CONCEPT OF FORMULATION DESIGN

Preformulation is branch of Pharmaceutical science that utilizes biopharmaceutical principles in the determination of physicochemical properties of the drug substance.

Prior to the development of any dosage form new drug, it is essential that certain fundamental physical & chemical properties of drug powder are determined.

This information may dictate many of subsequent event & approaches in formulation development.

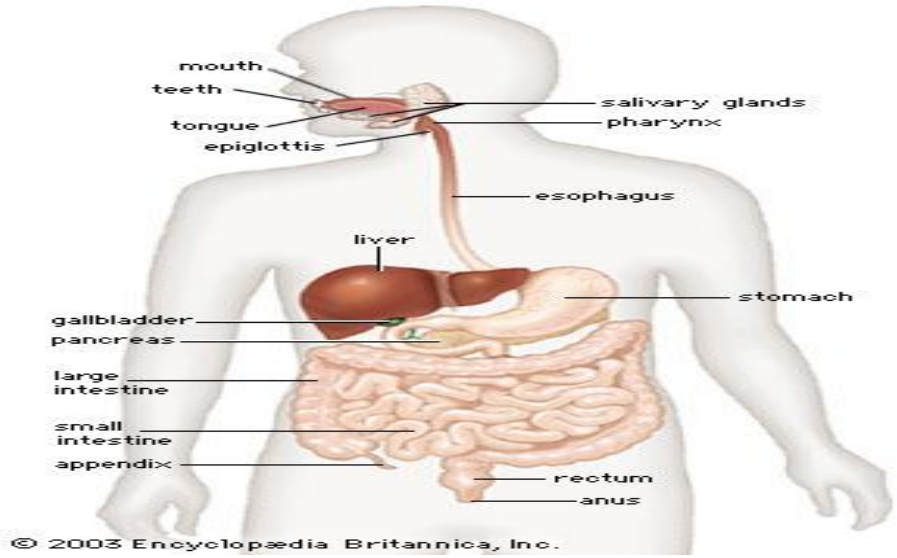
This first learning phase is called as preformulation.

1. M. E. Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

Design of dosage form **Biopharmaceutical factors**
Therapeutic aspects

- Introduction of absorption.
- Structure of the Cell Membrane.
- Gastro intestinal absorption of drugs.
- Mechanism of Drug absorption.
- Factors affecting drug absorption

GASTRO INTESTINAL ABSORPTION OF DRUGS



MECHANISM OF DRUG ABSORPTION

1) Passive diffusion
2) Pore transport
3) Carrier- mediated transport
    a) Facilitated diffusion
    b) Active transport
4) Ionic or Electrochemical diffusion
5) Ion-pair transport
6) Endocytosis

1. M. E. Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,

INFLUENCE OF DRUG pKa AND GI PH ON DRUG ABSORBTION

Drugs	Site of absorption
Very weak acids (pKa > 8.0)	Unionized at all pH values Absorbed along entire length of GIT
Moderately weak acids (pKa 2.5 – 7.5)	Unionized in gastric pH Ionized in intestinal pH Better absorbed from stomach
Strong acids (pKa <2.5)	Ionized at all pH values Poorly absorbed from GIT
Very weak bases (pKa < 5)	Unionized at all pH values Absorbed along entire length of GIT
Moderately weak bases (pKa 5 – 11)	Ionized in gastric pH Unionized in intestinal pH Better absorbed from intestine
Strong bases (pKa >11)	Ionized at all pH values Poorly Absorbed from GIT

1. M. E. Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,

FACTORS AFFECTING GASTRIC EMPTYING

Volume of Ingested Material	As volume increases initially an increase then a decrease. Bulky material tends to empty more slowly than liquids
Type of Meal	Gastric emptying rate: carbohydrates > proteins > fats
Temperature of Food	Increase in temperature, increase in emptying rate
Body Position	Lying on the left side decreases emptying rate and right side promotes it
Git PH	Retarded at low stomach PH and promoted at higher alkaline PH
Emotional state	Anxiety promotes where as depression retards it
Disease states	gastric ulcer, hypothyroidism retards it, while duodenal ulcer, hyperthyroidism promotes it.

1. M. E. Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,

SOLID DOSAGE FORMS: TABLET

Tabletting properties: compressibility and fluidity consolidation study

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.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 293-345

TABLET INGREDIENTS

• **Drugs** • Fillers, diluent, bulking agent To make a reasonably sized tablet • **Binders** To bind powders together in the wet granulation process To bind granule together during compression • **Disintegrants** To promote breakup of the tablets To promote rapid release of the drug • **Lubricants** To reduce the friction during tablet ejection between the walls of the tablet and the walls of the die cavity	• **Glidants** Reducing friction between the particles To improve the flow properties of the granulations • **Antiadherants** To prevent adherence of the granules to the punch faces and dies • **Dissolution (enhancers and retardants)** • **Wetting agents** • **Antioxidants** • **Preservatives** • **Coloring agents** • **Flavoring agents**

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 325-328.
2. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 449-452.

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 10 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

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

RATIONALE FOR GRANULATION

- To prevent segregation of the constituent of the powder mix
- To improve flow properties of the mix
- To improve the compaction characteristics of the mix
- Miscellaneous reasons

GRANULATION PROPERTIES

- Particle size and shape
- Surface area
- Density
- Strength and friability
- Flow properties

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 410-423.

GRANULATION MECHANISMS

To form granules, bond must be formed between powder particles so that they adhere and these bonds must be sufficiently strong to prevent breakdown of granules.

These are five primary bonding mechanisms between particles

- Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles
- Interfacial forces in mobile liquid films with the granules
- The formation of solid bridges after solvent evaporation
- Attractive forces between solid particles
- Mechanical interlocking

Mechanisms of granule formation

I. Nucleation

II. Transition

III. Ball growth- Four possible mechanisms of ball growth are,

- Coalescence, Breakage
- Abrasion transfer, layering

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 410-423.

EVALUATION OF GRANULES

Angle of Repose

$$\tan \theta = h/r.$$

where, θ = angle of repose.

