Pharmacy

Pharmaceutical Technology

Tablets

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CONTENTS

Introduction

Solid medicaments may be administered orally as **powders**, **pills**, **cachets**, **capsules** or **tablets** .These dosage forms contain a quantity of **drug** which is given as a single unit and they are known collectively as solid unit **dosage forms,** even in the case of sustained action preparations which, technically, contain the equivalent of several normal doses of drug .The stringent formulation requirements of modern medicaments, the many advantages of tablet and capsule medication, coupled with expanding health services and the commitment need for large-scale economic manufacture, have led to a steady decline in the prescribing of powders and pills .Tablets and capsules, on the other hand, currently account for well over two third of the total number and cost of medicines produced all over the world.

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**.

Disadvantages of Tablet dosage form are:
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, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.
4. 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.

General properties of Tablet dosage forms:
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. Must have a chemical stability over time so as not to follow alteration of the medicinal agents.

Different types of Tablets
(A) Tablets ingested orally:
1. Compressed tablet, e.g. Paracetamol tablet
2. Multiple compressed tablet
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
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: Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.

Multiple compressed tablets: For incompatible components these are:
A) Layered tablet- either two layered (for two components) or three layered (for three components) tablet.
B) Compressed coated type- either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons
1. To separate physically or chemically **incompatible** ingredients.
2. To produce repeat action or prolong action product.

Repeat action tablet: Sugar coated or multiple compressed tablets are used for this purpose .The core tablet is usually coated with shellac or an enteric polymer so that it will not release its drug in stomach but intestine.

Delayed action and enteric-coated tablet: This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the GIT into another. All **enteric coated** tablets are type of **delayed action tablet** but all delayed action tablets are not enteric or not intended to produce enteric action.

Sugar coated tablet: Primary role is to produce an elegant, glossy, easy to swallow, widely utilized in preparing multivitamin and multivitamin mineral combination. **Sugar coating** doubled the tablet weight. Now polymers are used with sugar solution.

Film coated tablet: One type of coated tablet in which drug is not required in coating. This is an attractive method within one or two hours. Polymers such as hydroxypropylcellulose, hydroxypropylmethyl cellulose, and colloidal dispersion of ethylcellulose are commonly used. A 30% dispersion of ethyl cellulose is known as aquacoat. Advantage of film coated over sugar coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.

Chewable tablet: These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid, bitter or foul testing drugs are not suitable for this type tablet.

Buccal and sublingual tablet: These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrate but slowly dissolve.

Troches and lozenges: Used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in common cold. They may contain local **anesthetics**, **antiseptic**, **antibacterial agents**, **demulcents**, **astringent** and **antitussive**. The tablets are dissolving slowly over a period of 30 minutes.

Dental cone: These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding.

Implantation tablets: designed for substances implantation to provide prolonged drug effect from one month to a year, tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy. Generally used for administration of growth hormone to food producing animal.

Vaginal tablets: These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to antibacterial, antiseptic and astringent to treat vaginal infection.

Effervescent tablets: Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active ingredient with mixture of organic acid such as citric acid or tartaric acid and sodium bicarbonate.

Dispersing tablets: Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.

Hypodermic tablets: These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.

Tablet triturates: Usually are made from moist materials using a triturate mold, which gives them the shape of cylinder. Such tablet must be completely and rapidly soluble.

Tablet Ingredients
In addition to active ingredients, tablet contains a number of inert materials known as additives or excipients. Different excipients are:
1. Diluent
2. Binder and adhesive
3. Disintegrents
4. Lubricants and glidants
5. Colouring agents
6. Flavoring agents
7. Sweetening agents

1. 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.

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
8. Sorbitol

9. Sucrose- Sugartab, DiPac, Nutab
10. Dextrose

Lactose: most widely used diluent in tablet formulation. Lactose has no reaction with most drugs, whether it is used in **hydrous** or anhydrous form. **Anhydrous** lactose has advantage over lactose that it does not undergo Maillard reaction which is browning & discoloration of tablet due to the interaction of amine drug with lactose. Spray dried lactose in conc 20-25% of active ingredient is used for direct compression.

Starch obtained from corn, wheat, potatoes is used as diluent, Sta-Rx 1500 is free flowing, direct compressible starch used as diluent, binder and /or disintegrating agent. Two hydrolyzed starch Emdex and Celutab, which are combination of 90-92% of dextrose and 3-5% of maltose, are free flowing and direct compressible.

Sucrose is used as diluent. Some sugar-based diluents are used for direct compression. These are:
a) Sugartab: 90-93% sucrose and 7-10% invert sugar
b) DiPac: 97%sucrose and 3% modified dextrin
c) Nu Tab: 95%sucrose & 4% invert sugar with small amount of corn starch & magnesium stearate.

Microcrystalline cellulose, having trade name Avicel is used for direct compression. These are two types: PH101 (Powder) and PH102 (Granules). Dibasic calcium phosphate and calcium sulphate used as diluents but reduce bioavailability of tetracycline tablet.

2. Binders and Adhesives: These materials are added either dry or in wet- form to form granules or to form cohesive compacts for directly compressed tablet.
Example: Acacia, tragacanth- Solution for 10-25% Conc.
　　　Cellulose derivatives- Methyl cellulose, Hydroxy propyl methyl
　　　cellulose, Hydroxy propyl cellulose
　　　Gelatin- 10-20% solution
　　　Glucose- 50% solution
　　　Polyvinylpyrrolidone (PVP)- 2% conc.
　　　Starch paste-10-20% solution
　　　Sodium alginate
　　　Sorbitol

3. Disintegrants: Added to a tablet formulation to facilitate its breaking or disintegration when it contact in water in the GIT.
Example: Starch- 5-20% of tablet weight.
　　　　　Starch derivative – Primogel and Explotab (1-8%)
　　　　　Clays- Veegum HV, bentonite 10% level in colored tablet only
　　　　　Cellulose
　　　　　Cellulose derivatives- Ac- Di-Sol (sodium carboxy methyl
　　　　　 cellulose)
　　　　　Alginate
　　　　　PVP (Polyvinylpyrrolidone), cross-linked
Superdisintegrants: Swells up to ten fold within 30 seconds when contact water.

Example: Crosscarmellose- cross-linked cellulose, Crosspovidone- cross-linked povidone (polymer), Sodium starch glycolate- cross-linked starch. These cross-linked products swell upto 10n fold with in 30 seconds when in contact with water.

A portion of disintegrant is added before granulation and a portion before compression, which serve as **glidants** or **lubricant**. Evaluation of carbon dioxide in **effervescent tablets** is also one way of disintegration

4. Lubricant and Glidants: 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.

Glidants are intended to promote flow of granules or powder material by reducing the friction between the particles.
Example: Lubricants- Stearic acid, Stearic acid salt - Stearic acid, Magnesium stearate, Talc, PEG (Polyethylene glycols), Surfactants
 Glidants- Corn Starch – 5-10% conc., Talc-5% conc., Silica derivative - Colloidal silicas such as Cab-O-Sil, Syloid, Aerosil in 0.25-3% conc.

5. Coloring agent: The use of colors and dyes in a tablet has three purposes:
   (1) Masking of off color drugs
   (2) Product Identification
   (3) Production of more elegant product
All coloring agents must be approved and certified by FDA. Two forms of colors are used in tablet preparation – FD &C and D & C dyes. These dyes are applied as solution in the granulating agent or Lake form of these dyes. Lakes are dyes absorbed on hydrous oxide and employed as dry powder coloring.
Example: FD & C yellow 6-sunset yellow
          FD & C yellow 5- Tartrazine
          FD & C green 3-   Fast Green
          FD & C blue 1- Brilliant Blue
          FD & C blue 2 - Indigo carmine
          D & C red 3- Erythrosine.
           D & C red 22 – Eosin Y

6. Flavoring agents: For chewable tablet- flavor oil are used
7. Sweetening agents: For chewable tablets: Sugar, mannitol.
 Saccharine (artificial): 500 time's sweeter than sucrose
Disadvantage: Bitter aftertaste and carcinogenic
Aspartame (artificial)
Disadvantage: Lack of stability in presence of moisture.

Granulation technology on large scale by various techniques

1. Direct compression: Processing steps are**:**
Raw material →   Weighing → Screening → Mixing → Compression.

Direct compression consists of compressing tablets directly from powdered materials without modifying physical nature of materials. This method is applicable for crystalline chemicals having good compressible characteristic and flow properties

such as: Potassium salt (chlorate, chloride, bromide), Sodium chloride, Ammonium chloride, Methenamine etc.

If necessary, direct compression vehicles can be used which are having good flow and compressible characteristics. Commonly used directly compression diluents are: MCC (Microcrystalline cellulose (Avicel), Spray dried lactose, Starch - (Sta Rx 1500, Embdex, Celutab), Sugar (Sugartab, Nutab), Dicalcium phosphate dihydrate (Di-Tab), Mannitol for chewable tablet.

Advantages: 1. Low labour input

2. A dry process

3. Fewest processing steps

Disadvantages: 1. Stratification may occur due to differences in particle size and bulk density which results poor content uniformity.

2. A large dose drug may cause problem in direct compression. It requires diluents. The tablet becomes large in size which is difficult to swallow and also costly.

3. During handling of dry materials static charge may form which may present uniform distribution of drug.

4. Direct compression diluent may interact with the drug. For example, amine drug with Lactose produce discoloration of tablet.

2. Dry granulation: Processing steps are :

Raw material →   weighing → Screen → Mixing → Slugging →   Milling → Screening → Mixing → Compression

When tablet ingredients are sensitive to moisture and/or unable to withstand elevated temperature during drying and when the tablet ingredient have insufficient cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation. This technique is used in preparation of aspirin, aspirin combination, acetophenetidin, thiamine hydrochloride, ascorbic acid, magnesium hydroxide.

A comparative processing chart of different granulation techniques

Processing step	Wet	Dry	Direct
Raw material	X	X	X
Weigh	X	X	X
Screen	X	X	X
Mix	X	X	
Compress (slug)		X	
Wet mass	X		
Mill	X		
Dry	X		
Mill	X	X	
Mix	X	X	
Compress	X	X	X

Compression granulation involves the compaction of the components of a tablet formulation by means of flat punch. These compact masses are called slug and the process is called slugging. Slugs are then milled and screened to produce a granular form. On large scale operation compression granulation can be performed on specially designed machine called Roller compactor (Chilsonator roller compactor)

Chilsonator roller compactor : Roller compactor ,utilizes two rollers that revolve towards each other which produce a known pressure on powdered materials that flows between the roller. Powdered material is feed between the rollers by screw conveyer system. After passing through the roller, the compact mass is breaked by breaker. The segments are then screened or milled for production of granules.
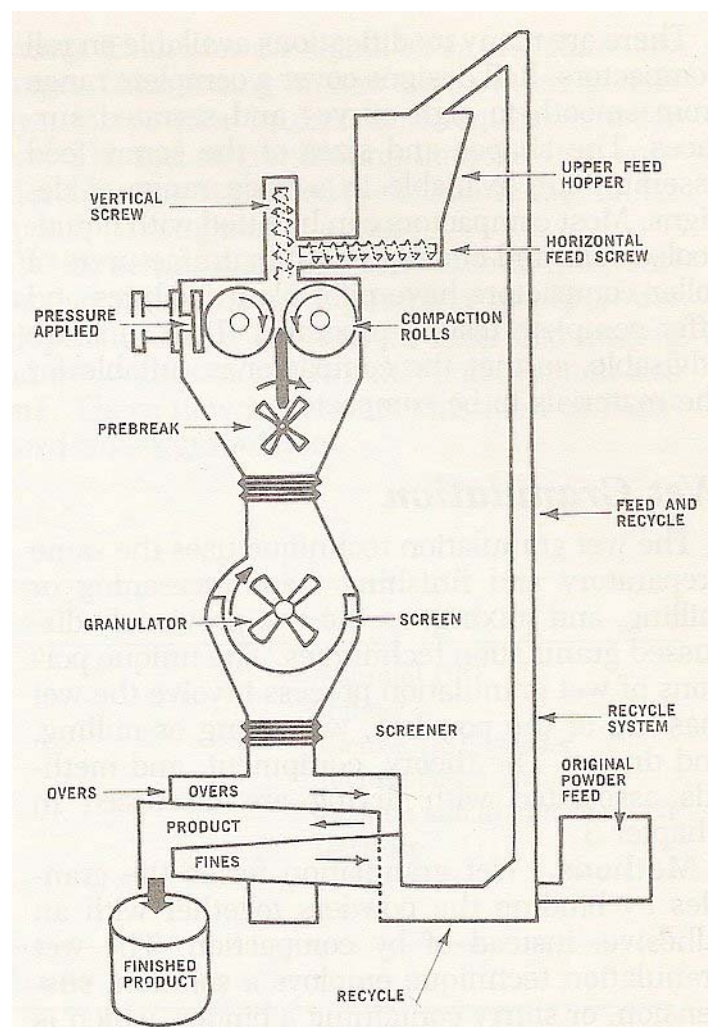

