आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

NAAC ACCREDITED

E-Content

IFTM University, Moradabad

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.

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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

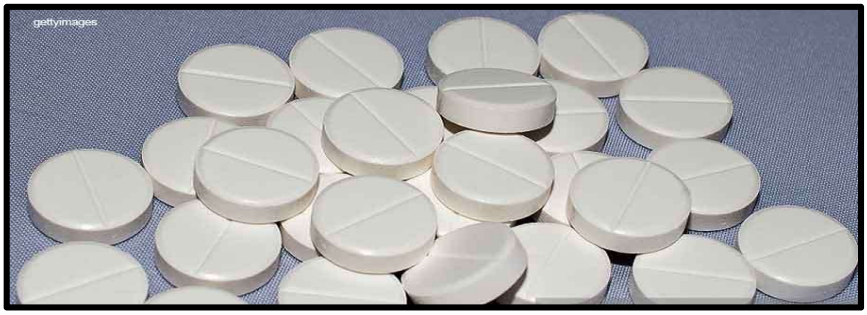
(d) T<u>ablets used to prepare solutions:</u>

- 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).



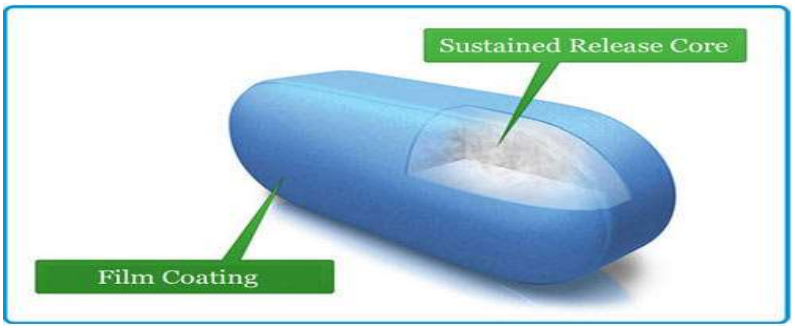
(2) Multiple compressed tablets / Layered tablets-

- 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.

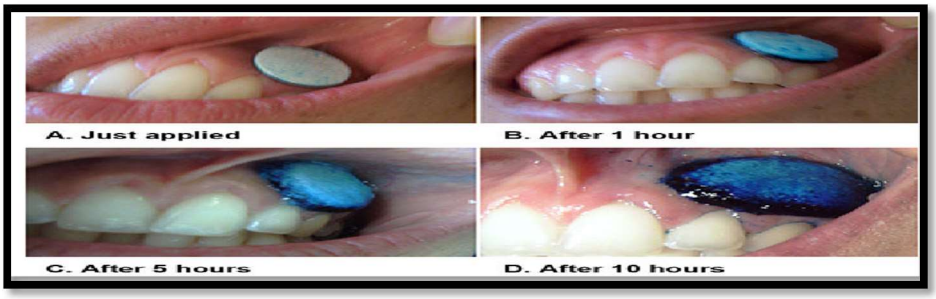
(7) Chewable tablets:

- 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

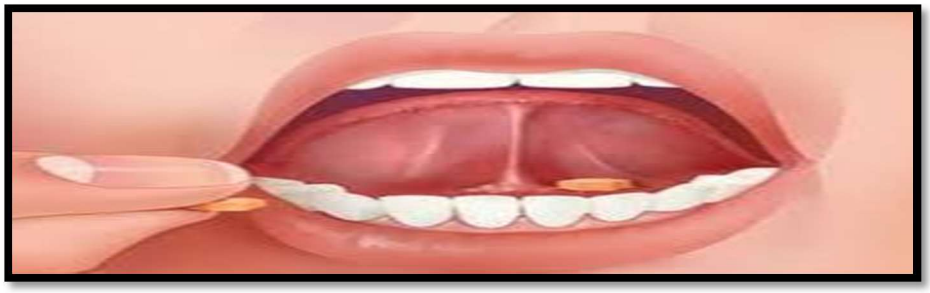
(1) Buccal tablets:

- 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.