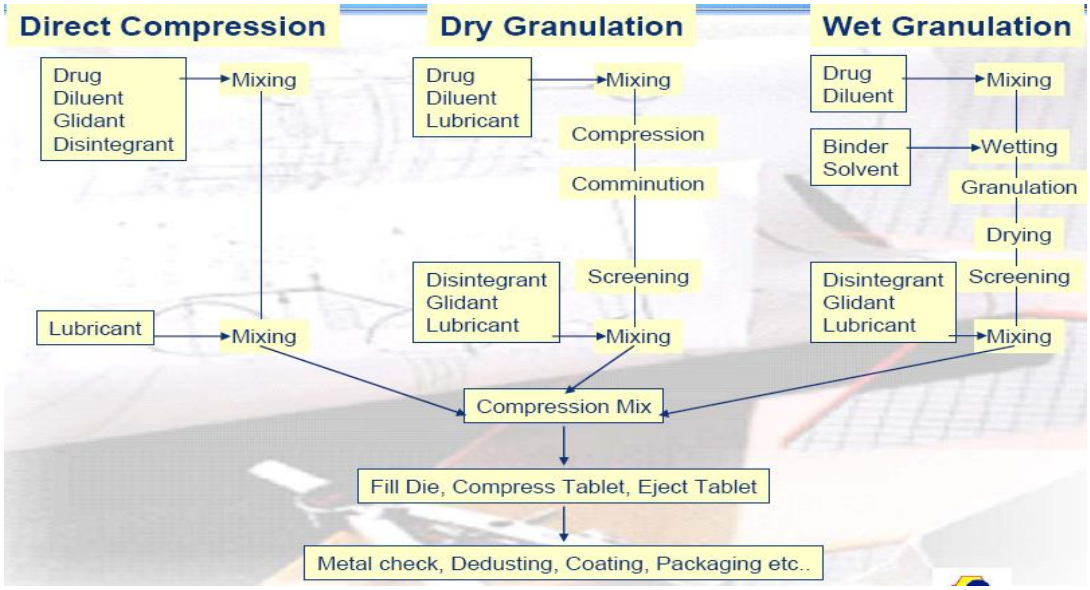
h=height of pile.

r= radius.

$$\text{CARR'S INDEX(\%)} = \frac{(\textit{TAPPED DENSITY} - \textit{POURED DENSITY})}{\textit{TAPPED DENSITY}} \times 100$$

Hausner's Ratio

Granulation technology on large scale by various techniques



1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

SLUGGING (DRY GRANULATION)

- A dry powder blend that cannot be directly compressed because of poor flow or compression properties.
- This is done on a tablet press designed for slugging, which operates at pressures of about 15 tons, compared with a normal tablet press, which operates at pressure of 4 tons or less.
- Slugs range in diameter from 1 inch, for the more easily slugged material, to ¾ inch in diameter for materials that are more difficult to compress and require more pressure per unit area to yield satisfactory compacts.
- If an excessive amount of fine powder is generated during the milling operation the material must be screened & fines recycled through the slugging operation.

ROLLER COMPACTION

- Granulation by dry compaction can also be achieved by passing powders between two rollers that compact the material at pressure of up to 10 tons per linear inch.
- Materials of very low density require roller compaction to achieve a bulk density sufficient to allow encapsulation or compression.
- One of the best examples of this process is the densification of aluminum hydroxide.
- Pilot plant personnel should determine whether the final drug blend or the active ingredient could be more efficiently processed in this manner than by conventional processing in order to produce a granulation with the required tabletting or encapsulation properties.

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 422-423.

2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 293-345.

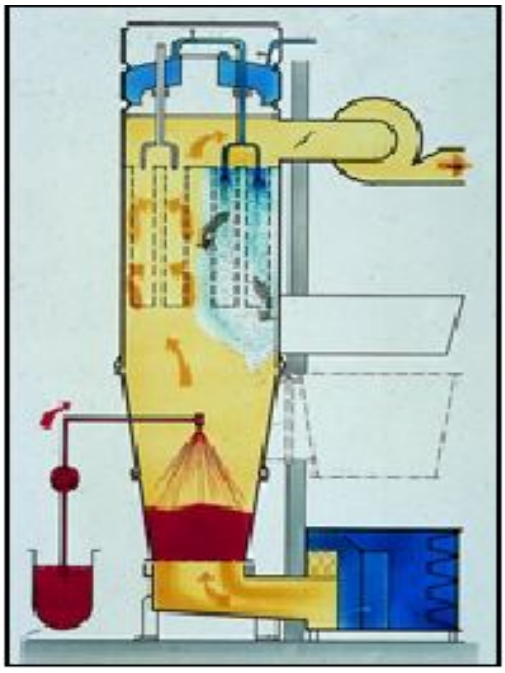
FLUID BED GRANULATION

ADVANTAGES

- All process such as mixing, massing, granulation, drying etc. is performed in the single unit
- Saves labour costs, transfer losses of time.
- The process is automated once the conditions affecting granulation are optimized.

DISADVANTAGES

- Expensive
- Optimization of operating variable is critical



1. M. E. Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,

EXTRUSION

Advantages

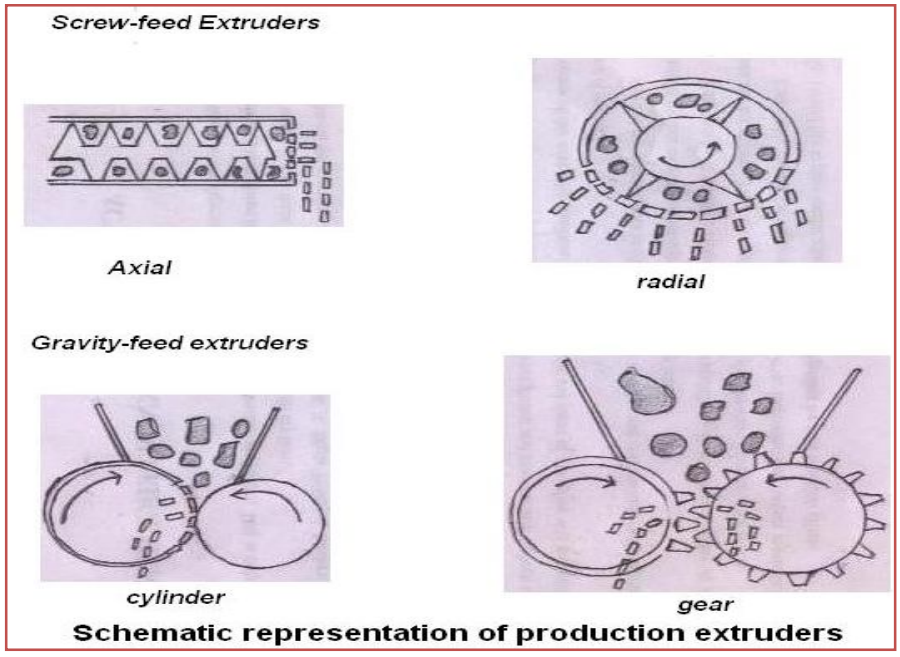
Extrusion-spheronization is a versatile process capable of producing granules or spheres having unique physical properties.

- It may be more labor and time-intensive

Disadvantage

- Care must be taken to understand the desired properties and the formulation and process variables capable of achieving them

EXTRUDERS



Schematic representation of production extruders

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,

MELT SOLIDIFICATION

ADVANTAGES

- Neither solvent nor water used in this process.
- Fewer processing steps needed thus time consuming drying steps eliminated.
- Entire procedure simple, continuous and efficient.

