Tablets

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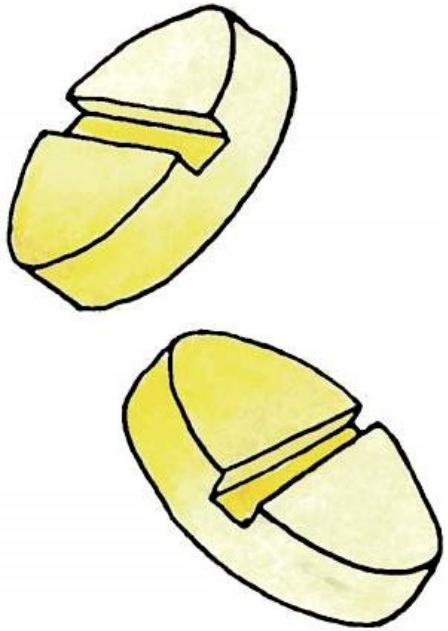


TABLETS

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 drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. **It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet.** All medicaments are available in the Tablet form except where it is difficult to formulate or administer

The advantages of the Tablet dosage form are:

1. They are unit dosage form and offer the greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
2. Cost is lowest of all oral dosage form.
3. Lighter and compact.
4. Easiest and cheapest to package and strip.
5. Easy to swallowing with least tendency for hang-up.
6. Sustained release product is possible by enteric coating.
7. Objectionable odour and bitter taste can be masked by coating technique.
8. Suitable for large scale production.
9. Greatest **chemical and microbial stability over all oral dosage form.**
10. Product identification is easy and rapid requiring no additional steps when employing an **embossed and/or monogrammed punch face.**
11. **Tamperproof dosage form**

Disadvantages:

1. Difficult to swallow in case of children and unconscious patients.

2. Some drugs resist compression into dense compacts, owing to **amorphous nature, low density character.**

3. Drugs with poor wetting, slow dissolution properties, may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

4. Bitter tasting 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.

5. Patient can not got perticular properties of a medicine such as demulcent action of linctus, can not effectively obtained with a tablet

6. Liquid medicine can not be satisfactorily formulate as a tablet

Ideal characteristics of tablet

1. A tablet should have elegant product identity while free of defects like chips, cracks, discoloration, and contamination.

2. Should have sufficient strength to withstand mechanical shock during its production, packaging, shipping and dispensing.

3. Should have the chemical and physical stability to maintain its physical attributes over time

4. The tablet must be able to release the medicinal agents in a predictable and reproducible manner.

5. Suitable size and shape for ease of administration

Types of tablets:

(A) Tablets ingested orally:

1. **Compressed tablet, e.g. Paracetamol tablet**
2. **Multiple compressed tablet, eg. coldrin**
3. **Repeat action tablet,**
4. **Delayed release tablet, e.g. Enteric coated Bisacodyl tablet**
5. **Sugar coated tablet, e.g. Multivitamin tablet**
6. **Film coated tablet, e.g. Metronidazole tablet**
7. **Chewable tablet, e.g. Antacid tablet**

(B) Tablets used in oral cavity:

1. **Buccal tablet, e.g. Vitamin-c tablet**
2. **Sublingual tablet, e.g. Vicks Menthol tablet , angina pain tablet**
3. **Troches or lozenges**
4. **Dental cone**

(c) Tablets administered by other route:

1. Implantation tablet
2. Vaginal tablet, e.g. Clotrimazole tablet

(D) Tablets used to prepare solution:

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet
4. Tablet triturates e.g. Enzyme tablet (Digiplex)

- Compressed Tablets (CT)
- Are formed by compression and contain no special coating.

- They are made from powdered, crystalline or granular materials, alone or in combination with binders, disintegrants, controlled-release polymers, lubricants, diluents and, in many cases, colorants

- **Multiple Compressed Tablets (MCT)** - These are compressed tablets made by more than one compression cycle.
- Layered Tablets OR Laminated tablet - 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. Special tablet presses are required to make layered tablets. The Compression speed is slower in multiple compression than standard compression tablet

- **Compression-Coated Tablets - dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. The outer tablet of compression coated tablet provide initial dose, rapidly disintegrating in stomach, inner tablet formulated with the component that are insoluble in gastric media but are released in intestinal environment.**
- **Core tablets- Have central core over which another layer of material is compressed, They are made by two successive compression. The core tablet usually coated with shellac or an enteric polymers so that it will not release its drug in to stomach**
- **Purpose of prepared these tablets-**
- **To separate physically or chemically incompatible ingredients**

Controlled-Release Tablets –

Controlled release tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, referred to as Prolonged-Release or Sustained-Release dosage forms as well. These tablets categorized into three types:

(1)those which respond to some physiological condition to release the drug, such as enteric coatings;

(2) those that release the drug in a relatively steady, controlled manner and

(3) those that combine combinations of mechanisms to release “pulses” of drug,

Repeat-action tablets

Repeat Action tablets Multiple doses in single tablet One dose in core-coated with enteric polymer Another dose in coat-sugar coat Now a days – Outdated Uncontrolled/ unpredictable Time consuming

Delayed action tablet

Intended to release a drug after some time delay or after the tablet has passed through one part of GIT to another. Eg of D A tablet is enteric coated tablet

All enteric coated tablets are D A tablets but not all D A tablets are enteric coated, enteric coated tablets are used for those drug which are inactivated or destroyed in acidic media or which irritate gastric mucosa

C A P, Polyvinyl acetate pthalate, HPCP etc

Sugar-Coated Tablets (SCT) –

These are compressed tablets containing a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors, and in protecting materials sensitive to oxidation.

Four main stages involved in process

1. Sealing- Shellac or CAP which prevent moisture also prevent impairment of drug release
2. Subcoat- Adhesive coat of gum (like acacia, gelatine etc) and sucrose used to round off the edge and kaolin or cal carbonate like dusted substance used to harden the coat.
3. Smoothing- 70% v/v sucrose syrup and opacifiers such as TiO_2
4. Polishing- solution of wax like material in organic solvent apply in final stage,

   colorant is added into final polishing stage

Automated spray coating gun with high efficient drying pan used for sugar coating.

Coating is relatively brittle, prone to chipping and cracking, 50% wt gain

Film-Coated Tablets (FCT) –

These are compressed tablets which are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of a greatly

-Reduced time period required for the coating operation.

-Better mechanical strength of coating based on elasticity and flexibility

- Wt gain significantly less

Chewable tablet

Tablets are chewed in moth prior to swallowing and are not intended to be swallowed intact

Specially used for children, elderly and those who have difficulty in swallowing a tablet intact, these tablets have acceptable taste and flavors, should disintegrated in short time and produce cool sweet taste but formulation does not containing DT agent, Mannitol, sorbitol, lactose dextrose etc used

Bitter types of drugs are not good candidates

- **Tablet used in oral cavity**

- **Buccal and Sublingual Tablets:**
- **These are small, flat, oval tablets.**

  Tablets intended for buccal administration by inserting into between cheek and teeth or in the cheek pouch where as sublingual placed beneath the tongue, tablet must containing sweetening agent and excipients used in tablet formulation which are not stimulate salivation, tablets deigned not to disintegrate but may dissolve slowly over 15-30 min period; therefore, they are formulated and compressed with sufficient pressure to give a hard tablet. Drug administered by this routs are intended to produce systemic drug effect by avoiding first pass metabolism
- **Advantages:- gastric decomposition is avoided, - onset of drug action is more rapid,- first pass effect is avoided**

