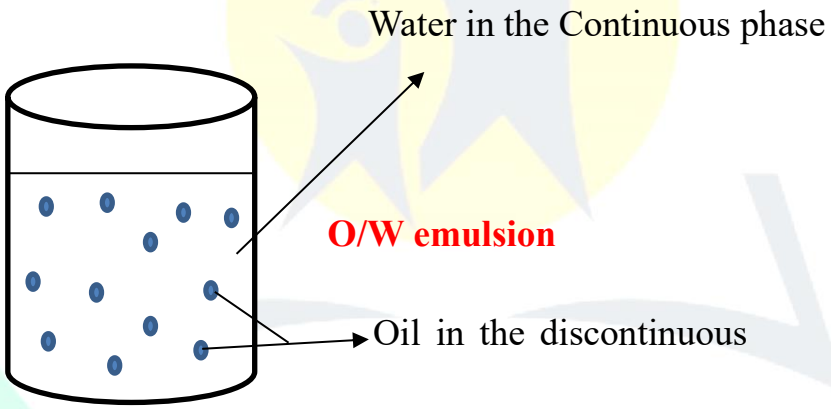
Chapter 5

EMULSION

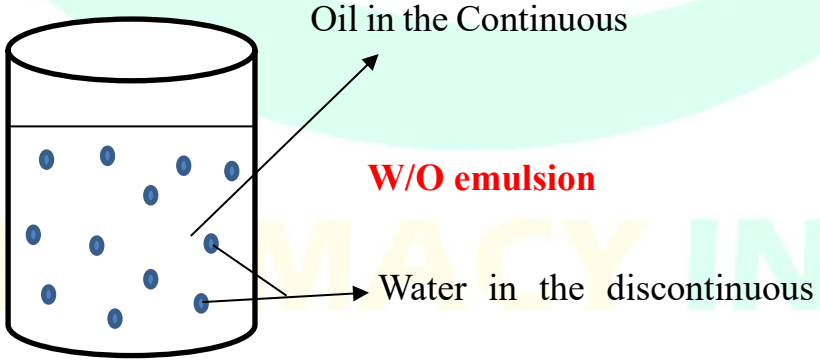
- Emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible.
- These are coarse dispersions having the globule diameter in the range from about 0.1 to 100 micrometers.
- Emulsions are also called heterogenous systems or more precisely biphasic system.

OR

- An emulsion is a thermodynamically unstable system consisting of at least two immiscible liquid phases one of which is dispersed as globules in the other liquid phase stabilized by a third substance called emulsifying agent.
- Examples of emulsion include milk, rubber, paints, polishes. Some emulsions themselves have medical properties for example, liquid paraffin is used as purgative and laxative.



The dispersed liquid is known as the Internal or Discontinuous phase. The droplet phase is called the dispersed phase or internal phase.



Whereas the dispersion medium is known as the External or Continuous phase. The liquid in which droplets are dispersed is called the external or continuous phase.

CLASS	EXAMPLES
1. Surface active agents	

• **Cationic**	• Quaternary ammonium compounds
	  ○ Cetrimide
	  ○ Benzalkonium chloride

• **Nonionic**	• Polyoxy ethylene fatty alcohol ethers $C_{12}H_{25}(OCH_2CH_2)nOH$ • Sorbitan fatty acid esters • Polyoxyethylene sorbitan fatty acid esters • Polyoxyethylene polyoxypopylene block copolymers • Lanolin alcohols and ethoxylated lanolin alcohols

• **Anionic**	• Soaps
	  ○ Mono valent
	  ○ Polyvalent
	  ○ Organic
	• Sulphates
	• Sulphonates $(CH_3(CH_2)n\ CH_2SO_3 – Na+)$

2. Hydrophilic colloids	
• **Semisynthetic**	• Sodium carboxymethyl cellulose • Hydroxyl propyl cellulose • Methyl cellulose

• **Natural**	• Plant origin
	  ○ Acacia
	  ○ Tragacanth
	  ○ Agar
	  ○ Pectin
	  ○ lecithin
	• Animal origin
	  ○ Gelatin
	  ○ Lecithin
	  ○ Cholesterol
	  ○ Wool fat
	  ○ Egg yolk

3. Finely divided solids	
• **Colloidal clays**	• Bentonite $(Al_2O_3.4SiO_2.H_2O)$ • Veegum (Magnesium Aluminium silicate) • Magnesium trisilicate
• **Metallic hydroxides**	• Magnesium hydroxide • Aluminium hydroxide

THEORIES OF EMULSIFICATION

1. **Monomolecular Adsorption and Film Formation**
   - Surfactants adsorb at the oil-water interface and form a monomolecular film.
   - Example – Adsorption of sodium cetylsulfate (hydrophilic) and cholesterol (Lipophilic).

Chapter 8

PREFORMULATION STUDIES

Stage of development during which physical and chemical properties of drugs in questions which are considered important in formulation of a stable, safe and effective dosage form.

STATE	PROPERTIES
(A) Study of physical properties of drug:	Fine particle characterization
	Bulk density
	Powder flow properties
	Solubility Analysis: Intrinsic solubility, pKa determinations, Salts formation, Dissolution, Intrinsic dissolution rate, Common ion effect.
	Hygroscopicity
(B) Study of chemical properties of drugs:	Crystallinity and Polymorphisms
	Hydrolysis
	Oxidation-reduction
	Racemization
	Polymerization

GOALS OF PREFORMULATION STUDY

- To establish necessary physicochemical parameter of new drug substance.
- To determine its kinetic rate profile.
- To determine its physical characteristics.
- To establish its compatibility with common excipients.

STATE	PROPERTIES
1. Bulk Characterization	Crystallinity and Polymorphism
	Hygroscopicity
	Fine Particle Characterization
	Bulk Density
	Powder Flow Properties
2. Solubility Analysis	Ionization Constant-pKa
	pH Solubility Profile
	Common lon Effect- Ksp
	Thermal Effects
	Solubilization
	Partition Coefficient
	Dissolution
3. Stability Analysis	Stability in Toxicology Formulations
	Solution Stability: pH Rate Profile
	Solid State Stability: Bulk Stability and Compatibility

A) Study of physical properties of drug:

1. **Fine particle characterization**
   - Size, shape, and surface morphology of the drug particles can affect the bulk flow, formulation homogeneity, and surface area of powder, which in turn are important parameter which governs controlled drug dissolution and chemical reactivity.
   - A light microscope with a calibrated grid usually provides adequate size and shape characterization for drug particles
   - In conjunction with light microscopy, stream counting devices, such as the Coulter counter and HIAC counter, often provide a convenient method for characterizing the size distribution of a compound.

METHODS TO DETERMINE PARTICLE SIZE

METHODS	SIZE (IN μ)
Seiving	5-50
Microscopy	0.2-100
Sedimentation Rate Method	1-200
Light Energy Diffraction	0.5-500
Laser Holography	1.4-100

2. **Bulk Density**
   - Bulk density of a compound varies substantially with the method of crystallization, milling, or formulation.
   - Once a density problem is identified, it is often easily corrected by milling, slugging, or formulation.

$$\textbf{Bulk density} = \frac{mass\ of\ powder}{bulk\ volume}$$

3. **Powder Flow Properties**
   - Pharmaceutical powders may be broadly classified as free-flowing or cohesive (non-free-flowing).
   - Most flow properties are significantly affected by changes in particle size, density, shape, electrostatic charge, and adsorbed moisture, which may arise from processing or formulation.

ANGLE OF REPOSE

- When only gravity acts upon it, a static heap of powder will tend to form a conical mound. One limitation exists: the angle to the horizontal cannot exceed a certain value and this is known as the angle of repose (θ).
- Methods used for determination-
  - **Fixed cone method**

    $\theta = \tan^{-1}\frac{h}{r}$

    Where, θ → angle of repose

    r = radius of the base of pile

    h = height of pile
  - **Rotating cylinder method**
  - **Tilted box method**

ANGLE OF REPOSE	POWDER FLOW
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

- Other small inorganic counter-ions, other than CI-, such as nitrate, sulfate and phosphate, have also been implicated.
- To identify a common ion interaction, the IDR of the hydrochloride (or inorganic) salt should be compared between (a) water (b) water containing 1.2% w/v NaCl and (c) 0.05 M HCl and 0.9% w/v NaCl in 0.05 M HCI.
- Both saline media contain 0.2M Cl-, which is typically encountered in fluids *in-vivo*. A common ion effect with CI- will result in a significantly reduced IDR in the presence of sodium chloride.

5.Hygroscopicity

- Many drug substances, particularly water-soluble salt forms, have a tendency to adsorb atmospheric moisture.
- Adsorption and equilibrium moisture content can depend upon the atmospheric humidity, temperature, surface area, exposure, and the mechanism for moisture uptake.
- Deliquescent materials adsorb sufficient water to dissolve completely, as is observed with sodium chloride on a humid day.
- Other hygroscopic substances adsorb water because of hydrate formation or specific site adsorption.
- With most hygroscopic materials, changes in moisture level can greatly influence many important parameters, such as chemical stability, flowability and compatibility.
- The degree of Hygroscopicity is classified into four classes:

Degree of Hygroscopicity	Description
Slightly hygroscopic	increase in weight is ≥ 0.2% w/w and < 2% w/w
Hygroscopic	increase in weight is ≥ 0.2 % w/w and < 15 % w/w
Very hygroscopic	increase in weight is ≥ 15% w/w
Deliquescent	sufficient water is adsorbed to form a solution

- Analytical methods which is used are:
    1. Gravimetry
    2. Karl Fischer Titration
    3. Gas chromatography

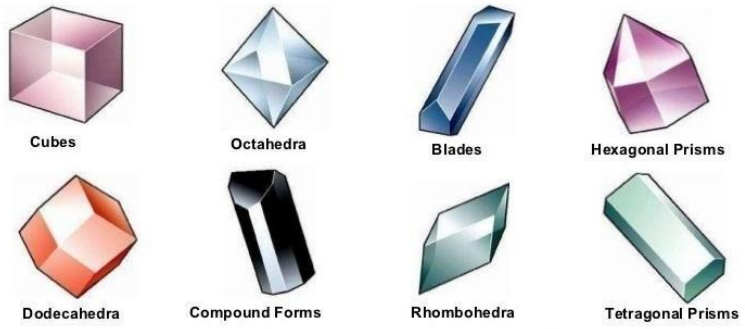
B) Study of chemical properties of drugs:

1. Crystallinity and Polymorphisms

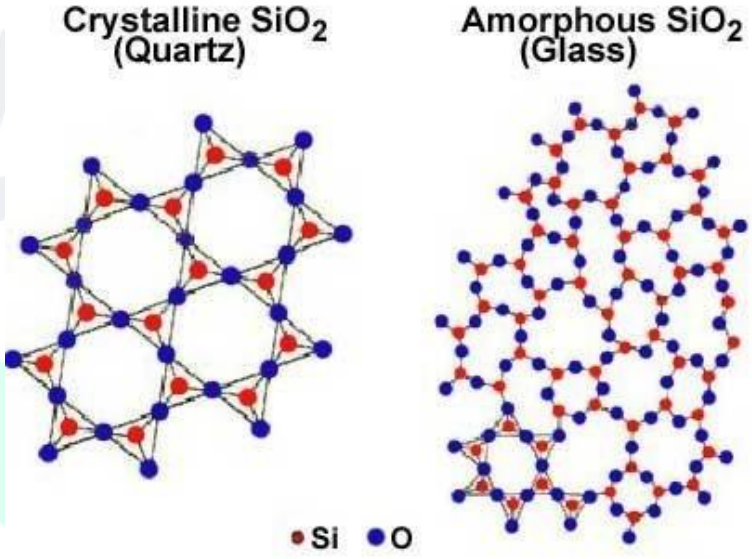
- Crystal habit & internal structure of drug can affect bulk & physicochemical property of molecule.
- Crystal habit is description of outer appearance of crystal.
- Internal structure is molecular arrangement within the solid.
- Change with internal structure usually alters crystal habit.
- Eg. Conversion of sodium salt to its free acid form produce both change in internal structure & crystal habit.
- Depending on internal structure compounds is classified as
  1. Crystalline
  2. Amorphous
- Crystalline compounds are characterized by repetitious spacing of constituent atom or molecule in three-dimensional array.
- In amorphous form atom or molecule are randomly placed.
- Solubility & dissolution rate are greater for amorphous form than crystalline, as amorphous form has higher thermodynamic energy.
- Eg. Amorphous form of Novobiocin is well absorbed whereas crystalline form results in poor absorption.