DISADVANTAGES

- Requires high energy input.
- The melt solidification technique is that the process cannot be applied to heat-sensitive materials owing to the elevated temperatures involved.

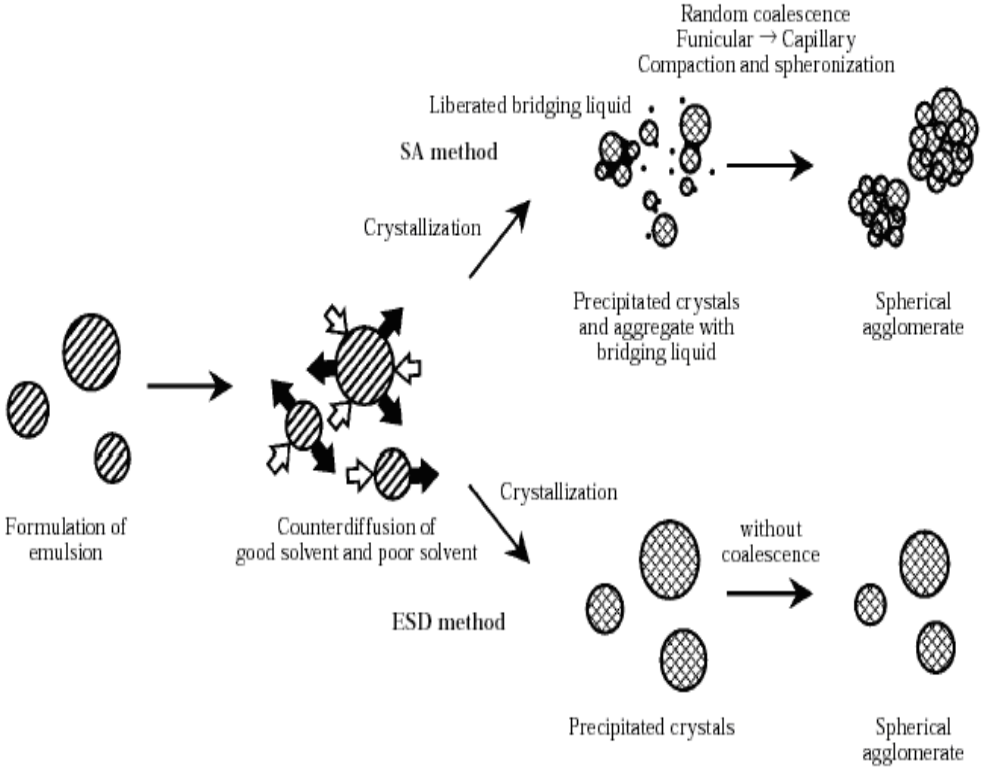
TECHNIQUES FOR MELT GRANULATION

- Spray congealing
- Tumbling melt granulation
- Melt agglomeration
- Melt extrusion

SPHERICAL CRYSTALLISATION

TECHNIQUES

- Spherical agglomeration
- Emulsion solvent diffusion
- Ammonia diffusion method



HECKEL EQUATION

- Heckel plot is density Vs applied pressure.
- Follows first order kinetics.
- As the porosity increases the compression force will increase.
- The Heckel equation is described as follows. It is based on the assumption that powder compression follows first-order kinetics, with the interparticulate pores as the reactant and the densification of the powder bed as the product.
- Where
  - D= relative density of a powder
  - P=compact at pressure P.
  - Constant k = measure of the plasticity of a compressed material.
  - Constant A =die filling and particle rearrangement before deformation and bonding of the discrete particles.
- Thus, a Heckel plot allows for the interpretation of the mechanism of bonding.

$$\ln \frac{1}{1-D} = kP + A$$

Ref.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 82-83
2. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 471-472.

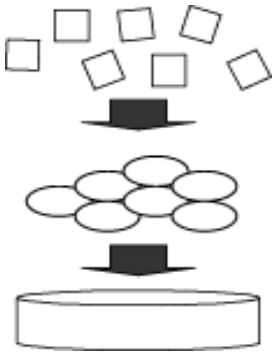
KAWAKITA EQUATION

- The Kawakita equation is described as follows. This equation describes the relationship between the degree of volume reduction of the powder column and the applied pressure.
- The basis for the Kawakita equation for powder compression is that particles subjected to a compressive load in a confined space are viewed as a system in equilibrium at all stages of compression, so that the product of the pressure term and the volume term is a constant. Where,
    - C = degree of volume reduction of a powder compact at pressure P.
    - constants (a and b) =evaluated from a plot of P/C versus P.
    - a= total volume reduction for the powder bed [carr's index]
    - b= constant that is inversely related to the yield strength of the particles.
- The data from this study were modeled via the Kawakita equation in an attempt to evaluate the relationship between the volume reduction and applied pressure for each studied DC binder.

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 82-83.
2. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 471-472.

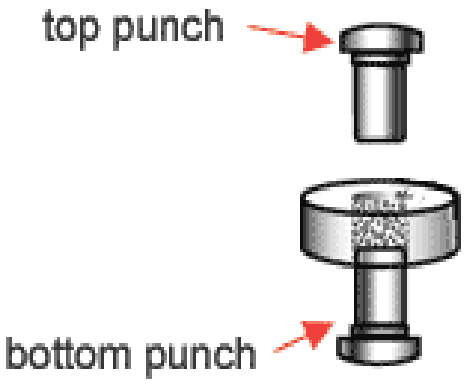
Physics of tablet compression, machines and equipments



- When external mechanical forces applied to a powder mass there is reduction in bulk volume as follows
- Repacking
- Particles deformation
- Elastic deformation-e.g. acetyl salicylic acid, MCC
- Plastic deformation-at yield point of elastic.
- Brittle fracture – e.g. sucrose
- Microquashing-irrespective of larger particles, smaller particles may deform plastically.

Compaction	Consolidation
• It is defined as the formation of solid specimen of defined geometry by powder compression. • The compression takes place in a die by the action of two punches, the lower and the upper by which compression force is applied.	• It is in increase in mechanical strength of material from particle particle interactions.