Fig. 1 Schematic diagram of a Chilsonator Roller Compactor in a granulation production system
(Courtesy: The theory and practice of Industrial pharmacy Leon Lachman, third Edition)

3. Wet granulation: Processing steps are:
   Raw materials → Weighing → Screening → Wet massing → Sieving/Milling → Drying → Screening → Mixing → Compression

The most widely used and most general method of tablet preparation is the wet granulation method. The active ingredient, diluent and disintegrents are mixed or blended well. For large-scale production twin shell blender, double cone blender, planatory mixer, sigma blade mixer, ribbon mixer etc. are commonly used. Solutions of the binding agent are added to the mixed powder with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow. If

the granulation is over wetted the granules will be hard, if not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication. The wet mass is forced through a 6 or 8 mesh (Mesh no. is the number of wires passing through an inch) screen or several mills can be used .Moist materials from wet milling steps is placed on large trays and placed in drying chambers with a circulating air current and thermostable heat controller. Commonly used dryers are tray dryer, fluidized bed dryer. After drying, the granulation is reduced in particle size by passing smaller mesh screen. The screen size depends on the diameter of the punch as follows:

Tablet upto 3/16 in diameter ----------------------- 20 mesh
Tablet upto 7/32 into 5/16 in diameter ------------16 mesh
Tablet upto11/32 into13/32 in diameter ----------14 mesh
Tablet upto 7/16 in and more -----------------------16 mesh

After drying granulation, the lubricant or glidants is added as fine powder to promote flow of granules. These granules then compressed to get tablet.

Types of Granulators

Different types of granulators are available which perform granulation & drying at same equipment such as Fluid bed spray granulator.

Mixer	Dryers	Granulator
1.Tumbling mixer (Twin-shell blender) 2. Double cone mixer 3. Planatory mixer 4. Sigma blade mixer 5. Ribbon mixer 6. High speed chopper blade mixer	1.Tray dryer 2. Spray dryer 3. Fluidized bed dryer	1.Fluid bed spray granulator 2. Double cone mixer dryer processor 3. Nauta processor

Equipments:
MIXER
Twin shell blender: The materials are placed in the V-shaped chamber and rotate on its horizontal axis. Due to tumbling action materials are mixed uniformly.
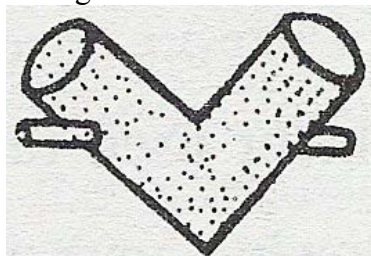

Fig. 2 Twin shell blender
(Courtesy, Remington, The science and Practice of Pharmacy, 20th Edition)

Double cone blender: The materials to be mixed are placed inside the conical chamber and rotate along its horizontal axis.
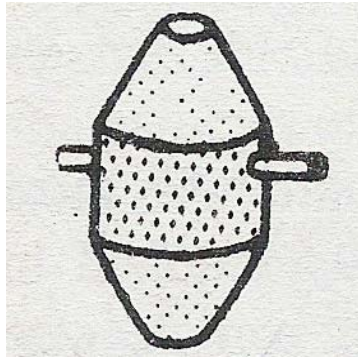
Fig. 3 Double cone blender
(Courtesy, Remington, The science and Practice of Pharmacy, 20th Edition)

Sigma blade mixer: Sigma type blades are rotates in same direction along horizontal axis. Suitable for powder, semisolid material
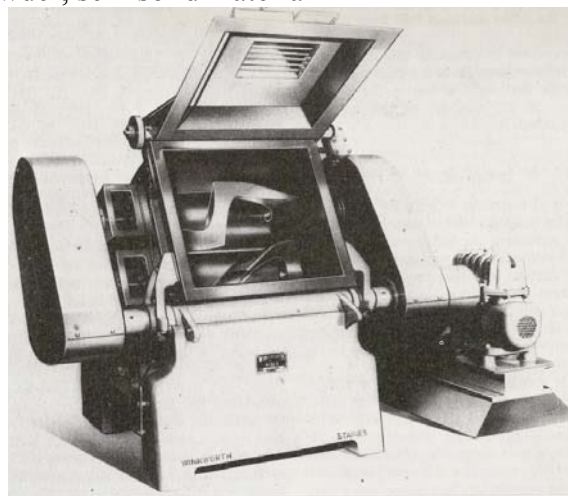

Fig. 4 Sigma"Z"blade mixer
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Ribbon mixer: Two spiral ribbons are fixed on a horizontal shaft, which rotates the ribbon. The bending of the ribbon is such that two ribbons move materials in two opposite direction and promote uniform mixing.
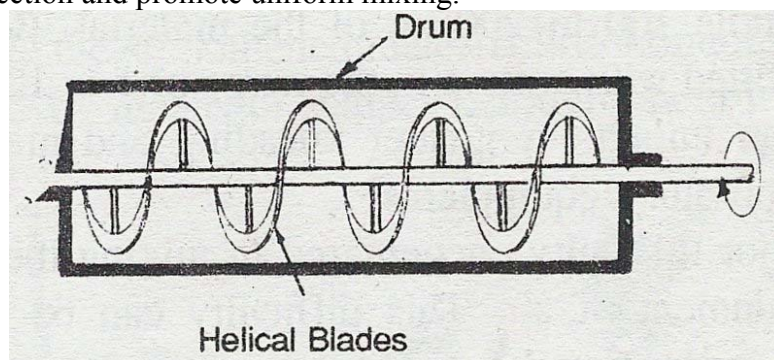

Fig. 5 Ribbon mixer
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Planetary mixer: A set of mixing blade rotates as planet around the mixing bowels.
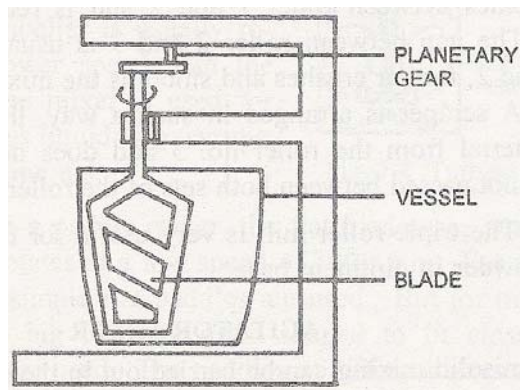
Fig. 6 Planetary mixer
(Courtesy The theory and practice of Industrial pharmacy Leon Lachman, third Edition

High-speed chopper blade mixer: The mixer consists of a bowl mounted in vertical position. A high-speed mixer blade revolves around the bottom of the bowl. The mixer also contains a high-speed chopper blade which functions as lump or agglomerate breaker.
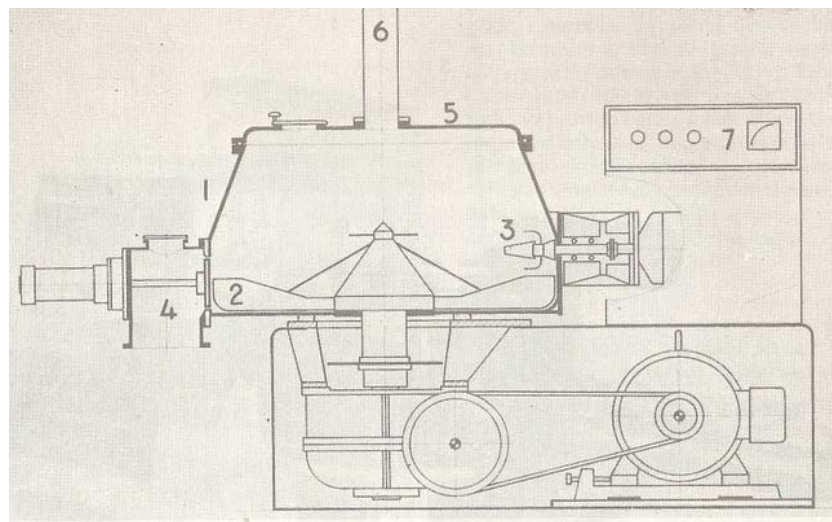

Fig. 7 High-speed chopper blade mixer.

(1) Mixer bowel (2) High-speed mixer blade (3) High-speed chopper blade (4)   Pneumatic discharge port. (5) Mixed lid. (6) Exhaust air sleeve. (7) Mixer control panel.
(Courtesy The theory and practice of Industrial pharmacy Leon Lachman, third Edition

DRYER
Tray dryer: Also called shelf, cabinet or compartment dryer.
Area of each tray: 4 to 8 sq.ft.
Load thickness: 0.5 –4 inches.
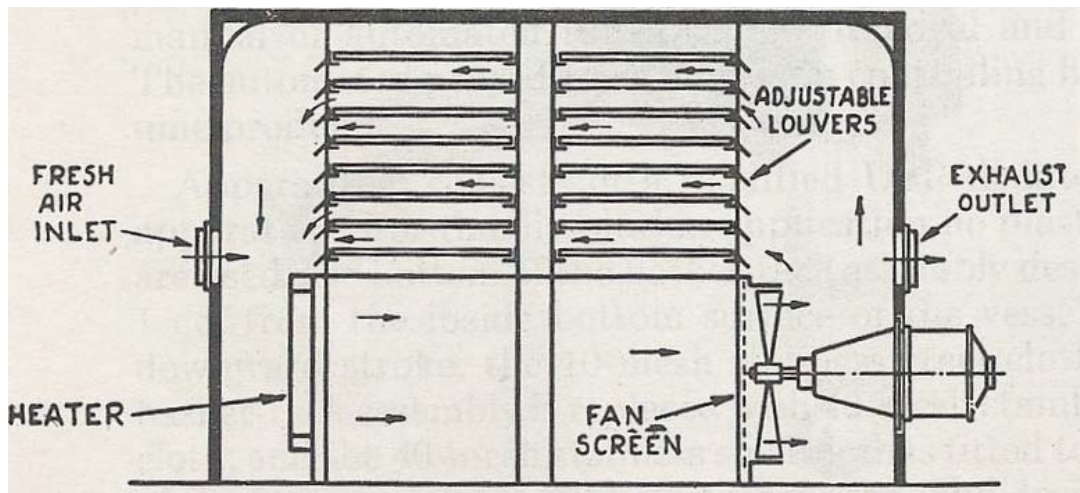Capacity: 500-2000lb/batch

Fig. 8 Tray dryer
(Courtesy, Remington, The science and Practice of Pharmacy, 20th Edition)

Spray dryer: Can handle only liquid as solution, Slurries, dispersed as fine droplets into a moving stream of hot gas. The solvent evaporates and dried product collected by gas current-gravity flow collection system.
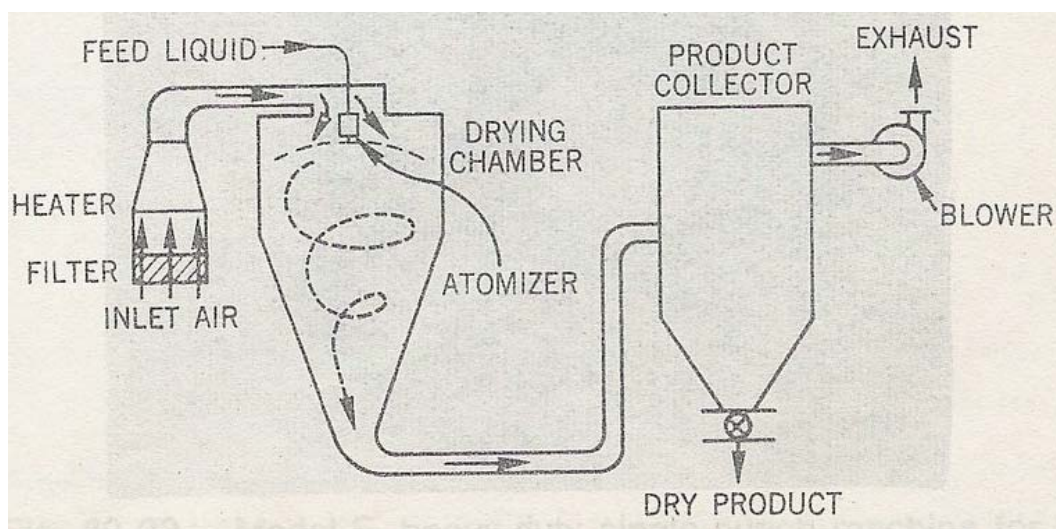