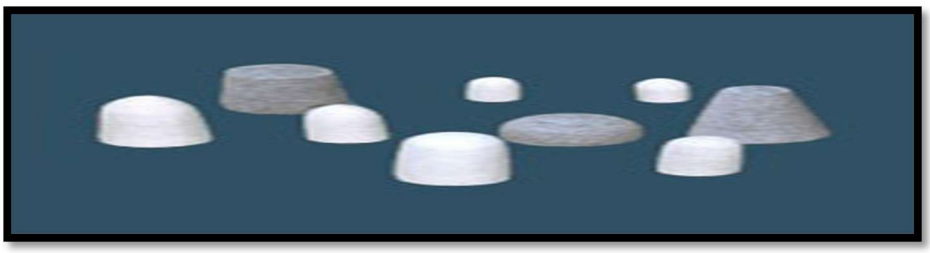
(3) Lozenges tablets:

- 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.

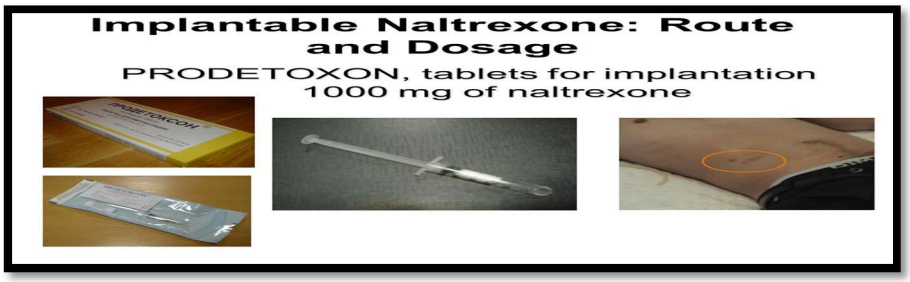
- These tablets contain an excipient like lactose, sodium bicarbonate and sodium chloride. These cones generally get dissolved in 20 to 40 minutes time.



(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:

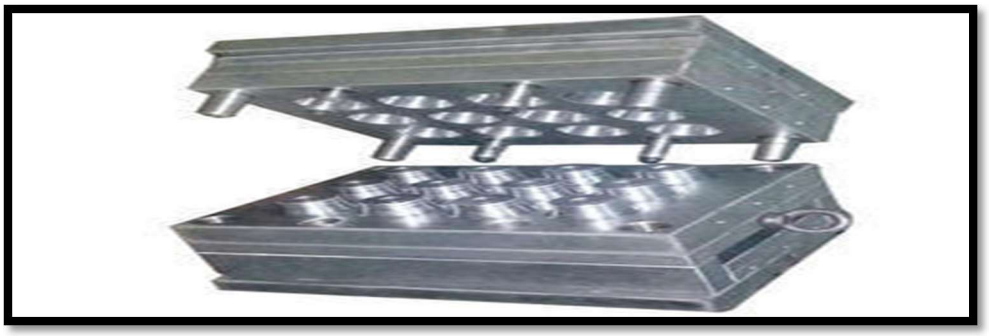
- These tablets provide a convenient quantity of potent drug that can be readily convert into powders and incorporate into liquids, thus circumventing the necessity to weigh small quantities. these tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed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