Single Punch Machine



Multi-station rotary presses

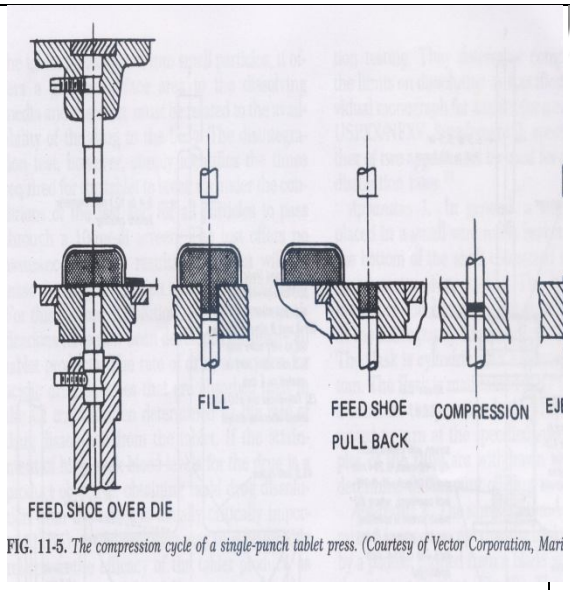


FIG. 11-5. *The compression cycle of a single-punch tablet press. (Courtesy of Vector Corporation, Mari*

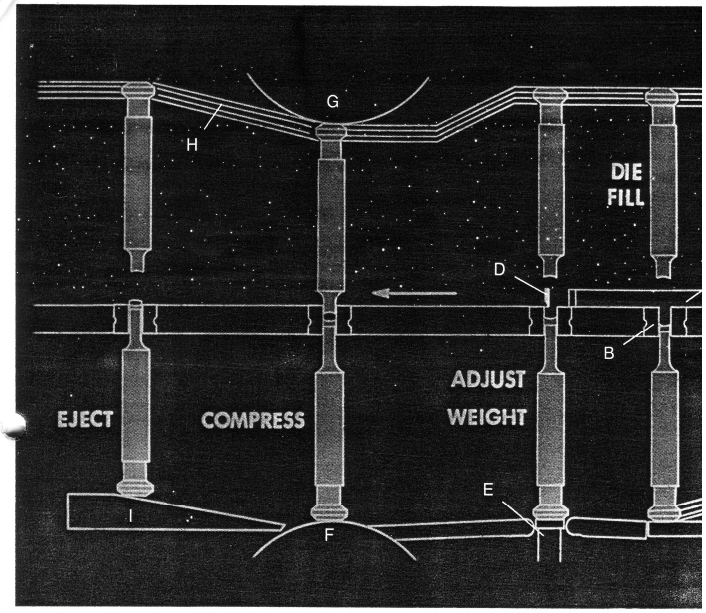


FIG. 11-6. *The compression cycle of a rotary tablet press. (See text for explanation of lettered labels.) (Courtes Engineering, Hoffman Estates, IL.)*

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

CHEWABLE TABLETS

I. Advantages over other types of tablets

i. Better bioavailability through by passing disintegration.

ii. Patient convenience through the elimination of the need for water for swallowing .

iii. Substitute for liquid dosage forms where rapid onset of action is needed.

iv. Improved patient acceptance through pleasant taste.

v. Product distinctiveness from a marketing perspective.

II. Formulation factor

A. Taste and flavour

Taste Is a sensory response resulting from a chemical stimulation of the taste buds on the tongue. Salty and sour taste are derived from substances capable of ionizing in solution, bitter response is for organic medicinal compound and sweet taste is given by most saccharides, disaccharides, aldehydes and few alcohols. Substance which do not cause any sensory stimulation are said to have bland taste.

Flavour Refers to a specific combined sensation of taste and smell. Honey flavour having sweet taste and characteristic smell.

B. **Aroma** Pleasant smell are generally referred to as aromas. Chewable tablets should have a characteristics sweet and sour taste and aroma of fresh orange.

C. **Mouth feel** The term mouth feel is related to the type of sensation or touch a tablet produces in the mouth upon chewing. In general, gritty or gummy is undesirable where as a soothing and cooling sensation with smooth texture is desirable mouth feel.

D. **After effects** Most common after effect is after taste eg: iron salts leave a " rusty " after taste and saccharin in high.

III. FORMULATION TECHNIQUES

I. Coating by wet granulation

II. Microencapsulation

III. Solid dispersion

IV. Adsorbate formation technique:

i. Solvent method

ii. Melting method

V. Ion exchange

VI. Spray congealing and spray coating

VII. Formation of different salts and derivatives

VIII. Inclusion complex

1. Lieberman H.A., Pharmaceutical Dosage Forms: tablets Volume 1, Second Edition, 367-406.

MOUTH DISSOLVING TABLET

Mouth dissolving tablets are also called as fast disintegrating tablets, rapidly dissolving tablets, disintegrating dosage form, fast melting tablet, fast dispersing tablet.

Some features of mouth dissolving tablets:

- ✓ Ease of administration for patients who are mentally ill, disable and uncooperative
- ✓ Requires no water
- ✓ Quick disintegration and dissolution of dosage form.
- ✓ Overcome unacceptable taste of the drug
- ✓ Can be designed to leave minimal or no residue in the mouth after administration and also to provide a pleasant mouth feel
- ✓ Allows high drug loading
- ✓ Adaptable and amenable to existing processing and packaging machinery
- ✓ Cost effective.
- ✓ Simple processing
- ✓ Using conventional pharmaceutical facilities
- ✓ Low manufacturing cost
- ✓ Relatively strong in hardness and friability
- ✓ Excellent taste and rapid disintegration

Characteristics

1. Ease of administration
2. Taste of measurement
3. Hygroscopicity
4. Friability
5. Mouth feel

Techniques

1. Tablet molding
2. Direct compression
3. Freeze drying
4. Spray drying
5. sublimation
6. Taste masking
7. Mass extrusion

EFFERVESCENT TABLETS

Effervescent tablet are designed to produce a solution rapidly with the simultaneous release of co_2.

General characteristics

i. **Moisture content**: Reaction occurs between soluble acid source and an alkali material carbonate to produce co_2 gas which serves as tablet disintegrate. If small amount of water is bound or absorbed on raw material it initiates the reaction earlier making it physically unstable and decomposes.

ii. **Solubility**: if the tablets components are not soluble, the effervescent reaction will not occur and the tablet will not disintegrate quickly; affecting the solubility rate ideally all tablet components should have similar rates of solubility.

A. Acid source

1. Food Acids

i. Citric acid

ii. Tartaric acid

iii. Malic acid

iv. Formic acid

v. Adipic acid of succinic acids are also used.

2. Acid anhydrides

3. Acid salts

B. Carbonase source

Sodium bicarbonate

Sodium carbonate (soda ash)

Potassium bicarbonate and carbonate, L-lysine carbonate, Arginine carbonate, Amorphous carbonate are also used.

Special condition

A maximum of 25% relative humidity at a controlled R.T. of 25°c or less is used to avoids problems due to atmospheric moisture. Relative humidity is expressed as grains of moisture per pound of air at a specified temperature.

A. Wet granulation

1. With the use of heat
2. With Non-reactive liquid
3. With reactive fluids

B. Dry granulation :

C. Fluidized bed granulation :

D. TABLET EVALUATION IPQC

E.