Troches and lozenges

Intended to exert local action in mouth or throat, these are commonly used to treat sore throat or to control coughing in common cold

Lozenges are originally termed as pastilles, but are commonly called cough drops, containing sugar candy base

Lozenges made by compression but are usually formed by fusion or candy molding process

Troches are made by compression

These tablets are designed not to disintegrate in mouth but dissolve or slowly erode over a period of 30 min or less

Dental cones

Are relatively minor tablet that are intended to be placed in a empty socket remaining follow tooth extraction, their usually purpose is to prevent multiplication of bacteria and reduce bleeding by antibiotics and astringent or anti coagulants

Usually vehicle is sodium bicarbonate, NaCl or amino acid

Tablet should dissolve or erode slowly in presence of small volume of serum or fluid over a 20-40 min of period

Tablets administered by other routes

Implantation tablet: Depot tablet

Designed for subcutaneous implantation in animal or human

Tablets usually small, cylindrical, rod shaped etc, typically not more than 8 mm length and are sterile in form

Purpose is to prolong release of drug ranging from one months to year

Special types of ken injector are used to administered rod shaped tablet, other shape surgery is require

Disadvantages is surgery require, once tablet administer it will difficult to remove when skin reaction arise

Generally water in soluble and steroidal drugs are used

Vaginal tablet

Are designed to under go slow dissolution and drug release in vaginal cavity, they are substitute for traditional pessaries

Tablets are typically ovoid or pear shaped to facilitate retention in vagina

Component of the tablets should be compatible with plastic tube inserter, which are used to kept tablet in to the upper region of the vaginal tract

Generally antibacterial, antiseptic or astringent are used to treat vaginal infection

Tablet used to prepare solution

Effervescent Tablets:

- In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric or citric.
- In the presence of water, these additives react and liberating carbon dioxide which acts as a disintegrator and produces effervescence.
- Except for small quantities of lubricants present, effervescent tablets are soluble.
- Tablet produce a pleasantly flavored carbonated drink which assist in masking the taste of certain drug

- **Molded Tablets [Tablet Triturates (TT]**

- Tablet triturates usually are made from moist material using a triturate mold which gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water soluble
- Alcohol is commonly used in TT to wet the powder mass
- TT are soft and friable

- **Dispensing Tablets (DT) –**

- These tablets provide a convenient quantity of potent drug that can be used to produce solution by pharmacist or consumer by dissolving in a given vol. of water. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.
- Material that have been commonly incorporated in dispensing tablets include mild silver propionate, bichloride of mercury, quaternary ammonium compound
- D T must typically comprise totally soluble component

- **Hypodermic Tablets (HT)** –
- Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Tablets are intended to be added in sterile water or water for injection, all drug and additives must be highly purify
- Main adv is portability of tablets for injection
- Disadvantage is medical situation is required

- Tablet Ingredients
- In addition to the active or therapeutic ingredient, tablets contain a number of inert materials(excipients). They are classified according to the part they play in the finished tablet.
- 1- those which affect compression characteristics of the tablet (diluents, binders, glidants and lubricants).
- 2- those which affect, biopharmaceutics, chemical and physical stability and marketing consideration of the tablet
- (Disintegrating agent, colors, flavours and sweetner etc)

Diluent:

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

Selection of the diluent

Is based partly on the experience of the manufacturer as well as on diluent cost and compatibility with other tablet ingredients

- **However, in the formulation of new therapeutic agents, the compatibility of the diluents with the drug must be considered, e.g:**
- **calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract.**
- **When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems.**

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 101 and PH 102)
5. Dibasic calcium phosphate dehydrate
6. Calcium sulphate dihydrate
7. Mannitol
8. Sorbitol
9. Sucrose- Sugartab, DiPac, Nutab
10. Dextrose

•Lactose

- Hydrous, anhydrous lactose and spray dried commonly used
- Are available in two grades 1. 60-80 # - course, 2. 80-100 # - Regular
- The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, moisture results in tablets which leads to brown- millard reaction, that is due to presence of 5-(hydroxy)-2-furaldehyde
- Hydrous form gives millard reaction while anhydrous form have less tendency, some time they produce brownish color slowly
- Spray dried lactose- directly compression,
- Diluents used in direct compression formulas have been subjected to prior processing to give them flowability and compressibility.
- Brand name- Pharmattose, tablettose,

Starch

- Source- corn,wheat, or potatose
- Uses- diluent, binder, disintigrants and film former
- Available in different forms they are differentiate mainly based on presence of moisture content, starch USP- contain more moisture (11-14%) than dried starch (2-4%)
- Sta-Rx 1500 (modified corn starch) 10% moisture
- Two hydrolysed starch (8-10% moisture) Emdex and Celutab are basically 90-92% dextrose and about 3-5% maltose, generally used in place of mannitol in chewable tablet because of their sweet teste smooth feeling and good flowabiliy - directly compressible
- These modified starch also aids in rapid release of drug from the tablet

MCC

- Microcrystalline cellulose (Avicel) usually is used as an excipient in direct-compression formulas. Two gades- PH 101 (powder) and PH 102(granules)
- Provide good flow properies, excellent compression charecteristics and producing cohesive compacts and also act as secondary binder, disintegrating agent and lubricants (when less than 20% of API) due to less static friction
- Disadv- expensive

- Mannitol
- Mainly used in chewable tablet because of their good mouth feeling and palatibility properties its due to nagative heat of the solution and slow solubility
- It has been reported 72% sweeter than sucrose
- Due to their non hygroscopicity vitamins and antacid along with used
- Poor flow properties, produce soft tablet compare to sucrose and dextrose and relatively expensive
- Brand- mannogen 2080

Sorbitol

- Is an optical isomer of manniol, used in sometime with manniol to reduce formulation cost, however sorbitol is hygroscopic in nature
- Both are low caloric content and non carcinogenic
- Brand- Neosorb 60, sorbidex P

Dextrose- same reaction occur as lactose

Trade name- Cerelose – in two form hydrous and anhydrous, some time combined in formulation to replace some qty of spray dried lactose, which may reduce tendency of the resulting tablets to darken

- Sucrose or sugar
- Main disadv is some manufacture avoid use of sugar as diluent in case of diabetic patient, some of following sugar based diluents availables in named
- Sugartab- (90-93% sucrose+7-10% invert sugar)
- DiPac- (90% sucrose +3% modified dextrine)
- Nu Tab- (95% sucrose and 45% invert sugar with small amount of corn starch and magnesium stearate)
- Used in direct compression and with or without mannitol in chewable tablet

- **Dibasic calcium phosphate dihydrate N F,**

Normally used as diluents and binder as directly compression, Marketed name Emcompress- composed of 40-200 # material, is non hygroscopic and contain about 0.5% moisture, in DC formula it require mag stearate

Other Brand- fujicalin, Di Tab.

Miscellaneous

Elcema- microfine cellulose (α- cellulose) available in powder, fibrous and granular form

Rexcel- Food grade natural source of α and amorphouse cellulose

- Binders

- Binders are used in wet granulation to form granules or to promot cohesive compacts for direct compressed tablet
- Commonly used binders include: starch, gelatin and sugars as sucrose, glucose and dextrose
- Natural and synthetic gums which have been used include acacia, sodium alginate, carboxy- methylcellulose, methylcellulose, polyvinyl pyrrolidone, Veegum, disadv- is variable in their composition and performance based on their natural origin
- The quantity of binder used has considerable influence on the characteristics of the compressed tablets.
- The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies.
- Usually materials which have no cohesive qualities of their own will require a stronger binder than those with these qualities.

