

Chapter 1

Pharmaceutics

Pharmaceutics- Theory

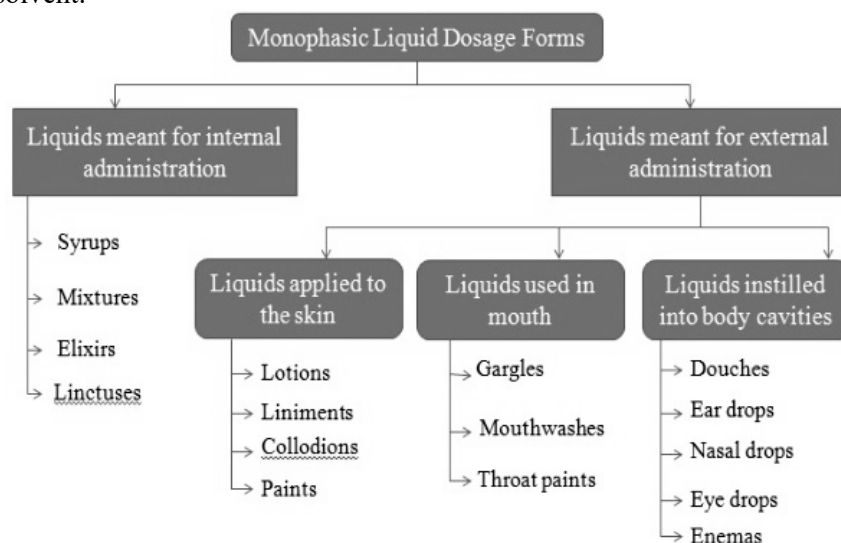
1.1 Liquid Dosage Forms

Liquid dosage forms are essentially pharmaceutical products in the form which involves a mixture of active drug components and nondrug components (excipients). Liquid form of a dose of a drug used as a drug or medication intended for administration or consumption.

- It may be defined as “A solution is a liquid-preparation that contains one or more soluble chemical substances dissolved in a specified solvent”
- Liquid dosage forms are intended for External, Internal or parenteral use.
- The component of the solution which is present in a large quantity is known as “SOLVENT” where as the component present in small quantity is termed as “SOLUTE”
- They mainly classified in to two category namely as –
 - (i) Monophasic Liquid dosage forms.
 - (ii) Biphasic liquid dosage forms.

Monophasic Liquid Dosage Forms

Monophasic dosage form refers to liquid preparation containing two or more components in one phase system; it is representing by true solution. A true solution is a clear homogenous mixture that is prepared by dissolving solute in a suitable solvent.



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Solubility:

Type	Solubility
Soluble	From 10 to 30 part
Freely Soluble	From 1 to 10 part
Very Soluble	Less than 1 part
Slightly Soluble	From 100 to 1000 parts
Very slightly Soluble	From 1000 to 10000 parts
Sparingly Soluble	From 30 to 100 parts
Insoluble	more than 10000 parts

- A solution should be designed in which the solubility of the solute is not exceeded even at Temperature low as 4°C.
- **pH:** The pH of solution greatly affect the solubility of a solute.
- **Co-solvency:**
 - The mechanism responsible for solubility enhancement through co solvent that it works by reducing the **interfacial tension** between the predominately aqueous solution and the hydrophobic solute.
 - The example of cosolvents is ethanol, Sorbitol, glycerine, propylene, glycol, and several members of polyethylene glycol.
- **Dimethylacetamide** is used as cosolvent in **parenteral** products.
- **Dielectric Constant**
 - The absolute solubility of a solute may vary in two different solvents of the same dielectric constant.
 - Every solute shows a maximum solubility in any given solvent system, at one or more specific dielectric constant
 - The solubility profiles as a function of dielectric constant appears to be similar for a solute in different solvent systems.
- **Solubilizing agent**-The lyophobic surface active agents with HLB value higher than 15 are act best solubilizing agents.
- **Preservatives:**
 - **Acidic preservatives** usually used in oral preparations.
 - **Neutral, mercurial, and quaternary ammonium compounds** widely used in ophthalmic, nasal and parenteral products.
 - The **neutral preservatives** are volatile alcohols.
 - Mercurial, and quaternary ammonium compound are good preservatives but subject to a variety of **incompatibilities**.
 - Methyl and propyl paraben used together in a ratio of **10:1** respectively
 - Syrup containing 85% of sugar act as **self-preservative** by virtue of their osmotic effect on microorganisms.
 - Syrup containing less than 85% of sugar but having sufficient quantity of polyols also have osmotic effect on microorganisms.

Table Some pharmaceutical used preservatives and their usual concentration

Class	Preservatives	Concentration
Acidic	Phenol	0.2-0.5
	Chlorocresol	0.05-0.01
	O-phenyl of Para benzoic	0.005-0.01
	Alkyl ester of para benzoic acid	0.1-0.3
	Benzoic acid and its salts	0.5-1.0
	Boric acid and its salts	0.05-0.2
	Sorbic acid and salts	0.06-0.2
Neutral	Chlorobutanol	0.5
	Benzy alcohol	1.0
	β-phenyl ethyl alcohol	0.2-1.0
Mercurial	Thimerosal	0.001-0.1
	Phenyl mercuric acetate and nitrate	0.002-0.005
	Nitromserosol	0.001-0.1
Quaternary	Benzalkonium chlorides	0.004-0.02
AmmoniumCompounds	Cetylpyridinium	0.01-0.02

- **Sweetening agents:**

- Sucrose 85% concentration is widely used as sweetening agents. It is chemically and physically stable in a pH range of **4.0 to 8.0**. It is widely used in conjunction with sorbitol, glycerine, and other polyols to reduce the tendency of sucrose to crystallize.
- Liquid glucose is prepared by the partial hydrolysis of **starch with strong acids**. Its main components are **dextrose with small amounts of dextrin and maltose**.
- Saccharine is also widely used as sweetening agents and it is approximately **250-500** times sweetener. Than sucrose. It is **having a bitter after taste**.
- **Aspartame** is another synthetic sweetening agents and approximately **200 times** sweetener than sucrose and **has no bitter after taste**. It is the **methyl ester aspartic acid and phenylalanine**. It is very stable in dry powder but in aqueous solution it is stable between **pH 3.4 – 5.0** and refrigerated temperature. Its taste property can be improved using sodium **bicarbonate, gluconate salt, and lactose**.

- **Viscosity control:** The viscosity of a solution can be improved by a) increasing the sugar concentration b) incorporating viscosity controlling agents like polyvinylpyrrolidone or cellulose derivatives like methyl cellulose of sodium carboxy methyl cellulose etc.

Biphasic Liquid Dosage Forms

- The liquid which consist of two phases are known as a biphasic liquid dosage forms.
- They are sub categorized into two different forms namely as –
 - (i) Emulsion
 - (ii) Suspension

Emulsion

Emulsion is a biphasic liquid preparations containing two immiscible liquid (Continuous Phase & dispersed phase) made miscible. The liquid which is converted into minute globules is called as dispersed phase & the liquid in which the globules are dispersed is called the continuous phase. 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.

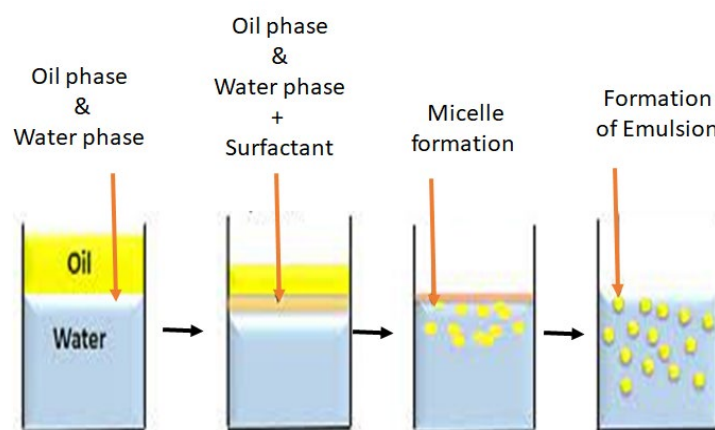


Fig Representation of formation of emulsion.

- An emulsion is
 - (a) A thermodynamically unstable dispersed system
 - (b) Consisting of at least two immiscible liquid phase
 - (c) Stabilized by the presence of emulgent (s)
- Ordinary emulsion is white or off-white in colour. This is due to the particle diameter of the dispersed phase generally extends from about 0.1 to 10 μm , and the dispersed globule diameter is higher than the wave length of light.
- An assembly of closely packed monodisperse spherical droplets as the internal phase can occupy no more than approximately 74% of the total volume of the emulsion.
- The dispersed particles having a diameter of less than $\frac{1}{4}$ the wave length of visible light. i.e less than approximately **120 nm**.
- **Type of emulsion:**
 - Oil-in-water (o/w) type of emulsion e.g. - **Milk & Vanishing cream**
 - Water-in-Oil (w/o) type of emulsion e.g.- **Butter, Cold cream & Salad cream**
 - **Multiple emulsions** or three phase emulsion or emulsion with in emulsion with emulsion. (o/w /o)\. Multiple emulsions may be used for prolongation action of drug action, or intramuscular therapy.
 - **-Micro emulsions:** These may be defined as dispersions of insoluble liquids in a second liquid that appear clear and homogeneous to the naked eye. They contain globules of size about **0.01 μm** .
 - **-Fine emulsions:** normally these have milky appearance and the globule size ranges from **0.25-25 μm** .
- **Determination of emulsion type:-**
The following method are used for of determining the type of an emulsion.

Table Various methods for determination of emulsion type

Test	Observation	Comments
Dilution test	Emulsion can be diluted only with external phase	Useful for liquid emulsion only
Dye test	Water soluble solid dye tints only O/W emulsions and reverse. Microscopic observation usually helpful.	May fail if ionic emulsifier is present.
CoCl₂/filter paper	Filter paper impregnated with CoCl ₂ and dried, (blue) Changes to pink when O/W emulsion is added	May fail if emulsion is unstable or breaks in presence of electrolyte
Fluorescence	Since oil fluorescence under UV light, O/W emulsion exhibit dot pattern, W/O emulsions Fluorescence throughout.	Not always possible
Conductivity	Electric current is conducted by o/w emulsions, owing to presence of ionic species in water	Falls in non-ionic w/w emulsions.

- **Application:**

- Emulsion may be used as
 - Oral preparation
 - Parenteral preparation
 - Topical preparation
- Total Parenteral Nutrition (TPN), a product recently available in the market to maintain debilitated patients in form of emulsion. When **Bicarbonate** added to TPN formulation it causes an incompatibility problem.

- **Mechanical equipment's used for emulsion:**

- Mechanical stirrer, Colloidal mill, Homogenisers and used Ultrasonic devices equipment are used in the preparation of emulsion.
- A homogenizer generally consists of a pump that raises the pressure of the dispersion to arrange of **500 to 5000 psi**.
- The pressure required range in an ultrasonicator 150 to 350 psi.
- Given below are ratio of oil: water: gum for preparing primary of different oil
 1. Fixed oil 4:2: 1
 2. Mineral oil 3:2: 1
 3. Volatile oil 2:2: 1
 4. Oleo-resin 1:2: 1

- **Emulsifying agents:**

- The nature of emulgent is selected for a type of emulsion is based upon Bancroft's rule.
- Bentonite, veegum, graphite, magnesium, hydroxide are the example of finely divided solid particle used as emulgents.
- Cetrimide is a synthetic emulsifying agents.
- Bentonite is an example of inorganic emulsifying agents.
- Surfactants of HLB range 15 to 18 are ideal solubilizing agent's used to form clear emulsions.
- Emulsions made with tween are usually o/w.
- Auxiliary emulsifying agents (Glyceryl monostearate, Stearic acid, CMC sodium, Methyl cellulose, steraryl alcohol) act as thickening agents and help to stabilize the emulsion.

Table Emulsifying agents and their mechanism of action

Emulsifying Agents	Mechanism of Action
Surface active agents (eg. Soaps, Spans, Tweens)	They reduce interfacial tension
Hydrophilic colloids (Accacia, gelatin)	They tend to form a multimolecular film around the globules and prevent coalescence
Finely divided solids (Bentonite, vee gum)	They adsorb at the oil-water interface and form rigid film of closely packed solids and act as a mechanical barrier and prevents the coalescence of globules.

- **Stability:**
 - The physical instability of emulsions is related with phase inversion, creaming or sedimentation, Ostwald ripening and cracking of the emulsion.
 - For a stable emulsion, the phase volume ratio is generally about 52:48.
- **Physical stability markers**
 - (a) Flocculation : It is due to interaction of attractive and repulsive forces
 - (b) Creaming : It is due to density difference between two phases.
 - (c) Coalescence : Agglomeration of particles in emulsion.
 - (d) Breaking : Completely separation of oil and aqueous phase
 - (e) Phase inversion : The change of emulsion type from o/w to w/o or vice versa.

Points to Remember

The factor responsible for cracking or splitting or breaking of an emulsion are

- Centrifuging
- Addition of electrolytes
- Heat
- Freezing
- Bacterial growth
- Addition of a liquid in which both phases soluble
- Addition of a chemical that is incompatible with the emulsifying agent like calcium and magnesium salts to emulsion stabilized with anionic surfactants.
- Addition of higher percentage of alcohol to an emulsion stabilized with hydrocolloids.
- Creaming may occur upward & downward
- According to Stok's law: -
 - The creaming of emulsion is indirectly proportional to viscosity of medium.
 - Rate of settling is directly proportional to particle diameter
- When **sodium chloride** is added to sodium oleate emulsion, the emulsion is destabilized.
- In a macro emulsion the dispersed globules having radius below the range of **10-75nm**.

Suspension

Introduction

A pharmaceutical suspension is a type of disperse system in which one (or more) substance (the dispersed phase) is distributed in particulate form throughout another (the continuous phase)

Formulation additives:

The additives of a suspension formulation such as –

- Vehicles,
- Thickeners,
- Buffers,
- Stabilizers,
- Preservatives,
- Colours and flavours,

In case of suspension formulation of hydrophobic drugs, it is very difficult to disperse the drug particle in aqueous media. The surface of such drug particles is better wetted by the incorporation of a suitable wetting agent having the HLB value 7 to 9. The wetting agents act by reducing the “contact angle” between the spreading liquid and the solid surface of the drug particles help in wetting the particle with vehicle. The contact angle between a liquid and solid may be 0° signifying complete wetting for it may approach to 180° , at which wetting is insignificant.

Dispersing Agents

The agents help in causing the dispersion of the solid particles to be evenly distributed in the suspension. Especially in deflocculated suspension, the individual particle should remain dispersed. In some materials where the quantum of surface charge is not sufficient, the particles tend to come together. To overcome this tendency some material which carry good charge and can get easily absorbed into the

- Dispersed phase particle can be added. These are dispersing agents. Eg. **Darvans, Daxods** etc. They increase the “Zeta potential” considerably, thus discouraging the particles in the suspension to come together.
- The surface of the dispersed drug particles may be charged due to preferential adsorption of a particular ion (cation or anion) or due to ionization of a particular ionisable group attached to the solid surface of the drug particles.
- Naturally a potential known as “Nernst potential” or electro thermodynamic potential is developed at the surface of the solid, which will attract oppositely charged counterion or gegenion in the tightly bound solvent layer around the surface of the solid.
- Now depending upon the number of ions adsorbed at as the surface of the solid and the counterion in the tightly bound solvent layer, the surface of the tightly bound layer may charge.
- The zeta potential is defined as the difference in potential between the surfaces of the tightly bound layer and the electro neutral region of the solution.
- This may be positive, zero or negative Good dispersing agents increase the magnitude of zeta potential there by help the individually dispersed solid particles to retain their individually due to the repulsive force experienced between two approaching particles.

Method of Preparation of Suspension

There are several methods of preparing flocculated suspension. For instance in the preparation of the oral suspension of a drug, clays such as diluted bentonite magma are commonly employed as the flocculating agent. Electrolytes can also act as flocculation agents, apparently by reducing the electrical barrier between the particles of the suspension and forming a bridge so as to link them together.

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Levigation (wet grinding) process followed in small scale manufacturing of suspension where as in industry the mixture is passed through colloid mill to break the clumps and to produce a homogenous suspension.

Suspension containing diffusible Solids

Some insoluble powders are light and easily wettable, hence they readily mix with water and, on shaking, diffuse evenly through the liquid for long enough to ensure even distribution in each dose, such substances are known as diffusible or dispersible solids. Eg. Calcium carbonate, Light kaolin, Magnesium carbonate, Magnesium trisilicate, rhubarb powder etc.

Suspension Containing Indiffusible Solids

Indiffusible solids will not remain evenly distributed in a vehicle long enough to ensure uniformity of dose. The simplest way of correcting the problem is to increase the viscosity of the vehicle by adding a thickening agent. Some examples of indiffusible solids are aspirin, chalk, phenobarbitone, succinylsulphathiazole, sulphadimidine, calamine, hydrocortisone, sulphur, zinc oxide etc.

Suspensions Produced by chemical Reactions

Very occasionally the insoluble active constituent of a lotion etc. is formed by a chemical reaction. A Filter precipitate is obtained if dilute solutions of the reactants are mixed, hence, the reacting substances

Should be dissolved separately in approximately half volumes of the vehicle and the two parts mixed prepared in the manner the precipitate is diffusible and no suspending agents is necessary. An official example of this kind of preparation is zinc sulphide lotion B.P.C which is used to treat acne and scabies.

Physical Stability of Suspension

In most cases suspension formulation are not physically stable due to the sedimentation of the dispersed particles. Hydrocolloids used as suspending agents are very susceptible to microbial growth resulting in gas and color formation. Discoloration and loss of viscosity along with others. Therefore suitable preservative should be incorporated along with other necessary stabilizers.

The factors influencing the rate of sedimentation is expressed by **Stoke's law** as follows

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\eta} = \frac{2r^2(\rho_1 - \rho_2)g}{9\eta}$$

Where,

V = Velocity of the settling particles

g = Acceleration due to gravity

d = Average diameter of the particle

r = Average radius of the particle

ρ_1 = Density of the particle

ρ_2 = Density of the liquid / dispersed mediums

η = The viscosity of the dispersion medium

Points to Remember

- A wetting agent is included in the formulation of a suspension, particularly when the suspended particles are **hydrophobic**.
- When charcoal powder is dusted on the surface of water, the contact angle that the charcoal exhibits is **108°**

- Suspension and emulsion are coarse dispersion when particle size is usually 1-100 micron
 - **Electrolyte, Surfactant & polymer** are used to make flocculated suspension are stability of suspension can be predicated by measuring **Zeta potential**.
 - The most commonly used flocculating agents is **bentonite magma**.
 - A suspension is not suitable dosage for **intravenous** type of injection.
 - **Pseudo plastic flow & Thixotrophy** are the properties are desirable in a pharmaceutical suspension.
 - A suspension is said to be colloid able when particle size is usually **1-500 micron**.
 - The characteristics of particles in an ideal suspension are, **particle should be aggregated**.
 - Brownian movement of particle in suspension depends upon density of the particle, density of the medium and viscosity of the medium.
 - Suspensions containing high concentration (50% or more) of deflocculated particles represents **Dilatant flow**.
 - The initial rate of setting of particle is determined by floc size & porosity of aggregated mass.
 - The ratio of volume of the sediment and original volume of suspension is called **Sedimentation volume**.
 - The pH of an antacid suspension is around 8.
 - Sorbitols, Menitol, Potassium citrate, Sodium Citrate are the agents added to **prevent gelling**.
 - **Magnesium hydroxide** is used along with aluminium hydroxide gel in the antacid preparation because magnesium hydroxide has **laxative action** which counters the **constipation action** of aluminium hydroxide.
 - The antioxidants like sodium formaldehyde sulfoxylate USP is added in suspension with high solids content because **it prevent the color** formation during storage.
 - The suspension made by dispersion process is achieved by **Pulverization** of solid by **micro ionization** technique.
 - The suspensions made by controlled crystallisation, a supersaturated solution should be formed and then quickly cooled with rapid stirring.
 - The suspension stability can be evaluated by a) Sedimentation volume b) Rheological method c) Electro kinetic technique d) Particle size determination.
- The **silicon is coated** glass is used for packing the suspension products due to
- (a) Improve drainage of suspension
 - (b) Minimize the leaching of alkali from glass in to the product.
- **Polyacrylic acid(Carbopol)**, a pure synthetic polymer is widely used in preparation of external lotion and gel.
 - Clay suspension and gels contains non-ionic preservatives like paraben esters and benzoates. But quaternary preservatives are ineffective.
 - A maximum sedimentation volume will be obtained when zeta potential is **Zero**.
 - When aluminium chloride or Calcium hydrogen phosphate is dissolved in water, the suspension exhibits a **negative apparent zeta potential**.
 - When is dissolved in water? The apparent zeta potential initially is **negative**.
 - Protective colloids differ from surfactant. In respect that
 - (a) They do not **reduce interfacial tension** like surfactants

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- (b) They are used in **higher concentration** than surfactants.
- (c) They have ability to **increase the Zeta-potential**
- **Hydrophilic** colloidal material is used commonly in the preparation of a structured vehicle.
- The isoelectric point of insulin is **pH 5**
- The isoelectric point of protamine zinc insulin is **pH 6.9 to 7.3**
- The protamine zinc insulin suspension is prepared by a method like **altered pH precipitation**.

1.2 Pharmaceutical Engineering

Size Reduction

Size reduction is a process of reducing large solid unit mass (vegetable or chemical substances) into small unit mass, coarse particles or fine particles. This is also termed as comminution or diminution or pulverization. Size reduction can be achieved by two processes-

- Precipitation method,
- Mechanical process.

Precipitation Process:

The substance is dissolved in appropriate solvent. Subsequently, it is finely precipitated by the addition of another solvent, which is immiscible with the first, but in the later the substance is insoluble. Inorganic chemical such as calcium carbonate, magnesium carbonate and yellow mercuric oxide, are prepared by precipitation method.

Mechanical process:

In this process the substances is subject to mechanical forces using grinding and cutting equipment.

Table General Characteristics of Various Types of Mills

Name of the Mill	Action	Product size	Uses	Not for used
Cutter mill	Cutting	20-80 mesh	Fibrous, crude animal and vegetable drugs	Friable material
Roller mill	Compression & attrition	20-200 mesh	Fine grinding of abrasive material	Abrasive material
Hammer mill	Impact	4-325 mesh	All most all drugs	Abrasive material
Ball mill	Attrition & Impact	20-200 mesh	Brittle drugs	Soft material
Fluid energy mill	Attrition & Impact	1-30	Moderately hard & friable material	Soft & sticky material
Edge runner mill	Crushing & shearing	20-80 mesh	All most all the drugs	Sticky material
End runner mill	Crushing & Shearing	20-80 mesh	All most all the drugs	Sticky material
Colloid mill	Shearing	3-75 μm	All most all the drugs	Dry milling
Disintegrator	Impact & grinding		Hard drugs	
Pin mill (Reddrop-periflo mill)			Fine grinding substances with low melting points such as resin, soap, sugar etc.	

Table Some of mill used for size reduction and their specifications

Name of the mill	Action	Use	Variants
Cutter mill	The cutting action is attained by two sets of stationary and rotating knives. The rotor disc is allowed to rotate 200-900 revolutions per minute	Medicinal plants, Plant parts, and animal tissues are normally converted into small parts.	Double runner disc mill Single runner disc mill
Roller mill	The degree of the size reduction can be attained by adjusting the gap between the two follers.	It is used for crushing and cracking of seeds before extraction of fixed oils. It is also used to crush soft issues to help in the penetration of solvent during extraction process.	
Hammer mill	The hammers are made up of stainless steel and the impact surface is made of haystellite and carbaloy . The hammers are to be in a continuous motion 8000-15000 revolution per minute.	It is used to mill dry materials, wet filter press cakes, ointments, slurries etc.	1.Fitzpatrick communicating machine (Fitz mill) 2. Stokes tornado mill 3. Micro pulveriser
Ball mill (Tumbling mill)	The cylinder contain ball that occupy 30-50% of the mill volume. The drug to be reduced in size should fill in the cylinder of 60% volume.	Brittle drugs	Harding mill Continuous ball mill Vibrating ball mill
Fluid energy mill/ Jet mill/ micronizer/ ultrafine grinder	It consists of an elliptical pipe, which has a height of about 2 meter long and diameter ranging from 20 to 200 millimetres. Normally compressed air is used at 600 kilopascal to 1.0 mega pascals .	It is mostly used to reduce the particle size of most of the drugs such as antibiotics and vitamins .	1.Centrifugal impact pulveriser
Edge runner mill	The size reduction done by crushing (compression) due to heavy weight of stones.	It is used for plant based products.	
End runner mill	The size reduction done by crushing (compression) due to heavy weight of steel pestle.	It is used for fine grinding products.	
Colloid mill	The clearance between rotor and stator can be adjusted from 0.05-0.75mm . The rotor is moving at 3000-20000 revolution per minute. During milling heat is generated and may rise the temperature up to 40°C hence cold water circulation is provided to reduce the temperature up to 20°C . The capacity of mill ranging from 2-3L/min for small mills to 440L/min for the large mills.	Usually suspension and emulsion are placed in this mill.	