F. General Appearance
G. Size & Shape
H. Unique identification marking
I. Organoleptic properties
J. Hardness and Friability
K. Friability
L. Weight Variation test
M. Content Uniformity Test
N. Disintegration Test
O. Dissolution Test

1. Lieberman H.A., Pharmaceutical Dosage Forms: tablets Volume 1, Second Edition, 286-320.

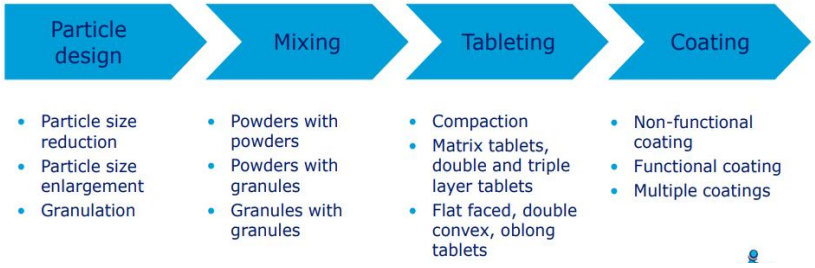
PROCESSING PROBLEMS AND REMEDIES

CAPPING and LAMINATION	POOR FLOW
PICKING And Sticking	POOR MIXING
MOTTLING	PUNCH VARIATION
WEIGHT VARIATION	HARDNESS VARIATION
GRANULE SIZE AND SIZE DISTRIBUTION BEFORE COMPRESSION	DOUBLE IMPRESSION

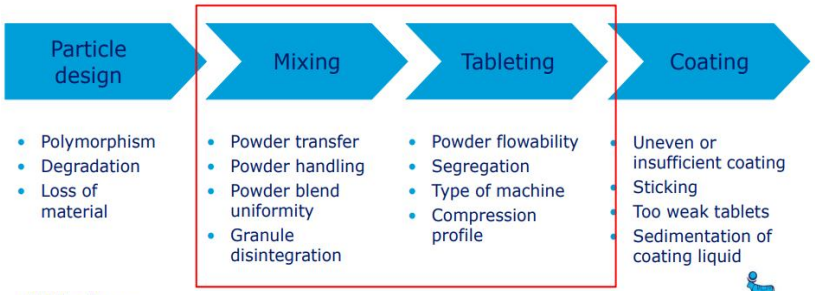
1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

Concept of Scale up and technology transfer of Tablet

Work Flow of Tablet Manufacturing



Problematic Areas of the Process Steps



Mixing

Small scale
- Small amounts are handled
  - Varying from 60 mg to 200 g
- Powder transfer
  - By spatula or spoon
- Mixing
  - Geometric series
  - By hand using mortar and pestle
  - Small scale turbula mixing

Large scale
- Varying amounts of powder
  - From 10 to 500 000 g
- Powder transfer
  - Manual lifting
  - Automatic handling
  - Intermediate bulk container
  - Stainless steel containers
  - Drums
- Mixing
  - Planetary mixers
  - Diffusion mixers
  - Any SUPAC listed mixers

Mixing

- Most often tumbling blenders are used in large scale
  - V-blender
  - Double-cone
  - BIN-blender
- Tumbling blenders are used due to
  - Large capacities
  - Low shear stresses
  - Ease of cleaning
- Variables during the mixing
  - Rotation speed
  - Time of mixing or number of revolutions
  - Filling rate

Tableting

Small scale
- Batch sizes from 15 to 300 tablets
- Powder is weighed by hand and poured into a die
- Batches of 100 tablets, a funnel can be used
- Single press tableting machine
- Rotary machine having only one pair of die and punches

Large scale
- Batch sizes from 50 to millions of tablets
- Rotary machine
- Increased production speed
- Powder can be force fed into the die

Tablet press

- To increase batch size and output of process, tablet instrument is changed from a single press into a rotary press

- 15 – 200 tbl/ min
- One pair of punches
- Fixed die
- One sided compaction
- Hopper moves

- Up to 10 000 tbl/ min
- 6 – 60 pair of punches
- Dies are attached to a moving table
- Double sided compaction
- Hopper fixed

Tableting – changes due to the tablet press

- The change from single press to rotary press affects to
  - Powder feed rate
  - Compression profile (one sided, double sided, pre-compression, profile shape)
  - Compression time (dwell time)
  - Tablet ejection speed and force
- Faster tableting sets more requirements for the powder properties
  - Flowability
  - Segregation
- Flowability and segregation both contribute to the quality of the end product, i.e. tablet

COATING PROCESS

- Tablet Coating is the process of a coating composition to a moving bed of tablets with the concurrent use of heated air to facilitate evaporation of solvent.
- The distribution of coating is accomplished by the movement of tablets either perpendicular or vertical to the application of the coating composition.

TYPES OF COATING PROCESSES

- Sugar Coating
- Film Coating
- Compression Coating

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	

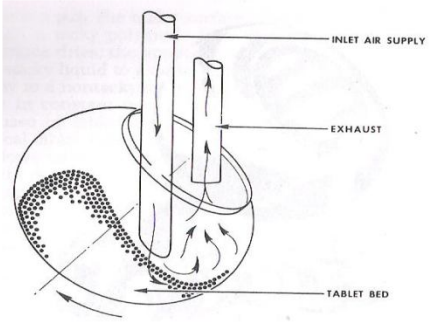
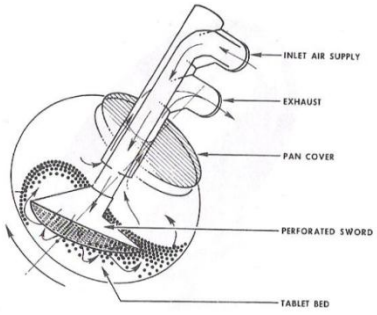
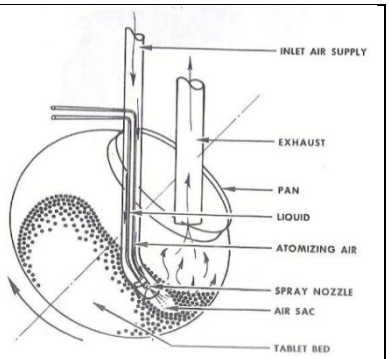
Enteric coating polymers: Cellulose acetate phthalate, Acrylate polymers, Hydroxypropyl methyl cellulose phthalate, Polyvinyl acetate phthalate