- Binders are used both as a solution and in a dry form depending on other ingredients and method of preparation.
- The same amount of binder in solution will be more effective than in a dry form. So it is preferable to incorporate the binding agent in solution.
- If the drug substance is adversely affected by an aqueous binder , a non aqueous binder can be used or binder can be added dry.
- The direct-compression method for preparing tablets requires a material that not only is free-flowing but also sufficiently cohesive to act as a binder.

Starch paste - dispersing starch in water then apply heat for prescribed time, during heating starch under go hydrolysis to dextrin and to glucose, prepared paste translucent rather than clear which would indicate complete conversion to glucose

- Sucrose solution commonly used in conc beween 50-70%, are produce hard but some what brittle compacts, this material have adv- being low cost adhesives
- Some of the modified natural polymers eg alginates, cellulose derivatives are used as dry form in direct compression and also aqueous solution have adhesive properties and other polymers like HPC, EC, PVP are used as anhydrous adhesive by dissolving in non aqueous solvent

- **Disintegrants**
- Is a substance, or a mixture of substances, added to a tablet to facilitate its breakup or disintegration after administration.
- Materials serving as disintegrants have been classified chemically as starches, clays, celluloses, algins, gums and cross-linked polymers.
- The oldest and still the most popular disintegrants are corn and potato starch which have been well-dried and powdered.
- Starch has a great affinity for water and swells when moistened, thus facilitating the rupture of the tablet matrix.
- Others suggested that its disintegrating action in tablets is due to capillary action rather than swelling.

- Starch 5%, is suggested, but if more rapid disintegration is desired, this amount may be increased to 10 or 15%.
- Usually disintegration time would decrease as the percentage of starch increased.
- A group of materials known as super disintegrants have gained in popularity. As Croscarmelose, crospovidone and sodium starch glycolate
- The name comes from the low levels (2 to 4%) at which they are completely effective.
- Sodium starch glycolate swells 7-12 fold in less than 30 seconds. Croscarmelose swells 4-8 fold in less than 10 seconds.
- Modified starch primogel and explotab are low substituted carboxymethyl starch (1-8% , optimum 4% repored)

The disintegrating agent usually is mixed with the active ingredients and diluents prior to granulation.

In some cases it may be advantageous to divide starch into two portions:

- One part is added to the powdered formula prior to granulation, and the remainder is mixed with the lubricant and added prior to compression.
- Incorporated in this manner, the starch serves a double purpose; the portion added to the lubricant rapidly breaks down the tablet to granules, and the starch mixed with the active ingredients disintegrates the granules into smaller particles.
- **Other factors affect the disintegration time of compressed tablets:**

1- The binder
2- Tablet hardness
3- Lubricant.
4- Evolution of carbon dioxide. As in effervescent tablets.

Lubricants, Anti adherants and glidants

▶Lubricant functions in tablet manufacture.

1.Prevent adhesion of the tablet material to the surface of the dies and punches.

2.Reduce inter particle friction.

3.Facilitate the ejection of the tablets from the die cavity.

4. May improve the rate of flow of the tablet granulation.

▶Commonly used lubricants include: talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, sodium benzoate and PEG.

▶Most lubricants, with the exception of talc, are used in concentrations less than 1%. When used alone, talc may require concentrations as high as 5%.

- Lubricants are in most cases hydrophobic materials. Poor selection or excessive amounts can result in “waterproofing” the tablets, resulting in poor tablet disintegration and or delayed dissolution of the drug substance

- Anti adherants:

  reduce sticking and adhesion of the tablet granulation or powder to the faces of the punches or to the die walls. material used as antiadherant are colloidal silica such as cab-O-sil, sylloid, talc, SLS, mag stearate,

- **Glidants**

  promote the flow of the tablet granulation or powder materials by reducing friction among particles, generally effectiveness of glident in order of fine silica > magnesium searate > purified talc

Colorants

Colors and dyes serve to:

1. Disguise off-color drugs.
2. Provide product identification.
3. Produce a more elegant product.

- Food, drug, and cosmetic dyes (solution form) and lakes (dry form) are available in various colors, specially the color of dye that are near the mid-range of visible spectrum (yellow to green) which shows least amount of mottling.

Differentiating character	lakes	Dyes
Solubility Characteristics	In soluble in most of the solvent	Soluble in water and propylene glycol
Method of addition	Dispersion form	Solution form
Amount of pure dye	10-40%	90-93%
Concn needed for coloring	0.1-0.3%	0.01-0.03%
Size of particle	<0.5 micron	12-200#
Color intensity	Does not depends on dye content	Depends on pure dye content
Shade of color	Depend on amount Of pure dye	constant

▶Flavoring agents

Are usually limited to chewable tablets or tablets intended to dissolve in the mouth.

▶(a) Generally, water-soluble flavors have poor stability; hence, flavor oils or dry powders usually are used.

▶(b) Flavor oils may be added to tablet granulations in solvents, dispersed on clays and other adsorbents, or emulsified in aqueous granulating agents. Usually, the maximum amount of oil that can be added to a granulation without influencing its tablet characteristics is O.5%—O.75%.

▶If flavor oil are volatile in nature then added just before compression

▶**Sweeteners**,

Sweeters and flavors, are usually used only with chewable tablets or tablets dissolve in the mouth for improving taste.

(a) Some sweetness may come from the diluent (e.g., mannitol, lactose); agents, such as saccharin and aspartame, can also be added.

(b) Saccharin has an unpleasant after taste and carcinogenic.

(c) Aspartame is not stable in the presence of moisture.

▶**Adsorbents**

(e.g., magnesium oxide, magnesium carbonate, bentonit, silicon dioxide) are substances capable of holding quantities of fluid in an apparently dry state.

Highly adsorbent substances, e.g, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed after administration.

Co-processed Excipients

- Are the mixture of one or more excipients, which are commonly used in conjunction with each other to improve their characteristics, these excipients possess better tabletting properties compared to individual components.
- Coprocessing of excipients- It is the process in which the components are modified physically with out changing its chemical structure
- These excipients must have better binding and blending properties and also they should be economical compared to individuals

- Disadvantages- they are unofficial, not included in pharmacopoeia
- Ratio of individual components is fixed

- Example-
- Cellactose (MCC and lactose)
- Dipac (Sucrose and dextrin)
- Ludipress(lactose ,pvp, crosspovidone)
- Prosolv(MCC and colloidal sillica)

- **Tablet preparations**

  There are three general methods of tablet preparation:

  1-the wet granulation method,

  2- the dry-granulation method and

  3- direct compression

- **After compression, the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and content uniformity which are also influenced by both :**
- **the method of preparation and by**
- **the added materials present in the formulation**.

General methods of tablet preparation:

▶Wet Granulation

- ▶The most widely used and most general method.
- ▶This due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets.
- ▶Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on a large scale.
- ▶The steps in the wet method are:

1-weighing, 2-mixing, 3-granulation, 4-screening the damp mass

5- drying, 6-dry screening, 7-lubrication and 8-compression.

- The active ingredient, diluent and disintegrant are mixed or blended well.
- The powder blend may be sifted through a screen to remove or break up lumps, this screening affords additional mixing.
- The screen selected always should not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys

- Solutions of the binding agent are added to the mixed powders with stirring.
- The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar.
- If the 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.

- Tray drying was the most widely used method of drying tablet granulations in the past, Notable among the newer methods being introduced are the fluid-bed dryers.

- In fluidization, the material is suspended and agitated in a warm air stream while the granulation is maintained in motion.