Polymorphism

- It is the ability of the compound to crystallize as more than one distinct crystalline species with different internal lattice.
- Different crystalline forms are called polymorphs.
- Polymorphs are of 2 types-
  - Enatiotropic
  - Monotropic
- The polymorph which can be changed from one form into another by varying temp or pressure is called as Enantiotropic polymorph. Eg. Sulphur.
- One polymorph which is unstable at all temp. & pressure is called as Monotropic polymorph. Eg. Glyceryl stearate.



- The first major distinction is whether the solid is crystalline or amorphous.
- Crystals are characterized by repetitious spacing of constituent atoms or molecules in a three-dimensional array, whereas amorphous forms have atoms or molecules randomly placed as in a liquid.



Analytical methods for the characterization of polymorphs

1. Microscopy
2. Hot stage microscopy
3. Thermal analysis
4. X-ray diffraction
5. Infrared (IR) spectroscopy
6. Proton magnetic resonance (PMR)
7. Nuclear magnetic resonance (NMR)
8. Scanning electron microscopy (SEM)

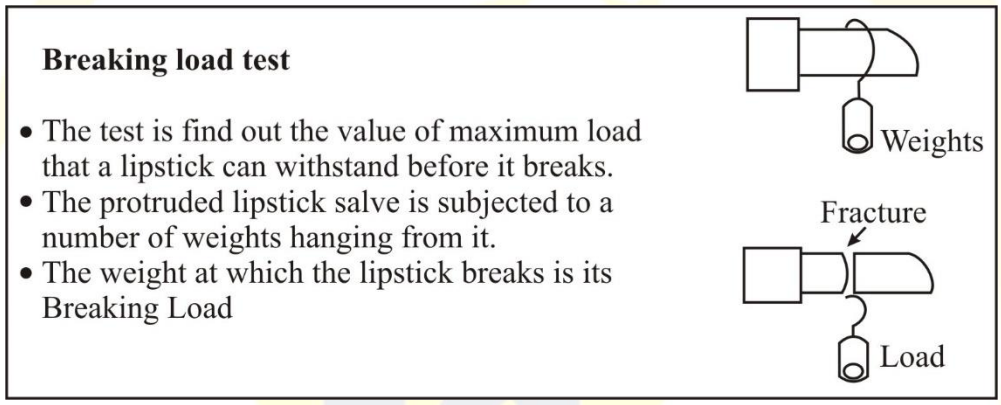
STERILIZATION METHOD	MECHANISM	APPLICATION	VALIDATION
Dry heat	Oxidation of proteins	Glassware, porcelain and metal equipments. Fats, oils, powder.	**Physical –** Temperatur e Recording Charts **Chemical –** Browne's the Bowie Dick heat sensitive tapes. Spores of *Bacillus Subtilis* and *Clostridium Sporogens*
Moist heat	Denaturation and coagulation of proteins	Aqueous solution and suspension. Surgical dressings, plastic and rubber closures. Metal instruments, Glass apparatus.	*Bacillus Stearethamo ph Bacillus cogulans*
Ethylene oxide **Gaseous Sterilisation**	Alkylation of – SH, -NH, COOH, OH group of proteins	Surface sterilsation of powders, syringes, needles, catheters. Geiger Muller Counter	Chemical – Reyce Sac *B. subtilis Var. Niger*
Formaldehyde	Alkylating agent (Same as above)	Fumigation of empty rooms	
UV-rays (Non- ionizing radiations)	Nuclear protein damage by UV of 253.5 nm	Treatment of air in sterile areas and hospitals and thin layer of water.	**Chemical –** Dorimeters *Bacillus pumilus Bacillus Sphaerians*
Ionizing radiations γ rays	Denaturation of enzymes, DNA by excitation, ionization free radical formation	Plastic syringes, Catheters, Hypodermic needles, Catgut	*Micrococus radiofena*
Filteration **(Dessicators destroys the spore)**	Retention of bacteria	Thermolabile liquids and solutions, Antisera	Physical – **Bubble point pressure test** ***Pseudomonas diminuta Serrata marcesens***

3. **COLOR MIXTURE:** Insoluble dyes and lake colors are used as main color. **Eg –** Ti02 is used to modify the shades of basic pigment.
4. **ANTIOXIDANTS: -** BHA, BHT, Propyl gallate
5. **FLAVOURS: -** to mask the fatty odour of the base.

NOTE: - Lip Slave:- Do not contain color and form a adherent moisture resistant film on lip, used to protect lips during winter.

EVALUATION OF LIPSTICKS

1. **DROP POINT TEST: -** Temperature at which liquid start oozing out or flatten out from within in case is known as drop point.
2. **BREAKING POINT TEST: -** Determine the strength of lipstick.



3. **TEST FOR PENETRABILITY: -** Indicates rheological properties of lipsticks. A specific diameter of needle is allowed to penetrate the lipstick and depth of penetration is noted**.**
4. **TEST FOR FORCE OF APPLICATION: -** Lipstick is applied on the piece of paper at an angle of 45 degree and force is read from balance.
5. **STABILITY TEST:** - By mean of accelerated stability test in which lipstick for surface defects , perfume, colour and application characteristics.

DENTRIFRICES

Preparation intended to clean the food debris, prevent calculi, plaque formation, polish to impart luster to the teeth and to leave refreshing feeling in mouth.

TYPES: -

1. **Tooth powder**
2. **Tooth paste**

Tooth powder is a powder containing abrasive, detergent, sweetening, agent etc meant for cleaning agent.

FORMULATION (TOOTH POWDER): -

1. **Abrasives and polishing agent:** eg – calcium carbonate, dicalciumphosphate, sodium metaphosphate.

Chapter 1

STATES OF MATTER

INTRODUCTION

In our everyday life, we can observe four different states of matter, namely solid, liquid, gas and plasma. However, there are numerous other states that can be seen to exist but only under extreme conditions. The ones worth mentioning are glass and Bose-Einstein condensates.

They are all differentiated on the basis of differences in their quality. For example, their characteristics can be stated as:

STATES OF MATTER	VOLUME	SHAPE	PARTICLES POSITION
Solid	Fixed	Fixed	Close together and fixed
Liquid	Fixed	Not fixed, Adapts to the shape of the container.	Particles close but move freely
Gas	Variable	Variable	Particles not close or fixed
Plasma	Variable	Variable	Neutral atoms, and large number of ions and electrons that move freely.

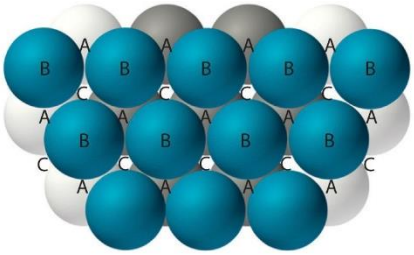
Solid: The particles, or the atoms, ions and molecules, are packed together closely. The particles are free to vibrate but are not free to move. They can only change their volume and shape when external force is applied, or when they are cut into smaller pieces,

SOLIDS ARE OF TWO TYPES

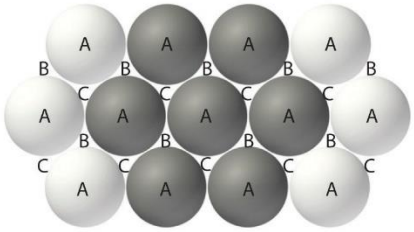
- **Crystalline solids**
- **Amorphous Solids**

S. NO.	CRYSTALLINE SOLIDS	AMORPHOUS SOLIDS
1.	Long range orderly arrangement of constituents.	Short range, random arrangement of constituents.
2.	Definite shape	Irregular shape
3.	Generally crystalline solids are anisotropic in nature	They are isotropic* like liquids
4.	They are true solids	They are considered as pseudo solids (or) super cooled liquids
5.	Definite Heat of fusion	Heat of fusion is not definite
6.	They have sharp melting points	Gradually soften over a range of temperature and so can be moulded.
7.	Examples: NaCl , diamond etc.	Examples: Rubber, plastics, glass etc.

Liquid: They are incompressible matter in liquid form that is not dependent on pressure. They have a fixed volume, if the pressure and temperature are kept unchanged. When solid is exposed to temperatures higher than their specific melting points, they have a tendency to transform into the liquid state, subject to pressure properties.



(b)most open, loosest, or cubic packing – 48%porosity



4. Flow properties

A. Angle of repose-

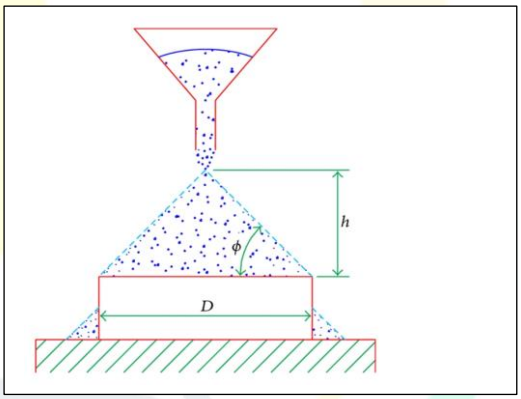
- It is the maximum angle possible between surface of the pile of the powder and horizontal plane.
- Methods used for determination-
  - **Fixed cone method**

    $\theta = \tan^{-1}\frac{h}{r}$

    Where, θ → angle of repose

    r = radius of the base of pile

    h = height of pile
  - **Rotating cylinder method**
  - **Tilted box method**



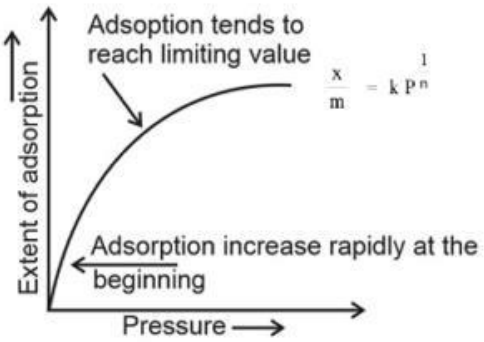
Angle of repose	Powder flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

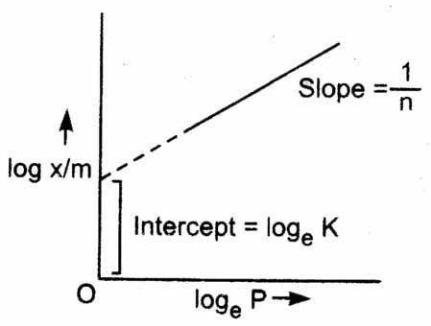
B. Carr's consolidation index

- A volume of powder is filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping is measured.

$$\textbf{Carr's index} = \frac{\textbf{Tapped density} - \textbf{bulk density}}{\textbf{Tapped density}} \times 100$$

- **Also known as compressibility.**
- It is the relationship between powder flowability and % compressibility.
- In free-flowing powder the bulk density and tapped density would be close in value. Therefore, the Carr's index would be small.
- In poor flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater. Therefore, the carr's index would be larger.





$$\text{Log } \frac{x}{m} = \text{Log k} + \frac{1}{n} \text{Log p}$$

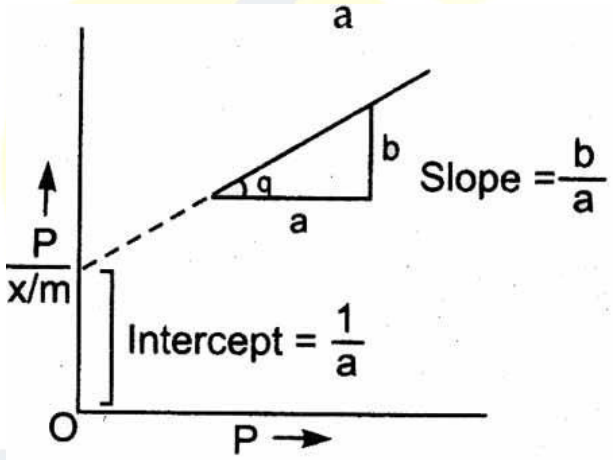
Where,

y → mass of gas adsorbed per unit weight of absorbent

k, n → constant

p → equilibrium gas pressure

3. **Langmuir adsorption isotherm**



$$p/y = 1/y_{mb} + p/ y_m$$

where,

y_m → mass of gas & needed to form a monolayer per gram of adsorbent

b → constant

4. **BET equation**

$$\frac{p}{y(p_0 - p)} = \frac{1}{y_m b} + \frac{b-1}{y_m b}\frac{p}{p_0}$$

where,

P → pressure of the adsorbate molecules

y → the mass of vapour adsorbed per gm of adsorbent

p_o → saturation vapour pressure

Factors affecting adsorption

1. **Solute –** increase in conc. of solute increases adsorption.
2. **Surface area -** increase in surface area of adsorbent increases adsorption.
3. **Temperature** - increase in temperature will decreases adsorption.
4. **Removal of adsorbed impurities –** Increase in impurities will decrease adsorption.
5. **pH of the medium –** adsorption would increase or decrease with change in pH.

