INDUSTRIAL PHARMACY-I

UNIT II-TABLETS AND LIQUID ORALS

CLASS:10

Topic :Granulation methods

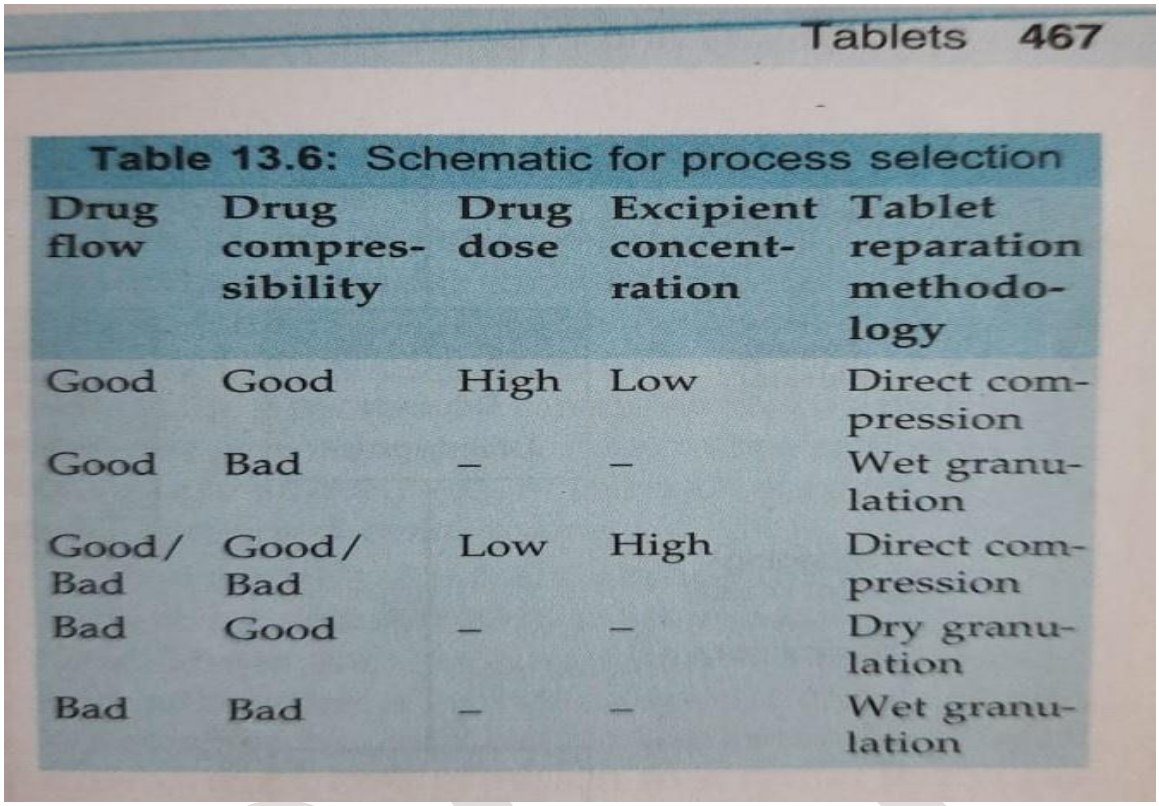
Tablet manufacturing

Manufacture of tablets involves certain well defined steps: namely,
Pulverization and mixing
Granulation Compression
Coating (if required).

Methods to manufacture tablets

Direct compression
Compression granulation
Wet granulation

Process selection



Tablets 467

Table 13.6: Schematic for process selection

Drug flow	Drug compressibility	Drug dose	Excipient concentration	Tablet reparation methodology
Good	Good	High	Low	Direct compression
Good	Bad	–	–	Wet granulation
Good/ Bad	Good/ Bad	Low	High	Direct compression
Bad	Good	–	–	Dry granulation
Bad	Bad	–	–	Wet granulation