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

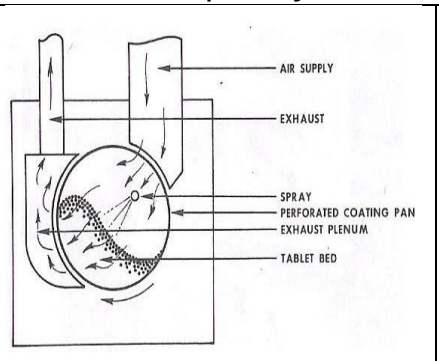
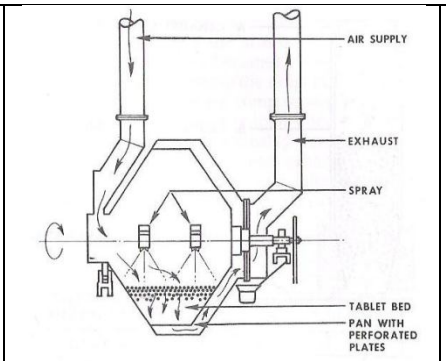
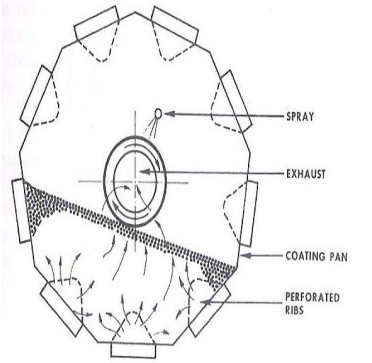
1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

TABLET COATING EQUIPMENTS

Standard coating pan

		
Pellegrino pan system	Immersion sword system	Immersion tube system

Perforated pan system

		
Accela cota system	Hicoater system	Driacoater system

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

Why is film coating favoured over sugar coating ?

Film coating	Sugar coating
Tablet appearance ✓ Retains shape of original core ✓ Small weight increase of 2-3% due to coating material ✓ logo or 'break lines' possible	Tablet appearance ✓ Rounded with high degree of polish ✓ Larger weight increase 30-50% due to coating material ✓ Logo or 'break lines' are possible
Process ✓ Can be automated e.g. Accela Cota ✓ Easy training operation ✓ Single stage process ✓ Easily adaptable for controlled release allows for functional coatings.	Process ✓ Difficult to automated e.g. traditional coating pan ✓ Considerable training operation required ✓ Multistage process ✓ Not able to be used for controlled release apart from enteric coating.

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

EVALUATION OF COATED TABLET

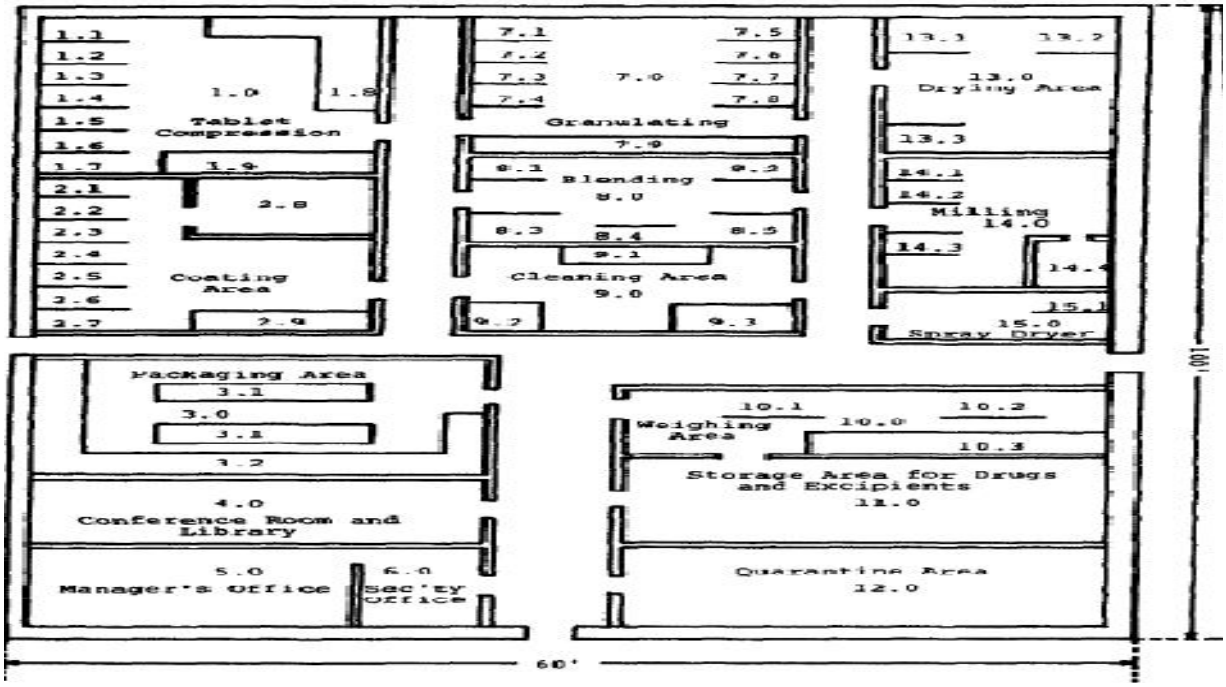
Adhesion test: to measure the force required to peel the film from tablet surface using tensile strength tester. Apart Diametral crushing strength, disintegration, dissolution and stability studies of coated tablet should be performed.

FILM DEFECTS

STICKING	FILLING
PICKING	BLISTERING
ROUGHNESS	HAZING/DULL FILM (BLOOM)
ORANGE PEEL EFFECT	COLOR VARIATION
BRIDGING	CRACKING

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier,
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House,

LAYOUT OF TABLET SECTION



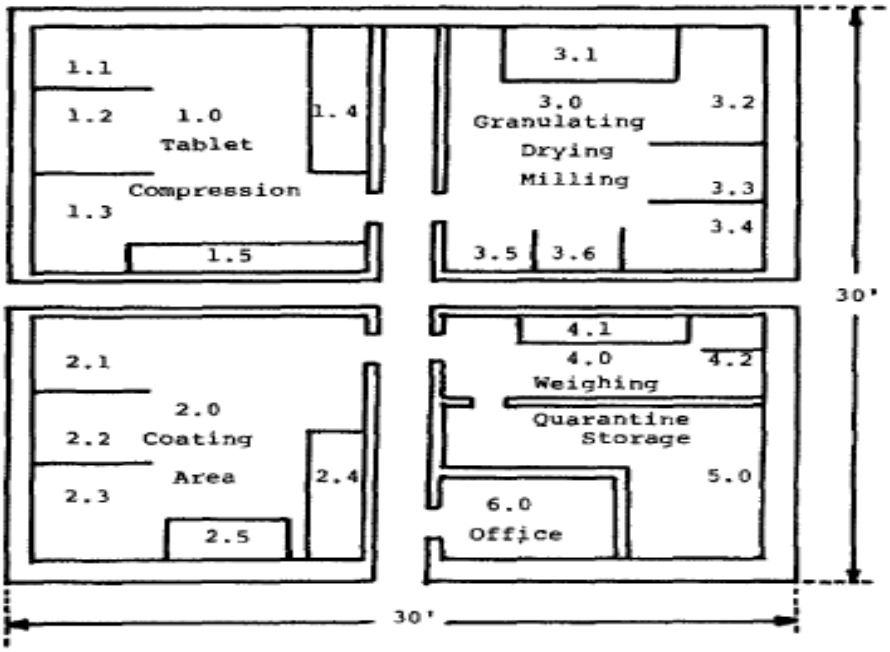


Figure 5 Floor plan for a small pilot plant for tablet development.