- Comparing the fluidized bed and a tray dryer indicated that the former was 15 times faster than the conventional method of tray drying. In addition to the decreased drying time, the fluidization method have advantages such as better control of drying temperatures, decreased handling costs.

- In drying, it is desirable to maintain a residual amount of moisture in the granulation. This is necessary to maintain the various granulation ingredients such as gums in a hydrated state.
- Also, the residual moisture contributes to the reduction of the static electric charges on the particles.
- In the selection of any drying process, an effort is made to obtain a uniform moisture content, the stability of the products containing moisture-sensitive active ingredients may be related to the moisture content of the products.

- Previously it was indicated that water-soluble colorants can migrate toward the surface of the granulation during the drying process, resulting in mottled tablets after compression.

- Migration can be reduced by drying the granulation slowly at low temperatures or using a granulation in which the major diluent is present as granules of large particle size. The presence of microcrystalline cellulose in wet granulations also reduces migration tendencies.

- After drying, the granulation is reduced in size by passing through screen.
- After dry granulation, the lubricant is added as a fine powder.
- It usually is screened through 60- or 100-mesh nylon cloth to eliminate small lumps as well as to increase the covering power of the lubricant.
- The presence of some fines is necessary for the proper filling of the die cavity.

•Dry Granulation

- **When tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures during drying, and when the tablet ingredients have sufficient inherent binding or cohesive properties, slugging may be used to form granules.**

- **This method is referred to as dry granulation, pre compression or double-compression. It eliminates a number of steps but still includes weighing, mixing, slugging, dry screening, lubrication and compression.**

- One of the constituents, either the active ingredient or the diluent, must have cohesive properties. Powdered material contains a considerable amount of air; under pressure this air is expelled and a fairly dense piece is formed. The more time allowed for this air to escape, the better the tablet or slug
- The compressed slugs are comminuted through the desirable mesh screen either by hand, or for larger quantities through the comminuting mill.
- The lubricant remaining is added to the granulation, blended gently and the material is compressed into tablets.
- Aspirin is a good example where slugging is satisfactory.

Direct Compression

- **Direct compression consists of compressing tablets directly from powdered material without modifying the physical nature of the material itself.**
- **Reserved for a small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet. This group includes chemicals such as potassium salts (chlorate, chloride, bromide, iodide, nitrate, permanganate), ammonium chloride.**
- **For tablets in which the drug itself constitutes a major portion of the total tablet weight, it is necessary that the drug possess those physical characteristics required for the formulation to be compressed directly.**

- These commercially available direct- compression vehicles may contain small quantities of other ingredients (e.g, starch,) as processing aids.
- Di-Tab is chemically odorless, tasteless and non- hygroscopic. Since it has no inherent lubricating or disintegrating properties, other additives must be present to prepare a satisfactory formulation
- Compressible sugar consists mainly of sucrose that is processed to have properties suitable for direct compression. It also may contain small quantities of dextrin, starch or invert sugar. It is a white crystalline powder with a sweet taste and complete water solubility. It requires the incorporation of a suitable lubricant at normal levels for lubricity. The sugar is used widely for chewable vitamin tablets because of its natural sweetness.

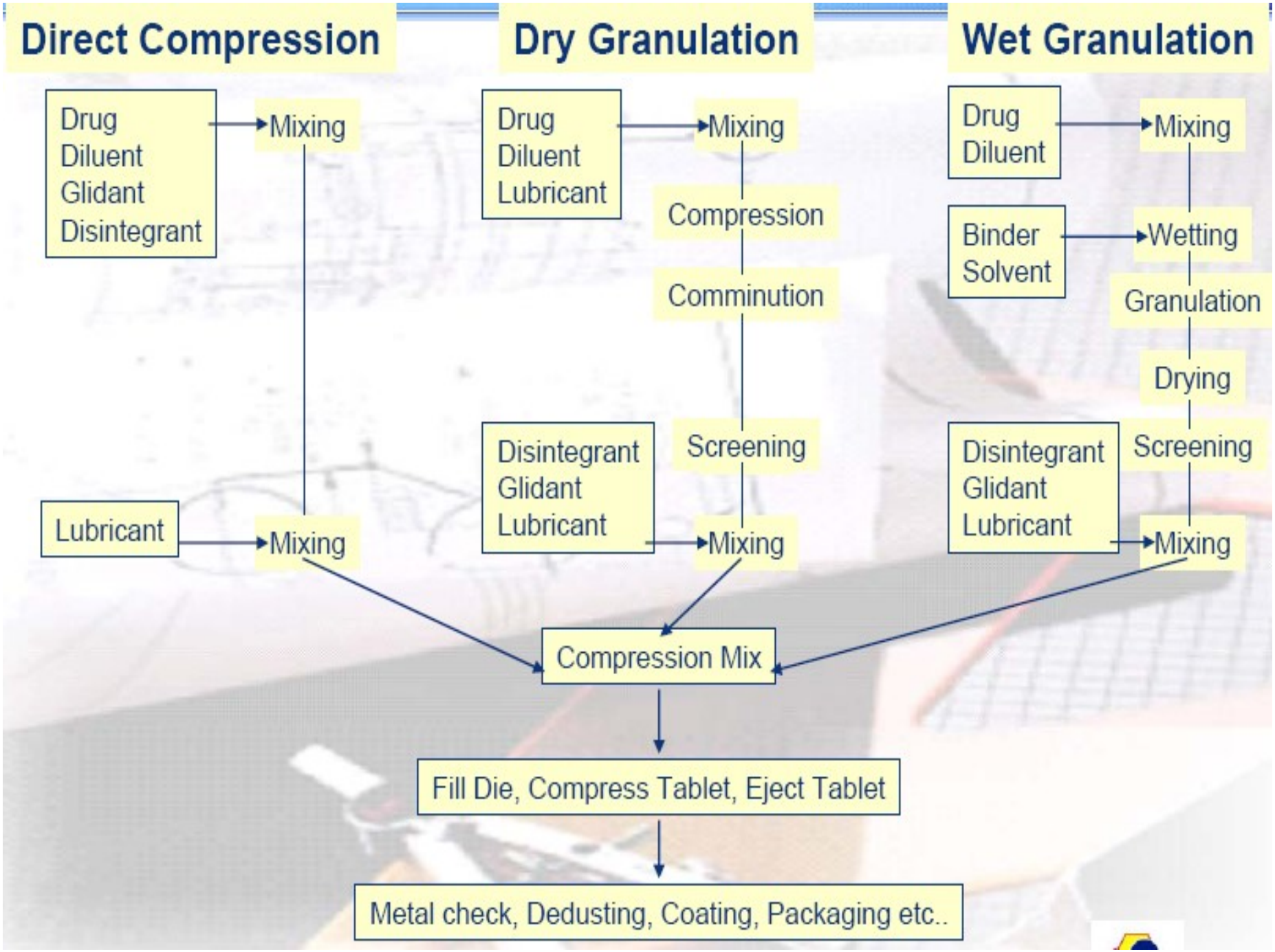
* One commercial source is Di-Pac (Amstar) prepared by the cocrystallization of 97% sucrose and 3% dextrins.

* Some forms of lactose meet the requirements for a direct-compression vehicle. Hydrous lactose does not flow and its use is limited to tablet formulations prepared by the wet granulation method, Both anhydrous lactose and spray dried lactose have good flowability and compressibility and can be used in direct compression provided a suitable disintegrant and lubricant are present.

- microcrystalline cellulose (Avicel, FMC).