- **Griffith theory** -The amount of force to be applied depends on the crack length and focus of stress at the atomic bond of the crack apex.
- **Hooke's law**-Stress is proportional to strain
- **Young modulus**-Express the stiffness or softness in dyne per square centimetre
- **Kick's law**-The energy required for size reduction is directly related to the reduction rati
- **Bond low**-The energy required for size reduction

Points to be Remembered

- The size of micro ionized particle is typically **less than 10µm**.
- Micro calorimetry process, Dynamic vapour sorption process, inverse gas chromatography process (IGC) are used to detect the **change in crystallinity of the drug** particle & other surface property of powder during size reduction.
- Laser light scattering technique is used, to detect distribution of particle sizes.
- Malvan Masersizer is used to measure particle sizes.
- Malvan Masersizer works on the principal of laser **diffraction**.
- Fraunhofer& Mie’s light scattering theory is applied to determine to **measure particle size**.
- Aerosizer is used to measure particle sizes. It works on the technique of **light scattering**.
- The sizer of colloid particles are preferably determined by **quasi elastic light scattering** technique.
- Couter determines particle size by Electrical Zone sensing technique.
- Photon correlation spectroscopy (PCS) and single particle optical sizing (SPOS) technique are used to measure **particle sizes**.
- Krypton & gas is used to determine surfaces area of drug particles by gas adsorption method
- $S_t = \frac{V_{\text{mom}} N A_{\text{cs}}}{M}$ is the equation is used for surface area determination of the drug particles for the BET isotherm for Type –II adsorption methods.
- **Displacement of liquid** method is most commonly used method in the pharmaceutical industry for measuring true density.
- **Helium** is taken as references during the true density measurement by Gas picnometry method

Table Particle size range and their specifications

Technique	Size range
Laser light scattering (Quasi elastic)	0.001 – 1 µm
Electrical Zone sensing	1 – 200 µm
Electron microscopy	0.001 – 5 µm
Woven wire sieving	20 – 125, 000 µm
Sedimentation by centrifugation	0.01 – 5 µm
Optical microscopy	5 – 150 µm
Sieving by perforated plate	1000 – 125000 µm

Size Separation

Size Separation is a pharmaceutical process by which the particles of different sizes are separated from a mixture. Also called as,

- Sifting.
- Sieving.
- Classifying.
- Screening.

Table Official standard for powders

Grade of powder	Sieve size all particles pass through	Nominal mesh aperture size	Sieve through which 40% particles pass	Nominal mesh aperture size
Coarse	#10 sieve	1.7 mm	#44 sieve	355 μm
Moderately coarse	#22 sieve	710 μm	#60 sieve	250 μm
Moderately fine	#44 sieve	355 μm	#85 sieve	180 μm
Fine	#85 sieve	180 μm	-	-
Very fine	#120 sieve	125 μm	-	-

Table The list of method of size reduction and the particle size related to it:

Match the method of size separation	Particle size
Microscopy	0.4 to 150 μm
Sieving	10 to 50 μm
Sedimentation	1 to 200 μm

Types of sieves:

1. Woven wire sieves : These sieves are included in roller mill, ball mill.
2. Blotting cloth sieves : Silk, nylon, and cotton are generally woven from twisted multi-trend fibres. These are used for separation of fine powders. Hum-mer screen uses this type of screens.
3. Bar screen : These are used handling large and heavy pieces of materials. Grizzlies use this type of screens.
4. Punched plate : These types are used for coarse sizing. And used in hammer mill.
5. Herringbone design : This is the punched plate type of sieve. It consists of a series of slotted holes repeated across the surface of the seven. These are made at an angle of degree to the length of the screen.

Sieve number: Sieve number indicate the number of meshes per liner length of 25.4 millimetres.

Nominal mesh aperture size: It indicates the distance between the two adjacent wires. It represents the side of a square aperture. It is expressed in mm or μm .

Sieve shaker machine: It is a mechanical shaker apparatus and the standard sieves of different mesh numbers are fixed vertically. A sample of 50 gm of powder is placed on the top sieve and shaken for 20 minutes of time. After the powder retained in each sieve is weighed and the percentage retention is calculated.

Cyclone separator: In cyclone separator centrifugal forces is used to separate the solids from fluids. It's also used to separate solids from gases.

Elutriation: This is a size separation method based on sedimentation principle it may be used to separate the coarse and fine particle present in a paste after levitation.

Mixing

Mixing is defined as the unit operation that combines two or more components together by agitation, shear or mixers. The final product of mixture contains uniform distribution of both components of mixture.

Example of mixers: Blenders, Planetary mixtures, Propellers etc.

Table Mechanism of mixing

Method	Mechanism
Trituration	Rubbing or grinding a substance in a mortar
Spatulation	Small amount of powder is blended
Levigation	Adding a suitable agent to form a paste & then rubbing
Pulverization	Reducing & subdividing a substance by adding as easily removed
Tubling	Process of mixing powder in a large container rotated by electric motor
Geometrical mixing	Method used when potent substances are to be mixed

Table Various instruments and their specification which are used for mixing

Equipment's	Rate of rotation	Mechanism	Mixing materials
V cone blender	Smaller – 35 rpm Larger – 15 rpm	Tumbling	
Double cone blender	30 -100 rpm	Tumbling	Powder
Fluidized mixture		Air supported blending	Wet granulation of tablet
Barrel type of continuous mixture		Rotating shell and rotating blade	
Zig-zag continuous mixture		Rotating shell and rotating blade	
Ribbon blender		Stationary shell and rotating blade	Mixing of glident with tablet granules before punching
Sigma blade mixture		Stationary shell and rotating blade	Wet granulation of tablet Stiff paste and ointment
Planetary mixture	Varied as per desireness	Shear	Wet granulation of tablets
Emulsifier (Silver son mixer)		Shear & Turbulence	Emulsion and cream of fine particle size
Colloid mill			Emulsion
Ultrasonic emulsifier		Ultrasonic vibration	Emulsion
Triple roller mill			Suspension, paste & ointment

Filtration

Filtration is a separation technique used to concentrate or purify substances based on their physical or chemical properties. It is a simple and routine method used in many laboratories to remove insoluble particles from solutions and to prepare samples for analysis. Filtration is used to reduce sample complexity, improve clarity of viscous samples, and reduce background signals resulting in increased signal-to-noise ratios in analytical tests.

Table Filtration according to particle size

Pore size (micron)	Particle removed
0.22 µm	All bacteria
0.45 µm	All coliform group bacteria
0.2 µm	All bacteria
0.8 µm	All airborne particle
1.2 µm	All non-living particles considered dangerous
0.45 µm	All coliform group bacteria

Table List of material and their filtration performance

Fibres used for filter	Temperature recommends	Performance
Safe limits °F		
Cotton	210	Poor
Polyester	200	Very Good
Dynelmodacyclic	300	
Acrylic	475	Excellent
Saran	160	
Polyethylene	165	
Polypropylene	175	
Polyvinylchloride	165	Good
Wood	210	
Teflon	475	
Rayon & acetate	210	Poor
Glass	750	Excellent
Nylon		Fair
Wool		Very Good

Mechanism of filtration:

- (a) Straining : The particles larger cannot pass through the smaller pore size of the filter medium.
- (b) Impingement : Solids having the momentum move along the path of streamline flow and strike the filter medium. Thus the solids retained on the filter medium.
- (c) Entanglement : Particles becomes entwined in the mass of fibres due to smaller size of particles then the pore size.
- (d) Attractive force: Solids are retrained on the filter medium as a result of attractive forces between particles and filter medium, as in case of electrostatic precipitation.

Theory of filtration:

Darcy's equation:
$$V = \frac{KA\Delta P}{\eta L}$$

Poiseuille's equation:
$$V = \frac{\pi\Delta Pr^2}{8\eta L}$$

Kozeny- Carman equation:
$$V = \frac{A}{\eta S^2}, \frac{\Delta P}{KL}, \frac{\varepsilon^2}{(1-\varepsilon)^2}$$

Drying

- **Bond moisture:** It is the minimum moisture held by the material that exerts an equilibrium vapour pressure less than the pure water at the same temperature.
- **Unbound moisture:** It is the amount of moisture held by the material that exerts an equilibrium vapour equal to that of pure water at the same temperature.
- **Equilibrium Moisture content (EMC):** It is the amount of water present in the solid which exerts a vapour pressure equal to the vapour pressure of the atmosphere surrounding it.

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- For zero humidity, EMC of all material is zero. As the temperature of air increase, the EMC of solid decreases.
- **Free Moisture content (EMC):** It is the amount of moisture that is free to evaporate from the solid surface.

Table Type of dryer and their mechanism

Type of dryer and mechanism	Example	Use
Static Bed Dryer System in which there is no relative movement among the solid particle being dried, although may be bulk motion of the entire drying mass.	Tray dryer and freeze dryer	Sticky material, Plastic substance, granular mass or crystalline material, precipitates and pastes can be dried in a tray dryer.
Moving Bed Dryer System in which the drying particles are partially separated so that they flow over each other.	Drum dryer	It is useful for drying solutions, suspension, slurries etc. Usually the products dried are milk products starch products etc.
Fluidised Bed Dryers System in which the solid particles are partially suspended in an upward moving heated gas system	Fluidised bed dryer	It is used for drying of granules in the production of tablets. I can be useful for three operations such as mixing, granulation and drying.
Pneumatic Dryer System in which drying particles are entrained and conveyed at a high velocity gas stream.	Spray dryer	
Freeze Dryer Freeze drying, is also known as lyophilization. In freeze drying, water is removed from the frozen state by sublimation.	Freeze dryer	It is used in the production of blood plasma, and its fractioned products, Bacterial and viral cultures, Antibiotics and plant extracts, steroids, Vitamins and enzymes, Human tissue etc.
Vacuum Dryer In vacuum dryer, material is dried by the application of vacuum is created; the pressure is lowered so that water boils at a lower temperature. Hence water evaporates faster.	Vacuum dryer	It is used for heat sensitive materials, Dusty and hygroscopic materials, Drug containing toxic solvents, Drugs which are required as porous end products and friability dry extracts.

1.3 Semisolid Dosage Forms

- Semisolid dosage forms meant for external application
- Semisolid dosage forms subcategorized are as-
 - Creams
 - Paste
 - Jellies
 - Ointment
 - Suppositories
- The suppositories are also included in this category but it is a unit dosage forms.

Creams

- These are viscous semisolid emulsions, which are meant for external use.
- Cream is divided in to two types namely as
 - (i) Aqueous creams
 - (ii) Oily creams

- In case of aqueous creams the emulsions are o/w type & it is relatively non greasy. The emulsifying waxes are anionic, cationic & non –ionic used. Generally polysorbate, triethanolamine soap are used as emulsifying agent.
- In case of oily creams w/o type & it is relatively greasy. The emulsifying agent such as wool fat, wool alcohols, and beeswax & calcium soap is used.
- The cream should be store in collapsible tube & supplied in well closed container to prevent evaporation & contamination.

Pastes

- Pastes are semisolid preparations intended for external application to skin.
- The pastes are generally very thick & stiff.
- They do not melt at ordinary temperature & thus forms a protective coating over the area where they are applied.
- Pastes are differ from ointment as they contain a high proportion of finely powdered medicaments.
- They are mainly used as a antiseptic, protective, soothing dressings.
- Pastes should be stored & supplied in containers made of materials which do not allow absorption or diffusion of content.

Jellies

- Jellies are transparent or translucent, non greasy, semi solid preparations mainly used for external application to skin.
- These are also used for lubricating catheters, surgical gloves & rectal thermometer.
- The substance like gelatin, starch, tragacanth, sodium alginate & cellulose derivatives are used for the formulation of jellies.
- Jellies are of three types namely as
 - Medicated jellies
 - Lubricating jellies
 - Miscellaneous jellies

Ointments

- Ointments are semisolid preparation meant for application to skin or mucous membrane.
- The ointments are mainly used for their protective or emollient properties
- It may be defined as a medicament or medicaments dissolved, suspended or emulsified in ointment base.
- There is no single ointment base which possesses all the qualities of ideal ointment base, so it become necessary to use more than one ointment base in the preparation of ointment.

Table Base for the Ointments and ointment types

Name of base	Ointments
Hydrocarbon base	Soft paraffin, Hard paraffin, Liquid paraffin
Absorption base	Wool fat (Anhydrous lanolin), Wool alcohol, Bees wax, Cholesterol, Lanolin (Hydrous wool fat) etc.
Water-Miscible bases	Anionic, cationic non-ionic emulsifying base
Water soluble base	Polyethylene glycol

Table Other Ingredients of Ointment bases

Name	Example
Vegetable oils	Arachis, castor, coconut, olive etc
Synthetic esters oil fatty acid	Isopropyl myristate
Higher fatty alcohols	Cetyl, sterayl, cetosteary alcohols etc.
Silicons	-
Propylene glycols	-

- Determination of iodine value depends upon addition of iodine at the **double bond of fatty acids**.
- **Plastibase** is a common ointment vehicle. It is a mixture of **mineral oil and hydrocarbon waxes**.
- The following procedures help to improve the absorption of a drug into the skin-
 - Application of the ointment and covering the area with an occlusive bandage or saran wrap
 - Incorporating an oil-soluble drug in polyethylene glycol ointment rather than white ointment.
 - Applying the medicated ointment on the back of the hand rather than on the palms.
 - Increasing the concentration of the active drug in the ointment base.
- The substances which have been shown to increase the permeability of the skin are sodium lauryl sulphate, Chloroform, Benzene, Dimethyl sulfoxide etc.
- The substances which have been shown to **increase the permeability** of the skin are sodium lauryl sulphate, Chloroform, Benzene, Dimethyl sulfoxide etc.
- **Aqueous solutions** may be incorporated in to the entire following ointment base like lanolin, Aquaphor Unibase, polysorb etc.
- Silicones are useful in ointment formulas since they are good water repellents.
- Lassar's paste is a zinc oxide paste with salicylic acid.
- Hudrophlic petrolatum contains Cholesterol as an emulsifier.
- Petrolatum rose water ointment is a synonym for cold cream USP.
- Iodine **value** may be defined as the weight of iodine absorbed by **100 parts by weight** of the sample of fat of oil.
- The liberation of oil or water from ointment base is called bleeding.
- The term greasiness is suitable used for water dispersible base & o/w base.
- The effect of temperature on the consistency of an ointment base can be analysed by rotational viscometer.
- Melting point range of paraffin wax is 35-75°C
- Crup testing is applied to analyse the viscoelastic property of Ointment.
- Ceresin is a mixture of Ozokerite (mined wax) & Paraffin wax.
- Stearic acid is used in water removable creams as an emulsifier.
- Promulgen G is a mixture of Stearyl alcohol & Ethoxylated cetearyl alcohol.
- During preparation of a topical ointment, the preservative efficacy of the formulation is determined by using Tat broth.
- AS per the microbiological guideline, the limit for the raw material used for Baby product is Not more than (nmt) 500 microorganisms per gram of millilitre.

- About the eye- nmt 500 microorganisms per gram or millilitre.
- Oral products – nmt 1000 microorganisms per gram or millilitre.
- All other products nmt 10500 microorganisms per gram or millilitre.
- Methyl paraben and propyl paraben are tend to irritate to eye or nasal passage, So quaternary ammonium compounds or phenyl mercuric salts are suitable preservatives for ophthalmic and nasal preparations.
- The paraben esters of p-hydroxybenzoic acid is less effective against gram negative bacteria.
- Germall II (Imidazolidine urea) (0.1-0.5%) is used in combination to increase the activity.
- Liqa per is an emulsion of p-hydroxybenzoic acid esters. A 50% by weight oil-in-water emulsion. The oil phase is a mixture of p-hydroxybenzoic acid esters –n-butyl, isobutyl and iso propyl. The aqueous portion contains water with emulsion stabilizers.
- Dowicil, chemically cis isomer 1-(3chlorolloyal)-3, 5, 7-triaza-1-azoniaadamantane is IA broad spectrum anti-microbial agent and not inactivated by non-ionic, anionic, or cationic formulation ingredients.

Table Various type of base and their example with composition

Base	Example and their water number with composition
Oleaginous base	Lanolin
Absorption base	Kersolin, Wool fat, Aquaphor
Emulsion base	Mineral oil
Water soluble base	Polyethylene glycol
Petrolatum	9 to 15 water number
Wool fat	185 water number
Cocoa butter	Mixed glycerides
Cotmar	Partially hydrogenated cotton seed oil
Dehydag	Hydrogenated fatty alcohol & esters
Wecobee R	Glycerides of saturated fatty acid
Wecobee SS	Triglycerides derived from coconut oil
Eitpsol	Triglycerides of saturated fatty acid

Different values

Iodine value

Water number

Acid value

Saponification value

Hydroxyl value

Definition

Number of grams of iodine that reacts with 100 g of fat

Amount of water in grams that can be incorporated in 100 g of fat

KOH required to neutralize the free acid

KOH required to neutralize the free acids & saponify the esters

Measuring an esterified position of glyceride molecules

Gels

- Gels may be defined as semisolids, being either suspension of small inorganic particles or large organic molecules interpenetrated with liquid.
- On the basis of the nature of the colloidal phase the Gels may be classified into-
 1. **Inorganic gels:** Bentonite magma.
 2. **Organic gells:** Natural gum (Accacia, carageen xanthan gum, anionic polysaccharide)
 - Polyethylenes
 - Metalic stearates

Polypeptides (Gelatin)

Synthetic block polymers (ploxamers)

- On the basis of the nature of the solvents the Gels may be classified into –
- **Hydrogel:** Bentonite meagma&Gelatin
- **Organogels (With non-aqueous solvent):** Low molecular weight polyethylene dissolved in mineral oil and shock cooled metallic stearates in oils.
- Solid gels with very low solvent concentration are known as **xerogels**. Eg. Dry gelatin, tragacanth ribbons and acacia tears.
- Liquid of the gel is pressed out naturally after standing for sometimes. This process is called **Syneresis**.
- Sometimes the gel structure would converted to solution structure, which again in a undisturbed stage converted to gel structure. This phenomenon is known as **Thixotrophy**.
- The stability of visco elastic material of gel can be measured by **penetrometer**.
- When gels can accommodate small amount of liquid without measurable increase in the volume, the process is known **imbibition**.
- Pectin paste is a **Jelly**.

Table Different type gels and their example

Different types of gels	Definition / example
Gel	Solid or semisolid system in which at least two constituents condensed in which liquid is interpenetrated
Jelly	Coherent matrix is rich in water
Xerogel	Frame work of gel in fee from liquid
Hydrogels	Water containing gels
Organogels	Organic liquid containing gels
Organic hydrogel	Tragacanth jelly
Inorganic hydrogels	Bentonite gel
Animal organogel	Theobroma oil
Soap base organogel	Mineral oil gel
Hydrocarbon type organo-gel	Petrolatum
Hydrophillicorgano-gel	Carbowax base

Suppositories & Pessaries

“**Suppositories**” are solid medicated preparations designed for insertion in the rectum where they melt, dissolve or disperse and exert a local or systemic effect.

“**Pessaries**” are similar solid medicated preparation designed for insertion into the vagina, usually to exert a local effect.

“**Bougies**” are urethral suppositories.

- **Suppository bases:** There are two main classes of suppository base.
 - Fatty base designed to melt at body temperature. : eg. Theobroma oil, Synthetic hard fat.
 - Water soluble or water miscible base designed to dissolve or disperse with the body eg. Glycero-Gelatin, Macrogels (PEG) like Macrogel- 400, 1000, 1540, 4000, 6000.

Displacement value: The number of parts by weight of medicaments that displace one part by weight of the base-

- Glycerin suppositories contain 92% glycerine and are solidified by the use of sodium stearate.
- A group of substances used as suppository bases that dissolve rather than melt are carbowaxes
- Most commercial vaginal suppositories use a base of Polyethylene glycol.
- Suppositories may be used as a deodorant.

Table Cocoa butter and their boiling point

Cocoa butter form	Boiling point
α – form	24°C
β – form	28 to 31°C
β' – form	34 to 35°C
γ – form	18°C

Table Represents different values for ideal suppository

Different values for ideal suppository	
Acid value	0.2
Saponification value	200 to 245
Iodine value	7

1.4 Cosmetics

Lipstick

Lipsticks are the lip cosmetic molded into sticks are essentially dispersion of colourings matter in a base consisting of suitable blends of oil, fats, and waxes.

Ingredients of Lipstick

1. Colouring material:

- (i) Eosin
- (ii) Halogenated fluorescein (Tetrachlorotetrabromo fluorescein, di-iodofluorescein)
 - Eosin produces purple red stain above pH4
 - Halogenated fluorescein produces brilliant bluish stain.

2. Pigments:

- (i) Titanium dioxide (It is the most effective white pigment used as opacifying agent.)
- (ii) D&C Red No.36, and D&C Orange No.17 (These are insoluble in both water & oil used as pigments)
- (iii) Lakes (Calcium lakes, Barium lakes, Aluminum lakes)

3. Base:

- (a) Natural oil – Castor Oil (30-40%)
- (b) Fatty alcohol (Lauryl - C_{12} , Steryl - C_{18} , Myristyl- C_{14} , Oleyl- C_{18} , Cetyl - C_{16} ,
- (c) Hexadecyl alcohol)
- (d) Ester (Adipic, Sebcic)
- (e) Polyethylene glycols (Carbowaxes)
- (f) Monoakanolamide (Loramine)
- (g) Polychol-5 (It is an ethylene oxide derivate of lanolin alcohol)
- (h) Valpoa-3 (It is a polyoxethyleneoleyl ether)

4. Other base ingredients:

- Carnumba wax – It is used for raising melting point and providing contraction properties in the molding process.
- Candeilla – It serves some function as carnauba wax but having low melting points and less brittle.
- Ozokeriatic wax- It gives short – fibred texture to the products.
- Microcrystalline wax – It is used to modify the rheology of the products.
- Bees wax – It is used as shifting agent for castor oil.
- Lanolin – They have eosin solvent property. They act as binding agent for other ingredient and acting as plasticizer.
- Petroleum jelly – They have eosin solvent property. They act as binding agent for other ingredient and acting as plasticizer.
- Lecithin – It act as dispersing agent for pigments.
- Silicon wax- These are used as cosmetic solvent & colouring agents. eg. Organosilicon block Polymer, hydrocarbon silicon polymer, Silphenylene co-polymer.

5. Perfumes: (2-4%) e.g. Rose oil, Aniseed oil, cinnamon Oil, Clove oil, lemon oil, orange oil Etc.

- **Manufacture of lipsticks**

The lipstick manufacture involves three stages.

- The preparation of component blends, that is oil blend, color dispersion, and wax blend.
- Blending of the intermediates too form the lipstick mass.
- The molding of lipstick mass into the sticks.

- **Transparent lipsticks**

- These type of lipsticks does not contain any insoluble opaque pigment or lakes but instead uses soluble or solubilized dyes.
- This allows light to shine through it.
- Giving sparkle.
- The staining action of these days is enhanced by the use of suitable solvent such as Loramine OM-101 or dipropylemne glycol methyl ether.

- **Liquid lipstick**

The liquid lipstick consists of

- Alcoholic solution of alcoholic soluble dyes-e.g. - Alcoholic soluble halogenated fluorescins.
- Suitable film forming resins- e.g. – Ethyl cellulose, polyvinyl alcohol and polyvinay acetate.
- Plasticizers - e.g – Triethylcitrtate, dioctyl acetate, methyl abietate or Polyethylene.

- **Evaluation of lipsticks**

Lipsticks are evaluated by means of following tests:

1. Droop point test – The temperature at which the lipstick starts oozing out oil or flatten out from within the case is known as droop point.
2. Breaking point test – This determines the strength of lipstick. The lipstick is held horizontally in a socket and a gradually increasing weight is applied on the lipstick half an inch away from the base, and the weight at which breaks is taken as breaking point.

3. Test for penetrability – This test indicates the rheological property of the lipstick. A needle of specific diameter 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 (kept in a balance at an angle of 45°, and the force required for applying is read from the balance.
5. Stability test – Stability of lipsticks can be determined by means of accelerated stability test in which lipstick formulation is kept at higher temp. (Say 45°C) and assessing the lipstick for surface defects, perfume, color and application characteristics.

Shampoos

Shampoo is a preparation meant for cleaning hairs of dust, grime, crust and to impart gloss to hairs.

Characteristics of a Good Shampoo-

- Effectively remove soil, sebum, and residues of hair setting lotions or oils from the scalp
- Good amount of foam to satisfy psychological needs of the customer.
- Easily removed on rinsing of hairs.
- Makes the hair soft, lustrous and manageable.
- Pleasant fragrance.
- Non-toxic and non-irritant.

Formulation of shampoos

1. Surfactants
2. Conditioning agents
3. Thickening agents
4. Chelating agents
5. Antidandruff agents
6. Colours
7. Perfumes
8. Preservatives

- **Surfactants:** These are principle surfactants used in shampoo. Cationic surfactants are only used as conditioners and not as principle surfactants because of their irritation potential. Non-ionic are also used but they do not good foaming ability. Soaps were used earlier as they are cheap but they are highly alkaline and they make hair dull. Further they also leave deposits of calcium and magnesium with hard water. Examples of surfactants used include **Sodium lauryl sulphate, Triethanolamine lauryl sulphate, monoethanol lauryl sulphate etc.**
- **Conditioning agents:** These agents improve manageability, feel luster of the hairs. Various materials used as conditioning agents include lanolin, mineral oil, egg albumin, amino acids, lecithin and herbal extracts like shikakai and henna.
- **Thickening agents:** This make shampoo viscous so that they are easy to pour and handle. Example of thickening agents employed in shampoos include natural gum like gum karaya, gum tragacanth, cellulose derivatives like **CMC, HPMC**, polymers like **Polyvinylalcohol, carbopol 934P** etc.
- **Chelating agents:** These are used to prevent the deposition of calcium and magnesium salts of soaps on hairs eg. **Disodium edentate, polyphosphates, citric acid etc.**

Types of Shampoo

1. Liquid shampoo
2. Liquid shampoo

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3. Cream based shampoo
4. Powder Shampoo
5. Aerosol shampoo
6. Antidandruff shampoo
7. Baby shampoo

Table Some important material used in Antidandruff shampoo for the treatment of Dandruff

Name of the material	Usual conc. %
Thymol	0.05-0.2
Selenium sulphide	0.1-2.5
Quaternary Ammonium compound	15-20
1,2 Bithional	0.5-1.0
2-pyridinethiol-oxide	2
Zink pyridinethiol-oxide (ZPTO) it is used in Head& Shoulder the popular anti dandruff shampoo	2
2-mercapto-quinoxaline-1-okide	
2-mercapto-quinoline-1-oxide	

- **Baby Shampoo:** The baby shampoo's mild ness is provided by choosing non-irritant surfactants that produce limited detergency. The most common surfactants are amphoteric imidazoline dervatives and the fatty sulphosuccinate esters and amides are usually combined with ethoxylated sorbitan or mannitan ester to give sting free composition.
- Tween 20 is combined with a complex obtained from tridecyltrilethoxy sulphate and N-(2-cocoamidoethyl) diethanolamine is used in the **Johnson & Johnson's** popular baby shampoo 'no more tears'

Nail Preparations

Nail polish/ Nail enamels: A distinction is drawn between those polishes which by abrasive action bestow a gloss on the nail surface & a nail varnish.