Fig. 9 Spray dryer
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition)

Fluidized bed dryer: In FBD, the fluidizing air stream is introduced by a fan or blower mounted in at the top of the apparatus. The air is heated to the required temperature in an air heater and flows upward through the wet materials, which contained in a drying chamber fitted with a wire mesh supported at the bottom
Capacity: 5-200 kg
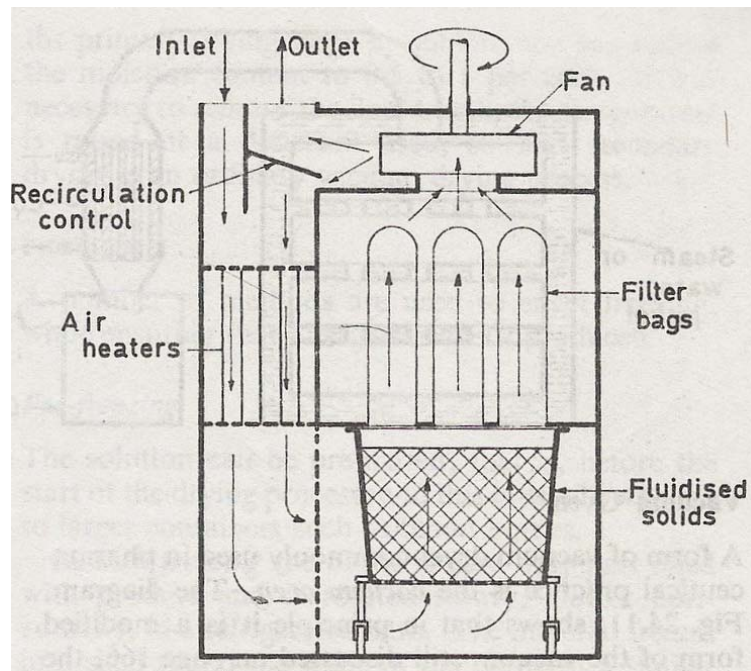Drying time: 20 to 40 mins.
Type: Batch type

Fig. 10 Fluidized bed dryer
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

GRANULATOR

Fluidized bed spray granulator: The unit is same as fluidized bed dryer. When the unit is used as granulator the dry ingredients are placed in the chamber and fluidized while the granulating liquid is sprayed into the bed causing the particles agglomerate into granules.
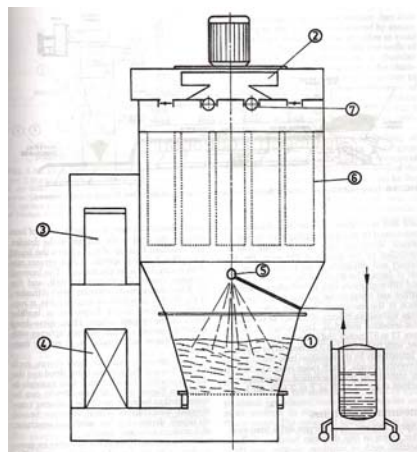
Fig. 11 Fluidized bed spray granulator
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

Double cone mixer dryer processor: This is modified double cone blender used to perform operation – mixing, wet massing, agglomeration and drying. Liquid feed system is through the trunion of the machine and sprayed. Vacuum system is through same or opposite trunion providing a nilon filter. Agitators rotate within the powder mass.

Nauta Mixer Processor: A screw assembly is mounted in a conical chamber within the screw lifting the powder from bottom to top. The screw assembly orbits around the conical chamber wall to ensure more uniform mixing. The operation is power mixing with incorporation of the liquid granulating agents, wet massing and drying as hot, dry air is passed through the wet materials.

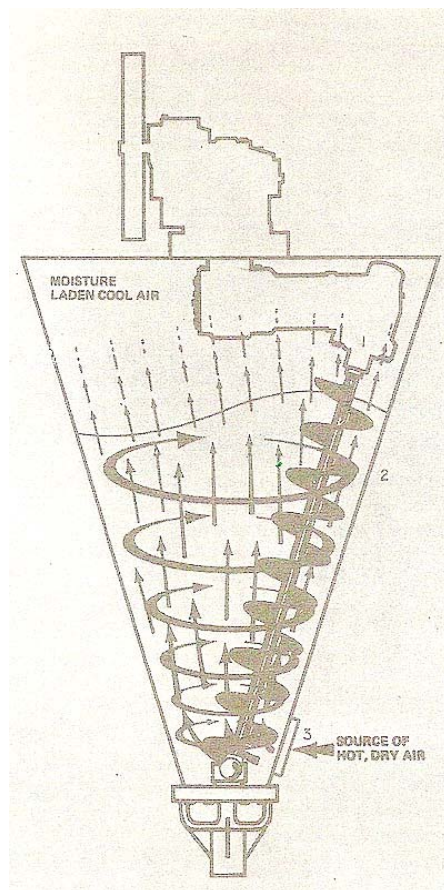

Fig. 12 Nauta processor
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

Granulation Characteristics

The characteristics of a tablet like compactness, physical and chemical stability, **efficacy**, rapid production capability depends on the quality of granulation. Granules must posses two characteristics, **fluidity** and compressibility. Good flow properties are essential for the transport of materials through the **hopper**, **feed** frame and **into dies**. Tablet materials should be in a physical form that flows smoothly and uniformly. The ideal physical form for this purpose is **a sphere**, which offers minimum contact surface between themselves and with the wall of the machine parts. Therefore granulation process improves the flow of powdered materials by forming sphere like aggregates called granules.

Granulation Properties: Following properties should be verified before compression:
1. **Particle size & shape:** Particle size of granulation affect the average tablet weight, weight variation, disintegration time, **friability**, granule flow ability. The methods for determine particle size and size distribution are **sieving**, **microscopy** and **sedimentation.**

2. **Surface area:** Dissolution of a drug depends on surface area of powder materials or granules. The most common method for determination of surface area is gas adsorption and air permeability.

3. **Density:** Granule density may influence compressibility, tablet porosity, dissolution and other properties. Generally three types of density arises for granules:

(a) True density (l_p) = Wt/ True Volume
$$= W/V_p$$

(b) Bulk density (l_b) = Wt/ Bulk Volume
$$= W/V_b$$

(c) Granule density = Wt/ Granule volume
$$= W/V_g$$

True Volume = Vol. excluding inter & intra granular space

Bulk Volume = Vol. including inter & intra granular space

Granule Volume = Vol. excluding inter granular space but including intra granular space.

True density can be measured by Mercury, helium displacement method and also using low surface tension liquid like benzene with the help of Pyenometer.

Bulk density can be measured by taking a known wt. of materials in a graduated measuring cylinder and tapping upto a constant reading.

Porosity directly related with true density and bulk density.

Porosity = Total empty space / Bulk volume
$$= V_b - V_p / V_b$$
$$= 1 - V_p / V_b$$
$$= 1 - m/l_p / m/ l_b$$
$$= 1 - l_b/ l_p$$

Therefore % Porosity = $(1 - l_b/ l_p) \times 100$

Compressibility of a tablet also depends on bulk density of granules.

% Compressibility = $P_b - P_u / P_b \times 100$

Where P_u = Bulk density at untapped condition or loose bulk density or untapped bulk density.

Bulk density depends on granule size as granule size decreases, bulk density decreases.

4. Strength & Friability: After formation of granules these are used for tableting. Granules are aggregation of component particles that is held together by bonds of infinite strength. Measurement of granule strength is estimation of attractive forces seeking to hold the granules together. Friability is the ability to formation of fines or fragments. Strength can be measure by placing the granules between two anvils (flat face) and force required to break the granules is measured.

5. Flow properties: For the movement of granules from hopper to die cavity sufficient flow properties are essential. Improper flow cause weight variation of content uniformity. Factors affecting flow properties are:

(a) Frictional forces

(b) **Surface tension** forces

(c) Mechanical forces caused by interlocking of particles of irregular shape

(d) Electrostatic forces

(e) **Cohesive** or **Van der Waals** forces.

Flow properties of granules can be measure by two methods:

  (a)   **Angle of repose:** It is maximum angle between the surface of a pile of powder and horizontal plane, when powders are allowed to flow freely from a certain height. It can be measured by fixed funnel and cone method. Powder or granulation is allowed to flow through the funnel until the apex of conical pile just touches the tip of the funnel. Measuring the radius (r) and height (h) of pile repose angle can be measured.

          Angle of Repose$\leq 30 \rightarrow$ Free flowing material

          Angle of Repose $\geq 40 \rightarrow$ Poorly flowing material

  (b)   **Hopper Flow rate:** Granules are allowed to flow from the conical hopper onto a recording balance device and dw/dt is calculated

5. Compaction: This measure the force applied during compression. Tabletpresses are instrumented by affixing transducers to measure the forces. The signals produced by transducers are converted to digital output by computer.

Processing Problems

1. Capping & Lamination: Complete or partial loss of top and bottom crowns of a tablet from the main body is called *capping.* The separation of a tablet into two or more distinct layers is called *lamination.* These problems occur immediately after compression, however may occur after several hours or days.

  Cause: 1. Air entrapment

          2. Deep concave punch

          3. Claw formation of Punch

          4. Wear ring formation in die wall

          5. Incorrect setting of the press

          6. Compression of too dry material

  Remedy: 1. By precompression

          2. Slowing tableting

          3. Reducing final compression force

          4. Using flat punch

          5. Using hygroscopic materials to maintain proper moisture level

            eg. - PEG-4000 and Methyl Cellulose

 2. Picking & Sticking: Surface materials from a tablet that is sticking to the punch and being removed from the tablet surface is *picking.* Sticking refers to tablet materials adhering to the die wall. When sticking occurs, additional force is required to overcome the friction between the tablet and die wall during ejection.

Cause: 1. Picking occurs when punch tips are engraving or embossing. Small enclosed areas in letters A.

3. Mottling: It is an unequal distribution of colors on a tablet with light and dark areas on tablet surface.

Cause: 1. Use of a drug whose color differs from tablet excipients

       2. Use of a drug whose dehydration products are colored

Remedy: 1. The use of colorant may solve the problem but can create another Problem. A dye can cause mottling by migration to the surface of a Granulation during drying to overcome this difficulty. Change the Solvent system, reduce drying temperature.

2. Disperse a dry color additive during powder binding steps.

4. Weight Variation: Variation of tablet weight also causes variation of active medicament which change the bioavailability.

Cause: (a) Granule size & size distribution: Variations in the ration of small to large granules and difference in granule size determine how the void space between particles are filled. Since volume of die cavity remain same , different proportions of large and small particles may change
the weight of fill in each die.

(b) Poor Flow: The die fill process in based on a continuous and uniform flow of granules from the hopper through the feed frame. When the granulation does not flow uniformly some dies are incompletely filled. Dies are also not filled properly when machine speed is in excess of granulations flow capability. With poor flow the addition of a **glidant** such as talcum or colloidal silica may be helpful.

Depending on the geometry of the hopper, poor flow give rise to another problems like arching or **bridging** & **rat holling**

(1) Arching or Bridging: Granules separate at the neck of the hopper and flow stops completely. Addition of glidant to prevent flow can overcome the problem.
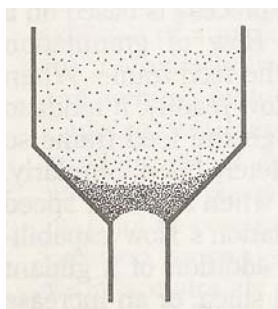

Fig. 13 Bridging

(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

(2) Rat Holling: In this case particles segregate near the wall of the hopper and at the center flow continues forming hole. In rat holling flow rate decreases which can overcome by using glidant

Fig. 14 Rat holling

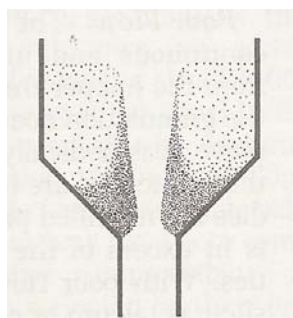(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

(c) Punch Variation: When length of lower punches is unequal, the fill in each die varies which causes weight variations of tablet.