Micellisation

Chapter 4

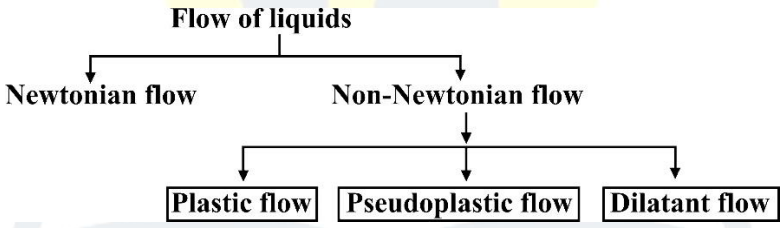
RHEOLOGY

INTRODUCTION

- The term **—rheology,** from the Greek *rheo* (—to flow‖) and *logos*(—science), was suggested by Bingham and Crawford (as reported by Fischer1) to describe the flow of liquids and the deformation of solids.
- **Rheology** is involved in the mixing and flow of materials, their packaging into containers, and their removal prior to use, whether this is achieved by pouring from a bottle, extrusion from a tube, or passage through a syringe needle.
- **Rheology** describes the deformation of a body under the influence of stresses.
- **Ideal fluids** such as liquids and gases deform irreversibly –they flow.
- **Ideal solids** deform elastically.

Terminologies

- **Shear:** is the movement of material relative to parallel layer.
- **Shear stress(F)**is the force applied per unit area to make liquid flow (Force/Area).
- **Shear rate (G)** difference in velocity dv, between two planes of liquids separated by distance dr (i.e. dv/dr).



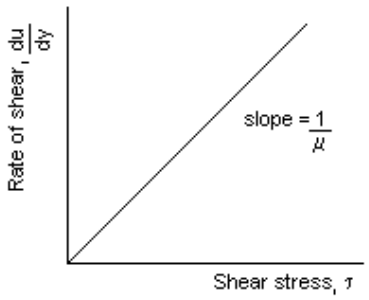
Newtonian flow

Newton was the first to study flow properties of liquids in a quantitative way. He recognized that the higher the viscosity of a liquid, the greater is the force per unit area (*shearing stress*) required to produce a certain rate of shear. Rate of shear is given the symbol *G*. Hence, rate of shear should be directly proportional to shearing stress.

$$\text{States that viscosity} = \frac{Shearing\ stress\ (F)}{Rate\ of\ shear\ (G)}$$

$$\eta = \frac{F}{G} = \frac{F'/A}{dv/dr}$$

Examples – Water, Glycerine, Chloroform, castor oil, olive oil, ethanol, solution of syrup, very dilute colloidal solution.



Newtonian Fluid

Absolute (dynamic) viscosity

- The fundamental unit of viscosity measurement is the poise.
- Shear force required to produce a velocity of 1 cm/sec between two parallel planes of liquid each 1cm2in area and separated by 1cm
- Fluidity; it is the reciprocal of viscosity Ø = 1/ η its unit is inverse poise.

Kinematic viscosity

Kinematic viscosity is the absolute viscosity [as defined in divided by the density of the liquid at a specific temperature.

$$\text{Kinematic viscosity} = \frac{\eta}{\rho}$$

The units of kinematic viscosity are the stoke (s) and the centistoke(cs).

Temperature dependence

When temperature increases viscosity decreases.

$$\eta = Ae^{Ev/RT}$$

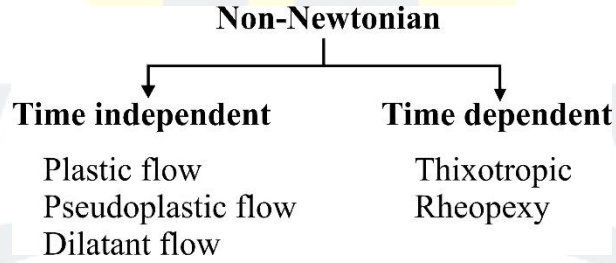
Where, E_v – activation energy to initiate flow between molecules.

A – constant depending on molecular weight and molar volume.

Non-Newtonian flow

The majority of fluid pharmaceutical products are not simple liquids and do not follow Newton's law of flow. These systems are referred to as non-Newtonian.

Non-Newtonian behaviour is generally exhibited by liquid and solid heterogeneous dispersions such as colloidal solutions, emulsions, liquid suspensions, and ointments.



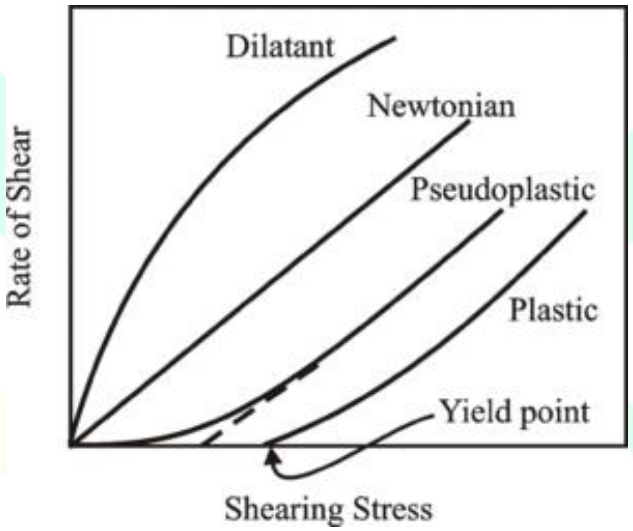


Figure- Rheogram

Plastic flow

- Plastic flow curves do not pass through the origin but rather intersect the shearing stress axis (or will if the straight part of the curve is extrapolated to the axis) at a particular point referred to as the yield value.
- Also known as **BINGHAM BODIES.**
- A Bingham body does not begin to flow until a shearing stress corresponding to the yield value is exceeded.
- At stresses below the yield value, the substance acts as an elastic material.
- Associated with flocculated particles or concentrated suspension.
- Yield value (f) is an indication of the force that must be applied to a system to convert it to a Newtonian System.

The equation describing plastic flow is –

$$U = \frac{F-f}{G}$$

Where, U = plastic viscosity
f = yield value (N/m^2)
G = rate of shear (S)
F = shear stress (N/m^2)

Examples → Flocculated particles in concentrated suspension / Suspension of ZnO in mineral oil, certain paints, ointments

Pseudoplastic flow

- Curve for a pseudoplastic material begins at the origin
- There is no yield value
- Also called **SHEAR THINNING SYSTEM**
- Because no part of the curve is linear, the viscosity of a pseudoplastic material cannot be expressed by any single value.
- The viscosity of a pseudoplastic substance decreases with increasing rate of shear.
- Exponential equation for pseudoplastic flow-

$$F^N = \eta' G$$

N = 1 (Newtonian flow)
N > 1 (Non-Newtonian flow)

Examples → Liquid dispersions of natural and synthetic gums (tragacanth, soidum alginate, methyl cellulose, and sodium carboxy methyl cellulose).

Dilatant flow

- Certain suspensions with a high percentage (upto 50%) of deflocculated solids exhibit an increase in resistance to flow with increasing rate of shear.
- Such systems actually increase in volume when sheared and hence termed dilatant and phenomenon as **rheopexy.**
- No yield values.
- Curve begins at the origin.
- Also known as **SHEAR THICKENING SYSTEM.**
- When stress is removed, a dilatant system returns to its original state of fluidity.
- Exponential equation for dilatant flow-

$$F^N = \eta' G$$

N< 1 (degree of dilatancy increases)
N = 1 (Newtonian flow)
N > 1 (Non-Newtonian flow)

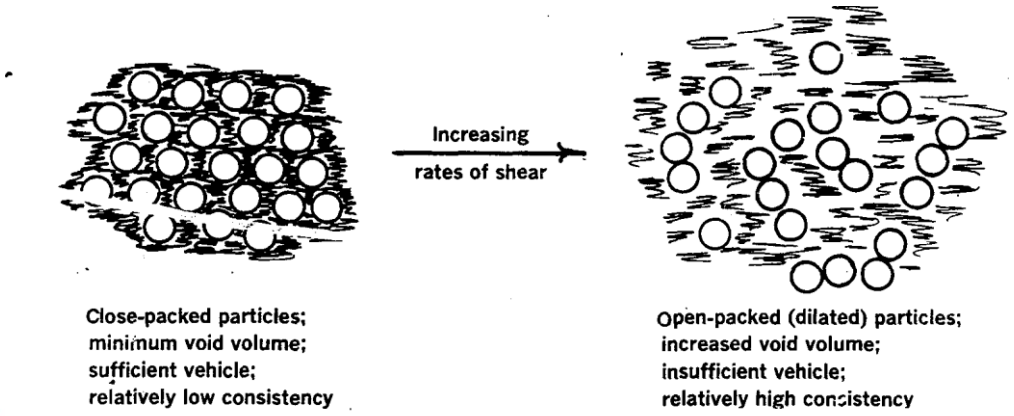


Fig. 20–3. Explanation of dilatant flow behavior.

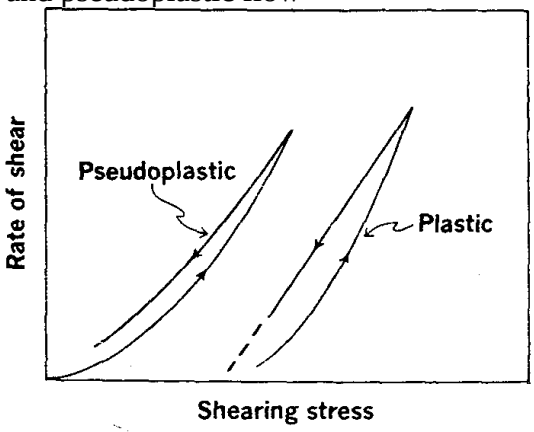
Examples → Suspension of corn starch in water; Suspension containing high concentration of solids; Inorganic pigments in water; kaolin in water; zinc oxide in water.

Thixotropy

- **GEL-SOL-GEL** system.
- **Shear thinning system**.
- Non-Newtonian
- Time Dependent behaviour
- Down curve displaces left to up curve for shear thinning system
- It is the decrease in viscosity as a function of time upon shearing, then recovery of original viscosity as a function of time without shearing.
- Loose network through sample.
- At rest, its Rigidity is like Gel
- As shear applied, the structure begins to break and the material undergo Gel-to Sol transformation.
- Finally, at rest the structure is restored again (Sol to Gel)

Example → Procaine penicillin G (40-70% w/v in water)

Thixotropic effect on plastic and pseudoplastic flow-



Negative/ Antithixotropy

- **SOL-GEL-SOL system**
- **SHEAR THICKENING system**
- Also called **rheopexy**
- Viscosity increases so, downward curve more towards right.

