***Scope**: Once a person goes through this module he / she will be able to understand about the importance played by various pharmaceutical additives in different dosage forms where they are added and how they play a vital role in work ability of a dosage from.*

***Other highlights that can be understood by students**: 1. The student will also be able to have a clear knowledge about various existing as well as novel manufacturing techniques involved in drug product development. 2. Equip himself / herself with knowledge to overcome few challenges that are other faced during formulation of a potent pharmaceutical dosage form.*

Contents of the present module: *Preformulation Studies: Introduction to preformulation, goals and objectives, study of physicochemical characteristics of drug substances. a. Physical properties: Physical form (crystal & amorphous), particle size, shape, flow properties, solubility profile (pKa, pH, partition coefficient), polymorphism b. Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization BCS classification of drugs & its significant Application of preformulation considerations in the development of solid, liquid oral and parenteral dosage forms and its impact on stability of dosage forms.*

Introduction:

The most challenging situation or night mare for any formulation scientist or pharmaceutical company is the time when the most successful drug or its formulation or promising dosage form has to be recalled due to unexpected changes. One of the recent example in this context is the Ritonavir story which has really posed to be a challenge for Abbott laboratories. This is the stage where a planned preformulation study really helps in avoiding such effects to a larger extent[1]. Preformulation studies found its way in to practical field by 1950 and early 1960.

Preformulation:

This term can be defined as a phase of formulation development process where the formulation chemists analyses and characterizes various properties of the new drug substance in order to figure out a stable, safe and effective dosage form for better management of diseased conditions.

Objectives of Preformulation Studies:

The prior investigations before formulation helps to give an idea that major and significant challenges associated with a potent compound of interest to be developed in to commercial product can be analyzed and removed. Further the formulation chemist can use these information to design and develop a more stable dosage form[2].

Steps of Preformulation Study:

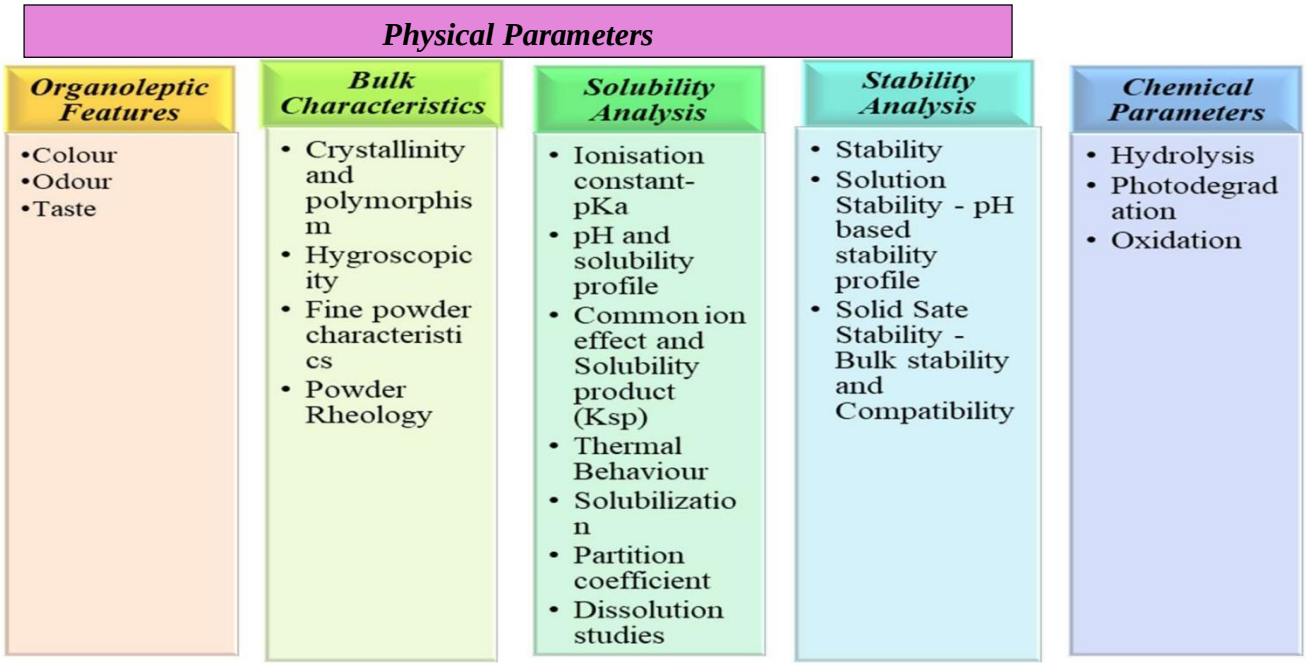


Figure -1: Various steps of preformulation studies.

A detailed description about various parameters:

Organoleptic properties:

Color: A poor visual appealing system is usually not accepted by patients, so a thorough study is needed either based on visual perception or instrumental method to analyses that each formulated batch does not vary with respect to chromatic features. In cases where needed coating with suitable color become mandatory in order to have compliance.

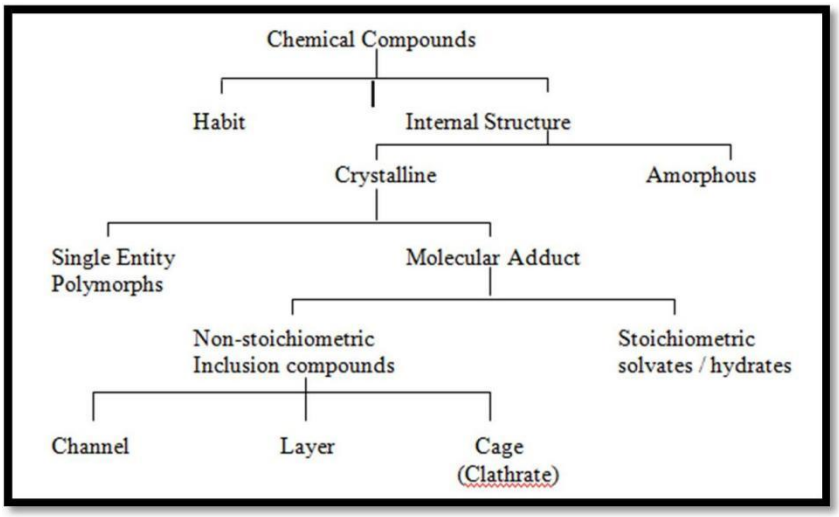
Olfactory perception and palatability: An active ingredient must be palatable as well as have a good aroma in case it's not the case then additives like flavours or coating can be done to mask out the taste or hide the intense smell which is otherwise not acceptable. For example: Pungent or sulphur smelling ingredients must be covered with an acceptable odorous compound similarly bland or bitter drugs can be masked for taste.

Bulk characterization studies:

The need of this study is to identify all possible forms that may exist for a substance at various points of synthesis for example presence of polymorphs (the ritonavir case). Here we normally characterise the bulk properties such as particle size, bulk density, surface morphology which may otherwise lead to an un-predictive phenomenon that may either alter

the efficacy of the drug or the question the stability. The studies undertaken under this head is depicted in Figure-1.

Crystal Morphology, Polymorphism, Hydrates and Solvates:



The active ingredient or the excipients can exist in different crystalline or amorphous states based on their method of synthesis, isolation from mother liquor, phases of crystallizations and geometric configurations. Based on their arrangements sometimes many different physical forms arise and this phenomenon is defined by the term polymorphism. Each polymorph that is obtained is different from the other form significantly which usually influences predominantly the parameters of bioavailability and stability of the drug. Even the polymorphs play a critical role during the compression stage of tabletting in case of few drugs like paracetamol, valsartan etc[3]. In case of paracetamol it is seen that orthorhombic forms are preferred over monoclinic forms during compaction. The crystals that are generally disordered and do not possess sharp melting point like that of crystals as well as demonstrates slow change with rise in temperature are defined amorphous products. The point where amorphous substance exhibits this change is called as glass transition temperature. Thus, it is important to understand crystal habits and other properties to ensure that a dosage form does not deviate from bioavailability or stability.

Factors affecting crystal habit:

1. If super saturation is not controlled it leads to transformation of a prism shaped crystals to a needle shaped one.

2. Similarly if rate of cooling rate and agitation are ultered then crystal habit changes super saturation degree, e.g. thin plates of naphthalene is developed if it gets rapidly recrystallized in cold ethanol or methanol solvent system, whereas controlled evaporation yields prisms.

3. The mother liquor affects habit by preferential assimilation on to certain faces, inhibiting their growth. For example: Resorcinol needles are obtained from benzene while squat prisms from butyl acetate.

4. Poisoning of mother liquor yields orients growth of crystals in different direction. An example to understand this is the Sodium chloride crystal demonstrates usually cubic structure, but in presence of urea produces an octahedral habit.

Amorphous forms:

The solids that exist in this form usually do not have any defined internal structure. They have atoms or molecules randomly placed as in a liquid. For example - Amorphous form of Novobiocin[4].

Glass transition temperature, Tg:

Tg is a characteristics feature of an amorphous form. Below *Tg* the amorphous form are brittle and is defined as glassy state. Above *Tg* the solid tend to behave as to be in plastic or rubbery state. So *Tg* is the minimum temperature at which the solid becomes amorphous i.e. (plastic) from glassy state.

***Application of glass transition temperature*:**

1. Glass transition temperature can be brought down by addition of plasticizers where they either disturb or deform the molecular arrangements, thus they reduce the *Tg.*

2. During the unit operation like milling, all the solids must remain below *Tg*.

3. Amorphous novobiocin is more soluble and has higher bioavailability than its crystalline form.

Difference between crystalline and amorphous form

Crystalline forms	Amorphous forms
(i) Crystalline forms have defined internal structure (ii) These forms are more stable than amorphous forms. (iii) These forms of active principles have lesser solubility than their amorphous form. (iv) Crystalline form has lesser inclination to change its form during storage.	(i) Amorphous forms do not have any defined internal structure (ii) Amorphous forms have higher thermodynamic energy than crystalline counter parts. (iii) These forms are less stable than crystalline forms. (iv) Amorphous forms have greater solubility than its crystalline forms. (v) Amorphous substance have a tendency to return back to more stable forms during storage.

Table -1:Highlights of difference between crystals and amorphous substance

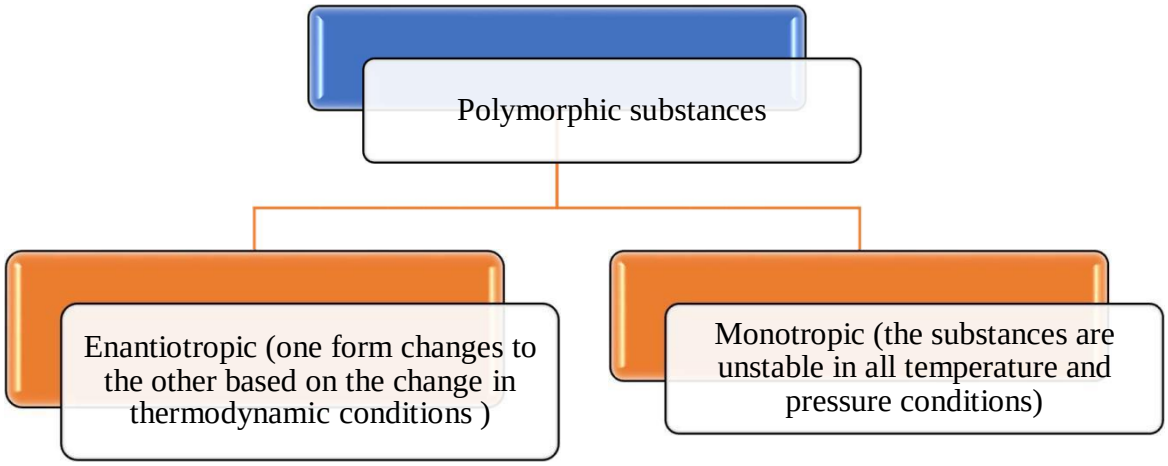
Polymorphism*:* As described earlier when crystals exhibits more than one physical form in accordance to its internal structure (i.e. packing pattern) the various crystalline forms are called *polymorphs* and the phenomenon is known as *polymorphism*. Based on thermodynamic stability, the polymorphs are categorised in to stable, metastable and unstable forms. Unstable form has a inclination to convert into stable form. Metastable forms in dry state will remain stable, but if melted or dissolved will form stable polymorph.

Features of polymorphs:

Features of polymorphs	***Stable form***	***Metastable form***	***Unstable form***
Packed arrangement of molecules in crystal lattice	Tightly packed	Less tightly packed	Loosely packed
Melting point	Highest	Moderate	Lowest
Rate of dissolution	Lowest	Moderate	Highest

Table-2: Representation of the features of the polymorphs

Classification of polymorphs*:* The polymorphic substances can be categorised as follows:

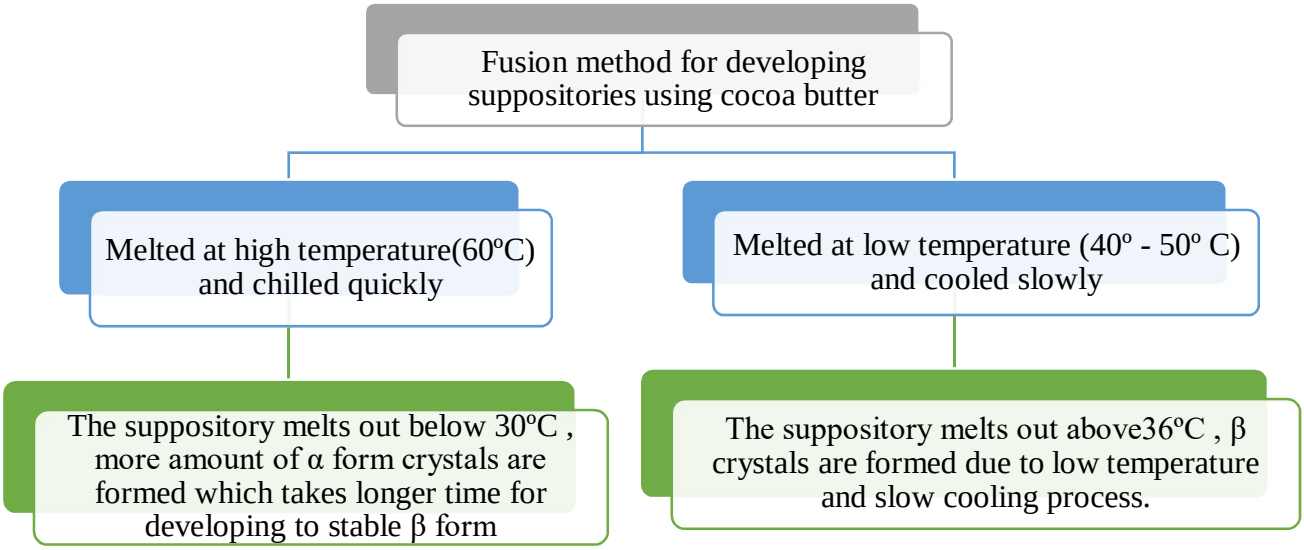


Effects of polymorphism in bioavailability of drugs:

Quite a large number of drugs are hydrophobic by nature; this implies that they have low aqueous solubility. That means these substances in their most stable form will produce the slowest rate of dissolution followed by low bioavailability. While in case of a highly aqueous soluble drugs dissolution does not get hindered. For example: Chloramphenicol palmitate exhibits three polymorphs (stable- α), (metastable- β) and (unstable- γ). Similarly aspirin demonstrates polymorphic forms when isolated from 95% ethanol and n-hexane. Where the n- hexane isolated aspirin has high solubility in aqueous medium compared to the one isolated from 95% ethanol.

Effects of polymorphism on melting point:

Polymorphic forms are found in case of Cocoa Butter or Theobroma oil, it's a base used for preparation of suppositories. Theobroma oil demonstrates 3 polymorphic forms with respect to melting points α - 20º C (meta stable), β - 36º C (stable), γ - 15º C (unstable). Below is depicted few descriptions about how fusion process of developing suppositories gets influenced under the influence of temperature using cocoa butter base.



Effect of polymorphism and cake formation in suppositories:

Basically in suspensions the suspended particles tend to settle down as a result they get closer to each other and proximity distance decreases. Other than this a suspension formulation experiences various range of temperature during storage. The rise in thermal factors tend to dissolve the metastable polymorph in the stagnant layer and during reduction of thermal value the particles may bridge out among themselves along with stable forms leading to irreversible caking. As a result redispersion becomes difficult.

Molecular Adducts

During the process of crystallization, some substances tend to entrap the solvent molecules within the lattice being formed. These defined as molecular adducts and can be classified as follows:

1. Non-Stoichiometric inclusion compounds (or adducts)

In these crystals mother liquor molecules are trapped within the crystal lattice and the number of solvent molecules are not included in stoichiometric number. Based on the shape they are of three types:

(1) Channel:

Where the crystal contains continuous channels in which the mother liqour molecule can be included. For example: Urea forms channel.

(2) *Layers:* Here solvent is trapped between layers of crystals.

(3) ***Clathrates (Cage)****:* Solvent molecules are entrapped within the cavity of the crystal from all sides.

2. Stoichiometric inclusion compounds (or stoichiometric adducts):

These molecular complexes entrap the mother liquor molecules into specific sites within the crystal lattice and have stoichiometric number of solvent molecules complexed.

If the incorporated solvent is water, then the complex is called hydrates while if the solvent is other than aqueous system, then complex is defined as solvates. Depending on the ratio of water molecules within a complex these can be categorized as follows:

(i) ***Anhydrous*** : 1 mole compound + 0 mole water

(ii) ***Semi hydrate***: 1 mole compound + ½ mole water

(iii) ***Monohydrate****:* 1 mole compound + 1 mole water

(iv) ***Dihydrate*** : 1 mole compound + 2 moles water

Properties of solvates / hydrates:

(i) Very commonly, the anhydrous form of a drug has greater aqueous solubility than its hydrates. This is due the fact that the hydrates are in equilibrium with water and therefore have less necessity for water. For example; anhydrous forms of theophyline and ampicillin have higher aqueous solubility than their hydrates.

(ii) On the other hand the non aqueous solvates have greater tendency for aqueous solubility than the non-solvents. For example; chloroform solvates of griseofulvin are more water soluble.

Polymeric materials:

Polymers are very large molecules and are flexible thus are not aligned perfectly to form crystals. They have two regions one ordered region within their structure and the other is the disordered one that surrounds the ordered region. Thus polymers are said to be semi crystalline substance and their degree of crystallinity depends on their synthesis process and experimental conditions there off.

Equipments used to characterise a solid substance (for its various nature like crystal, amorphic forms, and polymorph): there are few analytical instruments that help us to determine the nature of the solid drug substances like:

1. Optical microscopy
2. Scanning Electron Micorscopy (SEM)
3. Hot stage microscopy
4. Differential Thermal Analysis
5. Differential Scanning Calorimetry
6. Thermogravimetric Analysis (TGA)
7. X-ray powder diffraction
8. IR-Spectroscopy

Detailed study on Instruments used for characterising the solid substances:

Microscopy: The instrument works on principle of passing light through cross-polarizing filters. As a result any substance that is super cooled or has crystal lattice will demonstrate refractive index while amorphous systems will not exhibit this behavior.

Differential Scanning Calorimetry *(DSC):* In this method the difference of energy inputs i.e. ΔH values of test sample and that of reference sample is determined based on controlled temperature programming. Mostly samples that are studied under this are powders, fibers, crystals, polymers etc. the study finds its application in various sections like determination of purity of sample, number of polymorphic forms of a substance, heat of salvation, compatibility of drug and excipients, glass transition phase of a given polymeric sample. Similar to DSC there is yet another technique that assists in determination of physical nature of solids i.e. *Thermogravimetric Analysis (TGA):* this method uses the variation in sample weight with respect to change in time or temperature. It's basically used to study the desolvation and decomposition processes.

X-Ray Powder Diffraction*:* This study is based on Bragg's law of diffraction; it's mostly exhibited by crystalline powders. Amorphous systems do not demonstrate this property under diffraction study. The diffraction pattern is specific based on the lattice arrangement of the given crystal. It's also called finger print pattern of a crystal.

Hygroscopicity*:* Active ingredients basically aqueous soluble salt forms having pharmaceutical importance usually take up moisture from atmosphere and are defined as hygroscopic materials.

There are yet another category of materials called *Deliquescent substances* that absorb moisture from environment and dissolve out completely.

How to determine hygroscopic materials*:* there are few analytical instruments that can help us out to identify hygroscopic material to name a few of them are Gravimetry, Thermogravimetric analysis (TGA), Karl-Fischer titration (KF-titration), Gas chromatography (GC). These substances need at most care while they are to be formulated to a dosage form.

Significance of Hygroscopicity determination*:* The determination of hygroscopic materials in a given pharmaceutical bulk system plays vital role like it helps to decide about the method of storage to be adopted for such substances, helps to determine condition of storage with respect to temperature and humidity. It also enables to decide upon the packaging material needed for packing the material, it also helps us to determine the effect of moisture level in the compound and how it will affect flow behavior, consolidation or compaction stages during tabletting or filling of capsules. The study also enables the formulation chemist with the idea that in case there is formation of hydrates then how this is going to influence the dissolution of the drug or how presence of moisture is going to degrade an active principle.

Fine particle characterization and powder flow behavior properties: The study includes analysis of powder based on particle size and size-distribution, shape of the particle, surface topography study etc. even few instrumental methods also help us to characterize particles nature like sieve analysis, optical micrometer, light microscope techniques, coulter counting techniques, etc.

Fine particle characterization

Sieve Analysis: The study is based on IP method of determination of particles using sieve of standard sizes. In this study the given powder sample is passed through a standard sieve set as per the procedure mentioned in IP. The particle size is plotted against % weight retained on each sieve. The method finds utility to measure the particle size mostly when our powder sample is course natured.

Size and size distribution of the given active ingredient can be determined by sieve analysis method[5]. In this method the given sample is separated in to various size fractions by sieving those using standard sieves of different aperture size. For example 12, 14, 16, 18 and 22 (mesh apertures i.e. 1.4 mm, 1.18 mm, 1.0 mm, 0.85 mm and 0.71 mm respectively) for 5 min. After 5 min sample that is retained on each sieve are collected separately and weighed.

The study is usually conducted in triplicate and mean particle size of powder samples are calculated using the following formula,

$$Mean\ particle\ size = \sum(mean\ particle\ size\ of\ the\ fraction\ X\ weight\ fraction\ /\sum weight\ fraction$$

Stream Scanning method or coulter counter method: There are few instrumental methods that work out on the principle of stream counting for determining the particle size of a sample. Some of the instruments are:

a) Coulter counter or Anderson pipette method works based on electrical sensing

b) HIAC counter works on the principle of optical sensing

c) Malvern particle and droplet sizer works based on laser diffraction technique

Procedure:

In this method the sample under study is suspended in a conducting medium (vehicle) and a few drops of surface active agents are also used to distribute the particles uniformly in the medium. A known volume approximately 0.5 to 2 ml of this suspension is pipetted into a tube through a small opening of 0.4 to 800 μm diameter over which a voltage is applied. As the particle pass through the opening, the particle is counted and size is determined based on the electrical resistance the particle displays while forcing out the particle volume from the medium. The obtained size distribution is determined from the graph obtained from the software. Unlike other methods this method also has its own disadvantage i.e. it too much time consuming.

Surface topography study: Scanning electron microscopy helps us to determine the surface characteristic of a given powder sample in black and white image form. In this study we get a magnified image of the particle using electron wave instead of photons.

Procedure:

The sample under study is dried with precaution to prevent it from shrinkage, and then the sample is coated using gold by help of sputter-coater. Post this process the sample is placed in the vacuum chamber of the microscope unit and exposed to high beam of electrons through a series of magnetic lenses system focused on to a fine zone. Thus, capturing the image and helping to know about surface texture whether it is rough or smooth or whichever texture feel we can note.

Powder characteristics: the powder can be characterized by the following parameters. Bulk density, tapped density, true density, flow behavior etc.

Bulk density: It's also called the apparent bulk density of a powder and is expressed in terms of g/cm^3. It is calculated by the formula:

$$Apparent\ Bulk\ Density = {}^{Weight\ of\ the\ powder}/_{Bulk\ volume}$$

Why do we measure Bulk density: Bulk density is a required parameter when compaction or filling of capsule with high dose active ingredient is an operation in manufacturing process. If at all the drug has low bulk then it has to be aided with excipients. Even in case of low dose drugs a large difference between drug and excipient is a challenge in manufacturing unit.

Similarly, the *Tapped Density* also expressed in terms of g/cm^3 is expressed by the equation

$$Tapped\ Density = {}^{Weight\ of\ the\ powder}/_{Tapped\ volume}$$

Why do we measure Tapped density: as bulk density tapped density helps us to know the compactability of the powder bed when formulating tablet and in case of capsule helps to select the size of capsule for filling the active principle based on dose.

True Density (g/cm^3): It's defined as the density of a powder bed excluding the volume of its pores either (open or closed). True density usually explains about packability and behavior of the powder when used in binary mixtures at various proportions. It's basically determined by displacement method utilizing either an insoluble solvent or through gas displacement using helium gas.

Apparent density: Unlike true density this parameter measures the density of powder bed taking the volume of closed pores in to account. This is useful study about the behavior of powder bed when under the influence of die filling and compaction

Porosity: its synonym is void fraction and its measurement of void spaces or empty spaces of a powder bed. It is calculated as ratio of volume of voids: total volume. It lies between 0 and 1. This parameter plays a significant role in deciding the powder behavior, selection of composition of final formulation, the selection of various unit operations that may be needed for developing the final product. The porosity also decides upon various parameters like selection of granulation method, hardness of formulate tablets, disintegration of tablets, dissolution rate, thereof.

How to determine void volume and porosity: the following formula can be used to determine porosity,

$$Porosity = \frac{Void\ volume}{Bulk\ volume} = m^{\left(\frac{1}{\rho bulk} - \frac{1}{\rho true}\right)} \Big/ \frac{m}{\rho bulk} = 1 - \frac{\rho bulk}{\rho true}$$

Flow behavior: this parameter is characterized by various sub parameters like particle size, density, shape, charge of powder bed, moisture content etc. powder being used for formulation basically tablet may demonstrate few problem like developing cohesive nature due some factors. This issue that may arise needs to be solved by adapting to few techniques like: enhancing densification of powder through slug preparations, granulating the sample, changing to a suitable formulation instead of the one selected previously. Flowability of powder and chemical stability depends on the habit and internal structure of a drug.

Angle of repose: it is the simplest of all parameters but plays a predominate role in describing the inter-particle cohesion. If the cohesive force is dominant in a powder sample then its flow will be poor while it's reversed true when cohesive forces are less.

Why inter-particle cohesion is found: it may be due to existence of non-specific Vanderwaal's force or may be due to high moisture content of the sample; it may also be resultant of surface tension between the sample and media absorbed by it. It may also be attributed to the forces experienced due to contact or friction that the powder sample experiences while in contact with the equipment[6,7,8].

Sl. No.	***Method of determination adopted***	***Angle value obtained in terms of***	***How to interpret angle of repose***

1	Fixed height	Angle of repose	*$\theta < 25^o$ implies very good flow behaviour*
2	Fixed base cone	Angle of repose	
3	Tilting surface	Angle of repose	*$25^o < \theta < 50^o$ implies satisfactory flow*
4	Rotating cylinder	Dynamic Angle of repose	
5	Ledge	Drained Angle of repose	
6	Crater	Drained Angle of repose	*$\theta > 50^o$ implies unsatisfactory flow behaviour*
7	Platform	Drained Angle of repose	

Table-3: Methods to determine angle of repose and interpretation of angle of repose

Compression behavior study: The compression properties (basically the parameters like elasticity, plasticity, fragment ability) for minor amount of a new drug or existing drug candidate can be established. This property is used in proper selection of the formulation ingredients. It is characterized by Carr's index and Hausner ratio.

Compressibility index or Carr's index: It is expressed in terms of ratio between tapped bulk density and fluffy bulk density of a given powder sample.

$$\%\, Compressibility = \frac{\rho t - \rho 0}{\rho t}\, X\, 100$$

Where the terms are ρ_t = tapped bulk density and ρ_0 = fluffy bulk density.

Similarly another parameter i.e. Hausner ratio also helps out in determining the compressibility ability of a given sample of solid system. It is the ration between tapped density and pre tapped density. It is expressed by the following formula;

$$Hausner\ ratio = {Df}/{Do}$$

Where *Df* is the tapped density while *Do* is the pre tapped density.

How to interpret the datas of compressibility index and Hausner's ratio: it is said that if the value of *Hausner's ratio* is higher it indicates that the sample is cohesive natured due to which the sample will exhibit poor flow behavior. Similarly, *Compressibility index* with a

higher range value implies more cohesiveness and poor flow. The table below depicts the type of flow behavior with respect to compressibility index:

Compressibility index (%)	***Flow behavior exhibited***	***Illustrations about the Samples that depict the mentioned flow***
>40	Extremely poor	Cohesive powders have very poor flow
35-38	Very poor	Cohesive powders but fluidised
28-35	Poor	Cohesive powders natured but fluidised
23-28	Poor	Demonstrates fluidised behaviour
18-23	Fair	Granules of powdered nature exhibit this flow
12-18	Good	Exhibited by free flowing powdered granules
5-15	Excellent	Free flowing granules

Table-4: Various Compressibility index (%) values and flow behavior exhibited by the samples

Solubility profile (pKa, pH, Partition coefficient) and its significance

One vital aspect of the preformulation study is to design a suitable method for obtaining a solution form of the drug in a suitable media. This is a need because to have a good therapeutic efficacy of a drug it has to enter in to the systemic circulation and the very first media it encounters is aqueous natured so, it should possess aqueous solubility. It has been demonstrated by insoluble compounds that they get poorly absorbed. Thus, focus of study mainly lies on solubility parameter and the inter molecular forces of attraction within the substance and force of attraction between solute and solvent. This implies there is need overcome the solute-solute interaction forces, the solvent-solvent interaction forces and attain the solute-solvent attraction (drug-body fluid interaction). For example: if we want to understand about the solubility of an orally administered drug then we need to study about its solubility in simulated gastric fluid (SGF). A new drug entity is always evaluated for its solubility profile. For example if a drug has low aqueous solubility there is a fair chance of it to suffer from absorption problems in bio fluids.

Factors on which the solubility of a drug depends:

Solubility is influenced by temperature, physicochemical properties of a drug, nature of vehicle or solvent in with which it has to interact, the pressure above it, acidity and basicity of the solution, the rate of agitation to which it is subjected while being dissolved in the solvent.

Methods adopted for solubility analysis:

a) Determination of solubility profile

b) Determination of pKa value

c) Common ion effect

d) Partition coefficient

e) Membrane permeability

Methods adopted to improve the drug solubility profile:

Few of the adopted measures for improving drug solubility are: Chemical modification of the drug into salt or its ester forms by use of a suitable solubilising agent, by usage of co-solvents, by adopting to micronization or nanonization techniques, developing solid dispersion system of the drug or by adjusting the pH of the solvent in which the drug can be dissolved[9].

a) Intrinsic Solubility determination: it is definite that all factors that influence solubility and dissolution of a drug must be fixed. While determining the intrinsic solubility the first step is to disperse a slight excess amount of drug in the vehicle at constant temperature, agitation and with respect to time withdraw a small amount of the solution and either filtrate it out or centrifuge it. Then assay of collected sample for drug content is determined using UV, HPLC, GC or other analytical instruments and the value estimated is recorded.

b) pKa and pH determination: there exist unique relation between dissociation constant, lipid solubility and pH at site of absorption which is based on the principle of pH-partition theory. As described earlier quite a large number of drugs are either weak acids or bases. The ionisation and dissociation features of a drug molecule often are governed by degree of ionization which is dependent on pH of a solution and pKa value. The individual information about a drug on pH and pKa is always a need as it govern the absorption of drug to systemic circulation. The pKa and pH values can be determined over by using Henderson-Hasselbach equation.

For acidic drug compounds

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

pH = pKa + log [ionized] / [unionized] = pKa + log $[A^-]$ / [HA] = pka + log [base] / [acid]

For Basic drug compounds

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

$$pH = pKb + \log [\text{Unionized}] / [\text{ionized}] = \text{pKa} + \log [B] / [BH+]$$
$$= \text{pKa} + \log [\text{base}]/[\text{acid}]$$

Significance

a) the determination of pH as a solution basically is needed to design ophthalmic and parenteral products as these dosage forms need through consideration of pH since below pH value of 3 the patient to whom the product is administered may feel pain while above the pH of 9 the person may exhibit tissue damage so these dosage should be buffered suitably.
b) With the knowledge of solubility profile and pKa, pH of a solution can be determined.
c) The pH equation can helps to determine solubility profile of the salt.
d) Helps in determining suitable media from which the drug will be absorbed. For example, acidic drugs will be absorbed from acidic region while basic drugs will be absorbed from basic environment.

Partition coefficient-This is the oil/water partition coefficient that measures drug molecules lipophilic characters that is, whether the drug has affinity for hydrophilic or lipophilic solvent. This parameter decides upon the development of dosage form. The distribution of the solute between two immiscible solvents i.e. it is defined as ratio of unionized drug in organic layer versus ionized drug in aqueous layer at equilibrium.

$$K_{o/w} = \{C_{oil} / C_{water}\} \text{ at equilibrium}$$

Drug molecules with higher $K_{O/W}$ will cross the lipid bio-membrane.

Dissolution studies: Dissolution rate is defined as the rate at which the active ingredient dissolves with the media. Dissolution mostly depends on the parameters like drug's solubility, dissociation constant and partition coefficient. These factors can be used as indicative measure to know about the potential and efficacy of drug post administration. Noyes-Whitney equation helps to determine the dissolution constant of a drug and also explains how surface area or particle size influences dissolution. Less is particle size of the sample higher will be dissolution profile.