(d) Poor Mixing: Some times lubricants and glidants are not thoroughly distributed. The flow of particles then impaired and the granules do not move efficiently into the dies.

5. Hardness Variation: Hardness depends on the weight of materials and space between upper and lower punch at the moment of compression. If the volume of materials and distance between the punches varies hardness also alters.

6. Double Impression: This involves only punches that have monogram or engraving. If the monogram present in upper punch, slight rotation of punch after precompression produce double impression. If monogram present in lower punch after compression is over lower punch move slightly downward to free the tablet and produce double impression. This problem can overcome using non-rotating cam track.

Tabletting Technology

The compaction process-Both tablet machines and ram presses have been used to investigate the compaction behavior of pharmaceutical substances. Pressure in the range 300 to 3000kg/cm2 is usual for tablet machines, but the upper limit may be higher for mechanical or hydraulic ram presses. The use of flat- faced punches simplifies subsequent treatment of the data. Where the time taken for compression is short, as the tablet machine, transducers must be used to convert the compaction forces, punch displacements, etc. into electrical signals, which can be recorded, usually by an ultraviolet oscillograph.

The downwards thrust of the top punch in the die -bore during compaction causes movement of material relative to wall of the die. The movement is resisted by frictional effects, in part within the bed of material but mainly between that material and the die wall. As a result, the maximum force transmitted to the lower punch (Fb) is less than the maximum force. (Fa) applied by the top punch to the contents of the die -cavity by an amount (Fd), that is the force 'lost' to the die-wall. As compaction also squeezes the compacting material into close contact with the wall of the die this latter experiences a maximum radial force (Fr). Even when the top punch has been removed from the die, residual stresses within the tablet give rise to a load normal to the die-wall and therefore an ejection force, maximum value (Fe), must be applied to the compact by the lower punch to overcome friction and initiate ejection. The extent to which the material in the die has been compacted may be evaluated from the relative volume (Vr), relative density (Pr) or porosity of the tablet. By loading the edge s of the tablet across a diameter the minimum crushing force (Fc), just sufficient to rupture the tablet, may be found. If, as is often the case, the tablet dimensions are maintained in an experimental series, (Fc) provides a comparative measure of tablet hardness. By finding the values of the parameters described in table at a number of preselected maximum upper punch pressures the compaction behavior of a substance may be studied. Higuchi et al (1953) determined these values for sulphathiazole compacts made in a ram press. In each case the upper punch pressure (Pa) was raised to its preselected maximum value over a period of 20 to 60 s. where as the logarithm of the disintegration time was found to be proportional to Pa. Thus, the compaction pressure had a much greater effect on the disintegration time then on hardness. The porosity of the tablets progressively decreased, as the pressure was increased bur the specific area rose to a maximum at about 1600 kg/cm2 and subsequently decreased. This was attributed to fragmentation of granules during initial stages of compaction followed by bonding of the freshly formed surfaces at higher pressure.

Train(1956)compacted alternate layers of normal and colored magnesium carbonate. When the die- wall was lubricated with graphide the layers compressed evenly,

whereas, in the absence of the lubricants, the layers curved downwards from the wall of the die towards the centre of the compact indicating that friction had restricted movement of the particles near the die -wall. Due to intense local shear action a hard 'skin' of distorted strongly bonded particles was formed where the compact had been in contact with the die. this 'skin' is often formed on tablets and provides resistance to abrasive damage. The degree of compaction was assessed by measuring the thickness of the layers in each region and was found to be higher in a peripheral ring near the top punch and in a lower central region The later may explain why the 'core' often seen towards the end of a disintegration test, breaks down more slowly than the rest of the tablet. A plot of Vr as a function of log Pa was not a smooth curve showed a several abrupt changes of slope. The initial decrease in Vr was due to closer packing of magnesium carbonate but this was eventually limited by the available space in the die-cavity. Thereafter, the slope increased abruptly and during the second stage the load was supported by temporary structures of compacting material. At still higher pressures the structures collapsed and the material failed by crushing and plastic flow(third stage) until, in the fourth stage, there was sufficient rebonding of the freshly created surfaces to give a compact with enough strength to involve the normal compression characteristics of solid magnesium carbonate in any future reduction of volume.The data of Higuchi et al. (1953, 1954b) and Shotton and Ganderton(1960a),when plotted in the form used by Train, show that the third and fourth stages of compaction also occur with aspirin, lactose, sulphathiazole, sulphadiazine and sodium chloride .In the cases of the first four substances the abrupt changes in the slope of the log Pa/Vr plot occur at approximately the same compaction pressures as the maxima in the specific surface area curves. This would be expected if, as Train suggested, fragmentation and rebonding are competitive processes with the later predominating in the fourth stage of compaction.

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) A feeding mechanism for moving granulation from hopper into the
         dies
Tablets presses are classified either single punch or multi-station rotary presses.

In case of single punch machine all of the compression is applied by the upper punch, making the single punch machine a "stamping press".

Multi station presses are termed rotary because the head of the tablet machine that holds the upper punches, dies, and lower punches in place rotates. As their head rotates, the punches are guided up and down by fixed cam tracks, which control the sequence of filling, compression and ejection. The portion of the head that hold the upper and lower punches are called upper and lower turrets `respectively, and the portion holding the dies is called the die table. At the start of compression cycle granulation stored in a hopper emptied into the feed-frame, which has several interconnected compartments. The pull down cam(C) guided the lower punches to the

bottom of their vertical travel, allowing the dies to overfill. The punches are then passed over a weight control cam (E), which reduces the fill in the dies to the desired amount. A wipe -off blade (D) at the end of the feed frame removes the excess granulation and directs it around the turret and back into the front of the feed-frame.
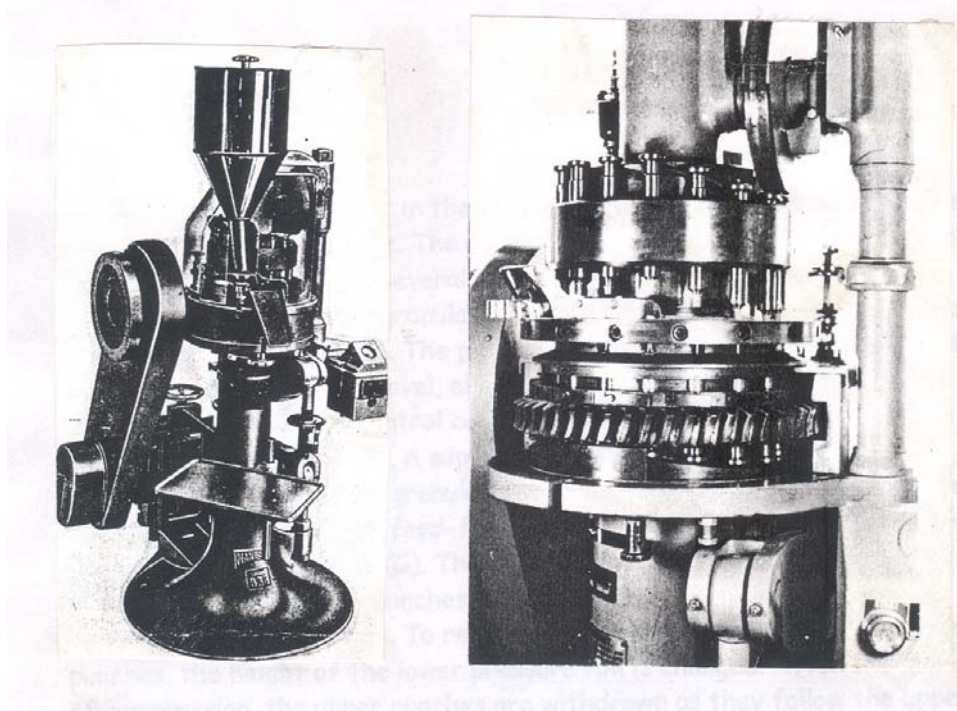

Fig. 15 Single punch tablet machine (left) & 16 station rotary tablet machine(R)
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Next, the lower punches travel over the lower compression roll (F) while simultaneously the upper punches ride beneath the upper compression roll (G). The upper punches enter a fixed distance into the dies, while the lower punches are raised to squeeze and compact the granulation within the dies. To regulate the upward movements of the lower punches, the height of the lower pressure is changed. After the moments of compression, the upper punches are withdrawn as they follow the upper punch raising cam (H); the lower punches ride up the cam(I), which brings the tablets flush with or slightly above the surface of the dies. The tablets strike a sweep off blade affixed to the front of the feed- frame (A) and slide down a chute into receptacle. At the same time, the lower punches re- enters the pull down cam(C), and the cycle is repeated.

In general, all rotary presses are engineered for fast and economical production of all kind of tablets. Larger machines can readily produce several million tablets each in a working day.

Special adaptations of tablet machine allow for the compression of layered tablets and coated tablets. Pre-compression station is also available to help in compressing difficult granulations. Available with certain Fette machines is a device that chills the compression components to allow for compression of low melting point substance such as waxes, thereby making it possible to compressed products with low melting point such as **suppositories**.

Compression Machine Tooling

The size and shape of a tablet as well as certain identification makings are determined by the compression machine tooling each tooling set consist of a die and upper and lower punches. The most common tools employed are referred as BB tooling and are 5.25 inches in length, and have a nominal barrel diameter of 0.75 inches and 1-inch head diameter's tooling is identical to BB type except that the lower punch is only 39/16 inches longed tooling is popular for large tablets, utilizing a 1-inch barrel diameter, 1.25- inch head diameter, and 5.25- inch length .the dies that are used with the above punches are either a 0.945 – inch outside diameter(OD) die capable of making a 7/16 – inch round tablet or 9/16-inch capsule shaped tablet.

Several types of steel are normally used in manufacturing of compression tooling. This steel differs in toughness, to withstand the cyclic compacting forces (ductility), and in wear resistance. The selection of the best steel for a specific application must be best on experience and an accumulated history of the product being tabletted. On e should also consider the shape of the punch tip, whether or not debossing is to be employed on the tooling , the expected compression forces involved, and whether the materials to be processed are abrasive or corrosive.

The size, shape and contour of a tablet are almost unlimited within the given limits of the specified die size. Tooling can be made with certain other information to aid in producing visible unique tablet product Company names and symbol, trade names , dosage strength, or National Drug Code (NDC) numbers can be cut or engraved into a punch face, or the punches may be scored to produced uniquely embossed or engraved tablets. When the tip of the upper punch is not round, it must not rotate, or it will strike the edge of the die hole as it descents for compression .To prevent this, a slot is curt longitudinally into the barrel of the punch, and a key is inserted. This key protrudes a short distance so that it engages a similar slot cut into the upper punch guides on the tablet press. Lower punches do not need keys because their tips remain within the die bore, which control the axial movement of the punch. Because keyed punches cannot rotate, wear is distributed unevenly, and punch life is shortened.

When a press is set up with keyed punches the upper punches are inserted first to determine the placement of the dies. Once the dies are properly aligned and seated, they are locked in place, and the lower punches are inserted. The more curvature that is built into a tablet contour, the more difficult is to compress, especially if the tablet tends to laminate or cap. The engraving or embossing on a tablet must be designed to be legible, must not add to compression problems, and must fit on the tablet surface.
Because of its hard steel structure tablet tooling may appear to be indestructible. During normal use, however, the punches and die become worn, and the cyclic application of stress can cause the steel to fatigue and break. The punch tips are especially delicate and susceptible to damage if the tips make contact with each other, the dies or the press turret upon insertion or removal of the tools from the tablet machine.

To avoid tooling damage, compressive loads or pressure at the pressure rolls must be translated into a circulation of pressure at the punch tips. As tablet punch diameter decreases, less force is required to produce the same pressure at the punch face, since the face represents a smaller fraction of a unit area (square inch). The formula for area of a circle is $\pi r2$ where r is the radius of the circle. Given a flat punch face, the area of

a ¼ - inch diameter punch would thus be 3.14*(1/8)2 or 3.14*1/64 or approximately 1/20 square- inch .If a 1-ton load is being applied by the pressure roll, this area is translated as 2000 pounds on 1/20 square inch, or 40,000 pounds on 1 square inch, a gross overload.