Chapter 5

COLLOIDAL DISPERSION

INTRODUCTION

- A dispersed system is defined as a system in which one phase the dispersed phase is distributed uniformly as particles throughout another phase called the dispersion medium or continuous phase.
- Dispersed phase can be classified on the basis of the physical state of two phases-

DISPERSION MEDIUM	DISPERSED PHASE	EXAMPLES OF COLLOIDAL DISPERSIONS	EXAMPLES OF COARSE DISPERSIONS
Gas	Liquid	Fog	Spray
Gas	Solid	Smoke	Dust
Liquid	Gas	Foam (Aerosol)	Foam
Liquid	Liquid (immiscible)	Oil globules	Emulsions
Liquid	Solid	Colloidal gold in water	Suspension of kaolin in water
Solid	Gas	Solid foam (Aerosol)	Solid foam
Solid	Liquid	Mineral oil in wax	Solid emulsion
Solid	Solid	Colloidal gold in glass	Solid suspension

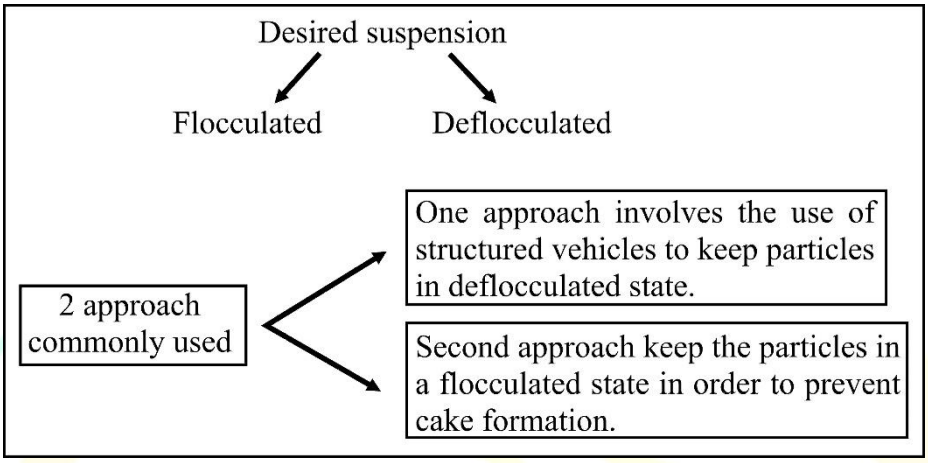
- Dispersed system can also be classified as –
  1. Molecular dispersion (true solutions)
  2. Colloidal dispersions
  3. Coarse dispersions

PROPERTY	MOLECULAR DISPERSION	COLLOIDAL DISPERSION	COARSE DISPERSION
Particle size	Less than 1nm	1nm to 1µm	Greater than 0.5µm
Filter paper	Can pass	Can pass	Cannot pass
Semipermeable membrane	Can pass	Cannot pass	Cannot pass
Optical property	No tyndall effect	Tyndall effect is produced	Tyndall effect is observed
Visiblity under microscopy	Not visible	Visible under ultra microscope	Visible under normal ultra-microscope
Diffusion	Undergo rapid diffusion	Diffuse very slowly	Particles do not diffuse
Appearance	Clear	Clear or turbid	Turbid

Colloidal Dispersions

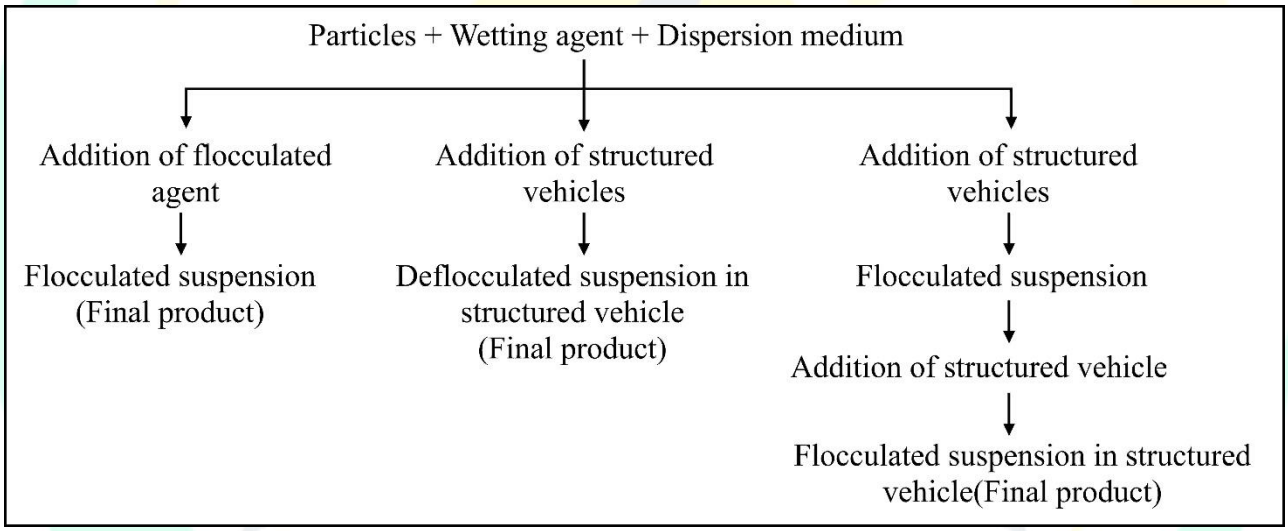
- Term colloid implies → glue like substance
- Colloidal system is a dispersion where in dispersed particle are uniformly distributed in a dispersion medium.
- Size ranges - 1nm to 1µm
- **Types of colloidal dispersion-**

Formulation of pharmaceutical suspension



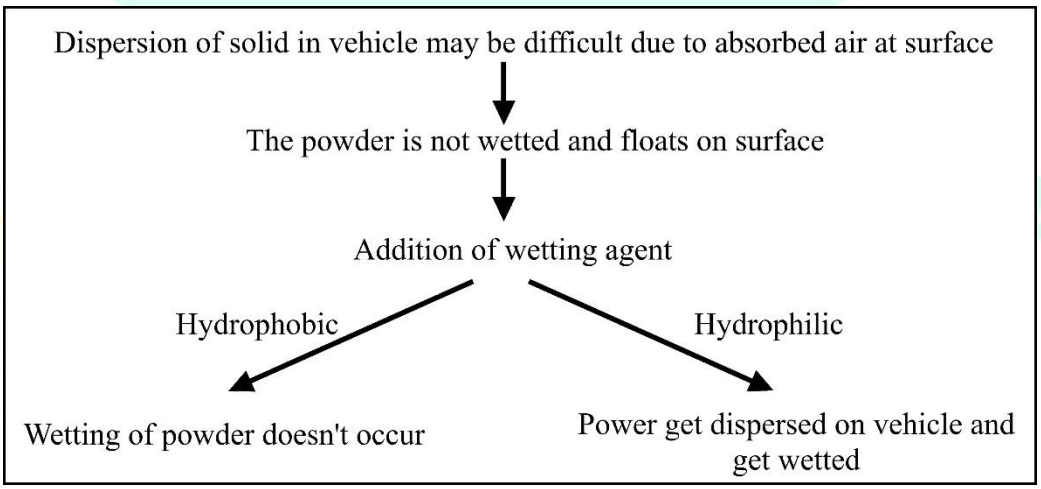
- Third method uses a combination of these approaches to prevent settling

Approches used in formulation of suspensions



Wetting Phenomenon

- In industry large quantities of powders such as talc or charcoal are added to water. These powders do not get wetted properly in spite of their higher densities than water., instead these floats on the surfaces.
- Wetting is an adsorption process in which an intimate contact of the solids with liquid phase is achieved.



Chapter 8

KINETICS AND DRUG STABILITY

INTRODUCTION

- Chemical kinetics is the study of the rate of chemical changes taking place during chemical reactions.
- In pharmaceutical formulations, it is the study of –
  - physical and chemical reactions in drugs and dosage forms
  - factors influencing the rate of these chemical reaction
  - accelerated stability testing and prediction of shelf life of formulations.

Rate of Reaction

- The rate of chemical reaction is defined as the velocity with which a reactant or reactants undergo chemical change. The rate of reaction is given by:

$$\pm\frac{dc}{dt}$$

- The + or – sign indicates an increase or decrease respectively in concentration dc with a time interval dt.

Rate constant or order of reaction

- Acc. To law of mass action, the rate of a chemical reaction is proportional to the product of the molar concentration of the reactants each raised to a power usually equal to the number of molecules, a and b of the substances A and B undergoing reaction.

$$aA + bB \rightarrow \text{products}$$

- the rate of reaction is given by:

$$\text{Rate} = -\frac{1}{a}\frac{d\,[A]}{dt}$$

$$\text{Rate} = -\frac{1}{a}\frac{d\,[A]}{dt}$$

$$\text{Rate} = k\,[A]^a\,[B]^b$$

$$k \rightarrow \text{rate constant}$$

- **Order of reaction →** the sum of the powers of the concentration terms involved in the rate equation. Thus, the order of the above reaction is (a + b).

Molecularity of the reaction

- The molecularity of a reaction refers to the number of molecules, atoms or ions reacting in an elementary process to give the reactants.
- **Unimolecular reaction –** If only one type of molecule undergoes a change to yield the product.

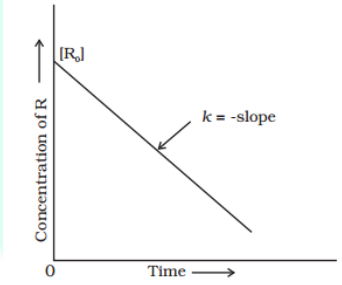
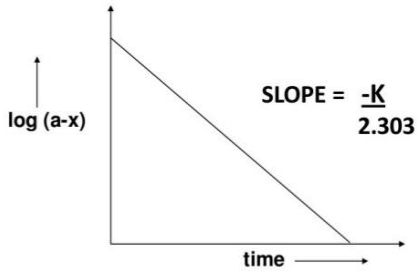
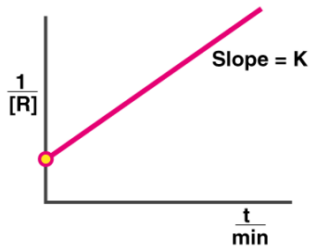
$$Br_2 \rightarrow 2Br$$

- **Bimolecular reaction –** two types of molecules are stoichiometrically involved in reaction.

$$H_2 + I_2 \rightarrow 2HI$$

- **Half-life –** It is the time required for the concentration of the reactant to reduce to half of its initial concentration.
- **Shelf life (t_{90}) –** It is defined as the concentration of the reactant to reduce to 90% of its initial concentration.

Order of reaction

ZERO ORDER	FIRST ORDER	SECOND ORDER
Rate of reaction is independent of the concentration of the reacting species.	Rate of the reaction is directly proportional to the first power of the concentration of a single reactant.	Rate of the reaction is directly proportional to the second power of the concentration of a single reactant.
Rate equation $K = \frac{Ao - At}{t}$ A_o → initial concentration A_t → concentration after t time	**Rate equation** $K = \frac{2.303}{t} \log \frac{a}{a-x}$ a → initial concentration x → decrease in concentration t → time	**Rate equation** $K = \frac{1}{at} \frac{x}{a-x}$ Initial concentration of a and b are not equal $a \neq b$ $K = \frac{2.303}{a-b} \log \frac{b(a-x)}{a(b-x)}$
Half life $t_{1/2} = \frac{Ao}{2K}$	**Half life** $t_{1/2} = \frac{0.693}{K}$	**Half life** $t_{1/2} = \frac{1}{ak}$
Shelf life $t_{90} = \frac{0.1\ Ao}{K}$	**Shelf life** $t_{90} = \frac{2.303}{K} \log \frac{Co}{0.9\ Co}$ **or** $t_{90} = \frac{0.1052}{K}$	
Graph 	**Graph** 	**Graph** 
Unit **K = moles/ litre/ second**	**Unit** **K = second^{-1}**	**Unit** **K = Litre.mole^{-1} second^{-1}**

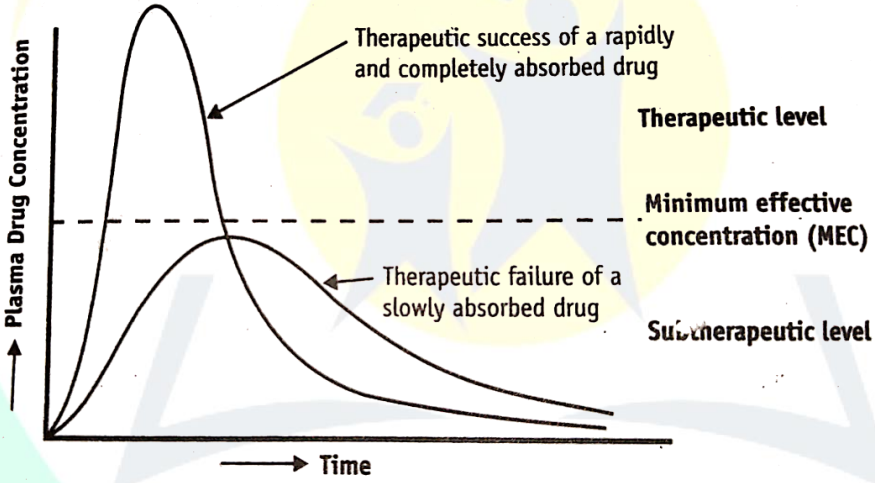
Methods of determining order of reactions

1. **Graphical method**
   - More reliable because deviations from the best fit line can be easily observed.
   - The kinetic study is conducted and data are collected on the time of changes in the concentration of the reactants.
2. **Substitution method**
   - The kinetic study is conducted and data are collected on the time of changes in the concentration of the reactants.
   - Data are substituted in the integral equations of zero, first and second order reactions to get the k values.
3. **Half-life method**
   - The average k value is calculated using the data for zero, first and second orders as given in substitution method or graphical method.
   - Then, the $t_{1/2}$ values are calculated for each time period in the kinetic study.