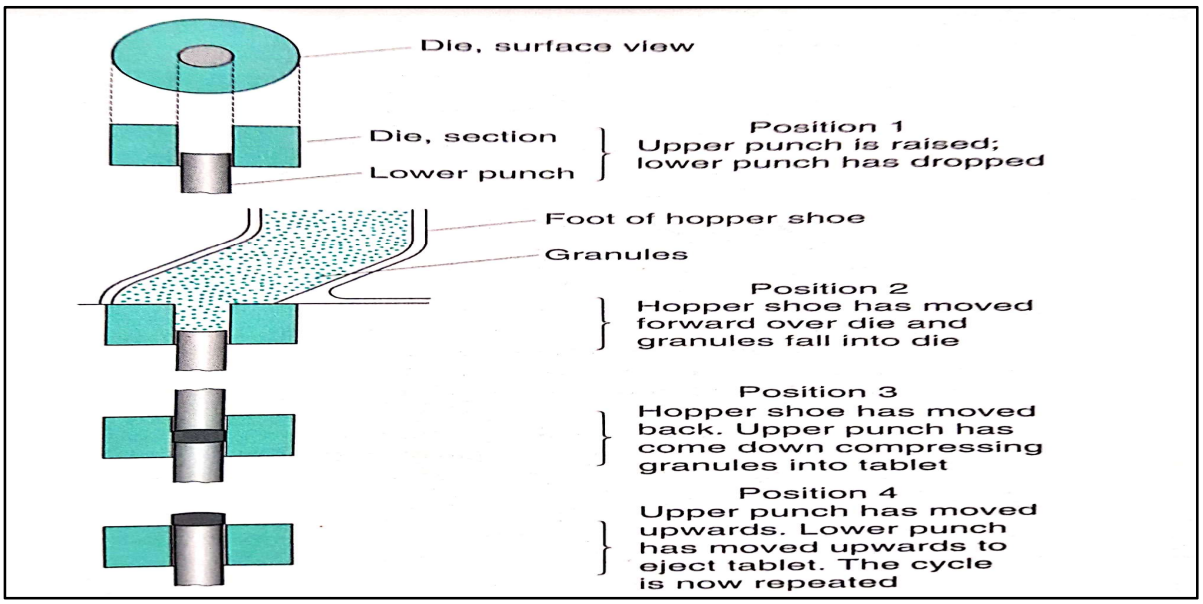


Fig.2. Sequence of events involved in the formation of tablets.

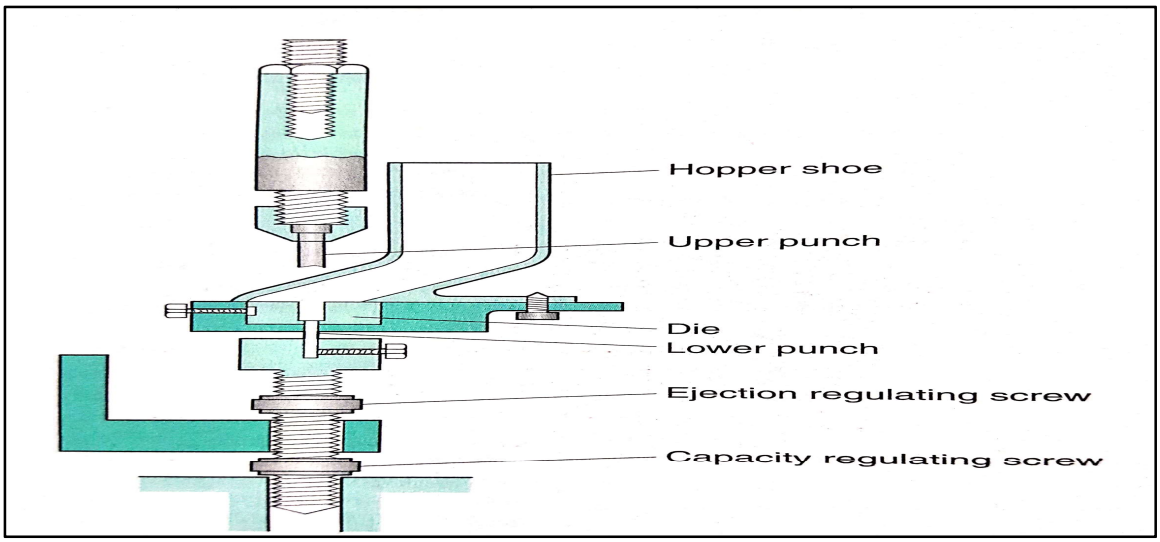


Fig.3. A single punch tablet press.