The formulation includes as-

1. Film former
 2. Solvent
 3. Plasticizers
 4. Colours
 5. Pearlescent pigments
 6. Perfume
- **Film former:** Cellulose nitrate, Cellulose acetate, Cellulose acetobutyrate, ethyl cellulose, Stannic acid, powered silica, methacrylate and vinyl polymers are used as film formers in nail lacquers. But ethyl cellulose is most widely used film formers.
 - **Solvent:** Usually a mixture of high boiling, medium boiling, and low boiling solvents are employed in nail enamels. The mixture of solvents is so balanced that precipitation of cellulose nitrate is prevented. The example of solvents are-
 - High boiling – butyl lactate, ethyl oxalate, isoamyl acetate etc.
 - Medium boiling – Isopropylacetate, touene, methyl acetate, ethyl acetate etc.

- Low boiling – Ether, Carbon disulphide, acetone, methyl acetate, ethyl acetate etc.
- **Plasticizers:** These impart flexibility and gloss to the film, and also help in adhesion of fill to the nails e.g. Dibutyl phthalate, resorcinol diacetate, castor oil, butyl acetyl ricinolate etc.
- **Pearlescent:** These impart pearly appearance to the film. E.g. 2-amino, 6-oxypurine (crystalline guanine), bismuth oxy chloride coated pigments.
- **Enamel Remover:** These are the preparations intended to remove enamel from the nails and basically consists of simple mixture of solvents such as acetone, amyl acetate or ethyl acetate. Gamma-Valerone (GVL) is used as strong enamel remover.

Dentifrices

Dentifrices are the preparations intended to clean the teeth of food debris, prevent calculus and plaque formation, polish to impart lustre for the teeth and to leave a refreshing feeling in mouth. They are two types tooth powder and tooth paste.

Formulation of the Tooth Powder:

1. Abrasives and polishing agents: (Calcium carbonate (2-20 μ m particle size), Dicalcium phosphate, sodium metaphosphate etc.
2. Detergent and foaming agents: Sodium lauryl sulphate, Sodium lauryl sarcosinate, Sodium lauryl sulphosuccinate and soap like sodium palmitate etc.
3. Saccharine sodium is the most commonly used sweetening agents.
4. Flavouring agent: Anise oil, peppermint oil, cinnamon oil etc.

Table Formulation of tooth paste with example

Ingredients	Example		Composition
Abrasives and polishing agents	Calcium carbonate (2-20 μ m particle size). Dicalcium phosphate Sodium metaphosphate		15-56%
Detergent and foaming agents	Sodium lauryl sulphate, Sodium lauryl sarcosinate, Monoglyceride sulphate		1-2%
Gelling or binding agents	Hydrophilic colloids which disappears in aqueous medium are mainly used.	Gum tragacanth, Karaya gum, Sodium alginate, SCMC Hydroxy ethyl cellulose Irish moss	1.0%
Humectants	Glycerine, propylene glycol, sorbitol		10-30%
Preservatives	Methyl paraben or propyl paraben Tricoslan (It is now a days most widely used in tooth paste)		0.1-0.2%
Flavouring agent	Anise oil, Peppermint oil, cinnamon oil, eugenol		1-1.5%
Anti caries agent	Sodium fluoride, Sodium lauryl sarcosinate		
Desensitizers	Potassium nitrate and strontium chloride are used to reduce the sensitivity of teeth to hot and cold		

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- When the fluorides like sodium fluoride or sodium mono fluorophosphates is added to tooth paste the abrasive must be chosen carefully because the free calcium ions present in calcium carbonate will quickly precipitate as calcium and the characteristic activity will be lost.
- In this case the abrasive like sodium metaphosphate and special grade of calcium pyrophosphate is used.
- Evaluation of dentifrices:
 1. **Abrasive action-** A very techniques are commonly used to test abrasive action.
 - Shadograph method
 - Surface profile method
 - Interference microscopy,
 - Replication technique
 - Radio tracer method (This is the most widely accepted method in the world)
 2. **Particle size:** The particle size should be remain with a range of 2-20 μ m
 3. **pH**
 4. **Consistency**

1.5 Novel Drug Delivery System

The main objective of sustained/controlled/prolonged release formulation

The formulation is designed ion such a way that minimum effective plasma concentration (MEC) level drug should attain quickly and thereafter the rate of entry of drug to the body should equal with the rate of total eliminator or inactivation of drug from the body, as a result the plasma drug concentration curve will run parallel to the time axis just above the MEC level.

Few Latest Delivery Systems

1. **Microencapsulation:** In this technique the drug along with a suitable polymer (s) are transformed to numerous micro- capsules. Few hundreds of such a solid microcapsules containing a definite amount of drug is then taken in hard gelatine capsule shell of compressed into a quickly disintegrating tablet for administration to the patient. This formulation now-a-days is widely used as sustained release formulation as the entrapped drug release slowly from the microcapsule.
2. **Nano-particles:** In this case also the entrapped or adsorbed drug is released slowly giving sustained action and the sizes of the particles permit.
3. **Transdermal drug delivery system:** Our skin can absorb a considerable amount of a drug to initiate and continue physiological response. The drug with moderate lipid water partition co-efficient (not too hydrophilic or too lipophilic) can be delivered as transdermal patch along with pressure sensitive adhesive. The patient is directed to fix up the patch when the drug action is not required.

Examples include:

- (a) Transdermal scopolamine control motion sickness
 - (b) Transdermal testosterone
 - (c) Transdermal oestrogen to female during post-menopausal period
 - (d) Transdermal antianginal preparation.
4. **Liposomal drug delivery system.**
 5. **Multiple emulsions.**
 6. **Monoclonal antibody tagged drug delivery system.**

7. Drug loaded erythrocytes.
8. Iontophoretic techniques.
9. Controlled release suppositories.
10. Prodrug for sustained drug action.

Table Some terminologies related to novel delivery system and their definition

Type of release	Definition
Delayed release	Use of repetitive, dosing of drug from one or more immediate release unit incorporated into a single dosage form
Sustained release	Drug delivery system that achieves slow release of drug over an extended period of time
Controlled release	Successfully maintained constant drug level in the blood or target tissue.
Prolonged release	unsuccessfully maintained constant drug levels but extend the duration of action over that achieved by conventional delivery
Site-specific release	Targeting of a drug directly to a specific biological location
Reservoir release	the target is a certain organ or tissue for receptor release
Reservoir device for sustain release	A core of drug is surrounded by a polymeric membrane
Matrix device for sustain release	Drug dissolved or dispersed drug is distributed uniformly throughout an inert polymeric matrix

Different type of products

Name of the products

Reservoir diffusion products	Measurin tablet, Bronkodyl SR capsule, Nitrospan tablet
Matrix diffusion products	PBZ to SR, Choleadyl SA tablets, Dospan tablet, Fero-Gard 500
Encapsulated dissolution products	Hispril, Diamox, Artane
Matrix dissolution products	Nicobid, Mestinon
Ion exchange products	Lonamin capsule, Tussiones, Biphedamine capsule

- **Osmotic Pump** a pharmaceutical technology utilized to achieve rate controlled & sustained released solid dosage forms.
- **Galactomannose** a hydrophilic polymer is used as a retardant in matrix tablet formulation.
- The most common mechanism utilized in rate controlled pharmaceutical products is **Erodible system** controlled by the erosion of a polymeric matrix.
- The half-life a drug is suitable for formulated in to a sustained release dosage form is **2 to 4 hours**
- **KCI** is the osmotic active substance is used in osmotic pressure controlled release system.
- **PVC** is an insoluble, inert polymer, used as a retardant in matrix tablet formulations.
- The release of drug from a reservoir device is governed by **Ficks 1st law of diffusion**.
- Absorption of poorly soluble drug is dissolution rate limited.
- The flux of diffusion constant decreases with increasing of partitioning, particle size and molecular weight.
- Phase separation **concertation** is used in **Microencapsulation** process.
- **ZYO** is referred to Modified release tablet.
- **Liposomes** interest with cell membrane by Fusion, Adsorption and Endocytosis.
- Release of drug is the first rate limiting step for controlled drug delivery system.

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- **Scopolamine & Nitroglycerine** drug can be introduced by transdermal drug delivery system
- Liposomes are **Uni or multi layered vesicles of phospholipids**.
- **Propylene glycol** is a non-ionic surfactant used as a penetration enhancer in the preparation of mucoadhesives.

Table Micro encapsulation and approximate particle size

Approximate Particle Size	Approximate Particle Size (µM)
Air suspension	35 to 5000
Conservation phase separation	2 to 5000
Multiorifice centrifugal	1 to 5000
Pall coating	600 to 5000
Solvent evaporation	5 to 5000
Spray drying and congealing	600

Table List of various material used in encapsulation

Core Material	Purpose of Encapsulation
Acetaminophen	Taste masking
Activated charcoal	Selective Absorption
Aspirin	Taste masking and reduction of gastric irritation
Progesterone	Sustained release
Potassium chloride	Reduced gastric irritation
Urease	Permeability of enzyme
Vitamin A palmitate	Stabilization of enzyme
Islet of Langerhans	Sustained normalization of diabetic condition

1.6 Pharmaceutical Calculation

Calculation based on density

$$\text{Density} = \text{weight} / \text{Volume}$$

$$\text{Volume} = \text{weight} / \text{density}$$

$$\text{Weight} = \text{Density} \times \text{Volume}$$

Example: Calculate the volume of 5 kg of glycerine. The density of glycerine is 1.25g/ml.

$$\begin{aligned}\text{Volume} &= \text{weight} / \text{density} \\ &= 5000 / 1.25 \text{g/ml} \\ &= 4000 \text{ ml}\end{aligned}$$

Example: Calculate the weight of 1 liter of fixed oil whose density is 0.9624g/ml

$$\begin{aligned}\text{Weight} &= \text{Density} \times \text{Volume} \\ &= 0.9624 \times 1000 \\ &= 962.4 \text{ g}\end{aligned}$$

Alcohol dilution

Formula: Volume of stronger alcohol used = $\frac{\text{Volume required} \times \text{Percentage required}}{\text{Percentage used}}$

Example: What volume of 50% v/v alcohol could be prepared from on liter of 95% v/v alcohol?

Formula: Volume of stronger alcohol used = $\frac{\text{Volume required} \times \text{Percentage required}}{\text{Percentage used}}$

$$1000 \text{ ml} = \frac{\text{Volume required} \times 50}{95}$$

$$\text{Volume required} = \frac{1000 \times 95}{50} = 1900 \text{ ml}$$

Example: What is the percentage of alcohol in a mixture obtained by mixing 5L of 25% , 1L of 50% and 2L of 95% alcohol?

$$500 \text{ ml} \times 25\% = 1250$$

$$1000 \text{ ml} \times 50\% = 500$$

$$2000 \text{ ml} \times 95\% = 1900$$

$$8000 \text{ ml} \quad 3650$$

$$3650:8000:: X:100$$

$$X = \frac{3650 \times 100}{8000} = 45.6\%$$

Therefore the percentage strength of the mixture is 45.6

Example: What is the strength of ZnO in an ointment prepared by mixing 400g of 10% and 50g of 5% ointment?

$$400 \text{ g} \quad 10\% = 40$$

$$100 \text{ g} \quad 20\% = 20$$

$$50 \text{ g} \quad 5\% = 2.5$$

$$550 \text{ g} \quad 62.50$$

$$62.50:550:: X : 10$$

$$X = \frac{62.50 \times 100}{550} = 11.36\%$$

Therefore the percentage strength of the mixture is 11.36

If a diluent is to be added along with the component of known quantity and strength to obtain mixture the diluent is generally taken to be zero % strength.

Example: What is the % strength of an alcoholic mixture obtained by mixing 500ml of 40% alcohol, 2L of 20% alcohol and 500 ml of water?

$$500 \text{ ml} \quad X \quad 40\% \quad = 200$$

$$2000 \text{ ml} \quad X \quad 20\% \quad = 400$$

$$\underline{500 \text{ ml}} \quad X \quad 0\% \quad = \underline{0}$$

$$300 \text{ ml} \quad \quad \quad 600$$

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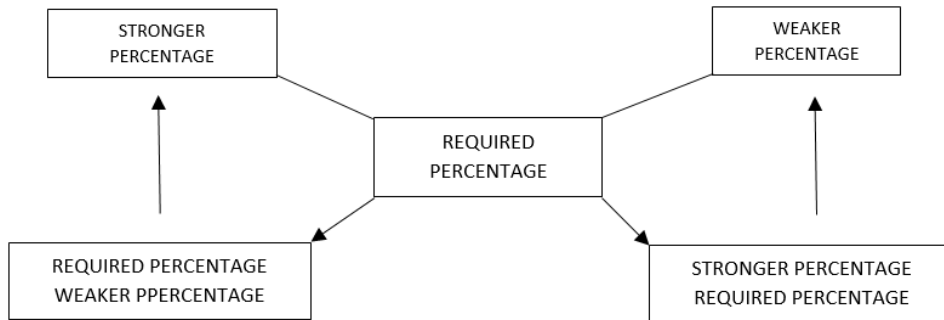
$$X = \frac{600 \times 100}{3000} = 20\%$$

Therefore the percentage strength of the mixture is 20%

Allegation method:

When the calculation involves mixing of two similar preparation of different strength, to produce a preparation of intermediate strength, the allegation method is used.

For calculation purpose the figures are written as given below:-



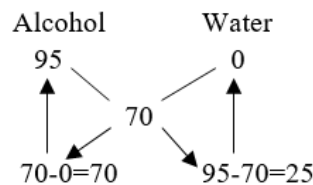
Example: Calculation the volume of 95% alcohol required to prepare 600 ml of 70% alcohol.

Volume required = 600 ml

% of alcohol required = 70

% of alcohol used = 95

By using allegation method

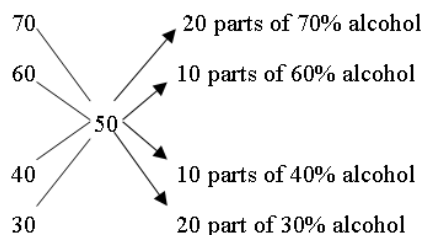


70 parts of 95% alcohol and 25 part of water will produce the required percentage alcohol.

$$\text{Quantity of 95\% alcohol required} = \frac{600 \times 70}{95} = 442.10 \text{ ml}$$

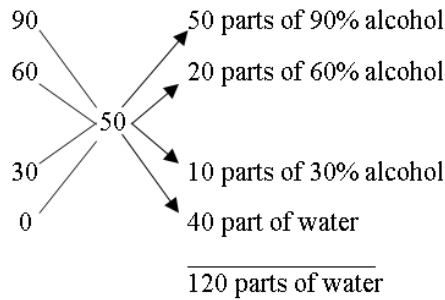
$$\text{Quantity of water required} = \frac{600 \times 25}{95} = 157.9 \text{ ml}$$

Example: Calculation the amount of 70%, 60%, 40%, 30% alcohol should be mixed to get 50% alcohol.



Therefore when 20 parts of 70% alcohol, 10 parts of 60% alcohol, 10 parts of 40% alcohol, and 20 parts of 30% alcohol are mixed together the resulting solution will produce 50% alcohol.

Example: Calculation the volume each of 90%, 60%, 30% and water are required to produce 500ml or 50% alcohol.



Therefore when 50 part of 90% alcohol, 20 parts of 60% alcohol, 10 part of 30% alcohol and 40 part of water are mixed together the resulting solution will produce 50% alcohol

1. Volume of 90% alcohol required
= 120part: 500 ml :: 50 part : v

$$V = \frac{500 \times 50}{120} = \frac{2500}{12} = 208.33$$

2. Volume of 60% alcohol required
= 120part: 500 ml :: 20 part : v

$$V = \frac{500 \times 20}{120} = \frac{1000}{12} = 83.33$$

3. Volume of 30% alcohol required
= 120part: 500 ml :: 10 part : v

$$V = \frac{500 \times 10}{120} = \frac{500}{12} = 41.67$$

4. Volume of water required
= 500-208.33 + 83.33 + 41.67 = 166.67ml

Proof Spirit

Proof means pure or absolute alcohol b means of proof degrees. It means 100 proof spirit contains 50% (by volume) or 42.49% (by weight) of ethyl alcohol and specific gravity is 0.91976.

In India 57.1%v/v alcohol is 100 volume of proof spirit.

- The term 10° UP (under proof) signifies that 100 volumes of spirit contains 90 volumes of proof spirit + 10 volume of water.
- 30° OP indicates that 100 volumes diluted with water yields 130 volume of spirit.

Proof spirit = % strength of alcohol X 1.7530

Proof spirit in USA = % strength in alcohol X 2

Proof strength = (% strength of alcohol X 1.7530) – 100

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Example: Find out proof spirit of an elixir containing 30% v/v alcohol.

$$\begin{aligned}\text{Proof spirit} &= \% \text{ strength of alcohol} \times 1.7530 \\ &= 30 \times 1.753 \\ &= 52.59 \text{ proof spirit}\end{aligned}$$

Example: Find out the proof strength of an alcoholic product containing 55% v/v alcohol solid at U.S.A

$$\begin{aligned}\text{Proof spirit in USA} &= \% \text{ strength in alcohol} \times 2 \\ &= 55 \times 2 \\ &= 110 \text{ proof spirit}\end{aligned}$$

Example: Find out the proof strength of an alcoholic product containing 25% v/v

$$\begin{aligned}\text{Proof strength} &= (\% \text{ strength of alcohol} \times 1.7530) - 100 \\ &= (25 \times 1.7530) - 100 \\ &= 43.8 - 100 \\ &= -56.2 \text{ or } 56.2^\circ \text{ U/P (since negative number)}\end{aligned}$$

Example: Find out the proof strength of an alcoholic products containing 65% v/v alcohol sold in U.S.A

$$\begin{aligned}\text{Proof strength in USA} &= (\% \text{ strength in alcohol} \times 2) - 100 \\ &= (65 \times 2) - 100 \\ &= 130 - 100 \\ &= 30^\circ \text{O/P}\end{aligned}$$

Example: Calculate the real strength of 30° O.P and 40°U.P

30 Over proof means 100 = 3

Alcohol strength = $130 / 1.753 = 74.15\% \text{ v/v}$

40 U.P means $100 - 40 = 60$. Alcohol strength = $60 / 1.753 = 34.23\% \text{ v/v}$

Calculation of Doses

1. Young's formula

$$\text{Dose of child} = \frac{\text{Age in years}}{\text{Age} + 12} \times \text{Adult dose}$$

This is formulation is used for calculating the doses for children under 12 years of age.

Example: If the adult dose of a drug is 200mg. what will be the dose for a child of 8 years.

According to the young's formula, the dose will be

$$\frac{8}{8+12} \times 200 = 80\text{mg}$$

2. Dilling's formula

$$\text{Dose of child} = \frac{\text{Age in years}}{20} \times \text{Adult dose}$$

This formula is used for calculating the doses for children in between 4-20 years of age.

Example: 25 mg of ephedrine hydrochloride can be given to an adult. What will be the dose for a boy of 16 years?

According to the Dilling's formula, the dose will be

$$\frac{16}{20} \times 25 = 20\text{mg}$$

3. Cowling's formula

$$\text{Dose of a child} = \frac{\text{Age in years} + 1}{24} \times \text{Adult dose}$$

Example: If the adult dose of a drug is 25mg, what will be the dose for a boy of 15 years.

According to the Cowling's formula, the dose will be

$$\frac{15+1}{24} \times 25 = 17\text{mg}$$

4. Clark's formula

$$\text{Dose of a child} = \frac{\text{Wdight in pounds}}{150} \times \text{Adult dose}$$

Example: If the adult dose of a drug is 100mg, what will be the dose for a child of weighing 15 pounds.

According to the Clark's formula, the dose will be

$$\frac{15}{150} \times 100 = 10\text{mg}$$

5. Bastedo's formula

$$\text{Dose of a child} = \frac{\text{Age in years} + 3}{30} \times \text{Adult dose}$$

Example: If the adult dose of a drug is 300mg, what will be the dose for a boy of 12 years old?

According to the Bastedo' formula, the dose will be

$$\frac{12+3}{30} \times 300 = 150\text{mg}$$

6. Fried's Formula

According to the Fried's formula, the dose will be

$$\text{Dose of a child} = \frac{\text{Age in month}}{150} \times \text{Adult dose}$$

This formula is used for calculating the doses for children under 2 years of age.

Example: If the adult dose of a drug is 100mg what will be the dose for a infant of 10 month old?

According to the Fried's formula

$$\frac{10}{150} \times 100 = 6.7\text{mg}$$

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Milliequivalents

1 equivalent = 1000 milliequivalent

I.e. 1 mEq = 1Eq. wt. / 1000

e.g. one mEq of K^+ (ion) combines with 1mEq of Cl^- to give 1mEq of KCl

The eq. wt of KCl \cong 74.5 g of KCl \cong 74500 mg of KCl

\therefore 1mEq of KCl \cong 74.5 g pf KCl (1mEq K^+ is 39mg + 1 mEq Cl^- is 35.5mg)

Example: A solution that contains 409.5 mg of NaCl / 100 ml has how many mEq of Na and Cl?

Ans: 1 mEq of NaCl = 58.5mg

i.e. 58.5 mg = 1 mEq of NaCl

1 mg = 1/58.5 mEqwt of NaCl

\therefore 409.5 mg = 409.5 / 58.5 mEq wt

= 7

\therefore 7 mEq wt/ of NaCl is to be dissolved to make 500 ml solution containing 500 mEq of Na^+ .

Isotonic Solutions

Calculation of Isotonicity based on Freezing point method: The lachrymal secretion contains several solutes in I and has a freezing point of -0.52°C . All solution which freeze at -0.52°C will be isotonic with the lachrymal fluid. Human blood plasma also freezes at this temperature and hence solution having freezing point at -0.52°C . Will be isotonic with blood plasma as well. Adjustment of tonicity is simplified if the freezing point of the medicament and the inert salt (Adjusting substance) are known for various strengths of their solution. Freezing points are usually expressed in terms of 1% solution and on can calculate the quantity by multiplying the freezing point with the factor.

Freezing point of tear secretion or human or human blood plasma = freezing point of drug + Freezing point of the adjusting substance.

Therefore the amount of adjusting substance required may be calculated from the equation.

$$W = \frac{0.52 - a}{b}$$

Where

W = the weight in gram of the added substance in 100 ml of the final solution.

a = the depression of the freezing point produced by the medicament already present in solution.

Calculated by multiplying the value for the medicament by the strength of the solution expressed as a percentage w/v

b = the depression of the freezing point of water produced by 1% of the adjusting substance.

Example: Find the concentration of sodium chloride required to render a 1.5% solution of procaine hydrochloride iso-osmotic with blood plasma. (The freezing point of a 1% (w/v) solution of procaine hydrochloride is -0.122°C , and that of a 1% (w/v) solution of NaCl is -0.576°C .)

Ans:
$$\frac{0.52 - (0.122 \times 1.5)}{0.576} = 0.585\% \text{ w / v}$$

Calculation of Isotonicity based on Molecular concentration:

The osmotic pressure of blood plasma and lachrymal secretion is approximately 6.7 atmosphere; hence, the molarity of these fluids is $6.7 / 22.4 = 0.3$ M approximately. Consequently, a 0.3 M solution of any non-ionizing solute will be iso-osmotic with plasma and tears.

Example: Find the concentration of anhydrous dextrose needed to produce a solution iso-osmotic with blood plasma.

Ans: The molecular weight of dextrose is 180 and it is non-ionising.

Therefore $0.3 \times 180 = 54$ g per litre required.

If the solute ionizes in solution this is assumed to be complete and the following formulation is used.

$$W = \frac{0.3M}{N}$$

Where, W = Amount required in g per litre.

M = Molecular weight of solute

N = No. of ions produced from each molecule of the solute.

Example: Find the concentration of Sodium chloride needed to produce a solution iso-osmotic with blood plasma.

Ans: The molecular weight of sodium chloride is 58.5 and it dissociates into 2 ion.

$$\text{Therefore } W = \frac{0.3M}{N} = \frac{0.3 \times 58.5}{2} = 8.8 \text{ g per litre (0.88 w/v)}$$

Calculation of HLB of a Blend of Emulsifying Agents

When a blend of emulsifying agents is used, the total HLB of the mixture is the arithmetic addition of the contribution of each part.

Example: What is HLB of mixture of 50% of Span 80 and 50% of Tween 80?

(HLB of span 80 = 4.3 and HLB of Tween 80 = 15.0)

HLB X % of mixture

Span 80 X 4.3 X 50% = 2.15

Tween 80 X 15.0 = 7.50

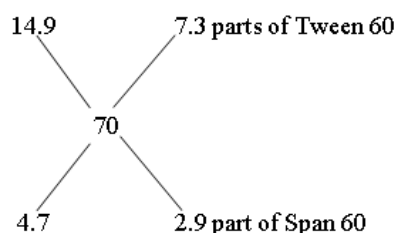
HLB of the mixture = 9.65

Calculation of Relative Amount of emulsifier to obtain a Required HLB value

The calculation involves the use of allegation alternate.