Chapter 2

ABSORPTION OF DRUGS

- **Drug absorption** is defined as the process of movement of unchanged, drug from the site of administration to systemic circulation.
- Following absorption, the effectiveness of a drug can only be assessed by its concentration at the site of action.
- However, it is difficult to measure the drug concentration at such a site. Instead, the concentration can be measured more accurately in plasma.
- There always exist a correlation between the plasma concentration of a drug and the therapeutic response and thus absorption can also be defined as the process of movement of unchanged drug from the site of administration to the site of measurement i.e. plasma.



Drugs that have to enter the systemic circulation to exert their effect can be administered by three major routes:

1. **The Enteral Route**: includes peroral i.e. gastrointestinal, sublingual/ buccal and rectal routes. The GI route is the most common for administration of majority of drugs.
2. **The Parenteral Route**: includes all routes of administration through or under one or more layers of skin. While no absorption is required when the drug is administered i.v. it is necessary for extravascular parenteral routes like the subcutaneous and the intramuscular routes.
3. **The Topical Route**: includes skin, eyes or other specific members. The intranasal, inhalation, intravaginal and transdermal routes may be considered enteral or topical according to different definitions.

- GI lining constituting the absorption barrier allows most nutrients like glucose, amino acids, fatty acids, vitamins, etc. to pass rapidly through it into the systemic, circulation but prevents the entry of certain toxins and medicaments. Thus, for a drug to get absorbed after oral administration, it must first pass through this biological barrier.

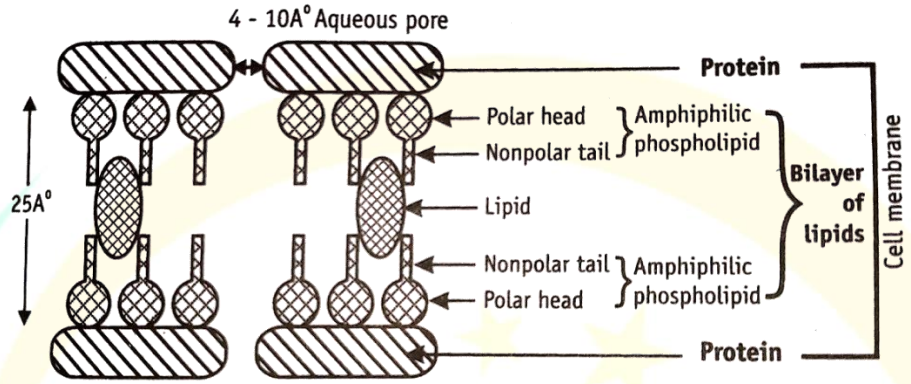


Figure: Basic structure of functional cell membrane

MECHANISMS OF DRUG ABSORPTION

- The principal mechanisms for transport of drug molecules across the cell membrane in order of their importance are:

MECHANISM	DESCRIPTION
• **Transcellular/ Intracellular transport**	Passage of drugs across the GI epithelium.
○ **Passive Transport Processes**	Donot require energy
➢ Passive diffusion.	Also called **non-ionic diffusion.** Major process for absorption of more than 90% of the drugs. The driving force for this process is the **concentration** or **electrochemical gradient**. It is defined as the difference in the drug concentration on either side of the membrane.
➢ Pore transport	Also called as **convective transport**, **bulk flow** or **filtration**. This mechanism is responsible for transport of molecules into the cell through the protein channels present in the cell membrane.
➢ Ion-pair transport	Absorption of drugs like quaternary ammonium compounds and sulphonic acids, which ionise under all pH conditions, is ion-pair transport. Despite their low o/w partition coefficient values, such agents penetrate the membrane by forming reversible neutral complexes with endogenous ions of the GIT like mucin. Such neutral complexes have both the required lipophilicity as well as aqueous solubility for passive diffusion.
➢ Carrier mediated transport	Carrier is required for the transport of drug across the cell membrane.

INFLUENCE OF DRUG PKA AND GI PH ON DRUG ABSORPTION

Drugs	pKa	pH/ site of absorption
Very weak acids (pKa > 8.0)		
Phenobarbital	8.1	Unionised at all pH values; absorbed along the entire length of GIT
Hexobarbital	8.2	
Phenytoin	8.2	
Ethosuximide	9.3	
Moderately weak acids (pKa 2.5 to 7.5)		
Cloxacillin	2.7	Unionised in gastric pH and ionised in intestinal pH; better absorbed from stomach
Aspirin	3.5	
Ibuprofen	4.4	
Phenylbutazone	4.5	
Stronger acids (pKa < 2.5)		
Disodium cromoglycate	2.0	Ionised at all pH values; poorly absorbed from GIT.
Very weak bases (pKa < 5.0)		
Theophylline	0.7	Unionised at all pH values; absorbed along the entire length of GIT
Caffeine	0.8	
Oxazepam	1.7	
Diazepam	3.7	
Moderately weak bases (pKa 5 to 11.0)		
Reserpine	6.6	Ionised at gastric pH, relatively unionised at intestinal pH; better absorbed from intestine
Heroin	7.8	
Codeine	8.2	
Stronger bases (pKa > 11.0)		
Mecamylamine	11.2	Ionised at all pH values; poorly absorbed from GIT

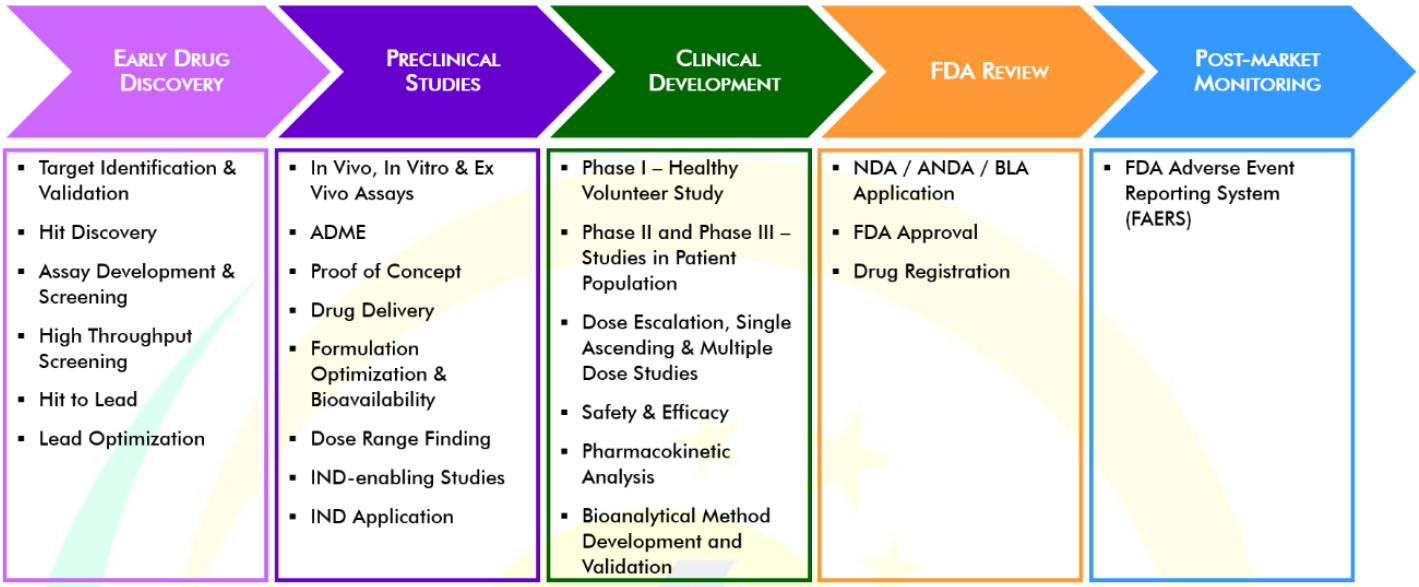
METHODS FOR STUDYING DRUG UPTAKE

1. ***In vitro experiments***:
   - used to study the transport of drugs through different types of membranes or biological materials.
   - Such experiments may utilize
     (a) Diffusion cells
     (b) Segments of GIT of laboratory animals – Two well-known established techniques are –
         (i) Everted sac technique
         (ii) Everted ring technique
     (c) Cell cultures of gut epithelium e.g. Caco-2 cells.
2. ***In situ experiments:***
   - simulates the in vivo conditions for drug absorption and are based on perfusion of a segment of GIT by drug solution and determination of amount of drug diffused through it.
   - The two perfusion methods used in laboratory animals are –
     (a) Dissolution method
     (b) Single pass perfusion

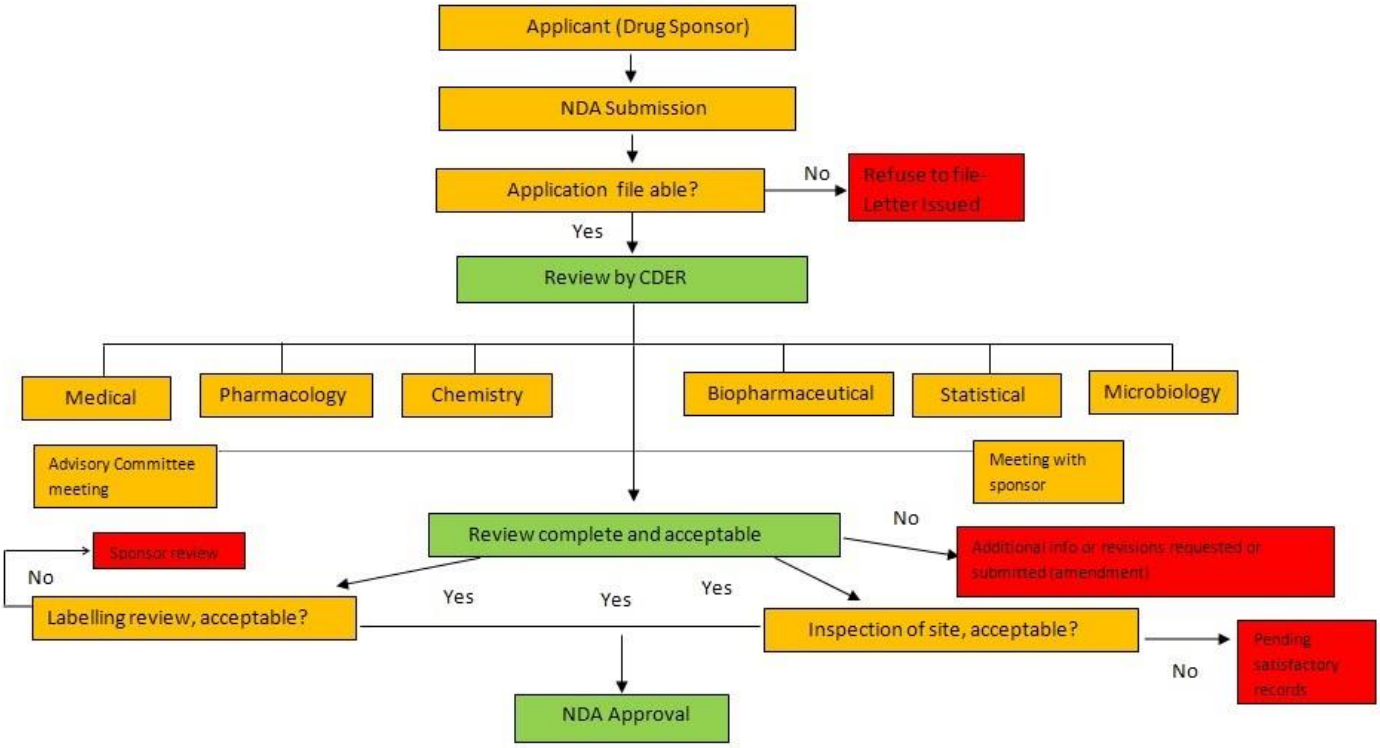
PERCUTANEOUS ABSORPTION OF DRUGS

- Certain ionic drugs are not absorbed transdermally despite the use of chemical penetration enhancers in the topical formulations.
- Percutaneous absorption of such drugs can be affected by novel techniques such as –
  1. **Iontophoresis –** Iontophoresis drug delivery implies delivery of ionic drugs into the body by means of an electric current.
  2. **Phonophoresis** – Phonophoresis is defined as the movement of drug molecules through the skin under the influence of ultrasound.