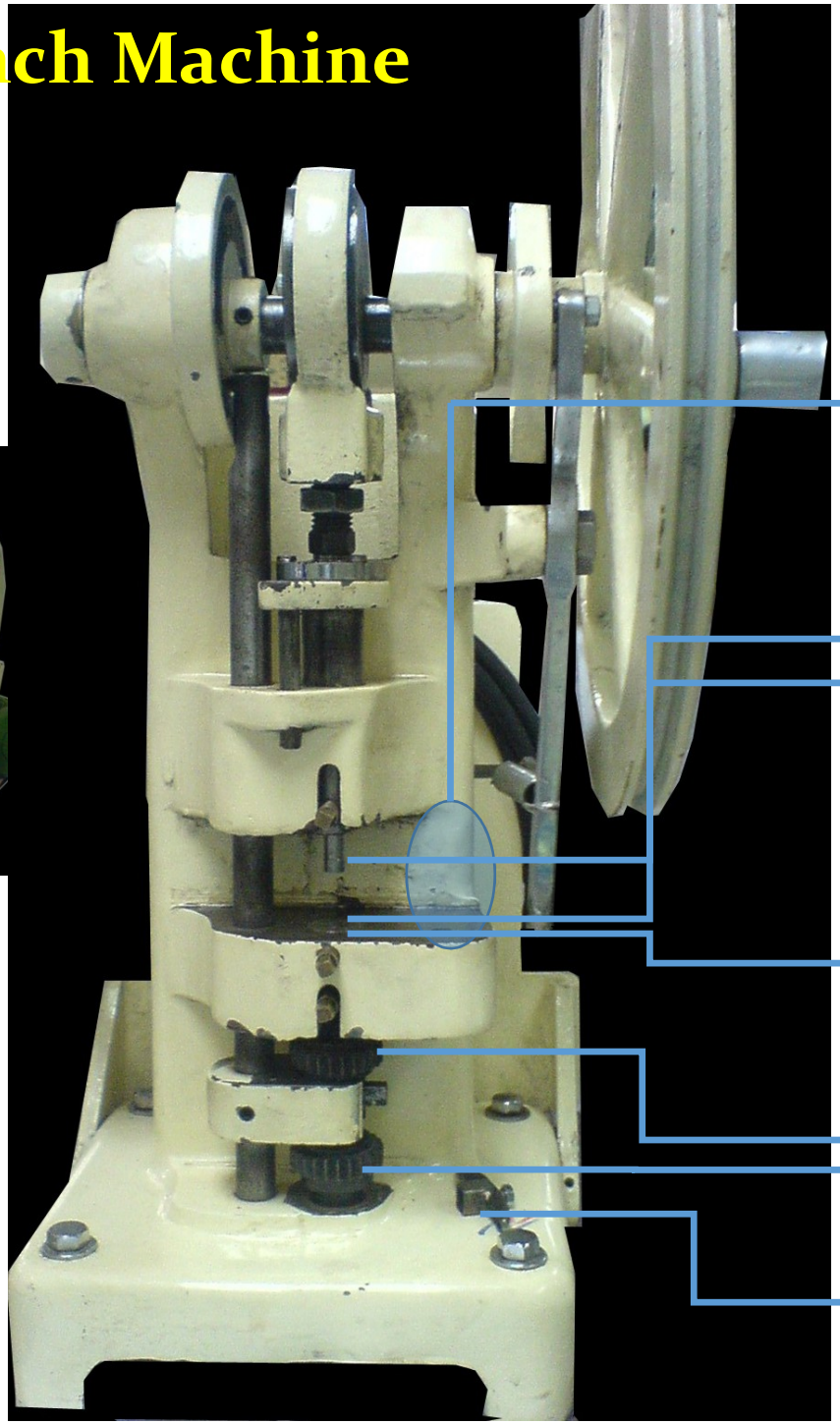
This non fibrous form of cellulose is obtained by spray-drying washed, acid-treated cellulose and is available in several grades which range in average particle size from 20 to 100 um. It is water insoluble but the material has the ability to draw fluid into a tablet by capillary action;

It swells on contact and thus acts as a disintegrating agent. The material flows well and has a degree of self-lubricating qualities, thus requiring a lower level of lubricant as compared to other excipients.


Direct Compression
Drug
Diluent
Glidant
Disintegrant
Mixing
Lubricant
Mixing
Dry Granulation
Drug
Diluent
Lubricant
Mixing
Compression
Comminution
Disintegrant
Glidant
Lubricant
Screening
Mixing
Wet Granulation
Drug
Diluent
Mixing
Binder
Solvent
Wetting
Granulation
Drying
Disintegrant
Glidant
Lubricant
Screening
Mixing
Compression Mix
Fill Die, Compress Tablet, Eject Tablet
Metal check, Dedusting, Coating, Packaging etc..

Step	Wet	Dry	direct
Raw material	Y	Y	Y
Weigh	Y	Y	Y
Screen	Y	Y	y
Mix	Y	Y	Nil
Compress	Nil	Y	Nil
Wet mass	Y	Nil	Nil
Mill	Y	Nil	Nil
Dry	Y	Nil	Nil
Mill	Y	Y	Nil
Mix	Y	Y	Nil
compress	y	y	y

Single Punch Machine (Tablets)

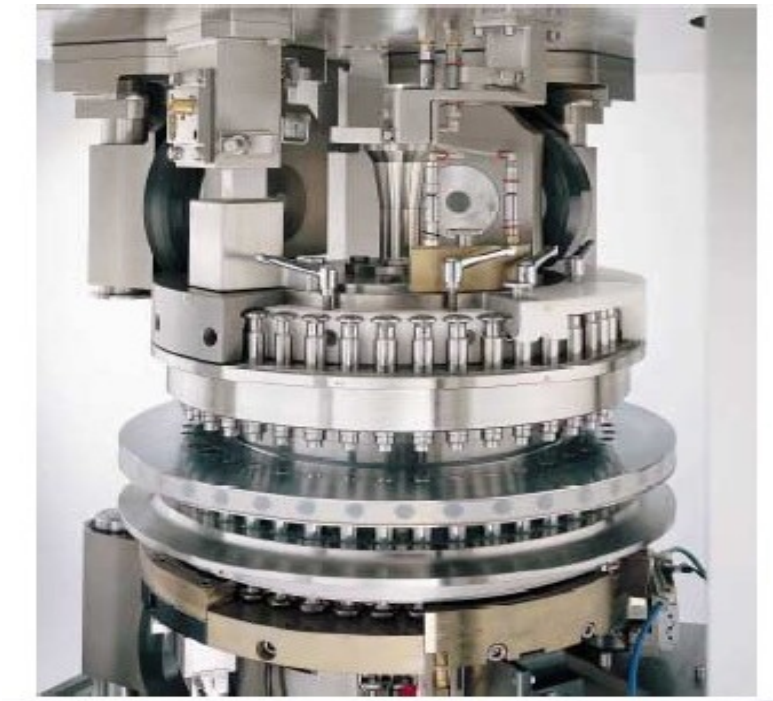


Tablet Compression Machine

Tablets are made by compressing a formulation containing a drug or drugs with excipients on stamping machine called presses. Tablet presses are designed with following basic components:

1) Hopper for holding and feeding granulation
2) Dies that define the size and shape of the tablet.
3) Punches for compressing the granulation within the dies.
4) Cam tracks for guiding the movement of the punches.
5) Feeder a feeding mechanism for moving granulation from hopper into the dies.