Flow chart-Tablet manufacture

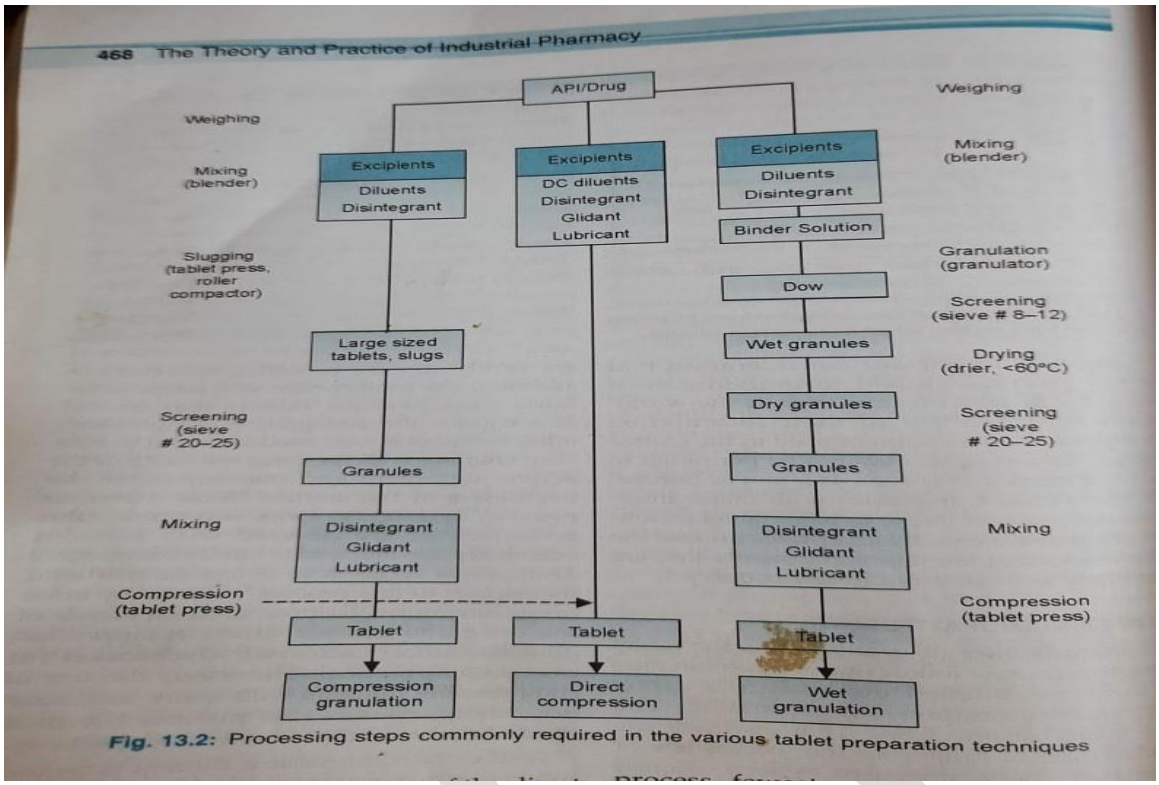


Fig. 13.2: Processing steps commonly required in the various tablet preparation techniques

Direct compression method

Wetgranulation and dry granulation methods having series of unit operations, both time consuming and potentially costly.

Potentially more attractive option for the manufacture of tablets involves powder mixing and subsequent compression of the powder mix, thereby obviating the need for granulation. This process is called direct compression.

The mechanism of particle-particle interactions in tablets produced by direct compression are similar to those operative in tablets produced by dry granulation and roller compaction.

- Defined as basically mixing and processing of formulation ingredients then compressing into tablets

  Drugs suitable for direct compression

  Relatively soluble drugs can be processed as coarse particles(to ensure good flowability)

  Relatively potent drugs-present in few mg can be relatively mixed with coarse excipient particles

- Production involves two steps
  Powder mixing
  Tabletting

Manufacturing of tablets involves three processes
First induced die feeders
Adding Dry binders and last directly compressible vehicles

Induced die feeders prevent segregation and compliments the powder to flow down the die cavity of tablet compression machine
Employing induced die feeder usually minimizes the air entrappment and increase density of the filling powder and thereby suceptibility of compaction

Use of binders ensures that the active and inactive ingredients held together
Substances used as dry binders must have required cohesion properties so as to ensure that the tablets are of the required hardness and crispiness
Low binder to drug ratio to be maintained to ensure satisfactory sizes of tablets contain high doses of dugs
Ex:MCC and PEGs

Excipients for direct compression

Diluents : MCC, Spray dried lactose
Flow improvers colloidal silica
Lubricant
Glidant

Properties of direct compressible vehicles:

Excepients require large qc tests before processing
Must be inert, tasteless,reworkable,able to disintegrate and inexpensive
Modified diluents, binders etc. are available in the market which assure spherical shape of the granules to modify flow property.