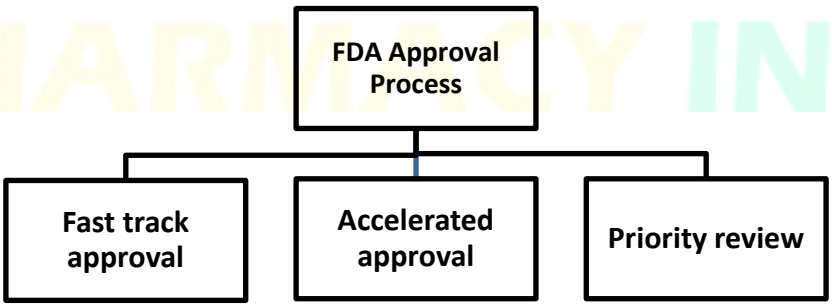
NEW DRUG DEVELOPMENT AND REVIEW PROCESS

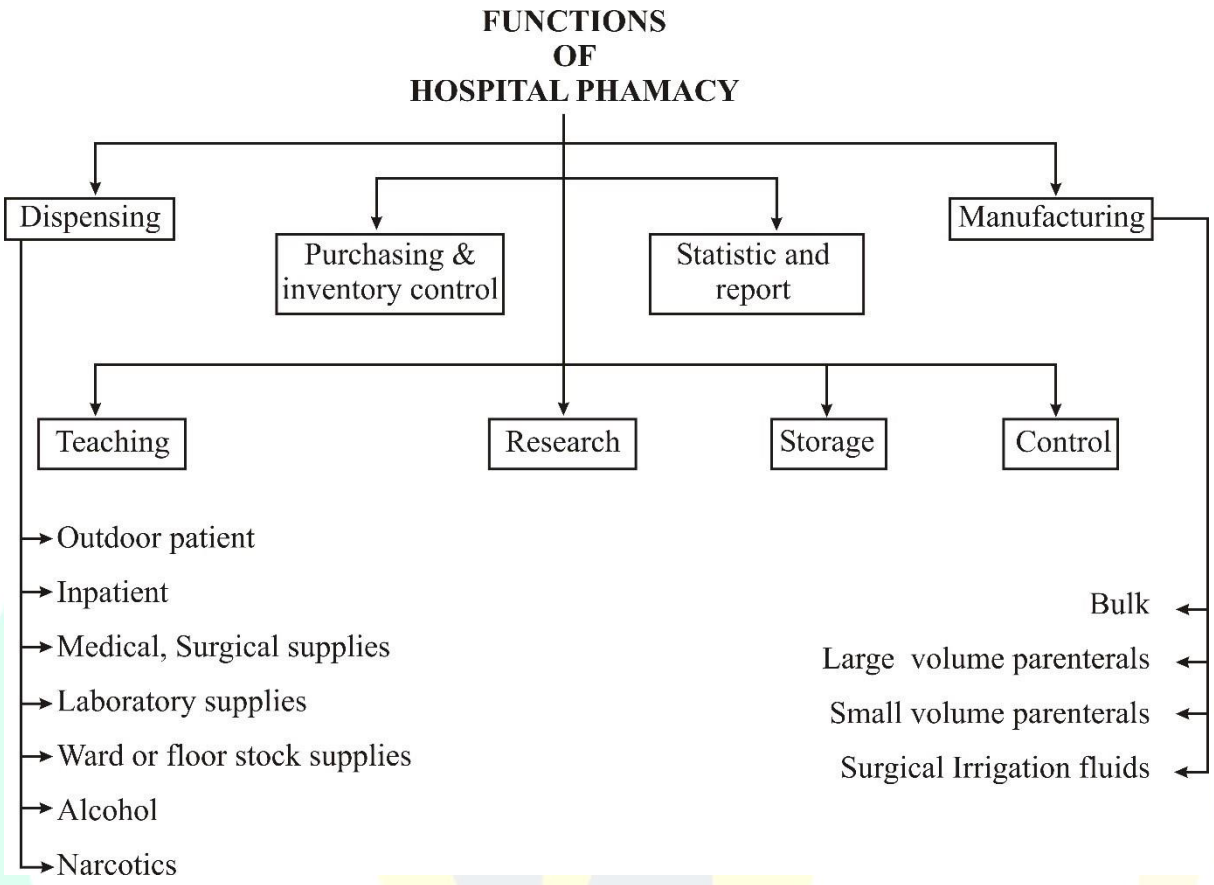


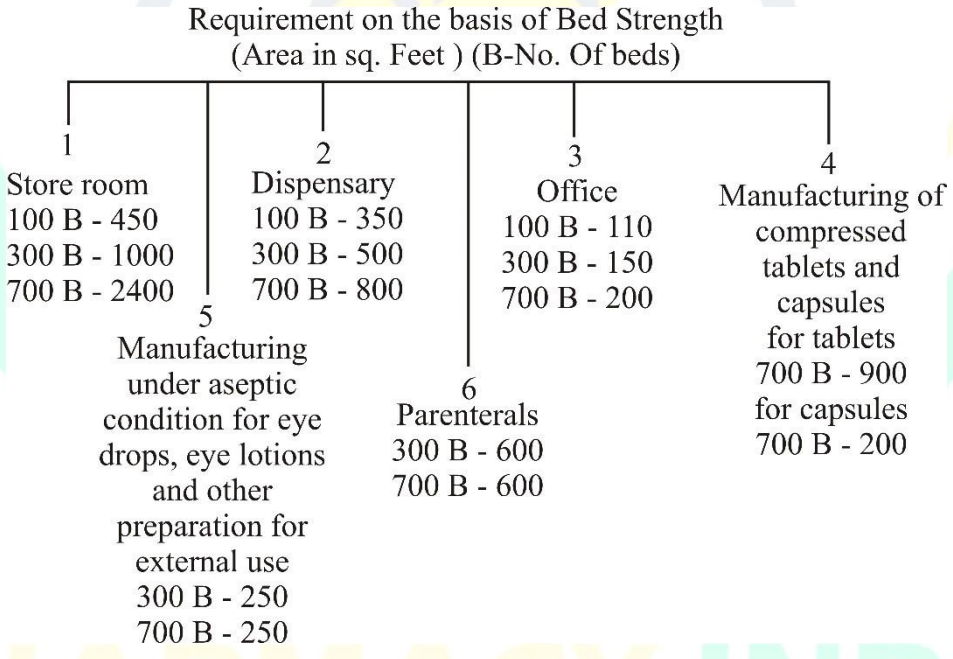
NDA REVIEW PROCESS



FDA Approval Process







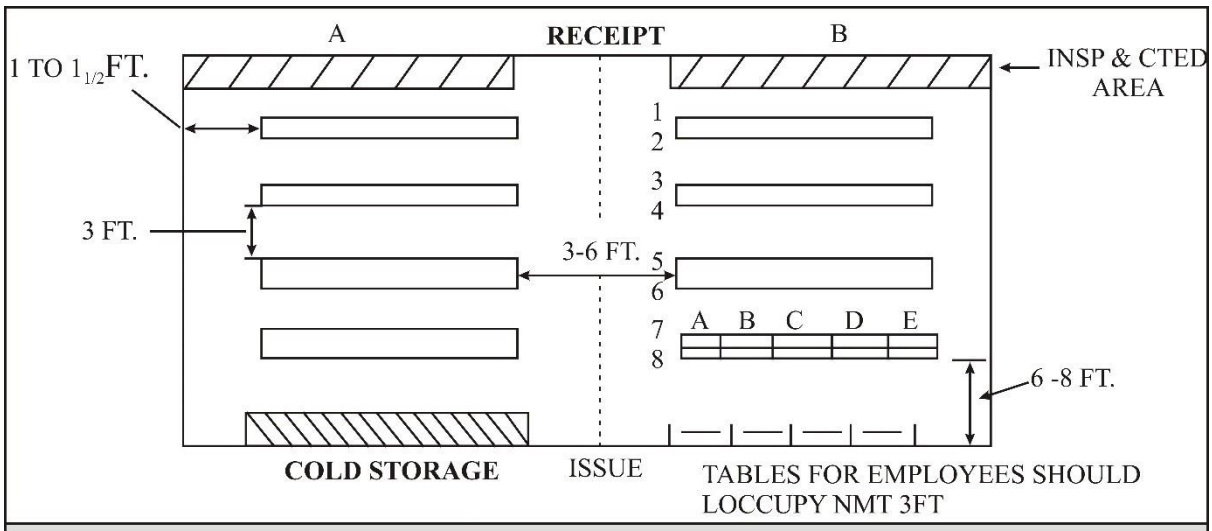


Fig: Layout of a store

Types of Material Stocked

- Poisons , Narcotics & psychotropic & schedule X drugs should be stored separately under lock & key.
- Vaccines and other thermolabile drugs are required to be stored at cold stores 2 C – 10 C.
- Antibiotics , vitamins , liver preparations etc , should be stored at cool temperature (15 C to 20 C)

STORAGE CONDITIONS		
CONDITIONS	**TEMPERATURE**	**EXAMPLES**
Cold storage	2 C – 8 C	Sera , vaccines , whole human blood , normal human plasma , insulin preparation etc.
Cool temperature	8 C – 25 C	• Penicillin preparartion , tetracycline preparations etc. • Vitamin preparations (A, B1, B2 , B6 , C , D) • Vitamin K injection • Vitamin K preparations • Heparin injection • Anaesthitic ether
Room temperature	Temperature prevailing in working area	
Warm	30 C – 40 C	
Excessive heat	Above 40 C	

Inventory Control -Drug store management is based on principles of a inventory control.

Techniques of Inventory controls

The commonest and most widely used tools and techniques which are applied fro – planning , acquisition , storage movement and control of materials in a hospital are –

<table>
<tr><th>S.NO</th><th>TOOLS & TECHNIQUES</th><th>COMMENT</th></tr>
<tr><td>1</td><td>A.B.C analysis</td><td>Basic tool with selective approach for concentration upon item .according to this items classified into 3 category
<table>
<tr><th>Class</th><th>% of Item</th><th>% of Annual Expenditure</th></tr>
<tr><td>A</td><td>10-15</td><td>70-80</td></tr>
<tr><td>B</td><td>20-25</td><td>15-20</td></tr>
<tr><td>C</td><td>60-70</td><td>5-15</td></tr>
</table></td></tr>
<tr><td>2</td><td>V.E.D. analysis
(V = Vital)
(E = Essential)
(D = Desirable)</td><td>VED analysis is based on the importance of the item and its effect on the functioning and efficiency of hospital.
• Vital drugs – These are those drugs whose absence can not be tolerated
• Essential Drugs – these are those drugs without which hospital can function but may affect the quality.of service.
• Desirable Drugs – These are those drugs whose absence will not affect the functioning of hospital.</td></tr>
<tr><td>3</td><td>EOQ (Economic Order Quantity)</td><td>It is the quantity of material to be ordered at one time which minimizes the cost</td></tr>
<tr><td>4</td><td>Lead time</td><td>It is the time taken between the placing of order and receipt of drugs to the departments. Longer the lead time the larger the safety stock.</td></tr>
<tr><td>5</td><td>Buffer stock</td><td>Buffer stock is used in emergency to meet the unforeseen demands.
Buffer stock = (maximum consumption rate /day average – consumption rate / day) x lead time</td></tr>
</table>

Drug distribution system

Out Patient services – it refers to patients not occupying the bed in a hospital clinics .Out patient is known as O.P.D

Hospitals generally break down their out patient load into three categories

Emergency	Person given emergency or accidental care for conditions which require immediate medical attention.
Referred out patient	He is referred directly to out patient department by his attending medical practioner for specific treatment
Primary care	It describes range of services adequate for meeting the great majority .
Ambulatory patient	An ambulatory patient is able to walk and since outpatient receive primary health care and walk off , they are wrongly called ambulatory patients .majority of the outpatients are ambulatory.