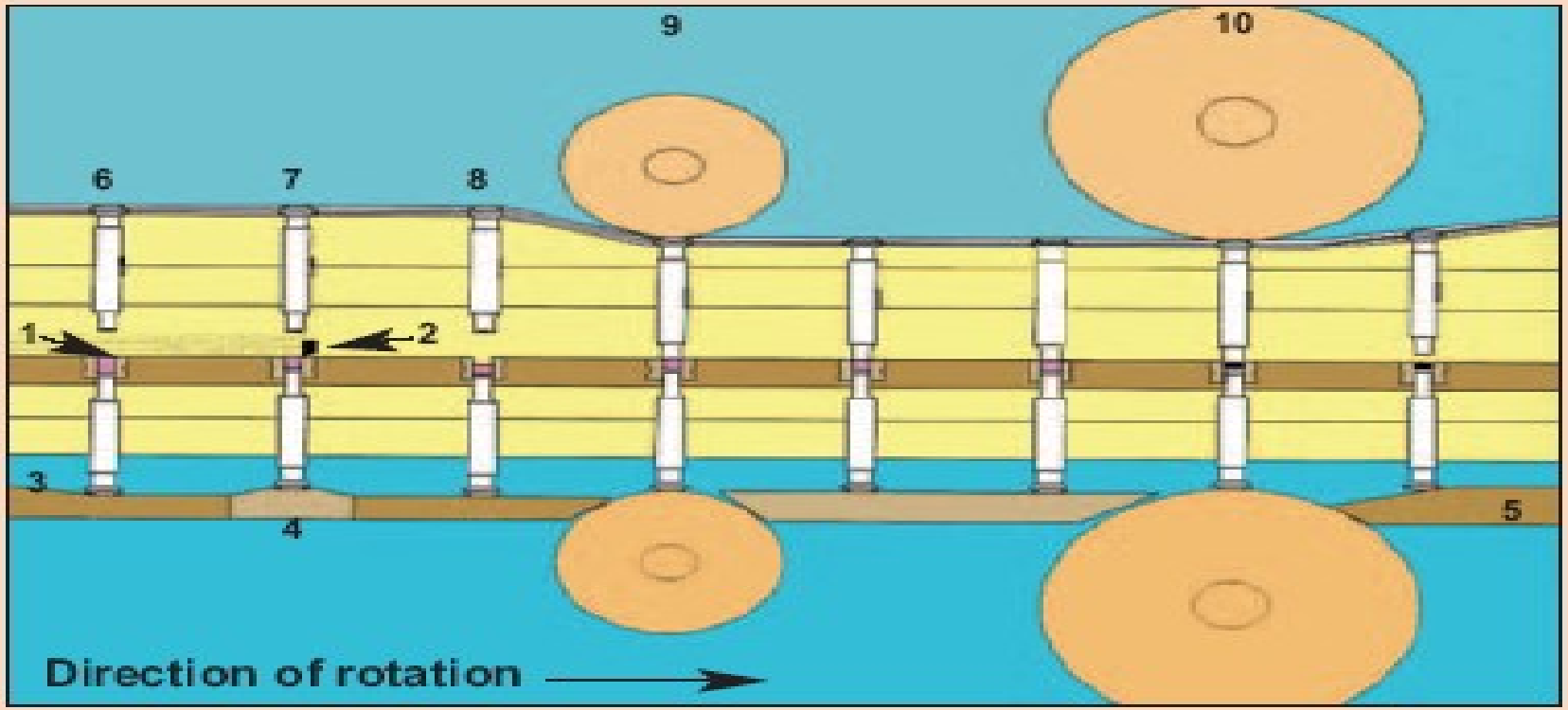
Rotary Tablet Press



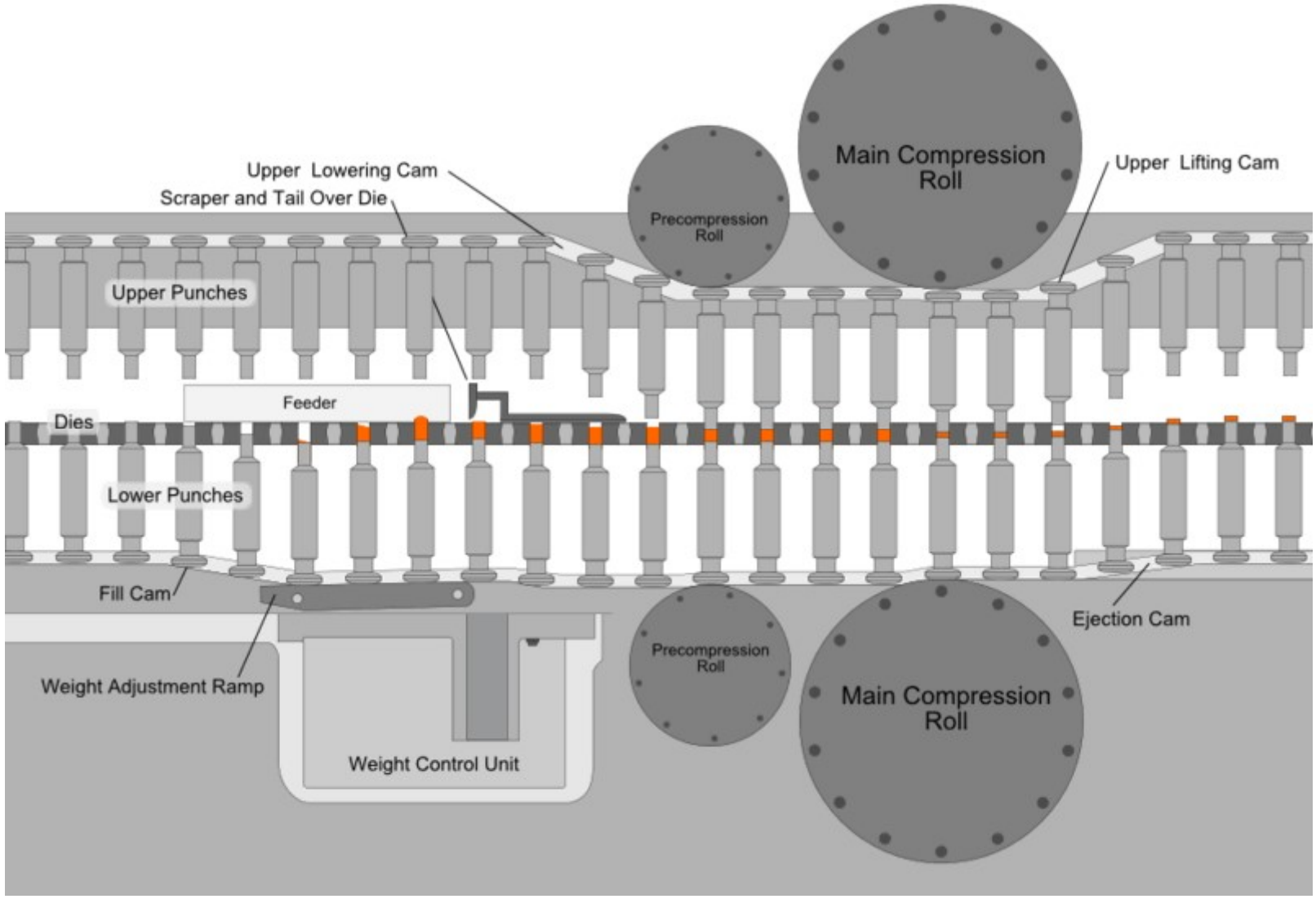
Compression process

- Filling
  - By gravitational flow of powder from hopper via the die table into die. The die is closed at its lower end by the lower punch.
- Compression
  - The upper punch descends and enters the die and the powder is compressed until a tablet is formed.
  - During the compression phase, the lower punch can be stationary or can move upwards in the die.
  - After maximum applied force is reached, the upper punch leaves the powder i.e. the decompressed phase.
- Ejection
  - During this phase, the lower punch rises until its tip reaches the level of the top of the die. The tablet is subsequently removed from the die and die table by a pushing device.