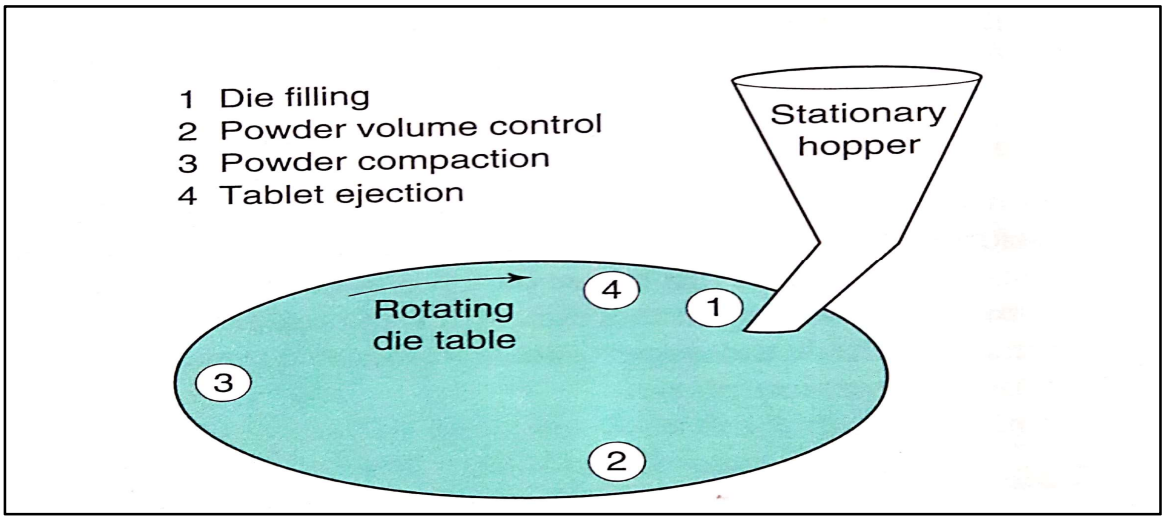
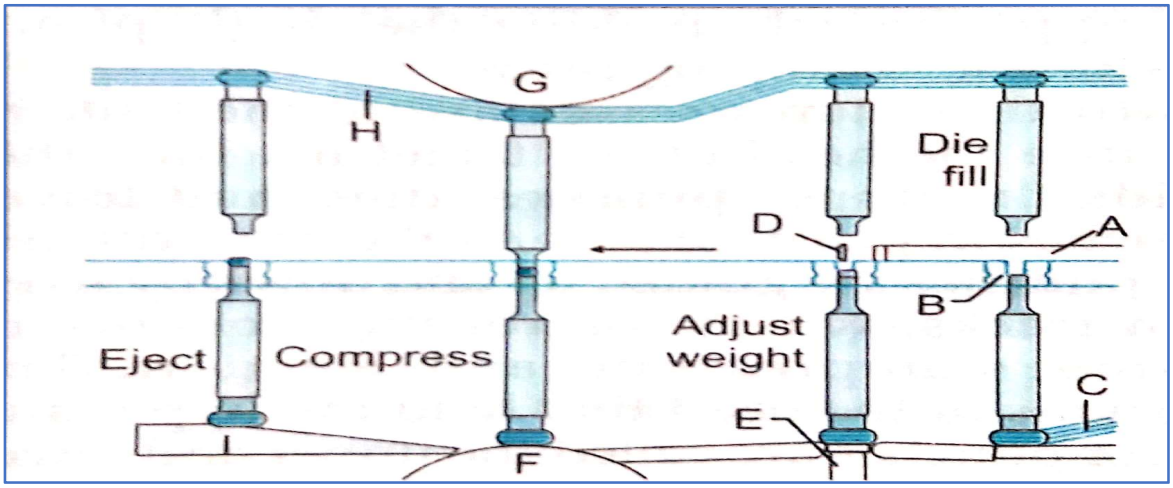
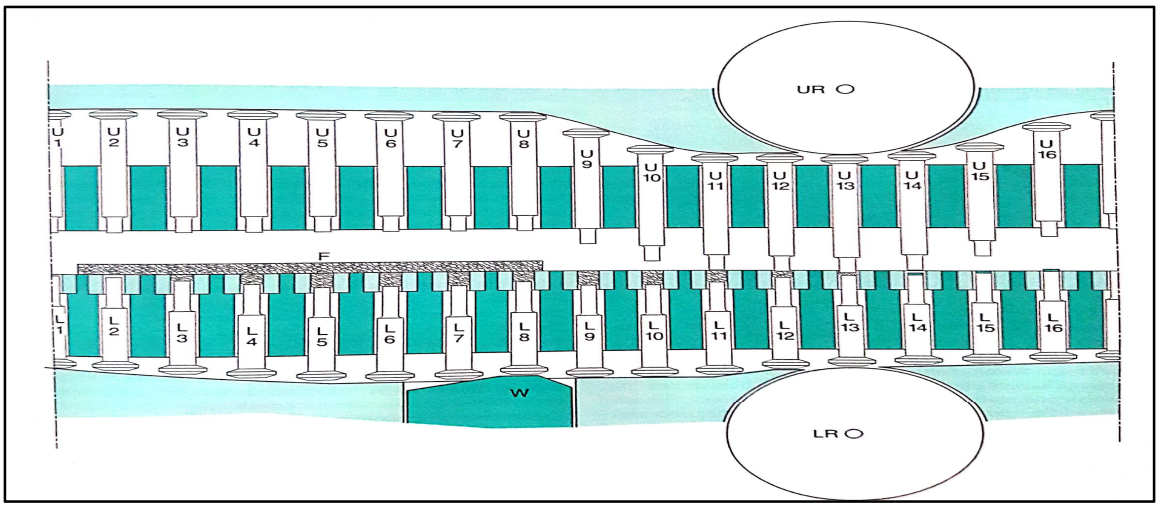