Example: In what proportion should Tween 60 and Span 60 to be blended to obtain a required HLB of 12.0 (HLB of Span 60 = 4.7 and HLB of Tween 60 = 14.9)

By allegation



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Relative amount of Tween 60: Span 60

$$7.3: 2.9$$

$$\text{Or } 71.5\% : 28.5\%$$

Displacement Value of Medicaments

This displacement value of medicament is defined as that proportion which displace on part of the standard calibrating substance. (oil oi Theobroma or cocoa butter) This displacement values (butter known as density factor i.e density of a medicament relative to cocoa butter) as reported in books are with reference to the oil of Theobroma and hence when other bases e.g. gelato-glycerine, polyethylene glycols etc. are used, the displacement values are to be calculated accordingly.

Example: Supply 12 suppositories of boric acid each weighing 4 gm and containing 300 mg of boric acid (the displacement value of boric acid = 1.5)

12 suppositories require $12 \times 300\text{mg} = 3600$ mg of boric acid.

The displacement value of boric acid = 1.5

The total amount of cocoa butter displacement by 3.6 gm of boric acid = $3.6/1.5 = 2.4$ gm

Hence the quantity of base required = $(12 \times 4) - 2.4 = 45.6\text{g}$

The formula for 12 suppositories would be

Boric acid = 3.6g

Cocoa butter = 45.6g

Conversion Formula

1. Conversion of mEq to mmol per litre

$$\text{mmol} = \frac{\text{mEq}}{\text{Valency}}$$

2. Conversion of % w/v strength to mmol per litre

$$\text{mmol per litre} = \frac{\% \text{ w / v strength} \times 10000}{\text{mg of substance containing 1 mmol}}$$

3. Conversion of mmol per litre to % w/v strength

$$\% \text{ w/v strength} = \frac{1 \text{ mmol} \times \text{mmol per litre}}{10000}$$

4. Conversion of mg per litre to mmol per litre

$$\text{mmol per litre} = \frac{\text{mg per litre}}{\text{mg of substance containing 1 mmol}}$$

5. Conversion of mmol per litre to mg per litre

$$\text{Mg per litre} = \text{mmol per litre} \times \text{mg of substance containing 1 mmol}$$

6. Conversion of °C (degree centigrade) into °F (degree Fahrenheit)

$$F = 32 + \frac{9}{5}C$$

7. Conversion of °F (degree Fahrenheit) into °C (degree centigrade)

$$C = (F - 32) \times \frac{5}{9}$$

1.7 Aerosols

- Aerosol or pressurized package is defined as a system that depends upon the power or a compressed or liquefied gas to expel the contents from the container.
- The aerosol products consists of
 1. Propellant
 2. Container
 3. Valve & actuator
 4. Products concentrate

1. Propellant

- The propellant is responsible for the development of proper pressure within the container and it expel the products when the valve is opened.
- The fluorinated hydrocarbon such as trichloromonofluoromethane (propellant 11), dichlorodifluoromethane (propellant 12), and dichlorotrifluoroethane (propellant 114) are widely used in oral and inhalational aerosol.
- Hydrocarbons like propane, butane, and isobutene and compressed gases like nitrogen, nitrous oxide and carbon dioxide are used in topical pharmaceutical aerosols.

2. Container

- The aerosol containers which must withstand pressure as high as 140 to 180 psig at a 130 °F
- Aluminium used to manufacturing seamless aerosol container. It has less chances of incompatibility due to its seamless nature.
- The combination of ethanol and propellant 11 in an aluminium container has been shown to produce hydrogen acetyl chloride, propellant 21, aluminium chloride and other corrosive product.
- Stainless steel container has been used for a large number of aerosols pharmaceutical. It is available in with or without plastic coating.
- Glass container – If the total pressure of the system is below 25 psig and there is not more than 15% of propellant, a glass can be safely used, pressure up to 33 psig can be utilized if the glass container having a double plastic outer coating.

3. Valve

- (a) An aerosol valve consists of many different parts like
- (b) Ferrule or mounting cap
- (c) Valve body or housing
- (d) Stem
- (e) Gasket
- (f) Spring
- (g) Dip tube

(a) Ferrule or mounting cap

- The mounting cap is used to attach the valve proper to the container. The cup is made from teen plate steel, at the aluminium also can be used. In the underside of the valve cup a single or double epoxy or vinyl coating can be added to increase resistance of corrosion.

(b) Valve body or housing

- The housing is generally made up of Nylon or Delrin. It has a opening at the point of the attachment of the dip tube is about 0.013 to 0.080 inch. The housing may or may not

contains another opening that is a vapour tap which prevents valve clogging with product containing insoluble material. The vapour tap opening is about 0.013 to 0.08 inch.

- A recent development that is useful for pharmaceutical is the aquasol valve. It is used in water based aerosol system where only active ingredient and water are dispensed (Propellant is in vapour state and present only in extremely small quantity). There is no chilling effect as occurs with hydrocarbon propellant.
- The chief difference between the Aquasol system and three phase system is that the former dispenses a fairly drug spray with very small particles.

(c) Steam

- It is also made up of Nylon or Delrin. But metal such as brass and stainless steel are also used. One or more orifice is set into the stem. They range from one orifice of about 0.013 inch to 0.030 inch to three orifices of 0.040 inch each.

(d) Gasket

- Buna- N and Neoprene rubber are commonly used for gasket.

(e) Spring

- Spring is made up of stainless steel. The spring folds the gasket in place and returns the valve to its closed position.

(f) Dip tube

- Dip tubes are made from polyethylene or polypropylene. The inside diameter of commonly used dip tube is about 0.120 to 0.125 inch. Capillary dip tubes are 0.050 inch. For highly viscous products it may be 0.195 inches.
- Metered valves are applicable to the dispensing of potent medication. Approximately 50 to 150 mg \pm 10% of liquid can be dispensed at one time with the use of such valves.

(g) Actuator

- Actuator is an integral part of almost every aerosol package to ensure that the aerosol product is delivered in the proper and desired form.

4. Products concentrate

- Product having low pH and containing water utilize organic lining of epoxy and vinyl resins. As compared to vinyl resin the epoxy resin has greater degree of heat stability. The vinyl resin forms a tough film and cannot be utilized for products that must be heat sterilized.

• **Manufacture of pharmaceutical aerosols utilize**

- ✓ Pressuring filling apparatus
- ✓ Cold filling apparatus
- ✓ Compressed gas filling apparatus

Pressuring filling apparatus: This cannot be used to fill inhalation aerosol whereas cold filling apparatus should not be used to fill hydrocarbon aerosols.

Cold filling apparatus: This method requires chilling of all components including concentrate and propellant to temperature -40°F , whereas the pressure filling method is carried out at room temperature.

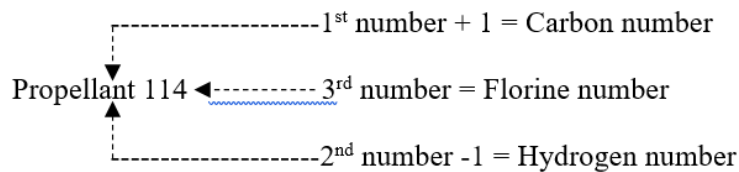
• **Evaluation**

- Testing of pharmaceutical aerosol includes flame projection, flash point, vapour point, vapour pressure density, moisture content etc.

- The flash point is determined by use of the standard Tag open cup apparatus, this aerosol products is chill to temperature of about -25°F ,
- A can punching device is available for accurately measuring vapour pressure.
- The density of aerosol system can be accurately determined through the use of a hydrometer or a pycnometer.
- The moisture content can determined by Karl Fisher method and Gas chromatography.
- Gas chromatography and infrared spectrophotometer have been used to identify the propellant.
- Particle size of aerosol is determined by the cascade impactor and light scatter decay method.

Calculation (Naming)

1. Propellant 114

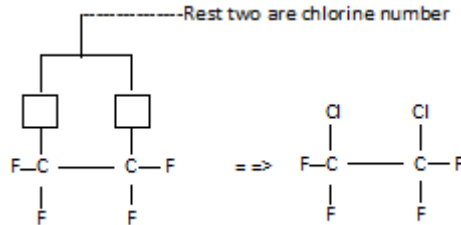


So,

C => $1+1 = 2$

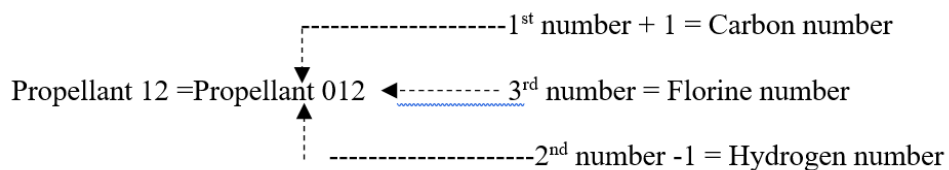
H => $1-1 = 0$

F => 4



Naming- Dichlorotetrafluoro ethane (Propellant 114)

2. Propellant 12



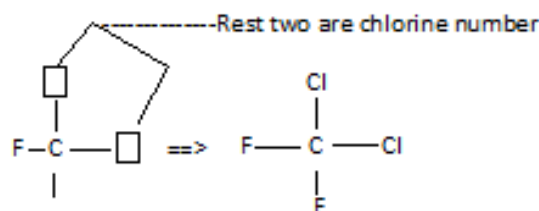
So,

C => $0+1 = 2$

H => $1-1 = 0$

F => 2

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Naming- Dichlorodifluoro methane (Propellant 12)

1.8 Solid Dosage Forms

Tablet

Tablets are solid dose pharmaceutical preparation containing drug substances usually prepared with the aid of suitable pharmaceutical excipients. They may vary in size, shape, weight, hardness, thickness, disintegration, and dissolution characteristics and in other aspects, depending on their intended use and method of manufacture.

Important characteristics

- Tablet is essentially tamperproof dosages from
- They offer the greatest capabilities of all oral dosage forms for the greatest dose precision & the least content variability.

Evolution

1. Size

At the constant compressive load, tablet thickness varies with

- Changes in die fill
- With particle size distribution
- Packing of particle mix being compressed.
- Total weight
 - With a constant die fill thickness varies with compressive load.
 - **The crown thickness of a tablet is measured with micrometre.**
 - **The total crown thickness of tables is measured with Side calliper.**
 - Tablet thickness should be controlled with in a $\pm 5\%$ variation of standard value,

2. Shape

- Shaped tablet required slotting punches
- Round tablet requires conventional punches
- **More convex the tablet surface, the more likely it is to cause capping problems.**

3. Colour

- The quantities colour evaluation may be done with
 - Reflectance spectrophotometry
 - Tristimulus calorimeter
- To measure the colour uniformity and gloss on a tablet surface – Micro reflectance photometer.

4. Hardness & Friability

The hardness of a tablet can be determined by

- (a) Monsanto tester
- (b) Strong Cobb tester
- (c) Pfizer tester
- (d) Erweka tester
- (e) Schleuniger tester
- (f) At a constant die fill a hardness increase and thickness decreases.
- (g) At a constant compression force (fixed distance between upper & lower hardness increases with increasing die fills & decreasing with lower die fills.
- (h) Vickers, Brinell Static test and dynamic tests associated to determine hardness.
- (i) Brinell hardness can be calculated by the equation
$$\text{BHN} = \frac{2F}{\pi D_1 \sqrt{(D_1 - D_1^2 - D_1^2)}}$$
- (j) Vickers hardness can be calculated by the equation.
$$\text{Hv} = \frac{2F \sin 68^\circ}{d^2}$$

Factors effecting for harder of tablet

- Tablets are harder after several hour of compression than after immediately compression.
- Lubricants if used in a high concentration or mixed for a prolonged period of time can affect hardness.
- Large tablets requires greater force and therefore less harder than small tablets.
- In a given granulation a Flat bevelled tool produces a tablet more harder than a deep cup tool.

5. Friability Test

- The laboratory friability tester is known as **Roche friabilator**.
- This works in the principal of **abrasion and shock**.
- It revolves at **25 RPM**.
- It drops at a distance of **6 inches**.
- During test it is operated for **100 revolutions**.
- Conventional compressed tablets that lose less than **0.5 to 1 %** of their weight are generally considered acceptable.
- Usually **chewable tablets** have higher friability value.
- **Very dry granulation** result high friability value.
- In a large scale industry, where the large no. of tablets are products, the friability evaluation is performed by **Rough handling test**. This test includes a. **Vibration test**, b. **Drop test**, c. **Incline plate impact test**
- **(When concave or deep concave punches are used they produce whispering at the tablet edge.)**
- **2 to 4 % moisture in granules act as binder.**

6. Weight Variation Test

- 20 tablets to be weighed individually and calculate average weight than compare with the individual tablet weight with the average weight.
- If no more than **2 tablets** are outside the percentage limits and if no tablet differs by more than **2 times** the percentage limit then the tablets are accepted.

Table Weight variation tolerance for uncoated tablets

Average wt. of a table in (mg)	Maximum percentage difference allowed
<130	± 10
130 – 324	± 7.5
> 324	± 5

7. Disintegration Test

- The height of disintegration tube is **3 inch long**.
- The temperature maintained during disintegration is $37^{\circ}\text{C} \pm 2^{\circ}\text{C}$
- During the test the tablets remain 2.5 cm below the surface of liquid on their upward movement & descend not closer than 2.5 cm from the bottom of the beaker.
- 28-32 cycles are maintained per minute.
- Perforated plastic disc may be placed on the top of the tablet which imports an abrasive action to the tablets.
- **Un coated tablets** have disintegration time below **5 to 30 minutes**.
- For **enteric coated tablets** the disintegration time is **1 hour** in gastric fluid, then in intestinal fluid for **2 hour**.
- Disintegration test mesh size **10 mesh**.
- Disintegration test basket mesh size is **40 mesh**.
- Croscarmellose sodium Sodium starch glycolate & Crospovidone are super disintegrants. Among all **Crospovidone** is having **high wicking activity**.

8. Dissolution Test

- The temperature of the medium $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$
- AS per IP the dissolution apparatus type 1 is **basket type**.
- **Electronic devices such as a Thomas Tablet Sentinel, Pharmakontroll and the Kilian Control System – MC, Monitor the tablet weight.**

Tablet Doffect

Capping: It is a term used to describe the partial or complete separation of the top or complete separation of the top or bottom crown of a tablet from the main body of tablet.

Lamination: It is the separation of a tablet into two or more distinct layers.

Cause: Deformational property of the formulation during & immediately following compression.

Table Formulation defects

Capping & Lamination cause	Solution
Rapid decompression	- Precompression. - Slowing the tableting rate - Reducing the final compression pressure
Deep concave punch (Capping)	Use of flat punch
Too dry granulation	Addition of hygroscopic substances such as sorbitol, methyl cellulose or PEG- 4000
Die develops a wear “ ring “ the area of compression	To turn the die over so that compression occurs in an unknown are over the ring.
Incorrect set up at the press	Correct set up at the press.

- **Brittle Fracture Index test (BFI)** is used to measure capping and lamination.
- In a tablet batch manufacturing process the lamination for BFI is **NOT more than 0.8**
- **Strain Index and Bonding Index** is associated with **Capping of a tablet**
- In a tablet batch manufacturing process the limitation for BFI is a **not more than 0.8**

Picking & Sticking

- Picking is a term used to describe the surface material from a tablet that is sticking to and being removed from the tablet surface by a punch. It is particularly concern with punch tips above engraving or embossing with letter 'B', 'A', 'O'.
- Sticking refers to the tablet materials adhering to the die wall.
- Chipping refers to the serious sticking at ejection of tablets cause chipping of tablet edges and can produce rough edge.

Remedies

- Lettering should be designed as large as possible.
- Plating of the punch faces with chromium is a method of avoiding picking and sticking.
- Colloidal silica may be added as polishing agents and make the punch faces smooth.
- Sometimes low melting point such as stearic acid & PEG may soften from the heat of compression to cause sticking. This can be avoided by either reducing low melting point ingredients or adding the ingredient with high melting point.
- When a low melting point medicaments are present high concentration. Refrigeration of the granulation may be made.
- Excess moisture may cause sticking. This may avoid by further drying of the granulation.

Mottling

- It is an equal distribution of colour on a tablet.
- Cause: The drug colour differs from the colour of tablet excipients.
- The drug whose degrading product are coloured both can be avoided by using colorants.
- A dye can cause mottling by migrating to the surface of granulation during drying. This can be overcome by changing solvent system, binding system, reducing the drying temperature.
- Coloured adhesive gel solution may not be distributed well because they must be hot & may lead to mottling. This can be overcome by incorporating fine powder adhesive such as acacia and tragacanth into the products before adding the granulating fluid or to disperse a drug colour additive during the powder blending step.

Orange Peel Effect

Cause: Inadequate spreading of the coating solution before drying.

Bridging

Causing: The film may shrink & pull away from the sharp corner

Weight Variation

Cause:

1. Granule size and size distribution before compression.
 - The apparent volume in the die is essentially same if the size of granules is filled inside the die. The void spaces between the granules may cause weight variation of tablets.
 - This can be avoided by filling the die with different size of granules so that the void space is minimized and hence the variation minimized.
2. Poor flow
 - Arching or bridging and Rat-holing at Hooper side are the prime cause of poor flow. It may be controlled with the vibrato attached with it.
 - Recent a patent is issued for a new feed frame design that accommodated excessive flow from the Hooper without compromising uniform weight variation.
3. Poor mixing
 - Inadequate mixing cause unsatisfactory granulation flow.
4. Punch variation
 - When lower punches are unequal length, they cause weight variation.
5. Hardness variation
 - If the volume of the material or the distance between punch varies, hardness varies and hence weight also varies.
6. Double impression
 - This involves only punches that have monogram or other engraving on them.

Table Tablet weight variation test

Average Weight (MG)	Wt. Variation
130 or less	10%
130 to 324	7.5%
More than 324	5%

Tablet Granulation

- Granulation is in part of pharmaceutical process that attempts to improve the flow of powdered materials by forming sphere like regularly shaped aggregate called granules.

$$\text{The shape Co-efficient of } (a_{vs}) = \frac{a_s \text{ (surface shape factor)}}{a_v \text{ (volume shape factor)}}$$

- The shape co-efficient of a sphere is 6
- The shape co-efficient of a cubic is 6.8

Determination of Granulation Characteristics

- Particle size and shape (By microscopic method)
- Surface area (By gas adsorption and air permeability method)
- Density (By pycnometer)
- Strength & Friability (By compression strength or friability measurement)

Flow Properties

- Fine powders $\leq 150\mu\text{m}$, the magnitude of the frictional and vander walls forces usually predominate.
- The larger particles $\geq 150\mu\text{m}$, such as granules produced by wet granulation process frictional forces normally predominate over Vander wall force.
- Repose angle and Hopper flow measurement are common methods to determine flow properties.
- Value of angle of repose $\leq 30^\circ$ usually indicate free flow and $\geq 40^\circ$ indicate poor flow.
- Shear cell method, Hausner ratio method & Carry index method are used to measure powder flow properties.

Compaction

- Transducers are used to measure the forces applied during compression process.
- Avalanching Behaviour is associated with powder flow property.
- Hackel equation is mostly used to describe Compaction of pharmaceutical powder.
- Hackel equation is in $\left[\frac{1}{1 - D_r} = k p + A \right]$

Manufacture of Granules

By dry manufacturing method

- Roller compactor is used in large scale for compression granulation.
- In this compactor first the material are formed in to ribbon like structures, which can than screened or milled into a granulation suitable for compression into tablets.
- Slugging is a process by which compacted mass (slug) are produced by a tablets press or by a special designed machinery followed by milling an screening to produce granules.

Wet granulation

These can be prepared by

1. LittelfordLodige mixture
2. Diosna mixture
3. Littelford MGT mixture
4. Gral mixture

Tablet Design & Formulation

Excipients

1. Diluent
2. Binder
3. Disintegrate
4. Lubricant
5. Colorant
6. Flavors
7. Sweeteners

Diluent

- Round tablets are in a size of 3/16, to 1/2 inch. And weight about 120 to 700mg.
- Oval tablets are up to 800 mg.
- Tetracycline product made with a calcium phosphate diluent has less than the half of the bioavailability of standard product.
- Divalent and trivalent cations form insoluble complexes and salts with a number for amphoteric or acid functionally antibiotics greatly reduces absorption.

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- When amine drugs prepared commonly with lactose diluents in presence of magnesium stearate or any metal stearate (lubricant), the resultant tablets were discoloured.
- The diluents which exist in their common salt of hydrate contain water as water of crystallization. These are not excellent diluents for water sensitive drugs because during storage condition at elevated temperature the products might be exposed. However the diluents like Dibasic calcium phosphate & calcium sulphate even contain water of crystallization, the water content does not release until the temperature is approximately 80°C is reached. Such excipients have low remaining moisture and superior to any anhydrous diluent.

Table Specification of lactose

Types of Lactose	Property	Disadvantages
Lactose	It is commercially available in 60 to 80 meshes (coarse) and 80 to 100 mesh (Regular) grades.	-
Anhydrous lactose	It does not undergo Maillard reaction which may lead to browning and discoloration of certain drugs.	-
Hydrous lactose	It is used in wet granulation process	It undergoes Maillard reaction which may lead to browning and discoloration of certain drugs.
Spray dried lactose	It is used for direct compression	It is prone to darkening in presence of moisture, amines and other compounds owing to the presence of a furaldehyde. A neutral or acid lubricant is used when spray dried lactose is used.
Corn, wheat, Potato starch	It contains a moisture of 11 to 14%	
Sta Rx 1500	It is used in direct compression It contains a moisture of 10 to 15% It is used as binder, diluent, and disintegrating agent. It has self-lubricant action but during preparation of little amount of drug (5 to 10 %), It is mixed with 0.25% of colloidal silicon dioxide.	
EM dex & Celutab	These are hydrolysed starches and used as direct compression It contains a moisture of 8 to 10% They contains basically 90 to 92 % of dextrose & 3 to 5 of maltose They are used in place of mannitol in chewable tablets because of their sweetness and smooth feeling in mouth.	

Dextrose

- It is available in hydrous and anhydrous form.
- Dextrose is combined with spray dried lactose **to reduce the tendencies** of tablets resulting darkness.

Mannitol

- It has a characteristic of **negative heat of solution**, low solubility and **pleasant testing** hence widely used in chewable tablets.
- It is non hygroscopic and used in vitamin formulation.
- These are having poor flow properties and require high lubrication labels.

Sorbitol

- It is optical isomer of **mannitol**.
- It is combined with mannitol to reduce its cost.
- It is hygroscopic at humidities **above 65%**

Sugar tab

- It is used in direct compression
- It contains 90 to 93 % sucrose + 7 to 1 % invert sugar.

Di pac

- It is used in direct compression.
- It contains 95% sucrose + 3% modified dextrin

Nu tab

- It is used in direct compression.
- It contains 95% sucrose + 4% invert sugar with small amount of corn starch and magnesium stearate.
- **Avicel (Microcrystalline cellulose)** it is used in direct compression.
- It exists in two tablet grades **PH (101) – Powder & PH (102) – granules**.
- It is a **unique diluent in that while producing cohesive compact**.
- These materials also act as **disintegrant**.

Points to Remember

- Jivraj et al (2000) is usually used as **filler for direct compression**.
- **Ludipres** is lactose monohydrate + Polyvinylpyrrolidone + Croscopolvidone
- **Cellactose** is Microcrystalline cellulose + Lactose
- **Cel-O-Cal** is Calcium sulphate + compressed microcrystalline cellulose.

Table Example of various binder & adhesives with their properties

Binder & Adhesives	Properties
Acacia & Tragacanth	<ul style="list-style-type: none"> - These are natural gums - They are added in dry or liquid form in a solution ranging from 10% to 25% concentration. - They are more effective when added in form a solution. - They often contaminated with bacteria and in wet granulation masses should be quickly dried at a temperature above 37° to reduce microbial proliferation.
Gelatin	It is a natural protein and used in combination with acacia.
Starchpaste	During preparation starch undergo hydrolysis to dextrin & glucose
Liquid glucose (50%)	It is also used as binding agent.
Modified natural polymer a. Alginate b. Methyl cellulose c. Hydroxy propyl methyl cellulose d. Hydroxy propyl cellulose	<ul style="list-style-type: none"> - In dry form all are used as binder and in aqueous solution they have adhesive properties. - HPMC is used an alcoholic solution to provide an anhydrous adhesive - Ethyl cellulose is used only as alcoholic solution. They also retard the disintegration & dissolution time of drugs.
Polyvinylpyrrolidone	- It is a synthetic polymer and used as adhesive in either aqueous or alcoholic solution.

Disintegrant

1. Starch USP - 5 to 10 % of tablet weight
2. Primogel & Explotab (Low substituted carboxy methyl cellulose) - 1 to 8 % (4% is optimum)
3. Pregelatinised starch - 5% concentration
4. Vegum V and bentonite - 10%
5. Microcrystalline cellulose -
6. Ac – Di- Sol - (it is an internally cross linking form of sodium cmc)
7. Super disintegrant - Sodium starch glycolate, Cross povidone, Carmellose

Lubricant

These are intended to reduce the friction during tablet ejection between the walls of tablet and the wall of die cavity in which the tablet is formed.

1. Stearic acid : It is salt and derivatives.
2. Talc : Due to presence of iron in it, sometimes the drug whose breakdown is catalysed by iron.
3. PEG : Used as water soluble lubricant.