Methods and Equipments used to Compress Tablets

The only limitation of commercially manufactured tablets is that they are available only in fixed dosage strengths and combinations. To provide the flexibility of compounded formulations, pharmacists can extemporaneously prepare molded and compressed tablets for their patients. Molded tablets are compounded using a tablet triturate mold. Compressed tablets can be made using a pellet press or a single-punch tableting machine.

Moulded Tablets: One of the advantages of **moulded tablets** is that they quickly disintegrate in the presence of moisture. And since the tablets are actually compressed powder mixtures, the pharmacist can easily adjust the composition for any number of dosages. Their chief disadvantage is their small size, which will limit their use to substances effective in small doses.

Moulded tablets are generally prepared by mixing the active drug with lactose, dextrose, sucrose, mannitol, or some other appropriate diluent that can serve as the base. This base must be readily water-soluble and should not degrade during the tablet's preparation. Lactose is the preferred base but mannitol adds a pleasant, cooling sensation and additional sweetness in the mouth.

The base ordinarily used for molded tablet triturates is lactose containing 10% - 20% sucrose, the latter being added to make a firmer tablet. Drugs that react chemically with sugars require special bases such as precipitate calcium carbonate, precipitated calcium phosphate, kaolin, or bentonite. A liquid is added to moisten the powder mixture so it will adhere while being pressed into the mold cavities. Mixtures of alcohol and water in varying proportions (typically about 50 - 80% alcohol) are employed; the alcohol will speed up the drying of the liquid and the water will cause the sugars to dissolve and bind the tablet. If the tablet contains ingredients that are very soluble in water, water can be omitted altogether and alcohol alone can be used.

Tablet triturate molds are made of metal. There are two plates; the *cavity plate* is the plate that has only holes and the *peg plate* that has pegs. The mold will indicate the capacity of one cavity in the cavity plate but that indication is only an approximation. Typical die plate cavity sizes are 60 mg and 100 mg.

The volume of the cavities always remains constant, but the weight of the tablet made will depend nature of the material. Different bases will have different densities and so the cavity capacity must be determined for each base, e.g., the mould must be calibrated. (This is the same reason why all molds must be calibrated for each base.)
Calibration of the mold:

1. Tablets that contain only the powder base are made first. The tablets produced are weighed as a batch and the average weight per tablet for that base is calculated.

2. The average weight per tablet of the active drug is determined. Generally, just a few cavities are used in this determination. Tablets containing only the active drug are made and the average weight per tablet for the drug is calculated.
3. The quantity of drug that will be required in the prescription per tablet is divided by the average weight per tablet of the active drug. This will give a percentage of the cavity volume that will be occupied by the active drug
4. Subtracting the percentage in step 3 from 100% will give the percentage of the cavity volume that will be occupied by the tablet base.
5. The percentage of active drug in the cavity volume and the percentage of base in the cavity volume are used to calculate the appropriate amounts of base and drug to weigh. For example, if the mold contains 50 cavities and each will hold approximately 100 mg, then 5000 mg of mixture will be needed to fill the mold. The amount of base and drug to weigh can be determined by multiplying 5000 mg by the two different percentages determined in the preceding steps.
6. It is prudent to prepare a slight excess of powder mixture (5 - 10%). This will allow for any variance in the approximate and actually capacity of the mold, and will also allow for powder loss during the compounding procedure.

To compound the molded tablets, prepare the powder mixture by proper techniques and sift the mixture through an 80-100 mesh sieve. Then moisten the powder mixture until the mass has the consistency of "Play Dough." Press the mass into the cavities of the cavity plate. Have the plate on an ointment tile or glass plate. A hard rubber spatula should be used to press the material into the cavities; stainless steel spatulas will scratch the surface of the metal plate. Sufficient pressure should be applied to tightly pack each cavity with base. It is important to insure that all cavities are equally filled especially the marginal cavities. Both sides of the cavity plate should be inspected to make sure that all of the space in each cavity is filled. When the cavity plate is loaded, the plate is placed on the peg plate so that the pegs are aligned with the holes. The cavity plate is then carefully pressed onto the peg plate. As the cavity plate falls, the tablets are pushed out of the cavity plate onto the tops of the pegs. The tablets are left on the pegs until they dry.

Single-punch Tablet Machines: Tableting machines are commonly used in pharmaceutical industry. They are high-speed machines that create thousands of tablets in a small period. The compounding pharmacist uses a variation of these machines. It is called a single-punch tablet press and makes one tablet at a time. A "punch" has two pieces of casted tubular metal. The bottom metal piece has a small cavity in one end of the tube; the top metal piece has one end that is tapered into a small rod that will just fit into the small cavity in the other piece. The rod does not go all the way to the bottom of the cavity, but leaves a small gap. The punch is fitted into a press so that when the handle is depressed and released, the rod goes into and then comes out of the bottom piece. To make a tablet, the powder material is placed into the bottom piece, and the handle is depressed and released. The powders are compressed and occupy the size of the gap designed in the punch.

Punches come in many sizes, which allow the production of tablets of different sizes and compression strengths. But each punch is a matched set; it is not possible to interchange the top and bottom pieces of different punches.

Chewable tablets, effervescent tablets, and compressed tablets can be made using a tablet press. Chewable tablets are generally made using mannitol because it has a sweet, cooling taste and is easy to manipulate. Other ingredients may include binders (e.g., acacia), lubricants (e.g., stearic acid), colors, and flavors. The powder mixture is prepared; the desired quantity of mixture is weighed, and then pressed with a single-punch tablet machine.

Effervescent tablets generally contain ingredients such as tartaric acid, citric acid, and sodium bicarbonate. These powders would be appropriately mixed and pressed into tablets using the same procedure as chewable tablets. They will not require a disintegrant since they will effervesce when placed in water. Compressed tablet mixtures generally contain the active drug, a diluent (e.g., lactose), a disintegrant (e.g., starch), and a lubricant (e.g., 1% magnesium stearate).

Rotary Tablet Press: It is also called multi station tablet press. Steps involved are:

Over fill → Corrected Fill → Compression → Ejection

Multi station presses are termed rotary because the head of the machine that holds the upper punches, dies and lower punches in place rotates. As the head rotates the tablet granulation runs from the hopper through the feed frame into dies. Feed frame promotes a uniform fill of the die. Compression takes place as the upper and lower punches pass between a pair of rollers. The up and down movement of the punches are guided by fixed cam tracks. The portion of the head that hold the upper and lower punches are called upper and lower turrets and the portion holding the dies are called the die table.

At the start of a compression cycle, granulation from hopper empties into the feed frame (A), which has several interconnected compartments, These compartments spread the granulation over a large area to provide time for the dies (B). Pull down cam (C) guide the lower punches to bottom of their vertical travel, allowing the die to the cam (E), which reduces the fill in the dies to the desired amount. A wipe-off blade (D) at the end of the feed frame removes the excess granulation and backs it into the front of the feed frame. Next, the lower punch travel over the lower compression roll (F) and upper punches rides below the upper compression roll (G) The upper punch enter a fixed distance into the dies, while the lower punches are raised and compact the granulation within the dies. To regulate the upward movement of the lower punches, the height of the pressure roll is changed. After compression, the upper punches are withdrawn by upper punch raising cam (H) and lower punch ride up by the cam (I), which bring the tablet above the surface of the dies. The tablet strike a sweep off blade attached at the front of the feed frame and slide down to the receiver. At the same time, the lower punch reenters the pull down cam (C) and cycle is repeated.

Evaluation of Tablet
1. General Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

1. Size & Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

2. Unique identification marking: These marking utilize some form of embossing, engraving or printing. These markings include company name or symbol, product code, product name etc.

3. Organoleptic properties: Color distribution must be uniform with no mottling. For visual color comparison compare the color of sample against standard color.
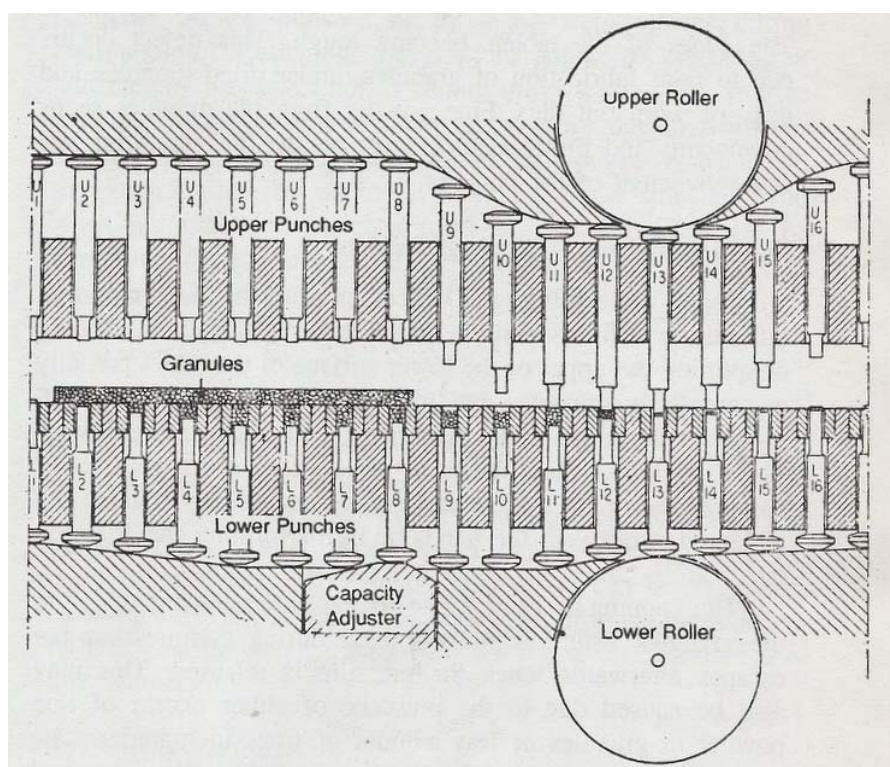

Fig. 16 The compression cycle of a rotary tablet press

(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

The presence of odor in a batch of tablet indicates a stability problem such as the characteristics odor of acetic acid in aspirin tablet. Presence of odor could be characteristic of the drug (Vitamin), added ingredients (flavoring agent) or the dosage form (film coated tablet have a characteristic odor) For chewable tablet presence or absence of specified taste can be checked. A tablet level of flaws such s chip, cracks, contamination from foreign solid substances (hair, drops of oil, dirt), surface texture (smooth vs rough) and appearance (shining vs dull) may have zero defect

2. Hardness and Friability: Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. The strength of a tablet was determined by following ways;

(a)   By cracking the tablet between 2nd and 3rd fingers with the thumb acting as a fulcrum. If there is a sharp snap, the tablet is an acceptable strength.

(b)   Tablet hardness can be defined as the force required breaking a tablet in a diametric compression. In this test the tablet is placed between two anvils, force is applied to the anvils, and the crushing strength that just causes the tablet to break is recorded. Generally used Hardness testers are:

                (1) Monsanto Tester
                (2) Strong-Cobb Tester
                (3) Pfizer Tester
                (4) Erweka Tester
                (5) Schleuniger Tester
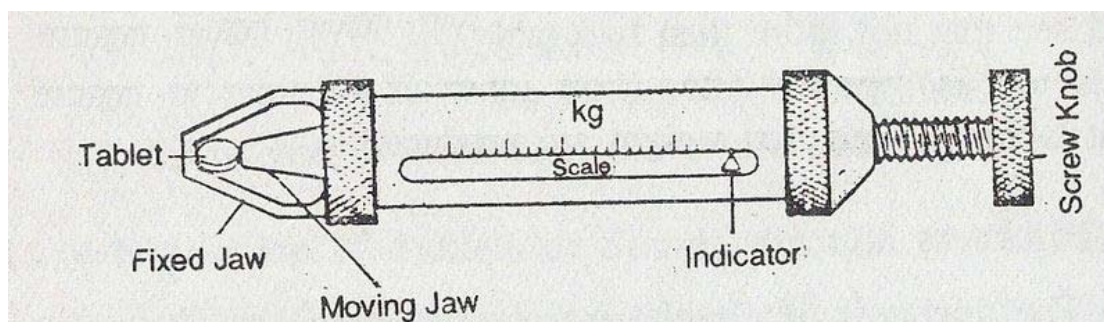
Hardness for compressed tablet is 5 to 8 kg.