Advantages:

Simplicity, low labor input and hence economy

Dry process-risk of deterioration of drug is decreased

Tablets disintegrate into their primary particles rather than granular aggregates – increased SA-fast drug release-dissolution

Direct compression method

Disadvantages:

Difference in particle size and bulk density b/n drug and diluent may lead to – stratification within the granulation-poor content uniformity

Non –compressible Large dose drugs require high diluent concentration make it difficult to swallow and costly

Diluent may interact with drug

Ex:Amine drugs and SDL –yellow discoloration

Dry nature results in static charge buildup on the drug –prevent uniform distribution

Direct compression method

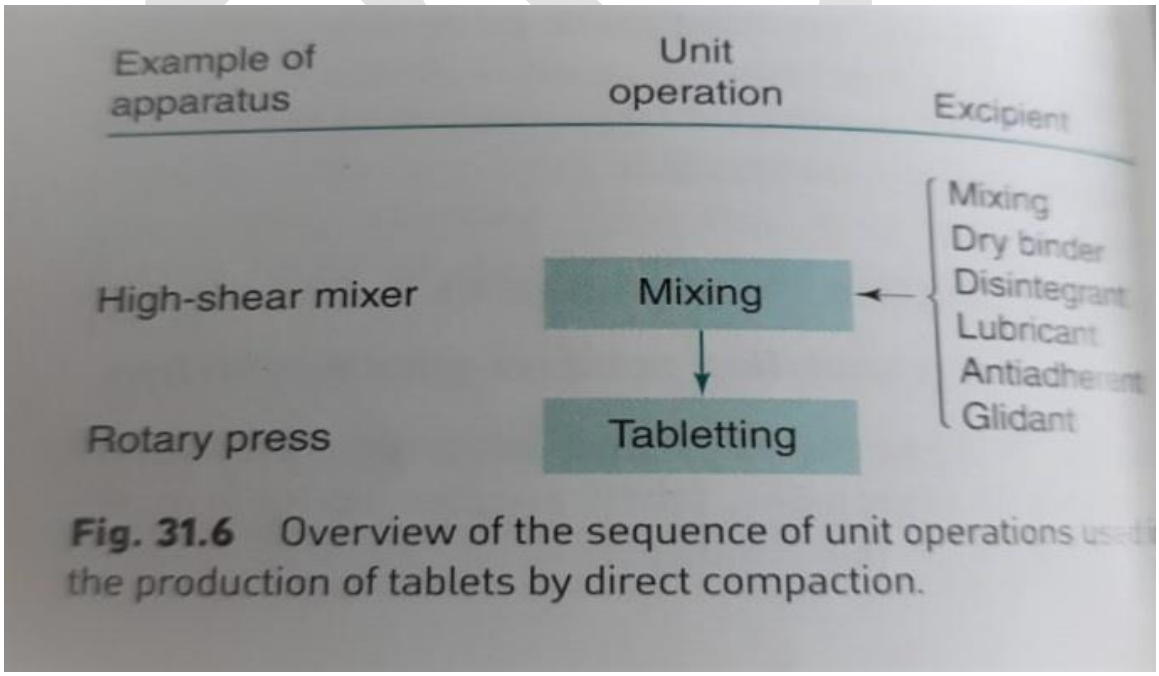


Fig. 31.6 Overview of the sequence of unit operations used in the production of tablets by direct compaction.

Dry granulation/compression granulation

Dry granulation is followed in situations where
The effective dose of a drug is too high for direct compaction,
if the drug is sensitive to heat, moisture or both, which precludes wet granulation.
e.g. Many Aspirin and vitamin formulations are prepared for tabletting by compression granulation

Steps of granulations

Compaction of the components by tablet press
Milling
Weighing
Screening
Blending
Slugging –initial blend of powders blend to large capacity tablet press –compacted by flat faced punches-compact mass (slug)
Granulation (Dry)
Lubrication
Compaction

Slugging

Slug may described as poorly formed tablets or, may be described as compacted mass of powdered material.
Purpose: To impart cohesiveness to the ingredients, so as to form tablets of desired properties.
Method: It is done either by
(i) high capacity heavy duty tablet press
(ii) Chilsonator roller compactorBlend is forced into dies of large capacity tablet press and compacted using flat faced punches.
compacted masses are called slugs and process is called slugging.
Slugs milled or screened to produce good free flowing granules for compression.