Fig.4. Schematic diagram for the formation of tablets with rotary press.



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.

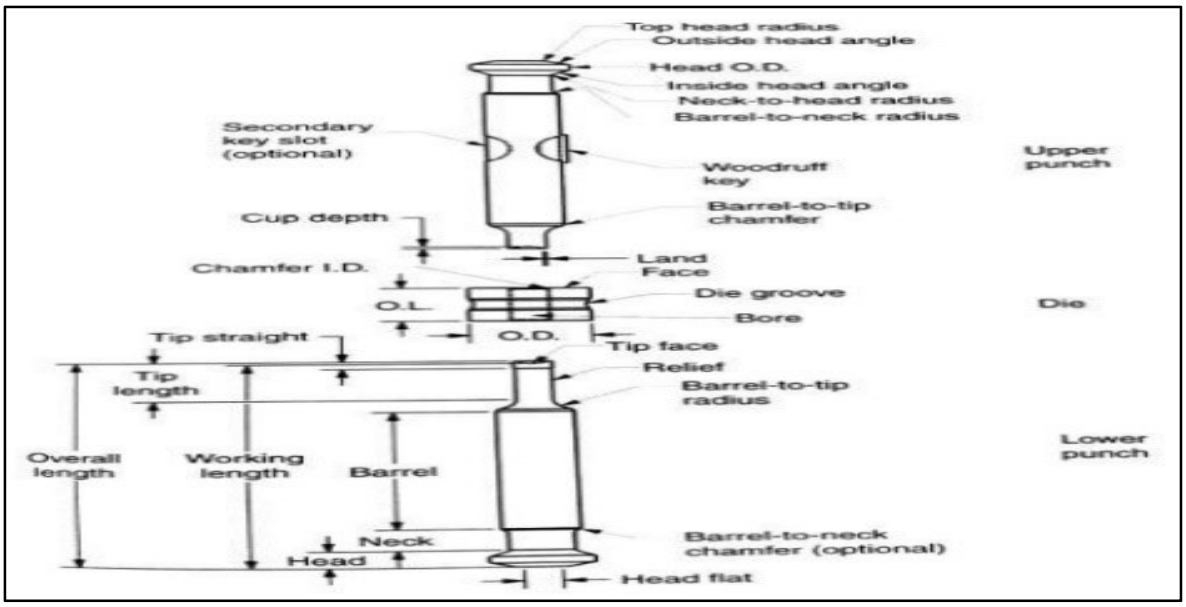
Gradually modification made in machines by using hydraulic or pneumatic pressure to control pressure roll in place of spring for smoother pressure.