Fig. 17 Monsanto hardness tester
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Friability of a tablet can determine in laboratory by Roche friabilator. This consist of a plastic chamber that revolves at 25 rpm, dropping the tablets through a Distance of six inches in the friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compress tablet that lose less than 0.5 to 1.0 % of the Tablet weigh are consider acceptable.
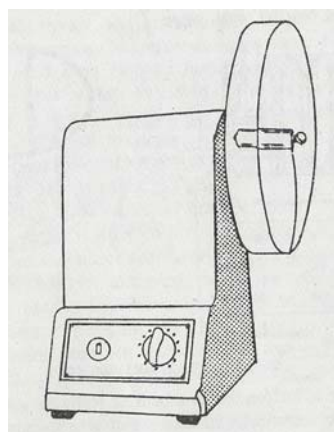

Fig. 18 Roche Friability test apparatus
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

3. Drug Content and Release:

(I)   **Weight Variation test (U.S.P.):** Take 20 tablet and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the U.S.P. test if no more that 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

(II)   **Content Uniformity Test:** Randomly select 30 tablets. 10 of these assayed individually. The Tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content.

> If these conditions are not met, remaining 20 tablet assayed individually and none may fall out side of the 85 to 115% range.

(III)   **Disintegration Test (U.S.P.):** The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2^0 C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet.

According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass.

Disintegration time: Uncoated tablet: 5-30 minutes
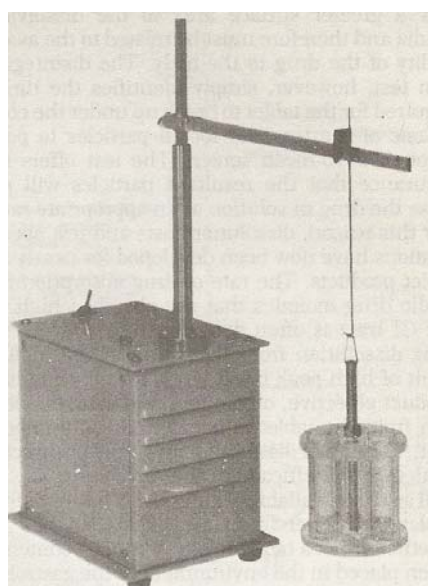> Coated tablet: 1-2 hours

Fig. 19 Disintegration test apparatus
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

(IV)   **Dissolution Test (U.S.P.):** Two set of apparatus:

Apparatus-1: A single tablet is placed in a small wire mesh basket attached to the bottom of the shaft connected to a variable speed motor. The basket is immersed in a dissolution medium (as specified in monograph) contained in a 100 ml flask. The flask is cylindrical with a hemispherical bottom. The flask is maintained at 37 ± 0.5^0C by a constant temperature bath. The motor is adjusted to turn at the specified speed and sample of the fluid are withdrawn at intervals to determine the amount of drug in solutions.

Fig. 20 Dissolution test apparatus
(Courtesy Indian Pharmacopoeia, 1996)

6.3 to 6.5 or
9.4 to 10.1 mm

vent hole, 2.0 mm diameter

retention spring with
3 tangs on 120° centers

5.1 ± 0.5 mm

clear opening
20.2 ± 0.1 mm

screen O.D.
22.2 ± 1.0 mm

27.0
± 1.0
mm
open
screen

36.8
± 3.0 mm

screen, with welded seam:
40 x 40 mesh, 0.254 mm
dia. (0.01 inch with 0.015-
inch openings); where 20-
mesh screen is specified,
use 20 x 20 mesh (0.016
inch with 0.034- inch
openings)

A

NOTE— Maximum allowable
runout at "A" is ±1.0 mm when
the part is rotated on ₵ axis
with basket mounted.

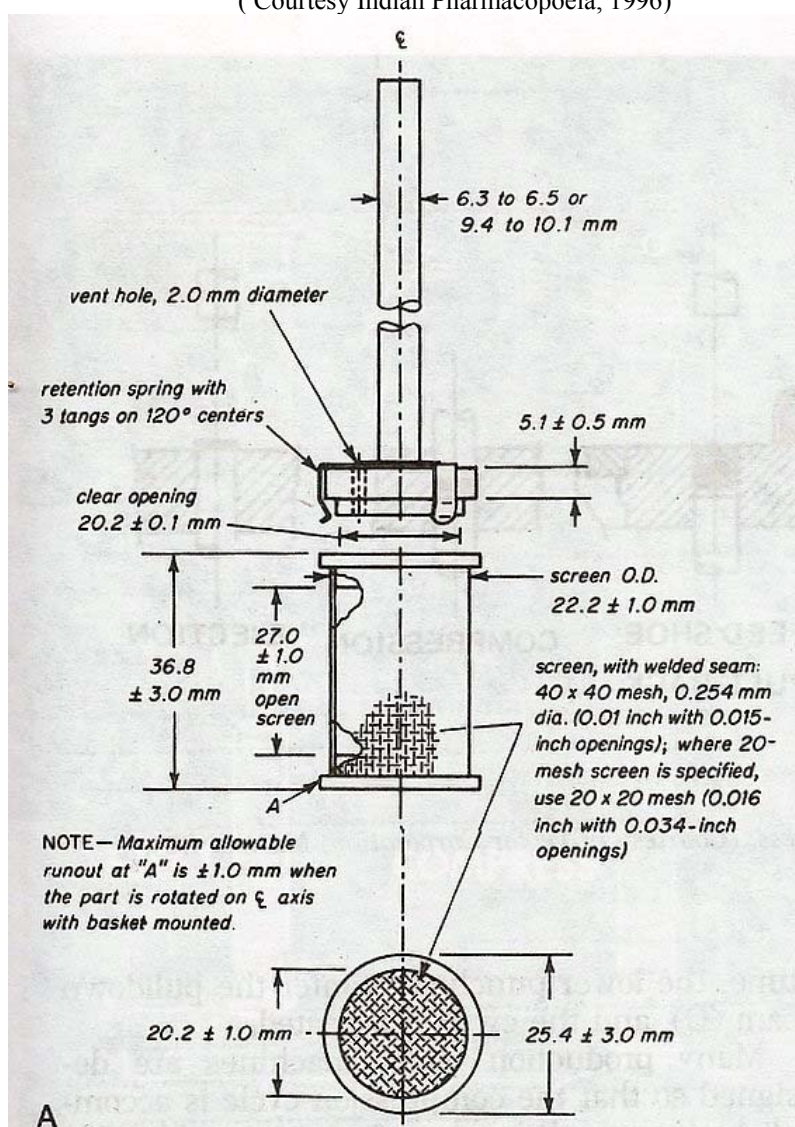20.2 ± 1.0 mm

25.4 ± 3.0 mm

A

Fig. 21 USP dissolution apparatus 1
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition
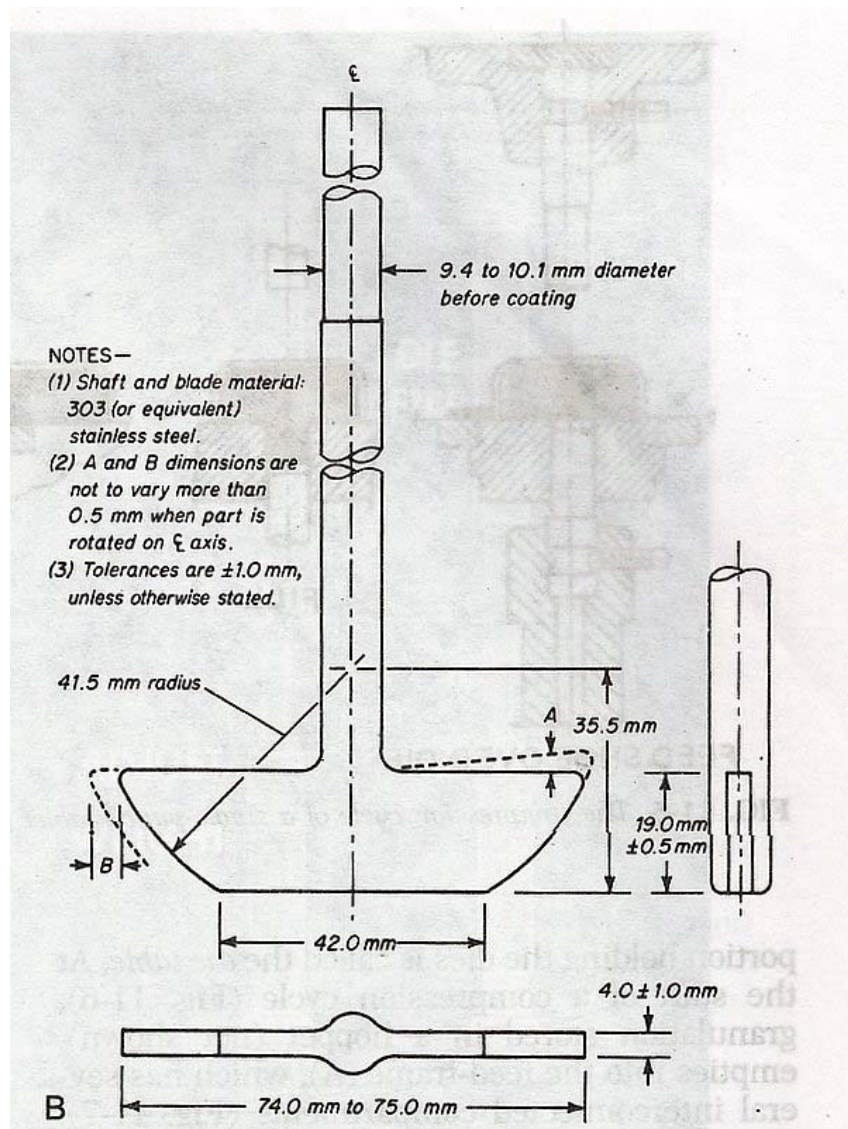
Fig. 22 USP dissolution apparatus 2
(Courtesy, The theory and practice of Industrial pharmacy Leon Lachman, third Edition

Apparatus-2: It is same as apparatus-1, except the basket is replaced by a paddle. The dosage form is allowed to sink to the bottom of the flask before stirring. For dissolution test U.S.P. specifies the dissolution test medium and volume, type of apparatus to be used, rpm of the shaft, time limit of the test and assay procedure for. The test tolerance is expressed as a % of the labeled amount of drug dissolved in the time limit.

Dissolution testing and Interpretation can be done in three stages:

1. **Stage 1:** Six tablets are tested and are acceptable if all of the tablets are not less than the monograph tolerance limit (Q) plus 5% if fail
2. **Stage 2:** Another six tablets are tested. The tablets are acceptable
   Take 6 tablets, test individually, Avg. weight 12 tablets is greater or equal to but no one less than (Q-15) %
   If the average of the twelve is greater than or equal to Q and no unit is less than (Q-15) % if fail

3. **Stage 3:** Another 12 tablets are tested. The tablets are acceptable if the average of all 24 tablets is greater than or equal to Q and if no more than 2 tablets are less than (Q-15) %

Tablet Coating

Tablet coatings perform one or more of the following functions. They may: *mask* the taste of unpalatable drugs, protect the drug from deterioration due to light, oxygen or moisture, separate incompatible ingredients, control the release of medicament in the gastrointestinal tract, and provide an elegant or distinctive finish to the tablet.

The materials used for coating may largely comprise sucrose (sugar coating), water-soluble film-forming polymers (film coating) or substances which are soluble in the intestinal secretions but not in those of the stomach (enteric coating). These types of coating can all be applied by the pan or fluid-bed processes; the compression coating technique is suitable for sugar and enteric coatings, but not for film coating.