Antiadherent

- These reduce sticking or adhering of any tablet granulation or powder to the faces of punches or to the die wall.
- All water insoluble lubrication usually act as antiadherent.
- Talc, Magnesium stearate, starch and starch derivative also act as antiadherent.

Glident

They promote the flow of the tablet granulation or powder materials by reducing friction between particles.

1. Talc – 5%
2. Corn starch - 5 to 10 %
3. Colloidal silica
 - Cab-O-Sil - 0.25 to 3%
 - Syloid - 0.25 to 3%
 - Aerosil - 0.25 to 3%

Colours – FD & C and D&C dyes

Flavours – Flavour oils added with 0.5 to 0.75%

Sweeteners

1. Mannitol - 72% AS sweet as Sucrose
2. Saccharine - IT is only an artificial sweetener.
 - It is 500 times sweeter than sucrose
 - Its major disadvantage is that it has bitter after taste and it is carcinogenic.
3. Aspartame - It is largely replaced by sucralose.
 - Its disadvantage is lack of stability due to presence of water.

Type of Tablets

Compressed Tablets

- The category referred to standard uncoated tablets

Multiple Compressed Tablets

These are

1. Layered Tablets
 2. Compressed coated tablets
- These are unusually prepared to separate physically or chemically incompatible ingredients or to produce repeat action or prolonged action products.

Repeat action tablets

- In this preparation the core tablet is usually coated with shellac or enteric polymer so that it will not release its drug load in the stomach. The second dose of drug is then added in the sugar coating which is allowed to coat on the surface of tablets. This coat is allowed to its drug load in the stomach. Ultimately the tablet produces repeat action in stomach & intestine.

Enteric coated tablet / Delayed action tablet

- All the enteric coated tablets remain intact in the stomach but quickly release in the duodenum.
- In the disintegration test the enteric coated tablets are immersed in water at room temperature for 5 minutes.
- Cellulose acetate phthalate or polyvinyl acetate phthalate or Hydroxypropyl methylcellulose phthalate are commonly used for enteric coating.
- The pH gastric fluid is – up to 4
- The pH of duodenum is – 4 to 6
- The pH of intestine is - 7 to 8
- The drug like erythromycin is prepared as enteric coated because it destroys in low pH.

Sugar coating tablets

- These types of tablets permit separation of incompatible ingredients between coating and core.
- The above principle helps for the preparation of multivitamin & multi mineral or vitamin combination.
- Water soluble polymers are often incorporated in sugar coating solution to reduce the coat weight of tablets (may be 50% less).
- Automation spray coating equipment is used in this coating process.

Film coated tablets

- An article spray coating procedure is typically for film, coating composition.
- This is the coating preparation where drug is not required coating.
- Polymers such as Hydroxypropyl cellulose, HPMC is dissolved in water with an appropriated plasticizer are used to produce immediate release film coating.
- The colloidal dispersion of Ethyl cellulose in water makes it possible to produce slow or controlled release film coating without the use of organic solvents.
- Aqua coat trade name of 30% Ethylcellulose dispersion is marketed under FMC Corporation.
- The film coated tablets have better mechanical strength of the coating based on the elasticity & flexibility of the polymer coating.

Chewable tablet

- The antacid tablets are prepared in chewable form because the dose of antacid is too large to swallow and if the tablet chewed prior to swallowing better acid neutralization may be possible

Tablet Classes

Buccal & Sublingual tablets

- When these preparation held in the mouth, they release their drug for absorption through oral mucosa an intended to produce systemic circulation.
- They avoid to first pass metabolism
- They are designed not to disintegrate but to slowly dissolve typically over a 15 to 30 minute period.

Troches & Lozenges

- They designed not to disintegrate in mouth but to dissolve slowly over a period of 30 minutes or less.
- Lozenges are formed by fusion or by candy molding process.
- Troches are formed by direct compression.

Dental cones

- The usually vehicle for the preparation is sodium bicarbonate, sodium chloride, or an amino acid.
- The drug content of the tablet is dissolved slowly for 20 to 40 minute period.

Implantation tablet

- They are typically shaped and not more than 8mm length.
- Keron injector is used to implant the tablet.
- They are restricted to use month to a year.
- They are restricted to use in humans because of surgical technique and tissue toxicity at the site of application.
- They usually applied to administration of growth hormones to food producing animals.

Effervescent tablet

- The tablet is typically prepared by compressing the active ingredients with a mixture of organic acid such as citric acid or tartaric acid and sodium bicarbonate.
- The effervescent tablet is specially packed in Hermetic-type-foil and various acid anhydrides may be used in combination with sodium glycine carbonate and various sesquicarbonates

Important Chart to Remember

Ingredient	Use
Calcium phosphate	Adsorbent diluent
Calcium hydrogen phosphate	Used for direct compression
Colloidal silica	Improve granular flow
Anhydrous dextrose	Adsorb moisture at high relative humidity
Dextrose (spray dried)	direct compressible but absorbs moisture at high
Lactose	Inexpensive & gives granules by moist granulation
Lactose (Spray dried)	useful for direct compression & incompatible with primary amine
Lactose anhydrous	direct compressible but prevent moisture uptake

Starch	Direct from used as absorbent & used as disintegrate
Mannitol	Gives cooling defect in the mouth

Material	(Lubricant)
Boric acid	External lubricant + Lubricant die wall
Colloidal silica	Lubricant + Glidant
Hydrogenated vegetable oil	Internal Lubricant + Lubricant die wall
Magnesium stearate	External Lubricant + Lubricant die wall
Polyethylene glycol	Internal Lubricant + Lubricant die wall
Stearic acid	die wall
Talc	Lubricant + Glidant

Tablet Coating

Objective

- To make the taste, odor, or colour of the drug.
- To provide physical and chemical protection.
- To control the release of the drug.
- To protect the drug gastric environment.
- To improve the pharmaceutical elegance.
- To incomplete another drug or formula adjuvant in the coating to avoid chemical incompatibility.

There are three primary component involved in table coating

1. Tablet preparation.
2. Coating process (Coating equipment)
3. Coating material or composition.

There are three types of equipment are generally used for tablet coating

1. The standard coating pan
2. The perforated coating pan
3. The fluidized bed (air suspension coater)
 - The standard coating pan consist of a circular metal pan of **8 to 60 inches** in diameter and rotated on
 - It is horizontal axis.
 - The improved standard coating pans are Pellegrini pan, immersion sword an immersion tube.
 - The perforated pan system consists of a perforated or partially perforated drum that is rotated on its horizontal axis. The perforated pan system includes.
 - (a) Acclacota
 - (b) Hi-coater
 - (c) Dria coater
 - The **Glatt coater** is the latest perforated pan coater.
 - The fluidized bed to basic types of system is used.
 1. High pressure, air less
 2. Low pressure, air atomised.

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- In the air less system liquid is pumped at high pressure (250-3000psig) through a small orifice (0.009-0.020inch in diameter)
- In the low pressure air atomized system liquid is pumped at low pressure i.e. **5-50 psig** through a somewhat larger orifice (0.02 inch to 0.060 inch in diameter)
- **Air capacity:** - This value represents the quantity of water or solvent that can be removed during the coating process.
- There are two type of tablet coating process.
 1. Sugar coating
 2. Film coating
 - Sealing
 - Sub coating
 - Syruping (Smoothing)
 - Finishing
 - Polishing

Sealing

- Seal coating prevent the moisture penetrating into the tablet core.
- Shellac is an effective seal coating agent but the disintegration and dissolution times increased because polymerization of shellac.
- Zain is an alcohol soluble protein derivative from corn which is also used for seal coating.

Sub coating

- The sub coating is done to increase the tablet weight and to round the edges.

Syruping (Smoothing)

- The purpose of syrup coating is to cover and fill the imperfection of the tablet surface caused by the sub coating step and to impart the desired colour.

Polishing

- Polishing is the final step and is done by canvas – lined polishing pan or clean standard coating pans. The bees wax or cornouba wax or worm wax or worm solution of these waxes in naptha.

The film fottmers are two types-

1. Non enteric material
2. Enteric material

The non-enteric materials are:

Hydroxy propyl methyl cellulose.

Methyl hydroxyl ethyl cellulose

Ethyl cellulose

Hydrox propyl cellulose

Povidine

Sodium carboxy methyl cellulose

Acrylate polymers

- HPMC is a material of choice for air suspension and pan coating system. HPMC is ideal polymer for film coating.
- Ethyl cellulose is completely insoluble in water and gastrointestinal fluid. This material is available as Aqua coat (30% ethyl cellulose)
- Povidone is a synthetic polymer available as four different viscosity grades. I.e. K-15, K-30, K-60 and K-90. The most commonly used povidone is K-30. Povidone is soluble in both acidic and basic medium.
- Acrylate polymer i.e. Eudragit E is a cationic polymer which is only Eudragit material freely soluble in gastric fluid up to pH 5.

The enteric materials:

- They deliver drug included for local action in the intestine and by pass systemic absorption in the stomach, they are resistant to gastric fluid.
- Example: Cellulose Acetate phthalate (CAP)
Acrylate polymers
Hydroxy propyl methyl cellulose
Polyvinyl acetate phthalate
- CAP is most widely used acrylate polymer and has and disadvantages. i.e. dissolve only above pH 6.
- Two forms of acrylic resins are Eudragit L and Eudragit S. Eudragit L and S are soluble in pH 6 and 7.
- Plasticizers used in tablet coating are castor oil, Propylene glycol, glycerine, low molecular weight PEG and surfactant i.e. Tweens and Spans.
- Colorants: - The inorganic materials (iron oxides) and the natural colouring materials (Anthocyanin, Carmel, Carotenoids, Chlorophyll, Indigo turmeric) are also used to prepare coating solution.
- Opalux: - opaquant colour concentrate for sugar coating.
- Opaspray: - Opaquant colour concentrate for film coating.
- Opaquant extenders: - The most commonly used material is titanium dioxide. Some other material is silicates, carbonates, sulphate oxide and hydroxides.
- Extrusion & Spheronisation are the process used to obtain spherical particles, suitable for coating to produce controlled release formulation.
- Side vented pan is mostly used for film coating.
- A polymer which has optimal dissolution profile for enteric coating is HPMCP

Film Defect

- Sticking and Picking: - Over weighting or excessive film thickness causes tablet to stick to each other, or to the coating pan.
- Orange peel effect: - Inadequate spreading of the coating solution before during causes a bumpy or orange peel effect on the coating.
- Bridging and filling: - During drying the film may shrink and pull away from the sharp corners resulting in a bridging of the surface depression.
Filling is caused by applying too much solution resulting in a thick film that fills and narrow the monogram or bisect.
- Blistering: - When coated tablets required further drying, too rapid evaporation of the solvent from the core results in blistering.

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Hazing / Dull film: - This is sometimes called bloom. It can occur when too high processing temperature is used for a particular formulation.

Cracking: - Cracking occurs if internal stress in the film exceeds the tensile strength of the film.

Table Some important solution with example

Different Solutions	Name
Seal coating solution	Dextrin, PEG-4000
Sub coating solution	Gelatine, Sugar cane
Polishing solution	Naphtha
Sub coating powder	Dextrin
Syrup solution	Syrup USP

Table Some example with their trade name and composition

Trade Name	Composition
Methocel	Methyl cellulose
Carbomer	Carboxypolymethylene
Povidone	Polyvinyl pyrolidone
Atlas	Sorbitan esters
Calgon	Polymetaphosphate

Table Some of polymeric powder with their specification

Types of Polymer	Example	Characteristic
Water soluble polymer	Hydropropyl cellulose Hydroxyprop cellulose Povidone	-
Water insoluble polymer	Ethyl cellulose, sodium alginate	-
Homo polymers	-	consist of a single monomer
Copolymers	-	consists of more than two monomer
Natural polymer	Cellulose, proteins	-
Synthetic polymer	Dacron, Cellulose	-

Table Polymer and their trade name with their specification

Trade Name	Extended to Release products type
Disintegrants	Avicel & Explotab
Lubricant	Talc
Coating agent	Castorwax
Enteric coat	CAP
Sustained release agent	Keltrol & Ethyl cellulose & HPMC

Table pH range inside body fluid

Fluid	pH
Stomach	6.5 to 8.0
Duodenum	5.0 to 6.0
Jejunum & large Intestine	1.2 to 3.5

Capsule

- **Capsules** are solid dosage forms in which medicinal agents and / or inert substances are enclosed in a small of gelatine.
- Mother & Dublin invented single piece of gelatine capsule.
- Murdock invented two piece telescopic capsule.

HRAD Capsules

- The capsule are mainly made of **gelatineblends** and may contain small amount of certified dyes.
 - Opaquing agents, plasticizers and preservatives.
- Gelatine is a heterogeneous predicts derived by irreversible hydrolytic extraction of treated animal collagen.
- Common sources of collagen are animal bones, hide portions and Frogen pork skin.
- **Blends of bone** and **pork skingelatin**s normally used for hard capsule production.
- The pork skin gelatin contributes **plasticity and clarity** to the bend and thereby reducing haze and clarity to the bend.
- **Type Agelatin** is derived from an acid treated precursor and exhibits an isoelectric point at **pH 9.0**
- **Type B gelatin** is derived from an alkali treated precursor an exhibits an isoelectric point at **pH 4.7**
- **“Green” (Fresh)** bones are used for the preparation of a gelatin of the **Type “B”**.
- **“Acid bones”** are used for the preparation of a gelatin of the **Type “A”**.
- Titanium dioxide **is used as** Opacifier for **gelatin mass (0.2 to 1.2%)**

Preparation of Capsule Shell

- Gelatin capsule are formed by dipping cool stainless steel mould pins & by centrifugal casting method.
- Automatic capsule production machine include the steps like dipping, spinning, drying, tripping, trimming and joining.
- The stainless steel mould pins are used to form the capsules and the tolerance is held with in fractions of a thousand of an inch.
- A number of (About 150) pair on pins is dipped in to a molten gelatin solution aform caps and bodies separately. The capsules are striped from the pins by bronze jaws and trimmed to definitive length. The cap and body sections are joined and finally ejected from the machine.
- The entire cycle is completed by 45 minutes.
- Thickness of the capsule wall is controlled by the viscosity of the gelatin solution and the speed and time of dipping.
- The size of the empty capsule may be varied due to variation of moisture content.
- Empty capsule usually receive the moisture of 12% to 15%
- Below 10% moisture content in gelatin shell caus brittle and may shrink to the point.
- Above 16% moisture content in gelatin shell cause size problem in the filling equipment.
- The solubility limit for empty capsules are
 - (a) Water resistant fails to dissolve in water at 20 to 30 °C in 15 monute.
 - (b) Acid solubility – dissolves in less than 5 minuts in 0.5% aqueous HCl (w/w) at 36 to 38 °C

Table List of filling equipment with their capacity and specification

Company	Model	Filling Capacity	Filling Material	Specific Feature	
Eli-Lilly	ROTOFIL	1200 Capsule/minute	Pellets		
Farmatic	2000/15	40000/hour	Powder	It's function is based in a continues motion with dosator- type powder feeding units	
	2000/30	80000/hour			
	2000/60	160000 / hour			
Hofiger and Karg	GKF - 303	303 / Minute	Pallets, Powder, Tablets Thixotropic liquids (The first three models)		
	GKF - 602	602 / Minute			
	GKF - 1500	1500 / Minute			
	GKF - 2500	2500 / Minute			
Mocofar	MT- 12	35000 / hour	Powder	It is function is based in a rectification and filling.	
	MT – 13/1	5000 / hour			
	MT – 13/2	10000 / hour			
mG2	G36/2	300 / minute	Powder	It is function is based in a rectification and filling.	
	G36/4	150 / minute	Granule		
	G36	600 / minute	Pellete		
	G37N	1600 / minute			
	G38	1000 / minute			
Osaka	R-180	70000 to 135000 / minute	Powder granule		
Perry	CF ACOFIL	600000 / hour	Powder	It has a powder dose control capacity which is a unique feature	
Zanasi	LZ-64	4000 / hour	Powder, Pallet and Tablet		
	AZ-20	9000 to 20000 / hour			
	BZ-40	30000 / hour	Powder, Pallet and Tablet (BZ-72 & BZ-40) Powder & Granule (BZ-110)		
	BZ-72	60000 / hour			
	BZ-110	110000 / hour			
	BZ-150	150000 / hour	Powder (BZ-150)		
	Z-5000R1	70000 / hour			Powder, Granule and tablet
	Z-5000R2	110000 / hour			
Z-5000R3	150000 / hour				

Capsule Filling

- The empty capsules can be handled in the area having humidity level of 30-45%
- Capacity of hard gelatin capsules ranges from numbers 000 to 5 9600 to 30 mg)
- Approximately capacity of empty gelatin capsule areas follows-

Size	000	00	0	1	2	3	4	5
Vol.	1.40	0.95	0.68	0.50	0.37	0.30	0.21	0.13
- During the filling by Eli-Lilly (Rotofil), Hofiger and Karg (GKF), Oskar (R-180) and Perry (CIACOFIL) models, the powder must have flow characteristics. For example when the acetyl salicylic acid is filled by the above model, the excipient should be flow able corn starch. The ideal lubricant is metallic stearate.
- During the filling by Zanasi ,(LZ, BZ, ZR,) Macofar(MT), Farmatic (2000) and mG2 (G) models the powder must have sufficient cohesiveness to retain its slug form during delivery to the capsules. For example when the acetyl salicylic acid us filled by the above models the excipient should be microcrystalline cellulose. The ideal lubricant is mineral oil.
- The glidants usually used (less than 2%) during filling a capsule are glycol esters, silicones, silicon dioxide, Metallic stearate, stearate acid and talc.

Evaluation

1. Weight variation test

- 20 intact capsules are individually weighed and the average weight is determined. If none of the individually weights are less than 90% or more than 110% of the average the it meets the test requirements.
- If the above test does not meet the requirements, then the individual net weight is determined and these are averaged. Then the difference is determined. If the difference does not exceed 10% of the average in more than 6 of 60 capsules, and if in no case any difference exceed 25% then it meets the test requirement.
- ROTOWEIGHT is high speed capsule weighing machine. The capsules are gravity – fed onto vacuum Pins which measure the reflected energy (backscatter) of a low power X-ray beam directed at each capsule.
- This reflected energy is proportional to the weight of the filled capsule. The machine operates 73000 capsules per hour.
- VERICAP 2000 is a high speed capsule weight machine. It operated by detecting capacitance variation, as filled capsules are propelled at high speed by compressed air between two charged plates. The measured change in dielectric constant thus produced is correlated to the weight of the capsule. The machine operates 73000 capsules per hour.

Capsule Dusting / Polishing Machine

The following method is used for Polishing of capsules.

1. **Pan polishing:** Accelacota tablet coating pan may be used to polish the capsule. A polyuthrane Or Cheese cloth liner is placed in the pan and the liner is used to trap the removed dust as well as to impart to gloss to the capsule.
2. **Cloth dusting:** In this method bulk filled capsule arte rubbed with a cloth.
3. **Brushing:** In this method capsules are fed under rotating soft brushes.
4. **Rotosort:** This is equipment used for dedusting and polishing of capsules. It is also used t o separate unfilled capsules. Filled or unfilled bodies and loose caps. The machine handles 15000 capsules per hour.
5. **Erweka KEA:** This is equipment used for polishing of hard gelatin capsules. It moves the capsules between soft plastic tassels against a perforated plastic sleeve, under vacuum.
6. **Seidenader model:** This is an equipment offers two units may be used separately or may be combined in the (PM-60) finishing of the filled gelatin capsules. If removes unfilled capsules. The PM-60 unit used to polish the finished capsules. It consists of two lamb wool belts moving in the opposite direction. The capsules are carried on the lower belt and both belts are under suction.

Special Techniques

Imprinting: This is the process by which the company print the products and identification information on capsules surfaces. The different companies which provide the machines are as follows.-

Company	Capacity	Types of Printing
Ackely	50000 / hour	Straight line and circumference
Markem	60000-250000 / hour	Straight line but not circumference
Harnet	500000 / day	Straight line and circumference

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- Fluidised bed drier is used in the pharmaceutical industry for the drying of powders before filling.
- Capsule all liquid. Solution and suspension for capsulation should be homogeneous, air free and flow by gravity at room temperature.
- Water soluble and volatile constituents can migrate into the hydrophilic shell and volatilize from its surface.
- The products cost of capsule is directly proportional to **shell thickness**.

Table Ingredients used in preparation of capsules shell

Purpose	Ingredients used in Preparation of Capsules Shell
Preservative	Propyl paraben (0.2%)
Aids solubility	Fumaric acid
Organoleptic additive	Essential oil
Opacifier	Titanium dioxide

Table List machine used in capsule preparation

Name of the machine	Use
a. Rotosort	1. Capsule sorting machine
b. Erweka KEA	2. Capsule dedusting and polishing machine
c. Seidenader model PM-60	3. Capsule polishing machine
d. 0.2% Markem model 280 A	4. Capsule imprinting machine
e. Vericap 1200, Rotoweigh	5. Capsule weighing machine
f. Hartnett Model	6. Capsule imprinting machine
g. Osaka, Accofil	7. Capsule filling machine

Table Disintegration time of capsules

Capsule	Disintegration Time
Hard capsule	30 minutes
Soft capsule	60 Minutes

Soft Capsule

- The custom manufacturers are specialist in production of these soft gelatins.
- The soft gelatins are useful in oral, suppository, topical, ophthalmic and otic preparations.

Method of Manufacture

Method	Weight variation in the net content
Plate process	20-40%
Rotary die process	±3%
Reciprocating die process	Negligible
Accogel machine	Negligible

Nature of Capsules Shell

- The capsules shells principally composed of Gelatin, Plasticizer, and water. It may also contain preservatives, colorants, opacifying agent's flavourings, sugars and acids.

Gelatin strength

- The bloom strength or gel strength of gelatin is the cohesive strength of the cross – linking that occurs between gelatin molecules and this strength is proportional to the molecular weight of the gelatin.
- Bloom is determined by measuring the weight in grams required to move a plastic plunger that is 0.5 inches in diameter 4 mm into a $6\frac{2}{3}$ % gelatin gel that has been held at 10°C for 17 hours.
- The normal bloom strength of a gelatin is usually 150-250g.
- The higher bloom strength becomes more physically stable capsule shell.
- The cost of the gelatin is directly proportional to bloom strength.

Viscosity of gelatin

- The viscosity of gelatin determined on a $6\frac{2}{3}$ % concentration of gelatin in water at 60°C.
- The viscosity of gelatin is 38 ± 2 milipoise (25 – 45 milipoise).
- Low viscosity (25-32 milipoise) with high Bloom (180 to 250g) gelatins are used for the capsulation of gygroscopic vehicles or solids.

Iron content

- The iron content present in gelatin used for manufacturer of soft capsules should not more than 15 ppm.

Plasticizers

- The role of plasticizer in capsule is it determines the hardness of shell.
- Gelatin is plasticized by addition of glycerine. Sorbitol or other polyol.
- The ratio by weight of water to dry gelatin is, Water (0.7-1.3) : dry gelatin (1.0)
- Gelatin and glycerine are used for the preparation of lamellas in specified ratio 5:1.

Table Specification for hardness of capsules

Ratio of dry glycerine and dry gelatin	Types of hardness
0.4: 1	Hard
0.6: 1	Medium
0.8: 1	Soft

- Usually medicaments to the gelatin mass are not added. But benzocaine is added (3mg / capsule shell) in chewable cough capsules)

Colorants

- Usually darker colour are used large size capsules (14 to 20 minim oblong).
- Clear type colour is used in clear type filling materials and opaque colours are used in suspensions.
- Before the colour is chosen, mixture should be checked by addition of water to ascertain.
- In the preparation of vitamins and minerals, as the iron is present in the gelatin, the water soluble iron sensitive ingredients migrated from the filling material in to shell an cause darks spots.
- FD & C and D&C water soluble dyes, certified lakes pigments, and vegetable colour alone or in combination is used as colorants.

Table Additional component of gelatin mass

Use	Name	Concentration
Preservative	Methyl paraben and propyl paraben In ratio of 4:1	0.2%
Opacifier	Titanium dioxide	0.2 to 1.2%
Flavoring agent	Ethly vanillin Essential oils	(0.1%)
To produce chewable shell and taste	Sucrose	(up to 2%)
Aids solubility (Reduces aldehydes Tanning of gelatin)	Fumaric acid	5%

Table The nature of the capsule content

Soft gelatin capsule size and shapes	Maximum volume for human intake
Oblong	20 minim
Oral	16 minim
Round	9 minim

Liquids

Full volume

- The minimum fill volume may be calculated from the specific gravity of liquid.
- The size of capsule depends on the dosage required.
- The die size and shape may be chosen from the nominal capacities in minims.
- The content of the soft gelatin capsule is liquid or a combination of miscible liquids, solutions suspension, etc.
- Liquids those are water miscible and volatile in nature cannot be included as a major constituent of capsule because they can migrate into the hydrophilic gelatin shell and volatilize from its surface.
- Gelatin plasticizer like glycerine and polyethylene glycol cannot also be the major constituent of the capsule because they will make the capsule softer. However water and alcohol up to 5% if capsule content can be used as co-solvent to aid in the preparation of solutions.
- The plasticizer like glycerine and propylene glycol up to 10% of capsule content can be used as co-solvents with polyethylene glycol.
- The most widely used liquid for human use are as follows-

Oil Active ingredients	Vegetable oils	Non-ionic suffocative agents	Fish oil
Clofibrate	Soyabain oil	Polysorbate 80	Shark liver oil
		Polyethylene glycol 400	
		Polyethylene glycol 600	

- The viscosity of liquids ranging from 0.222 cp to 3000 cp (at 25°C) is allowed to be encapsulated but the liquid like glycerine (954cp at 25°C) cannot be encapsulated because it can cause binding of slide valves and pumps filling machine.
- The pH of liquids to be encapsulated should have been between 2.5 to 7.5
- The organic or inorganic solids which is to be encapsulated in suspension form should be 80 mesh or finer particles.