CAPSULE

Solid dosage form, the drug is enclosed within either a hard or soft shell. Shell is typically made of gelatine.

SHELL COMPOSITION

Gelatin: protein, prepared from hydrolysis of collagen (animal bones and skin)

- type A : pI = 7-9, pig skin
- type B : pI = 5, animal bones

Colorants

Various soluble synthetic dyes ("coal tar dyes") and insoluble pigments are used. Not only play a role in identifying the product, but also may play a role in improving patient compliance

Opaquing agents

Titanium dioxide may be included to render the shell opaque.

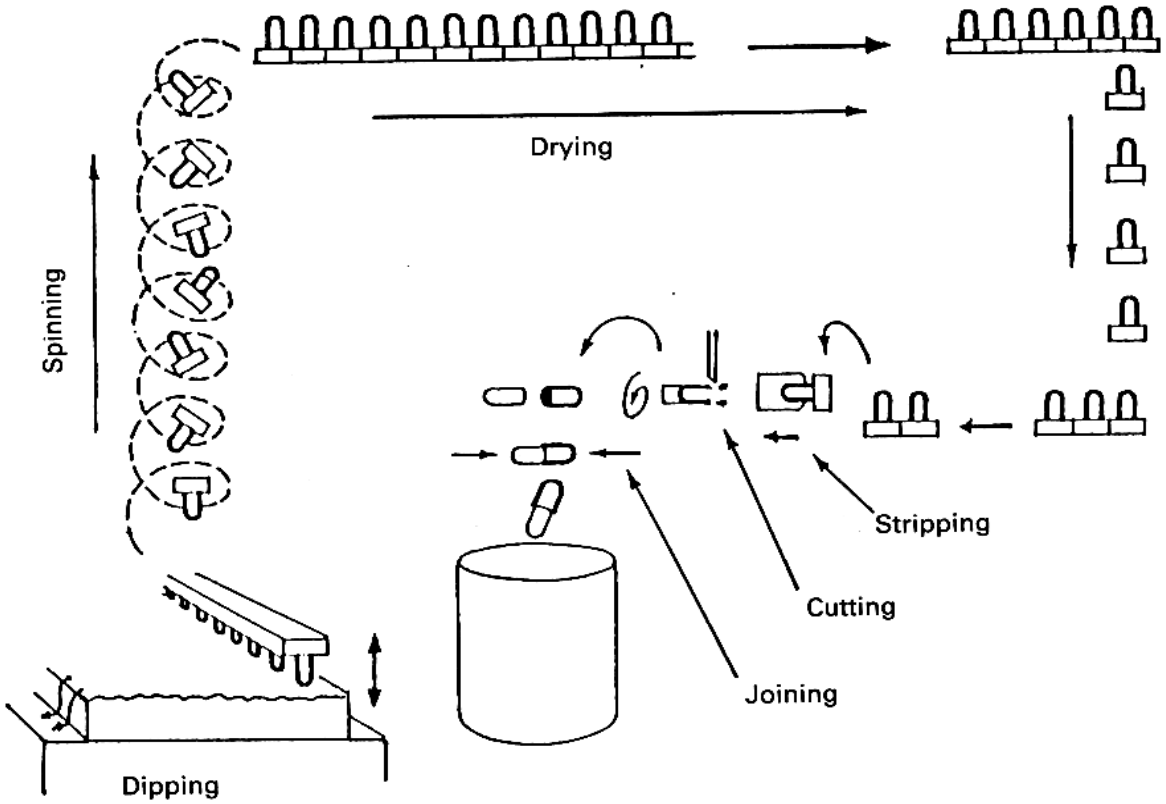
Opaque capsules may be employed to provide protection against light or to conceal the contents.

Preservatives

When preservatives are employed, parabens are often selected.

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 515.

SHELL MANUFACTURE



Dipping , Rotation , Drying , Stripping ,Trimming , Joining

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 515.
2. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc.,338-339

IMPORTANT SPECIFICATIONS OF GELATIN

Bloom or gel strength: It is a measure of cohesive strength of cross-linkage that occurs between molecules and is proportion to the molecular weight of gelatin.

Bloom is determined by measuring the weight in grams required to move a plastic plunger of 0.5inches in diameter, 4mm into a 62/3% gelatin that has held at 10°C for 17 hrs.

The unit of bloom is grams and it is between 150-250g

Viscosity: Is determined on a 62/3% gelatin of water at 60°C and it is a measure of the molecular chain length. Standard used: 25-45 mill poise.

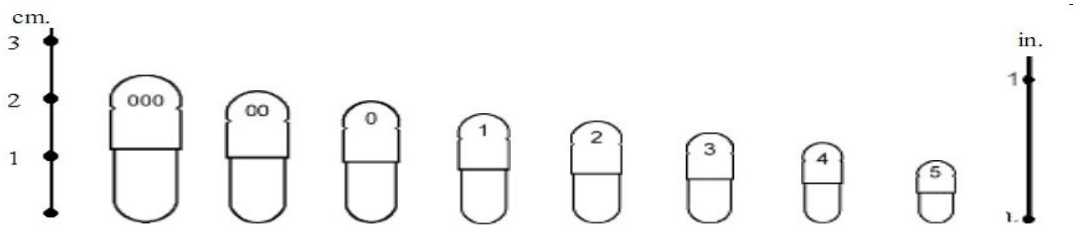
Iron content: Iron is always present in raw gelatin, and its concentration usually depends on the iron content of the large quantities of water used in its manufacture .Amount should not exceed 15ppm

In hard gelatin capsule the plasticizer and gelatin ratio is

0.4 : 1

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 400.

SIZES AND SHAPES



The largest size of the capsule is No: 000; The smallest size is No: 5

The standard shape of capsules is traditional, symmetrical bullet shape.

Size	Volume	Fill weight(g) at 0.8 g/cm^3 powder density
000	1.37	1.096
00	0.95	0.760
0	0.68	0.544
1	0.50	0.400
2	0.37	0.296
3	0.30	0.240
4	0.21	0.168
5	0.15	0.104

1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc., 340-342.

2. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 518.

Various Filling Machine Available

- Eli-lily and Co
- Farmatic
- Hofliger and Karg
- Zanasi
- Parke-Davis; These machine differ in there design and output

STEPS IN CAPSULE PRODUCTION

1. Mixing of ingredient
2. Granulation and lubrication
3. Making of capsules
4. Filling of capsules
5. Uniformity testing
6. Packing and labeling

Polishing

Pan Polishing : Acela-cota pan is used to dust and polish.

Cloth Dusting : Capsule are rubbed with cloth.