Types of Coating

Different coating processes are: Pan coating, Fluid Bed Coating, Compression coating

A. Pan   Coating

In this process the tablets are tumbled in a bowl or pan which rotates about an axis inclined about 30^0 to the horizontal (Fig.23). With the correct pan load a three dimensional circulation is established and sufficient coating solution is added to wet the tablet surfaces. Internal baffles (Sutaria 1968) or hand manipulation of the wetted tablets ensures that the solution is evenly distributed and a satisfactory tumbling action maintained while the coating is dried by a stream of warmed air. Small amounts of dusting powder may be applied to reduce tackiness and cohesion of the tablets during the drying stage. The volume of coating solution for each application is critical; inadequate wetting leads to irregular coating, whereas with too large a volume the tablets agglomerate and do not tumble well. The cycle of alternate wetting and drying is continued to build up a coating of the required properties. Initially, the tablets are subject to considerable abrasive action and for this reason should be more highly compressed than the corresponding uncoated tablets.
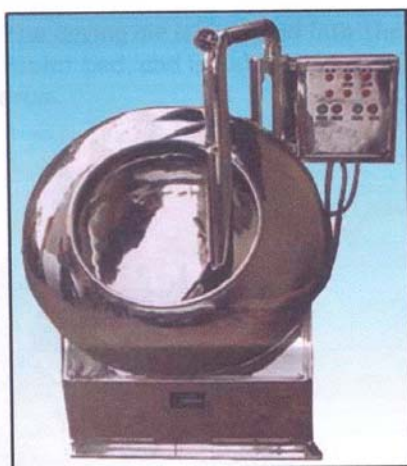

Fig. 23 Tablet coating pan
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Sugar Coatings

This traditional coating imparts a smooth, rounded, elegant appearance to the tablet. Stephenson and Smith (1951) have given a detailed discussion on the composition of sugar coatings.

Advantages: 1. It gives a smooth & shining surface

2. It mask the bitterness & sweet in taste

3. It increases the elegance of the product.

Disadvantage: It increases the weight of the tablet & it is hygroscopic

Sealing. After all dust has been removed from the tablet a dextrin, gelatin or acacia coat may be applied to ensure good coating adhesion. Where protection against the effects of water in subsequent coating solutions is required a 30 to 50 percent solution of shellac in alcohol or other suitable solvent is employed for sealing, care being taken to avoid over generous application as this leads to a prolongation of the disintegration time.

Subcoating. To minimize the amount of material, which must be used to round the tablet edges, the cores are made on deep concave punches. The subcoat is build up in successive layers by wetting the tablets with an adhesive solution, dusting with filler and then thoroughly drying, as retained moisture may cause later cracking of the coat or deterioration of the core. The subcoating solution is usually an aqueous solution of sucrose to which is added acacia, gelatin or both, to impart adhesive properties. Talc and precipitated calcium carbonate are widely used in the subcoating filler together with some sucrose and a small proportion of acacia. A small proportion of inert filler, e.g., talc, may be added to the subcoating solution, which, if it contains gelatin, should be used warm to avoid gelling. Too heavy an application of filler must be avoided as the excess forms 'granules' with the coating solution and these interfere with the formation of a smooth subcoat. This stage of the process is continued until the tablets have a rounded appearance and the edges are well covered. When complete, the tablets are removed from the pan and thoroughly dried.

Smoothing and polishing. The application of a smoothing solution (60 per cent sucrose in water is satisfactory) causes limited wetting of the subcoat, which has been hardened by drying, so that it is smoothed out by the tumbling action. Soluble dye or a lake colour may be added to the smoothing solution if a coloured coating is required. As soon as the coat has become comparatively smooth the volume of smoothing solution per application should be reduced and the tablets dried without the aid of heat. In the final stages, tumbling is limited by 'inching' rather than rotating the bowl so that the coating is not scratched or otherwise damaged. At this stage the tablets will have a perfectly smooth but matt appearance and are thoroughly dried before polishing in a pan specially set aside for the job and coated with a beeswax, carnauba wax or similar waxy mixture.

Film Coating

Sugar coating doubles the weight and increases the size of a tablet and this is obviously undesirable if the tablet, in the uncoated state, is already large. Film coating provides an alternative means of masking the taste of the medicament and providing protection against adverse climatic conditions without significantly altering the tablet weight or size. The obvious advantages of excluding water from the coating process may be secured with film-forming polymers, such as ethylcellulose,

polyvinylpyrolidone or hydroxymethylpropyl cellulose, that are soluble in both water and anhydrous organic solvents. Some 3 to 10 percent of the foregoing materials can be dissolved in an acetone-alcohol mixture together with 5 to 10 percent of diethyl phthalate or other plasticizer to produce a film coating solution which may be applied by the pan technique. The plasticizer stops the film becoming brittle with age. Methylene chloride is often added to the solvent to reduce fire hazards, while undue absorption of expensive film forming agent is prevented by the prior application of a shellac-sealing coat to the core tablets.

Advantages: 1. It does not increase the weight of the tablet
2. It protects the tablet from moisture
3. It increases the elegance of the tablet

Enteric Coating

Tablets are enteric coated if the medicament is decomposed in the acid secretions of the stomach, if it causes gastric irritation, or if it is intended to exert its main effect only on the intestine. Some official tablets coated in this way include those containing biscodyl, bismuth and emetine iodide, and erythromycin. Enteric coatings resist the acid conditions of the stomach but readily dissolve in the more nearly neutral fluids of the small intestine. They are also used in the formulation of sustained action preparations as the release of medicament is delayed by the time taken for the tablet to pass from the mouth to the intestine.

Formalized gelatin, keratin, salol, shellac, sandarac, stearic acid and cetyl alcohol have all been used to produce enteric coatings but are either difficult to apply or erratic in their action. The compositions of the fluids in the gastrointestinal tract are not constant but vary with time and from person to person. It is clearly important that the enteric action shall largely be independent of such variations in compositions. Cellulose acetate phthalate is widely used for enteric coating and was reported by Antonides and DeKay (1953) to be the only cellulose derivative of the fourteen evaluated that was satisfactory for this purpose. Only one of the phthalic acid carboxyl groups is attached to the cellulose, the other being free for reaction. The polymer dissolves in a variety of solvents, gives water-soluble salts with a number of bases and forms coatings which are insoluble in, but slightly permeable to, water (Malm et al., 1951). An important feature is the solubility of cellulose acetate phthalate films in buffers having a pH as low as 5.8; thus the requirements for enteric action are a medium with a pH higher than this value which can contribute ions to the coating to form a soluble salt. Such conditions are found in the intestine but not in the stomach.

In addition to 5 to 15 percent of cellulose acetate phthalate the enteric coating solution may contain a plasticizer such as castor oil or butyl stearate together with a soluble or a lake dye if a colored finish is required. The materials are dissolved or dispersed in a volatile solvent comprising alcohol, acetone, and, to reduce flammability, methylene chloride.

Advantages: 1. It gives a sustained action.
2. It protects the tablet from moisture
3. It releases the medicament in the intestine.

Automated Pan Coating

Successful use of the pan coating technique depends, in large measure, on the skill of the operator: it is also time consuming. Due to their higher volatility the solvents used

for film coating permit rapid drying of tablets after each addition of the coating solution. As with moist granulation, spraying rather than pouring the coating solution is a more controllable technique that relies less on the operator's skills and which is more readily adapted to automatic control. In the case of enteric coated tablets, performance is determined by the thinnest part of the film and for reproducible characteristics between and within batches the coating must be of known uniform thickness. According to Lachman and Cooper (1963), enteric coatings complying with the foregoing criteria may be obtained by means of an automated film coating process. The tablets are tumbled in a baffled pan and a solution of cellulose acetate phthalate together with fillers in suspension is sprayed on to the tablets in repetitive 'bursts' alternating with longer drying periods. The spray gun for applying the coating solution and the hot or cold air flow for removing solvent are controlled by a punched tape programming device. The coating time for an 85 kilogram batch of tablets (90 minutes) is half that required by the corresponding manual procedure, and the weight of the coating is reduced and is more uniform.

Fully automated equipment for pan coating is now commercially available. Provision is made for programmed control of the coating composition, spray application and drying air-flow at each stage of the process. The different paths taken by tablets in a pear-shaped bowl leads to a lack of uniformity in the thickness of coating applied to tablets within the batch. This problem is avoided in the Manesty Autocota by the adoption of a cylindrical coating vessel rotating about a horizontal rather than inclined axis.

Film forming materials
The film forming materials used in film coatings are ethyl cellulose, polyvinylpyrolidone, hydroxymethylpropyl cellulose. These are soluble in water as well as in nonaquous organic solvents. The other agents are Methyl hydroxyethylcellulose, Povidone USP, Sodium CMC, PEG-4000, Acrylate polymers.

Formulations of coating solution: The constituents of coating solutions used for sugar coating are given below:

Seal coating	Sub coating	Syrup coating	Polishing soln.
Zein/Shellac	Gelatin	Colorant	Carnauba wax
Oleic acid	Acacia	Sub coating powder	(yellow)
Propylene glycol	Sugar cane powder	Cal. Carbonate	Bees wax
PEG 4000	Corn syrup	Cane sugar powder	(white)
Methylene chloride	Syrup	Corn starch	Paraffin wax
Alcohol	Distilled water	Syrup	Naphtha
		Distilled water	

Enteric coating polymers: Cellulose acetate phthalate, Acrylate polymers, Hydroxypropyl methyl cellulose phthalate, Polyvinyl acetate phthalate

Solvents used for coating: Ethanol, Methanol, Isopropanol, Chloroform, Acetone, Methylene chloride, Methylene ethyl ketone

B. Fluid-Bed Coating

Wurster (1959) first described the application of sugar or film coatings to tablets suspended in an air stream. In that equipment the coating solution is introduced into the fluidizing air stream at the base of a tall vertical tube in which tablets circulate as they are coated. Evaporated solvent and air are removed at the top of the chamber. The fluid-bed moist granulation equipment described earlier has now been modified by the makers for fluid-bed coating. As the tablets circulate in the air stream they are subjected to considerable abrasive action and for this reason they are compressed with extra firmness on punches which give a well rounded profile.

C. Compression Coating

As noted earlier it is desirable on occasion to separate tablet ingredients to avoid incompatibilities, to facilitate manufacture or to produce a sustained action product. Layer tablets provide an acceptable means for ingredient separation but the protective effect of the coat enveloping the tablet is lacking. It is not an easy matter to ensure a sugar coat of the same thickness for all tablets in a batch by pan coating and although reasonable variation in coat thickness and weight is not significant in plain sugar coating such variation can not be tolerated if the coat contains a potent medicament. The idea of applying granular coating materials to a performed core was conceived by Noyes in 1896 but could not be commercially exploited until the problem of core centration and the automatic rejection of coreless tablets had been solved. The expected advantages of a compression coating process are:

(i) Core tablets are not subjected to abrasive action and need not be especially hard,
(ii) The process is 'anhydrous' and sealing coats are not required,
(iii) The disintegration time of a coated tablet can be comparable with that of the uncoated   variety, due to the above,
(iv) Good control of coating weight can be obtained,
(v) Chemically incompatible ingredients may be separated,
(vi) The core and coat may be formulated for different properties e.g., for a sustained action tablet the coating would provide the prompt dose and the core the sustained dose,
(vii) The process is continuous, completely mechanized and removes much of the element of skill from tablet coating.

Compression Coating Machines
The essential stages of coating by compression are (Fig.24), deposition of the bottom fill of coating granules, transfer and centration of the core tablet, deposition of the side and top fill and finally compression to bond the coat to the core. The machine described by Whitehouse (1954), the Kilian Prescoter, used preformed cores which were fed into holes on the periphery of a transfer disc and deposited on the lower fill of coating granules as the lower punch dropped in readiness for the top fill. The core was centred by a light tap of the top punch, the top fill deposited and the coating bonded to the core by compression. The force developed during compaction in the presence of a core was sufficient to cause slight deflection of the overload release but failed to do so in the absence of a core. A switch connected to the overload release provided an electrical signal which, when fed to a memory unit, actuated a gate on the collection chute such that coreless tablets were rejected.
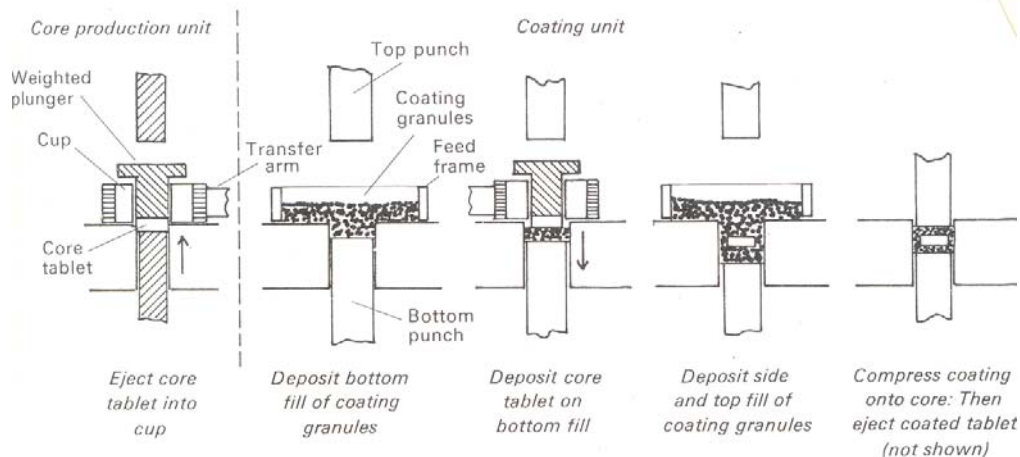
Fig.24 Compression coating of tablet
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