- The formulation of suspension for soft gelatin encapsulation depends upon the technique base adsorptions of the solids to be suspended. Base adsorption is expressed as the number of grams of liquid base required to produce a capsulatable mixture when mixed with one gram of solid.
- The base adsorption is used to determine the “minim per gram” factor (m/g) of the solid. The minim per gram factor is the volume in minims that is occupied by one gram of the solid plus the weight of liquid base required to make a capsulatable mixture.

Capsule Manufacturer Processing and Control

- Except the gelatin preparation area the temperature range of manufacturer area is 20-22°C and the humidity level in is a maximum of 40% in the operating areas and a range of 20-30% in drying areas.

Gelatin Preparation

- The gelatin is weighed on a printomatic (most accurate) scales and mixed with the accurately metered and chilled (7°) liquid constituents in a pony mixer. The mixing process requires about 25 minute for 270 kg of mass.
- The resultant fluffy mass is transferred to melting tanks and melted under vacuum (29.5”HG) at 93 for 3 hours.
- The mass is then maintained at a temperature of 57-60 before an during capsulation process.

Material Preparation

1. **Weighing-** All materials used for preparation for encapsulation must be weighed with. Printomatic scales for exact measurement and control record.
2. **Blending-** All weighed ingredients are kept in a mixture like Cowells for initial blending of solids with the liquids base.
3. **Milling-** After initial blending the materials are put through a milling or humanizing process. The equipment used in this process such as the homoloid mill, stone mill hopper mill or the Urschel Comitrol. The purpose of milling operation is to break up the agglomerates of solid and to make certain that solids are “wet” with the liquid carriers so as to achieve a smooth and homogenous mixture.
4. **Deaeration-** Then all mixture are subjected to deaeration. This is necessary to achieve uniform capsule fill weights and this also protects against loss of potency through oxidation prior to and during capsulation. This is the process by most liquids and suspension may be deaerated by means of equipment designed to expose thin layer of material continuously to vacuum (29.5”Hg) and at the same time transfer the material from the mixing tank to the container that will be used at the capsulation machine.

Capsulation Rotary Die Process

- The gelatine mass is fed by gravity to a metering device, this device control the flow of the mass onto air cooled (13-14°C) rotating drums.
- Gelatine ribbon of controlled ($\pm 10\%$) thickness are formed. The wet shell thickness may vary from 0.022 to 0.045 inch.
- The ribbons are feed through a mineral oil lubricating bath, over guide rolls, and down between the wedge and the die rolls.
- The materials to be capsulated flow in to the gelatine ribbons between die rolls.
- Now the filled, shaped and hermetically sealed capsule cut from the gelatine ribbon.
- The sealing of the capsule achieved by mechanical pressure on the die fills and the heating (37 to 46°C) of the ribbons by the wedge.
- The capsules are now conveyed through neptha wash unit to remove mineral oil.

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- The capsules are now dried by infrared drying steps or allowed to come equilibrium with forced air condition of 20-30% relative humidity at 21-24°C, capsules at equilibrium with 20-30% RH at 21-24°C are considered dry and the shell of such a capsule contains 6-10% water.
- The moisture content of the shell is determined by toluene distillation method.
- The capsules thereafter sent for heat branding or ink printing or ink printing for purpose of identification.

Physical Stability

- Physical stability of capsule product depends upon –
 - a. Types of gelatine
 - b. Gelatine formulation
- The physical stability soft gelatine capsule is associated primarily with the pick-up or loss of water by the capsule shell.
- The capsule shell is dried at the equilibrium with 20-30% at 21-24°C
- The ratio between dry glycerine to dry gelatine is 0.5:1
- The ratio between water and dry gelatine is 1:1
- The low humidifies (>20%RH), low temperature (<2°C) and high temperature (>38°C) or combination of these condition have only transient effects.
- The accelerated physical stability test is strictly relevant to the integrity of the gelatine shell and should not be constructed as stability of test ingredients.
- The resultant of ‘soft spot’ pm a capsule is due to slower drying.
- The rotating- bottle method is used for dissolution study of capsules.

Important Point to Remember

- Ingredient used for capsulation is soft capsule should flow by gravity at a temperature not exceeding 35°C.
- The soft gelatine capsule is soft, globular having gelatine shell is thicker than hard gelatine capsule.
- The type of soft gelatine is discarded are a. overfills b. underfills c. foregin
- Equipment which are used in capsulation for milling or homogenization a. Homoloid mill b. stone mill c. urchelcomitrol mill
- The scaling temperature of soft gelatine capsule is usually in the range of 37 to 40°C.
- While making soft gelatine capsules, gelatin mass is fed by gravity to a metering device known as spreader box which controls the flow of mass on to air cooled rotating drum.
- The thickness of wet shell of soft gelatine capsules is between 0.025-0.032 inches.
- The ideal bloom strength for manufacturer of hard gelatin shells is 230-275.
- The viscosity of the solution used to manufacturer hard gelatin shells is 3.3-4.7 mPas.
- The water content permissible in hard gelatin is 13-15%.
- The relative humidity where the hard gelatin capsule filed are 30-50%
- Cross linking of gelatin which is sometimes present at trace level in excipients is catalysed by formaldehyde.
- Auger method, piston temp method, Dosator methods are the independent method for powder and granulate filling in capsules.
- Osaka machine is used for powder & granulate filling method by dependent method.
- Zanasi machine is used to examine lubricity requirement of formulations being filled with dosator machine.
- In liquid encapsulation microscopy sealing (LEMS) process, 50% water + 50% ethanol is the sealing fluids which sprayed on the joint between the cap & body.

- The alternative material for gelatine offered by capsule manufacturer is Starch & HPMC.
- During manufacturer of soft gelatin capsules, the oxygen sensitive drug can be protected by filling under Nitrogen.

Microencapsulaton

- Microencapsulation provides the desired coating properties such as-
 - a. Strength and flexibility
 - b. Imermebility
 - c. Optical prooertues
 - d. stabilising and sustained release
- The method which are suitable for microencapsulation are
 - a. Air suspension
 - b. Pan coating
 - c. Polymerization
 - d. Coacervation
- Microencapsulation is a process by which solid, liquid or even gases may be encapsulated into microscopic size particles.
- Blisters are made up of **Polyvinyl chloride**.
- Polychlorotrifluoroethylene film is laminated to protect the content in Blister package from moisture
- A water soluble substance used as coating material in microencapsulation process is Hydroxy ethyl cellulose

Ingredients in Gelatin	Concentration
Methyl Paraben and propyl paraben	0.2%
Titanium dioxide	0.2 to 0.2%
Ethyl vanillin	0.1%
Essential oil	2.0%
Sugar	5%
Fumaric acid	1%

1.9 Sterile Products

Parenteral drug products are the dosage forms intended for administration by a route that does not involve the gastrointestinal (GI) tract (thus, parenteral). Most of the parenteral drug products are injectable dosage forms that are intended for administration by injection using a syringe and a needle.

Vehicle

- The most common vehicle for sterile product is water for injection. Sometimes non-aqueous solvents are also used.
- The conductivity of WFI is 0.99 micromhos.
- The total solid content of WFI is 10 ppm.
- The non-aqueous solvents are two types. 1. Water miscible, 2. Water immiscible.
- The solvent which is miscible with water usually used in combination with water as vehicle. These are for example dioxolanes, dimethylacetamide, butyl glycol, polyethylene glycol 400 and 600, propylene glycol, glycerine, ethyl alcohol, N-(β -hydroxyethyl) -lactamide, etc.
- The solvent which is not miscible with water includes fixed oils, ethyl oleate, isopropyl myristate, benzyl benzoate.
- The most frequently used non aqueous solvent is polyethylene glycol, propylene glycol, and fixed oils.

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- In non-aqueous injection the oil used as solvent are sesame oil cotton seed oil, corn oil and peanut oil.
- The most suitable vehicle for cardiac glycosides is 40% Ethyl alcohol.
- The capacity of buffer for parenteral preparation should be Moderate.
- Most suitable vehicle for Amylobarbitone sodium is WFI free from CO₂.
- Most suitable vehicle for progesterone injection BP is a sterile solution in Ethyl oleate.
- Water for injection differs from sterile distilled water as it is free from pyrogens.
- Bacteriostatic water for injection should be packed in containers of 30 ml.
- For aseptic processing Class 100-room process is used.

Pyrogens

- Pyrogens are water soluble & non-volatile in nature. Chemically they are Lipo polysaccharides. The main source of pyrogens is Gram-ve bacteria.
- 1 hour after injection the pyrogens produce clinical symptoms in human body.
- The containers used for the preparation of parenteral products may be rendered free from pyrogens.
- By heating usually at 210 or 3-4 hours or 650 for 60 second.
- The limits endotoxin content in WFI 0.25 units/ml.

Solutes

(a) Antioxidants

The antioxidants are three types.

- (a) Reducing agents Eg. Ascorbic acid, Sodium bisulfite, Sodium metabisulfite, Sodium formaldehyde, sulfoxylate, Thiourea
- (b) Blocking agents. Eg. Ascorbic acid ester, Butylhydroxytoluene (BHT), Tocopherols
- (c) Synergistics Eg. Citric acids, Citranic acid, Phosphoric acid, Tartaric acid.

(b) Tonicity

- The compounds contributing to the isotonicity of products reduce the pain of injection in areas.
- They also contribute to the colligative properties of the preparation.
- Dextrose 5%, sodium chloride 0.9%, serve as tonicity contributors.
- The isotonicity of the solution can be determined by a. freezing point depression method, haemolytic method by using red blood cell.

Table Classes and example of parenteral additives

Additive class	Example of parenteral additives	Usual concentration (%w/v)
Antimicrobial	Benzalkonium chloride	0.01
	Benzyl alcohol	1-2
	Chlorobutanol	0.25-0.5
	Phenol	0.25-0.5
	Butyl p-hydroxybenzoate	0.015
Antioxidant	Ascorbic acid	0.01-0.5
	Cysteine	0.1-0.5
	Sodiumbisulfide	0.1-1.0
	Tocopherols	0.05-0.5

Table Contd...

Additive class	Example of parenteral additives	Usual concentration (%w/v)
Buffers	Acetates	1-2
	Citrates	1-5
	Phosphates	0.8-2.0
Bulking agents	Lactose	1-8
	Mannitol	1-10
	Sorbitol	1-10
Chelating agents	Salts of ethylene diaminetetra acetic acid	0.01-0.05
Solubilising agents	Ethyl alcohol	1-50
	Glycerine	1-50
	Lecithin	0.5-2.0
	Polythene glycol	1-50
Surfactants	Polyoxy ethylene sorbitan monooleate	0.1-0.5
	Sorbiton monooleate	0.5-0.25
Inert gases	Nitrogen or carbon dioxide	

Container

1. Plastic Container

- The principal ingredient of the various plastic containers is the thermoplastic polymer.
- All of the thermoplastic polymer can be autoclaved during parenteral preparations except

Polyethylene and Polystyrene

- A new group of plastic **propylene** and the copolymer **polyethylene – polypropylene** belonging to polyolefin is most widely now days used. Polypropylene is a liner polymer that can be produced to be highly crystalline. Because of its crystallinity, it has high tensile strength, a high melting point of **165°C**, and relatively low permeability to gases and water vapour. It is translucent, abrasion-resistant and high surface gloss.
- **Flexible polyethylene containers** are used for **ophthalmic containers** and flexible polyvinyl chloride bags used for **intravenous solutions**.

Evolution of plastic materials:

The test procedure for evaluating the toxicity of plastic material consists of following phases

- (a) Implanting small pieces of plastic material IM in rabbits
- (b) Injecting elutes using sodium chloride injection, with or without alcohol IV in mice.
- (c) Injecting elutes using PEG – 400 and sesame oil intraperitoneally in mice.
- (d) Injecting all four elutes subcutaneously in rabbits.

Result: The reaction from the test samples must not be significantly greater than non-reactive control samples.

2. Glass Container

- The two general types of glasses are Soda lime and borosilicate. They are also divided into various types like Type – I, Type – II, Type – III, NP, depending on chemical resistance.

Chemical Resistance

- The most chemical resistant glass is composed entirely of the Silicon dioxide.
- The brittleness and high melting point characteristic of chemical resistance glass can be modified by Boric oxide.
- The chemical resistance of glass is evaluated by powder glass test and water attack test. The test result measures the amount of alkaline constituents leached from the glass.
- The borosilicate glasses are Type – 1 type and they are highly resistance to chemicals. They are preferred for most sterile products. Buffered and unbuffered aqueous solutions. Powder glass test is used to evaluate the chemical resistance of glass.
- The treated soda lime glasses are Type -11 type. They are preferred for the product has a non-aqueous vehicle or the period of contact with the aqueous vehicle is less. They may be used for buffered aqueous solutions with pH less than 7, dry powder and oleaginous solutions. Water attack test is used to identify the alkalinity of the glass.
- The general purpose soda-lime glasses are **NP type**. They **are least resistant** to chemicals. They are not used for parenteral. They are used for tablets oral solutions, and suspensions, ointments, and external liquids.
- Soda-lime glasses are **Type- III type**; they are preferred for the products of dry powders and oleaginous solutions. Powder glass test is used to evaluate the chemical resistance of glass.

Physical Characteristics

- Glass containers are sometimes coated internally with silicone fluid to produce a hydrophobic surface. To achieve permanency, the silicon must be baked at a temperature of approximately **150°(300°F)**
- Volume of container: For single dose not more than **1000 ml** and for multiple dose not more than **30 ml**

Rubber Closers

- Rubber closers are made-up of principle, natural rubber (latex) or by synthetic polymer.
- The elastomer used in rubber stopper formulation is butyl neoprene, Polysoprene, and silicon
- The other ingredients present are sulphur (**vulcanizingagents**), accelerator, 2-mercaptobenxothiazol (active organic compound), zinc oxide (**activator**) lime stone (**filters**), antioxidants, lubricants etc.

Evaluation

Bioburden test is done to determine

- a. number of microorganism present in a parenteral products
- b. Type of microorganism present in parental products

Leaker test

It is intended to detect incompletely sealed ampoules. Tip sealed ampoules are most likely to be incompletely sealed than that of pull – sealed. **0.5 – 1.0% methylene blue dye** is used in leaker test. It is usually detected by producing negative pressure within an incompletely sealed ampoule. **The vacuum 27 inches Hg**. For is released for **30 minutes** to carry out the test. **A spark tester probe** is applied to for the leaker test of vials and bottles.

Clarity test

- The limitation permitted for particles in the larger volume of infusions are 50 particles of 10 µm or larger and 5 particles of 25 µm and larger per millimetre.

- The particulate count and size distribution of a liquid in a parenteral product can be done by utilizing. The principles of light
- Scattering, light absorption, and electrical resistance.
- A video image projection coupled with electronic circuit detector is used for the clarity test of 1-5 ml containers.

Pyrogen test

The different method used for pyrogen testing is a. Rabbit test b. LAL test

- The veins of rabbits are selected to perform this test.
- If pyrogen is injected to the vein of a rabbit, an elevation temperature occurs within 3 hours.
- Minimum volume of preparation above which pyrogen test should be performed is **15ml**.
- Limulus amoebocyte lysate test is rapid in vitro test for parenteral to detect the **presence of Pyrogens**.
- During the test, in the presence of pyrogenic endotoxins from gram negative bacteria, a firm gel is formed within 60 minutes when incubated at **37°C**.

Table Important charts to remember

Material	Additive present	Water vapour permeation	Gas permeation (O ₂)	Physical Properties
Polyethylene	Low	High	Low	Translucent + Flexible
PVC	High	High		Translucent + Flexible
Polypropylene	Low	Moderately		
Butyl rubber	Moderately	Low		Opaque + Flexible
Soda lime glass	High	No		Optically clear + rigid
Borosilicate glass	Low	No	None	Optically clear + rigid
Silicone rubber	Moderately	Very high	Very high	Translucent + Flexible
Neoprene rubber	High	Moderately		Opaque + Flexible
Polyvinyl chloride		High		
Polyamide		High		Translucent + rigid + tough
Natural rubber		Moderately	Moderately	Opaque + Flexible
Polyisoprene rubber		Moderately	Moderately	Opaque + Flexible
Polystyrene			High	Translucent + rigid
Teflon			Low	
Polycarbonate				Translucent + rigid

Important Points to remember:

- The pH range for a parenteral preparation by subcutaneous route is **3-6**.
- Citrate buffer is preferably selected for parenteral products whose pH is restricted within **2.1 – 6.2**.
- The osmolality of parenteral products should be between **280-290 mOsm/L**.
- **Cardarone IV & Etoposide IV** is used as surfactants used in parenteral products.
- **Cardarone IV** is 10% of Polysorbate 80.
- **Hydroxypropyl β – cyclodextrin** is suitable for parenteral use.
- **Un substituted α & β cyclodextrin** are not suitable for parenteral preparation because they cause **Nephrotoxicity**.
- **Lypholization** is a process applied in pharmaceutical industry to remove unwanted water portion from a parenteral products.

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- The concentration of antioxidants like disodium edetate, Ascorbic acid, & sodium metabisulfite used in parenteral preparation is **0.005, 1, and 0.003 present respectively**.
- The most popular excipient combinations used for aqueous suspension in parenteral products is PEG/ Tween -80 & CMC /Tween – 80.
- The size of Liposomes used in parenteral is **less than 3000nm**

Table Important chart to remember

Ingredients	Use
Calcium phosphate	Adsorbent diluent
Calcium hydrogen phosphate	Used for direct compression
Colloidal silica	Improve granular flow
Anhydrous dextrose	Adsorbs moisture at high relative humidity
Dextrose (spray dried)	Direct compressible but absorbs moisture at high
Lactose	Inexpensive & gives granules by moist granulation
Lactose (spray dried)	Useful for direct compression & incompatible with primary amine
Lactose anhydrous	Direct compressible & but prevent moisture uptake
Starch	Dried from used as absorbent & used as disintegrate
Mannitol	Gives cooling effect in the mouth
Barium sulphate	Used in roentgenography
Propylidone	A radio-opaque medium for broncho graphic use
Ethiodizedoid	Used in emphography
Ipodate sodium	Used in roentgenography
Iophendulate	For myclography
Ipodate calcium	Used as a contrast medium for cholecystography
Indocyanine green	To determine cardiac output, hepatic function & live blood flow
Methiodal sodium	A radio – opaque medium for retrograde pycelography
Ndigotindisulfonate sodium	In a kidney function test
Insulin	Diagnostic agent for evaluation of glomerularfiltration
Phenol sulfonphthalein	For determining kidney function
Evans blue	A diagnostic agent used in blood volume estimation
Azuresin	An ion to exchange resin used as indicator
Congo red	Used in th detection of amyloidosis
Povidone	Non enteric material
Cellulose acetate phthalate	Enteric material
Ingredients	Purpose
Titanium Dioxide	Opacifier
Ethyl vanillin	Flavouring
Methyl Paraben and propyl paraben	Preservative
Essential oils	Flavoring agent
Ethrosine sodium	Dental disclosing agent used to identify areas of plaque on the teeth
Fluorescein sodium	As an ophthalmic diagnostic aid
Ascorbyl Palmitate	An antioxidant used in food & pharmaceuticals
Butylated hydroxyanisole	An antioxidant in cosmetics
Butylated hydroxytoluene	As oxidant employed to rtard oxidative degradation of oils & fats
Chlorobutanol	It has antibacterial & germicidal properties
Sodium bisulfate	Antioxidant & stabilizer

Table Contd...

Ingredients	Use
Monothioglycerol	Used as a preservation
Sorbet acid	Mold & yeast inhibitor
Chlorobutanol	Antibacterial & germicidal
Potassium sorbate	To inhibit the growth of mould & yeast
Sulphur dioxide	A – bleaching agent
Carmel	Colouring agent
Ginger	Flavouring agent
Ethyl vanillin	Flavouring agent
Sodium metabisulfite	Preservative
Vanillin	Only as a flavour
Compressible sugar	Tableting excipient & sweetening agent
Calcium sulphate	Diluent
Carnauba wax	Polishing agent
Calcium stearate	Lubricant
Micro crystalline cellulose	Diluent & Disintegrate
Cellulose acetate phthalate	Enteric tablet coating material
Citric acid	Anticoagulant
Dextrin	An excipient & emulsifier
Dextrose	As a supplement to milk for infant feeding

1.10 Interfacial Phenomena

- Surface tension is defined as the force in dynes, acting on the surface of the liquid at right angles to any line of length of surface 1 cm.
- The units of surface tension are dyne / cm in CGS systems and Newton's / meter in MKS systems.
- The inter molecular attraction between similar molecules is called as **cohesive forces** & the inter molecular attraction between dissimilar molecules is called as adhesive forces.

Example of liquids and Intermolecular Interaction

Polar (Water)	Hydrogen bonding
Semi Polar (Benzene)	London and inductive forces
Non Polar (Carbon tetrachloride)	London type forces

Table Determination of surfaces & Interfacial tension

Methods	Equation	Instruments used
1. Capillary rise method	$\gamma = \frac{1}{2} r h g$	Capillary tube
2. DuNouy Ring method	$\gamma = \frac{\text{dial reading (dynes)}}{2.2\pi} \times \text{Correction factor}$	Du Nouy tensiometer
3. Drop count method	$\frac{n(\text{liquid}) \times \rho(\text{liquid})}{n(\text{water}) \times \rho(\text{water})} \times \gamma(\text{water})$	Stalpmeter

- Surface free energy is defined as the work required to increase the area of a liquid by 1sq.cm.

Surface Active Agents

Surface active agents are defined as the substances which preferentially get adsorbed at the interface

And exhibits self-association in the bulk of solution at a specific concentration. These substances reduce interfacial tension. They have hydrophilic and lipophilic portions in their structure. The functional

Groups such as alcoholic (-OH), carboxylic acid (-COOH), Sulphate (-SO₄) and quaternary

Ammonium (-NH₄⁺) contribute to the hydrophilic portion. Alkyl chain contribute to the lipophilic nature

Application of Surface active agents

1. Pharmaceutical adjuvant (Solubilizing, Wetting, Suspending, Emulsifying, Foaming agents and Detergents)
2. Influence on the drug action. (Surfactants on **low concentrations** enhance the penetration of hexylresorcinol into pinworms, round worms etc.)
3. Antibacterial activity Ionic surfactants adsorb on the cell surface by **electrostatic interaction**. Both gram negative and gram positive organisms are susceptible to the action of **cationic quaternary compounds**. Whereas the gram positive organisms are attacked more easily by **anionic agents** than gram negative organisms.

Hydrophilic – Lipophilic Balance (HLB)

- The HLB system used to classify surfactants.
- HLB of sodium lauryl sulphate is 40.0
- Tween 20 is a hydrophilic surfactant.

Table The HLB range of different agents are given below

Different Agents	HLB Value
Antifoaming agents	1.5 to 8
W / O emulsifying agents	3 to 6
Emulsion o/w	8 to 18
Wetting and spread agent	7-9
Antifoaming agents	1-3
Foaming agents	8
Solubilizing agents	16-19
Detergents	13-16
No dispersion	1.5 to 3.7
Poor dispersion	3.8 to 5.5
Clear solution	13.1 to 20.0
Milky dispersion (stable)	9.5 to 10.3
Milky dispersion (unstable)	6.1 to 8.6
Translucent to clear dispersion	10.5 to 13.0

Table HLB values of different surfactants

Different Agents	HLB Value
Span 20 (SORBIRAL MONOLAUATE)	4.5
Span 40 (SORBIRAL MONOPALMITATE)	6.7
Span 60 (SORBIRAL MONOSTEARATE)	4.7
Span 80 (SORBIRAL MONOOLEATE)	4.3
Tween 20 (PolyoxyethylensorbitalMonolaurate)	13.3
Tween 40 (PolyoxyethylensorbitalMonopalmitate)	15.6

Table Contd...

Tween 60 (PolyoxyethylensorbitalMonosterarate)	9.6
Tween 80 (PolyoxyethylensorbitalMonooleate)	15.0
Propylene glycol monostearate	3.4
Propylene glycol monolaurte	4.5
Polyoxyethylene glycol monosterate	11.5
Polyozyethylene glycol monooleate	11.2

Type of surfactant	Example
Nonionic	Sodium lauryl sulphate, Polyoxyethylene lauryl ether, Sorbian mono-oleate, Polyoxyethylenesorbitan mono-oleate Sorbianmonopalmitate
Cationic	cetyltrimethyl ammonium bromide N-cetyl-N-ethyl morpholiumethosulfate Benzalkonium chloride
Ampholytic	Dimethyl dodecyl ammoniym propane sulfonate, Lecithin
Anionic	Trethanolamine

Dispersed Phase	Dispersion Medium	Example
Solid	Liquid	Solution
Solid	Gas	Smoke
Liquid	Liquid	Emulsion
Liquid	Gas	Fog
Gas	Liquid	Foam
Gas	Solid	Pumice

Wetting Phenomenon

- Wetting is an **adsorption process** in which intimate contact of the solid with liquid phase is achieved
- For the proper wetting of solids by liquids, the contact angle should be nearly **Zero**.
- The efficacy of wetting activity can be detected by **Draves test**.
- **Washburn equation**: It states that the distance that a liquid penetrates into a bed of powder in time is proportional to the square of $\cos\theta$. This is used to evaluate the wetting ability of powder by different vehicles.