STERILISATION

- **Sterilization** is a process in which all viable life forms are either killed or removed.
- **Aseptic technique:** Procedure that exclude the excess of viable microorganisms into the products.
- **D-Value or Decimal Reduction Time**: Time in minutes at any defined temperature to destroy 90% of viable organism.
- **Z-value or Thermal Destruction Time:** Number of degree of temperature change to produce a tenfold change in D-value.

7. Salicylates	Do not take on empty stomach
8. Chewable Antacid Tablets	Do not swallow, Chew them.
9. Ophthalmic Preparation	If there is itching or burning, the patient is advised to discontinue use or consult the physician.

Normal Values Showing Hematologic Parameteres

TYPE OF PARAMETER	MEN	WOMAN	CHILDREN
1. R.B.C Count	4.5 to 5.5 Million/mm3	3.5 Million/mm3	4.00 to 5.5 Million/mm3
2. W.B.C. Count	Normal range is from 4000-11000 cell		

W.B.C differential analysis gives the distrubution of five major leucocytes:

W.B.C.	% COUNT	ACTURE COUNT
i. Basophils	0-1%	0-100
ii. Eosinophil	1-4%	40-400
iii. Monocytes	4-8%	160-800
iv. Lymphocytes	23-35%	1000-3500
v. Neutrophils	60-70%	2500-7000

TYPE OF PARAMETER	MEN	WOMAN	CHILDREN
3. Thrombocytes (Platelets) The normal range for plateletes is 1,50,000 to 3,00,000 / mm3			
4. Hemoglobin			
	13-18 g/dl	11.5-16.5g/dl	7.5-14.5g/dl
5. E.S.R	0-15±1	0-20±1	0.13±1 mm/1 hr
6. Clotting time of Blood – Clotting time is 4-9 minutes at 37°C			

Abnormal variations appear in the urine sample whenever there s pathological condition of the body. The following table shows the small constituents and their related disorders.

ABNORMAL CONSTITUENT	DISORDERS
1. Sugar (glucose)	Diabetes mellitus, endocrine disorder
2. Proteins (Albumin) Normal (50-80 mg/L)	If albumin is present in urine, it can be due to kidney damage
3. Bile pigments like bilirubin	Jaundice
4. Ketone bodies (Acetone, acetoacetic acid, normal (3-15 mg in 24 hrs)	Diabetes mellitus, Starvation, ketosis
5. Blood cells	Haematuria, T.B., cancer, acute inflammation of urinary organs, haemolysis.

Generally urine is examined physically, chemically and microscopically. Various physical tests like volume, appearance, pH, specific gravity are performed to obtain basic information of certain systemic diseases.

TEST	NORMAL VALUE	RELATED DISORDERS
1. Volume	700-2500 ml (in adults)	Increase in -Polyuria -Diabetes millitus, -Diabetes insipidus Decrease -Diarrheea

Drug Interactions Involving Over The Counter Preparation and Common Diet-Drug Interactions

DRUG/DIET	INTERACTING DRUG	DRUG INTERACTION
1. Antacid like sodium bicarbonate, sodium citrate	Salicylates, phenobarbitone	Increased elimination due alkalinization of urine.
2. Antacids (Aluminium salts)	Iron	Decreased iron absorp tion.
3. Caffeine	Anti-inflammatory drugs-Aspirin, in- domethacin, pheny butazone	Increased anti-inflam - matory action.
4. Ethanol	Folic acid	Ethanol may cause folk acid deficiency due R reduced folate absorption.

DIET	INTERACTING DRUG	DRUG INTEACTION
Ethanol	Paracetamol	Enhanced hepato toxicity of paracetamol.
Alcohol	Aspirin	Synergistic effect of alcohol and aspirin on the mucosal coating of stomach.
Aspirin	Indomethacin	Reduced absorption of indomethacin from G.I tract.
Aspirin	Penicillin	Reduces the elimination of penicillin from the body.
Almond, dairy products	Tetracyclines, antibiotics	Reduced therapeutic ef fect, increased gas trointestinal disturban ces.
Q. Cold beverage, aerated	Penicillin G Cloxacillin, Erythromycin	Therapeutic effect is decreased in acidic en vironment due to decomposition of drug.
1. Curd	Tetracycline	Reduce therapeutic effect.
2 Fruit juices	Cloxacillin Erythromycin Penicillin G	Therapeutic effect is decreased in acidic environment due to decomposition
3. Green vegetable	Antibiotics	Reduced therapeutic ef fect and increased gastrointestinal distur bance.
4. Sugar	Hypoglycaemics	Blocks drug action
5. Leafy vegetable	Anticoagulants	Anti-coagulant gets cancelled effect

List of the Drugs Administered to the Mother and their Effect on the Foetus

DRUGS (PREGNANT WOMEN)	CAN LEAD TO (IN FOETUS)
A. ANALGESICS	
1. Narcotics	1. Withdrawl syndrome
2. Salicylates	2. Decreased hyperbillirubin 1. Increased structural abnom 2. Platelet dysfunction 3. Decreased factor XII
B. ANAESTHETICS	
1. General	Respiratory depression
2. Local	Respiratory depression, bradycata Acidosis, meth hemoglobinsma
C. ANTIBIOTICS	
1. Isoniazid	Encephalopathy
2. Nitrofurantoin	Haemolysis

Cyathus vinousus	cyath, vin.	A wineglass
E lacte	e lact.	With milk
Ex aqua	ex aq. Isin	With water
Dexter	dext.	Right
Laevus	laev.	Left
Parti affectae applicandus	p.a.a. lino	To be applied on the affected part
Partibus affectis	p.a.	To the affected parts
Sinister	sinist.	Left
Auri	auri	To the ear
Naso		To the Nose
Oculis	ocul.	To the eyes
Pro oculils	pro ocul.	For the eyes

LATIN TERM	ABBREVIATION	ENGLISH MEANING
Time of Administration of Application		
(a) Times per day		
Semel in die	sem. in die	Once a day
Bis in die, Bis die Ter in die,	b.i.d., b.d.	Twice a day
Ter die	t.i.d., t.d.	Three times a day
Quater in die	q.i.d., q.d.	Four times a day
Sexies in die	sex in d.	Six times a day
Bis terve in die	b.t.i.d	Two or three times a day
Ter quaterve die	t.q.d.	Three or four times a day
Quotidie	ter quot.	Daily
Ter quotidie	jonb quot.	Three times daily
(b) Parts of the Day		
Primo mane	prim. m.	Early in the morning
Mane	m.	In the morning
Omni mane	o.m.	Every morning
Jentaculum	jentac.	Breakfast
Nocte	n.	At night
Inter noctem	inter noct.	During the night
Omni nocte	o.n.	Every night
Hora somni	h.s.	At bedtime
Nocte et mane	n. et. m.	Night and morning
Nocte maneque	n.m.	Night and morning
Hac nocte	hac noct.	To night
(c) Hour time		
Omni hora, Quaque hora	o.h., qq.h.	Every hour
Omni quarta hora, Quaque quarta hora	o.q.h. qq.q.h.	Every fourth hour
Singulis horis	sing. hor.	Every hour
Alternis horis	alt. hor.	Every two hours
Tertis horis	tert. hor.	Every three hours
Quartis horis	quart. hor.	Every four hours
Sextis horis	sext. hor.	Every six hours

PHARMACEUTICAL ENGINEERING

SIZE REDUCTION

DEFINITION

It is a unit operation in which reduction of materials to coarse particle or to fine powder before formulate into suitable dosage form.
Comminution, grinding, milling, pulverizing are other terms used for size reduction.

SPECIFIC OBJECTIVES

1. It increases surface area of the particle, hence increases rate of dissolution and absorption and bioavailability, and therefore increases therapeutic efficacy.
2. It facilitates mixing and drying by milling by increase surface area.
3. In ophthalmic, aerosol, inhalation and parenteral preparation where controlled particle size is required which facilitate by size reduction.

Factors affecting size reduction

1. Hardness: Harder the material, more difficult to reduce its size.
2. Toughness: Soft but tough material creates problem in size reduction and its toughness is reduced by decrease temperature.
3. Stickness: Gum and resinous substances cause problem in size reduction.
4. Moisture content: <5% moisture suitable for dry grinding and >50% for wet grinding.

TYPE OF MILL	ACTION	PRODUCT SIZE	USED FOR	NOT USED FOR
Cutter	Cutting	20- to 80-mesh	Fibrous, Crude animal and vegetable drugs	Friable materials
Revolving	Attrition and impact	20- to 200-mesh	Fine grinding of abrasive material	Soft material
Hammer	Impact	4- to 325 - mesh	Almost all drugs	Abrasive material
Roller	Compression	20- to 200-mesh	Soft material	Abrasive material
Attrition	Attrition	20- to 200- mesh	Soft and fibrous material	Abrasive material
Fluid-energy	Attrition and impact	1 to 30µm	Moderately hard and friable material	Soft and Sticky material

MECHANISM OF SIZE REDUCTION

METHOD/ PRINCIPLE	COMMON EQUIPMENT	APPROX PARTICLE SIZE (MICRON)
Cutting	Cutter mill	100–80000
Compression	Roller mill	50–10000
Impact	Hammer mill	50–8000
Attrition	Colloid mill, Roller mill	1–50
Impact and Attrition	Ball mill, Fluid energy mill	1–2000

SIZE SEPARATION

Particle Size Separation by Different Method

SIZE SEPARATION METHOD	PARTICLE DIAMETER (MICRON)
Sieving	5–10000
Sedimentation	5–1000

HUMIDITY MEASUREMENT

1. **Gravimetric Method**–It is the most accurate mean for humidity measurement. But it is slow and cumbersome.
   Procedure–A known amount of air is passed over a previously weighed moisture-absorbing chemical such as Phosphorous Pentaoxide and the resultant increase in weight of chemical is measured.
2. **Temperature Based**–These methods are rapid comparative to Gravimetric method.
   - Wet-bulb temperature determination method– Instrument used is Sling Psychrometer.
   - Dew point temperature determination method
3. **Hygrometer**–It uses certain materials whose properties changes on contact with air of different relative humidities.
   - Loss on Drying (LOD)–It is a method of expressing water content in solids on wet weight basis.
   - % LOD = (Weight of water in sample/Total weight of wet sample) × 100
   - LOD of wet sample is often determined by moisture balance.

Moisture Content (MC)-

- % MC = (Weight of water in sample/weight of Dry sample) × 100
- LOD values can vary in any solid-fluid mixture fromslightly above 0% to slightly below 100% but MC values can change from slightly above 0% and approach infinity.

THEORY OF DRYING

1. **Equilibrium moisture content (E.M.C.)**
   - It is the number of pounds of water per pound of dry solid at any given temperature and humidity.
   - This E.M.C. is low for non-porous solids and zero for sand, china clay and higher for fibrous and colloidal organic substances.
2. **Bound moisture (bound water)** -It is present as liquid in solids which exert vapour pressure less than of pure liquid at same temperature. The substance containing bound water is called Hydroscopic.
3. **Free moisture content-**It is amount of water removed from wet solid under given condition.
   Free moisture content = Total pound of water of dry solid–E.M.C.
4. **Unbound moisture**
   It exerts its full vapour pressure and held in voids of solid. Bound and Unbound water depend on property of material itself while E.M.C depend on particular conditions.

DRYER EQUIPMENTS (ACCORDING TO ITS PRINCIPLE)

A. Convection dryer

NAME OF DRYER	CHARACTERISTICS AND USED FOR	NOT USED FOR
Tray dryer (shelf dryer)	Drying of chemical, powder, crude drugs, equipments, tablet granules.	Continuous process only batch process.
Fluidized Bed dryer (FBD)	Short Drying time (30 min), drying of tablet granules, plastic material, coal, inorganic salt, in fertilizer also.	It produces explosion and attrition. Only for batch process.
Tunnel dryer (belt or conveyor dryer)	Drying of paraffin wax, gelatin, soap	Not for Batch process.
Rotary dryer (modified tunnel)	Drying of powder and granular solid.	Not for Batch process.