Dry compaction/Roller compaction

On a large scale compression granulation can also be performed on a roller compactor.

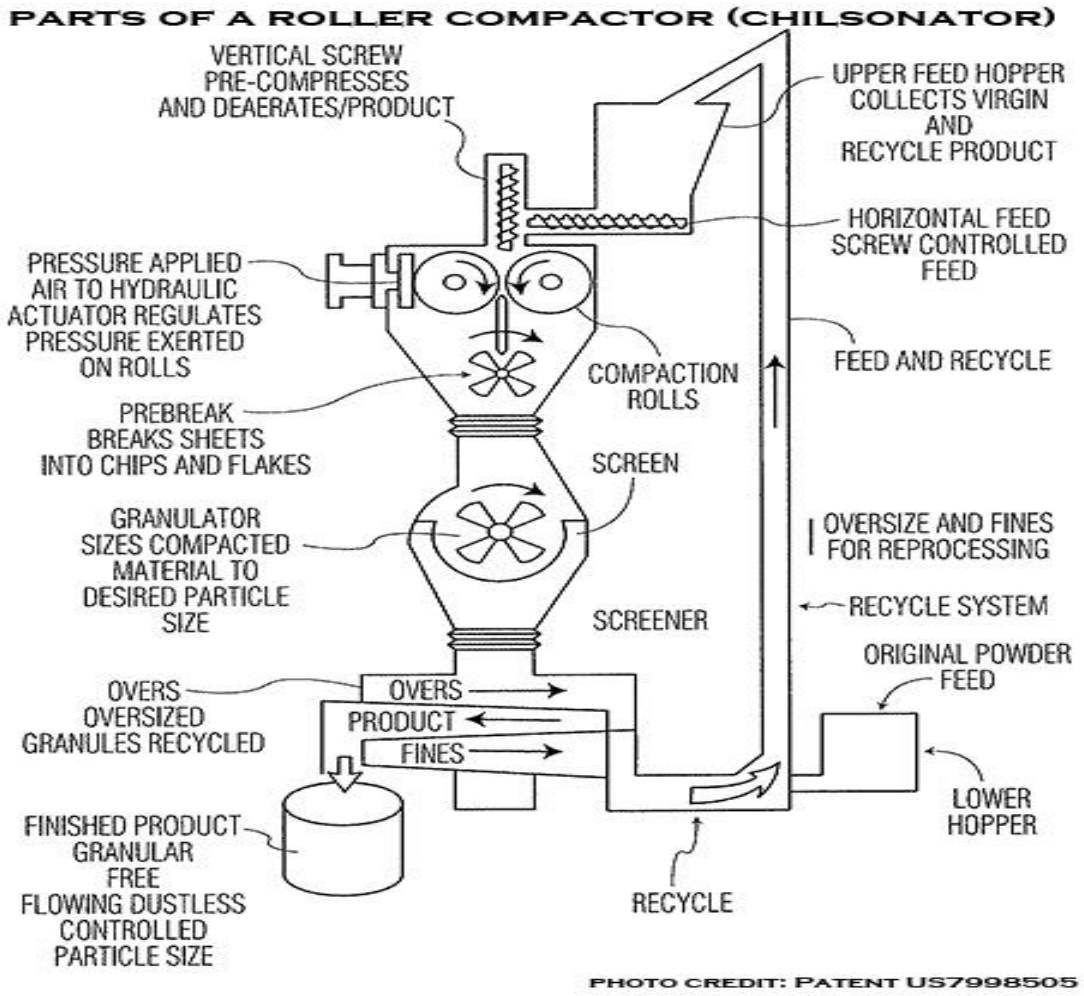
Granulation by dry compaction can also be achieved by passing powders between two rollers that compact the material at pressure of up to 10 tons per linear inch.