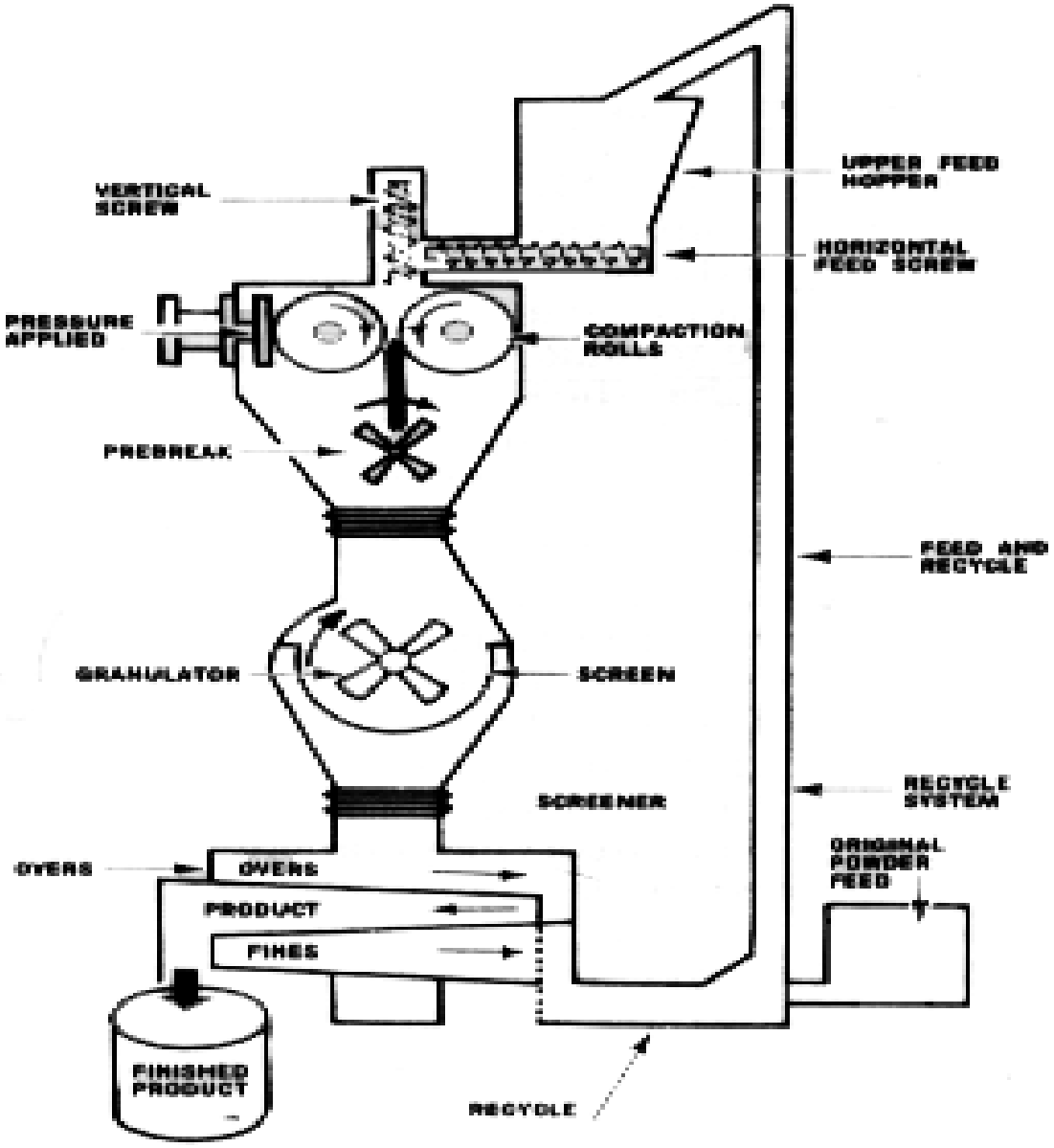
An illustration of the compression cycle



1. Product in feeder
2. Scraper
3. Fill cam (partial view)
4. Weight adjustment cam
5. Ejection cam
6. Fill position
7. Weight adjustment position
8. Pull-down position
9. Pre-compression
10. Main compression


Upper Lowering Cam
Scraper and Tail Over Die
Precompression Roll
Main Compression Roll
Upper Lifting Cam
Upper Punches
Feeder
Dies
Lower Punches
Fill Cam
Ejection Cam
Weight Adjustment Ramp
Precompression Roll
Main Compression Roll
Weight Control Unit

- **Roller compacter (chilsonator)**



Roller compacter (chilsonator)

- Variables
- Hydraulic pressure exerted on compaction rolls
- Rotational speed of compaction rolls

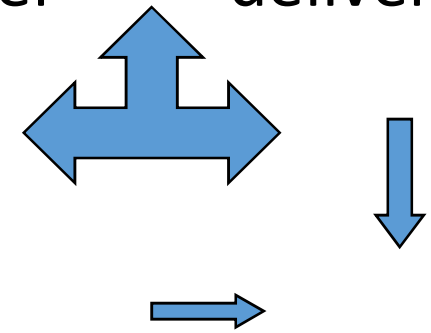
- Rotational speed of feed-screws

Horizontal

Picks up powder from hopper

Vertical

deliver to rolls



Greatest effect

Critical for uniform compaction

Processing problems

- a. **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 separation of a tablet into two or more distinct layers. Both of these problems usually result from air entrapment during processing.

- b. **Picking** is removal of a tablet's surface material by a punch.
- **Sticking** is adhesion of tablet material to a die wall. These two problems result from excessive moisture or substances with low melting temperatures in the formulation

- c. **Mottling** is an unequal color distribution on a tablet, with light or dark areas standing on otherwise uniform surface. This results from use of a drug with a color different from that of the tablet excipients or from a drug with colored degradation products.

Characteristics of ideal tablets

1- **Free of defects ,such as chips ,cracks ,discoloration &contamination**

2-Have the strength to withstand the mechanical stress of production

3-Chemically & physically stable over time

4-Release the medicinal agents in a predictable& reproducible manner

▶5. Tablet Evaluation and Control

▶1] General appearance:

Important for: a- consumer acceptance,

b- lot-to-lot uniformity

c- tablet-to-tablet uniformity

d- monitoring of the manufacturing process.

Tablet appearance includes visual identity and overall appearance. Control of appearance includes measurement of such attributes as size, shape, color, odor, taste, surface, textures physical flaws, consistency.

- **2] Hardness and resistance to friability:**

Are necessary for tablets:

1- To withstand the mechanical shocks of manufacture, packaging, and shipping,

2- To ensure consumer acceptance.

Hardness relates to both tablet disintegration and to drug dissolution. Certain tablets intended to dissolve slowly are made hard, whereas others intended to dissolve rapidly are made soft. Friability relates to the tablet's tendency to crumble.

- **(1) Tablet hardness testers measure the degree of force in kg required to break a tablet across the diameter**

(2) Friabilators determine friability by allowing the tablet to roll and fall within a rotating tumbling apparatus. The tablets are weighed before and after a specified number of rotations(100), and the weight loss is determined.

(a) Resistance to weight loss indicates the tablet's ability to withstand abrasion during handling, packaging, and shipping.