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

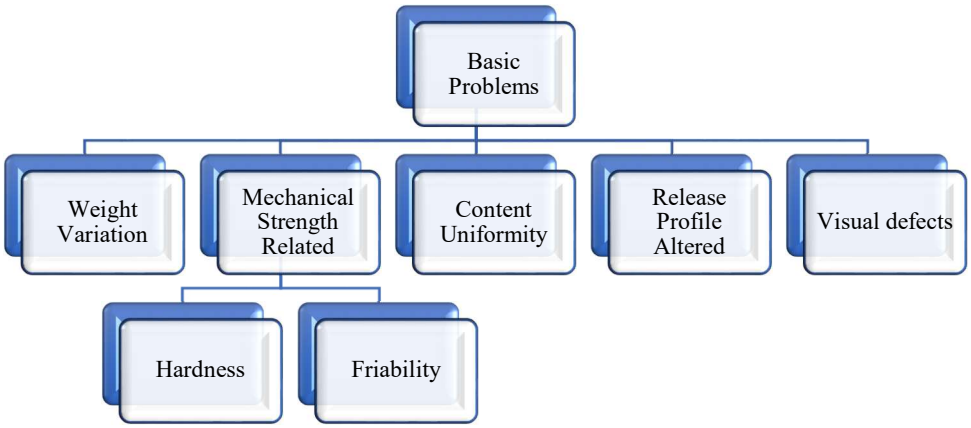
Tablet Processing Problems and its remedies-

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.

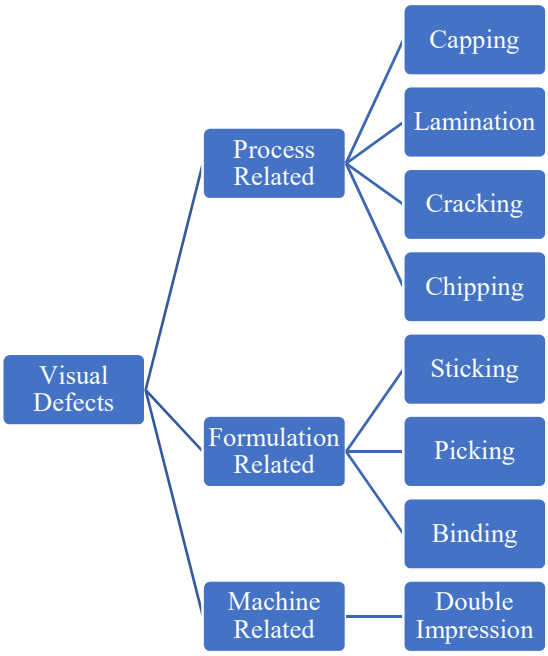


The **Imperfections** known as: 'VISUAL DEFECTS' are either related to Imperfections in any one or more of the following factors:

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 **$37^0 \pm 0.5^0$C.** 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.