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.

Roller compactor is capable of producing as much as 500 kg/hr of compacted ribbon like materials which can be then screened and milled in to granules for compression.

Equipment



Roller compactor

- Can produce 500 kg per hour or more of compacted ribbon like material
  Two rollers that revolves toward each other
  By means of a hydraulic ram forcing one of the rollers against other
  The machine is capable of exerting fixed pressure on any powdered material is fed between the rollers by screw conveyor system
  After passing through rollers the compacted mass resembles a thin wide ribbon fallen part into larger segments

Roller compactor

The segments are screened or milled for the production of granules
Compaction force controlled by
Hydraulic pressure exerted on compaction rolls
Rotational speed of the compaction rolls
Rotational speed of the feed screws

Roller compactor

Horizantal screw picks up the powder from hopper and maintains continuous flow to Vertical screw
Vertical screw delivers powder to compaction rolls and deaerate the powder
Vs delivers more material than compaction roll accept assuring constant loading
The speed of the compaction rolls controls the pressure dwell time has great effect on the density and hardness of the compact

Limitations of dry granulation

Dry granulation often produces a higher percentage of fines or non compacted products, which could compromise the quality or create yield problems for the tablet.
It requires drugs or excipients with cohesive properties.

Manufacturing of Tablets

Manufacture of tablets involves certain well defined steps: namely:-
Pulverization and mixing.

Granulation.
Compression.
Coating (if required)
Pulverization and mixing-
In this step the different solid / powder ingredients are reduced to the same particle size
since particles of different sizes will segregate while mixing.

Various equipments

like Cutter mill, Hammer mill, Roller mill and Fluid energy mill is
required to reduce the large lumps.
Granulation Technology-
Granulation: It is the process in which primary powder particles are made to adhere to form
large multi-particle entities.
Range of size: 0.2 mm to 4 mm. (0.2 mm to 0.5 mm)

Objectives of granulation

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

Procedure of Wet Granulation

Step-1 Milling of the drug and excipients

• Milling of the active ingredients, excipients etc. are milled to obtain a homogeneity in the final granulation.
• If the drug is given in solution then during drying it will come up to the surface.

To avoid this problem drug is mixed with other excipients in fine state.

Step 2: Weighing

Weighing should be done in clean area with provision of air flow system.

In the weighing area all the ingredients must not be brought at a time to avoid crosscontamination.

Step3: Blending

Mixing Commonly used blenders are:

(a) Double cone blender

(b) V – blender

(c) Ribbon blender

(d) Planetary mixer

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

Wet granulation

Step-IV Wet Massing

Wet granulation forms the granules by binding the powders together with an adhesive.

Binder solutions can be added in two methods:

Method-I	Method-II
Drug + Diluent	Drug + Diluent
Dry binder is added	Binder Solution is added
Blended uniformly	
Suitable solvent is added to activate the dry binder	
Blended in a Sigma - mixer or Planetary mixer till properly wet mass is formed	

Therefore, when

• (i) a small quantity of solvent is permissible, method-I is adopted and (ii) a large quantity of solvent is required method-II is adopted.

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

remains constant.

If granulation is over-wetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance.

If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

Step-V -Wet Screening

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

(i) passage through a hand screen (in small scale production) or,

(ii) passage through an oscillatory granulator of hammer mill equipped with screens

having large perforations (# 6 – 8 mesh screen).

Purpose

(i) Increase particle contact point

(ii) Increase surface area to facilitate drying.

Step-VI Drying

Drying is usually carried out at 600C. Depending on the thermolabile nature of the drug

the temperature can be optimized.

Drying is required in all wet granulation procedures to remove the solvent, but is not

dried absolutely because it will pose problems later on. Hence, certain amount of moisture (1 – 4 %) is left within the granules – known as the residual moisture.