Noyes-Whitney equation:

where, D = diffusion coefficient of the drug in the dissolution medium, h = thickness of the diffusion layer at the solid/liquid interface, A= surface area of drug exposed to dissolution medium, V = volume of the medium, C_S = Concentration of saturated solution of the solute in the dissolution medium at the experimental temperature, C=Concentration of drug in solution at time t.

$$\frac{dc}{dt} = \frac{DA}{hV}(C_S - C)$$

Significances:

a) Determination of dissolution study helps in finding any potential problems that may affect bioavailability in future.

b) It is assists in anticipating probable problems that may lead to poor absorption

c) This study aids in determining the effects of various factors like particle size, surface area, and excipients on release rate of the active agent.

Solubilization: for any drug candidate that has a poor solubility profile a study on how to enhance its solubility must be studied.

Methods to enhance solubility:

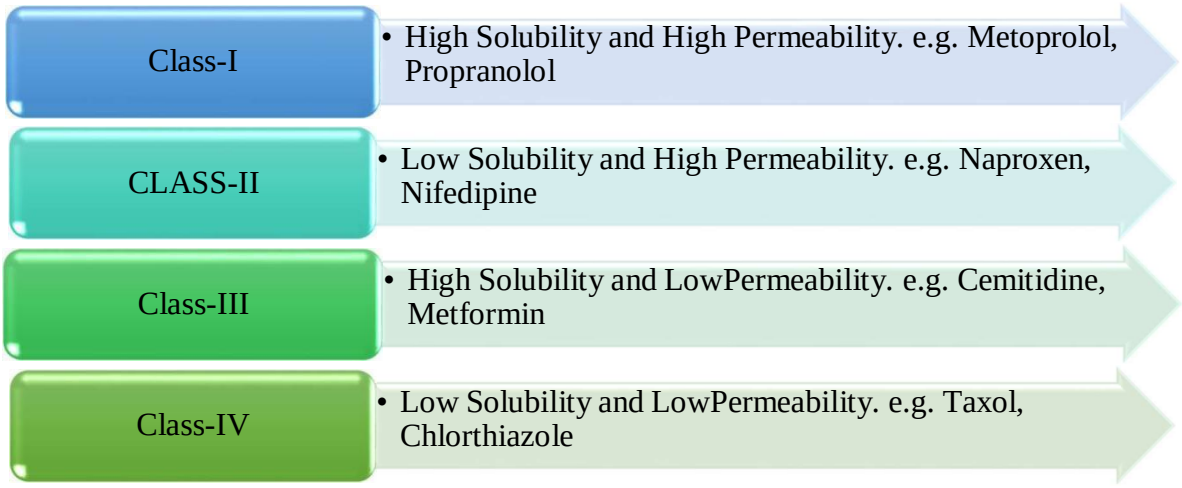
- Addition of a co-solvent to the aqueous system e.g. ethanol, propylene glycol and glycerin.
- Solubilization in micellar solutions such as surface active agent solution.
- Solubilization by forming molecular complexes e.g. para amino benzoic acid and caffeine complex.

- Solubilization by developing solid dispersion.
- By changing the pH of the solution
- By changing the polymorphs

Approaches of decreasing the solubility of drugs: like enhancing solubility of a sample there are methods to suppress solubility of a drug molecule, to name a few of them are esterification, coating with polymers of opposite natured, changing the polymorphic form of the molecule which has better solubility in a given media, or by using hydrate forms instead of anhydrous ones.

BCS classification of drugs & its significant:

The Biopharmaceutical Classification System was first developed in the year 1995, by a group of scientists (Amidon and his team). The Biopharmaceutical Classification System can be defined as a scientific model for categorizing the active principle (drug molecule) to different categories or classes based on its aqueous solubility and intestinal permeability.



Applications of BCS Classification: Helps to predict the *in-vivo* functioning of the drug base on solubility and permeability, assists in various stages of drug discovery, assists in identification of suitable drug delivery system, helps in scaling up a batch and bio equivalence data generation, can also help in bio-waiver analysis of drug.

Significance: it acts as predicting tool for bio equivalence study design through accurate in-vivo study. It also aids in *in-vitro in-vivo correlation study* (IVIVC) study[10].

Chemical Properties: Hydrolysis, oxidation, reduction, racemisation, polymerization:

Hydrolysis: Most of the drug molecules follow this common degradation path, thus water plays a huge role not only in solution but also solid dosage forms also even in its slightest value. Hydrolysis takes place due to nucleophilic attack of the water molecule on the hydrolytic bonds. Demonstrating a decrease in value in the order series of lactam > ester > amide > imine. The process is also influenced by pH. If the solvent is not water, solvolysis may take place in case there is incompatible reaction.

Oxidation: The phenomenon is influenced by environmental stresses like load of oxygen (or an oxidizing agent), light, and trace metals presences that are able to provoke the catalyzing process. The reaction is usually faster in case the process takes place due to molecular oxygen and is called as auto-oxidation. These responses usually involve free radical chain reactions. The reaction continues till an anti-oxidant stops it. These reactions generally produce high intensity coloured degradation products, which can be visually detected.

Photolysis: certain compounds have the tendency to absorb light which initiates the cleavage of bonds leading to photodegradation. This reaction is based on wave length and intensity of light. Maximum degradation occurs through UV light, of sunlight in the range of 290–1750 nm and sometimes due to artificial lighting such as fluorescent tubes of range 320–380 nm. Prevention of photodegradation is accomplished packing in suitable light resistive systems like foil wraps or amber glass.

Stability analysis:

The chemical stability of any new molecule can be quantified by preformulation study. The study design includes: stability study in toxicology formulation, stability study in solution state and finally stability study in solid state.

In toxicology formulations: The analyses help out in evaluating a toxicological formulation for stability and potential problems associated with the homogeneity. Usually an active principle is fed to the animals in their food, or by oral feeding of a solution or suspension of drug in an aqueous vehicle forcefully. Agents like water, essential vitamins, minerals, which can affect the shelf life of a drug and decrease stability thereof are fed to the animal along with the feed. The animal is kept under observation and any instability is detected and reported.

Solution stability: the study aims in establishing conditions that affect the stability of drug.

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Factors on which stability depends: Stability of a new drug may depend on quite a few parameters like pH, ionic strength, co-solvent, light, temperature, moisture and oxygen levels to which the drug is exposed.

pH stability study: in order to study the effect of extreme pH and temperature condition that affects the stability of the drug a study is designed as follows keeping temperature constant: a) Set-1(extreme acidic): 0.1N HCl solution at 90^0C. b) Set-2(neutral): Solution in water at 90^0C. c) Set-3(extreme basic): 0.1 N NaOH solution at 90^0C. this study assists in studying about rate of degradation of a sample in different environment.

Ionic strength: the pH of most of the pharmaceutical formulations should be compatible with body fluids as described earlier as basically when choice of route for their administration is parenteral. The ionic strength (μ) of the solution plays a vital role here for example ionic strength of an isotonic 0.9%w/v sodium chloride solution is 0.15. the ionic strength is calculated from the formula

$$\mu = \frac{1}{2}\sum m_i Z_i^2$$

Where m_i = molar concentration of the ion and Z_i = valency of the ion

Effect of temperature on stability: thermodynamic principles also play a vital role in stability of a drug molecule. Heat of solution, ΔH_s may give idea about either release of heat or energy or amount of heat absorbed during a process(when a mole of solute is dissolved in a large quantity of solvent).

Significance

- In most of the cases, the solubility process is an endothermic reaction. For instance if ΔH is positive then it implies that solubility increases with enhancement in temperature.
- Similarly in case of an exothermic process ΔH_S is negative implies solubility is lowered

Light: exposure of a drug to photons is very crucial basically during its storage period as any wrong exposure to photons may lead to instability. For example drugs like Naproxane is instable in all forms stray light, it needs to be store in dark room. Thus in order to preserve the nature of a drug the stability of the drug under influence of light should be carried out. For this study design sample are subjected to light exposure by storing in various container such as clear glass, amber coloured glass, yellow-green colour glass which are intended to be

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used in future to store the drug and these systems are studied over a period of time to identify the problems.

Temperature: The degradation rate constant (k) of a chemical reaction for a drug molecule will vary with change in temperature according to Arrhenius equation.

$$k = Ae^{-\mathrm{Ea/RT}}$$

$$\text{Or, } Ln = Ln\,A - {}^{Ea}/_{R}\,({}^{1}/_{T})$$

Where, k is the rate constant, A is defined as frequency factor, E_a is the energy of activation, R is gas constant, while T is absolute temperature. The above equation is used to study and estimate the shelf life of the drug.

Solid state stability

Objectives: this analysis is performed in order to understand and find a suitable storage conditions for active principle in its solid state and also identify the drug- excipients compatibility for a given formulation.

Characteristics: The rate of decay of the drug in its solid state is much more gradual, so the rate of appearance of the decay process is determined instead of determining the amount of drug remaining unchanged. In order to carry this analysis few analytical equipments are taken in to due considerations like TLC supported by UV/Visible spectroscopy, Differential Scanning Calorimeter, Infra-Red spectroscopy, reflectance equipments(to determine any change in colour intensity that take places on the surface of the sample due to oxygen stress.

Drug-excipient stability profile: in this study experimental dosage forms are prepared with various additives, at various concentrations and are exposed to various experimental conditions to study the interactions of drug and excipients.

Conclusions:

After carrying out the preformulation evaluation of new drug candidates, a complete report of it is prepared where the pharmaceutical problems associated with molecules are brought in to notice, this helps to develop the first phase of formulation and also assists in subsequent modifications if needed in order to develop a stable dosage form.

References:

1. Bauer J, Spanton S, Henry R, Quick J, Dziki W, Porter W, Morris J. "Array". Pharmaceutical Research 2001; 18: 859-866.

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2. Lachman L, Liebeman H. The theory and practice of Industrial Pharmacy .Indian Edition CBS publishers.2009.
3. Jones TM. The physico technical properties of starting materials used in tablet formulations. Int J Pharm Technol Prod Manuf 198; 2: 17-24.
4. Allen LV, Popovich NG and Ansel H.C: Ansels Pharmaceutical Dosage Forms and Drug Delivery Systems. Lippincott Williams and Wilkins, Wolters kluwer, New York, Edition 9, 2005: 431-492.
5. Viswanathan NB, Thomas PA, Pandit JK. Preparation of non-porous microspheres with high entrapment efficiency of proteins by a (water-in-oil)-in-oil emulsion technique. J Control Rel 1999; 58:9-20.
6. Jain NK and Sharma SN: A Text book of professional pharmacy. Vallabh prakashan, Pitampura Delhi, 2004: 317-333.
7. Lachman L, Lieberman H A and Joseph L K: The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Bombay, Edition 3, 1990: 171-196.
8. Banker GS and Rhodes CT: Modern Pharmaceutics. Revised and expanded, Marcel Dekker, Inc. Newyork, Edition 4, vol.121, 2008:167-185.
9. Gopinath R, Naidu RAS: pharmaceutical preformulation studies- current review. Int J of Pharm and Biological Archives 2011; 2: 1391-1400.
10. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12:413–420.

BP 502 T. Industrial Pharmacy-I (Theory)

UNIT-II

Tablets:

a. Introduction, ideal characteristics of tablets, classification of tablets. Excipients, Formulation of tablets, granulation methods, compression and processing problems. Equipment's and tablet tooling.

b. Tablet coating: Types of coating, coating materials, formulation of coating composition, methods of coating, equipment employed and defects in coating.

c. Quality control tests: In process and finished product tests

Liquid orals:

Formulation and manufacturing consideration of syrups and elixirs suspensions and emulsions; Filling and packaging; evaluation of liquid orals official in pharmacopoeia.

Introduction-

- According to USP, Tablet is defined as a compressed solid dosage form containing medicaments with or without Excipients.
- According to the Indian Pharmacopoeia, Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents

Advantages of tablet dosage form over other oral drug delivery systems

From patients stand point:

- They are easy to carry, easy to swallow and they are attractive in appearance.
- Unpleasant taste can be masked by sugar coating and they do not require any measurement of dose.
- Some of the tablets are divided into halves and quarters by drawing lines during manufacturing to facilitate breakage whenever a fractional dose is required.

From the standpoint of manufacturer:

- An accurate amount of medicament, even if very small, can be incorporated.
- Tablets provide best combined properties of chemical, mechanical and microbiological stability of all the oral dosage forms.
- Since they are generally produced on a large scale, therefore, their cost of production is relatively low, hence economical.
- They are in general the easiest and cheapest to package and ship among all oral dosage forms.
- Some specialized tablets may be prepared for modified release profile of the drug.
- Product identification is potentially the simplest and cheapest requiring no additional processing steps when employing an embossed or monogrammed punch face.

Disadvantages of tablet dosage form

- Difficult to swallow in case of children and unconscious patients.
- Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
- Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to oxygen may require encapsulation or coating. In such cases, capsule may offer the best and lowest cost.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

Types of tablets-

(a) <u>Tablets ingested orally:</u>

- Compressed tablets
- Multiple compressed tablets
- Enteric coated tablets
- Sugar coated tablets
- Film coated tablets
- Chewable tablets

(b) <u>Tablets used in the oral cavities:</u>

- Buccal Tablets
- Sublingual tablets
- Lozenges
- Dental cones

(c) <u>Tablets administered by other routes</u>:

- Implantation tablets
- Vaginal tablets

(d) T<u>ablets used to prepare solutions:</u>

- Effervescent tablets
- Dispensing tablets
- Hypodermic tablets
- Tablet triturates

(a) Tablets ingested orally-

(1) Compressed tablets:-

- These tablets are formed by compression and contain no special coating. They are made from powdered, crystalline or granular materials, alone or in combination with suitable excipients.
- These tablets contain water soluble drugs which after swallowing get disintegrated in the stomach and its drug contents are absorbed in the gastrointestinal tract and distributed in the whole body. e.g. Aspirin (Dispirin) paracetamol tablets (Crocin).

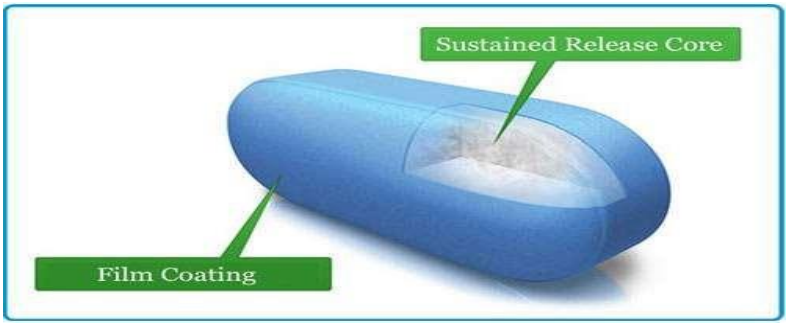
(2) Multiple compressed tablets / Layered tablets-

- These are compressed tablets made by more than one compression cycle. Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers.
- To avoid incompatibility, the ingredients of the formulation except the incompatible material are compressed into a tablet and then incompatible substance along with necessary excipients are compressed over the previously compressed tablet.

(3) Sustained action tablets:

These are the tablets which after oral administration release the drug at a desired time and prolong the effect of the medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required to maintain the maximum effective concentration of the drug in the blood throughout the period of treatment.

e.g. Diclofenac SR tablets.



(4) **Enteric coated tablets:**

- These are compressed tablet meant for administration by swallowing and are designed to by-pass the stomach and get disintegrated in the intestine only.
- These tablets are coated with materials resistant to acidic pH (like cellulose acetate phthalate, CAP) of the gastric fluid but get disintegrated in the alkaline pH of the intestine.

(5) Sugar coated tablets:

- These are compressed tablets containing a sugar coating. Such coatings are done to mask the bitter and unpleasant odour and the taste of the medicament. The sugar coating makes the tablet elegant and it also safeguard the drug from atmospheric effects.

(6) Film coated tablets:

- The compressed tablets having a film coating of some polymer substance, such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose and ethyl cellulose.
- The film coating protects the medicament from atmospheric effects. Film coated tablets are generally tasteless, having little increase in the tablet weight and have less elegance than that of sugar coated tablets.

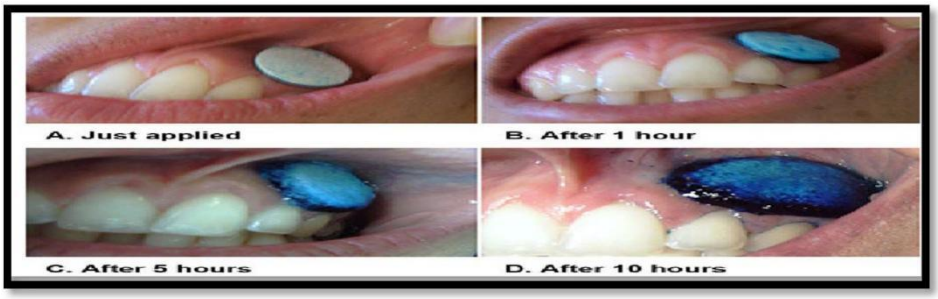
(7) Chewable tablets:

- These are the tablets which are required to be broken and chewed in between the teeth before ingestion. These tablets are given to the children who have difficulty in swallowing and to the adults who dislike swallowing.
- These tablets should have very acceptable taste and flavour. Ex- Antacid tablets (Digiene).

(b) Tablets used in oral cavity

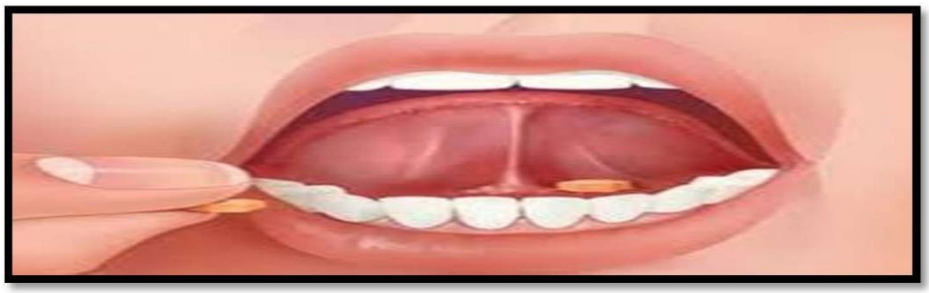
(1) Buccal tablets:

- These tablets are to be placed in the side of the cheek (buccal pouch) where they dissolve or erode slowly and are absorbed directly in the buccal cavity without passing into the alimentary canal.
- Therefore, they are formulated and compressed with sufficient pressure to give a hard tablets. e.g. Progesterone tablets.



(2) Sublingual tablets:

- These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT. e.g. tablets of nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate.



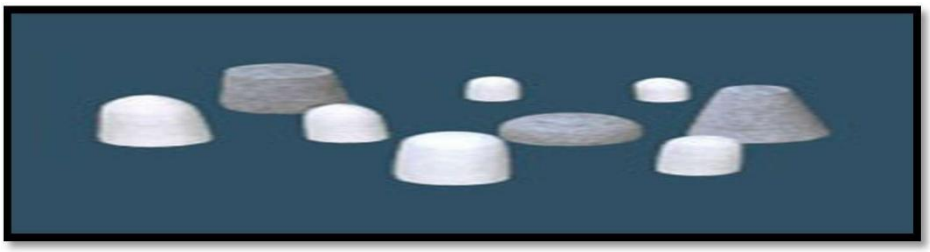
(3) Lozenges tablets:

- These tablets are designed to exert a local effect in the mouth or throat. These tablets are commonly used to treat sore throat to control coughing in common cold. They may contain local anaesthetics, antiseptics, antibacterial agents and astringents.
- These are prepared by compression at a high pressure by the moulding process and generally contain a sweetening agent, flavouring agent and a substance which roduces a cooling effect. e.g. Vicks lozenges, Strepsils.

(4) Dental cones:

- These are compressed tablets meant for placement in the empty sockets after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow-releasing antibacterial compounds or to reduce bleeding by containing the astringent.

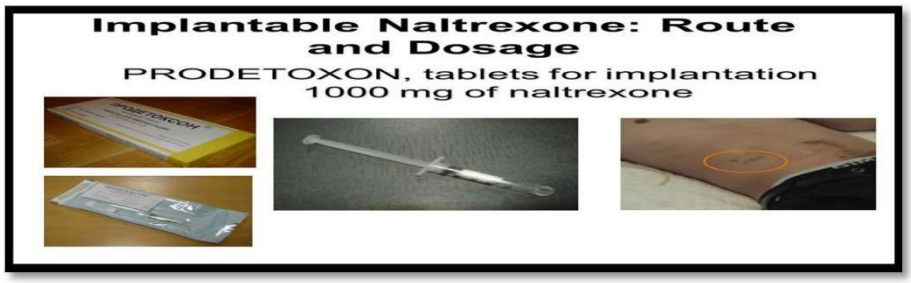
- These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride. These cones generally get dissolved in 20 to 40 minutes time.



(c) Tablets administered by other routes

(1) Implantation Tablets:

- These tablets are placed under the skin or inserted subcutaneously by means of minor surgical operation and are slowly absorbed. These may be made by heavy compression but are normally made by fusion. The ***implants must be sterile*** and should be ***packed individually in sterile*** condition. Implants are mainly used for the administration of hormones such as testosterone steroids for contraception. These tablets are very usefully exploited for birth control purpose in human beings.
- The disadvantages of implant tablets are their administration, changing rate of release with change of surface area and possibility of tissue reactions.



(2) Vaginal tablets:

- These tablets are meant to dissolve slowly in the vaginal cavity. The tablets are typically ovoid or pear shaped for the ease of insertion. these tablets are used to release steroids or antimicrobial agents. the tablets are often buffered to promote a pH favorable to the action of a specified antimicrobial agent. The contains easily soluble components like lactose or sodium bicarbonate.

(d) Tablets used to prepare solutions

(1) Effervescent tablets:

- These tablets along with the active medicament contain ingredients like sodium bicarbonate, citric acid and tartaric acid which react in the presence of water liberating carbon dioxide and producing effervescence leading to disintegration of the tablet, thus fastens solution formation and increase the palatability. Eg. Histac (Ranitidine)

(2) Dispensing tablets:

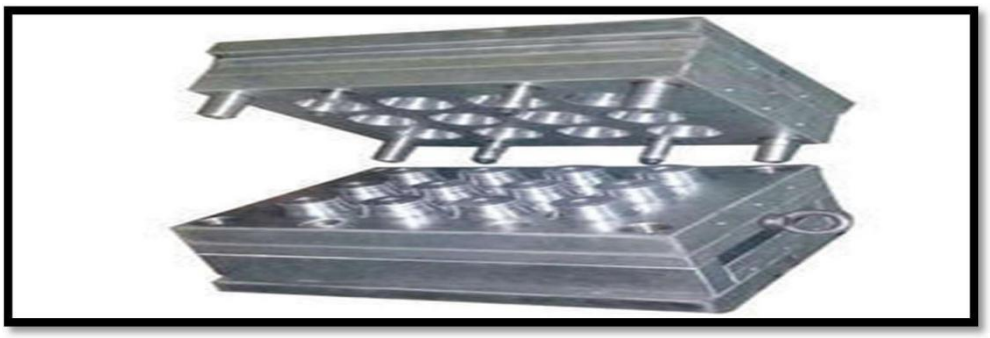
- These tablets provide a convenient quantity of potent drug that can be readily convert into powders and incorporate into liquids, thus circumventing the necessity to weigh small quantities. these tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as dosage form.
- e.g. The drugs commonly incorporated are mild silver potentiate, bichloride of mercury merbromin an quarterly ammonium compounds.

(3) Hypodermic tablets:

- Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. These tablets are dissolved in sterile water or water for injection and administered by parenteral route. these tablets are not preferred now-a-days because the resulting solution is not always sterile.

(4) Tablet triturates (Moulded tablets):

- These are powders moulded into tablets. They are flat, circular discs, usually containing a potent substance mixed with lactose, lactose and sucrose, dextrose, or other suitable diluent.
- Since they are intended to disintegrate very quickly in contact with moisture, water insoluble adjuncts are avoided. The name 'tablet triturate' is appropriate because they usually contain triturations (*trituration = dilution with an inert substance*).



Tablet Ingredients/ Excipients-

In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:

1. Diluent / Filler
2. Binder and adhesive
3. Disintegrants
4. Lubricants and glidants
5. Colouring agents
6. Flavoring agents
7. Sweetening agents

Function of excipients-

- Impart weight, accuracy, & volume.
- Improve solubility

- Increase stability
- Enhance bioavailability
- Modifying drug release
- Assist product identification
- Increase patient acceptability
- Facilitate dosage form design

1. Diluents

Definition- Diluents are fillers used to make required bulk of the tablet when the drug dosage itself is inadequate to produce the bulk.

Secondary reason is to provide better tablet properties such as improve cohesion, to permit use of direct compression manufacturing or to promote flow.

A diluent should have following properties:

1. They must be non-toxic and low cost.
2. They must be commercially available in acceptable grade
3. They must be physiologically inert, physically & chemically stable by themselves & in combination with the drugs.
4. They must be free from all microbial contamination.
5. They do not alter the bioavailability of drug.
6. They must be color compatible.

Characteristics of an ideal diluents

- They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
- They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
- They must be cheap compared to the active ingredients and must be physiologically inert.
- They must be chemically stable alone and/or in combination with the drug(s) and/or other tablet components.
- They must be color-compatible (should not produce any off-color appearance).
- They must have no negative effects on the bioavailability of the drug(s) in the product

Commonly used tablet diluents-

1- Lactose-anhydrous and spray dried lactose

2. Directly compressed starch-Sta Rx 1500

3. Hydrolyzed starch-Emdex and Celutab

4. Microcrystalline cellulose-Avicel (PH 101and PH 102)

5. Dibasic calcium phosphate dehydrate

6. Calcium sulphate dihydrate

7. Mannitol and Sorbitol

8. Sucrose- Sugartab, DiPac, Nutab

9. Dextrose

Lactose

- Lactose is the most widely used diluent for tablet formulation. It is obtained in hydrous and anhydrous form. The anhydrous form, picks up moisture when exposed to elevated humidity. Such tablets should be packed in moisture proof packets or containers. When a wet granulation method is employed, the hydrous form of lactose should generally be used.
- Two grades of lactoses are commercially available:

  (i) A 60 to 80 mesh – coarse

  (ii) a 80 to 100 mesh – regular grade

Advantages:

- Lactose has no reaction with most of the drugs, whether in hydrous or anhydrous form.
- Lactose formulations show good release rates. Their granulations are readily dried, and the tablet disintegration times of lactose tablets are not strongly sensitive to variations in tablet hardness.
- It is a low cost diluent.

Disadvantages:

- Lactose reacts with amine drug bases in presence of alkaline lubricants e.g. metal stearates (e.g. magnesium stearate) and gradually discolours (dark brown) with time due to the formation of furaldehyde. This reaction is called Maillard reaction.

Calcium salts ((DCP/TCP)

Dibasic calcium phosphate dihydrate (or dicalcium orthophosphate) (DCP) [$CaHPO_4$, 2 H_2O], Calcium sulfate dihydrate ($CaSO_4$, $2H_2O$).

Advantages:

- Diluents that exist in their common salt form as hydrates, containing appreciable bound water as water of crystallization. This bound water of calcium sulfate is not released below 80^0C. They possess very low concentration of unbound moisture. Hence, these

salts are excellent diluents for water-sensitive drugs. It is superior to anhydrous diluent, which has a moderate to high moisture demand.

Disadvantages:

- Tetracycline products made with calcium phosphate diluent had less than half the bioavailability of the standard product. Divalent cation (Ca^{++}) form insoluble complexes and salts with number of amphoteric or acidic functionality antibiotics, which generally reduces their absorption (*which is also why milk should not be co-administered with these drug*).

Spray dried lactose

Advantages:

- It is used for direct compression (containing drug + diluent + disintegrant + lubricant). In addition to the direct compression properties, spray dried lactose also has good flow characteristics. It can usually be combined with as much as 20 to 25% of active ingredients without losing these advantageous features.

Disadvantages:

- If spray dried lactose is allowed to dry out and the moisture content falls below the usual 3% level, the material loses some of its direct compressional characteristics.
- Spray-dried lactose is especially prone to darkening in the presence of excess moisture, amines, and other compounds owing to Maillard reactions. Hence, a neutral or acid lubricant should be used.

Starch

- Starch may be obtained from corn, wheat or potatoes and rice. It is occasionally used as a tablet diluent. USP grade of starch is usually possesses moisture content between 11 to 14%.
- Specially dried types of starch that have a standard moisture level of 2-4% are available, but are costly. Use of such starches in wet granulation is wasteful since their moisture level increase to 6-8% following moisture exposure.

Directly compressible starches

- **Sta–Rx 1500**– free flowing, directly compressible starch. It is used as diluent, binder, disintegrant.
- **Emdex and Celutab** – are two hydrolyzed starches – contains dextrose 90–92% and maltose 3–5%
- free flowing and directly compressible and may be used in place or mannitol in chewable tablets because of their sweetness and smooth feeling in the mouth.

Dextrose (D–Glucose)

- Available in two forms: as hydrates and anhydrous forms.
- Dextrose may sometimes be combined in formulation to replace some of the spray-dried lactose, which may reduce the tendency of the resulting tablets to darken.

Mannitol

Advantages

- Because of the negative heat of solution (cooling sensation in the mouth) its slow solubility, and its pleasant feeling in the mouth, it is widely used in chewable tablets.
- It is relatively non-hygroscopic and can be used in vitamin formulations.
- Low calorie content and non-carcinogenic.

Disadvantages

- Costly and has poor flow characteristics and usually require fairly high lubricant level.

Sorbitol

- It is an optical isomer of mannitol and is sometimes combined with mannitol formulations to reduce the diluent cost.
- Disadvantages:- It is hygroscopic at humidities above 65%.

Sucrose

- Some sucrose based diluents are:
- **Sugar tab**– 90 to 93% sucrose + 7 to 10% invert sugar
- **Di Pac** – 97% sucrose + 3% modified dextrins
- **Nu Tab**– 95% sucrose + 4% invert sugar + small amount of corn starch + Mg-stearate

Advantages: They are all used for direct compression.

Disadvantages: All are hygroscopic when exposed to elevated humidity.

Microcrystalline cellulose (MCC)

- Trade Name : Avicel – is a directly compression material
- Two grades are available PH 101 → powder

  PH 102→ granules
- Advantages: It acts as diluent and disintegrating agents.

2. **Binders and Adhesive**

Definition- Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators.

Objective of incorporating binders

- They impart a cohesiveness to the tablet formulation (both direct compression and wet–granulation method) which insures the tablet remaining intact after compression.
- They improves the free-flowing qualities by the formation of granules of desired size and hardness.

Characteristics of binder

Method-I

- Binders are used in dry form in the powder and then moistened with a solvent (of the binder) to form wet lumps.

Method-II

- Binders are often added in solution form. It requires lower concentration of binder.
- By Method-I the binder is not as effective in reaching and wetting each of the particles within the mass of the powder. Each of the particle in a powder blend has a coating of adsorbed air on its surface, and it is this film of air which must be penetrated before the powder can be wetted by the binder solution.

Method-III

- In direct compression method MCC, microcrystalline dextrose, amylose and PVP are used – those have good flow property and cohesiveness as well.
- It has been postulated that MCC is a special form of cellulose fibril in which individual crystallites are held together largely by hydrogen bonding. The disintegration of tablets containing the cellulose occurs by breaking intercrystallite bonds by the disintegrating medium.

Starch paste

Corn starch is often used in the concentration of 10–20%.

Method of preparation:- Corn starch is dispersed in cold purified water to make a 5 to 10% w/w suspension and then warming in water both with continuous stirring until a translucent paste is formed.. (Actually hydrolysis of starch takes place.)

Liquid glucose:- 50% solution in water is fairly common binding agent.

Sucrose solution:- 50% to 74% sugar solution is used as binder. They produce hard but brittle granules. Their cost is low.

Gelatin solution

- Concentration 10–20% aqueous solution
- Should be prepared freshly and added in warm condition other wise it will become solid.

Method of preparation

- The gelatin is dispersed in cold water and allowed to stand until hydrated. The hydrated mass is warmed in water bath to dissolve.

Cellulosic solutions

- HPMC (Hydroxy propyl methyl cellulose) Soluble in cold water.

Method of preparation: HPMC is dispersed in hot water, under agitation. The mixture is cooled as quickly as possible and as low as possible

- HEC (Hydroxy ethyl cellulose), HPC (Hydroxy propyl cellulose) are other successful binders.
- PVP (Polyvinylpyrollidone) Used as an aqueous or alcoholic solution. Concentration 2% and may vary.

3. Disintegrants

Definition:- A disintegrant is a substance to a mixture of substances, added to tablet to facilitate its breakup or disintegration after administration in the GIT. The active ingredients must be released from the tablet matrix as efficiently as possible to allow for its rapid dissolution.

Disintegrants can be classified chemically as: Starches, clays, celluloses, alginates, gums and cross-linked polymers.

Starch

- Corn starch, potato starch.
- For their disintegrating effect starches are added to the powder blends in dry state.

Mode of action*:*

- Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.
- Others have suggested that the spherical shape of the starch grains increases the porosity of the tablet, thus promoting capillary action.
- Normally 5% w/w is suggested and for rapid disintegration 10 – 15% w/w may be taken.

Superdisintegrants

Super disintegrants like Croscarmelose - cross linked cellulose, Crospovidone - cross linked polyvinyl pyrrolidone and Sodium starch glycolate- cross linked starch

Mode of action

- Croscarmelose swells 4 to 8 fold in less than 10 seconds
- Crospovidone acts by wicking or capillary action.

- Sodium starch glycolate swells 7 to 12 folds in less than 30 seconds.

Other materials

- Methyl cellulose, Agar, Bentonite, Cellulose, Alginic acid, Guargum, and Carboxymethyl cellulose.
- Sodium lauryl sulfate is a surfactant. It increases the rate of wetting of the tablet, thus decreases the disintegrating time.

4. **Lubricant and Glidants**

Objectives:

- Prevents adhesion of the tablet material to the surface of dies and punches.
- Reduce inter-particular friction, improve the rate of flow of tablet granulation.
- Facilitate ejection of the tablets from the die cavity.

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

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

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

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

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

5. **Coloring agent**

Objectives of using colors that (i) It makes the tablet more esthetic in appearance and (ii) Colour helps the manufacturer to identify the product during its preparation. Colorants are obtained in two forms dyes and lakes.