Brushing : Capsule are feed under soft rotating brush.

Storage

Finished capsules normally contain an equilibrium moisture content of 13-16%.

1. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 374-385.

SOFT GELATIN CAPSULES (SOFTGELS)

Definition

Soft Gelatin capsules are one piece, hermetically sealed, soft gelatin shells containing a liquid, a suspension, or a semisolid.

Soft gelatin is mainly composed of gelatin, plasticizers, preservative, colouring and opacifying agents, flavoring agents and sugars.

- consist of a continuous gelatin shell surrounding a liquid core
- formed, filled, and sealed in one operation
- shells are softened by addition of glycerin or polyhydric alcohol (ex. sorbitol)

In soft gelatin capsule the amount of plasticizers used is more

In soft gelatin capsule the plasticizer and gelatin ratio is

0.8 : 1

1. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 527-538.

I. Composition of the shell

- Similar to hard gelatin shells, the basic component of soft gelatin shell is gelatin; however, the shell has been plasticized.
- The ratio of dry plasticizer to dry gelatin determines the "hardness" of the shell and can vary from 0.3-1.0 for very hard shell to 1.0-1.8 for very soft shell.
- Up to 5% sugar may be included to give a "chewable" quality to the shell.

  The residual shell moisture content of finished capsules will be in the range of 6-10%.

II. Formulation

- Formulation for soft gelatin capsules involves liquid, rather than powder technology.
- Materials are generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic effectiveness and manufacture efficiency.
- The liquids are limited to those that do not have an adverse effect on gelatin walls.
- The pH of the lipid can be between 2.5 and 7.5.
- Emulsion can not be filled because water will be released that will affect the shell.

- The types of vehicles used in soft gelatin capsules fall in to two main groups:
    1. Water immiscible, volatile or more likely more volatile liquids such as vegetable oils, mineral oils, medium-chain triglycerides and acetylated glycerides.
    2. Water miscible, nonvolatile liquids such as low molecular weight PEG have come in to use more recently because of their ability to mix with water readily and accelerate dissolution of dissolved or suspended drugs.
- All liquids used for filling must flow by gravity at a temperature of 35^0c or less.
- The sealing temperature of gelatin films is 37-40^0C.

1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc., 372.

2. M.E.Aulton, Aulton's Pharmaceutics, The Design and Manufacture of Medicines, Third Edition, Churchill Livingstone Elsevier, 527-538.

Is manufactured by four methods

- ✖ Plate process
- ✖ Rotary die process
- ✖ Reciprocating die
- ✖ Accogel machine

MANUFACTURE PROCESS

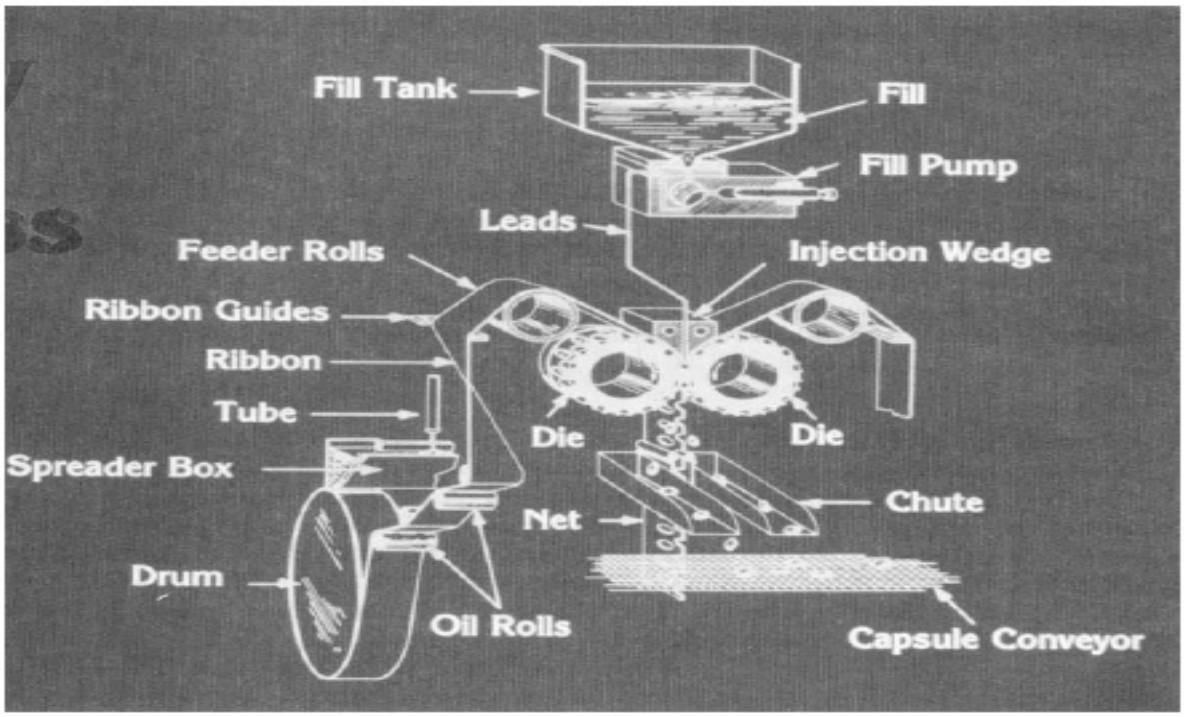
Plate process

- Placing the upper half of a plasticized gelatin sheet over a die plate containing numerous die pockets,
- Application of vacuum to draw the sheet in to the die pockets,
- Filling the pockets with liquor or paste,
- Folding the lower half of gelatin sheet back over the filled pockets, and
- Inserting the "sandwich" under a die press where the capsules are formed and cut out.

1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc., 373-374.

Rotary die process

- In this process, the die cavities are machined in to the outer surface of the two rollers.
- The die pockets on the left hand roller form the left side of the capsule and the die pockets on the right hand roller form the right side of the capsule.
- Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism.
- As the die rolls rotate, the convergence of the matching die pockets seals and cuts out the filled capsules.



1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc., 373-374.
2. Leon Lachmann, Herbert A. Libermann; Joseph L.Kanig., The Theory and Practice of Industrial Pharmacy, Third Edition, Varghese Publishing House, 407.

Accogel process

- In general, this is another rotary process involving
- A measuring roll,
- A die roll, and
- A sealing roll.
- As the measuring roll and die rolls rotate, the measured doses are transferred to the gelatin-linked pockets of the die roll.
- The continued rotation of the filled die converges with the rotating sealing roll where a second gelatin sheet is applied to form the other half of the capsule.
- Pressure developed between the die roll and sealing roll seals and cuts out the capsules.

1. Banker G.S., Rhodes C.T., Modern Pharmaceutics, Fourth Edition, Vol. 121, Marcel Dekker, Inc., 373.