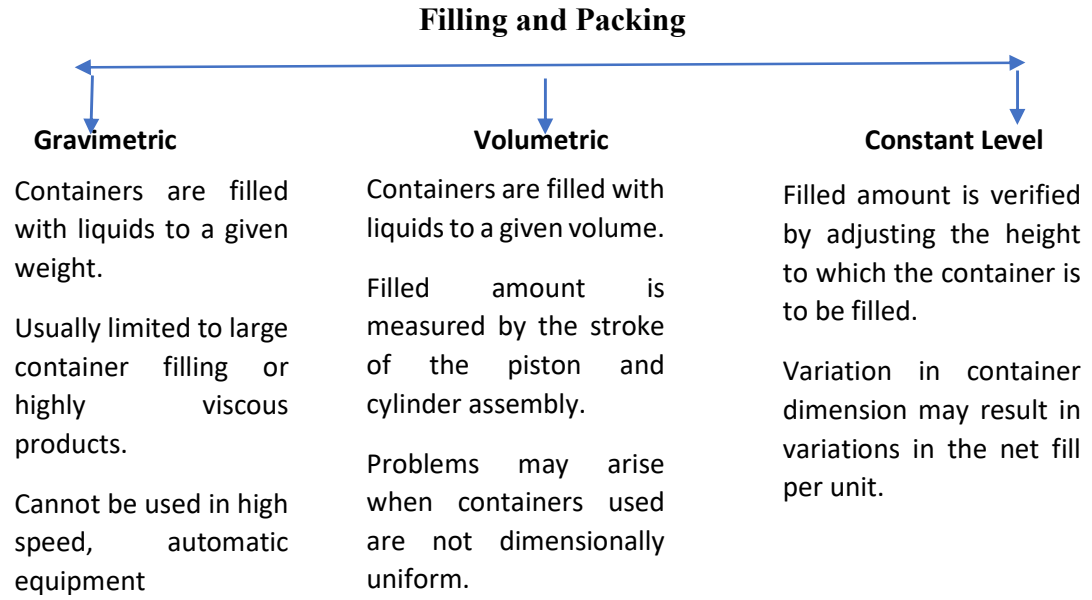
2. Measuring devices for large and small amount of solids and liquids. 3. Afiltration system e.g. filter press

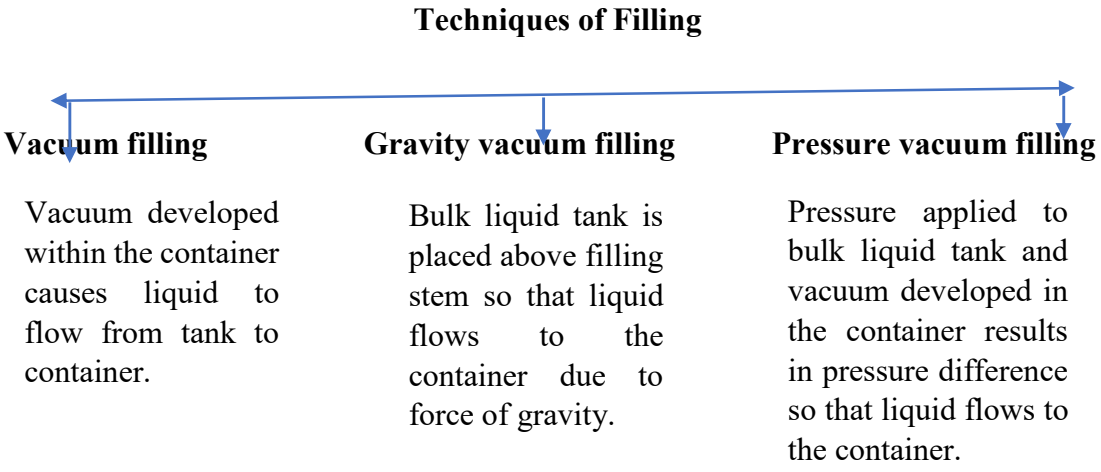
Cleaning of equipments

- All equipments must be thoroughly cleaned and sanitized before use.
- Disinfectants used: Dilute solutions of H2O2, 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.





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.

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