Dyes are dissolved in the binding solution prior to the granulating process. However, during drying their color may migrate to the surface and may produce mottling of the tablet. So another approach is to adsorb the dye on starch or calcium sulfate from its aqueous solution; the resultant powder is dried and blended with other ingredients.

Color lakes are dyes which are adsorbed onto a hydrous oxide of a heavy metal (like aluminium) resulting in an insoluble form of the dye.

6. **Flavours and Sweeteners**

Flavours are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder).

The use of sweeteners is primarily limited to chewable tablets. E.g. Sugar

- **Mannitol**– 72% as sweet as sugar, cooling & mouth filling effect
- **Saccharin**– Artificial sweetener, 500 times sweeter than sucrose

  Disadvantages (i) it has a bitter after taste and (ii) carcinogenic
- **Cyclamate**– either alone or with saccharin– it is banned
- **Aspartame (Searle)** – widely replacing saccharin

  Disadvantage – lack of stability in presence of moisture

Manufacturing of Tablets

Manufacture of tablets involves certain well defined *steps*: namely:-

- ❖ Pulverization and mixing.
- ❖ Granulation.
- ❖ Compression.
- ❖ Coating (if required)

Pulverization and mixing-

- In this step the different solid / powder ingredients are reduced to the same particle size since particles of different sizes will segregate while mixing.
- Various equipments like Cutter mill, Hammer mill, Roller mill and Fluid energy mill is required to reduce the large lumps.

Granulation Technology-

Granulation: It is the process in which primary powder particles are made to adhere to form large multi-particle entities.

Range of size: 0.2 mm to 4 mm. (0.2 mm to 0.5 mm)

Objectives:-

- ➢ To enhance the flow of powder.
- ➢ To produce dust free formulations and produce uniform mixtures.
- ➢ To improve compaction characteristics.
- ➢ To eliminate poor content uniformity of mix.
- ➢ To avoid powder segregation. As Segregation may result in weight variation.

Percolation Segregation:- air void Ex- Tea & Coffee jar.

Trajectory Segregation:- kinetic energy Ex- powder heap

(a) Wet Granulation-

Step-I <u>Milling of the drug and excipients</u>

- Milling of the active ingredients, excipients etc. are milled to obtain a homogeneity in the final granulation.
- If the drug is given in solution then during drying it will come up to the surface. To avoid this problem drug is mixed with other excipients in fine state.

Step-II <u>Weighing</u>

- Weighing should be done in clean area with provision of air flow system.
- In the weighing area all the ingredients must not be brought at a time to avoid cross-contamination.

Step-III <u>Mixing</u> Commonly used blenders are:

(a) Double cone blender

(b) V – blender

(c) Ribbon blender

(d) Planetary mixer

Any one of the blender may be used to mix dry powder mass.

Step-IV <u>Wet Massing</u>

- Wet granulation forms the granules by binding the powders together with an adhesive.
- Binder solutions can be added in two methods:

<u>Method-I</u>	**<u>Method-II</u>**
Drug + Diluent	Drug + Diluent
⬇	⬇
Dry binder is added	Binder Solution is added
⬇	
Blended uniformly	
⬇	
Suitable solvent is added to activate the dry binder	
⬇	

Blended in a Sigma - mixer or Planetary mixer till properly wet mass is formed

Therefore, when

- (i) a small quantity of solvent is permissible, **method-I** is adopted and

- (ii) a large quantity of solvent is required **method-II** is adopted.

However, **method-II will give more cohesiveness** than **method-I** if the amount of binder remains constant.

- If **granulation is over-wetted**, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance.
- If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

Step-V -Wet Screening

Wet screening process involves converting the moist mass into coarse, granular aggregates by

- (i) passage through a **hand screen** (in small scale production) or,
- (ii) passage through an **oscillatory granulator** of **hammer mill** equipped with **screens** having large perforations (# 6 – 8 mesh screen).
- **Purpose** (i) Increase particle contact point

  (ii) Increase surface area to facilitate drying.

Step-VI Drying

- Drying is usually carried out at **60^0C.** Depending on the thermolabile nature of the drug the temperature can be optimized.
- Drying is required in all wet granulation procedures to remove the solvent, but is not dried absolutely because it will pose problems later on. Hence, certain amount of moisture (1 – 4 %) is left within the granules – known as the *residual moisture*.

Methods: Drying can be carried out

Tray dryers – it may take 24 hrs of drying

Truck dryers – the whole cabinet can be taken out of the dryer

Fluid-bed dryer – carry out drying in 30 mins.

Step-VII Dry Screening

After drying, the granules are make monosize by passing through **mesh screen**.

For drying granules the screen size to be selected depends on the diameters of the punch. The following sizes are suggested:

Tablet diameter upto	**Mesh Size**
3/16 ”	# 20
3.5 / 16 – 5/16”	# 16
5.5/16 – 6.5/16”	# 14

7.0/16 or larger # 12

Step-VIII Lubrication of granules

- After dry granulation, the lubricant is added as a fine powder. It usually, is screened onto the granulation through 60 or 100 mesh nylon cloth to eliminate small lumps as well as increase the covering capacity of the lubricant.
- The lubricant is blended very gently using tumbling action to maintain the uniform granule size.
- Too much fine powder is not desirable because fine powder may not feed into the die uniformly causing variation in weight and density.
- Since, the very nature of lubricant produce hydrophobic surface on the particle hence over blending prevents the inter granule bonding that takes place during compression.

(b) **Dry Granulation**

Dry granulation is followed in situations **where** (i) the effective dose of a drug is too high for direct compaction and (ii) if the drug is sensitive to heat, moisture or both, which precludes wet granulation. e.g. many aspirin and vitamin formulations are prepared for tableting by compression granulation.

Steps of granulations

Milling→ Weighing → Screening → Blending → Slugging → Granulation (Dry) → Lubrication Compaction.

Slug:

Slug may described as poorly formed tablets or, may be described as compacted mass of powdered material.

Purpose: To impart cohesiveness to the ingredients, so as to form tablets of desired properties.

Method: It is done either by (i) high capacity heavy duty tablet press

(ii) Chilsonator roller compactor.

Advantages of dry granulation over wet granulation

- ❖ No application of moisture (required in wet granulation) and heat (for drying). So the drugs susceptible to either moisture or heat or both can be made by dry granulation. e.g. calcium lactate cannot be used by wet granulation. (Aspirin, Vitamin C).
- ❖ Dry granulation involves less steps and hence less time is required than that of wet granulation.
- ❖ Less steps requires less working space and energy.
- ❖ Since popularity of wet granulation is more that dry granulation because former will meet all the physical requirement for the compression of good tablets.

Direct Compression Method-

Milling → Weighing → Sieving → Blending → Compression

***Advantages*:** (i) It is much more quicker than any of the previous process

(ii) Minimum number of steps are required.

- Modified diluents, binders etc. are available in the market which assure spherical shape of the granules to modify flow property. However, they are not used extensively.
- If active medicament is less in amount then there will be no problem but in case of high dose large amount of active ingredient is to be replaced by specially treated vehicles to improve flow property or compressibility.
- These specially treated materials are **costly**.

Tablet Compression

It can reduce the volume by apply pressure, particle in die are re-arrange, resulting a closer packing structure and reduce space and at certain lode reduced space and increase inter-particulate friction will prevent farther interparticulate friction.

Elastic deformation:- Either whole or a part can change their shape temporarily.

Plastic deformation:- Change shape permanently.

Particle fragmentation:- Fracture into a number of smaller discrete particles.

Find new position- decrease the volume of powder bed- when force increase new particle again under go deformation-particle particle bonds can formed.

Time of loading:- Deformation of particle are **time independent** process in Elastic & Plastic deformation.

Deformation is **time dependent**, when its behavior is referred to Viscoelastic & Viscous deformation.

Degree of deformation:- Some quantitive chang in shape.

Mode of deformation:- type of shape change.

<u>Basic Component of Compression Machine</u>

Head- Contain upper punchs, dies, lower punchs.

Body- Contain operating machinaries.

Hopper- Holding feeding granules.

Dies- Define size, shape of tablet.

Punches – For compression with in dies.

Cam tracks – Guiding the movement of punches.

Feed frame- Guiding the granules from hopper to dies.

Upper turret- Holds the upper punchs.

Lower turret- Hold the lower punchs.

Die table- Contain the dies.

Single station – stamping press

Multi- station- Rotary press

Fig. 1. Tablet Compression Machine.

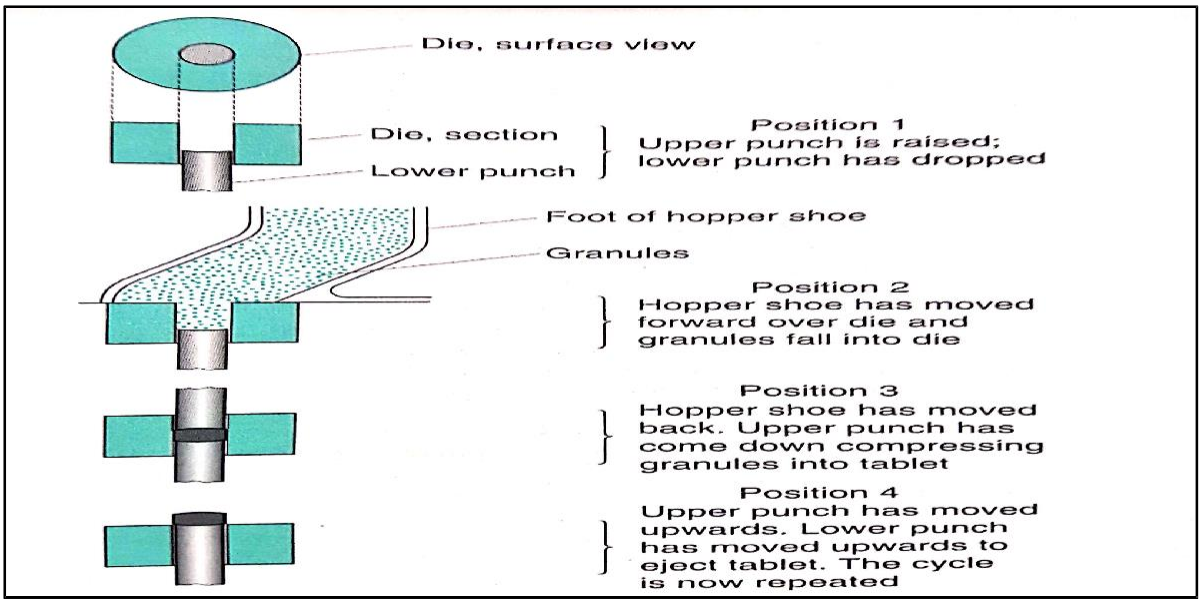


Fig.2. Sequence of events involved in the formation of tablets.

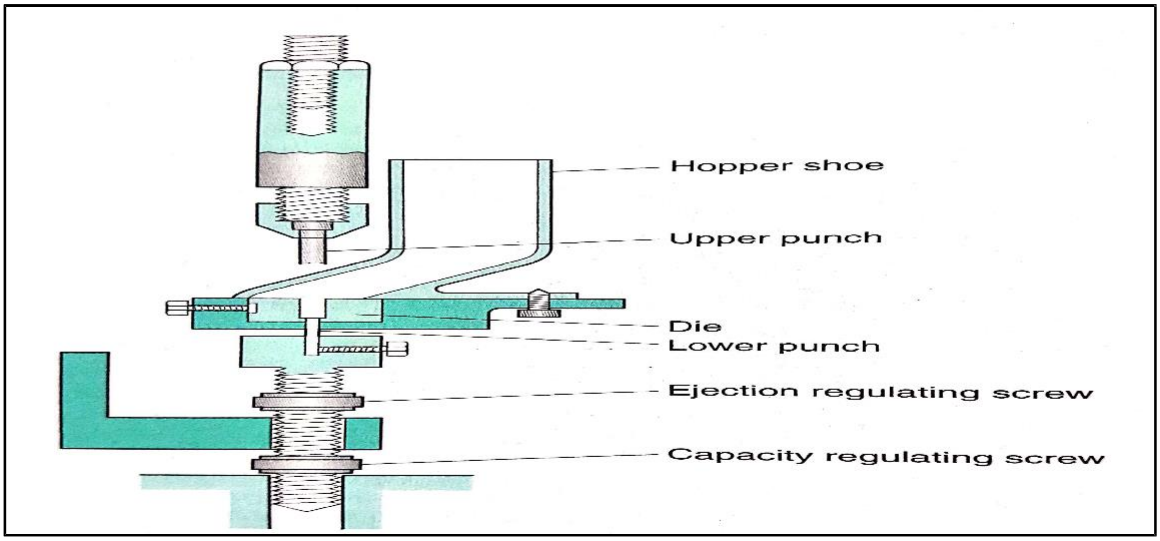


Fig.3. A single punch tablet press.

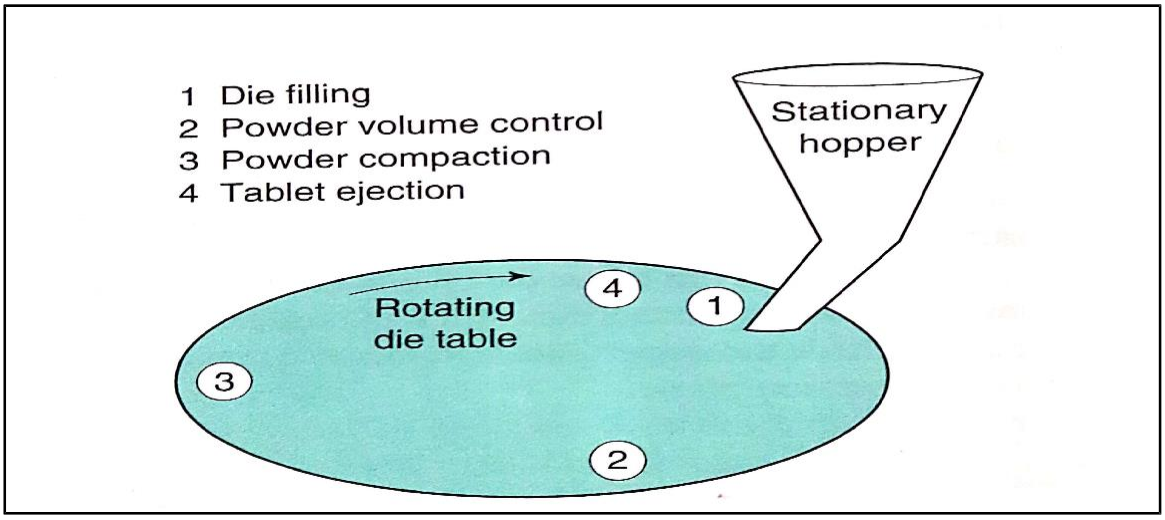
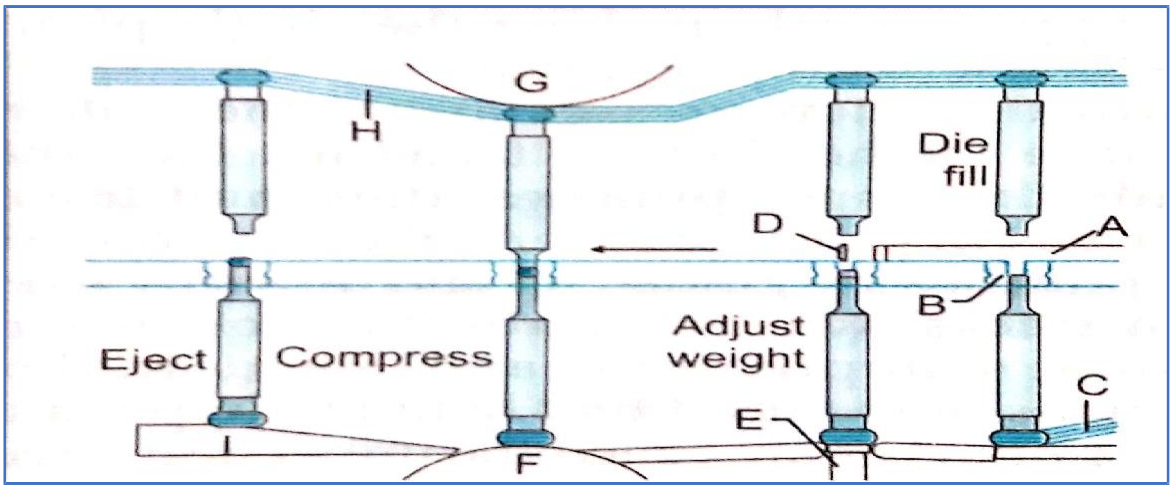
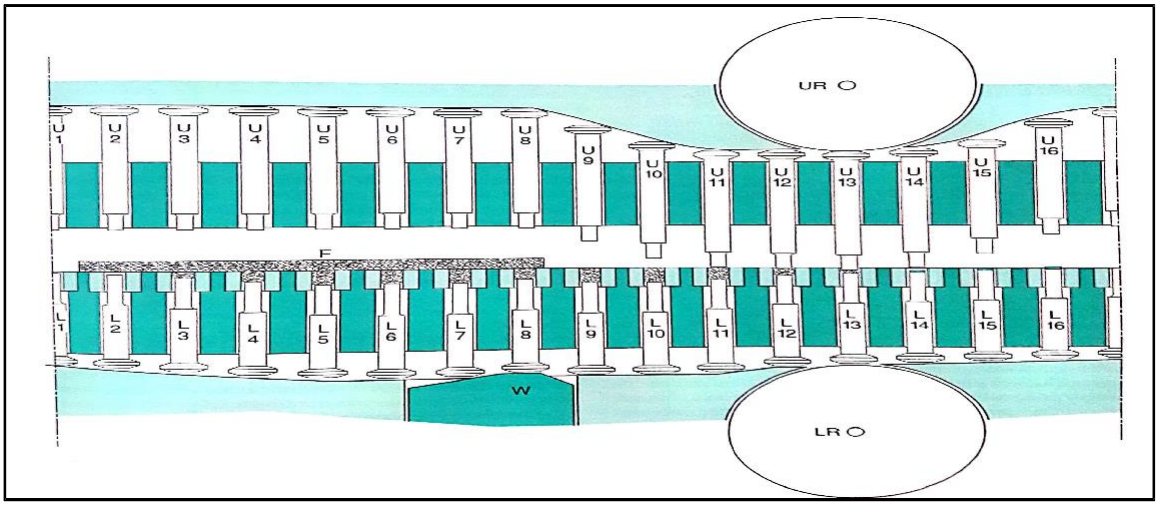


Fig.4. Schematic diagram for the formation of tablets with rotary press.



A- Feed frame, B- Die, C- Pull down cam, D- Wipe off blade, E- Weight control cam, F – Lower compression roll, G- Upper compression roll, H- Rising cam, I- Ride up cam



Tablet machine **out put** is regulated by three basic characteristic like:-

- No of tooling sets
- No of compression station
- Rotational speed of press.

Rotary presses are engineered for fast & economical production of all kind of tablet.

Ex- The monestry nova rotary tablet press.

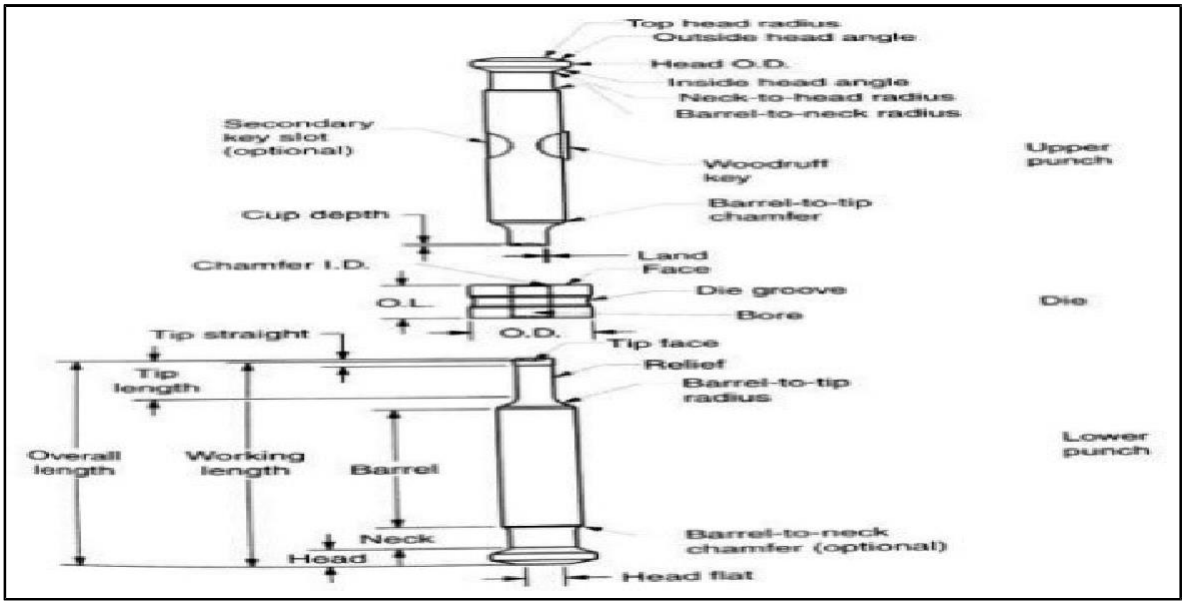
Gradually modification made in machines by using hydraulic or pneumatic pressure to control pressure roll in place of spring for smoother pressure.

Special type machine:-

Fette machine- Chill the compression(For low MP substance like wax)

Versa press- For multi-layer tablet

Tablet Tooling Set



- Its gives definite size, shape of tablet and certain identification marking.
- For this purpose different types of punches are used-
  - Flat faced bevel edged.
  - Shallow concave (Round / Capsule shaped)
  - Standard concave (Round / Capsule shaped)
  - Deep concave (Round / Capsule shaped)
  - Extra deep.
  - Modified ball

Auxillary Equipment-

- Mechanized feeder: Due to short D Well time (Monestry granulation feeding device)
- Mechanized hopper loading equipment:
- Bulk granulation container:
- Electronic monitoring device: To maintain fixed force

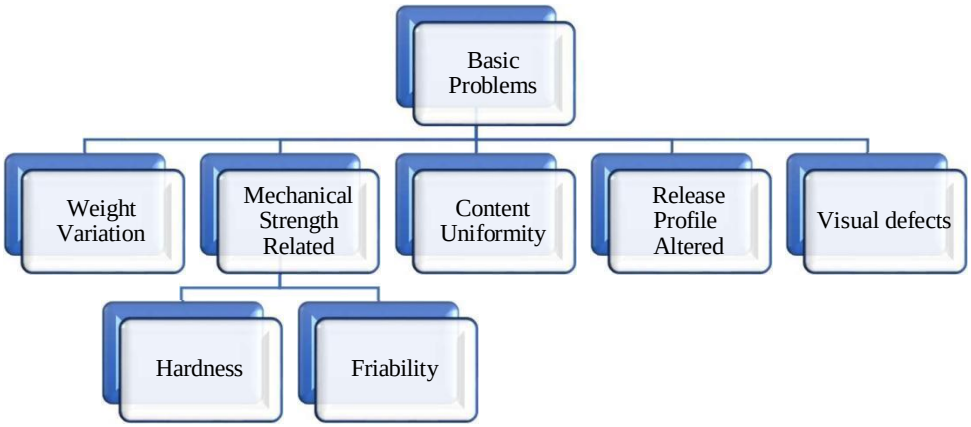
Tablet Processing Problems and its remedies-

An ideal tablet should be free from any visual defect or functional defect. With the development of technology, the production process had become more simplified and more mechanized.

But now the tablet punching machines are all mechanized, the mechanical feeding of feed from the hopper into the die, electronic monitoring of the press, but tablet process problem still persist.

An industrial pharmacist usually encounters number of problems during manufacturing. Majority of visual defects are due to inadequate quality or inadequate moisture in the granules

ready for compression or due to faulty machine setting. Functional defects are due to faulty formulation.

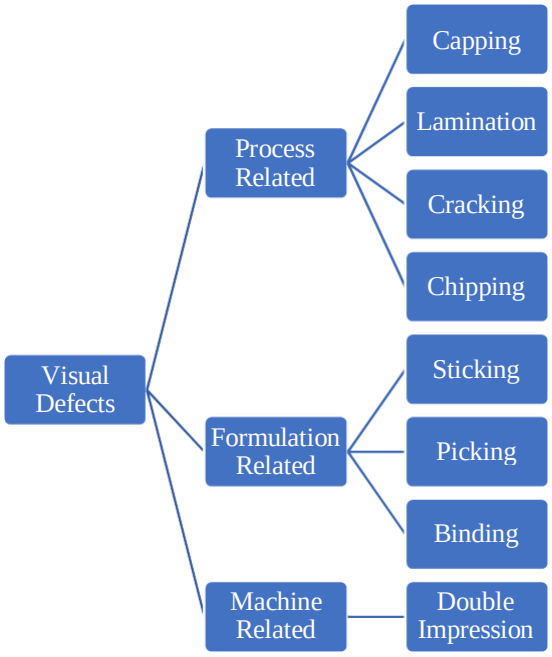


The **Imperfections** known as: 'VISUAL DEFECTS' are either related to Imperfections in any one or more of the following factors:

I. Formulation design

II. Tableting process

III. Machine



1. Capping and Lamination

Capping is the partial or complete separation of the top or bottom crowns of a tablet from the main body of the tablet.

- **Lamination** is the separation of tablet into two or more distinct layers. Usually these problems are apparent immediately after compression, or even hour or days later.

- **Detection**: Subjecting tablets to the friability test is the quickest way to reveal such problems.

Reason and Remedies

a) **Reason:** Entrapment of excess air in the granules during compression. If the granules are light and fluffy this type of problems are encountered frequently.

Remedies: Increasing the density of granules by adding more binder or changing the solvent of binder.

(b) **Reason:** New set of punches and dies are very tightly fitted; i.e. the clearance is very negligible hence air cannot come out.

Remedy: In that case punch diameter should be reduced by 0.005" (i.e. 5 thou)

(c) **Reason:** Granules should not be completely dried. if over dried or under dried then capping may take place.

Remedy: So moisture content should be kept within 1 – 4%.

(d) **Reason:** Tooling set used for longer period of time will form claw-shaped curve on tip of the punch or wear ring in die in compression area – this form capping.

Remedy: Punches and dies are changed.

2. Picking and Sticking

- **Picking**: -When some portion of the surface of the tablet is removed – it is termed as picking.
- **Sticking:** - Sticking refers to tablet materials adhering to the die wall. Serious sticking at ejection cause chipping.

Causes and Remedies of picking

Cause: When punch tips have engraving or embossing, usually of letters B, A, O are difficult to manufacture cleanly. These may produce picking.

Remedy:

(i) Lettering should be designed as large as possible, particularly on punches of small diameter.

(ii) Plating of the punch faces with chromium produces smooth, non-adherent face.

(iii) Colloidal Silica (Cab-o-sil) is added as polishing agent that makes the punch faces smooth; so that material does not cling to them.

Causes and Remedies of Sticking

***Causes*:** Excessive moisture may be responsible for sticking.

***Remedy*:** Further drying of the granulation is then required.

- During compression heat is generated and

(a) low m.p. lubricants e.g. **stearic acid** may produce sticking.

***Remedy*:** Low melting point lubricant are replaced with high melting point lubricants (e.g. **Poly ethylene glycol**)

(b) Low m.p. substances, either active ingredients or additives may soften sufficiently form the heat of compression to cause sticking.

***Remedies*:**

- Dilution of active ingredient with additional high m.p. diluents.
- Increase in the size of tablet.
- If a low m.p. medicament is present in high concentration then refrigeration of the granules and then compressing may be the order or using fette compression machine.

3. Mottling

Mottling is an unequal distribution of color on a tablet, with light or dark patches in an otherwise uniform surface.

***Cause*:** Migration of water soluble dyes to the surface while drying.

***Remedies*:**

- Change the solvent system and change the binder system
- Reduce the drying temperature
- Grind to a smaller particle size.
- Use lakes instead of water-soluble dyes.

Quality Control Tests for Tablets-

- **General appearance**: - Size, shape, and thickness: This is important to facilitate packaging and to decide which tablet compressing machine to use.
- **Organoleptic properties:** which include color, odor and taste of the tablets.
- **Weight uniformity and Content uniformity:** The tablet should contain the correct dose of the drug.
- **Dissolution test:** Drug should be released from tablet in a controlled and reproducible way.
- **Weight variation, thickness & diameter:** The appearance of tablet should be elegant & its weight, size & appearance should be consistent.
- **Hardness & friability:** The tablet should show sufficient mechanical strength to withstand fracture & erosion during manufacture & handling.

- These factors must be controlled during production and verified after production, hence called In-process control

Official Standards as per I.P.

A) **Uncoated tablet:**

- ❖ Uniformity of container content and Content of active ingredient.
- ❖ Uniformity of weight and Uniformity of content.
- ❖ Disintegration test.

B) Enteric coated tablet:

- ❖ Disintegration test.

C) Dispersible tablet:

- ❖ Uniformity of dispersion.
- ❖ Disintegration test.

D) Soluble tablet:

- ❖ Disintegration test.

E) Effervescent tablet:

- ❖ Disintegration/Dissolution/Dispersion test.

1. Weight Variation

This test is based on the fact that, if the weight variation is within the limits then it can be said that the amount of medicament will uniform considerably. Conversely, if the weight variation is not in limits then it can be concluded that the active medicament will ununiform considerably**.**

Sources of weight variation

Weight variation is solely dependent on the poor flow property of granules and filling of die cavity. Poor flow properties arise from: (a) improper lubrication, (b) size of granules and (c) adjustment of lower punch.

Weight variation test

The U.S.P. weight variation test is run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if "*not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit."*

2) Content Uniformity test

Weight variation test is applicable when the amount of medicament in the tablet is high.

- In potent drug the medicament is less in amount in comparison to the other excipients. The weight variation may meet the pharmacopoeial limitation but this will not ensure the correct variation of potency. hence, in this case the weight variation test is followed by content uniformity test.
- In this test 30 tablets are randomly selected for sample, and at least 10 of them are assayed individually according to the official assay method.
- 9 of the 10 tablets must have potency within ± 15 % of the labelled drug content. Only 1 tablet may be within ± 25%.
- If this condition is not met then the tablets remaining from the 30 must be assayed individually and none may fall outside ± 15% of the labeled content.

3) Disintegration Test of Tablets

- The time a tablet takes to disintegrate is the disintegration time.
- To test the disintegration time one tablet is placed in each tube, and the basket rack assembly is positioned in a 1-litre beaker of water, simulated gastric fluid or simulated intestinal fluid, **at $37^0C \pm 2^0C$**, such that the tablet remains 2.5 cm from the bottom of the beaker.
- A standard motor moves the basket up and down through a distance of 5 to 6 cm at a frequency of **28 to 32 cpm** (cycles per minute).

Disintegration testing condition and interpretation (IP)

Sr. No	Type of tablets	Medium	Temperature	Limit
1	Uncoated	Water/buffer	37 °± 2 °C	15 min or as per individual monograph
2	Film coated	Water	37 °±2 °C	30 min or as per individual monograph
3	Sugar coated	Water/0.1 N HCl	37 °±2 °C	60 min or as per individual monograph
4	Dispersible Tablets	Water	25 °±1 °C	03 min or as per individual monograph
5	Effervescent Tablets	Water	25 °±5 °C	05 min or as per individual monograph
6	Enteric-coated Tablets	0.1 M HCl mixed phosphate buffer pH 6.8	37 °±2 °C	02 hour in HCl: no disintegration 60 min in buffer : disintegrate
7	**Soluble Tablets**	Water	20 °±5 °C	03 minutes

4) Dissolution Test

- Disintegration test simply identifies the time required for the tablet to break up under the condition of the test but it does not ensure the drug release in the bulk of the fluid.
- Rate of dissolution is directly related to the efficacy of the drug. Rate of dissolution is a good index for comparing the bioavailability of two tablet products of the same drug.

Apparatus-I (Basket)

- In general, a single tablet is placed in a small wire mesh basket and immersed in the dissolution medium (as specified in the monograph) contained in a **1000 ml** flask at **37^0 ± 0.5^0C.** Generally it is rotated at **50 rpm** unless otherwise specified.

Apparatus-2 (Paddle)

- The same equipment is used. Instead of basket a paddle is introduced as the stirring element. The tablet is allowed to sink at the bottom of the flask before stirring.
- **Limit:** A value of $t_{90\%}$ (i.e 90% drug release) within 30 minutes is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is not less than 75% dissolved in 45 minutes.

5) **Tablet Hardness**

The resistance of the tablet to chipping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness.

Method:

A tablet is taken between the 2nd and 3rd finger and pressing it with the thumb as fulcrum. If the tablet breaks with a "sharp snap", yet, it does not break when it falls on the floor – is said to possess proper hardness.

Instruments used:

a) Monsanto Hardness Tester

b) Strong Cobb Hardness Tester -Manual mode.

c) Pfizer Hardness Tester.

d) Erweka Hardness tester. – Automatic.

e) Schleuniger Apparatus. – Operates without manual involvement.

Hardness of a tablet:

The hardness at which the tablet crushes is the hardness of the tablet.

- **Unit of hardness:** Kg/sq.in. or lb/ sq.in
- **Limit:** Generally maximum 5 kg/sq.in. hardness is required.

6) **Friability**

Tablet hardness is not an absolute indicator of strength since some formulations, when compressed into very hard tablets may produce chipping, capping and lamination problems. Therefore, another measure of tablet strength i.e. friability is often measured, i.e. the friability.

Instrument: Roche Friabilator

Objective of friability test:

This apparatus is designed to evaluate the ability of the tablet to withstand abrasion, in handling, packaging and shipping operation.

Method: 20 tablets, previously weighed are taken in the plastic chamber of the laboratory friability tester. In the plastic chamber the tablets are subjected to abrasion and shock by rotating the plastic chamber at 25 rpm for 4 mins (i.e. total 100 revolutions). The tablets are dedusted and reweighed.

Limit: - For conventional compressed tablet the weight loss should be within 0.5 to 1.0 %.