The Manesty Drycota (Fig.25) comprises two rotatory presses coupled by a transfer unit (Fig.26). The spring-loaded arms of the transfer unit engage with small collars on the upper turret to ensure accurate ejection of the core tablet into a cup fitted with a free sliding weighed plunger. Next, the cup passes over a 'bridge' where dust is removed to avoid contamination of the coating granules and then engages with the collar on the upper turret of the coating press. As the bottom punch drops, the tablet is pushed out of the cup on to the centre of the bottom fill of coating granules by the action of the weighed plunger. The cavity is then filled with granules for the sides and top of the coating, which are bonded to the core by compression. As the cups pass round the transfer unit the plungers are examined by feelers which operate microswitches. If a cup fails to pick up or deposit a core at the appropriate stage in the cycle the signal from the microswitches initiates action for the rejection of coreless tablets.
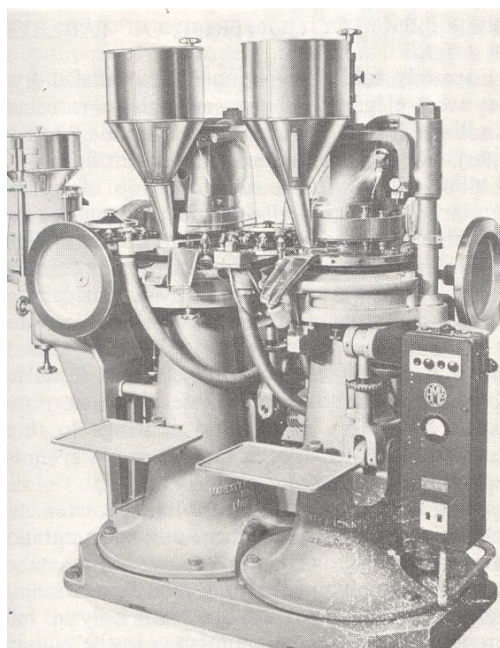

Fig.25 Compression coating machine.
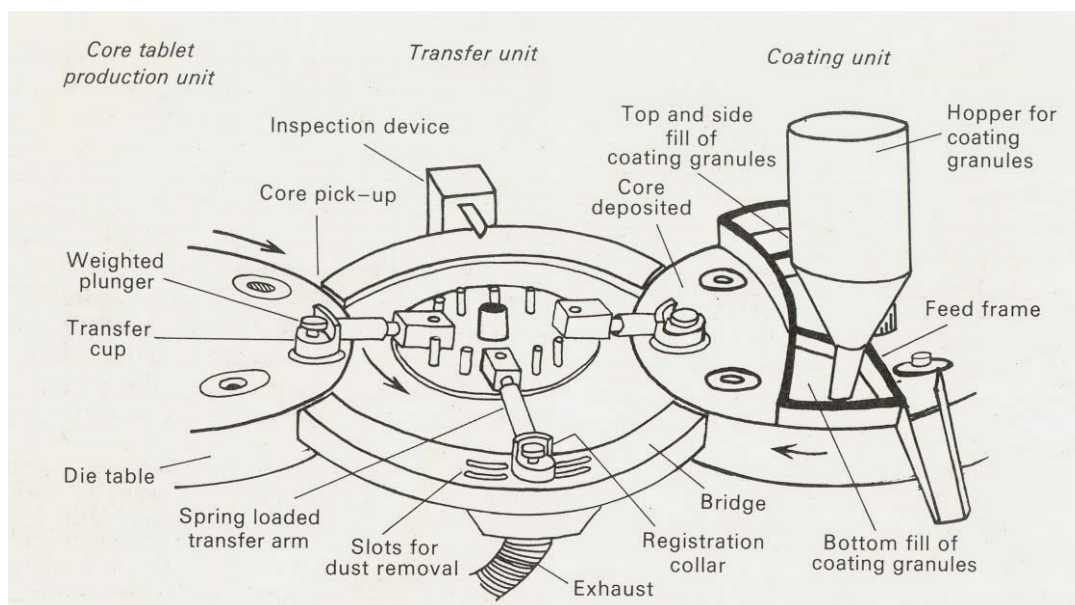(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Fig.26 Essential features of transfer mechanism of a compression coating machine.
(Courtesy, Bentley's text book of pharmaceutics, by E A Rawlins, eighth edition)

Requirements for Core Tablets and Coating Granules

Core tablets should be prepared from rather large granules and should be lightly compressed. The surface of a soft tablet made from large granules is somewhat porous and provides a good 'key' for adhesion of the coating. There is a second reason for light compression of the core tablet. Residual stresses in a tablet are not instantaneously relieved when that tablet is ejected from the die. Large residual stresses induced by a high degree of compression may be sufficient to split the coating some time after manufacture has been completed.

The gap between the core and die-wall should be at least 0.13 cm to facilitate uniform deposition of coating granules round the edges of the core tablet and hence to ensure adequate coating strength. For these reasons too, the granule size should not exceed a quarter of the edge coating thickness. On the other hand, excessive amounts of fines or fatty lubricants should be avoided, as these lead to poor coating strength and poor adhesion to the core.

Performance

Provided the requirements for edge thickness are met, the weight of the coating is maintained with considerable precision and may be varied over a wide range. It may be noted that the official test for weight variation applies to compression coated tablets but not to those having a film or conventional sugar coat. Centrifugal and tangential forces due to turret rotation may slant the bottom fill of coating granules and displace the core from its central position. Lachman et al. (1966) concluded that coating granules which gave minimum weight variation also tended to give less core displacement.

Coatings may be formulated for a wide range of properties but of these, enteric coatings are of particular interest. Blubaugh et al. (1958) have described the preparation of coating granules containing triethanolamine cellulose acetate phthalate

37

which, when applied by compression, produce a coating with enteric properties. In a more recent paper Srinivas et al. (1966) have reported on the use of a number of carboxylated polymers for the production of entire coating granules.

Other methods of coating equipments:

Perforated Pan Systems

Accela-Cota: It is a prototype of perforated cylindrical drum providing high drying air capacity. Therefofe it is preferred for film coating.

Fig.27 Accela-Cota

Hi-coater system: The drying air is directed into the drum is passed through the tablet bed, and is exhausted through the perforations in the drum.

Fig. 28 Hi-coater system

Fluid Bed Coater:

The Tablets are moving in stream of air passing through the perforated bottom of a cylindrical column. With a smaller cylindrical insert, the stream of core is rising in the center of the device together with a spray mist applied in the middle of the bottom. Very hard tablets (hardness>20N) have to be used for fluid bed coating, although surface smoothness is usually of a lower quality due to attrition of core material and frequent deformation of fresh film layers.

Fig. 29 Fluid Bed Coater:

Recent updates of Coating

Normal Film Coating

Ideal Cures manufactures and supplies the full range of tablet film coating systems under the brand name of INSTACOAT, for normal film coating and functional

coating. INSTACOAT has a wide range of products available. Depending upon the requirement, the customer can take help of our expert advice for choosing the right product for their application.

It is for film coatings, hydro alcoholic film coatings, tablet-coating films, cellulose film coating systems for various pharmaceutical solid oral dosage forms.

The brief details of film coating systems are as under:

Product	Description	Reconstitution level	Average weight gain *	Application ** examples
Instacoat Aqua	HPMC based Aqueous System	11 %	2.5 %	Amoxycilin, Azithromycin Atenolol, Amlodipine, Acelofenac, Amtriptyline, Ampicilin HCI, Ciprofloxacin, Cefadroxil, HCI, Celecoxib, Cimitidine, Calcium Tablets, Certizine, HCI, Clarithromycin, Chloroquine Phosphate Erythromycin estoate, Erthromycin striate, Enalpril, Maleate, Elctronxib, Ferrous, fumarate, Famotidine Flupenthixol Fluoxetine Felodipine, Gatifloxacin, Gliclazide, Ibuprofen, Indapamide, Ketorolac, Ketoprofen, Levofixation, Levocetrinzie, Losartan, Potassium, Levamisole, Metormin, Methylopa, Metra + Tetraozole, Metronidozole, Methyl, Comblamine, Mefenamic acid, Metropralal Nifedipne, Norfloxacin, Nifedopine, Norfloxacin Norflax+Tindazole, Oflaxacin, Oflaxacin+Omidazole, Olazzapine, Orridazole, Oflexacin + Omidazole Paracetamol, Pravastain, Prmethazine, Quinine, sulphate, Primaquine, Ramipril,Tindazole, Tiri+Doxicycline Tiri + Tetracyline, Valdecoxib, Verapamil, All herbal & Neutraceuticls
Instacoat Sol	HPMC based Organic Solvent System	5%	2.5%	
Instacoat Universal	HPMC based Aqueous / Organic / Hydro-Alcoholic System	Aqueous 11 % Organic Solvent - 5% Hydro Alcoholic - 9%	2.5%	
Instacoat Aqua -II	Grafted PVA based Aqueous System	20%	2.5%	
Instacoat Aqua -III	HPMC based Aqueous System	15%	2.5%	
Instacoat - P4	SA based Aqueous System	20%	2.5%	
Instacoat Herbo	Customized Polymer based Aqueous/ Organic System	Aqueous 11% to 20 % Organic - 5%	5%	
Instacoat Natcol	Aqueous / Organic System with Natural Colourants	Aqueous 11% to 20 % Organic - 5%	5%	

SUPERCELL™ Tablet Coater

Revolutionary tablet coater that accurately deposits controlled amounts of coating materials on tablets, even if they are extremely hygroscopic or friable.

Fig. 30 The SUPERCELL™ Tablet Coater

Tablet coating technology in the pharmaceutical industry has remained fundamentally unchanged for the past 50 years. Until now inconsistent and imperfect, this "standard" practice of tablet coating often delivers a non-homogenous product. Because the tablets are loaded in large rotating pans and vented for hot air drying, tablet edges can get grounded off, intagliations can get filled in by coating material, and edges and corners may not be coated with the same thickness as the tablet faces. The inaccuracy of deposition of coating material limits the use of modified release coatings. In a laboratory setting, it is necessary to coat several kilograms of tablets at one time, making Research & Development of a tablet dosage form costly and difficult.

In addition, extremely hydroscopic tablets cannot be coated with current technology, nor can flat or other odd shapes be consistently coated. The process must be run slowly to prevent "twinning", where two or more tablets stick together. Tablets may also be coated in a Wurster-type coating apparatus, but tablet attrition generally prevents all but the hardest tablets from being coated this way

Fig. 31 The SUPERCELL™ Tablet Coater

SUPERCELL™ **Tablet Coater** from Niro Pharma Systems effectively solves all of these problems using a small, modular design. The tablets are coated in batches ranging from 30 to 40 grams, which linearly scale up production capacities. The tablets are coated with the coating spray in the same direction as the drying gas, resulting in a more efficient process.

Due to SUPERCELL™ **Coating Technology's** unique air distribution plate design, the tablets move quickly and predictably through the spray zone, receiving only a small amount of coating per pass, and therefore achieving higher coating accuracy. The process time is short, seconds or minutes as opposed to hours, and therefore gentler on the tablets. SUPERCELL™ **Coating Technology** allows for coating of friable tablets, as well as, flat or highly oblong tablet shapes. Drying is very fast, making it possible to coat extremely hydroscopic tablets. The accuracy of deposition is great enough that Active Pharmaceutical Ingredients can be layered onto tablets, and uniform layers of taste masking or modified release coatings can be added in a single continuous batch without resulting in any problems.

Unique Features of SUPERCELL™ Coating Technology:

- Continuous coating
  - Short processing time
  - No scale-up parameters
- Flexible modular design
  - R & D batch size (Minimum batch size of 30 grams)
  - Production capacity of 6 cells coats 200,000 tablets per hour of 120 mg tablets
- Enhancing technology
  - Difficult-to-coat shapes
  - Friable tablets
  - Multi-layer coating
- Enabling Technology
  - "Low humidity process" suitable for moisture sensitive materials
  - Accuracy of coating (RSD less than 1% demonstrated)

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