* Compressed tablets that lose less than 0.5%- 1 % of their weight are generally considered acceptable.

(b) Some chewable tablets and most effervescent tablets are highly friable and require special unit packaging.

3] Tablet thickness

- The thickness of the tablet from production-run to production-run is controlled carefully.

- Thickness can vary with no change in weight due to:

  a- Difference in the density of the granulation

  b- The pressure applied to the tablets.

  c- The speed of tablet compression.

- tablet thickness important in reproducing tablets identical in appearance but also to insure that every production lot will be usable with selected packaging components. If the tablets are thicker than specified, a given number no longer may be contained in the volume of a given size bottle. Tablet thickness also becomes an important characteristic in counting tablets using filling equipment.

- **A plus or minus 5% may be allowed, depending on the size of the tablet.**

4] Uniformity of Dosage Forms:

Weight variation

tablets containing 50 mg or more of drug substance in which the drug substance represents 50% or more (by weight) of the dosage form unit.

- Twenty tablets are weighed individually and the average weight is calculated.

  The variation from the average weight not more than two of the tablets must not differ by more than the percentage listed; no tablet differs by more than double that percentage. Tablets that are coated are exempt from these requirements but must conform to the test for content uniformity if it is applicable.

- Content uniformity
- 10 tablet 100mg-----85-115%
- Non outside this range-----75-125%
- Only one between the two ranges
- Non of the tablet must be outside 75-125% range
- If content of one tablet outside range 85-115% further20T are assayed &all must fall within85-115%

5] Tablet Disintegration

It is recognized generally that the in vitro tablet disintegration test does not necessarily bear a relationship to the in vivo action of a solid dosage form. To be absorbed, a drug substance must be in solution and the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles. Generally, this test is useful as a quality-assurance tool for conventional (non sustained-release) dosage forms.

- comparing disintegration times and dissolution rates or initial absorption rates of several brands of aspirin tablets, it was found that the faster absorbed tablets had the longer disintegration time. Regardless of the lack of significance as to in vivo action of the tablets, the test provides a means of control from one production batch to another. It is used as a control for tablets intended to be administered by mouth, except where tablets are intended to be chewed before being swallowed or where tablets are designed to release the drug substance over a period of time

- The apparatus consists of a basket rack holding six plastic tubes, open at the top and bottom; the bottom of the tubes is covered with 10-mesh screen
- The basket rack is immersed in a bath of suitable liquid, held at 37°, preferably in a 1 -L beaker. The rack moves up and down in the fluid at a specified rate.

- The volume of the fluid is such that on the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom on the downward stroke. Tablets are placed in each of the six cylinders along with a plastic disc over the tablet unless otherwise directed in the monograph. The end-point of the test is indicated when any residue remaining is a soft mass having no soft core

- The plastic discs help to force any soft mass which forms through the screen. For compressed uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets and sublingual tablets. Disintegration times are included in the individual tablet monograph.

- For most uncoated tablets the period is 30 minutes although the time for some uncoated tablets varies greatly, from this. For coated tablets up to2 hours may be required, while for sublingual tablets, the disintegration time is 3 minutes.

6] Dissolution Test

- For tablet containing slowly or poorly soluble drug determination of dissolution rate may be more important than measuring tablet disintegration time
- The dissolution test measures the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an in vitro test.

- It provide a step towards the evaluation of the physiological availability of the drug substance, but it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate in vivo studies and clinical evaluation. It provides an in vitro control procedure to eliminate variations among production batches.

- All 6 tablets must meet the requirements specific. If one or two T failed, repeat the test on 6 additional T. In most cases the amount of drug dissolved should not be less than 70% of quantity contained in tablet after 45min.

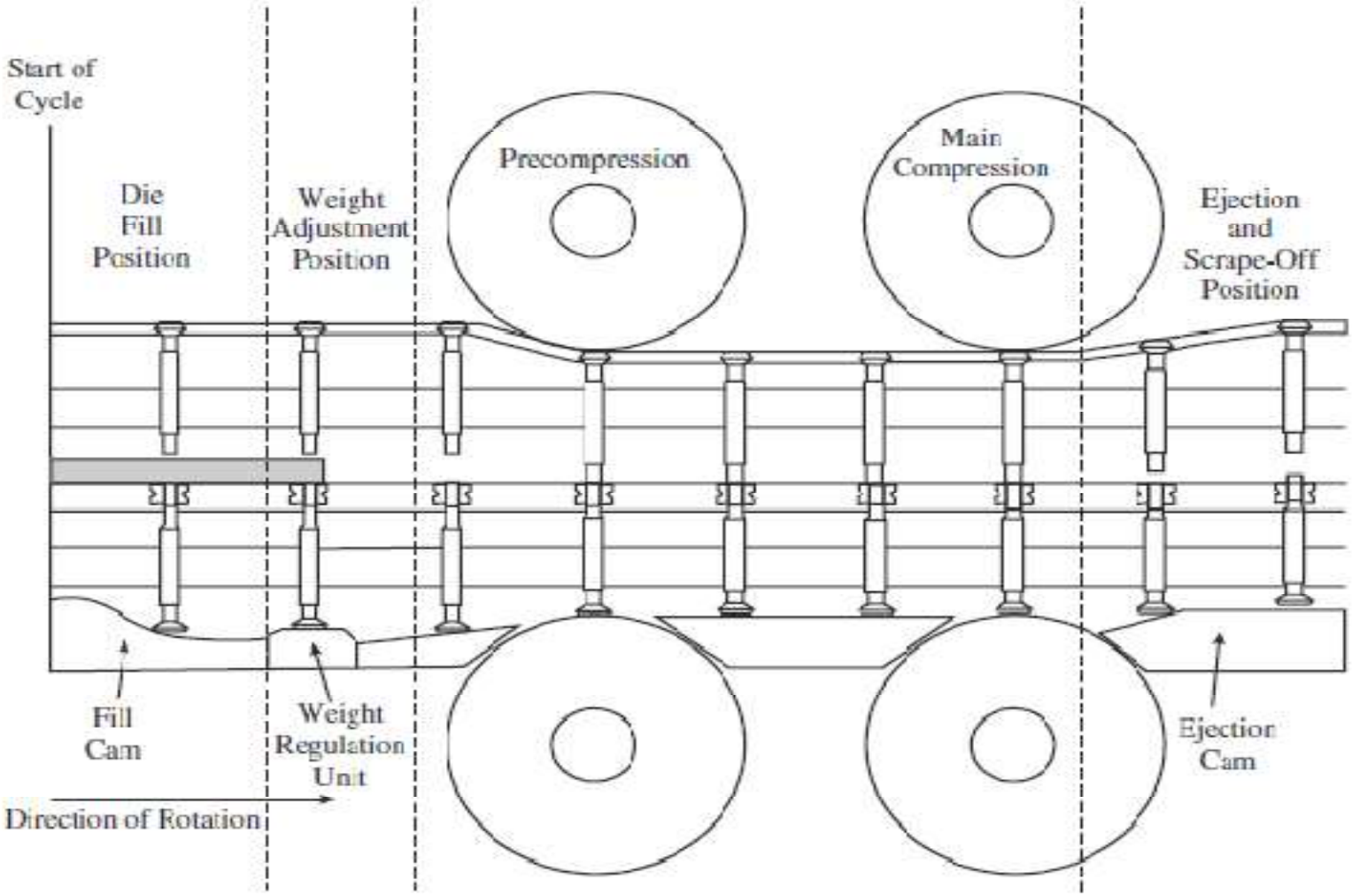


Fig. 4 Rotary press (sequences of compression).