Tablets Coating

Reasons Behind Coating of Tablets:

- To mask the taste, odour or colour of the drug. Improving the product appearance, particularly where there are visible differences in tablet core ingredients from batch to batch.
- Provide physical protection, facilitates handling, particularly in high speed packaging / filling lines.
- To provide chemical protection from its surrounding environment (particularly air, moisture and light).
- To control the release of drug from the tablet e.g. sustained release tablets, repeat action tablets.
- To protect the drug from the gastric environment of the stomach with an acid resistant enteric coating.

Components Considered in Tablet Coating

Tablet Properties: - Shape, Tolerance, Surface area.

- Tablet to be coated must possess the proper physical characteristics like spherical shape and uniform surface.
- To tolerate attrition of tablets during coating process they must be resistant to abrasion and chipping.
- As the tablet surfaces that are brittle and soften in presence of heat or effected by coating composition and tend to become rough in the early stages of coating process are unacceptable for film coating.

Coating process: -

A. Coating equipment

B. Coating parameters.

C. Facility & ancillary equipment.

D. Automation of coating process.

Coating composition: - which involves polymers, color, plasticizer, solvent.

Types of Coating-

(A) Sugar Coating.

1) Sealing-

***Objectives*-** (i) To prevent moisture penetration into the tablet core, a seal coat is applied and (ii) To strengthen the tablet core without a seal coat, the over wetted tablets would absorb excess moisture, leading to tablet softening, and may affect the physical and chemical stability.

Ingredients

- Alcoholic solutions of Shellac (10 – 30% solid) or alcoholic solution of zein,
- Alcoholic solution of cellulose acetate phthalate (CAP) or alcoholic solution of polyvinyl acetate phthalate.

2) Sub-coating-

Objectives-To round the edges and build up the tablet size. Sugar coating can increase the tablet weight by 50 to 100% at this step.

Method:- The sub-coating step consists of alternately applying a sticky binder solution to the tablets followed by a dusting of sub-coating powders and then drying. Subsequent coatings are applied in the same manner until the tablet edges have been covered and the desired thickness is achieved.

3) Smoothing (Syruping)-

Objectives-To cover and fill in the imperfections in the tablet surface caused by the sub-coating step.

Ingredients-Simple syrup solution (approximately 60–70%(w/w)). Often the smoothing syrups contain a low percentage of titanium dioxide (1–5%) as an opacifier. This gives a very bright and reflective background for the subsequent coloring step.

4) Color coating-

***Objective*-**To impart an elegant and uniform colour.

***Ingredient*-**Syrup (60 – 70% sucrose) containing the desired color.

***Method*-**Syrup solutions containing the dyes are coated upto 60 individual applications until the desired color is achieved. After each application of color, the coatings are dried. In the finishing step a few clear coats of syrup may be applied.

5) Polishing-

***Objective*-**To produce the desired luster on the surface of the tablet.

***Ingredients*-**Mixtures of waxes (like beeswax, carnauba wax, candella wax or hard paraffin).

***Method*-**Either this mixture of waxes is applied as powder or as dispersions in various organic solvents in a polishing pan (canvas line pan).

6) Printing-In order to identify sugar-coated tablets often it is necessary to print them, using pharmaceutical grade ink, by means of a process of offset rotogravure.

(B) Film Coating

Film coating adds 2 to 5% to the tablet weight. Film coating is a complex process that involves the application of thin (in the range of 20-200 μm) polymer-based coatings to an appropriate substrate (tablets, pellets, granules, capsules, powders, and crystals) under conditions that permit:

1. Balance between (and control of) the coating liquid, addition rate and drying process.
2. Uniformity of distribution of the coating liquid across the surface of product being coated.
3. Optimization of the quality (both visual and functional) of the final coated product.

Advantage-

- Substantial reduction in quantity of coating applied (2-4% for film coating, compared with 50-100% for sugar coating).
- Faster processing times and Improvement in process efficiency and output.
- Greater flexibility in optimizing formulations as a result of the availability of a wide range of coating materials and systems.
- Ability to be applied a wide range of pharmaceutical products.

Types-

1) Pan-pour method-

Viscous coating materials are directly added from some container into the rotating pan moving with the tablet bed. Tablets are subjected to alternate solution application, mixing and then drying.

Disadvantages:

- The method is relatively slow and it relies heavily on the skill of the operator.
- Tablets always require additional drying to remove the latent solvent.
- Aqueous film coating is not suitable for this method because localized over wetting will produce physicochemical instability.

2) Pan-spray method-

Coating material is sprayed over the tablet bed from nozzles and hot air is passed through the tablet bed to dry it. The variables to be controlled is pan-spray film coating process are:

(a) Pan variables:

Uniform mixing is essential to deposit the same quantity of film on each tablet.

1. *Pan design or baffling*: Some tablet shapes mixes freely while other shapes may require a specific baffling arrangement to ensure adequate mixing.

Disadvantages: Baffles may produce chipping and breakage if not selected properly.

(b) Pan speed

- Pan speed affects mixing and the velocity at which the tablet pass under the spray.
- Too slow speed cause localized over-wetting resulting in tablets sticking to each other or to the pan.
- Too high speeds may not allow enough time for drying before the same tablets are reintroduced to the spray. This results in a rough coating appearance on the tablets.

Optimum pan speed: 10 – 15 rpm for nonaqueous film coating.

3 – 10 rpm for aqueous film coating

3) Fluidized bed process (air suspension coating)

This process have been successfully used for rapid coating of tablets, granules and capsules.

Process variables are as follows: (a) Chamber design and air flow rate controls the fluidization pattern, (b) Tablet shape, size and density, (c) Volume and rate of air flow either too high rate produce attrition and breakage of tablets or too low rate → mass does not move fast enough through the spray region → over-wetting occurs and (d) Inlet and exhaust air temperature.

Examples-

Non-enteric materials: e.g. Hydroxypropyl methylcellulose (HPMC), Methyl hydroxy ethyl cellulose (MHEC), Ethyl cellulose (EC), Polyvinyl pyrrolidone (PVP), Sodium carboxymethyl cellulose (Sod. CMC), Polyethylene glycols (PEG), Acrylate polymers e.g. Eudragit E

Enteric materials: e.g. Cellulose acetate phthalate (CAP), Acrylate polymers (Eudragit L, S), Hydroxypropyl methylcellulose phthalate (HPMCP), Polyvinyl acetate phthalate (PVAP).

(c) <u>Spray variables</u>

1) Rate of liquid application.
2) Spray pattern.
3) Degree of atomization

These three spray variables are interdependent. For spraying two types of systems are there: (a) High-pressure, airless system and (b) low-pressure, air atomization system.

(d) Process air variables (temperature, volume, rate) are required for optimum drying of the coating by evaporation of the solvent. The balance between the supply and exhaust air flow should be such that all the dust and solvent are confined within the coating system

(C) Enteric Coating

1) Pan-pour method.
2) Pan-spray method.
3) Fluidized bed process (air suspension coating)

Oral Liquids-

Oral Liquids are homogeneous liquid preparations, usually consisting of a solution, an emulsion or a suspension of one or more medicaments in a suitable vehicle. Liquid dosage forms are either monophasic or biphasic. A monophasic liquid dosage form is one which contains only one phase. A biphasic liquid dosage form contains two phases.

Liquid preparations for oral use are either supplied in the finished form or, with the exception of Oral emulsions, may also be prepared just before issue for use by dissolving or dispersing granules or powder in the vehicle stated on the label.

The vehicle for any liquid preparation for oral use is chosen having regard to the nature of the active ingredient(s) and to provide organoleptic characteristics appropriate to the intended use of the preparation. Liquid preparations for oral use may contain suitable antimicrobial preservatives, antioxidants and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilizing, stabilizing, flavouring and sweetening agents and authorized colouring matter.

Classification of Liquid Orals

Liquid dosage forms are broadly classified into two groups:

a) Monophasic liquid dosage forms b) Biphasic liquid dosage forms

1. Monophasic liquids dosage forms are mixtures, elixirs, syrups, linctuses, draughts and drops etc.

2. Biphasic liquids dosage forms are suspensions and emulsions.

Advantages of Liquid Dosage Forms

i) They are the most suitable dosage form for infants, children and geriatric patients.

ii) The unpleasant taste of the drugs can be masked by adding sweetening and flavouring agents.

iii) It is attractive in appearance and gives beneficial psychological effects.

iv) The drug is rapidly available for absorption.

Disadvantages of Liquid Dosage Forms

i) The liquid dosage forms have less stability when compared to solid dosage forms.

ii) Liquids are bulky and therefore inconvenient to transport and store

iv) Accidental breakage of the container results in loss of whole dosage form.

Formulation consideration:

The common excipients used in liquid formulation are

(1) Vehicles

(2) Solubilizers

(3) Preservatives

(4) Stabilizers

(5) Organoleptic agents

(1) Vehicles

Solvents: In liquid pharmaceutical formulations, vehicles are major components used as a base in which drugs and other excipients are dissolved or dispersed. They function by breaking of bond and reducing effective charge on ions thus increasing solute-solvent forces of attraction which are eventually greater than solute-solute and solvent-solvent forces of attraction. Eg: water, hydro-alcoholic liquid systems, polyhydric alcohols, acetic acid, ethyl acetate and buffers. These may be thin liquids, thick syrupy liquids, mucilage or hydrocolloid bases. The oily vehicles include vegetable oils, mineral oils, organic oily bases or emulsified bases etc.

Co-solvent: are defined as water- miscible organic solvents that are used in liquid drug formulations to increase the solubility of poorly water soluble substances or to enhance the chemical stability of a drug. Co-solvent increases the solubility of a drug. An ideal co-solvent should possess values of dielectric constant between 25 and 80. The most widely used system that will cover this range is a water/ethanol blend. It should not cause toxicity or irritancy when administrated for oral or parental use. Other co-solvents are sorbitol, glycerol, propylene glycol and syrup.

Water : They contain large number of dissolved and suspended particles as impurities like inorganic salts sodium, potassium, calcium, magnesium and iron as chlorides, sulfates and bicarbonates, organic impurities are either soluble or insoluble state. Microorganism is other impurities present in water. Drinking water contains less than 0.1 % of total solid. For the preparation in pharmaceutical formulation IP refers water as clear, odorless, colorless and neutral with slight deviation in pH due to dissolved solids and gases. Purified water IP is commonly used as vehicle or as a component of vehicle for aqueous liquid formulations but not for those intended for parenteral administration. Ethanol, frequently referred as alcohol is the most commonly used solvent in liquid pharmaceutical formulation next to water. It is generally used as hydro-alcoholic mixture to dissolve water and soluble drugs and excipients. Diluted ethanol is prepared by mixing equal volumes of ethanol IP and purified water IP is a most useful solvent in various pharmaceutical processes and formulations to dissolve poorly soluble substances Glycerol is called glycerin is a clear, colorless liquid with thick, syrupy consistency, oily to the touch, odorless, very sweet and slightly warm to taste. They are prepared by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95% of absolute glycerin. It is soluble in all proportions, in water or alcohol; also soluble in a mixture of 3 parts of alcohol and 1 part of ether, but insoluble in ether, chloroform, carbon di-sulphide, benzene, benzol, and fixed or volatile oils.

(2) Solubilizers: To increase the solubility of the drug

pH adjustment : By addition of buffer to the formulation .buffers act by binding hydrogen formulations to control potential changes in the pH. Buffers act by binding hydrogen ions in acids and donating hydrogen ions in bases. The selection of as suitable buffer should be based

on suitability of acid-base form for use in oral liquids, stability of the drug and excipients in the buffer, and compatibility between the buffer and container. The stabilizing effect of buffers determines the potential reaction between excipients and drug. For example, buffers containing carbonate, citrate, tartarate and phosphate salts may precipitate with calcium ions by forming sparingly soluble salts. The other factors that may affect the solution pH include temperature, ionic, strength, dilution and the amount and the type of co-valents presents. For example the pH of acetate buffers is known to increase with temperature, whereas the pH of boric acid buffers decreases with temperature. It is important to know that the drug in solution may itself act as a buffer. If the drug is a weak electrolyte such as salicyclic acid or ephedrine, the addition of base or acids, respectively will create system in which the drug can act as a buffer Eg: phosphate buffers, acetate buffers, citric acid phosphate buffers etc.

Co-solvency: By addition of water miscible solvent in which drug has good solubility. The solvent known as co-solvent.

Complexation: Drug-complexing agent complexation formed when complexing agent is added to solution. It increase solubility of drug on the basis of Le Chatelier's principle or " The equilibrium law". Eg disodium EDTA, dihydroxy ethyl glycine, citric acid.

Micronization: The processes involve size reduction of drug particle 1 to 10microns either by spray drying or fluid energy mill.

Hydrotrophy : Drug dissolve in the cluster of hydrotropic agent. Also there is drug-hydrotrophy agent complexation formation to increase drug solubility.

Wetting agents and surfactants:

In pharmaceutical formulations wetting agents are routinely used, they air adsorbed at solid particles surfaces keep them away from vehicles which ultimately promotes penetration of the vehicle into pores and capillaries of the particles. For non-aqueous based formulations mineral oils are commonly we use wetting agents because hydrophobic drug particles are difficult to wet even after the removal of adsorbed air. In such cases it is necessary it is necessary to reduce the surface tension between the particles and the liquid vehicles. Surface active agents that work as wetting agents, comprises of branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups.

For example- Sodium lauryl sulphate is one of the most commonly used surface-active agents as a wetting agent. When dissolved in water, it lowers the contact angle of water and support in spreading of water on the particles surface to remove the air layer at the surface and replace it with the liquid phase.

(3) Preservatives

Microbial contamination is major problem encountered by aqueous based liquid dosage forms. Use of preservatives becomes unavoidable in such cases to prevent the growth of micro-organisms during production and over storage time. In fact, it is desirable to develop a preservative-free formulation to avoid unwanted effects of these excipients. The majorities of preservatives are of both acid and non-acid types and are bacteriostatic rather than bactericidal.

Preservatives must have following criteria: Effective against broad spectrum of microorganisms. Physically, chemically and microbiologically stable for lifetime of the product. Non toxic, non sensitizing, soluble, compatible and with acceptable taste and odour.

Types of Preservatives

Acidic: phenol, benzoic acid, sorbic acid

Neutral preservatives: Chlorobutanol, benzyl alcohol

Quarternary ammonium compounds: Benzalkonium chloride

(4) Stabilizers

Oxidation, photolysis, solvolysis and dehydration are common transformations taking place in liquid dosage forms. Amongst them for oxidation and photodecomposition of drug are very common pathways of drug decomposition and are very difficult to control due to low activation energies. Trace amounts of impurities, which are invariably present in the drug or excipient intitates the oxidation reaction. Drugs exists in reduced form show increased susceptibility when it is consistently exposed an open environment. The pH of the solution may contribute in the oxidation of drugs because ionized forms of these drugs at particular pH are very prone oxidation

Physical stability: A stable formulation retains its viscosity, color, calarity, taste and odour throughout its shelf life Color can be measured spectrophotometrically. Clarity can be determined by measurement of its turbidity or light scattering equipment. Viscosity can be measured by use of viscometers. Taste and odour can be determined either by pharmaceutical investigator or by a panel of unbiased, taste sensitive individuals.

Chemical stability of the formulation is affected by pH, temperature, Ionic Strength, Solvent effects, Light, Oxygen. Instability can be prevented by use of: Buffering agents, Antioxidants, Proper packaging (eg: use of amber bottle for light sensitive products)

Antioxidants act as chain terminators where it reacts with free radicals in solution to stop the free-radical propagation cycle. A combination of chelating agents with antioxidants is often used to exert synergistic effect. This is because many of these agents act at differing steps in the oxidative process. Oxidation of formulation component leads to products with an unpleasant odor taste appearance, ppt, discoloration or even a slight loss of activity. Some substances prone to oxidation include unsaturated oils/fats, compounds with aldehyde or phenolic groups, colors, flavors, sweeteners, plastics and rubbers, the latter being used in containers for products. Eg: acetone sodium bisulfite, acetylcysteine, ascorbic acid, thiourea.

Emulsifying agents which prevent coalescence of the dispersed globules. Forms barriers at interface, and reduce interfacial tension Eg sodium lauryl sulphat, cetrimide, macrogols

Antifoaming agents: the formation of foams during manufacturing processes or when re constituting the liquid dosage forms can be undesirable and disruptive. Antifoaming agents are effective at discouraging the formation of stable foams of stable foams by lowering surface

tension and cohesive binding of the liquid phase. Eg: Simethicone, organic phosphates, alcohols, paraffin oils etc.

Suspending and Viscosity Enhancing Agents: The selection of an appropriate suspending agent is one of the most crucial factors in formulating a pharmaceutical suspension. Suspending agents impart viscosity and thus regard particle settling. Other factors considered in the selection of the appropriate suspending and viscosity enhancing agent include desired reheological property supendability in the system, chemical compatibility with other excipients, pH stability, hydration time, reproducibility, and the cost. Eg: clays, natural gums, synthetic gums In many formulations these excipients are employed in combination for enhanced effects.

Humectants: are hygroscopic substances that help to retard evaporation of aqueous vehicles from dosage forms. These excipients are used at 5% strength in aqueous suspension and emulsion for external application. They are also used to prevent drying of the product after application to the skin as well as prevent drying of product from the container upon opening. It also helps to prevent cap-locking caused by condensation onto neck of container-closure at first opening Eg propylene glycol, glycerol, polyethylene glycol.

Flocculating agents: prevent caking. Addition of an electrolyte reduces the magnitude of zeta potential of dispensed particles Eg: Starch, sodium alginate.

Chelating agents: are substances that form complexes with metal ion in activating their catalytic activity in oxidation of medicaments. These agents are capable of forming complexes with the drug involving more than one bond it's a complex compound contains one or more ring in its structure. Protect drug from catalysts that accelerate the oxidative reaction. Eg Disoium EDTA, dihydroxy ethyl glycine, citric acid and tartaric acid

(5) Organoleptic properties

Flavouring agents: are agent in liquid pharmaceutical products is added to the solvent or vehicle component of the formulation in which it is most soluble or miscible. That is water soluble flavors are added to the aqueous component of a formulation and poorly water soluble flavors are added to the alcoholic or other non-aqueous solvent component of the formulation. In a hydro-alcoholic or other multi-solvent system, care must be exercised to maintain the flavorants in solution. This is accomplished by maintaining a sufficient level of the flavorants solvent.

Sweetening agents: Sucrose enhances viscosity of liquids and also gives a pleasant texture in the mouth. The term sugar free solution include sweetening agents such as sorbitol, mannitol, saccharin and aspartame as alternative to sugar such as sucrose, fructose. In addition to sucrose, a number of artificial sweetening agents have been used in food and pharmaceuticals over the years. Some of these including asparatame, saccharin, and cyclamate have faced challenges over the safety by the FDA and restriction to their use and sale in fact in 1969, FDA banned cyclamates from use in US. Sucralose is most popular due to its excellent sweetness, non-cariogenic, low calorie wide and growing regulatory acceptability but is relatively expensive

Coloring agent: A distinction should be made between agents that have inherent color and those that are employed as colorants. Colors used in liquid dosage form must be certified by FDA as per D&C Act 1940. Certain agents- sulphur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green) cyanocobalamin (red) and red mercuric iodide (vivid red) have inherent color and not thought of as pharmaceutical colorants in the usual sense of the term. Although most pharmaceutical colorants in use today are synthetic, a few are obtained from natural mineral and plant sources. For example, red ferric oxide is mixed in small proportions with zinc oxide powder to give calamine its characteristic pink color, which is intended to match the skin tone upon application. The age of the intended patient should also be considered in the selection of the flavorings agent, because certain age groups seem to prefer certain flavors. Children prefer sweet candy-like preparations with fruity flavors, but adults seem to prefer less sweet preparation with a tart rather than a fruit flavor.

Manufacturing Consideration-

The manufacturing process for liquid preparations for oral use should meet the requirements of Good Manufacturing Practice (GMP). The following information is intended to provide broad guidelines concerning the critical steps to be followed during production of liquid preparations for oral use.

In the manufacture of liquid preparations for oral use, measures are taken to:

- ensure that all ingredients are of appropriate quality
- minimize the risk of microbial contamination
- minimize the risk of cross-contamination

Steps of Liquids Manufacturing Process

1. Planning of Material Requirements: Research and development of protocols and selection of materials; acquisition and analysis of raw materials; physical plant design, building, and installation; equipment selection and acquisition; personnel selection and initial training; and monitoring information system.

Raw Materials : Incoming raw materials should be tested as per specifications that is identity, purity, uniformity and microbial contamination .

Equipments : The following types of equipments may be used in the manufacture of liquid formulations:

1. Mixing tanks (SS 316 Stainless Steel) equipped with an agitator.

2. Measuring devices for large and small amount of solids and liquids. 3. Afiltration system e.g. filter press

Cleaning of equipments

- All equipments must be thoroughly cleaned and sanitized before use.
- Disinfectants used: Dilute solutions of H_2O_2, phenol derivatives.
- Sterilized by:Alcohol, boiling water, autoclaving, steam or dry heat.

2. Liquid Preparation: Research and development of protocols concerning liquid compounding; scale - up of the bulk product compounding; physical plant control and maintenance; equipment maintenance and renovation; continuous training of personnel and personnel compensation plan; and supervision of system reports.

3. Filling and Packing: Research and development of protocols concerning filling and packing; scale-up of the finished drug product filling and packing; physical plant control and maintenance; equipment maintenance and renovation; continuous training of personnel and personnel compensation plan; and supervision of system reports.

Filling and Packing

Gravimetric	Volumetric	Constant Level
Containers are filled with liquids to a given weight. Usually limited to large container filling or highly viscous products. Cannot be used in high speed, automatic equipment	Containers are filled with liquids to a given volume. Filled amount is measured by the stroke of the piston and cylinder assembly. Problems may arise when containers used are not dimensionally uniform.	Filled amount is verified by adjusting the height to which the container is to be filled. Variation in container dimension may result in variations in the net fill per unit.

Techniques of Filling

Vacuum filling	Gravity vacuum filling	Pressure vacuum filling
Vacuum developed within the container causes liquid to flow from tank to container.	Bulk liquid tank is placed above filling stem so that liquid flows to the container due to force of gravity.	Pressure applied to bulk liquid tank and vacuum developed in the container results in pressure difference so that liquid flows to the container.

4. Sales of Drug Products: Research and development of protocols concerning product storage; distribution process; continuous training of personnel and personnel compensation plan; and supervision of system reports.

5. Vendor Handling: Research and development protocols concerning precautions to maintain product stability; control of vendor stock; and sales system reports.

6. Customer Service: Research and development of protocols concerning home storage and handling to maintain product stability; relations with health insurance companies and health care professionals; educational materials for patient counseling; and customer service system reports.

Elixirs

Elixirs are clear, flavoured, sweetened, hydroalcoholic preparations for oral administration. They are more stable than mixtures. Elixirs are classified into two classes.

a) Non medicated elixirs: These elixirs do not contain any medicament but contain some aromatic or pleasantly flavoured substances. These are used as solvents for other liquid preparations.

b) Medicated elixirs: These elixirs contain some medicinal substance along with other ingredients.

Syrups

Syrups are liquid oral preparations in which the vehicle is a concentrated solution of sucrose or other sugars in water. The concentration of sugar in syrup is 66.7 % W/W. Syrups are further classified into 2 classes.

a) Simple syrups: The simple syrups do not contain any medicament, but contains some pleasantly flavoured substances. These syrups are used as a medium for other liquid preparations.

b) Medicated syrups: These syrups contain some medicinal substance along with other ingredients.

Advantages of syrups

• Syrups prevent oxidation and decomposition of drugs.

• Syrups are sweet in taste and therefore bitter taste of drugs can be reduced.

Disadvantages of syrups

• Syrups are not preferred for diabetic patients.

• On continuous take syrup promote dental decay.

Suspensions

Suspensions are the biphasic liquid dosage form of medicament in which the finely divided solid particles are suspended or dispersed in a liquid or semisolid vehicle with the help of suspending agent.The solid particle is the ‘dispersed phase’ or ‘discontinuous phase’ whereas the liquid vehicle is the ‘continuous phase’.

The solid particles act as disperse phase whereas liquid acts as a continuous phase. The medicaments that are insoluble or poorly soluble are formulated as suspensions. Suspensions contain a suspending agent. A suspending agent is a substance that is added to the preparation to suspend the insoluble particles in the preparation. It can be classified into four groups.

a) Oral suspensions: These suspensions are to be consumed by oral route.

b) Parenteral suspensions: The suspensions which are administered by parenteral route are called parenteral suspensions.

c) Ophthalmic suspensions: These are used for instilling into the eye.

d) Suspensions for external use: These are used for external applications.

Advantages:

- Can improve chemical stability of certain drugs.
- Higher rate of bioavailability, as order of bioavailability is: Solution>Suspension>Capsules>Compressed tablets

Disadvantages:

- Physical stability, sedimentation and compaction.
- Bulky, handling require care.
- Uniform drug delivery cannot be achieved sometimes.

Ideal properties of suspensions:

1. The dispersed particles should not settle readily and the settled particles should redisperse immediately on shaking.

2. The particles shouldn‘t form a cake on settling.

3. The viscosity should be such that the preparation can be easily poured.

4. It should be chemically stable.

5. Suspensions for internal use must be palatable and suspension for external use must be free from gritty particles.

Types of suspensions:

Depending upon particle nature/dispersed particle nature the suspensions are of two types:

1. Flocculated suspensions

2. Non-flocculated/deflocculated suspensions.

Flocculated suspensions:

Suspension in which particles are weakly bonded, settle rapidly, don’t form a cake and are easily resuspended with a minimum of agitation.

Deflocculated suspensions:

Suspension in which particles settle slowly and eventually form a sediment in which aggregation occurs with the resultant formation of a hard cake which is difficult to resuspend.

Stability of suspensions:

A stable suspension can be redispersed homogenously throughout its shelf life.The more stable pharmaceutical suspensions are flocculated i.e.,the suspended particles are bonded together physically to form a loose cake.

Packing of Suspensions

Suspensions can be packed in narrow mouth screw caped colour less plain bottle. Suspensions that are very thick require a container with wide mouth. Suspensions should be stored in a cool place.

Evaluation of suspension stability:

The following are commonly used for evaluating the physical stability of suspensions:

1.Sedimentation method.

2.Rheological method.

3.Electrokinetic method.

4.Micromeritic method.

1.Sedimentation method:

It is determined by keeping a measured volume of suspension in a graduated cylinder in an undisturbed position for a definite period of time, the ultimate volume (V0) and the initial volume (Vu) of the sediment is to be noted. Sedimentation volume is a ratio of the ultimate volume of sediment (V0) to the original volume of the sediment (VU) before settling. Sedimentation volume F=V0/VU

2. Rheological method:

- It provides information about settling behaviour.
- The arrangement of the vehicle and the particle structural features.
- Brookfield viscometer is used to study the viscosity of the suspension. If viscosity of the suspension increases, the stability of the suspension increases.

3. Electrokinetic method:

The determination of surface electric charge or zeta potential is helpful to find out the stability of suspension. Zeta potential can be calculated from the migration of particle measured by the electrophoretic method.

4. Micromeritic method:

The stability of suspension depends on the particle size of the disperse phase. The size of the particle in a suspension may grow and ultimately leads to the formation of clumps or caking.

So, any change in particle size distribution with reference to time gives a stable suspension. The particle size can be studied by microscopy or coulter countered method.

Emulsions

An emulsion is defined as a dibasic or heterogenous liquid preparation immiscible liquids which is dispersed as a minute globules in another liquid by adding emulsifying agent.

Medicines having an unpleasant taste and order can be made more palatable for oral administration in the form of an emulsion. Emulsions protect drugs against oxidation or hydrolysis.

• Emulsions are less stable.

• They are susceptible to microbial growth.

Classification of emulsions:

Emulsions can be classified into the following types:

1. Oil in water (o/w) type of emulsion.

2. Water in oil (w/o) type of emulsion.

3. Microemulsions

4. Multiple/double emulsion.

Advantages:

- Mask the unpleasant taste.
- Sustained release medication.
- Inert and chemically non-reactive.
- Reasonably odourless & cost effective.

Disadvantages:

- Packing, handling & storage is difficult.
- Thermodynamically unstable & have short shelf life.
- Leads to creaming & cracking.
- Leads to phase inversion.

Packing of Emulsions

Emulsions can be packed in narrow mouth screw caped colourless plain bottle. Emulsions that are very thick require a container with wide mouth. Emulsions should be stored in a cool place.

a) Oil in water type: This type of emulsion is the one in which the oil is dispersed in the water

b) Water in oil type: This type of emulsion is the one in which the water is dispersed in the oil. Emulsions may be liquid or semi-solid. Liquid emulsions can be classified as i) emulsions for oral administration, ii) emulsion for external uses, iii) emulsion for parenteral uses, and iv) emulsion for rectal use.

i) Emulsions for oral administration

Some medicaments are unpleasant in taste. For example fish liver oil, we can mask this unpleasant taste by converting it into an emulsion and can be given orally.

ii) Emulsions for external use

The external preparation of emulsion consists of three classes. Applications, lotions and liniments, these emulsions can be either oil in water or water in oil.

iii) Emulsions for parenteral use

Some patients are unable to ingest food in the normal way. We can administer oil in water emulsions of nutritive oils and fats to these patients. Vitamin K that prevents blood clotting is injected in this form.

iv) Emulsions for rectal use

Some emulsions are given by rectal route. Semi-solid emulsions are water in oil or oil in water type. The water in oil type semi-solid emulsions are oily creams while the oil in water semi-solid emulsions are aqueous creams. Creams are easy to apply and are less greasy.

Preparation of emulsions:

The emulsions are prepared by two methods:

1. Small scale method

a) Dry gum method

b) Wet gum method

c) Bottle method.

2. Large scale method.

Identification tests:

The type of emulsion can be determined by the following tests:

1. Dilution test.

2. Conductivity test.

3. Dye test.

4. Fluorescence test.

5. Cobalt chloride test ($CoCl_2$).

1. Dilution test: This test is based on the solubility of external phase of emulsion.

- o/w emulsion can be diluted with water.
- w/o emulsion can be diluted with oil.

2. **Conductivity test:** The basic principle of this test is that water is a good conductor of electricity. Therefore in case of o/w emulsion this test will be +ve as water is the external phase. In this test, an assembly is used in which a pair of electrodes connected to an electric bulb is dipped into an emulsion. If the emulsion is o/w type, the electric bulb glows.

3. **Dye test**: When an emulsion is mixed with a water soluble dye such as amaranth and observed under the microscope.

- If the continuous phase appears red, then it means that the emulsion is o/w type as water is the external phase.
- If the scattered globules appear red and continuous phase is colourless, then it is w/o type.

4. **Fluorescence test:**

Oil gives fluorescence under UV light, while water doesn't. Therefore, o/w emulsion shows spotty pattern when observed under UV, while w/o emulsion fluoresces.

5. **Cobalt chloride test:**

When a filter paper soaked in cobalt chloride solution is dipped into an emulsion and dried, it turns from blue to pink, indicating that the emulsion is o/w type.

Evaluation of emulsions:

1. Size distribution analysis.

2. Rate of phase separation.

3. Viscosity & rheological study.

4. Measurement of dielectric constant.

5. Conductivity measurement.

6. Influence of temperature.

7. Microwave radiation.

8. Microelectrophoretic measurement.

Stability of emulsions:

The following three changes usually occurs during the storage of emulsion:

1. Creaming.

2. Cracking.

3. Phase inversion.

1. **Creaming:**

Creaming may be defined as the upward movement of dispersed globules to form a thick layer at the surface of emulsion. The creaming depends on "Stokes law", the rate of creaming depends on the various factors. V=2r2(d1-d2)g/9n

2. Cracking:

Cracking means the separation of two layers of dispersed phase and continuous phase due to coalescence of dispersed phase globules. Cracking may be due to the following reasons:

a) By addition of emulsifying agent of opposite type.

b) By decomposition of emulsifying agent.

c) By addition of common solvent.

d) By microorganisms.

e) Changes in temperature.

3. Phase inversion:

Phase inversion means change of one type of emulsion into the other type i.e., o/w emulsion changes into w/o type and vice versa. It may be due to following reasons:

a) By the addition of an electrolyte. b) By changing the phase volume ratio. c)By temperature change. d)By changing the emulsifying agent.

Reference

1. Lieberman HA, Rieger MM, Banker GS. "Pharmaceutical Dosage Forms: Disperse System", vol.3; Second Edition,473-511
2. The theory and practice of industrial pharmacy by Leon Lachman, Herbert A. Liberman, Joseph L. Kanig; Third edition
3. Aulton, ME. "Pharmaceutics, The Science of Dosage Form Design", 2nd edition, Churchill Livingstone, London, 2002, pp 309-322.
4. Lachman L, Lieberman HA, Kanig JL. "The Theory and Practice of Industrial Pharmacy", 3rd edition, Varghese Publishing House, Bombay, 1991, pp 457-477.
5. Niazi SK. "Handbook of Pharmaceutical Manufacturing Formulation: Liquid products", CRC Press LLC, 2004.
6. Remington-The science and practice of pharmacy 21st edition pg 323,740-744.
7. Lachman L, Lieberman HA, Kanig JL. 'Theory and Practice of Industrial pharmacy'-Varghese publishing house, third edition-pg no-511.
8. Edward J, Pittsburgh B, Pennsylvania,' Pharmaceutical Packaging Handbook' USA Informa health care.

SUBJECT NAME: INDUSTRIAL PHARMACY –I (BP502T)

UNIT-III (CAPSULES) COURSE: B.PHARM SEM: 5TH

Abbreviation:

HGC: Hard Gelatin Capsule

SGC: Soft Gelatin Capsule

PEG: Poly Ethylene Glycol

GI: Gastro Intestinal

BA: Base Adsorption

M/g: Minim per Gram factor

MCC: Micro Crystalline Cellulose

CMC: Carboxy Methyl Cellulose

GMS: Glyceryl Mono Stearate

SUBJECT NAME: INDUSTRIAL PHARMACY –I (BP502T)

UNIT-III (CAPSULES) COURSE: B.PHARM SEM: 5TH

Definition:

Capsules are solid dosage forms in which the drug or a mixture of drugs with or without excipients is enclosed in Hard Gelatin Capsule Shells, in soft, soluble shells of gelatin, or in hard or soft shells of any other suitable material, of various shapes and capacities. They usually contain a single dose of active ingredient(s) and are intended for oral administration.