Crystallization equipment: According to super saturation method

CRYSTALLIZER	METHOD	USES AND CHARACTERISTICS
Tank Crystallizer	Cooling	Globar salts, synthetic sponge, for only batch process
SwensonWalker Crystallizer	Cooling	It has spiral agitator run at 7 rpm for to prevent accumulation of crystal.

CRYSTALLIZER	METHOD	USES AND CHARACTERISTICS
Krystal crystallizer	Cooling	
Krystal evaporator/ OLSO crystallizer	Evaporation	
Magma crystallizer	Evaporation	Propeller agitator used to lift magma. Not used when refrigeration temperature required to obtain good yield or solution has large B.P elevation and not used for salt which has flat solubility curve.

EVAPORATION

It is simply vaporization from surface of liquid. Means the removal of liquid from solution by boiling the liquor in suitable vessel and withdrawing vapour, leaving concentrate liquid residue and heat supply is latent heat of vaporization.

Factors Affecting Evaporation

1. **Surface area of liquid:** Greater the surface exposed to evaporation higher will be the rate of evaporation like in film evaporator.
2. **Temperature:** Higher the temperature, higher will be evaporation.
3. **Agitation:** It breaks scum or layer and increase rate of evaporation.

EVAPORATION EQUIPMENTS (EVAPORATOR)

EVAPORATOR	PRINCIPLE	CHARACTERISTIC AND USE
Evaporating pan	Natural circulation	It contain liner as pan and use for aqueous and thermo-stable liquor
Vacuum pan	Natural circulation	Use for thermo labile materials.
Evaporating stills	Natural circulation	Use for thermo labile materia
Horizontal tube evaporator	Natural circulation	Use for liquor that do not crystallize and not form scale and non viscous.
Vertical tube evaporator (CALENDRIA)	Natural circulation	Use in sugar industry, concentrate cascara extract and not for foamy liquid.
Vertical tube (basket type) evaporator.)	Natural circulation	Use for sugar, salts and heavy chemical.

EVAPORATOR	PRINCIPLE	CHARACTERISTIC AND USE
Falling film evaporator	Natural circulation	Use for viscous liquid and when high percentage of evaporation is required.
Wiped/Rotary film evaporator (AHSO LUWA)	Natural circulation	Its modified falling film evaporator Use for highly viscous liquid.

CENTRIFUGATION

CENTRIFUGATION

It is a unit operation employed for separating the constituents present in dispersion with aid of centrifugal force.

CLASSIFICATION OF CENTRIFUGE

TYPE	CHARACTERISTIC AND USE
Sedimentation centrifuge	Used for blood plasma separation, preparation of bacterial enzyme, manufacturing of insulin. Used for clarification of olive and fish liver oil
Filtration centrifuge	Used for obtained anhydrous product.
Ultracentrifuge	Used in colloidal research for separate solid from liquid. r.p.m-85000
Angle centrifuge	45–50 angle
High speed centrifuge	r.p.m-10000

EQUIPMENT

NAME	PRINCIPLE	CHARACTERISTICS AND USES
Perforated basket type	Filtration	Used for separating crystalline drug like aspirin.
NonPerforated basket type	Sedimentation	Used when deposited solids offer high resistance to flow.
Short cycle automated batch centrifuge	Filtration	Semi-continuous type.
Horizontal centrifuge	Sedimentation	Used for slurries contains 0.5 to 50% solids.
Super centrifuge	Sedimentation	Used for separating liquid phase of emulsion.
De Laval Clarifier	Sedimentation	Used in manufacture of antibiotics Separation of cream from milk, concentration of rubber wax removing solids from oils, inks.

RADIATION SOURCE	WAVELENGTH	APPLICATION
IR lamp	1 µm	High intensity radiation
Ceramic rods and panels Heated by gas or electricity	2 to 4 µm	Pharmaceutical purpose, thermo labile substance.

HEAT AND MASS TRANSFER

Heat flow from high region temperature to lower region temperature. According to principle of thermodynamic, whenever physical or chemical transformation occurs, heat flows into or leaves the system.

MECHANISM

1. **Conduction -** When heat flow in body is achieved by transfer of momentum of individual atoms or molecule without mixing. This mechanism is based on Fourier's law.
   Fourier's law - It states that the rate of heat flow through a uniform material is proportional to the area and temperature drop and inversely proportional to length of path of flow.

FLOW OF FLUIDS

It is the flow of substance that does not permanently resist distortion.
Manometers - These are the devices which are use for measuring the pressure difference.
1. Simple manometer: It helps in measuring the consumption of gases in the chemical reaction.
2. Differential manometer (two-fluid U-tube manometer): It useful for measuring small gas pressure.
Critical velocity - It is defined as average velocity of any fluid at which viscous flow changes into turbulent flow.
Reynolds number - It is used for measurement and type of flow determination.
Re = D× u × density of liquid/Viscosity of fluid
D = diameter of pipe, u = Average velocity
When Re<2000 then flow is laminar or viscous or streamline
Re>4000 then flow is turbulent
Re is 2000–4000 then flow is laminar or turbulent
Bernoulli's Theorem - When principle of conservation of energy is applied to the flow of fluids, the resulting is called as Bernoulli's Theorem.

MEASUREMENT OF RATE OF FLOW OF FLUIDS

1. Direct weighing or measuring
2. Hydrodynamic methods

NAME	CHARACTERISTIC AND USE
Orifice meter (variable head meter)	Normally used for testing purpose like for steam, lines.
Venturi meter (variable head meter)	Used in on-line installation and for measurement of gases.
Pitot tube (insertion meter)	It measures the velocity at one point only.
Rotameter (area meter)	It use in bulk drugs chemical industries and in fermenters for control of air supply

Valves - These are used to control the rate of flow of fluids in a pipeline.

NAME	CHARACTERISTIC AND USE
Plug Cocks valve	Use for handling compressed air
Globe valve	It contain seat ring and used in
Gate valve	It contains inclined seat type of gate.
Diaphragm valve	The rubber diaphragm coated with PTFE (polytetra fluoroethylene) is used. Used for fluid containing suspended solids and in production of sterile product.

Pumps - These are mechanical devices use to increase the pressure energy of a liquid.

A. **Reciprocating pumps:-** These are used for injection of inhibitors in polymerization units and corrosion inhibitors to high pressure system.

NAME	CHARACTERISTIC AND USE
Piston pump	Used in peristaltic and HPLC pumps and for spray system in sugar coating and film coating operations.
Plunger pump	Used for handling liquids at high pressure. Used for transport viscous liquid and liquid contain suspended solids.
Diaphragm pump	Used in transporting liquid containing solids. Hazardous, toxic and corrosive liquids can also handle.

- **Vacuoles →**
  - Vacuoles are sap- filled vesicles in the cytoplasm. These are surrounded by a membrane called tonoplast.
  - It facilitates the rapid exchange of solutes aid gases between the cytoplasm and adjoining fluids.

TISSUE CULTURE

- Tissue culture is the method of 'in vitro' culture of plant or animal cells, tissue or organ – on nutrient medium under aseptic conditions usually in a glass container.
- Tissue culture is sometimes referred to as 'sterile culture' or 'in vitro' culture.
- **Single cell cloning →** Culture of single cell.
- **Explant →** portion of the plant
- **Clone →** Culture derived from a single explant
- **Inoculum →** A small amount of substance containing bacteria from a pure culture which is used to start a new culture or to infect an experimental animal.

TYPES OF CULTURES

- **Plant culture →** If a seedling is cultured
- **Embryo culture →** an embryo is cultured
- **Organ culture →** shoot tips, root tips, leaf primordia, flower primordia or immature fruits are cultured.
- **Callus culture →** culture of unorganized tissues from cell proliferations of segments of plant organs is called callus culture.
- **Suspension culture/ cell culture →** When a single cell or small cell aggregate in a dispersed state is cultured.

❖ **Somatic hybridization →** The fused protoplast is grown in vitro with an aim to obtain a hybrid plant. So, the in vitro fusion of plant protoplasts derived either from somatic cell of same plant or from two genetically different plant.

❖ **Somato-gametic hybridization →** The protoplasts from vegetative cell and gametic cell are fused.

❖ **Somatic embryogenesis →** the process in which a single cell or a small group of cells follow a developmental pathway that leads to reproducible regeneration of non-zygotic embryos which are capable of producing a complete plant.

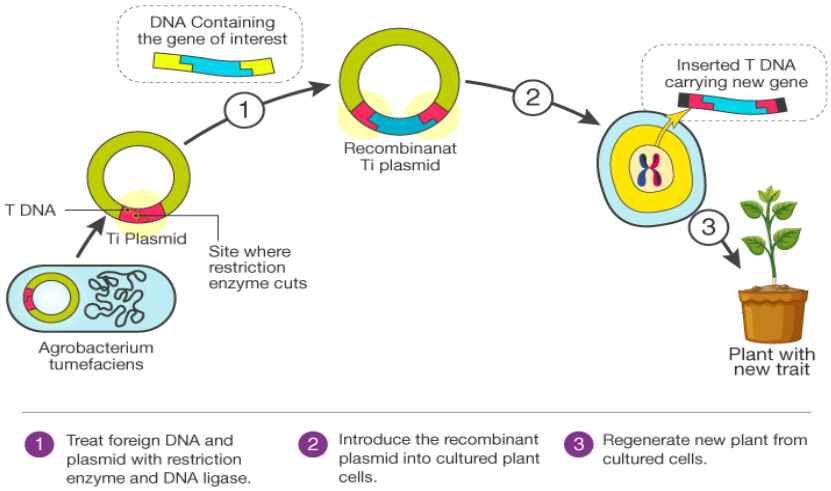
ENZYME IMMOBILIZATION

- Immobilization of enzymes (or cells) refers to the technique of confining/anchoring the enzymes (or cells) in or on an inert support for their stability and functional reuse.
- By employing this technique, enzymes are made more efficient and cost-effective for their industrial use.
- **Methods of immobilization**

Physical methods-	**Chemical methods-**
➢ Entrapment ➢ Adsorption ➢ Microencapsulation	➢ Covalent bonding ➢ Cross-linking

- **Applications of immobilized enzymes**
  - ✓ Manufacture of commercial products
  - ✓ Production of L-amino acids
  - ✓ Production of high fructose syrup
  - ✓ Glucose isomerase
  - ✓ Biochemical analysis

1. Isolation of genetic material
2. Cutting of DNA at specific locations
3. Recombinant DNA formation
4. Cloning of DNA



- **Enzymes used in recombinant DNA technology**

1. **DNA ligase** →The enzyme DNA ligase joins the DNA fragments with cloning vector.
2. **Reverse transcriptase:**
   - RT is used to synthesize complementary strand (cDNA) from mRNA template.
   - It is also known as RNA dependent DNA polymerase.
3. **Restriction endonuclease**
   - Restriction endonuclease enzyme recognize and cut DNA strand at specific sequence called restriction site.
   - There are 3 types of restriction endonuclease:
     - **Type I Restriction endonuclease** → It has both methylation and endonuclease activity.
     - **Type II Restriction endonuclease** → It cuts DNA at restriction site itself
     - **Type III Restriction endonuclease** → It cuts DNA about 25bp away from restriction site.
4. **Terminal transferase** → It is the enzyme that converts blunt end of DNA fragments into sticky end.
5. **Nuclease** →
   - The enzyme nucleases hydrolyses the phosphodiester bond on DNA strand creating **3'-OH** group and **5'-P** group.
   - Nucelase are of two types; endonuclease and exonuclease
6. **DNA polymerase** → DNA polymerase is a complex enzyme which synthesize nucleotide complementary to template strand. It adds nucleotide to free 3′ OH end and help in elongation of strand.
7. **Ribonuclease-H (RNase H)** → RNase-H removes mRNA from DNA-RNA heteroduplex and that mRNA is used to synthesize cDNA.
8. **Alkaline phosphatase** → removal of terminal phosphate group from 5′ end.
9. **Polynucleotide kinase** → It adds phosphate group from ATP molecule to terminal 5'end after dephosphorylation by alkaline phosphatase.

POLYMERASE CHAIN REACTION

- PCR or Polymerase Chain Reaction is a technique used in molecular biology to create several copies of a certain DNA segment.
- This technique was developed in 1983 by Kary Mullis, an American biochemist.
- **Principle of PCR**