Contact Angle

- Contact angle can be defined as an angle between the liquid droplet and surface over which it spreads.
- Wetting ability of a vehicle can be detected by observing **contact angle**.
- A low contact angle indicates that adhesive forces between the liquid and the solid predominate and wetting occurs, while a high contact angle indicates that cohesive forces of the liquid predominate
- The basic equation that applies to wetting is young's equation.

$$\text{Contact angle } \cos\theta = \frac{-\gamma_{st} + \gamma_s}{\gamma_s}$$

Detergency

- The HLB requirement for detergency is about 13 – 16.
- Cationic type of detergent are Zephiran (benzyltrimethylammonium chloride) and **Cetrimide** (cetyltrimethyl ammonium chloride)
- **Anionic** type of detergent are Soaps, Sodium lauryl sulphate etc.

Electrical Properties of Interfaces

- **Nernst potential (Electro thermodynamic potential):** It is defined as the difference in potential between the actual surface and the electro neutral region of the solution.
- **Zeta potential (Electro Kinetic potential):** It is defined as the difference in the potential between the surface of the tightly bound layer (shear plane) and the electro neutral region of the solution.
- If the zeta potential **falls below a particular value**, the attractive forces exceed the repulsive forces and this result in the **aggregation** of particles.
- Zeta potential decrease more rapidly when the concentration of electrolytes is increased or the valency of counter ions is higher.

Miscellaneous Points to Remember

- **Marasperse** is a deflocculating agent
- When non polar substances are dissolved in a polar solvent using surfactants, the process is called **solubilisation**.
- Ostwald pipette is used to measure **viscosity**
- The munsell system is associated with **colours**.
- The Crocker – Henderson system is used to classify **odours**
- Povan could be classified as **cyaninedye**.
- **Cloudpoint:** The temperature above which cloudiness suddenly appears for non-ionic surfactants in solution is known as **Cloudpoint**.
- **Kraftpoint:** The rapid increase in solubility of a surfactant solution above definite temperature is known as **Kraftpoint**.
- **Spreadingcoefficient:** The difference in the work of adhesion and the work o cohesion of liquids ion the surface of other liquid is known as **Spreadingcoefficient**.
- **Micellarsolubilisation:** The phenomenon of increasing the solubility of non-polar drugs by addition of surfactants is known as **Micellarsolubilisation**.
- Stalagometer is used for the measurement of **Surfacetension**.
- At critical temperature the surface tension is **Zero**.
- Electrolytes are added to **decrease** the Zetapotential.
- **Antonlff's rule** is applicable to slightly polar liquids against water.
- The HLB range for lipophilic surfactants is **2 to 9**.
- **Gegenions** mean ion having a charge opposite to the potential determining ions.
- In the thermodynamic treatment of dispersion of hydrophilic solids, **the Gibb's free energy change** and the **entropy change**, respectively, are negative and positive.
- Near critical micelle concentration, micelles of the surfactant molecules assume the shape of spherical.

Important Equations related to surface and interfacial phenomenon

Name	Equation
Kelvins equation	$\left(\frac{P}{P^0}\right) = \frac{2\gamma v}{rRT}$
Gibb's equation	$T_2^1 = -RT \frac{dy}{d\ln a_2}$
Langmuir equation	$\frac{c}{x/m} = \frac{1}{b} + \frac{c}{b}$ (It is used to describe the adsorption from solutions)
Freundlich equation	$I/k = \left(\frac{DKT}{2ne2z2}\right)^{\frac{1}{2}}$
Debye length	$\frac{x}{m} = Kc^{1/n}$
Vant Hoff	$\Pi = CRT$
Vanderwalls force	$F = Ad (Ad / 12x^2)$

- **Schulze Hardy rule:** It states the strong effect of the valence of electrolyte on the double – layer repulsive force.
- **DLVOR theory:** It is considered only the balance between electrostatic repulsive and Van der walls attractive forces.
- **Gibb's equation:** It states that a solute that concentrates in the interfacial region causes decrease in surface tension as the concentration of the solute is increased.
- **PZC:** Point of Zero change (PZC), which represents the pH at which the net surface charge is zero.
- **Mechanism of crystal growth:** The size distribution of dispersed systems may increase during aging, owing to three principle mechanisms. 1. Ostwald repining 2. Polymorphic transformation 3. Temperature cycling
- **Taub's rule:** The rule is that a polar adsorbent preferentially adsorb's the more polar component of a non-polar solution.

1.11 Micromeritics**Particle Size**

- Micromeritics involve the study of small particles and of the order of a few microns size.
- One micrometer (μm) = 10^{-3} mm or 10^{-6} m.
- One Milimicrometer = One nanometer (nm) = 10^{-6} mm = 10^{-3} μm = 10^{-9} m.

Table Particle size diameter and their specification

Surface diameter	Diameter of a sphere having the same surface area as that of the asymmetric particles
Volume diameter	Diameter of a sphere having the same volume as that of the asymmetric particles
Projected diameter	Diameter of a sphere having the same area of the asymmetric particles observed under microscope
Stroke's diameter or equivalent sphere diameter	Diameter of an equivalent sphere undergoing sedimentation at the same rate as the symmetric particles
Sieve diameter	Diameter of a sphere that passes through the same sieve aperture as the asymmetric particles
Volume-surface diameter	Diameter of the sphere having the same volume to surface area ratio as the asymmetric particles

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Particle shape

The shape factor of a particle can be expressed as the ratio of surface to volume factors.

$$\text{Shape factor} = \frac{a_s}{a_v}$$

- The minimum possible value for shape factor is **6 for a sphere**. If the ratio value **exceed 6**, it is considered as **asymmetric**.

Powder Characteristics

- If the powder contains particles of one size then it is called **monodisperse**.
- If the powder contains particles of different size then it is called **polydisperse**.
- Arithmetic mean of a powder is defined as the sum of the **particle** sizes divided by the **number** of particles.

$$\text{Volume surface mean diameter } d_{vs} = \frac{\sum nd^3}{\sum nd^2}$$

$$\text{Surface number mean diameter } d_{sn} = \sqrt{\frac{\sum nd^3}{\sum n}}$$

Determination of particle size: The methods to estimate particle size are

1. Optical microscopy (Particle size of 0.2 – 100 μm can be measured. Particle in suspension, emulsion, aerosol can be determined)
2. Sieving method (Particle size range of 50 – 1500 μm)
3. Sedimentation method (Particle size range of 1 – 200 μm)
4. Conductivity method (Particle size range of 0.5 – 500 μm)

Powder surface area

- **Air permeability method** is used to determine **particle surface diameter**. The **Kozeny-Carman equation** is used to determine the surface area by this method.

- The Kozeny-Carman equation $V = \frac{A}{\eta S_w^2} \frac{\Delta Pt}{KI} \frac{\epsilon}{(1-\epsilon)^2}$

Derived properties of powder

$$\text{True density} = \frac{\text{Weight of powder}}{\text{True volume of powder}}$$

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume}}$$

$$\text{Consolidation index} = \frac{\text{Tapped density} - \text{fluff density}}{\text{Tapped density}} \times 100$$

$$\text{Angle of repose } \theta = \tan^{-1} \frac{h}{r}$$

Relation between angle of repose and powder flow

Angle of repose	Flow
<25	Excellent
25 – 30	Good
30 – 40	Passable
>40	Very poor

% compressibility	Flow ability
5 to 15	Excellent
12 to 16	Good
23 to 35	Poor
<40	Very poor

Points to Remember

- **Surface area** of a particle significantly affects the physical, chemical and biological properties of the drug
- Due to the particles in a powder are irregular in shape it is difficult to express the size of particles in a meaningful diameter.
- When cumulative percent frequency on a probability scale is plotted against logarithm of the particle size, 50 percent on the probability scale gives the **geometric mean**.
- **Stoke's diameter** is important in the formulation development of emulsions and suspensions.
- Stoke's law cannot be used, if Reynolds number is **more than 0.2**.
- **Fisher subsieve sizer** is used to determine the surface area of the powder, The surface area is measured based on the change weight of powder when air is passed through the powdered pack
- **When Coulter-counter** apparatus is employed for powder analysis, **dispersion medium** should be in **conducting** stage
- In Coulter-counter, as the particles travel through the orifice, **resistance between the electrodes increases**.
- **High repose angle** of the granules **indicates roughness** of the granule surface.
- The term '**light**' as applied to pharmaceutical powders means: low granule density.
- Porosity of a porous powder is defined as **void volume/ bulk volume**.
- Shear cell method, Hausner ratio method, Carr Index method are used to **measure powder flow properties**
- **Avalanching Behaviour** is associated with Powder flow property.
- Hackle equation is mostly used to describe **compaction of pharmaceutical powder**.
- Hackle equation = $\ln \left[\frac{1}{1-Dr} \right] = K p +$

1.12 Rheology

Viscosity

Coefficient of viscosity

It is defined as the force per unit area required to maintain unit difference in velocity between two parallel layers in the liquid, one centimetre apart.

Kinematic viscosity- It is defined as ratio of viscosity of the dispersion to that of the solvent

Specific viscosity- It is defined as relative increase the viscosity of the dispersion over that of the solvent alone.

Reduced viscosity- It is defined as ratio of specific viscosity to the concentration.

- The units of viscosity is **poise or centipoise**
- The CGS units for poise are **dy.sec/cm². Or g.cm⁻¹.sec⁻¹**
- In SI system, one unit of poise is equal to **0.1Nsm²**

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- The unit of kinetic viscosity is **stokes** (s)centistokes (cs)
- The unit of Shear stress is **dy/cm²**

Flow of Liquids

Newtonian flow: Simple liquids exhibit Newtonian flow eg: Water, glycerine, Solution or syrup, Chloroform etc.

Non-Newtonian flow: The heterogeneous dispersions such as emulsion, suspensions and semisolids exhibit Non-Newtonian flow.

Non-Newtonian flow are three types

1. Plastic flow (Expressed in terms of Bingham equation) $U = \frac{F-f}{G}$
Where F = Shear stress, f = yield value, G = rate of shear.
2. Pseudo plastic flow: The viscosity of pseudo plastic follow cannot be expressed by a single value.
3. Dilatant flow: This viscosity exhibits where there is high concentration of solids.

Determination of flow properties

Types of flow	Types of viscometer	Example	Equation
Newtonian	Single Point viscometer	Ostwald viscometer	$\eta_1 = \frac{\rho_1 t_1}{\rho_2 t_2} \eta_2$
		Filling sphere viscometer	$\eta_1 = t(S_b - S_F)B$
Non-Newtonian	Multi point viscometer	Cup and bob viscometer (Rotational Viscometer)	$\eta = K_v \frac{W}{V}$
		Cone and plate viscometer	$U = C_1 \frac{T-T_1}{V}$

- **Brookfield viscometer** is also a **rotational** viscometer. The construction of this instrument is similar to as the Cup and bob viscometer.
- **Plug flow** is not observed in cone and plate viscometer.

Points to Remember

- Flocculated suspensions exhibit the **plastic flow**.
- Plug flow is NOT related to the **falling sphere viscometer**.
- A corresponding expression in Non-Newtonian fluids (in terms of viscosity) is **apparent**.
- Fluidity is a term associated with Newtonian fluids. An equivalent term in plastic flow fluids is **mobility**.
- -Dilatant flow is characterized as a reverse phenomenon of **pseudo plastic flow**.
- Deflocculated suspension with high concentration of the dispersed solids exhibits the **dilatant** type of flow
- In antithixotropy, the down-curve is frequently positioned to **right side** (with respect to up-curve)
- The pseudo plastic flow behaviour can be explained by **apparent viscosity**.
- Creep testing is applied to analyse the viscoelastic property of **ointment**.
- The system that undergoes gel-to-sol transformation is known as **shear thinning**.
- The type of viscosity specified in I.P. (Ostwald viscometer) is **kinematic viscosity**.
- After giving the I.M. injection of procaine penicillin G, the process of forming a depot in the muscle is due to **rapid thixotropic recovery**.

- Plug flow is NOT observed in cone and plate viscometer. The reason is **shear can be maintained uniformly**.
- Poiseuille's equation $\eta = \frac{\Delta P \pi^4}{8LQ}$

1.13 Colloids

- Kraft Point:** It is defined as the temperature at which solubility of the surfactant is equal to cmc.
- DLVO theory:** According to this theory, the distance between two dispersed particles mainly influences Particle-particle interactions.
- Gold number:** It is defined as the minimum weight in milligrams of a protective colloid (dry weight or dispersed phase) required to prevent a color change from red to violet in 10ml of gold solution on addition of 1ml of 10% solution of sodium chloride. Basically gold solution is a hydrophobic colloid and has a red color. When an electrolyte like sodium chloride is added. Coagulation of colloids is observed indicating the violet color. When protective colloid is added this is observed indicating the violet color. When protective colloid is added these stabilize the gold solution and prevent the change to violet color. Lower the gold number, greater the protective action.
- Lyophilic colloid:** Dispersed phase consists of large organic molecules.
Dispersions are stable in the presence of electrolytes.
- Amphiphilic colloids:** Dispersed phase consists of aggregates of small organic molecules
- Lyophobic colloid:** Unstable in the presence of small concentration of electrolytes

Protective colloid	Gold number	Products	Particle size
Gelation	0.005 to 0.01	Molecular dispersion	a. Less than 1.0 nm
Albumin	0.1	Colloidal dispersion	b. 0.5 μm to 1.0 nm
Acacia	0.1 to 0.2	coarse dispersion	c. more than 0.5 μm
Tragacanth	2		

Some Essential Chart of Physical Pharmacy

Mineral	Structural type
Kaolinite	Layer lattice non-expanding
Montmorillonite	Layer lattice expanding
Analcite	Zeolite open network lattice
Synthetic permutite	Amorphous alumina silicate gel

Material	Flowability
Celutab	Excellent
Star X-1500	Fair passable
Maize starch	Poor
Dicalcium-Phosphate dehydrate (fine)	Very Poor
Titanium dioxide	Very Poor

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Temperature

Cool

Cold

Warm

Room temperature

Excessive heat

Degree centigrade

8⁰ to 15⁰c

2⁰ to 8⁰c

30⁰ to 40⁰c

does not exceed 25⁰ c

above 40⁰c

Character

Non-hygroscopic

Slightly hygroscopic

Moderately hygroscopic

Very hygroscopic

Humidity

No increase of humidity

The increase of relative humidity but less than 40%

Moisture increase may occur less than 50%

Moisture increase at relative humidity's as low as 50%

Pharmaceutics MCQs

- Humectants added in cosmetic preparations generally act by
 - Hydrogen bond formation
 - Covalent bond formation
 - Complex formation
 - The action of London forces
- In the mixing of thymol and menthol the following type of incompatibility occurs:
 - Chemical incompatibility
 - Therapeutic incompatibility
 - Physical incompatibility
 - Tolerance incompatibility
- Bloom strength is used to check the quality of
 - Lactose
 - Ampoules
 - Hardness of tablets
 - Gelatin
- The characteristic of non-linear pharmacokinetics include:
 - Area under the curve is proportional to the dose
 - Elimination half-life remains constant,
 - Area under the curve is not proportional to the dose
 - Amount of drug excreted through remains constant
- Thioglycolic acid-like compounds have applications in following type of cosmetic formulations :
 - Depilatory preparations
 - Epilatory preparations
 - Vanishing creams
 - Skin tan preparations
- Which one of the following is a flocculating agent for a negatively charged drug?
 - Aluminium chloride
 - Bentonite
 - Tragacanth
 - Sodium biphosphate
- The healing agent used in hand creams is
 - Soft paraffin
 - Urea
 - bees wax
 - Stearyl alcohol
- Which one of the following is the commonly used bulking agent in the formulation of freeze dried low dose drug products?
 - Sodium chloride
 - Mannitol
 - Starch
 - HPMC
- The applicability of Noyes-Whitney equation is to describe
 - First order kinetics
 - Zero order kinetics
 - Mixed order kinetics
 - Dissolution rate
- Which filler can NOT be used for the preparation of tablets for amine containing basic drugs to avoid discoloration of the tablets?
 - Dicalcium phosphate
 - Microcrystalline cellulose
 - Starch
 - Lactose
- What quantities of 95 % v/v and 45 % v/v alcohols are to be mixed to make 800 mL of 65 % v/v alcohol?
 - 480 mL of 95 % and 320 mL of 45 % alcohol
 - 320 mL of 95 % and 480 mL of 45 % alcohol
 - 440 mL of 95 % and 360 mL of 45 % alcohol
 - 360 mL of 95 % and 440 mL of 45 % alcohol

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12. The role of borax in cold creams is
 - (a) Anti-microbial agent
 - (b) To provide fine particles to polish skin
 - (c) *In-situ* emulsifier
 - (d) Antioxidant
13. Drugs following one compartment open model pharmacokinetics eliminate
 - (a) Bi-exponentially
 - (b) Tri-exponentially
 - (c) Non-exponentially
 - (d) Mono-exponentially
14. Drugs in suspensions and semi-solid formulations always degrade by
 - (a) First order kinetics
 - (b) Second order kinetics
 - (c) Zero order kinetics
 - (d) Non-linear kinetics
15. In nail polish, following polymer is used as a film-former:
 - (a) Nitrocellulose
 - (b) Polylactic acid
 - (c) Hydroxypropyl methylcellulose
 - (d) Cellulose acetate phthalate
16. A drug (200 mg dose) administered in tablet form and as intravenous injection (50 mg dose) showed AUG of 100 and 200 microgram hr/mL, respectively. The absolute availability of the drug through oral administration is:
 - (a) 125% (b) 250 %
 - (c) 12.5% (d) 1.25%
17. How many mL of a 1:500 w/v stock solution should be used to make 5 liters of 1:2000 w/v solution?
 - (a) 750 mL (b) 1000 mL
 - (c) 1250 mL (d) 1500 mL
18. The Volume of distribution of a drug administered at a dose of 300 mg and exhibiting 30 microgram/mL instantaneous concentration in plasma shall be
 - (a) 10 L (b) 100 L
 - (c) 1.0 L (d) 0.10 L
19. It is required to maintain a therapeutic concentration of 10 microgram/mL for 12 hours of a drug having half life of 1.386 hr and Vd of 5 L. The dose required in a sustained release product will be
 - (a) 600 mg (b) 300 mg
 - (c) 30 mg (d) 60 mg
20. In which of the following techniques the sample is kept below triple point?
 - (a) Lyophilization (b) Spray drying
 - (c) Spray congealing (d) Centrifugation
21. Which of the following is not a semisolid dosage form
 - (a) Paste (b) Creams
 - (c) Ointments (d) Suspensions
22. Generally pastes contain
 - (a) High percentage of insoluble solids
 - (b) Low percentage of insoluble solids
 - (c) Both
 - (d) None
23. Most widely used hydrocarbon in semi-solid dosage forms
 - (a) Petrolatum (b) Mineral oil
 - (c) Both (d) None
24. Which of the following hydrocarbon waxes are employed in the manufacture of creams and ointments?
 - (a) Paraffin wax (b) Ceresin
 - (c) Both (d) None
25. Which of the following is not a vegetable oil
 - (a) Peanut oil (b) Almond oil
 - (c) Olive oil (d) Petrolatum
26. Which of the following fatty acid used in water removable creams as emulsifier
 - (a) Stearic acid (b) Palmitic acid
 - (c) Both (d) None
27. Combination of a surfactant with oilsoluble auxiliary emulsifier is known as
 - (a) Simple emulsifier system
 - (b) Mixed emulsifier system
 - (c) Both
 - (d) None

28. Promulgen means
- (a) Anionic emulsifiers composed of fatty alcohols & their ethoxylates
 - (b) Non-ionic emulsifiers composed of fatty alcohols & their ethoxylates
 - (c) Cationic emulsifiers composed of fatty alcohols & their ethoxylates
 - (d) All the above
29. Promulgen D contains
- (a) Cetyl alcohol & Cetareth-20
 - (b) Stearyl alcohol & Cetareth-20
 - (c) Both
 - (d) None
30. Promulgen G contains
- (a) Cetyl alcohol & Cetareth-20
 - (b) Stearyl alcohol & Cetareth-20
 - (c) Both
 - (d) None
31. With promulgen D, which type of emulsion generally obtained?
- (a) Liquid emulsion
 - (b) Thick consistency emulsion
 - (c) Both
 - (d) None
32. With promulgen G, which type of emulsion generally obtained?
- (a) Liquid emulsion
 - (b) Thick consistency emulsion
 - (c) Both
 - (d) None
33. Which of the following polyols used as humectants in creams
- (a) Glycerine
 - (b) Propylene glycol
 - (c) Sorbitol 70%
 - (d) All the above
34. The choice of humectants is based on
- (a) Rate of moisture exchange
 - (b) Viscosity and texture of preparation
 - (c) Both
 - (d) None
35. Which of the following is more hygroscopic at low concentration?
- (a) Sorbitol 70%
 - (b) Glycerine
 - (c) Both
 - (d) None
36. Due to which factors, petrolatum is most widely used as a hydrocarbon base in ointments
- (a) Its consistency
 - (b) Its neutral characteristics
 - (c) Its ability to spread easily on the skin
 - (d) All
37. Water number means
- (a) Maximum amount of water that can be added to 100 g of a base at given temperature
 - (b) Maximum amount of water that can be added to 10 g of a base at given temperature
 - (c) Maximum amount of water that can be added to 5 g of a base at given temperature
 - (d) All
38. Lanolin is which type of base
- (a) Hydrocarbon base
 - (b) Absorption base
 - (c) Both
 - (d) None
39. In the preparation of vanishing creams, which types of bases are used generally?
- (a) Absorption bases
 - (b) Water removable bases
 - (c) Hydrocarbon bases
 - (d) None
40. In the preparation of cold creams, which types of bases are used generally?
- (a) Absorption bases
 - (b) Water removable bases
 - (c) Hydrocarbon bases
 - (d) None
41. Water soluble bases are also known as
- (a) Greasy ointment bases
 - (b) Greaseless ointment bases
 - (c) Both
 - (d) None
42. In pastes, the concentration of insoluble powder substances in
- (a) 20%-50%
 - (b) 50%-100%
 - (c) 50%-75%
 - (d) None

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43. Jellies are generally
(a) Water-soluble bases
(b) Water-insoluble bases
(c) Both
(d) None
44. As per USP XX, the term “objectionable” means
(a) An organism can cause disease or the presence may interrupt the function of the drug or lead to deterioration of the product
(b) Pathogens if they produce disease or infection, in the newborn or debilitated persons
(c) Organisms or their toxins that is responsible for human disease or infection
(d) None
45. The success or failure of a preservative in protecting a formulation against microbial spoilage depends on
(a) Interaction between preservative with surfactant
(b) Interaction between preservative with active substances
(c) Sorption by packaging materials
(d) All the above
46. A suppository is generally intended for use in
(a) Rectum (b) Vagina
(c) Urethra (d) All the above
47. Vaginal suppositories also called as
(a) Pessaries
(b) Simple suppositories
(c) Bougies
(d) None
48. “Oleum theobromae” was first recommended by
(e) Taylor (b) Griffin
(c) Stocks’s (d) None
49. Weight of rectal suppository for adults is
(a) 1 g (b) 2 g
(c) 5 g (d) None
50. Weight of rectal suppository for children is
(a) 1 g (b) 2 g
(c) 5 g (d) None
51. Urethral suppositories also called as
(a) Pessaries (b) Bougies
(c) Both (d) None
52. Urethral suppositories having which shape
(a) Oviform shape (b) Torpedo shape
(c) Pencil shape (d) None
53. Weight of urethral suppository for males & females respectively
(a) 4 & 2 (b) 2 & 4
(c) 4 & 6 (d) 6 & 4
54. Shape of vaginal suppositories is
(a) Oviform shape (b) Torpedo shape
(c) Pencil shape (d) None
55. Rectal suppositories mainly used for the treatment of
(a) Constipation (b) Hemorrhoids
(c) Both (d) None
56. The number of milligrams of KOH required neutralizing free acids & saponify the esters contained in 1 g of fat is known as
(a) Iodine value
(b) Saponification value
(c) Water number
(d) Acid value
57. The number of grams of iodine that reacts with 100 g of fat is known as
(a) Iodine value
(b) Saponification value
(c) Water number
(d) Acid value
58. The number of milligrams of KOH required neutralizing free acids in 1 g of fat is known as
(a) Iodine value
(b) Saponification value
(c) Hydroxyl value
(d) None
59. The number of milligrams of KOH required neutralize the acetic acid used to acetylate 1 g of fat is known as
(a) Iodine value
(b) Saponification value
(c) Hydroxyl value
(d) Acid value

60. Which of the following method is used to manufacture suppositories
- Hand molding
 - Compression molding
 - Pour molding
 - All the above
61. Which of the following is most commonly used suppository base
- Cocoa butter
 - PEG 1000
 - PEG + Hexanetriol
 - None
62. Cocoa butter available in following forms
- α -form
 - β -form
 - γ -form
 - All
63. The solidification point of cocoa butter lies between
- 12 – 13o
 - 20 – 30o
 - 5 – 10o
 - None
64. Which of the following method is simple & oldest method of preparation of suppositories?
- Hand molding
 - Compression molding
 - Pour molding
 - All the above
65. Most commonly used method for producing suppositories on both a small & large scale is
- Hand molding
 - Compression molding
 - Pour molding
 - All the above
66. Which formula can be used to calculate the amount of base that is replaced by active ingredients?
- $f = 100 (G - E) + 1(G) (X)$
 - $f = 100 (E - G) + 100 (G) (X)$
 - $f = 100 (E - G) + 1 (G) (X)$
 - $f = 100 (E - G) + 10 (G) (X)$
67. Rancidity generally results from
- Auto oxidation
 - Decomposition of unsaturated fats
 - Both
 - None
68. Which of the following is not antioxidant
- BHT
 - BHA
 - Tocopherol
 - Theobroma oil
69. Suppositories are generally evaluated by
- Melting range test
 - Breaking test
 - Liquefaction
 - All the above
70. 3. Major 1. Which of the following materials are used in pharmaceutical packaging?
- Glass
 - Plastic
 - Metal
 - All the above
71. Which of the following packaging material is protect the drug content against light
- Plastic containers
 - Amber colored glass containers
 - Both
 - None
72. disadvantages of glass as a packing material are
- Fragility
 - Weight
 - Both
 - None
73. Composition of glass is
- Sand
 - Soda ash
 - Lime stone & Cullet
 - All the above
74. Soda ash also known as
- Pure silica
 - Sodium carbonate
 - Lime stone
 - Calcium carbonate
75. Which of the following one is a broken glass & acts as fusion agent
- Cullet
 - Soda ash
 - Lime stone
 - Sand
76. Which of the following methods are used in the production of glass
- Blowing
 - Drawing
 - Pressing & casting
 - All the above
77. To produce molten glass, which of the following method is used
- Blowing
 - Drawing
 - Pressing
 - Casting