Advantages:

- The drugs having unpleasant odour and taste can be administered by enclosing them in a tasteless shell.
- They are smooth, become very slippery when moist and can be easily swallowed.
- They are economical
- They are easy to handle and carry.
- The capsules release the medicament as and when desired in gastro-intestinal tract.
- Capsules are made from gelatin and hence they are therapeutically inert.
- Capsule have elegant appearance so that it enhance patient acceptance.
- The drug in the form of solid,liquid & viscous form can be encapsulated in capsule shell.
- Capsule formulation provide better stability of drug as compare to uncoated tablet & liquid dosage form

Disadvantages:

- Capsule are not usually used for administration of extremely soluble materials such as potassium chloride, potassium bromide etc. since there is sudden release of such compound in stomach & causes irritation.
- Capsule should not used for highly efflorescent material as material may cause the capsule to soften by losing water molecule to shell ,
- Capsule should not used for highly deliquescent powder as powder have tendency to absorb moisture from capsule shell & make it brittleness.
- The capsule shells can absorb water from the environment and develop problems with drug stability and capsule shell can become tacky
- it unsuitable for use with liquid formulations

Gelatin as a component of capsule shell:[1]

As the gelatin is the main source for production of capsule shell,we need to understand its source & process of manufacture .Gelatin is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen as it never occurs naturally.

The physical & chemical properties of gelatin are the function of parent collagen, method of extraction,pH value ,thermal degradation & electrolyte content. The main source of collagen which are required for production of gelatin are animal bones and frozen pork skin.

Generally two type of getatins are used to manufacture capsule shell.

Type A Gelatin:it is derived from the acid treated precursor and exhibit isoelectric point in region of pH 9.

Type B Gelatin: it is derived from an alkali treated precursor & exhibit isoelectric point in region of pH 4

[The **isoelectric point** is the pH at which a molecule carries no net electrical charge or is electrically neutral]

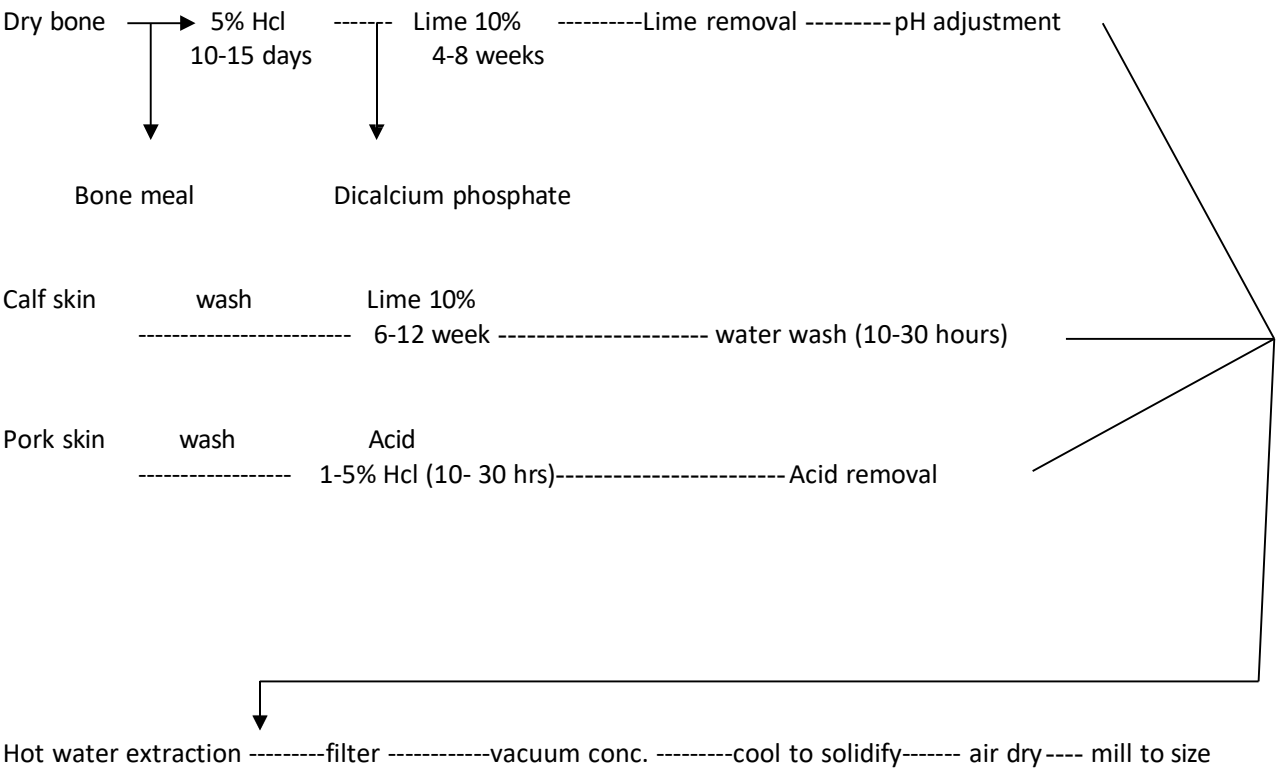


Fig.1 [The process of manufacturing gelatin] [1]

Type of capsule (based on type of shell)

1. Hard Gelatin capsule [HGC]
2. Soft Gelatin capsule [SGC]

Hard Gelatin capsule:it is the capsule in which medicament(s) with or without excipient in the dry powder form are enclosed in a shell which consist of cap & body.

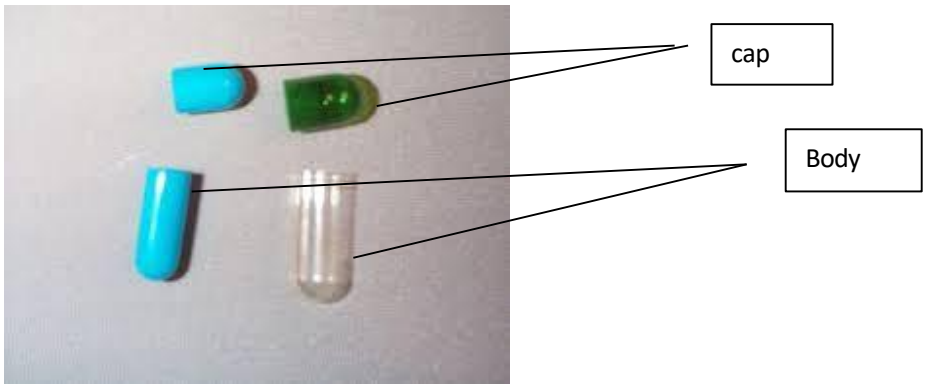


Fig.2 showing part of hard Gelatin capsule

Production of Hard gelatin capsule shell:[1]

The mechanism involved for production of hard gelatin capsule shell are

- Dipping
- Spinning
- Drying
- Stripping & Trimming
- Joining

Preparation of the gelatin solution (dipping solution): A concentrated solution of gelatin (35-40%) is prepared by dissolving the gelatin in demineralized water which has been heated to 60–70°C in jacketed pressure vessels.This is stirred until the gelatin has dissolved and vacuum is applied to removed entrapped air bubbles. At this stage, other processing aids may be added like plasticizer, colourant, opaquing agent etc.The viscosity of gelatin preparation has to be controlled as it may affect downstream manufacturing process & very importantly thickness of shell.

Dipping: Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatin solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan.

Spinning of the dip-coated pins: after adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is rotated more times to evenly distribute the gelatin solution around the pins,as uniform gelatin distribution being critical for correct and precise capsule wall thickness.

Drying of the gelatin-coated pins **:**once the gelatin is evenly distributed on the mould, a blast of cool air is used to set the gelatin on the mould. At this point, the gelatin is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Stripping & Trimming : After the gelatin is dried, the capsule is stripped off the mould and trimmed to the proper length

Joining of the trimmed capsule shell: Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

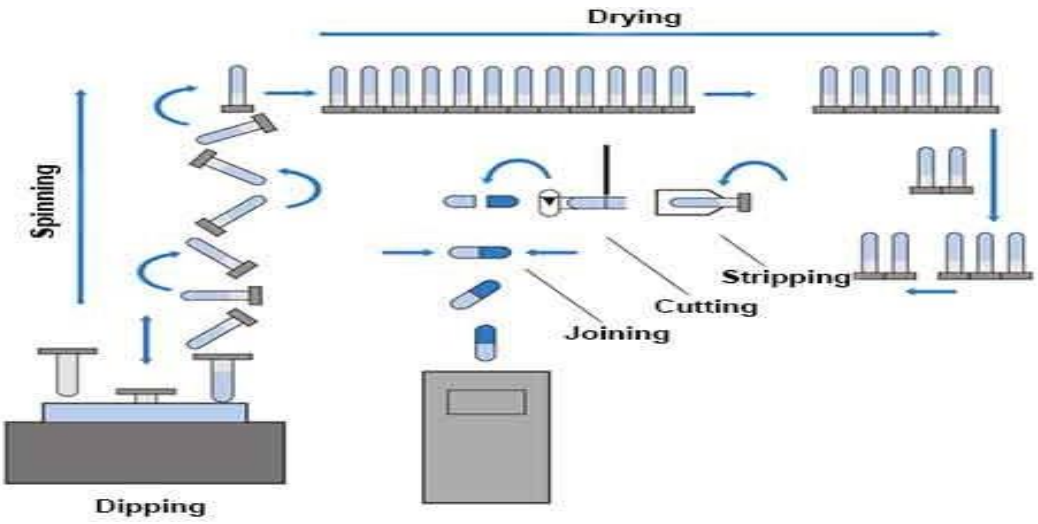


Fig.3 Sequence of two piece hard gelatin capsule shell manufacture [2]

Size of capsule:

Size	Volume (mL)	Fill weight (g) at powder density of 0.8/cm^3
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.13	0.104

Table -1 (capsule size & body fill volume) [3]

Filling of Hard Gelatin capsule: The several type of filling machine in use in the pharmaceutical industry have in common the following operation.

1. Rectification: The empty capsule are oriented so that all point the same direction, i.e body end downward. The capsule pass one at a time through a channel just wide enough to provide a frictional grip at cap end. capsule will always be aligned body end downwards regardless of which end entered the channel first.
2. Separation of cap from bodies: This process depend on the difference in diameter between the cap and body. The rectified capsule are delivered body end first into the upper portion of split brushing .A vacuum applied below pull the bodies down into the lower portion .the diameter of cap is too large to allow them to bodies into the lower portion
3. Dosing of fill material: various method like Auger principle, vibratory fill principle, piston- Tamp principle are employed for filling
4. Replacement of cap and ejection of filled capsule: The cap & body bushing portion are rejoined. Pins are used to push the filled bodies up into the caps for closure and to push the closed capsule out of the bushing. Compressed air also used to eject the capsules.

   Filling principles:

   a) Auger fill principle: The empty hard gelatin capsule are taken from hopper to the rectifying unit. the rectifier descend the the capsule such that caps are turned up and bodies are down.

- When vacuum is applied capsule from rectifying unit are placed one by one in the filling ring kept on rotating mode. The ring consists of upper and lower ring having cavities for for placing capsule. When all the cavities of ring filled, the upper ring is lifted which causes separation of bodies from caps.

- The lower ring is rotate with constant speed and the hopper containing powder is held over the ring. The auger drive the powdered drug into the capsule bodies. After bodies are completely filled ,the hopper is set aside & rotating ring is stopped. Now ring holding caps are placed over ring holding the bodies which are then joined together.

b) Vibratory fill principle: in this type of machine ,the feed is placed in the feed hopper & capsule bodies are pass under it. A perforated resin plate (connected to vibrator) is placed in feed hooper.Due to vibration of resin plate the powder flows freely through the pores into the capsule bodies.

- Pins are present below the capsule bodies for support. Capsule bodies are filled when the pins are pulled down. but when there is overfilling, The capsule bodies are pushed up to reach the level of disc plate and excess the powder is forced out by scrapping

c) Piston-tamp principle: automatic capsule filling machines work on piston-Tamp principle by using piston or Tamping pins. The piston tapmps alter the shape of powder by compressing the powder to form plugs (slugs).These plugs are transferred into empty capsule shell with the application of little pressure. This piston pump principle can be explained by two type of machine

i) Dosing-disc type machine
ii) Dosator type machine

d) Vacuum fill principle:The machine consist of an open ended cylinder. The upper end of this cylinder is fitted with piston. The lower end (open end) is placed in bulk powder. Vacuum is applied and the piston is moved upward by sucking the specific amount of powder,this result in filling of the cylinder, the powder is filled up to the piston height and the vacuum is held until the piston is positioned over empty capsule body. Now the vacuum and pressure in the form of compressed air is applied over the piston to transfer the powder into the capsule body.

Capsule filling methods:

1. Manual filling
2. Hand filling machine
3. semi-automatic machine
4. Fully automatic capsule filling machine

Manual filling method:

- This method is opted when number of capsule to be filled is less
- Initially the ingredients to be filled are triturated & make is uniform mixing.then put it on clean paper

- Now the required number of empty capsule are taken and caps are separated from body. Then individually powder has to be filled with the help of spatula to the capsule body. Then cap has to be fitted ovet it with little pressure

Hand filling machine :

- ✓ It consist of a bed having 200-300 hole, a loading tray having 200-300 holes, a powder tray, a pin plate having 200-300 pins, a sealing plate having a rubber top, a lever, a cam handle.
- ✓ The empty capsules are filled in the loading tray and it is palced over the bed. The cam handle is operated to separate the capsule caps from their bodies.
- ✓ The powder tray is placed in a proper position and filled with an accurate quantity of powder with scraper. The excess of the powder is collected on the platform of the powder tray. The pin plate is lowered and the filled powder is pressed by moving the pin downwards.
- ✓ After pressing the pin plate is raised and the remaining powder is filled into the bodies of the capsules. The powdered tray is removed after its complete filling. The cap holding tray is again placed in position. The plate with the rubber top is lowered and the lever is operated to lock the caps and bodies. The loading tray is then removed and filled capsules are collected.

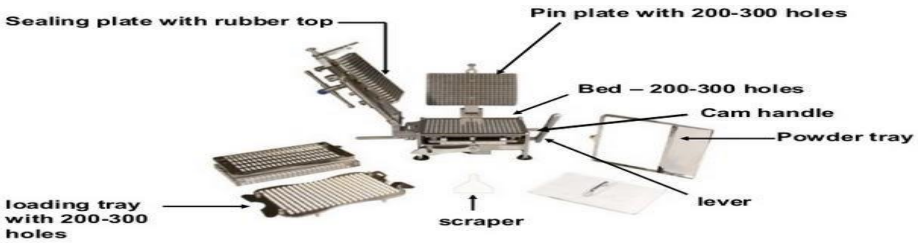


Fig 4.Hand filling capsule machine

Semi-automatic machine:

There are 3 stations in this semi-automatic capsule filling machine

- ❑ orientation of capsule
- ❑ powder filling
- ❑ capsule closing

The functions of first station include *:*

1. capsule feeding
2. Aligning
3. insertion into bores of holding ring
4. vacuum is used for separating capsule cap and body in first station.
5. After orientation of capsule, capsule cap can stay in upper holding ring and capsule body can stay in lower holding ring.

Powder filling:

Separate the holding ring, put the lower (body) holding ring on the rotary table, pull the powder hopper over the lower (body) holding ring, then auger inside powder hopper starts to run and fill powder into the capsule body. While Iower holding ring turns one circle, push powder hopper to its original position.

Capsule closing:

- Put upper holding ring and lower holding ring together, then position intact holding ring in front of peg ring .closing plate is pivoted to a position approximately 180 degrees
- Pneumatic pressure is applied to peg ring which finally push capsules inside the bores of holding ring the finished capsules will be collected into the container.

Fully automatic capsule filling machine:

Most automatic filling machines employs piston or tamping pin that lightly compress the powder into plugs,(some times referred as slugs) and eject the plugs into the empty capsule bodies.

The compression forces are low, often range from 50-150N, upto 100 fold less than that employed in typical tablet compression. Often plugs are very soft compacts and not able to recovered intact from filled capsule.there are two main type of these fillers: Dosator machine and dosing disc machine.

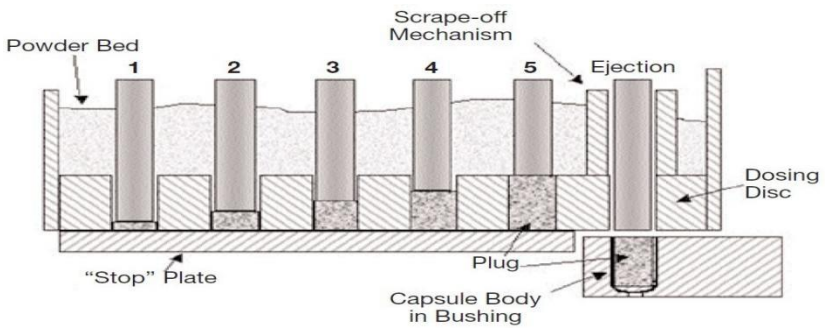


Fig.4 [Dosing disc type machine] [3]

The tamping pin type capsule filling process involves a number of stages. In this case, the machine has 5 stage tamping technology. This pan rotates continuously in a circular manner depending on the preset speed. Normally, as the dosing plate rotates below the powder bed, the filler material flows into each hole. The pins, which are in the tamping stations compress the powder to a controlled depth. That is, as the filler material flows into the first hole in the disc, tamping pin 1 compresses it to a predetermined depth. After this first step, the hole moves to the next stage where the powder again flows into the hole and tamping pin 2 compresses it to a predetermined depth. The force these tamping pins exert on the powder is just enough to compact it. That is, it may range from 50N to 150N.

This process continues until the holes with the powder reaches the last tamping pin (no. 5), where the machine ejects a compacted powder through the dosing plate into the capsule. After filling the capsule shell, it moves to the next stage (sealing/covering the capsule). This is a continuous process and the production speed will depend on the preset machine conditions.

Finishing of capsule: in order to make capsule more elegant, they under go the process of finishing .the commonly used step for producing finished capsule are as follows:

1. Cloth dusting: it is manual method in which small number of capsule are rubbed with a cloth or gauze which may or may not contain inert oil.
2. Polishing: special pan may be used for polishing the the filled capsule. these pan lined with cheese or polyurethane cloth which remove the dust or other powder adhere to capsule
3. Brushing: in this method capsule are projected under soft rotating brushes which remove the dust from capsule shell. This process is assisted under vacuum.

   Sorting: This operation is needed to separate the imperfect & damaged capsule. although in large scale it done manually, some automatic equipment are available e.g-Rotosort

Formulation of powder need to be fill capsule shell:

Ingredients type	purpose	example
API	Produce therapeutic effect	Amoxycilin
fillers	To increase bulk volume of formulation	Starch ,lactose
Lubricant	Reduce powder to metal adhesion	Magnesium stearate
Glidant	Improve powder flow	Colloidal silica
surfactant	Increase the wetting of powder mass	SLS,sodium docusate
Super Disintegrant	Disruption of powder mass	Crospovidone,Croscarmellose sodium
Hydrophylic agent	Improve the wettability of poorly soluble drug	Methyl cellulose,hydroxyl ethyl cellulose

Table .2[list of excipient used in powder formulation for capsule filling] [3]

Special technique of formulation used in hard gelatin capsule: [1]

1. **Imprinting** ; is a convenient method by which company and/or product identification information can be placed upon each capsule. The imprinting operation is best performed on empty capsule although filled capsule can be printed.
2. Solubility: For special purpose capsule attempt to retard solubility in some manner.

   a) formalin treatment has been employed to modify the solubility of gelatin capsule. exposure to formalin vapour or treatment with aq formalin produce unpredictable decrease in solubility of the gelatin film.

   This result may be noted if product being filled contain aldehyde materials of aldehyde flavor.it is difficult to control degree of insolubilization.

   b) various coating have been used to provide similarity modified solubility character. These coating include salol,shellac,cellulose acetate phthalate

3. separation of incompatible material: it invoving two phase fill in the capsule. one phase consist of either a soft capsule,a pill or suitably coated tablet that is filled into the capsule. in second phase a powder fill is added in usual manner.these changes include ,at minimum the necessary changes in machine operation to allow material to be loadedat two point during filling cycle.

4. filling of conventional two piece gelatin capsule with liquid & semisolid.the formulation used for filling are usually semisolid at ambient temperature, which are melted to allow filling or they are thixotropic formulation in which the shear developed in filling allows pumping but whose high viscosity when shear is absent prevent leakage after filling.

Manufacturing defect of hard gelatin capsule:

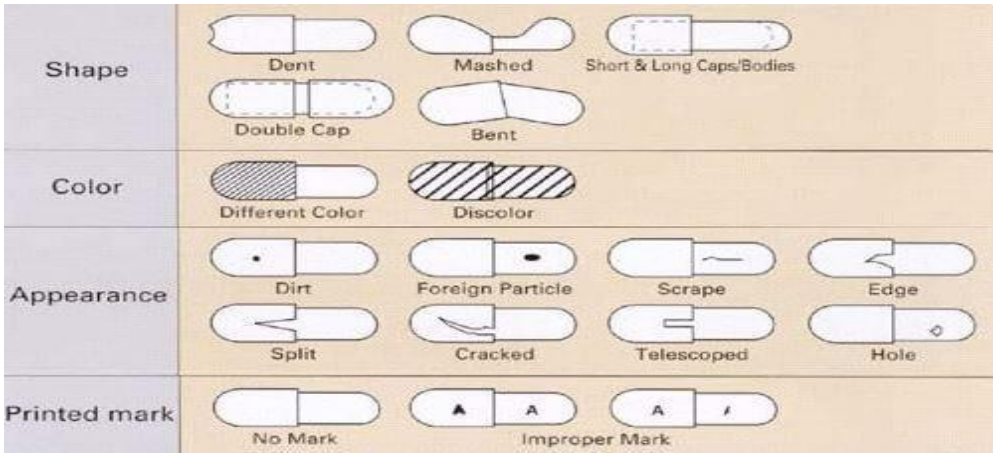


Fig.5 manufacturing defect of hard gelatin capsule

several defects that include;

- Shell surfaces not smooth
- Opacify not proper
- Empty capsules after the filling stage
- The foreign matter inside the capsules
- Capsules fitting not uniform during filling
- Capsules are not of the specified type
- Color variation and non-uniformity of appearance
- Surface spots and embedded particles on the capsules
- Capsule may have cracks, breaks, pinholes or splits, losing its integrity.

In process Quality control (IPQC) for capsules :

1. Mfg of Gelatin Shell.
2. Drying of shells in controlled humidity.
3. Mfg of granules.
4. Filling of Shells.
5. Packaging & Labeling. •

IPQC Checks During Gelatin Shell Manufacturing:

•% purity of gelatin
•Viscosity of gelatin solution 25-45 millipoise
•Bloom strength of gelatin solution 150-250 gm
•Iron content NMT 15 ppm
•Film Thickness
•Color, surface, appearance of empty shells
•Temperature of hot air, for drying of shells

•Length of Capsule & Body of the shell
•Moisture content 12-15%

Inspection of defects like:-

Hardening of shells
Softening of shells
Swelling of shells
Cracking of shells
Discoloration of shells
Misprinting of logo on shells

Finished product quality control test of capsule: [4]

1. **Appearance**:
Capsules produced on a small or a large scale should be uniform in appearance. Visual or electronic inspection should be undertaken to detect any flaws in the integrity and appearance of the capsule
2. **Size and Shape:** Hard capsules are made in a range of sizes,the standard industrial ones in use today for human medicines range from size from 000 (the largest) to 5 (the smallest) are commercially available. inspection must be done for size and shape.
3. **Unique Identification Markings:**
Capsule surfaces may bear symbols or other unique identification markings for better identification.
4. **Uniformity of weight**.: Weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible. To remove the contents of a soft capsule the shell may be washed with *ether* or other suitable solvent and the shell allowed to stand until the odour of the solvent is no longer detectable. Weigh the shell. The weight of the contents is the difference between the weighings. Repeat the procedure with a further 19 capsules. Determine the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in below and none deviates by more than twice that percentage.

Average weight of capsule Contents	Percentage deviation
Less than 300 mg	10
300 mg or more	7.5

TABLE 3 (percentage deviation for capsule weight)

5. **Uniformity of content**. This test is applicable to capsules that contain less than 10 mg or less than 10 per cent w/w of active ingredient.
Determine the content of active ingredient in each of 10 capsules taken at random using the method given in the monograph or by any other suitable analytical method of equivalent accuracy and precision. The capsules comply with the test if not more than one of the individual values thus obtained is outside the limits 85 to 115 per cent of the average value and none is outside the limits 75 to 125 per cent. If two or three individual values are outside the limits 85 to 115 per cent of the average value repeats the determination using another 20 capsules. The

capsules comply with the test if in the total sample of 30 capsules not more than three individual values are outside the limits 85 to 115 per cent and none is outside the limits 75 to 125 per cent of the average value

6. Disintegration. The disintegration test is not applicable to Modified-release Capsules. For those Hard Capsules and Soft Capsules for which the dissolution test is included in the individual monograph, the test for Disintegration is not required..

a) **Hard Capsules**. Comply with the disintegration test in monograph , Unless otherwise directed in the individual monograph use *water* as the medium. If the capsules float on the surface of the medium, a disc may be added. If the capsules adhere to the discs, attach a removable piece of stainless steel woven gauze with mesh aperture of 2.00 mm to the upper plate of the basket rack assembly and carry out the test omitting the discs. Operate the apparatus for 30 minutes unless otherwise directed

b) Soft Capsules. Comply with the disintegration test Unless otherwise directed in the individual monograph use *water* as the medium and add a disc to each tube. Operate the apparatus for 60 minutes unless otherwise directed

c) Enteric Capsules. Use the apparatus described under disintegration test (2.5.1), using one capsule in each tube. Operate the apparatus for 2 hours without the discs in *0.1 M hydrochloric acid*. No capsule shows signs of disintegration or of rupture permitting the escape of the contents. Replace the medium in the vessel with *mixed phosphate buffer pH 6.8*, add a disc to each tube and operate the apparatus for a further 60 minutes. Remove the apparatus from the medium and examine the capsules. They pass the test if no residue remains on the screen or on the underside of the discs, or, if a residue remains, it consists of fragments of shell or of a soft mass with no palpable, unmoistened core.

7. Content uniformity of drug: A sample of 30 capsule is taken and 10 are assayed individually.The drug content of a capsule should be within the limits of average drug content ±15% and the drug content of none of the capsule fall outside the average drug content ±25%. If 1-3 capsules falls outside the average drug content ±15%, the remaining 20 are assayed. The drug content of at least 27 out of 30 assayed should be within the average drug content ±15% limits. and the drug content of none of the capsules falls outside the average drug content ±25% limits. The test is prescribed for capsules when active ingredient is <10 mg or 10% of fill weight.

8. **Dissolution test**: The dissolution test is carried out using the dissolution apparatus as per U.S.P .

• The capsule is placed in a basket , and the basket is immersed in the dissolution medium and caused to rotate at a specified speed . The dissolution medium is held in a covered 1000ml glass vessel and maintained at 37^0 c +-0.5^0c by means of a constant temperature suitable water bath. The stirrer speed and type of dissolution medium are specified in the individual monograph

Stage	Number of capsule tested	Acceptance criteria
S1	6	Each unit is not less than Q + 5%.
S2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than Q – 15%.
S3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

Table. 4 [acceptenace criteria for dissolution study][1]

The quantity Q, is the specified amount of dissolved active substance, expressed as a percentage of the labeled content.

SOFT GELATIN CAPSULE (SGP): Soft gelatin capsules are one piece , hermetically sealed , and are made up of gelatin in which glycerin or polyhydric alcohol (sorbitol) are added , containing liquid , suspension or semisolid enclosed in it.

Advantages:

- Soft gelatin capsules are in sealed form so they protect the inner fill from oxidation and degradation.
- Opaque soft gelatin capsules also protect the inner fill from UV radiation and photo sensitive products.
- It enhance patient compliance due to its elegant appearance.
- Suitable for medicaments like semisolid, oils, liquid forms.
- Soft gelatin capsules increase the bioavailability of API.

Disadvantages:

- Few filling equipment available
- Manufacturing expensive
- Drugs from oily vehicle may pass into the shell
- Soft gelatin capsules having difficulties in dealing with water soluble materials.
- Soft gelatin capsules are highly sensitive to moisture.
- Soft gelatin capsules having difficulties in dealing with efflorescent materials.
- Soft gelatin capsules having difficulties in dealing with deliquescent material

Shape of capsule shell:

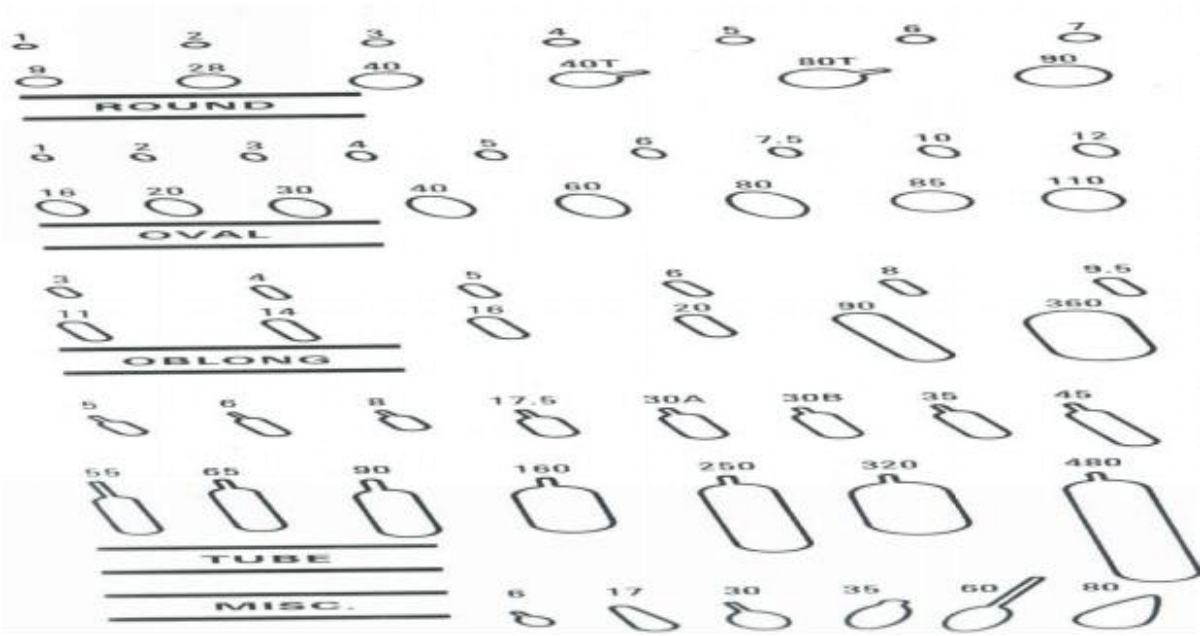


Fig.6[Size and shape of soft gelatin capsules. number represents the normal capacity in minims] [1]

Nature of capsule shell:

- The capsule shell **is** basically composed of gelatin, plasticizer & water. Additionally it may contain preservative, colouring agent, opacifying agent, flavor, sweetening agent to achieve desired effect.

- The gelatin is USP grade with additional specification required by the capsule manufacture. The additional specification concern the bloom strength,viscosity,iron content of gelatin used.
- Bloom or gel strength: is a measure of cohesive strength of cross linking that occurs between gelatin molecule and is proportional to the molecular weight of gelatin. Bloom is determined by measuring the weight in gram required to move a plastic plunger that is 0.5 inches in diameter 4mm into a 6 2/3 % gelatin gel that has been held at 10^{o}c for 17 hours. Bloom may vary from 150-250g.
- Viscosity: viscosity of gelatin determined on a 6 2/3 % conc of gelatin in water at 60^{0} c, is a measure of molecular chain length and determines the manufacturing characteristics of gelatin. The viscosity for gelatin can ranges from 25 to 45 millipoise.

- Iron is always present in the raw gelatin and its concentration usually depend on the iron content of the large quantities of water used in its manufacture.Gelatin used in manufacture of soft gelatin capsule should not contain more than 15 PPM of this element.

Hardness	Ratio Dry glycerin/Dry gelatin	Usage
Hard	0.4/1	Oral,oil based or shell softening product,designed for hot,humidity areas
Medium	0.6/1	Oral,water miscible based ,shell hardening product and designed for temperate areas
Soft	0.8/1	Tube,vaginal,water miscible based or shell hardening product and destined for cold,dry areas

Table .5 [Typical shell Hardness ratios and their uses] [1]

Capsule content:

- Content may be liquid, or a combination of miscible liquids, Solution of a solid(s) in a liquid(s) or Suspension of a solid(s) in a liquid. It can be a liquid like a volatile oil composition E.g. Vegetable oils like arachis oil or aromatic or aliphatic hydrocarbons, ethers, esters, or alcohols.
- Solids that are not Sufficiently soluble in liquids or in combination of liquids are capsulated as Suspension. Suspending agents used are Lecithin, Soyabean oil
- Liquids are important part of capsule content. only those liquid that are both water miscible & volatile cannot be included as major constituent of the capsule content since they can migrate into the hydrophilic gelatin shell and volatilize from its surface .water, ethyl alcohol fall inthis category.
- Similarly gelatin plasticizer such as glycerin and propylene glycol cannot be major constituent of capsule content owing to their softening effect on gelatin shell.
- Preparation for encapsulation should have a pH between 2.5 and 7.5,since preparation that are more acidic can cause hydrolysis and leakage of shell and preparation that are more alkaline can tan the gelatin and affect the solubility of shell.
- The maximum capsule size and shape for convenient oral use in human is the 20 minim oblong,the 16 minim oval,9 minim round.