Methods: Drying can be carried out

Tray dryers – it may take 24 hrs of drying

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

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

Step-VII Dry Screening

After drying, the granules are make monosize by passing through mesh screen. For drying granules the screen size to be selected depends on the diameters of the punch. The

following sizes are suggested:

• Tablet diameter upto Mesh Size

3/16 ” # 20

3.5 / 16 – 5/16” # 16

5.5/16 – 6.5/16” # 14
7.0/16 or larger # 12

Step-VIII Lubrication of granules

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

Wet granulation

Step 9: Tableting: Last step in which the tablet is fed into the die cavity and then compressed

Equipment

Mixing-sigmablade mixer, planetary mixer –dry mixing
Lodige,Diosna and Gral newer equipment for both dry mixing and and wet granulation in less time

Wet granulation method

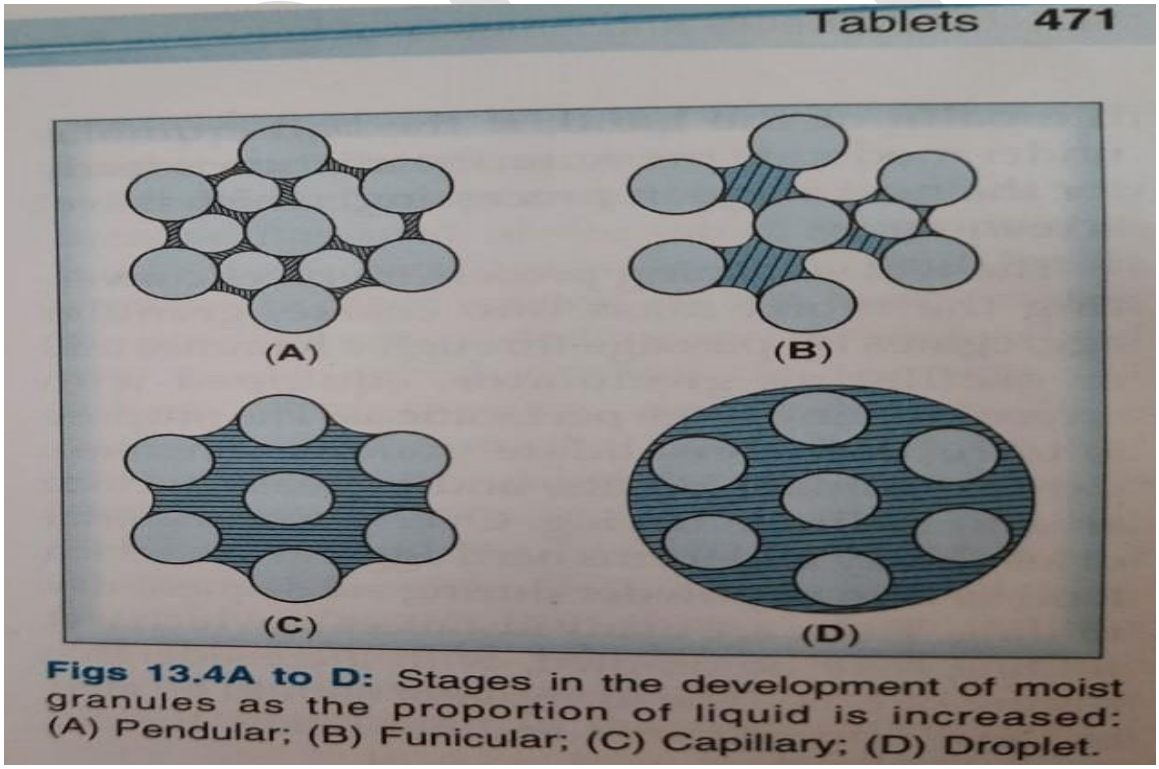
Addition of granulating liquid to a mass of powder involves following stages
Pendular state: has low mechanical strength
Powder particles wetted during initial stage liquid films will be formed on their

surface and may combine to produce liquid bridges at points of contact
Surface tension and negative capillary pressure produce cohesiveness

Stages in development of moist granules

Funicular state: as liquid concentration increases several bridges may coalesce give rise to funicular state
Capillary state: more liquid added –mass is kneaded to bring particles into closer proximity
Void spaces entirely eliminated
Bridging effected by interfacial forces at granule surface and negative capillary pressure through out the interior liquid filled space
Droplet stage: particles still held together by surface tension but with out intragranular force
Optimisation of granulation ensuring that this state is achieved

Stages in development of moist granules



Figs 13.4A to D: Stages in the development of moist granules as the proportion of liquid is increased: (A) Pendular; (B) Funicular; (C) Capillary; (D) Droplet.