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78. To protect the contents of a bottle from the effects of sunlight by UV rays, which glass is used?
(a) Amber glass (b) Red glass
(c) Both (d) None
79. To evaluate the chemical resistance of glass, which of the following tests are conducted?
(a) Powder glass (b) Water attack test
(c) Both (d) None
80. Which of the following test is performed on crushed grains, to evaluate the chemical resistance of glass?
(a) Powder glass (b) Water attack test
(c) Both (d) None
81. Which of the following test is performed on whole container?
(a) Powder glass (b) Water attack test
(c) Both (d) None
82. Type I glass is also known as
(a) Borosilicate glass
(b) Regular soda-lime glass
(c) Treated soda-lime glass
(d) None
83. The advantages of plastic containers over glass containers are
(a) Easy formation
(b) Resistance to breakage
(c) Freedom of design
(d) All the above
84. Plastic containers are generally made from the following material
(a) Polyethylene (b) Polypropylene
(c) Polystyrene (d) All the above
85. Which of the following ingredients are present in rubber stopper?
(a) Vulcanizing agent (b) Softner
(c) Antioxidant (d) All the above
86. Which of the following packaging systems are identified by the FDA?
(a) Blister pack (b) Strip pack
(c) Bubble pack (d) All the above
87. Which of the following packaging is commonly used for packaging of tablets & capsules?
(a) Blister pack (b) Strip pack
(c) Both (d) None
88. Which of the following materials offer moisture barrier properties?
(a) Aclar (b) Cellophane
(c) Polyester (d) All the above
89. Which of the following mechanism is responsible for release of encapsulated core materials?
(a) By disrupting the coating by pressure
(b) By offering permeability facilities
(c) By leaching of permanent fluid
(d) All the above
90. Pre - formulation studies mainly focus on
(a) Physical properties of new compound
(b) Chemical properties of new compound
(c) Physico-chemical properties of new compound
(d) None
91. Which of the following information is helpful in designing the preformulation evaluation of a new drug?
(a) Structure of a compound
(b) Formula & molecular weight of a compound
(c) Therapeutic indication of a new compound
(d) All the above
92. Which of the following problems commonly encountered in evaluating salt forms are
(a) Poor crystallinity (b) Hygroscopicity
(c) Instability (d) All the above
93. Which of the following salts generally used in pharmaceutical products?
(a) Acetate (b) Gluconate
(c) Lactate (d) All the above
94. Description of the outer appearance of a crystal is known as
(a) Crystal habit (b) Internal structure
(c) Both (d) None

95. Which of the following techniques used to prepare amorphous forms?
 (a) Rapid precipitation (b) Lyophilization
 (c) Rapid cooling (d) All the above
96. Amorphous forms generally having
 (a) Low thermodynamic energy & low solubility
 (b) High thermodynamic energy & high solubility
 (c) Both
 (d) None
97. Which of the following compound possess high aqueous solubility's?
 (a) Hydrates (b) Anhydrates
 (c) Both (d) None
98. Which of the following properties may change with changing of the internal structure of a solid?
 (a) Melting point (b) Density
 (c) Optical properties (d) All the above
99. Which of the following methods generally used for studying solid forms?
 (a) DSC (b) XRD
 (c) TGA (d) All the above
100. Which of the following methods generally used to measure heat loss or gain within a sample?
 (a) DSC (b) DTA
 (c) Both (d) None
101. Which of the following co-solvent can be used to increase the solubility of poor soluble drugs?
 (a) Ethanol (b) Propylene glycol
 (c) Glycerin (d) All the above
102. Partition co-efficient generally measures
 (a) Drug's lipophilicity
 (b) Ability of drug to cross cell membrane
 (c) Both
 (d) None
103. Dissolution of a drug particle is described by
 (a) Noyes-Whitney equation
 (b) Stock's equation
 (c) Drag's equation
 (d) None
104. The effect of temperature on drug stability can be described by
 (a) Noyes-Whitney equation
 (b) Stock's equation
 (c) Arrhenius equation
 (d) None
105. Unequal distribution of color on a tablet, refers to
 (a) Picking (b) Mottling
 (c) Capping (d) Sticking
106. Match the following and find out the correct combination
1. Capping (P) Separation of a tablet into 2 or more layers
 2. Lamination (Q) Unequal distribution of color on a tablet
 3. Mottling (R) Separation of top/bottom crowns of a tablet from the main body
 4. Sticking (S) Adherence of tablet material to the die wall
- (a) 2-P, 3-Q, 1-R, 4-S
 (b) 1-P, 2-Q, 3-R, 4-S
 (c) 3-P, 1-Q, 2-R, 4-S
 (d) 4-P, 1-Q, 3-R, 2-S
107. Which of the following one is responsible for sticking?
 (a) Excessive moisture (b) Low moisture
 (c) Both (d) None
108. Which of the following mixer is a first high shear powder blender/mixer
 (a) Diosna mixer
 (b) Littleford lodige mixer
 (c) Plow mixer
 (d) Gral mixer
109. If the dose of a drug is inadequate, then it generally requires the following one, to make up its bulk
 (a) Binders (b) Disintegrants
 (c) Lubricants (d) Diluents

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110. The first and most widely used diluents in tablet formulation is
 (a) Dextrose (b) Lactose
 (c) MCC (d) Starch
111. Anhydrous lactose has the advantage over hydrous lactose
 (a) Improved flow
 (b) Absence of millard reaction
 (c) Improved compressibility
 (d) High microbial load
112. Which of the following is not a commercially available starch product?
 (a) Sta-Rx 1500 (b) Celutab
 (c) Emdex (d) Sugar tab
113. Which of the following is a synthetic adhesive?
 (a) PVP (b) MC
 (c) HPMC (d) HPC
114. Which of the following is a water soluble lubricant?
 (a) Stearic acid
 (b) Mineral oil
 (c) PEG
 (d) Magnesium stearate
115. Find out the correct statements regarding a sweetener, saccharin
 (P) It is 500 times sweeter than sucrose, but it is carcinogenic
 (Q) It is 500 times sweeter than sucrose, but it has bitter taste
 (R) It is sweeter than sucrose, but it is safe
 (S) It is sweeter than sucrose, but it is unstable
 (a) P, S (b) P, R
 (c) P, Q (d) R, S
116. Aerosil is used as
 (a) Glidant (b) Lubricant
 (c) Antiadherent (d) None
117. What is the pH of duodenum?
 (a) 2-3 (b) 7-8
 (c) 4-6 (d) 10
118. Tablets, which are placed between cheek and teeth, are known as
 (a) Buccal (b) Sublingual
 (c) Lozenges (d) Troches
119. Which statement is not correct?
 (a) Buccal routes avoids first pass metabolism
 (b) Parenteral route avoids first pass metabolism
 (c) Sublingual route avoids first pass metabolism
 (d) Oral route avoids first pass metabolism
120. Match the following ingredients according to their purpose in the formulation of tablets and find out the correct set
 (i) Glidant (P) Pre- gelatinized starch
 (ii) Diluent (Q) Pyramine
 (iii) Adherent (R) Colloidal silica
 (iv) Disintegrant (S) Calcium sulphate
 (v) (T) Sodium alginate
 (a) 1-R, 2-S, 3-P, 4-T
 (b) 1-S, 2-R, 3-Q, 4-P
 (c) 1-R, 2-S, 3-T, 4-Q
 (d) 1-Q, 2-T, 3-R, 4-P
121. Enteric coating is achieved by using
 (a) HPMC (b) CMC
 (c) CAP (d) Povidine
122. The disintegration time for sugar coated tablets is
 (a) 30 minutes (b) 45 minutes
 (c) 60 minutes (d) 75 minutes
123. Flow rate of granules from the hopper can be improved by adding
 (a) Disintegrant (b) Glidant
 (c) Binder (d) Lubricant
124. Given below are equipment used in the manufacture of following products PT. Match them and find out correct answer
 (i) Zenasi (P) Tablet granules
 (ii) Hepa filter (Q) Tablet coating
 (iii) Chilsonator (R) Emulsion
 (iv) Accela cota (S) Injectables
 (v) (T) Capsule
 (a) 1-T, 2-S, 3-P, 4-Q
 (b) 1-P, 2-Q, 3-S, 4-R
 (c) 1-T, 2-R, 3-Q, 4-P
 (d) 1-S, 2-R, 3-P, 4-Q

125. Match the ingredients according to their purpose in the formulation and find out correct set
- Film coating (P) Sodium benzoate
 - Syrups (Q) Ethyl cellulose
 - Emulsification (R) Eudragit
 - Enteric coating (S) Sucrose
 - (T) Sodium oleate
- 1-P, 2-Q, 3-R, 4-S
 - 1-R, 2-S, 3-T, 4-Q
 - 1-T, 2-P, 3-S, 4-Q
 - 1-R, 2-S, 3-Q, 4-T
126. Match the following regions in GIT with the pH levels indicated from P-T and find out correct answer
- Mouth (P) 5-6
 - Stomach (Q) 6.8-7.5
 - Deodenum (R) 6.8-7
 - Large intestine (S) 3-5 (T) 1.5-3
- 1-Q, 2-T, 3-S, 4-R
 - 1-P, 2-R, 3-S, 4-T
 - 1-S, 2-T, 3-Q, 4-R
 - 1-R, 2-S, 3-T, 4-P
127. In sugar coating of tablets, sub-coating is done
- To prevent moisture absorption
 - To round the edge & build tablet size
 - To smoothen the surface
 - To prevent the tablet from breaking due to vibration
128. Some possible causes are mentioned in P-T, for the following defects during the film coating of tablets. Match them
- Chipping (P) Poor spreading during spraying
 - Cracking (Q) Over heating during spraying
 - Orange peel (R) Higher internal stresses in film
 - Blistering (S) Excessive coating process
 - (T) Precipitation of polymer due to high temperature/poor solvent
- 1-S, 2-R, 3-P, 4-Q
 - 1-T, 2-S, 3-R, 4-P
 - 1-P, 2-Q, 3-R, 4-S
 - 1-R, 2-P, 3-Q, 4-T
129. Sub coating is given to the tablets
- To increase the bulkiness
 - To avoid deterioration due to microbial attack
 - To prevent the solubility in acidic medium
 - To avoid stickness
130. The following ingredients are commonly used as coating agents for film coating except
- CAP
 - Carnauba wax
 - HEC
 - Sodium CMC
131. The ingredients mentioned in P-S are used in various stages of sugar coating of tablets. Match them and find out correct answer
- Seal coating (P) Gelatin
 - Sub coating (Q) Carnauba wax
 - Syrup coating (R) PEG 4000
 - Polyshing (S) Cane sugar
- 1-S, 2-P, 3-R, 4-Q
 - 1-Q, 2-S, 3-R, 4-P
 - 1-P, 2-Q, 3-R, 4-S
 - 1-R, 2-P, 3-Q, 4-S
132. The courster process can be used to
- Coat tablets
 - Determine the disintegration time
 - Gas sterilize parenteral solution
 - Automatic filling of capsules
133. Which of the following is the first process that must occur before a drug can become available for absorption from a tablet dosage form?
- Dissolution of the drug in GI fluids
 - Dissolution of the drug in epithelium
 - Ionization of the drug
 - Disintegration of the drug
134. Tablets are placed into coating chamber & hot air is introduced through the bottom of the chamber. Coating solution is applied through an atomizing nozzle from the upper end of the chamber. This technique is called
- Sealing before sugar coating
 - Coating by air suspension
 - Spray-pan coating
 - Chamber coating

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135. A synthetic sweetening agent which is approximately 200 times sweeter than sucrose & has no taste is
(a) Saccharin (b) Aspartame
(c) Cyclamate (d) Sorbitol
136. Shellac is used the purpose of coating tablets as
(a) Polishing agent
(b) Film coating agent
(c) Enteric coating agent
(d) Sub-coating agent for sugar coating
137. Dose dumping is a problem in the formulation of
(a) Compressed tab
(b) Suppository
(c) Soft gelatin capsules
(d) Controlled release drug products
138. Select the equation that gives the rate of drug dissolution from a tablet
(a) Fick's law
(b) Henderson-Hasselbatch equation
(c) Noyes-Whitney equation
(d) Michelis Menton equation
139. Which of the following substance is used as muco adhesive
(a) Acacia (b) Sodium CMC
(c) Burnt sugar (d) Saccharin
140. In the preparation of multi layer tablets, one of the following is used for hydrophilic matrix coating
(a) Shellac (b) CMC
(c) Stearyl alcohol (d) Bees wax
141. The diameter of the mesh aperture in the I.P. disintegration apparatus is given below. Choose the correct size
(a) 2 mm (b) 4 mm
(c) 1mm (d) 1.50 mm
142. Diclofenac tablet with CAP has been administered to a patient. Where do you expect the drug to be released?
(a) Stomach (b) Oral cavity
(c) Small intestine (d) Liver
143. Which of the following flavour is used in a formulation containing sour taste?
(a) Wild cherry (b) Vanilla
(c) Citrus (d) Chocolate
144. Durability of a tablet to combined effects of shock & abrasion is evaluated by using
(a) Hardness tester
(b) Disintegration test apparatus
(c) Friabilator
(d) Screw guage
145. A retardant material that forms a hydrophilic matrix in the formulation of matrix tablets is
(a) HPMC (b) CAP
(c) Polyethylene (d) Carnauba wax
146. A water soluble substance used as coating material in micro encapsulation process is
(a) Polyethylene (b) Silicone
(c) HEC (d) Paraffin
147. One of the following is used as a pH dependant controlled release excipient
(a) Carnauba wax
(b) HPMCP
(c) MC
(d) Glyceryl mono stearate
148. In the tablet coating process, inadequate spreading of coating solution before drying causes
(a) Orange peel effect (b) Sticking effect
(c) Blistering effect (d) Picking effect
149. Crown thickness of a tablet is measured by
(a) Micrometer (b) Pycnometer
(c) Hydrometer (d) All the above
150. Friabilator is operated at
(a) 100 RPM (b) 75 RPM
(c) 50 RPM (d) 25 RPM
151. Enteric coated tablet disintegrate in.....hours in simulated intestinal fluid
(a) 1 (b) 2
(c) 3 (d) 4
152. In dissolution test, flask is maintained at
(a) $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ (b) $41^{\circ}\text{C} \pm 1^{\circ}\text{C}$
(c) $39^{\circ}\text{C} \pm 0.6^{\circ}\text{C}$ (d) $40^{\circ}\text{C} \pm 1^{\circ}\text{C}$

153. Capping is prevented by using one of the following punches
 (a) Flat (b) Circular
 (c) Square (d) Rectangular
154. Plating of punch faces are done by
 (a) Chromium (b) Zinc
 (c) Iron (d) All
155. Sta-Rx-1500 contains% of moisture
 (a) 15 (b) 10
 (c) 18 (d) 50
156. Acacia tragacanth is used in the concentration of
 (a) 10%-25 % (b) 60%-70 %
 (c) 40%-50 % (d) 90%
157. Starch on heating hydrolyze into
 (a) Glucose
 (b) Fructose & Sorbose
 (c) Fructose & Mannose
 (d) Dextrin & Glucose
158. PH of the small intestine is
 (a) 1-2 (b) 3-4
 (c) 6 (d) 7-8
159. Aqua coat is a
 (a) 30% w/v of ethyl cellulose dispersion
 (b) Solution of HPMC
 (c) 2% w/v of methyl cellulose dispersion
 (d) None
160. Lozenges were originally named as
 (a) Capsule (b) ODT
 (c) Pastillies (d) Sustained axn tab
161. Implantation tab are NMT.....mm in length
 (a) 20 (b) 100
 (c) 40 (d) 8
162. Seal coating is done by using
 (a) Shellac (b) Acacia
 (c) Gelatin (d) None
163. Sub coating is done to
 (a) Round the edges
 (b) Increase the bulk of tablet
 (c) Both a & b
 (d) Make water resistant 60. CAP dissolves at PH
 (a) Above 6 (b) Below 6
 (c) 4 (d) 2
164. Which of the following one is used as opacifier
 (a) TiO₂ (b) Mgo
 (c) Siliactes (d) All of the above
165. Green bone is a source of
 (a) Type A Gelatin (b) Type B Gelatin
 (c) Both (d) None
166. Empty capsule has moisture content in the range of
 (a) 60% (b) 12%-15 %
 (c) 50%- 70% (d) 30%
167. Which treatment is used for solubility of gelatin
 (a) Heat (b) Formalin
 (c) Water (d) Alcohol
168. Which of the following is used to fill powdered dry solid into soft gelatine capsule
 (a) Aceo gel (b) Rotobil
 (c) Rotosort (d) Rotoweigh
169. Sealing of capsule is achieved by
 (a) 100°C (b) 20°C
 (c) 37°C-40°C (d) 70°C
170. Moisture content is determined by
 (a) Gas Chromatography
 (b) K-F Method
 (c) Both
 (d) None
171. Foam stability is measured by
 (a) IR Spectroscopy
 (b) UV Spectroscopy
 (c) Rotational viscometers
 (d) All
172. Particle size is determined by
 (a) Gas Chromatography
 (b) Cascade impactor
 (c) Light scatter decay
 (d) Both b & c
173. Chewable tablet contains the following base
 (a) Manitol (b) Glucose
 (c) Lactose (d) None

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174. Which of the following is not added in lozenges?
(a) Sweetener (b) Binder
(c) Disintegrant (d) All
175. Enteric coated tablet is disintegrated in
(a) Stomach (b) Liver
(c) Intestine (d) Mouth
176. The ability of a substance dissolves in a given solvent system is depends on
(a) Nature and intensity of the forces present in the solute
(b) Nature and intensity of the forces present in the solvent
(c) Interactions between solute and solvent
(d) All the above
177. Which of the following substances having poor water solubility
(a) Weak electrolytes
(b) Non-polar molecules
(c) Both
(d) None
178. The solubility of weak electrolytes & non-polar substances can be increased by adding water miscible solvents. This process is known as
(a) Co-solvency (b) Complexation
(b) Both (d) None
179. How co-solvents increase the solubility of poorly soluble drugs?
(a) By reducing the interfacial tension between the predominant aqueous solution and hydrophobic solute
(b) By reducing the interfacial tension between solute and solvent
(c) Both
(d) None
180. Which of the following co – solvents are used to increase the solubility of a drug
(a) Ethanol (b) Sorbitol
(c) Glycerin (d) All the above
181. Which of the following co – solvent is accepted as a co – solvent in parenteral products, but its use in oral liquids is limited
(a) Glycerol formal (b) Glycerol
(b) Dimethyl acetamide (d) None
182. Due to which factor, dimethyl acetamide is not been used as a co-solvent in oral liquids
(a) Due to objectionable odor
(b) Due to objectionable taste
(c) Both
(d) None
183. Thiomersal is belongs to which category preservative
(a) Acidic
(b) Neutral
(c) Mercurial
(d) Quaternary ammonium compounds
184. Which of the following are widely used and excellent preservatives
(a) Mercurial
(b) Quaternary ammonium compounds
(c) Both
(d) Acidic
185. Benzalkonium chloride is categorized as
(a) Acidic preservative
(b) Neutral preservative
(c) Mercurial preservative
(d) Quaternary ammonium compounds
186. At which concentration, phenol act as preservative
(a) 0.2 – 0.5 (b) 0.5 – 0.8
(c) 0.05 – 0.1 (d) None
187. Which of the following sugar has bitter taste
(a) Glucose (b) Sucrose
(b) Saccharine (d) None
188. Which of the following is a synthetic sweetener
(a) Glucose (b) Sucrose
(c) Sorbitol (d) Aspartame
189. To increase the viscosity of liquid, which of the following agents are used
(a) PVP
(b) Methyl Cellulose
(c) Sodium Carboxy Methyl Cellulose
(d) All the above
190. Which of the following agents are used as flavoring agents
(a) Menthol (b) Chloroform
(c) Both (d) None

191. Most widely used flavoring agent in food industry
(a) Menthol
(b) Chloroform
(c) Mono sodium glutamate
(d) None
192. Which of the following flavor is not responsible for sour taste
(a) Citrus flavours (b) Licorice
(c) Raspberry (d) Mint spice
193. The filling method of a pharmaceutical liquid depends on the following factors
(a) Viscosity of the liquid
(b) Surface tension of the liquid
(c) Compatibility with the materials used in the construction of the filling machine
(d) All the above
194. Which of the following methods are generally used in liquid filling
(a) Gravimetric
(b) Volumetric
(c) Constant level method
(d) All the above
195. In the formulation of suspensions, generally which types of drugs are selected?
(a) Hydrophilic (b) Hydrophobic
(c) Both (d) None
196. In the formulation, to facilitate the wetting of insoluble solids, which of the following agents used
(a) Suspending agents (b) Flavoring agents
(c) Wetting agents (d) None
197. How surfactants will facilitate or aid wetting of hydrophobic materials in liquid
(a) By decreasing the solid-liquid interfacial tension
(b) By increasing the solid-liquid interfacial tension
(c) Both
(d) None
198. Stoke's equation is expressed as
(a) $2V = 2r (d_1 - d_2) g / 9\eta$
(b) $2V = 2r (d_1 - d_2) g / 18\eta$
(c) Both
(d) None
199. The stability of suspensions can be evaluated by
(a) Sedimentation volume
(b) Degree of flocculation
(c) Re-dispersibility
(d) All
200. To identify the emulsion type, which of the following tests are conducted?
(a) Dilution test (b) Dye test
(c) Conductivity test (d) All
201. The temperature at which the inversion occurs depends on emulsifier concentration is known as
(a) Phase temperature
(b) Inversion temperature
(c) Phase inversion temperature
(d) All
202. Which of the following mechanical equipment can be used for emulsification?
(a) Homogenizers
(b) Mechanical stirrers
(c) Ultra sonifiers
(d) All
203. Which of the following is not used as an emulsifying agent?
(a) Surfactant
(b) Hydrophilic colloids
(c) Electrolytes
(d) Finely divided solids
204. HLB system was developed by
(a) Griffin (b) Stock's
(c) Dalla Valle (d) None
205. Gum Arabic is a
(a) Anionic polysaccharide
(b) Cationic polysaccharide
(c) Neutral polysaccharide
(d) None

Answer Key Pharmaceutics

- | | | | | | |
|-----|---|-----|---|------|---|
| 1. | a | 45. | d | 89. | d |
| 2. | c | 46. | d | 90. | c |
| 3. | d | 47. | a | 91. | d |
| 4. | c | 48. | a | 92. | d |
| 5. | a | 49. | b | 93. | d |
| 6. | a | 50. | a | 94. | a |
| 7. | a | 51. | b | 95. | d |
| 8. | b | 52. | c | 96. | b |
| 9. | d | 53. | a | 97. | b |
| 10. | d | 54. | a | 98. | d |
| 11. | b | 55. | c | 99. | d |
| 12. | a | 56. | b | 100. | c |
| 13. | d | 57. | a | 101. | d |
| 14. | c | 58. | d | 102. | c |
| 15. | a | 59. | c | 103. | a |
| 16. | c | 60. | d | 104. | d |
| 17. | c | 61. | a | 105. | b |
| 18. | a | 62. | d | 106. | c |
| 19. | b | 63. | a | 107. | a |
| 20. | a | 64. | a | 108. | b |
| 21. | d | 65. | c | 109. | d |
| 22. | a | 66. | c | 110. | b |
| 23. | c | 67. | c | 111. | b |
| 24. | c | 68. | d | 112. | d |
| 25. | d | 69. | d | 113. | a |
| 26. | a | 70. | d | 114. | c |
| 27. | b | 71. | b | 115. | c |
| 28. | b | 72. | c | 116. | a |
| 29. | a | 73. | d | 117. | c |
| 30. | b | 74. | b | 118. | a |
| 31. | b | 75. | a | 119. | d |
| 32. | a | 76. | d | 120. | a |
| 33. | d | 77. | a | 121. | c |
| 34. | c | 78. | c | 122. | c |
| 35. | a | 79. | c | 123. | b |
| 36. | d | 80. | a | 124. | a |
| 37. | a | 81. | b | 125. | b |
| 38. | c | 82. | a | 126. | a |
| 39. | b | 83. | d | 127. | b |
| 40. | a | 84. | d | 128. | a |
| 41. | b | 85. | d | 129. | d |
| 42. | a | 86. | d | 130. | b |
| 43. | a | 87. | b | 131. | a |
| 44. | a | 88. | d | 132. | a |

133. d
134. b
135. b
136. c
137. d
138. c
139. b
140. a
141. a
142. c
143. c
144. c
145. a
146. c
147. d
148. a
149. b
150. a
151. b
152. a
153. a
154. a
155. b
156. a
157. d

158. d
159. b
160. c
161. c
162. a
163. c
164. a
165. a
166. b
167. c
168. b
169. a
170. c
171. b
172. c
173. d
174. a
175. c
176. a
177. c
178. a
179. a
180. d
181. c
182. c

183. c
184. c
185. d
186. a
187. c
188. d
189. d
190. c
191. c
192. d
193. d
194. d
195. b
196. c
197. a
198. b
199. d
200. d
201. c
202. d
203. c
204. a
205. c