Formulation of filling material of SGC:

The various liquid phase filling matrices used in soft gelatin capsule are selected considering following criteria:

Compatibility with capsule shell
Ability to dissolve the drug
Rate of dispersion in the GI fluid after shell disintegration in the GIT
Ability to optimize the bioavailability of drug

Types of filling/Bases:

1. Hydrophilic Liquids: like PEG 400 having high mol weight are frequently used
2. Lipophilic liquid: soya bean oil commonly used. the drug like steroid, vitamin D are mixed with these oil
3. Microemulsion system: it consist of oil-surfactant-water system. blend of oil and surfactant together with the active ingredient is filled into the capsule
4. Emulsifying oil: mixture of pharmaceutical oil & non ionic surfactant like polyoxyethylene sorbitan mono oleate serve as self emulsifying oil matrix
5. Suspension: the drugs which are insoluble in liquid matrices of capsule & which are poorly soluble in GI fluid can be formulated as suspension.

Base adsorption:[1]

- In the formulation of suspension for soft gelatin encapsulation, certain basic information must be developed to determine minimum capsule size. so one of such tool is Base adsorption of solid(s) to be suspended.
- Base adsorption is expressed as the number of gram of liquid base required to produce a capsulatable mixture when mixed with one gram of solid(s).

The Base adsorption of solid influenced by

- Particle size & shape
- Its physical state (amorphous or crystalline)
- Density, moisture content, its oleophylic & hydrophilic nature

Determination of Base adsorption:
weigh a definite amount(40 g is convenient) of solid into 150 ml tared beaker. In a separate 150ml tared beaker , place about 100g of the liquid base. Add small increment of base to the solid and using the spatula ,stir the base into the solid after each addition until the solid is completely wetted & uniformly coated with base.
This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a 45^0 angle above the mixture.

Base adsorption = weight of base/weight of solid

Minim per gram factor(M/g):

- The base adsorptions used to determine the “minim per gram” factor (M/g) of the solid(s).
- The minim per gram factor is the volume in minims that is occupied by one gram of the solid plus the weight of the liquid base(BA) required to make capsulatable mixture.
- The minim per gram factor is calculated by dividing the weight of the base plus the gram of solid base (BA+S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V).
    - (BA+S) x V/W = M/g
- Thus lower the base absorption of the solids and higher the density of the mixture, the smaller the capsule will be.

Manufacture of soft gelatin capsule:

1. Plate process
2. Rotary die process
3. Reciprocating die process
4. Accogel capsule filling machine

Plate process:

- Place the gelatin sheet over a die plate containing numerous die pockets.
- Application of vacuum to draw the sheet in to the die pockets.
- Fill the pockets with liquid or paste.
- Place another gelatin sheet over the filled pockets, and
- Sandwich under a die press where the capsules are formed and cut out.

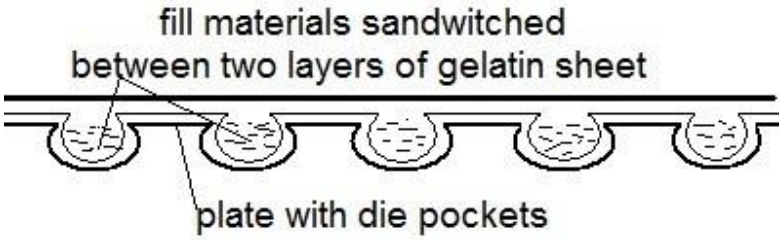


Fig.7 (plate process) [3]

Rotary die process:

1. In this machine the soft gelatin capsules are prepared & then filled immediately with liquid medicaments it is having two hoppers & two rotating dies
2) Liquid mixture is placed in one hopper & the liquid medicament in other Hooper.
3) The two rotating dies rotate in opposite directions when the fluid gelatin mixture enters the machine from the hopper it produces two continuous ribbons .
4) These half shell of the capsule is formed.
5) At this stage the measured quantity of the medicament is filled in to it with the stroke of a pump with the subsequent movement of the dies the other half capsule is formed.
6) The two halves' of the capsules are sealed together by the heat & pressure of the rotating dies
7) As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules

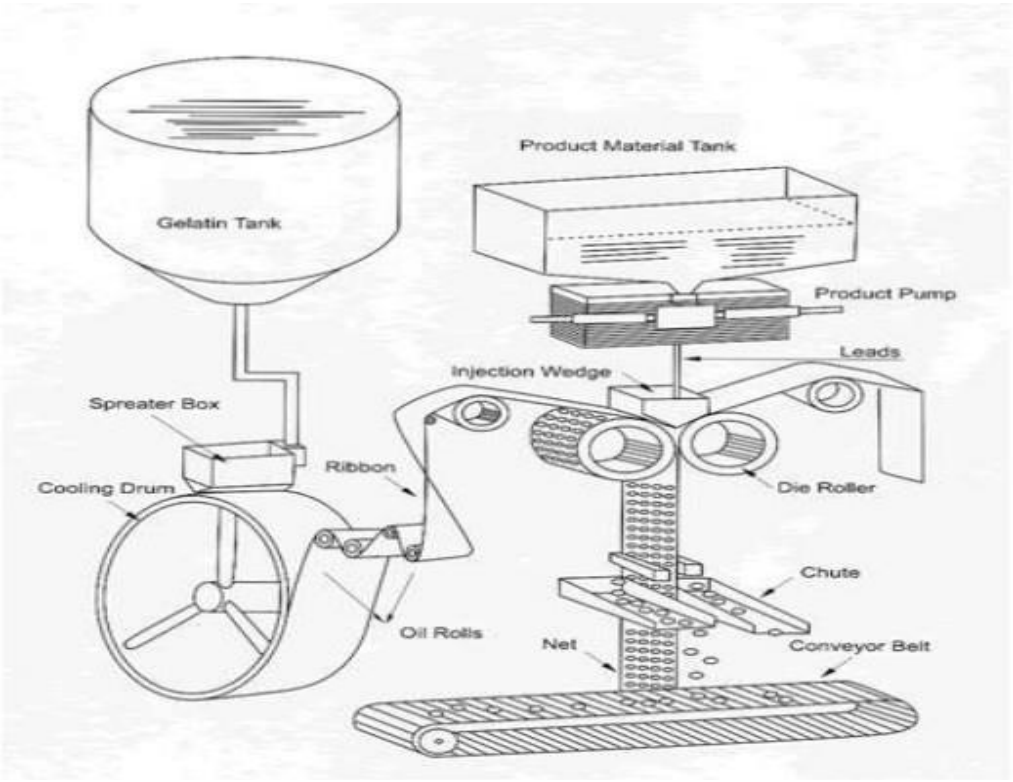


Fig .8 (Rotary die process)[1]

Reciprocating die process: This machine produces capsule completely automatically by leading two films of gelatin between a set of vertical dies. Rows after rows of pockets are formed across the gelatin film, filled with medicaments and as they process through the dies, are sealed, shaped and cut out of the film as capsules which drop into a cooled solvent bath

Accogel capsule filling machine: This is another rotary process involving a measuring roll, a die roll and a sealing roll. The measuring roll rotates directly over the die roll, and the pockets in the two rolls are aligned with each other. The powder or granular fill material is held in the pockets of measuring roll under vacuum. A plasticized gelatin sheet is drawn into the die pockets of the die roll under vacuum. As the measuring roll and die roll rotates, the measured dose are transferred to the gelatin lined pockets of the die roll.

Fig.9 (Accogel capsule filling machine)

In-process testing :

- During the encapsulation process the four most important tests are:-
- .The gel ribbon thickness;
- Soft gel seal thickness at the time of encapsulation;
- Fill matrix weight & capsule shell weight;
- Soft gel shell moisture level and soft gel hardness at the end of the drying stage.

For the determination of the fill weight each capsule is weighed and the contents removed by cutting open the capsule. The shell is then washed with petroleum ether, and the empty shell is reweighed. If necessary, adjustment can be made to obtain the proper fill weight.

Finished product testing: Test parameter almost same as hard capsule

Special quality control test on soft gelatin capsules:-

•Seal thickness:-Is measured under a microscope and it should one half to two third of the ribbon thickness.

•Total or shell moisture test:-Moisture content is determined by the toluene distillation method. Collecting the distillate over a period of one hour.

•Capsule fragility or rupture test:-Force required to rupture the capsule is determined.

•Determination of freezing and high temperature effect:-(>45^0 c for 30 days)

These are performed similarly to the shell integrity test.

Packaging & store of capsule:

The main aim of packaging of filled capsule is to prevent contamination & loss or gain of moisture during long term storage.

Many plastic container & various packaging technology such as blister packaging, strip packaging are used for it.

In some container dehydrating powder(desicants) is placed which retard the excessive moisture absorption by capsule.

Storage: storage of hard gelatin capsule shell for long time period require proper maintenance of temp & humidity

Storage condition	Relative humidity(%)	Temp (^{0}c)
Minimum	35	15
Best possible	50	20
Maximum	65	25

Table .6 (storage condition of capsule)

Very high humidity: capsules soften, stick together and lose shape

Very low humidity: capsules contract in size and become fragile

High or fluctuated temperatures: capsule forms lumps & condensation is seen on the surface of container.

Capsule physical stability:

- Unprotected soft gelatin capsules rapidly reach equilibrium with the atmospheric conditions under which they are stored.
- This inherent characteristic warrants a brief discussion of the effects of temp and humidity on the products.
- General statements relative to the effects of temp and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil with a gelatin shell having a dry glycerin to dry gelatin ratio of 0.5-1 and water to dry gelatin ratio of 1-1 and that is dried to equilibrium with 20-30% RH and 21-24^{o} c.
- The physical stability of soft gelatin capsules is associated primarily with the pick up or loss of water by the capsule shell .
- If these are prevented by proper packaging ,the above controlled capsule should have satisfactory physical stability at temp ranging from just above freezing to as high as 60^{0} c.
- As the humidity increases the moisture content pickup of capsules increases .
- ex- at 30%RH at room temp shows that gelatin retain about12%(48 mg) of water and glycerin 7%(14 mg) of water. at 60%RH the moisture content should be 17.4%.
- High humidity (>60%RH at 21-240 c)produce more lasting effects on the capsule shell

Since as moisture is absorbed, the capsules become softer, tackier and bloated.

- The capsule manufacturer routinely conducts accelerated stability tests on new product as an integral part of the production development program.

- The successful results are obtained by conducing at test conditions like

1.80%RH at room temp in an open container
2.40^{0} c in open container
3. 40^{0} c in closed container (glass bottle with tight screw cap)

→ chemists conducting the physical stability test in their own lab should keep two important points in mind:

1. prior to testing ,the capsule should be equilibrated to known atm conditions, preferably 20-30%RH at 21-240 c.
2. evaluation of the results of the previously described heat test should be made only after the capsules have returned to equilibrium to room temp

Temp	Humidity	Effect on capsule shell
21-24^{0}C	60%	Capsule become softer,tackier & bloated
> 24^{0}C	> 45%	More rapid & pronounced effect-unprotected capsule melt & fuse together

Table 7. (Effect of Temp,humidity on capsule shell) [1]

Application of soft gelatin capsule:[1]

1. They permit liquid medications to become easily portable.
2. Accuracy and uniformity of dosage ,capsule to capsule and lot to lot predominant advantage
3. the pharmaceutical availability of drugs formulated for this dosage form ,as measured by disintegration time or by dissolution rate often shows an advantage over other solid dosage form
4. the physiologic availability of drug is often improved since these capsule contain the drug in liquid form
5. the biopharmaceutical characterstics of such formulations can altered and adjusted more easily than those of other solid dosage form
6. orally administered drug ,particularly if used chronically ,can be irritating to the stomach .the dosage form of such drug can affect gastric tolerance indicated by study.

Pellet [4,5,6]**:** In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipient using appropriate processing equipment[4]

Pharmaceutical advantages:

- Uniformity of dose
- spheres have excellent flow properties
- Prevention of dust formation
- Controlled release application of pellets due to the ideal low surface area-to-volume ratio
- They can be blended to deliver incompatible bioactive agents simultaneously and/or to provide different release profiles at the same or different sites in the gastrointestinal (GI) tract

Disadvantage:

1. It is difficult to compress pellets into tablets as they are too rigid. Therefore, they are often delivered encapsulated in hard gelatin capsule shells.
2. Pelletization demands highly sophisticated and specialized equipment, thereby increasing the cost of manufacturing
.3.The control of manufacturing process is complicated with too many process variables as well as formulation

Formulation:[5]

1) Active Pharmaceutical Ingredient: This multiple unit dosage form technology has the potential for delivery of variety of APIs. The different drugs can be used to develop immediate release, sustained release pellets with diversified applications in different areas. Pellets technology is widely used to delivery GIT drugs at a specific site to release drug in a controlled manner.

2. Binder: They are also called as agglomerating inducers or bridging agents. These are adhesive materials that can be incorporated into pellet formulations to bind powders and maintain integrity on pellet formation and the addition of the binder may be as a solution than the dry form, which is considered to be more efficient than dry mixing followed by liquid addition. E.g- Gelatin, HPC, HPMC, MC, PVP, sucrose, starch

3. **Granulating fluid:** Moisture content of the wet mass prepared is the most crucial parameter for pellet growth as it imparts the required plasticity and cohesiveness to the wet mass to extrude

it and spheronize it to give a prefect spherical shape. examples are alcoholic or hydroalcoholic systems, ethyl ether, dilute acetic acid, isopropyl alcohol

4. **Spheronizing Enhancer:** Spheronization enhancers are formulation aids that improve the production of spherical pellets, mainly during spheronization and balling processes. They not only impart plasticity onto the formulation, but also impart binding properties that are essential for pellet strength and integrity.e.g- MCC ,sodium CMC

5. **Filler:** These are the excipients used to form the bulk of the material, in the process of pelletization 70 to 80% of the excipients is formed by fillers. Generally microcrystalline cellulose is used for this purpose. Avicel PH 101 is considered to be the pelletization aiding excipient in this process. Glyceryl mono stearate (GMS), Starch RX1500, spray dried lactose.

6. **Plasticizer:** Plasticizers improve the flexibility of polymers by reducing the tensile strength and glass transition temperature of the material. examples are Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate

7. **Lubricant**: In pelletization process, lubricants are rarely used as the high-speed rotary equipments are being used in the preparation of pellets. However, during compression and Extrusion-Spheronization, lubricants do play a crucial role in the successful manufacture of pellets. Their use reduces the friction between the die wall and material mix either during the compression process or in ejection phase.E.g- Calcium stearate, glycerin, PEG, Mg. Stearate

8. **Separating Agents:** Separating agents are materials which are adsorbed on the surface and promote the separation of pellets into individual units during a pelletization process, which are incorporated initially in the formulation or externally during processing to prevent pellets attracting one another due to surface charge development during the process.E.g- Kaolin, talc, silicon dioxide

9. **Surfactant:** In most pelletization processes, the initial pellet formation and subsequent growth into fully fledged smooth surfaced spherical pellets depends, to some extent, on the liquid bridges that hold the primary particles together, therefore, liquid (water in most cases) wetting the particles effectively is given more attention. Surfactants are added to the liquid to improve wettability by lowering the interfacial tension between the liquid and drug particles

10) pH adjusters: The pH adjusters are substances that are incorporated in pellet formulations which influence the microenvironment of drug molecules used for many reasons. Generally acid-labile drugs are protected from the pH conditions of the GIT by giving an enteric coating. Buffer systems may also be added to the core formulation to maintain the stability of core in a favorable range. Examples are Citrate, phosphate.

11. **Release modifiers:** The main requirement of pelletization process is to manufacture spherical drug cores that will be subsequently coated in a separate unit operation. It is also possible to prepare pellet cores that inherently possess specific release profiles in a single step which can be achieved by the incorporation of release modifiers along with drug during the core formulation. example are while water insoluble polymers, hydrophobic substances, inorganic salts, and hydrophilic polymers that swell and/or form gels are incorporated in pellets that retard release kinetics.(Ethyl cellulose, carnauba wax, shellac.)

12. **Flavoring agent:** The choice for the flavors changes from individual to individual depending upon the age, ethnicity and liking which plays a significant role in the taste fondness.

13. **Sweetening agent**: The sweet taste in formulation is more preferred especially in case of pediatric population. Natural sweeteners as well as synthetic sweeteners are used to improve the palatability of the formulations. The traditional source of sweetener is sucrose (derived from

cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose.

14. Coloring agents: Coloring agents are generally used in order to improve the appearance and make it more patient compliance. Pigments such as Titanium dioxide or FD&C approved coloring agents are used either in the dry form or mixed with the granulating fluid during the formulation.

Pelletization process : It involves three consecutive regions:

- Nucleation
- Transition and
- Ball growth.

However, based on the experiments on the mechanism of pellet formation and growth, the following steps were proposed: nucleation, coalescence, layering and abrasion transfer

Nucleation:

- Nucleation is a stage of Pelletization process that occurs whenever a powder is wetted with solvent system. The primitive particles are drawn together to form three-phase air-water-liquid nuclei system which are held together by liquid bridges that are pendular in nature.
- Further the size, the rate and the extent of nuclear formation depends upon the size of the particles, the moisture content, the viscosity of the binding particles, the wettability of the substrate and the processing conditions, such as tumbling and drying rates.

Transition phase:

- Nucleation is followed by a transition phase where the growth mechanisms affecting are coalescence and layering. Coalescence is defined as the formation of large-sized particles by random collision of well-formed nuclei, this mechanism require slightly excess moisture on the surface of the nuclei although the number of nuclei is progressively reduced even though the total mass of the system remains unchanged during this operation.
- Coalescence causes discrete size changes and leads to decrease in number of agglomerates but not their mass
- Layering is a slow growth mechanism and with the successive addition of fragments and fines on an already formed nuclei.
- The fines and the fragments produced through size reduction are taken up by larger pellets. Production of fines and subsequent coalescence and layering continues until the number of collisions declines rapidly, thereby leading to a reduction in the rate of growth of the pellets. At this point the third phase, the ball growth region, is reached.

Ball growth phase:

- The main mechanism in the ball growth phase is the abrasion transfer which involves the transfer of materials from one granule formed to another without any preference in either direction.
- This phase does not result in any change in the total number or mass of the particles. However, the particles undergo a continuous change in their size as long as the conditions that lead to the transfer of material exist.

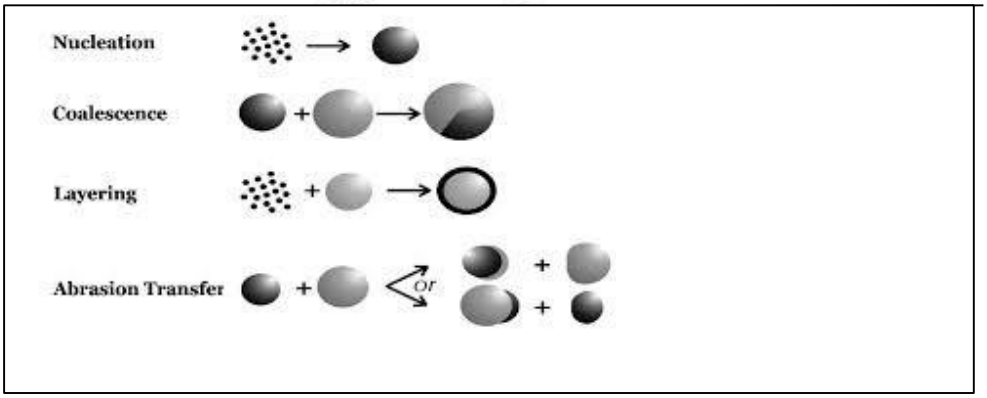


Fig.10 showing mechanism of pelettization process

Pelletization Techniques : [6]

Extrusion Spheronization
Layering Technique
Cryopelletization
Hot Melt Extrusion
Freeze Pelletization
MUPS (Multiple unit pellet system)

Extrusion Spheronization :

(a) **Dry Mixing:** Dry mixing of ingredients is done to achieve homogeneous powder dispersion using twin shell blender, planetary mixer, high speed mixer and tumbler mixer

(b) **Wet Massing:** Wet massing is done to produce a sufficient plastic mass for extrusion, by employing normal equipment and processes as employed in wet granulation for compaction. The most commonly used granulator is planetary mixer or Hobart mixer or sigma blade mixer and high shear mixer

(c) **Extrusion:** This is the third step in the process, which produces rod shaped particles of uniform diameter from the wet mass. The wet mass is forced through dies and shaped into small cylindrical particles with uniform diameter.

(d) **Spheronization:** consists of a static cylinder and a rotating friction plate where the extrudate is broken up into smaller cylinders with a length equal to their diameter and these plastic cylinders are rounded due to frictional forces. During Spheronization process different stages can be distinguished depending upon the shape

(e) **Drying:** A drying stage is required in order to achieve the desired moisture content. Drying rate also important an increase drying rate gave more porous pellets due to decrease pellet densification during that drying process

(f) Screening:

Screening may be necessary to achieve the desired size distribution, and for this purpose sieves are used

Layering Technique :

- This technique is further of two types: solution/suspension layering and powder layering
- In solution or suspension layering, powder feed material and other components are dissolved or suspended in the solvent. These solution or suspension is sprayed on the surface of the starter core and spread evenly as soon as it impinges on its surface.46 Spraying is followed by drying phase which allows dissolved material to get crystallized and thus between core and coating layer of the drug substance and among the consecutive layers of drug and polymers a solid bridges forms
- It has been demonstrated that drying method affects the structural and functional properties of pellets. Like fluidized bed drying increases the dissolution rate of pellets due to increase pore diameter whereas lyophilized pellets show increase dissolution due to increase porosity of pellets
- In powder layering, the seeds (e.g. sugar spheres) are charged into the pelletizer and on its surface; the binder liquid and the powdered feed material (drug+excipient) is sprayed tangentially. The powder is properly distributed on to the surface of seed along with the rolling movement of it which confirms its spherical shape. It involves successive deposition of fine powder (drug and other components) and on the surface of starting core with the help of bridging liquid
- Initially the drug particles get attached to the starter core with the help binding liquid that is sprayed on it; it forms a liquid bridge. Later on this liquid bridges gets replaced by the solid bridge which originates either from a binder in the solvent or from any material, that is soluble in the solvent medium.48 Conventionally coating pan was used for the manufacturing of pellets

Cryopelletization :

- Pellets were prepared by the utilization of Freeze drying method in this technique
- Here in this technique liquid nitrogen at -196°C is used as a fixing medium which causes freezing of droplet of liquid formulations into solid spherical particles which were then lyophilized to provide pellets. In this technique material gets freeze immediately and uniformly as a

result of rapid heat transfer between the droplets and liquid nitrogen. In the conventional freeze drier the pellets were dried. The total quantity of nitrogen required in this technique depends upon the temperature of the solution being fixed

Hot Melt Extrusion :

This method involves compaction and conversion of blend of powder into uniform shape product. Polymers were melted and forced these polymers and active ingredients along with other additives through an orifice or die that were placed under controlled temperature, pressure, screw speed etc, to form products of different shapes and sizes. Whole process can be classified into following steps:

1. Feeding of the extruder through a hopper
2. Mixing, grinding and kneading
3. Flow through the die, and
4. Extrusion from the die and further downstream processing

Freeze Pelletization :

- In this technique, a molten-solid carrier in which the drug is uniformly dispersed is allowed to enter as tiny droplets into an inert column of liquid in which the molten solid carrier is totally immiscible
- This droplet gets solidifies into spherical pellets. These pellets can move in either direction i.e. move upward or downward depending upon the density of the molten solid carrier with respect to the liquid in the column
- If the density of the molten-solid carrier is less than that of the liquid in the column then droplets are introduced from the bottom of the column, which then gets converted into solid pellets at the top portion of the column**.** Conversely, if the density of the molten-solid carrier is more than that of the liquid in the column then the droplets are introduced from the top of the column, and that gets solidify in the bottom portion of the column
- Melting point of solid carrier used for this process should be below 100ºC so that it remain in solid form at room temperature
- In order to prevent the blockage of the needles and also to maintain the homogeneity in shape and size of the pellets The viscosity of the drug matrix should be low. The optimum viscosity of the liquid in the column should range between 4 and 40 cP at 20ºC to obtain spherical pellets

MUPS (Multiple unit pellet system):

MUPS mainly emphasis on the final dosage form, if the multiparticulate were formulated into single-unit dosage forms such as filling them into hard gelatin capsules or compressing them into tablets these are called as MUPS

MUPS manufacturing process constitutes of 2 steps: (1) Pellets manufacturing and (2) Tablet containing pellets manufacturing.

Equipments for manufacture of pellet :

Mixer like sigma blade mixer, hexagonal mixer

Drying equipment like Fluidized Bed Dryer,spray dryer

Fluidized Bed processor

Freeze drying

Spheronizer

Coating pan, compression machine

References:

[1].The theory & practice of industrial pharmacy by Leon Lachman,H.A.Liberman,special indian edition 2009.

[2]Pharmaceutics, The science of Dosage form Design by Michael E.Aulton,second Edition 2002

[2].Modern Pharmaceutics by Gilbert S.Banker,Christopher T.Rhodes,fourth edition, Revised & Expanded, volume 121

[3] Indian pharmacopoeia, 2007 Edition

[4]International Research Journal of Pharmacy, 2013,4(4)-91-95

[5]International Journal of pharmaceutical sciences and Research, 2011; Vol. 2(6): 1337-1355

[6] Indian Journal of Pharmaceutical Education and Research 2016, Vol 50(3),146-160

Syllabus

Parenteral Products:

1. Definition, types, advantages and limitations. Preformulation factors and essential requirements, vehicles, additives, importance of isotonicity.
2. Production procedure, production facilities and controls, aseptic processing
3. Formulation of injections, sterile powders, large volume parenterals and lyophilized products.
4. Containers and closures selection, filling and sealing of ampoules, vials and infusion fluids. Quality control tests of parenteral products

Ophthalmic Preparations:

Introduction, formulation considerations; formulation of eye drops, eye ointments and eye lotions; methods of preparation; labeling, containers; evaluation of ophthalmic preparations.

Abbreviations: -

LVP: Large volume Parenteral

SVP: Small volume Parenteral

P: Partition coefficient

HEPA: High- efficiency Particulate Air

LAL Test: Limulus Amebocytes Lysate test

BET: Bacterial Endotoxin Test

IPC: In-Process Control

WFI: Water for Injection

RH: Relative Humidity

FTM: Fluid Thioglycolate Medium

SCM: Soyabean-casein digest Medium

1. Definition:

The term Parenteral has been derived from the Greek word **Para enteron**, which means outside the intestine**.** These are unique dosage forms as they are administered by injecting directly into the body tissues through skin and mucous membranes**.**

Parenteral products are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multi dose containers.

Types Parenteral Products:

The types of Parenteral products are based on Volume and the state of product according to USP.

Based on Volume:

- SVP – An injection that is packed in containers labeled as containing 100 ml or less.
- LVP – These are parenterals designed to provide fluid, calories and electrolytes to the body and the volume is more than 100ml.

Based on States of products:

- Injection: Injections contain sterile solutions and are prepared by dissolving the active ingredient and other substances in Water for Injection or other suitable non-aqueous base or a mixture of both. The solution to be injected may show sediments which can be dispersed easily by shaking the container. The suspension should remain stable in order to deliver a homogenous dose whenever withdrawal is made from the container.
- Infusions**:** These parenteral preparations are composed of sterile aqueous solution with water as its continuous phase. The preparations are free from bacterial endotoxins or pyrogens and are made isotonic with blood. They do not contain any antimicrobial preservatives.
- Powder for Injection: These are sterile solid compounds that are distributed in their final volume when the vial or container is shaken to form a clear particle-free solution.
- Concentrated Solutions for Injections**:** The concentrated solutions are diluted with water for injection before they are administered through injection or through intravenous infusion.
- Implants: These solid sterile preparations are implanted in the tissue in order to release the active ingredient for long periods. They are stored in sterile containers individually.
- Injectable Emulsion: These are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium. These products provide essential fatty acid and vitamins.
- Oily Injection: These are used to prepare parenteral controlled release dosage forms.

Advantages of Parenteral:

a) Parenteral products can By passes pre systemic or first pass metabolism and the Onset of action is quick

b) The drugs, which cannot be administered orally, can be administered by this route.
c) The patients who are vomiting or unconscious cannot take drug by oral route. In such cases, the drug can be administered by this route.
d) The drug action can be prolonged by modifying the formulation.
e) This route can deliver transfusion fluids containing nutritives like glucose and electrolytes such as sodium chloride.

Limitations:

a) Injection causes pain at the site of injection.
b) The trained persons are required to administer the drug.
c) The administration of drug through wrong route of injection may prove to be fatal.
d) It is difficult to save a patient when over dose is given.
e) There are chances of sensitivity reaction or allergic reaction of a drug by an individual. These reactions are sometimes fatal and lead to death.

Preformulation factors and essential requirements:

Preformulation involves the study about physical & chemical properties of drug substance prior formulation. These studies are performed under stressed conditions of temperature, humidity; light and oxygen so that the reactions are accelerated and potential reaction are detected. A few physicochemical properties that affect a drug substance are discussed below.

- **Melting point:** It is the Temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity.
- **Solubility**: This property is essential for developing solution to be injected either intraveneously or intramuscularly. It is a function of chemical structure: salts of acid or bases are the drugs that can achieve the desired degree of water solubility.
- **Molecular structure and weight**: These are the basic characteristics of the drug from which the potential properties and reactivities of functional groups can be determined.
- **Particle Size and Shape**: Study of particle size give information about Solubility, dissolution rate and absorption etc.These charcterstics are determined by Scanning electron microscope or an optical microscope with polarizing attachments.
- **Ionisation constant**: This property is used to determine the P^H-dependent solubility of a compound.Potentiometric PH titration or PH-solubility analysis is used for determining the P^{Ka} value.Ionisation constant of a compound also helps in determining the degree of ionization of an acid or base. Degree of ionization depends upon the P^H.
  For acidic drugs P^{Ka} ranges from 3-7.5 and for basic drugs P^{Ka} ranges from 7- 11.
- **Partition Coefficient (P);** It is a ratio of equilibrium concentration of drug in aqueous and oily phases in contact with each other at a constant temperature. Partition coefficient can be expressed as : $P = [C_{oil} / C_{water}]$,where, C_{oil}= organic phase concentration and C_{water} = aqueous phase concentration.

- **Hygroscopicity:** The tendency of a solid to take up water from atmosphere, as it is subjected to a controlled RH programe under isothermal condition. A high degree of hygroscopicity can adversely affect the physical and chemical properties of a drug substance.

Essential requirements for Formulation: The formulations of parenteral preparations need careful planning, thorough knowledge of medicaments and additives to be used. The excess use of additives in parenteral products should be avoided as some of these may interfere with the drug. In the preparation of parental products, the following substances are added to make a stable preparation.

1. Vehicles
2. Additives

a) Solubilizing agents b) Stabilizers c)Buffering agents d) Antibacterial agents e) Chelating agents f)Suspending ,emulsifying and wetting agents g)Tonicity factors

1. <u>Vehicles:</u>

There are two types of vehicles, which are commonly used for the preparation of injections

A) Aqueous vehicle - water is used as vehicle for majority of injections because water is tolerated well by the body and is safest to administer .The aqueous vehicle used are ;-

1) Water for injections.
2) Water for injection free from CO2 (carbon dioxide)
3) Water for injection free from dissolved air, water for injection is sterile water, which is free from volatile, non- volatile impurities and from pyrogens.

Pyrogens are by-product of bacterial metabolism. pyrogens are Lyposaccharide, thermostable, soluble in water ,unaffected by bactericide and can pass through bacterial proof filters. pyrogens can be removed from water by simple distillation process using an efficient trap which prevents the pyrogen to enter into the condenser .immediately after the preparation of water for injection ,it is filled in to the final container, sealed and sterilized by autoclaving .

Water for injection, contaminated with pyrogens may cause rise in body temperature if injected .Hence, test for pyrogen is done to ensure that water for injection is free from pyrogens.

B) Non -aqueous vehicles:-The commonly used non-aqueous vehicles are oils and alcohols.

Fixed oil, such as arachis oil,cottonseed oil ,almond oil and sesame oil are used as vehicle .the oily vehicles are generally used when a depot effect of drug is required or the medicaments are insoluble or slightly soluble in water or the drug is soluble in oil example dimercaprol injection by using arachis oil as vehicle.

Ethyl alcohol is used in the preparation of hydrocortisone injection .hydrocortisone is insoluble in water, hence the solution is made in 50% alcohol .Alcohol causes pain and tissue damage at the site of injection. Therefore, it is not used commonly.

Propylene glycol is used as a vehicle in the preparation of digoxin injection .it is relatively non-toxic but it causes pain on S/C or I/M injection.

Sometime polyethylene glycol and glycerine usually diluted with sterile water are used to prepare solutions for injections .they are used as solvent as well as to increase the stability of certain preparations.

2. Additives:

These substances are added to increase the stability or quality of the product .These additives should be used only when it is necessary to use them. While selecting the additives, care must be taken that they should be compatible both physical and chemical with the entire formulation, .They should be added in minimum possible quantity .The following additives are commonly used in preparing stable parental preparations.

a) Solubilising agents:- These are used to increase the solubility of drugs which are slightly soluble in water .the solubility of drug is increased by using surface active agent like tweens and polysorbate or by using co solvents.

b) Stabilizers:- The drugs in the form of solution are more liable to deteriorate due to oxidation and hydrolysis .The stabilizers are added in the formulation to prevent this .the oxidation can be prevented by adding a suitable antioxidant such as, thiourea,ascorbic acid ,sodium metabisulphite ,or the product is sealed in an atmosphere of Nitrogen or Carbon dioxide. hydrolysis can be prevented by using a non-aqueous vehicle or by adjusting the pH of the preparation.

Antioxidants:

Water soluble: Sulfurous acid salts, Ascorbic acid isomers, Thiol derivatives

Oil soluble; Propyl gallate ,Butylated hydroxyanisole ,Ascorbyl palmitate, alpha Tocopherol

c) Buffering agents: -The degradation of the preparation, which is due to change in pH, can be prevented by adding a suitable buffer to maintain the desired P^H .

pH	Buffer system	Concentration (%)
3.5-5.7	Acetic acid-acetate	1-2
2.5-6.0	Citric acid- citrate	1-5
6.0-8.2	Phosphoric acid- phosphate	0.8-2
8.2-10.2	Glutamic acid- glutamate	1-2

d) Antibacterial agents:- These substance are added in adequate quantity to prevent the growth of microorganism during storage. so these substances act as preservatives .antibacterial agents are added in single dose containers, where parenteral products are sterilized by filtration method and in multi dose containers to prevent microbial contamination .

Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.-

Benzyl alcohol (0.9% to 1.5%)

Methylparaben (0.18% to 0.2%)

Propylparaben (0.02%)

Benzalkonium chloride (0.01% to 0.02%)

Thiomersal (0.001% to 0.01%)

f) **Chelating agent: -** Chelating agents such as EDTA (Ethylene diamine Tetra acetic acid) and its salts, sodium or pottasium salts of citric acid are added in the formulation,to chelate the metallic ions present in the formulation. They form a Complex which gets dissolved in the solvent.

S. No.	Additives	Concentration range (%)
1	EDTA disodium	0.00368-0.05
2	EDTA calcium disodium	0.04
3	EDTAtetrasodium	0.01

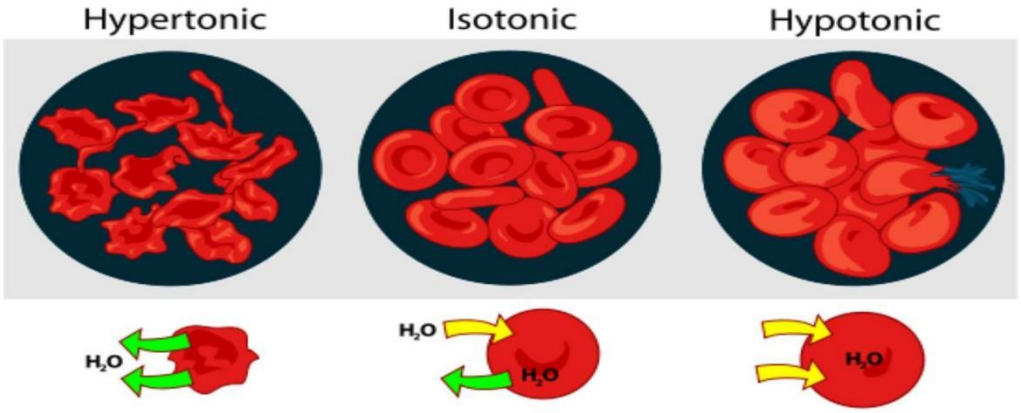
g) **Suspending, emulsifying and wetting agents:-** The suspending agents are used to improve the viscosity and to suspend the particles for a long time. Methyl cellulose, carboxy-methyl cellulose, gelatin and acacia are commonly used as suspending agents .Emulsifying agents are used in sterile emulsions .for this purpose lecithin is generally used .The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps. They also act as antifoaming agents to subside the foam produced during shaking of the preparation.

Additives	**Concentration range (%)**
Polyethylene glycol 300	0.01-50.0
Polysorbate 20	0.01
Polysorbate 40	0.05
Polysorbate 80	0.04-4.0
Povidone	0.2-1.0
Propylene glycol	0.2-50.0
Sorbitan monopalminate	0.05
Dimethylacetamide	0.01
Lecithin	0.5-2.3

h) **Tonicity factors:** - Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, dextrose and boric acid etc. in suitable quantities. These substances should be compatible with other ingredients of the formulation. Examples of Tonicity adjuster/modifier are Glycerin, lactose, mannitol, dextrose, NaCl, sodium sulfate and sorbitol

Importance of Isotonicity:

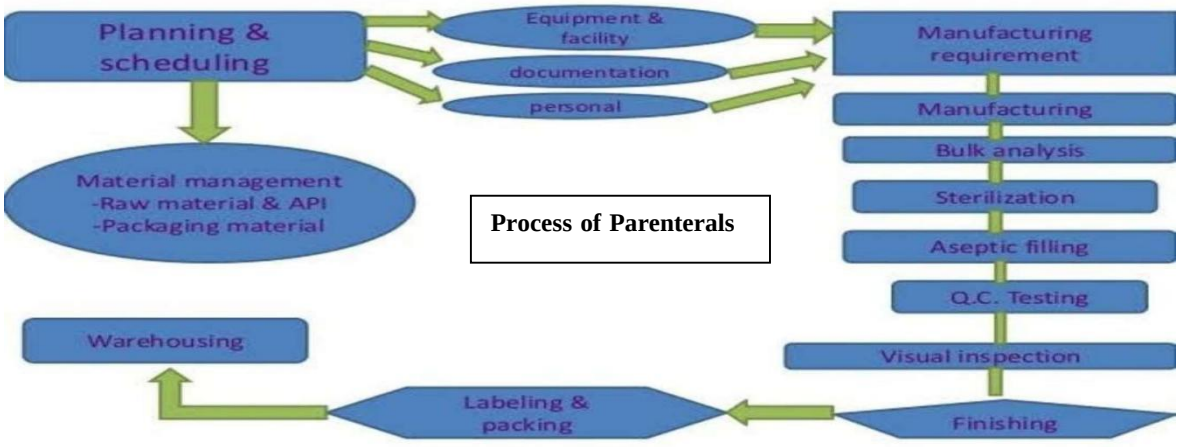
An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.Isotonicity is important for parenteral preparation because if the solution is isotonic with blood, the possibility of product penetrating the RBC and causing haemolysis is reduced. For hypertonic solution crenation and for hypotonic solution haemolysis will occur.



Crenation **Hemolysis**

2. Production procedure - Aseptic processing:

- The parenteral drug manufacturing (Drug Product Manufacturing) process includes compounding, mixing, filtration, filling, terminal sterilization, lyophilization, closing, and sealing, sorting, and inspection, labeling, and final packaging for distribution.
- The manufacturing process is complicated; requiring organization and control to ensure the product meets the quality and the specifications as shown in.
- Aseptic processing requirement adds more complication but assures that all dosage forms manufactured are free from any contamination of microbial, endotoxin, and visible particulate matter.
- The manufacturing process initiates with the procurement of approved raw materials (drug, excipients, vehicles, etc.) and primary packaging materials (containers, closures, etc.) and ends with the sterile product sealed in its dispensing package.



The manufacturing of parenterals involves the following steps;

1) Cleaning and washing of containers and closures
2) Preparation of solutions
3) Sterilization
4) Filling and sealing
5) Evaluation of parenterals
6) Packaging and labeling

1. **Cleaning of containers and closures:** - all the containers, closures and equipments which are required during the preparation of parental products are thoroughly cleaned with detergent and washing is done with tap water , followed by clean distilled water and finally rinsed with water for injection. Rubber closures are washed with hot solution of 0.5 % sodium pyrophosphate in water. The closures are then removed from the solution, washed with water followed by rinsing with filtered water for injection .on a small scale washing is done manually but on a large scale automatic washing machines are used.
2. **Preparation of Solution:-** The various ingredients of the formulation of parental preparations are weighed and collected in the preparation room. the raw materials required in the preparation of parenteral products should be pure. water for injection free from pyrogens and microorganisms are used in preparation of parenteral products. The Industrial pharmacist should decide the order of mixing and exact method of preparation to be followed before preparing the parenteral products . The parenteral preparation must be prepared under strict aseptic conditions . The ingredients are accurately weighed separately and dissolved in the vehicle as per method of preparation to be followed. The parenteral Solutions so formed is passed through bacteria proof filter ,such as ,filter candle, seitz filter, membrane filter, and sintered glass filters. the primary objective of filtration is to clarify the solution by removing foreign particles .if the parenteral preparations are required to be sterilized by means of bacteria proof filters, filtration should be done under strict aceptic condition to avoid contamination of filtered solution, before it is finally transferred into final container and sealed
3. **Sterilization**:-The parental preparations should be immediately sterilized after sealing in its final containers. The sterilization is done by any one of the methods of sterilization, which depends on the nature of Medicaments present in the parenteral preparations.

   For thermostable medicament ,the parenteral product are sterilised either by autoclaving at the temperature of 115°C to 116°C for 30 minutes or 121 degree centigrade for 20 minutes or in hot air oven at 160 degree centigrade for 2 hours. the thermolabile preparations are sterilized by filtration through a suitable bacteria proof filters. parenteral preparations which are sterilised by filtration method may contain a suitable bacteriostatic agent to prevent the growth of microorganisms .When the solutions are used for intravenous or intrathecal injection in doses exceeding 15 ml ,the bacteriostatic agent should not be used. The sterilised product is filled into the final containers and sealed .the process of filtration, filling and sealing are done under aseptic conditions.

4. **Filling and Sealing:-** The filtered product is filled into final container such as, ampoules, vials and transfusion bottles, which are previously cleaned and dried. ampoules are used for feeling single dose whereas , vials are used for filling multidoses .bottles are meant for filling transfusion fluids . On small scale feeling is done manually by using hypodermic syringe and needle .on the large scale feeling is done by automatic filling machine.The sterile Powders are filled into containers by individual weighing or by using automatic or semi automatic devices. The filling operation is carried out under strict aseptic precautions. During the filling of ampoules, the care should be taken that the solution should be filled below the neck of ampoules and the solution should not touch the neck of ampoules. this will prevent the cracking and stanining of the neck of ampoules at the time of Sealing. Sealing should be done immediately after filling .Ampoules are sealed manually on a small scale by rotating the neck of the ampoule in the flame of Bunsen burner but on a large scale ampoule sealing machine is used in which tip of ampoule is used to fused to seal it . The vials and transfusion bottles are sealed by closing its opening with rubber closures .The rubber closures are held in place by crimping the aluminium caps which is done manually or by mechanical means.
5. **Evaluation of Parenterals:-** The finished parenteral products are subjected to the following test ,in order to maintain quality control.

   a) Sterility test b) clarity test c) Leakage test d)Pyrogen test.

6. **Packaging and labeling:-** After evaluation of the parenteral preparation,the ampoules ,vials and transfusion bottles are properly labelled and packed. The label should state as :-

   a) Name of the preparation
   b) Quantity of the preparation
   c) Mfg.Lic .no.
   d) Batch no.
   e) Date of manufacture
   f) Date of expiry
   g) Storage condition
   h) Retail price
   i) Manufacturer's address

Production facilities and controls:

The production area where the parenteral preparations are manufactured can be divided into the following five sections.

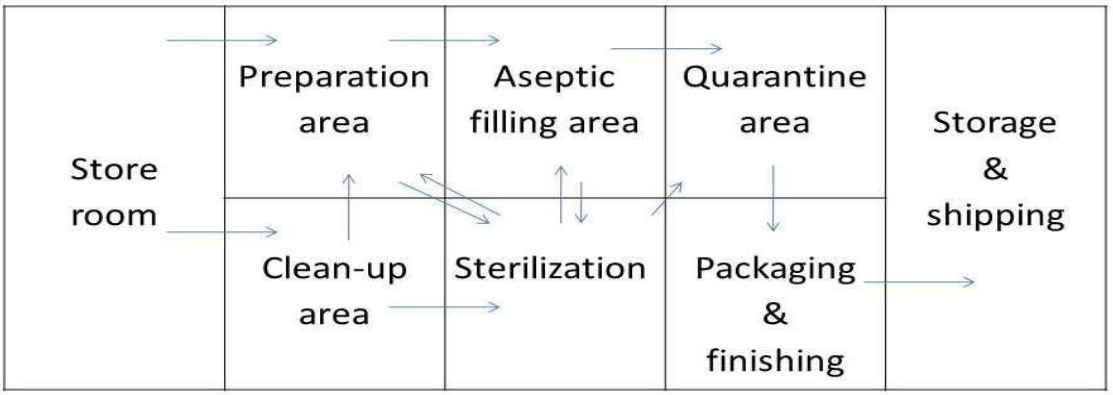
1) Clean-up area
2) Preparation area
3) Aseptic area
4) Quarantine area
5) Finishing & packaging area

1. Clean-up area:

- It is not aseptic area.
- All the parenteral products must be free from foreign particles & microorganism.
- Clean-up area should be withstand moisture, dust & detergent.
- This area should be kept clean so that contaminants may not be carried out into aseptic area.

2. Preparation area:

- In this area the ingredients of the parenteral preparation are mixed & preparation is made for filling operation.
- It is not essentially aseptic area but strict precautions are required to prevent any contamination from outside.



3. Aseptic area:

- The parenteral preparations are filtered, filled into final container & sealed in aseptic area.
- The entry of personnel into aseptic area should be limited & through an air lock.
- Ceiling, wall & floor of that area should be sealed & painted.
- The air in the aseptic area should be free from fibers, dust and microorganism.
- The High efficiency particulate air filters (HEPA) is used for air.
- UV lamps are fitted in order to maintain sterility.

4. Quarantine area:

- After filling, sealing & sterilization the parenteral product are held up in quarantine area.
- Randomly samples were kept for evaluation.
- The batch or product pass the evaluation tests are transfer in to finishing or packaging area.

5. Finishing & packaging area:

- Parenteral products are properly labelled and packed.
- Properly packing is essential to provide protection against physical damage.
- The labelled container should be packed in cardboard or plastic container.
- Ampoules should be packed in partitioned boxes

Controlled environment required for parenteral preparation:

Clean Room Classified Areas: Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments (clean rooms) in which these products are manufactured. The Critical and General area of clean room: The clean room divides into

1. Critical Area
2. General Area.

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area often protected by localized laminar flow clean benches and workstations. The General area is the rest of the clean room where contamination will not gain direct entry into the product but should be kept clean because of the transfer of contamination into the critical area. It is necessary that the critical area be cleaned most often with the best cleaning ability without introducing contamination.

Classification of Clean Rooms:-

The class is directly related to the number of particles per cubic foot of air equal to or greater than 0.5 micron.

1. Class 100,000: Particle count not to exceed a total of 100,000 particles per cubic foot of a size 0.5µ and larger or 700 particles per foot of size 5.0µ and larger.
2. Class 10,000: Particle count not to exceed a total or 10,000 particles per cubic foot of a size 0.5µ and larger or 65-70 particles per cubic foot of a size 5.0µ and larger.
3. Class 1,000: Particles count not to exceed a total of 1000 particles per cubic foot of a size 0.5µ and larger or 10 particles per cubic foot of a size 5.0µ and larger.
4. Class 100: Particles count not to exceed a total of 100 particles per cubic foot of a size 0.5µ and larger.

Class1: The particle count shall not exceed 3000 particles/m3 of a size 0.5µ.

Class 2: The particle count shall not exceed a total of 3000 particles/m3of a size of 0.5µ or greater; 2000 particles/m3of size 0.5µ or greater; 30 particles of a size 10µ.

Class 3: The particle count shall not exceed a total of 1,000,000 particles of a size of 1µ or greater; 20,000 particles/m3of size 5µ or greater; 4000 particles/m3of a size 10µ or greater; 300 particles of a size of 25µ or greater.

Class 4: The particle count shall not exceed a total of 200,000 particles of a size of 5µ or greater.

For the manufacture of sterile medicinal products normally 4 grades can be distinguished:

GRADE — 'A': The local zone for high risk operations. eg. filling zone, stopper bowls, open ampules and vials. GRADE — 'B': In case of aseptic preparation and filling, the back ground environment for grade — 'A' zone. GRADE — 'C' & 'D': Clean areas for carrying out less critical stages in the manufacture of sterile products.

Aseptic processing:-

The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which, whenever possible products intended to be sterile should be terminally sterilized by heat in their final container. Where it is not possible to carry out terminal

sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision should be taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing. Sterilization can be achieved by the use of moist or dry heat, by irradiation with ionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: the environment, personnel, critical surfaces, container/closure sterilization and transfer procedures, the maximum holding period of the product before filling into the final container and the sterilizing filter. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment. Filtration alone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is preferred.

3. Formulation of injections (Solution and suspension):-

Solutions:

A range of excipients may be included in parenteral solutions, including antioxidants, antimicrobial agents, buffers, chelating agents, inert gases, and substances for adjusting tonicity. Antioxidants maintain product stability by being preferentially oxidized over the shelf life of the product.

Antimicrobial preservatives inhibit the growth of any microbes that are accidentally introduced while doses are being withdrawn from multiple-dose bottles and act as adjuncts in aseptic processing of products.

It is Prepared by dissolving the drug and preservative, adjusting the pH and sterile- filtering the resultant solution through a 0.22 μm membranes filter. Drug solutions that resist heat are terminally autoclave sterilized after filling; this assures product sterility and package.

Suspension

A **suspension** for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for0.5-30% of the suspension. The vehicle may be aqueous, oil, or both.

- Caking of injectable suspensions is minimized through the production of flocculated systems, comprising clusters of particles (flocs) held together in a loose open structure.
- Excipients in injectable suspensions include antimicrobial preservatives, surfactants, dispersing or suspending agents, and buffers.
- Surfactants wet the suspended powders and provide acceptable syringeability while suspending agents modify the viscosity of the formulation.

General steps in manufacturing:

- Sterilization and milling of active ingredient (s).
- Sterilization of vehicle.
- Aseptic wetting and dispersion of the active ingredient (s).
- Aseptic milling of the bulk suspension.
- Aseptic filling of the bulk suspension in suitable containers

Formulation of sterile powders:-

Due to instability in water, many drugs are formulated as drug powders to be reconstituted prior to administration. eg.Penicillins, barbiturates, benzocain. Sterile water for injection is supplied with dry powders to make "solutions / or suspensions for injections". The obtained solution / suspension will meet with all the requirements of solution /suspension for parenteral. IV or IM route can give reconstituted solutions, however suspension is forbidden for IV administration.

Sterile powers are prepared by following methods.

1. Sterile recrystallization:
2. Lyophilization:
3. Spray drying

1. **Sterile Re-crystallization**: The drug is dissolved in a solvent and the obtained solution is sterilized through 0.22 μm membrane filter. A sterile anti-solvent is then added to crystalize the drug particles, which is filtered and dried aseptically.

   Advantages:

   This method is Flexible and economic.

   Disadvantage:

   This method represents variations from batch to batch and contamination.

2. **Lyophilization:** In this method, a solid substance is separated from solution by freezing the solvent and evaporating the ice under vacuum. The obtained drug solution is sterile filtered into sterile trays, which are aseptically loaded into a freeze dryer. The solution is then frozen at -50°C and then dried by vacuum to separate the drug powder.

   Advantage:

   This method involves removal of water at low temperatures.

   Disadvantage:

   i) In this method, the biological molecules are damaged by the stress associated with freezing, and drying.

   ii) This method is expensive and time consuming

3. **Spray drying**: In this method, the solution of the drug is sprayed into a dry chamber where it comes in contact with a hot steam of a sterile gas 80-100 °C temperature.

Advantage:

i) This method is Simple, Economical, scalable and faster.

ii)This method involves Coating of particles during drying prolonged release.

Disadvantage:

i) In this method, the high processing temperatures and high shear forces can easily damage drugs.
ii) In this method, higher levels of drugs are lost in comparison to freeze-drying.
iii) This method has a limited solvent choice for a given drug.
iv) In this method, product cannot be prepared directly in vials or plates.

Formulation of large volume parenterals: -

Large volume injections are intended to be administered by IV Infusion Fluids & are included in the group of sterile products & are known as large volume Parenterals. These consist of single dose injecting a volume of 100 ml or more than 100 ml sometimes additional drugs are added to them by either injecting svp to the administration sets or by piggyback method(small volume infusion of an additional drug is added to the intravenous delivery system).large volume parenteral products include:

1) Infusion fluid(Basic nutrition -Dextrose inj, Fluid replacement therapy-Normal saline)
2) Total parenteral Nutrition solution(TPN)
3) Intravenous antibiotics
4) Dialysis fluid
5) Irrigation solutions

Large volume parenterals should be terminally heat sterilized. Apart from water for injection as the main component, other ingredients that should be included are carbohydrates (e.g. dextrose, sucrose and dextran), amino acids, lipid emulsion, electrolytes (Nacl) and glycerol, sorbitol and mannitol.The LVP are mostly clear solutions, except for the oil- in –water emulsions. The emulsions for infusion are produced by highly specialized method as they are destabilized by heat. This result in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilization.

Production of LVP:

i) The manufacturing and filling of LVP fluids into containers are carried out in a a high standard clean room environment. High standards are required to prevent these products from getting contaminated with organisms, pyrogens and particulate matter.
ii) The fluids from a bulk container are filled into the product container using high speed filling machine. Before filling the fluid into the container, it is passed through an in-line membrane filter to remove the particulate matter.
iii) After filling, the neck of each glass bottle is immediately sealed with a tight fitting rubber closure held in place with a crimped aluminum cap.
iv) In case plastic bags are used, the pre-formed plastic bags are aseptically filled and heat-sealed immediately.
v) Blow –fill-seal system are adopted to minimizes the problems with product handling, cleaning and particulate contamination.

vi) The LVP products, including irrigation solution and dialysis fluids should be moist heat sterilized immediately after the containers are filled.

Lyophilization or freeze-drying:-

Lyophilization or freeze drying is a process in which water is removed from a product after it isfrozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes like; Freezing, Primary drying (sublimation), and Secondary drying (desorption).

Advantages of Lyophilization

- Ease of processing a liquid, which simplifies aseptic handling.
- Enhanced stability of a dry powder.
- Removal of water without excessive heating of the product.
- Enhanced product stability in a dry state.
- Rapid and easy dissolution of reconstituted product

Disadvantages

- Increased handling and processing time.
- Need for sterile diluent upon reconstitution.
- Cost and complexity of equipment

Steps involved in formulation of Lyophilized products:-

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22-micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers. There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products.

- Additionally, inspections have disclosed potency, sterility and stability problems associated with the manufacture and control of lyophilized products

4. Selection of containers and closures:

Selection of Containers & Closures should be such that it should ensure that the products must remain its purity, potency & quality during intimate contact with the container throughout its shelf life.

Glass:-

Glass is employed as the container material of choice for most SVIs. It is composed, principally, of silicon dioxide, with varying amounts of other oxides, such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. Glass is preferred for clarity reasons

Types:-

The USP provides a classification of glass:

- Type I, a borosilicate glass;
- Type II, a soda-lime treated glass;
- Type III, a soda-lime glass; and
- NP, a soda-lime glass not suitable for containers for parenteral.

Type I glass will be suitable for all products, although sulfur dioxide treatment is sometimes used for even greater resistance to glass leach-ables. Because cost must be considered, one of the other, less expensive types may be acceptable.

Type II glass may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass.

Type III glass is usually suitable for anhydrous liquids or dry substances.

Types II and III glass compounds are composed of relatively high proportions of sodium oxide (~14%) and calcium oxide (~8%). This makes the glass chemically less resistant. Both types melt at a lower temperature, are easier to mold into various shapes.

Type II glass has a lower concentration of the migratory oxides than Type III. In addition, Type II has been treated under controlled temperature and humidity conditions, with sulfur dioxide or other de alkalizers to neutralize the interior surface of the container.

The glass types are determined from the results of two USP tests:

The Powdered Glass Test

The Water Attack Test.

The Powdered Glass Test challenges the leaching potential of the interior structure of the glass, whereas the Water Attack Test challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation. Glass can be the source / cause of leach-ables / extractable, particulates (glass deamination or glass lamellae formation), adsorption of formulation components, especially proteins, and cracks / scratches.

Plastic:-

Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Plastic bottles for large volume injectable (LVIs) have been used for many years. Plastic vials for SVIs may be a wave of the future plastic packing offers such advantages of cost savings elimination of the problems caused by breakage of glass and increase convenience of use. Plastics are light weight, less fragile & easy to handle but not clear as that of glass.

Rubber:-

Rubber formulations are used as rubber closures, rubber plungers and other applications. The most common rubber polymers used in SVIs closures are natural and butyl rubber. Silicone and neoprene also are used but less frequently in sterile products. Butyl rubber has great advantages over natural rubber in that butyl rubber requires fewer additives, has low water vapor permeation properties and has good characteristics with respect to gaseous permeation reactivity with the active ingredient.

Rubber permits the entry of hypodermic needle into injection vials & also provide resealing of the vial after needle is withdrawn.

Filling and Sealing of Ampoules:-

Ampoules are thin-walled glass containers, which after filling, are sealed by either tip sealing or pull sealing. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filed – in product is in contact with glass only and the packaging is 100% tamper proof. The break system OPC(one –point cut) or the color break ring offer consistent breaking force. There are wide variety of ampoule types from 0.5 to 50ml volume.

- Here, the measured amounts of liquid deliver from the small orifice into the ampoule by filling machine.
- The size of the delivery tube is governed by opening in the container to be used, the viscosity and density of the liquid and the speed of delivery desired.
- The tube must free enter the neck of the container and deliver the liquid deep enough to permit air to escape without sweeping the entering liquid into the neck or out of the container.
- Filling machine parts should be constructed of non-reactive materials such as borosilicate glass or stainless steel.
- The solutions are usually filled in the bottle by gravity, pressure or vacuum filling device.
- Emulsion and suspension required specially designed filling equipment because of their high viscosity.
- Powders such as antibiotics, are more difficult to subdivide accurately and precisely into Individual dose containers than are liquid.
- Container should be sealed in the aseptic area in immediately adjacent to the filling machine.
- It is obvious that a sterile container that has been opened can no longer be considered to

be sterile. Therefore, temperature proof sealing is essential.

- Ampoules may be closed by melting a portion of the glass of neck to either form tip-seals or pull seals.
- **Tip-seals** are made by melting sufficient glass at the tip of the ampoule neck to form a bead of glass and close the opening. This is performed in a high temperature gas oxygen flame.
- **Pull-seals** are made by heating the neck of a rotating ampoule below the tip, then pulling the tip away to form a small, twisted capillary just prior to being melted closed. Pull sealing process is slower one, but the sealing done by this is more secure than that of tip sealing.
- Excessive heating of air and gasses in the neck causes expansion against the soft glass with the formation of fragile bubbles at the point of seal.

Filling and Sealing of Vials and Infusion bottle:-

The solutions, which sterilized through filtration, are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill. A liquid is more easily exposed uniformly into the container having the narrow mouth than is used for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling. The filling of liquids into containers with high accuracy involves the following methods

i) Volumetric filling

ii) Time/pressure filling

Volumetric filling machines have pistons or peristaltic pumps. These are most common used method. Time-pressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism.

By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly. This should be done by after filling with care, to prevent the contamination of the contents inside. Increased chances for contamination are the large opening in the vials than the ampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow. By using the aluminum caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole through the closure. A 500ml of infusion bottle is considered suitable for preparation of parenteral solutions. It is assumed that the bottle has been stored with a double cap protecting the mouth. The outer cap is discarded and the inner cap is removed. After ensuring that the bottle neck is not chipped, the solution is poured in and immediately the inner cap is replaced.

Quality Control Tests of Parenteral Products:-

The following are the evaluation test for the parenteral. They are as follows.

1. Sterility test
2. Clarity test
3. Leakers test
4. Pyrogen test

1. Sterility test: It is a method carried out to detect confirm absence of any viable form of microbes in product. The method used for sterility tests are

a. Direct transfer method

b. Membrane filtration method.

a. Direct transfer method: Open each sample container and with draw the require amount of the sample. Inject one-half of sample in a test tube containing fluid Thioglycolate Medium (FTM). Inject another half in the test tube containing Soyabean-casein digest Medium(SCM). Volume of the medium must be sufficient to promote and expedite microbial growth. Adequate mixing between the sample inoculums and the culture medium must take place to maximize interaction and facilitate microbial growth. If the product to be tested contains any anti-microbial agent, using suitable reagent it should be neutralized before the test.

b. Membrane filtration method (MF): This method is employed in the following cases:

1. Oil & oily preparations
2. Alcoholic preparations
3. For preparations miscible with or soluble in aqueous or oily solvents.

The steps involved in MF sterility test method are

i). The filter unit must be properly assembled and sterilized prior to use.

Ii). The contents are transferred to the filter assembly under strict aseptic conditions.

iii) The membrane is removed aseptically.

iv). Membrane is cut in half.

iv) One half is place in suitable volume of FTM and another in an equal volume of SCM.

Interpretation of results:

i). If there is no visible evidence of microbial growth, it may be interpreted that the sample is without intrinsic contamination and the product complies the test for sterility.

ii). If microbial growth is found, the product does not complies the test for sterility and the sterility test may be repeated.

2. Clarity test (particulate matter evaluation):-

Particulate matter in parenteral solutions has been recognized as an acceptable. Since the user could be expected to conclude that the presence of visible dirt would suggest that, the product is of inferior quality.

a). ***In visual method***, the entire product should be inspected by human inspectors under good light baffled against reflection into the eye and against black and white background. Dark background detects light particles and light background detects dark particles. Any container with visible particle if seen is discarded.

b). ***In Coulter counter method***; the principle is based on that there will be an increase in the resistance as a particle approaches and passes through the orifice (2 electrodes).

c). This method require destruction of the product unit since an electrolyte is added to the preparation before its evaluation.

d). Some other methods of clarity testing can be listed as Filtration method, Light scattering method, Light absorption, Light blockage methods, etc...

e). Once the particles are detected, then they are identified by various methods like microscopy,X-ray powder diffraction, mass microscopy, micro-chemical tests, polarized light microscopy and scanning electron microscopy.

3. Leakers test:-

Leaker test for ampoules is intended to detect incompletely sealed ampoules so that they can be discarded in order to maintain sterile condition of the medicines. Open capillaries or cracks at the point of seal result in LEAKERS.

- The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 inches of vaccum for a minimum of 15 mins.
- Detection of leaker is prominent when ampoules are immersed in a bath of dye during autoclaving as this has advantage of acomplishing both leaker detection and sterilization in one operation.
- Another means of testing for leakers is a high frequency spark test system, which detect presence of pinholes in ampoules.
- Bottles and vials are not subjected to such a vaccum test because of the flexibility of the rubber closure.

4. Pyrogen test:-

Pyrogens are the metabolic products of microbes. Most bacteria, moulds and viruses produce Pyrogen. Most potent pyrogenic substance called endotoxins are produced by gram negative bacteria .Pyrogens when injected into a human, shows marked rise in the temperature , chills, body aches, cutaneous vasoconstriction and increased arterial blood pressure. The most likely source of pyrogens are water, contaminated solutes and containers.

- The test involves measurement of the rise in body temperature of rabbits following the IV injection of a sterile solution into ear vein of rabbit.
- Dose not exceeding 10 ml per kg injected intravenously within a period of not more than 10 mins.
- Selection of animals - healthy, adult, not less than 1.5kg.
- Equipment and material used in test - glassware, syringes, needles.
- Retaining boxes - comfortable for rabbits as possible.
- Thermometers - standardized position in rectum, precision of 0.1°C.

Preliminary Test (Sham Test):

If animals are used for the first time in a pyrogen test or have not been used during the 2 previous weeks, condition them 1 to 3 days before testing the substance by injecting IV 10ml per kg

pyrogen free saline solution warmed to about 38.5°c. Record the temperature of the animals, beginning at least 90 mins before injection and continuing for 3 hours after injection. Any animal showing a temperature variation of 0.6° or more must not be used in main test.

Main Test:

The main test is carried out by using a group of 3 Rabbits. Dissolve the substance in,or dilute with, pyrogen free saline solution. Warm the liquid to approximately 38.5° before injection.Inject the solution under examination slowly into the marginal veins of the ear of each rabbit over a period not exceeding 4 mins. Record the temperature of each animal at half hourly intervals for 3 hours after injection. The difference between the initial temperature and the maximum temperature which is the highest temperature recorded for a rabbit is taken to be its response.

Interpretation of Result:

a). The test is carried out on the first group of 3 rabbits; if necessary on further groups of 3 rabbits to a total of 4 groups, depending on the results obtained.

b). Intervals of passing or failing of products are on the basis of summed temperature response. If the difference is negative, the result is counted as zero response.

No. of Rabbits	**Individual Temp. Rise(^oC)**	**Temp. Rise in group (^oC)**	**Test**
3 Rabbits	0.6	1.4	Passes
(If above not Passes)-: 3+5=8 Rabbits	0.6	3.7	Passes
If above Test not passes,the sample is said to Pyrogenic.			

Bacterial Endotoxin Test (BET) or Limulus Amoebocyte Lysate Test (LAL Test):-

The bacterial endotoxin test (BET) is a test to detect or quantify endotoxins from gram negative bacteria using Amoebocyte lysate from the horse shoe crab (Limulus polyphemus or Tachypleustridentatus) .

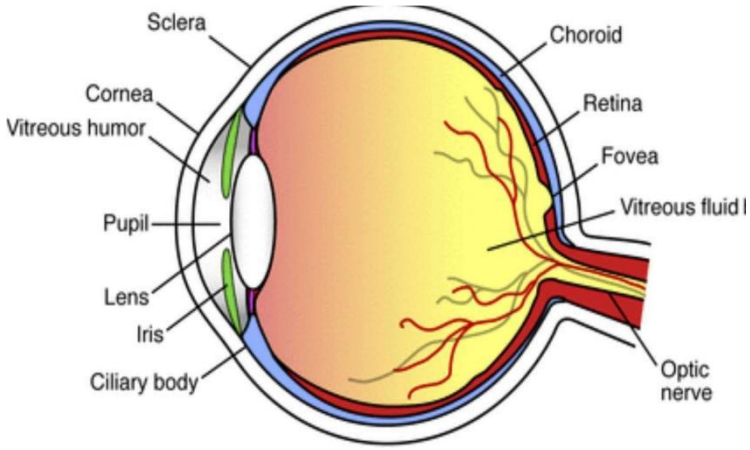
The endotoxins of gram-negative bacteria forms a firm gel within 60 mins in the presence of lysate of amebocytes of limulus polyphemus of horseshoe crab, when incubated at 37◦c. Hence, the test is only effective with gram-negative bacteria, which constitute the majority and the most potent of the pyrogens. The addition of a solution containing endotoxins to a solution of a lysate produces turbidity, precipitation or gelation of the mixture.

Ophthalmic Preparations:-

Introduction;

Ophthalmic preparations (eye preparations) are sterile, liquid, semisolid, or solid preparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The most commonly employed ophthalmic dosage forms are solutions, suspensions, and ointments. But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage.

Eye is the most easily accessible site for topical administration of a medication. Ideal ophthalmic drug delivery must be able to sustain the drug release and to remain in the vicinity of front of the eye for prolong period. The newest dosage forms for ophthalmic drug delivery are: gels, gel-forming solutions, ocular inserts, intravitreal injections and implants**.**



Anatomy of the human eye.

Formulation considerations:-

a) **Tonicity and Tonicity-Adjusting Agents:** The tonicity of aopthalmic solution should be adjust correctly(urge a osmotic pressure equal to that of tear fluids, generaly agreed to be equal to 0.9% NaCl) a range of 0.5-2.0% NaCl equvivalency does not cause a marked pain and range of about 0.2-0.7% sholud be acceptable for most persons. Common tonicity adjusting ingridient are:NaCl, Kcl, Buffer salt, dextrose, glycerine, propylene glycol and mannitol.

b) **pH Adjustment and Buffers:** pH adjustment is very important as pH affects:

- To render the formulation more stable
- The comfort, safety and activity of the product. Eye irritation→ increase in tear fluid secretion→Rapid loss of medication
- To enhance aqueous solubility of the drug.

- To enhance the drug bioavailability
- To maximize preservative efficacy Ideally every product buffered to a pH of 7.4(The normal physiological pH of tear fluid) If buffers are required, their capacity is controlled to be as low as possible.
- To enable the tears to bring the pH of the eye back to the physiological range
- To avoid effect of buffers on tonicity. Examples of buffer vehicles used:-Boric acid vehicle: pH ofslightly below 5-Isotonic phosphate vehicle: pH ranges from 5.9 -8.

c) Viscosity-Imparting Agents:

Polyvinyl alcohol, methylcellulose, hydroxyl propyl methylcellulose, hydroxylethylcellulose and carbomers are generally used in parentral preparation as viscosity imparting agent. They increase the ocular contact time thereby they decrease the drainage rate, increase the mucoadhessiveness and increase drug bioavilability.

d) Stabilizers & Antioxidants:

Stabilizers are the ingredients, which makes the preparation to decrease the rate of decomposition of active ingredient. Antioxidants are principle stabilizers added to some opthalmic preparation, primarily those containing epinephrine, and other oxidizable drugs.Example: Sodium bisulphite or metabisulphite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solution.

e) Surfactants:

The order of surfactant toxicity is anionic>cationic>>non-ionic. There are several non-ionic surfactant are used in low concentration to add in dispersing steroid in suspensions and to achieve or improve solution clarity. Some of the surfactant which are principally used are sorbiton ether esters of oleic acid (polysorbate or tween 20 and 80).

f) Preservatives:

Preservatives are included in multiple-dose eye solutions for maintaining the product sterility during use. Preservatives not included in unit-dose package. The use of preservatives is prohibited in ophthalmic products that are used at the of eye surgery because, if sufficient

concentration of the preservative is contacted with the corneal endothelium; the cells can become damaged causing clouding of the cornea and possible loss of vision. The most common organism is Pseudomonas aeruginosa that grow in the cornea and cause loss of vision. Examples: benzalkonium chloride, 0.004% to 0.01%;benzethonium chloride, 0.01%; chlorobutanol,0.5%; phenylmercuric acetate, 0.004%; phenylmercuric nitrite, 0.004%; and, thimerosal, 0.005%to 0.01%.

Formulation of eye drops:

Ophthalmic solutions are sterile solutions intended for instillation in the eye.In addition to sterility, these dosage forms require the careful consideration of such other pharmaceutical factors as the need for antimicrobial agents, osmolarity, buffering, viscosity, and proper packaging.

An eye drop formulation comprises of the following:

a) Active ingredients to produce desired therapeutic effect.
b) Vehicle(Aquous or Oily).
c) Inert antimicrobial preservatives to prevent microbial contamination and to maintain sterility.
d) Inert adjuvants for adjusting tonicity, Viscosity and PH to increase the stability of active ingredients.
e) Suitable container to maintain the preparation in a stable form and provide protection against contamination during preparation, storage and use.
f) Multi dose eye drops are added with an effective antimicrobial preservative system(a single substance cannot be successfully used as a preservative in ophthalmic solution) that should pass the test for efficacy of antimicrobial preservative. This ensures that the eye drops are sterile and non-contaminated.

Formulation of Eye Ointments:

Ophthalmic ointments must be sterile. Like suspensions, ointments can be more difficult to manufacture in sterile form. They can be terminally sterilized, or, alternatively, they must be manufactured from sterile ingredients in an aseptic environment. Filtration through a suitable membrane or dry heat sterilization is often used.

- The ointment base selected for an ophthalmic ointment must be non-irritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye.
- Ointment bases utilized for ophthalmics have a melting or softening point close to body temperature.
- Ophthalmic ointments have a longer ocular contact time when compared to many ophthalmic solutions.
- Ointment base is sterilized by heat and filtered while molten to remove foreign particulate matter**.**
- It is then placed into a sterile steam jacketed to maintain the ointment in a molten state and excipients are added.
- One disadvantage to ophthalmic ointments is the blurred vision that occurs as the ointment base melts and spread across the lens.
- The bases like; yellow soft paraffin, liquid paraffin and wool fat can be used for the preparation of eye ointment.

Formulation of Eye Lotions:-

Eye lotions are undiluted aqueous solutions, applied to an eye bath, which for first aid purposes. It is may allow a large volume of fluid to flow quickly over the eye.

It is iso-osmotic to tears, because compared to eye drops, lotions cause much greater dilution of the lachrymal fluid, hence cause discomfort if not adjusted.e.g. Sodium chloride (NaCl) eye lotion B.P.C. is used to remove foreign substance from the eye.

Thus these preparations should be very simple as well as the most common eye lotion consists of sterile normal saline. This preparation demonstrate the requirements of an eye lotion which are:

- Sterile as well as usually containing no preservative.
- Isotonic to lachrymal fluid
- Natural pH
- Large volume but not greater than 200ml
- Non-irritant to ocular tissue.

Methods of Preparation:

1) Preparation of the Solution: The aqueous eye drops vehicle containing suitable preservative , antioxidant , stabilizer, tonicity modifier , viscosity modifier, or buffer should be prepared, and added with the active ingredient and the vehicle to make up the volume.
2) Clarification: sintered glass filters or membrane filters having 0.45-1.2 µm pore sizes should be used. The clarified solution is either fillied directly into the final containers which are sealed before heat sterilisation or is temporarily filled into a suitable container before filtration. Clarified containers vehicle is used to prepare eye drop suspensions filled into final containers and sealed before sterilisation.
3) Sterilisation: This can be achieved by autoclaving at 115^{o}C temperature for 30 minutes or 121^{o}C temperature for 15 minutes . Filtration into sterile containers through a membrane filter having 0.22µm pore size is also a suitable method for sterililisation.Dry heat sterilisation at 160^{o}C temperature for 2 hours is best suited for non-aqueous preparations such as liquid paraffin eye drops.
4) After sterilisation, the eye drop containers should be covered with a readily breakable seal to distinguish between opened and unopened containers.

Labeling:-

The label should include:

(1) The name of the pharmaceutical product;
(2) The name(s) of the active ingredient(s); International Nonproprietary Names (INN) should be used wherever possible;
(3) The concentration(s) of the active ingredient(s) and the amount or the volume of preparation in the container;
(4) The batch (lot) number assigned by the manufacturer;
(5) The expiry date, the utilization period, and, when required, the date of manufacture;
(6) Any special storage conditions or handling precautions that may be necessary;
(7) If applicable, the period of use after opening the container;
(8) Directions for use, warnings and precautions that may be necessary;
(9) The name and address of the manufacturer or the person responsible for placing the product on the market;

(10) If applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and
(11) The statement "This preparation is sterile".

Storage:

Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Special storage recommendations or limitations are indicated in individual monographs.

Containers:

Traditionally, ophthalmic liquid products were packed in glass containers fitted with an eye dropper. Today, glass containers have limited use where product stability or compatibility issues exclude the use of flexible plastic containers made of polyethylene or polypropylene. Most liquid ophthalmic products on the market are packaged in plastic containers fitted with nozzles from which, by gentle squeezing, the contents may be delivered as drops.

- Plastic containers have several advantages over the glass-dropper combination such as minimizing the risk of the contents being contaminated with microorganisms by the replacement of the dropper which may have become contaminated by touching the infected eye or any other surfaces. Also, plastic containers are cheap, light in weight, more robust to handle and easier to use than glass-dropper type containers.
- Some plastic materials such as polyethylene can absorb some antimicrobial preservatives (e.g. benzalkonium chloride), or some drugs. They may also leach plasticizers into the product, or printing inks from the label can migrate through the plastic into the product.
- The challenge is to develop a packaging system for preservative-free products that maintains the sterility of the product throughout its shelf-life and during use.
- Unit-dose systems offer the easiest technical solution to this problem but have the disadvantage of higher cost of manufacture and of not being as compact as a multidose product containing equivalent doses.
- An alternative approach is to develop a multidose preservative free system. The container is required to be collapsible, and the suck-back of air, which could contain bacteria, has to be avoided. Containers are being developed that contain a valve mechanism to achieve this
- Plastic containers can also be permeable to water vapor and oxygen over prolonged periods of storage. This can lead to gradual loss of liquid product or oxidation of an unstable drug over time.
- Polyethylene containers are not able to withstand autoclaving and are usually sterilized by ethylene oxide or by irradiation before being filled aseptically with pre-sterilized product. Polypropylene containers can be autoclaved, but are not as flexible as polyethylene for eyedropper use.

- Semi-solid products have been traditionally packed in collapsible tin tubes. Metal tubes are a potential source of metal particles in ophthalmic products, and so the tubes have to be cleaned carefully prior to sterilization.
- Collapsible tubes made from laminates of plastic, aluminum foil and paper are good alternative to tin tubes. Laminate tubes fitted with polypropylene caps can be sterilized by autoclaving.

Evaluation of ophthalmic preparations:-

Ophthalmic preparations are evaluated as follows:

1) **Sterility:** The ophthalmic products should meet the standard requirements. If the ingredients used do not lend themselves to routine sterilization, ingredients that meet the sterility requirements should be used. The container for ophthalmic preparations should be sterilized at the time of filing and closing. They should be sealed and tamper-proof to maintain their sterility.
2) **Antimicrobial preservatives:** These should be added to multiple-dose containers, unless there are different directions provided in the individual monograph for multiple product withdrawal, the substance contains a radionuclide with a physical half of less than 24hours, he product itself is sufficiently microbicidal, or the added ingredients meet the requirements of antimicrobial agent content. Thus, acceptance criteria for the content of antimicrobial preservative in multiple-unit products should be established.
3) **Uniformity of Dosage Units**: This test should be performed for single-dose containers to evaluate the mass of dosage form as well as the content of the drug substance(s) in the dosages form. The test is performed by either content uniformity or weight variation.
4) **Uniformity in Containers:** Semisolid drug products undergo physical separation during manufacturing and /or during the storage period. To ensure the drug product integrity, the uniformity of the finished product at the time of batch release and throughout its shelf-life should be evaluated.
5) **Leachable and Extractables:** The packaging system and the preparation should not undergo any physical or chemical interaction to alter the strength, quality, or purity of the drug product. The packaging system should meet the requirements in elastomeric closures for injection, and glass or plastic containers.
6) **Container Closure Integrity:** The packaging system should be closed or sealed to prevent contamination or loss of contents. It should also be tamper-proof. Validation of container integrity should demonstrate no penetration of microbial, chemical or physical contaminants.

7) **Viscosity:** The residence time of the product in eyes increases in viscosity; but the diffusion of drug from the formulation in to the eye is inhibited. The ophthalmic ointments have a very high viscosity to prolong their residence time in the eyes.
8) **Antioxidant Content:** The content of antioxidants (if added in the drug product) should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should also be established based on the levels of antioxidant required to keep the product stable throughout its shelf-life.
9) **Particle Size and Particle Size Distribution:** The potential for any changes in the particle size of ophthalmic suspensions and emulsions should be evaluated through stability testing. the drop size for ophthalmic drops ranges from 20-70µm.However,the drop size should be controlled and maintained throughout the product shelf-life. Suitable substances should be added to the ophthalmic products to increase their stability, provided they do not cause any harm in the amounts administered and do not interfere with the therapeutic efficacy or responses to the specified assays and tests.

References:

1) Introduction to Pharmaceutical Dosage Forms. Ansel, HC— 4th ed. Philadelphia: Lea & Febiger; 1985:321–336.
2) Industrial pharmacy-I by KL Senthilkumar, AS Mundada and RS Kankate: Ist ed.Thakur Publication, pg. no.163-204.
3) Pharmaceutical dosage forms: parenteral medications of industrial pharmacy, Lachmann/ Lieberman's, 4th edition, pg.no. 864-871.

4). Dispensing pharmacy by R M Mehta, pg.no. 303-311.

5). The science & practice of pharmacy, Remington, 21st edition, pg.no. 1367-1374.

UNIT V

Cosmetics: Formulation and preparation of the following cosmetic preparations: lipsticks, shampoos, cold cream and vanishing cream, tooth pastes, hair dyes and sunscreens.

Pharmaceutical Aerosols: Definition, propellants, containers, valves, types of aerosol systems; formulation and manufacture of aerosols; Evaluation of aerosols; Quality control and stability studies.

Packaging Materials Science: Materials used for packaging of pharmaceutical products, factors influencing choice of containers, legal and official requirements for containers, stability aspects of packaging materials, quality control tests.

COSMETIC PREPARATIONS

- **Cosmetics** are defined as the Preparations intended to be rubbed or sprinkled or applied to any part of the external surfaces of the human body (Face, lips, nails) for cleansing, beautifying, promoting attractiveness or perfuming or protecting or altering the appearance or masking the body odour.
- Generally Cosmetic preparations are not used to prevent or treat any disease
- **Cosmetology** is defined as the science that deals with the laws governing the production, storage and application of cosmetic products

Classification of Cosmetic preparations/ Different types of Cosmetics

On the basis of Physical form, It is classified into

- Oils - Eg: Hair oils
- Emulsions - Eg: Cold Cream, Vanishing cream, Cleansing cream
- Suspensions - Eg: Calamine Lotion
- Pastes - Eg: Tooth paste
- Sticks - Eg: Lipstick
- Jellies - Eg: Brilliantine jelly
- Cakes - Rouge compacts, makeup compacts
- Powders - Face powder, Tooth powder
- Solutions - After shave lotions, Astringent lotions

- **On the basis of application in the organ**, it is classified into
- Cosmetics for Skin - Eg: Powders, Creams, Lotions, Suntan preparations
- Cosmetics for hairs - Eg: Shampoos, hair tonics, Shaving creams, Depilatories
- Cosmetics for nails - Eg: Nail polishes and polish removers, Manicure preparations
- Cosmetics for teeth and mouth - Eg: Dentrifices and Mouth washes
- For baby preparation Eg: Baby powders, Baby oils, Baby shampoos
- Other cosmetics Eg: Eye preparations, Foot powders etc

LIPSTICKS

- It is the cosmetic preparation prepared by disperion of colouring matter in a base consisting of mixture of oils, fats and waxes which are moulded into sticks.

Uses:

- To give attractive colour and appearance to the lips
- To prevent cracking and chapping of lips
- For emollient action (Soft and prevent drying)

Ideal Characteristics

- Free from grittiness
- Should have uniform color
- Stable through out the shelf life
- Should be safe dermotologically
- Should be easily apply

Formulation of Lipsticks or Ingredients used in lipsticks

Colouring agents:

- Colour is imparted to the lips in two ways
    - a) By staining the skin in which dye to be penetrate into the outer surface of lips
    - b) By covering lips with dye which hide roughness of lips
- Soluble dyes like methylene blue, Brilliant green, Erythrosine red
- Insoluble dyes like iron oxide colours, calcium, Barium, Strontium lakes of red

Bases:

- These are used to give proper consistency to the preparations.
- Oils, fats and waxes are used as bases in lipsticks.
- It produces greasy and emollient action which keep the lips soft and moist in appearance.
- Eg: Bees wax, Carnauba wax, Ozokerite, Hydrogenated Castor oil, Petroleum jelly, Liquid paraffin, Wool fat (Lanolin), Cetyl alcohol, Lecithin

Dye stuff Solvents

- For dissolving the colouring agents
- To give plasticity to the lipsticks
- Eg: Tetra hydro furfuryl esters, Polyethylene glycols

Wetting agents:

- Used to soubilize the dyestuff and improve the staining power
- Eg: Loramine wax, Polyethylene glycols

Preservatives:

- Prevents the microbial growth
- Eg: Methyl paraben, Propyl paraben

Fragrance:

- Mask the fatty odour of the base
- Eg: Rose oil, Jasmine oil

Method of Preparation of Lipsticks

Formula

Color	%	Wax & Oils &	%	Other ingredients	%
Eosin	2%	Beeswax	20%	Methyl paraben	0.8%
Eosol	22%	Lanolin	10%	Propyl paraben	0.2%
Titanium dioxide	8%	Ozokerite	6%		
Solvent		Cetyl alcohol	2%		
Polyethylene Glycol	10%	Liquid Paraffin	10%		
		Castor Oil	10%		

- Colouring agent is **dissolved** in Solvent. Then add other ingredients in solution and mix well.
- Wax and fats are **melted** separately. The melted base added to the dye stuffs.
- The whole contents are **milled** for several times to get smooth appearance
- Vaccum is applied to remove air.
- Perfume is added to the mass and **poured** into the moulds
- Moulds are chilled. By this sticks are formed.
- Then the sticks are removed and inserted in holders.
- Finally these are passed through flame for perfect and smooth finish.

DEFECTS IN LIPSTICKS

Formulation related

- **Sweating:** Due to high oil content or inferior oil blending capacity
- **Bleeding:** Separation of color from waxy base
- **Blooming:** Dull appearance instead of glossy appearance
- **Streaking:** Thin line of different color appears to the surface of finished products

Mould related

- **Laddering:** Ladder like appearance after congealing and setting due to uneven melting and cooling
- **Deformation:** Deformed structure appear on sides of lipsticks
- **Catering:** Dimples or spots appeared on the surface of lipstikcs.
- **Mushy failure:** Central core of stick are not strong enough to hold the base.

EVALUATION OF FINISHED PRODUCTS

- **Color Control:** Dispersion of pigment is checked stringently. It is checked by Calorimetric equipment. This provides the numerical reading of color shades. Matching the colour shades visually.
- **Melting Point:** Lipstick base should have melting point 55 C to 75C. It is measured by capillary tube temperature method.
- **Softening Point:** Lipstick should be resistant to varying temp both hot and cold weather. It is measured by Ring and Ball method.
- **Microbial testing:** Known amount of mass is placed in two culture media and analysed for suitable growth of bacteria and fungi. Limit is NMT 100 microorganism per gram.
- **Rancidity:** Rancidity is due to decomposition of fats, oils and lipids by hydrolysis or oxidation. It leads to color change, bad odour and taste. It is determined by its peroxide number
- **Breaking Load Test:** To find out the value of maximum load that a lipstick can withstand before it breaks.
- **Rupture test:** Crushing or rupturing of lipstick is measured when it is placed inbetween the two holders which contain weight.

SHAMPOOS

- Shampoos are cleansing agents containing synthetic detergents with various additives. After shampooing, it leaves the hair soft, nonsticky and free from oils, dirt, dandruff, pollutants and contaminant particles.

Functions of Shampoo:

- Cleaning agent - Removes dust and excess oils from the hair.
- Anitseborrhoeic agent - Agents used to prevent excessive secretion of sebum
- Antidandruff agents - This will treat dandruff and pruritis which are associated with fungal infections.
- Keratolytic agents - They remove the hard scales from the scalp.

Ideal properties

- Easily soluble even in hard water
- Easy spreading; no damage to hair, low toxicity, minimum eye irritation
- Good foaming ability
- Slightly acidic. Since basic environment weakens the hair by breaking disulfide bond of hair keratin.

FORMULATION OR COMPOSITION OF SHAMPOO:

- **Detergents:** Used to clean the hair. Surfactants like Anionic surfactants (Sodium Lauryl sulphate, Alkyl polyethylene glycol sulphates, alpha olefin sulphate), Non ionic surfactant (Amineoxides, Fatty acid alkanolamides), Cationic surfactants (Alkyl amines, Ethoxylated amines, Alkyl betains), Amphoteric surfactants.
- **Foam Boosters:** Stabilize the foam produced by surfactants Eg. Fatty acid alkanolamides, amine oxides.
- **Disinfectants and Germicides:** Used to prevent itching caused by bacteria. Eg: Hexachlorphene, Dichlorophene
- **Antidandruff agents:** To prevent formation of scaly scurf on skin under the hair Eg: Benzalkonium chloride, Cetrimide, Hyamines
- **Conditioning agents:** Gives smoothness and softness to the hair. Also known as pearlescent agents. Eg: Lanolin, Mineral oils, aminoacids
- **Preservatives:** Prevent microbial growth Eg: Parabens, PMN, PMA
- **Sequestering agent:** Prevent the calcium and magnesium like salts present in water which deposit on the hair Eg: EDTA, Pyrophosphates
- **Coloring agent:** Give attractive appearance to the formulation. Eg: Water soluble colours
- **pH modifier:** To make the formulation slightly acidic Eg: Citric acid, acetic acid
- **Perfumes:** To provide pleasant feeling. Eg: Lavendar oil, Rosemary oil, Jasmine oil are used

PREPARATION OF SHAMPOO: (Antidandruff Shampoo)

- Dissolve Part A in Water, heat at 40 C
- Dissolve Part B in water, heat at 40 C
- Mix these two phase at same temperature
- Make up the volume with water and mix well
- Cool the mixture and add perfume

EVALUATION/ QUALITY CONTROL TEST OF SHAMPOO

- Determination of pH
- Determination of solid content
- Foam Formation, Foam Quality and Retention test
- Viscosity
- Dirt dispersion
- Skin and Eye irritation test

FORMULA
Part A
Triethanolamine lauryl sulphate
Lauric monoethanolamide
Preservative
Color
Water
Part B
Hexachlorophane
Water
Part C
Water
Perfume

COLD CREAM

- This will produce smooth skin and also remove makeup. It produces cooling effect because slow evaporation of water present in emulsion. It is Water in oil type of emulsion

FORMULATION OR COMPOSITION

- Base: It melts at 70 °C and form smooth cream at room temperature when it mixed with suffecient amount of water
  Eg: Stearic acid, Cetosteryl alcohol, Cetomacrogol
- Emulsifying agent: Spans, Polysorbates
- Alkalis: Borax, Sodium hydroxide and Potassium hydroxide
- Preservatives: Parabens, Sodium Benzoate, Boronpol
- pH modifier: Sodium hydroxide, lactic acid

METHOD OF PREPARATION

- Melt Oil soluble ingredients at 70 °C
- Dissolve water soluble ingredients and heat at 70 °C
- Mix oil phase and water phase at same temperature and mix well
- Borax reacts with fatty acids from waxes and oils and forms soap which act as self emulsifying agent
- Cool the mixture and add perfume

EVALUATION

- Viscosity, Skin irritation
- Microbial growth and Rancidity
- Color and Physical appearance

FORMULA
Oil Soluble ingredients
Bees Wax
Mineral Oil
Paraffin Wax
Cetyl alcohol
Water Soluble ingredients
Borax
Preservative
Water
Perfume

VANISHING CREAM

- These are referred as Day creams. This provide emollient and protective action to the skin by forming occlusive film on the skin.
- They are oil in Wate type of emulsion. When applied on the surface of skin, it will disappear immediately and form thin film which is not visible to naked eye. Hence it is known as Vanishing cream.

FORMULATION OF VANISHING CREAM

- Main ingredient: Stearic acid, water and soap are basic constituents of stearate based creams. Soap is formed in-situ by the reaction between suitable alkali and stearic acid.
- Humectants: It prevents excessive drying out of cream. Eg: Glycerin, Sorbitol and propylene glycol
- Alkali: Potassium hydroxide, Borax, Sodium hydroxide, Sodium carbonate, Triethanolamine
- Emulsifying agent: Polysorbates, spans
- Preservatives: Parabens, Benzoates
- Perfume: Lavener oil, Terpineol, Sandal wood oil
- Purified Water

Formula
Water Soluble ingredients
Stearic acid
Oil soluble ingredients
Glycerin
Methyl paraben
KOH
Water
Perfume

PREPARATION OF VANISHING CREAM

- Stearic acid is melted to 70C
- KOH, Methyl paraben, Glycerin dissolved in water and heated to 70C
- Two phases are mixed at same temperature and mix well
- Cool the mixture to 50 C and add the perfume.

EVALUATION

- Viscosity, Skin irritation
- Microbial growth, Color and Appearance test.

TOOTH PASTES:

- It is a paste or gel dentrifice used with tooth brush to clean and remove the food debris and plaque adhere to the surface of the teeth.

Formulation or Compostion of Tooth paste

- Abrasives: Used to clean and polish the teeth and remove the debris. Eg: Calcium carbonate (Precipitated chalk), Dicalcium phosphate dihydrate, Tricalcium phosphate.
- Detergents: Used to produce foam and reduce the surface tension of adherents and staining. Eg: SLS, Sodium N lauryl Sarcosinate
- Humectants: Prevents drying of formulation. Eg: Glycerin, Sorbitol, Propylene glycol
- Binders: Give good consistency to the preparation. They provide protective colloidal effect stabilises and thicken the preparation. Eg: Tragacanth, Acacia, Carboxymethyl cellulose, Guar gum, Carageenan etc.
- Flavoring agents: They give good flavor and freshness to the preparation. Eg: Peppermint oil, Lavendar oil, Clove oil, Menthol
- Sweetening agents: Give pleasant taste to the preparation. Eg: Saccharine, Sodium cyclamate
- Preservatives: Binding agent in the form of mucilage will support microbial growth. To prevent microbial growth, preservatives are added. Eg: Parabens, Formalin, Benzoates
- Corrosion inhibitor: To prevent corrosion to the aluminium tube, Sodium silicate, silica are added.
- Colours: Erthyrosine, Eosin, Carmine are used to improve the appearance and palatability
- Flouride Actves: Increase resistance to enamel solubility. Eg: NaF, MFP

PREPARATION OF TOOTH PASTE

- Glycerol + Sorbitol + Preservative + SCMC → Mucilage
- Add Sod. Saccharine → Mass
- Abrasive + SLS → Mass
- Add mineral oil, peppermint oil to above solution

Tooth paste as Therapeutic agent

- Anticaries agent - Fluoride
- Antiplaque agent - Triclosan, SLS, Zn,Sn ions
- Anticalculus agent - Pyrophosphate, Zinc
- Antidentine hypersensitivity agent - Potassium salts
- Whitening agents - Dimethicone, Papain

EVALUATION OF TOOTH PASTE

- Test for abrasiveness
- Particle size
- Cleansing property
- Test for flouride
- Consistency, pH and Foaming character and stability of Foam
- Limit test for Arsenic and Lead, Volatile matters and moisture

FORMULA
Abrasives - 20-40%
Calcium Carbonate
Dicalcium Phosphate
Detergent and Binder - 1-2%
Sodium lauryl sulphate
Sodium carboxy methy cellulose
Sweetener & Preservative 1-2%
Sodium Saccharine
Methyl Paraben
Humectants - 20-40%
Glycerin
Sorbitol
Mineral oil
Water - 20%

HAIR DYES

- These are colourants or the cosmetic preparations which are used to change the natural hair color and to mask the greying of hair

Ideal properties

- Color distribution should be even
- Should not damage the hair and scalp
- Should remain for longer duration
- Natural moisture of hair should be retained

Formulation depends on the Classification of hair dye:

1. Temporary hair colourants
2. Semi permanent hair colourants/ Direct dyes
3. Oxidative dyeing systems
4. Gradual hair colorants
5. Natural dyes

Temporary hair colorants:

- They are leave in preparation. Not rinsed after application.
- Absorbed into the cuticle and cannot enter into the cortex of hair.
- It consists of dyestuff and acid. Dyes are azodyes, anthroquinone dyes, benzoquinoneimine dye, Triphenyl methane dye.
- Available in Powder, Crayons, Liquids and Shampoos.

Semipermanent Hair Colourants/ Direct dyes:

- Retain color for longer duration.
- Doesnot contain H2O2 and so it doesnt get bleached
- Composition of semipermanent hair colorants are
- Dye - O nitro anilines, Aminonitrophenols & their ethers, Azo dyes, Nitrodiphenylamine, Anthroquinone
- Aliphatic primary amines, Fatty acid, Thickener, Surfactant
- Water, Organic solvent,Perfume

Oxidative Dyeing Systems

- Also called Para dyes. Colorants are based on chemical reaction, produces color.
- Mostly oxidation, coupling and condensation reactions involved
- Composition are,
- Dyes - Aromatic compounds, Resorcinol, m-phenylene diamine, Diaminoanisole, hydrogen peroxide
- Vehicles - Water, Ethyl alcohol, Glycerine, Ethylene glycol monostearate
- Alkalis - Oxidation dyes are active in alkaline medium Eg: Ammonium hydroxide, Amm. Carbonate, Mono ethanol amine, Guanidine or Arginine, Diethanol amine
- Oxidizing agent - Induces the oxidation reaction with hair Eg: Ferric chloride, Kmno4, H2O2
- Antioxidant - During manufacturing, the amino dyes are darken in presence of air. Nitrogen is supplied in manufacturing vessel or Sodium sulfite are added

Gradual Colourant:

- This colorants require several applications on hairs to achieve required darkness
- It contains heavy metals like Lead, Bismuth salts in their composition
- But it produces negative effect on health

Natural dyes:

- Plant contain color pigments, which are used as Hair colorants
- It has very less side effects
- Henna: Leaves are powdered and it is mixed with water to form paste. It gives reddish to reddish brown color to the hair. Active constituent is 2 hydroxy 14 napthoquinone (Lawsone). Indigo leaves or synthetic indigo is added to henna to alter the color
- Chamomile: Flowers of chamomile are used to obtaine the colour. Powder is mixed with hot water to form paste. Navy blue color is achieved

Preparation or Manufacturing of Hair dye:

- Dye chemicals premixed with hot water
- Other ingredients like alkalis, surfactants, oxidizing agent, viscosity enhancer and buffers are dissolved in suitable solvents
- Dye Premix and Other mixtures are pumped in to manufacturing vessel and mix well.
- Remaining volume is makeup with water

EVALUATION

- pH, Viscosity
- Assay for H2O2
- Residue on ignition

SUNSCREENS

- It is a lotion or spray or gel that absorbs or reflects the sun's ultraviolet radiation and prevents the damaging effect of it.
- They can be used as Sunblock or sunscreens
- UV rays damage the skin cells and DNA in the form of Sagging, Wrinkling and Photo carcinogenesis
- UV light is artificially divided into 3 ranges
- UVA → 320-400 nm → Low energy → prevented by Ozone layer, doesnot reach the earth
- UVB → 290-320 nm → High Energy → Cause more immediate damage (Sun burn, Skin cancer)
- UVC → 100-290 nm → Very High Energy → DNA Damage

Mechanism or Principle of Sunscreens

- By reflecting or absorbing UV rays. Eg: ZnO and TiO2
- Filter the mid range UV rays (UVB). But allow the other range. All suntan preparations based on this principle. Eg: Chromophores, Inorganic particles
- Biologically active substances which prevents inflammation due to rays. Antihistamines substances are used to prevent inflammation
- By tanning the skin, which prevents the sun burn Eg: Dioxyacetone, Methoxypsoralene are taken 2 hrs before exposure to skin which induces tanning and avoids sunburn.

Ideal properties:

- Should be safe, chemically inert, non irritating and non toxic, Stable to heat, light and perspiration
- Retain the sunscreen property for several hours, Non stain and not be absorbed into the skin.
- Absorb UV rays in wide range

Classification of Sunscreens

- Physical preparation: Opaque formulation contains TiO_2, Talc, Kaolin, Zinc oxide, Ferric chloride, Which reflects the UV radiation due to large particle size
  Chemical Preparation: It contains PABA and its esters, Benzophenones, Cinnamates, Salicylates, Anthranilates which absorb UV radiation

SPF and Important of SPF

- SPF - Sun Protection Factor = $\frac{\text{Minimal Erythymeal dose for Product applied Protected Skin (MED - PS)}}{\text{Minimal Erythmeal dose for Product not applied unprotected Skin (MED - US)}}$
- Types of SPF

Type	Description	SPF Number	Character
I	Burn the skin easily & never tans	> 8	Sensitive
II	Burn the skin easily & minimum tan	6-7	Sensitive
III	Burn moderately & tan gradually	4-5	Normal
IV	Burn minimally & tans well	2-3	Normal
V	Barely burns & tans immediately	2	Insensitive
VI	Never burns & deeply pigmented	None	Insensitive

- Suitable base may be Aqueous, Alcoholic, Fats, Natural oils coconut oil, peanut oil, olive oil have absorption ability of UV light.
- Antioxidants also used in the preparation

Preparation or Manufacturing of Sunscreen: The product can be

- Aqueous or Oil type: Mixing and Dissolving the sunscreen and other ingredients in vehicle (Water and Oil). Perfume added atlast
- Cream type: These are emulsion type.
- Lotions type: These are solution type or emulsion type
- Gel type: Solution based Viscous preparation.

Preparation:

- Cetyl alcohol + Benzophenone + Ethyl hexyl methoxy cinnamate + Stearic acid + Glycerin + Stearyl Dimethicone Silicate → Melt in beaker
- Water + Triethanolamine → Taken in beaker → Heat to 80-85C
- Melted content is addded to the hot water solution slowly and stirred well
- Mixture is cooled to get uniform smooth cream.

FORMULA
Cetyl alcohol - 2%
Benzophenone - 1.5%
Ethyl hexyl methoxy cinnamate - 1.5%
Stearic acid - 4%
Glycerin - 2%
Triethanolamine - 1%
Water - 78%
Stearyl Dimethicone Silicate - 10%

Evaluation:

- Spectrophotometric evaluation: This will evaluate the UV absorption ability using UV Spectrophotometer
- Erythmeal damage: Erythema is estimated when the solar energy transmitted thro film of suntan preparation
- Sunscreen index - measurement of absorption coeffecient at 308 nm (Which is the effective UV rays wavelength which cause sun burn)
- Invivo skin testing - Sunscreens applied on the rabbit skin and exposed to radiation along with control unprotected skin for a period of time. The effects are observed at the end of period.