TABLETS

Excipients

Tableting methods – Controls

Tablet compression physics

Reasons for widespread use of tablets:

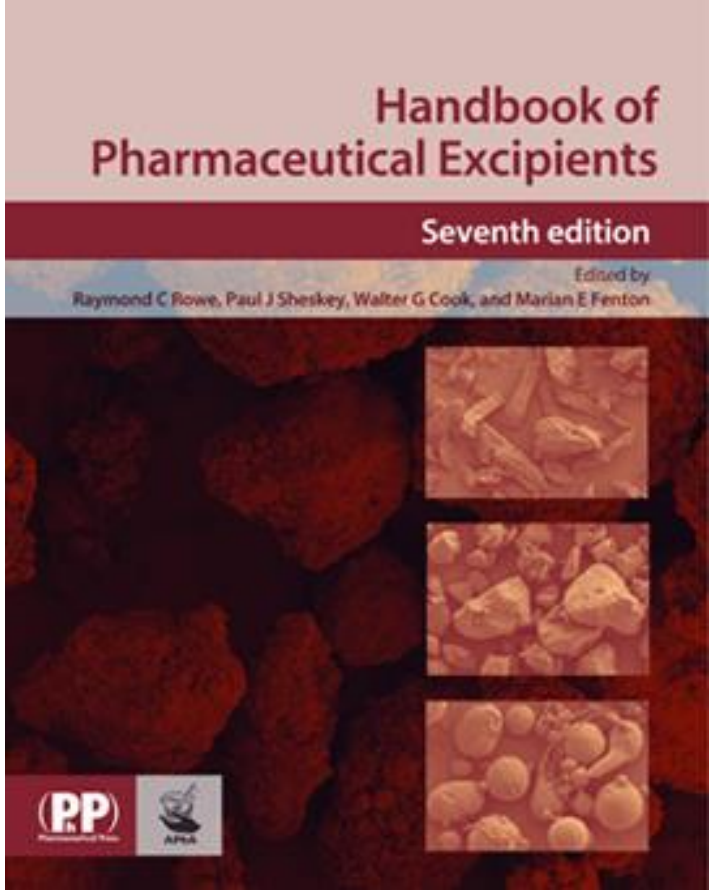
- It is easy for the patient to use, store, and carry the tablets.
- Due to their solid form, the physical and chemical stability of the active substance can be maintained for a long time.
- Content uniformity is high.
- Complete and predictable release of active substance is ensured.
- The unpleasant taste and odors of active substances can be masked.
- Since the production costs are low, this cheapness is reflected in the buyer.

However, tablet formulations should be carefully designed and prepared regarding;

- Bioavailability (BA) for active substances with low solubility
- Irritation to GI tract and mucosa
- Difficulty in swallowing

Excipients used in tablets

- Fillers – diluents
- Binders - adhesives
- Disintegrants
- Minor components
    - Lubricants
    - Glidants
    - Antiadherents
- Other excipients
    - Coloring agents
    - Flavours
    - Adsorbents



Properties of excipients

- They should be physiologically inert.
- They must be physically, chemically and microbiologically stable.
- They should not affect the bioavailability of the active substance.
- They should be commercially available in purity and form in accordance with pharmaceutical standards.
- They should officially comply with all existing requirements.

Fillers / Diluents

Unsoluble fillers	Soluble fillers
Mycrocrystal cellulose *Avicel® Emcocel ® Vivapur ®*	Lactose *Pharmatose®; Spherolac®; Granulac®*
Powdered cellulose *Solca Floc®; Vitacel®*	Sucrose
Dibasic calsium phosphate *Di-Tab®; Emcompress®*	Dextrose
Tribasic calsium phosphate *Tri-Tab®*	Mannitol *Parteck®M ; Pearlitol®; Mannogem®*
Calsium sülfate *Compactrol®*	Sorbitol *Sorbifin® ; Neosorb®*
Calsium carbonate	Starch!

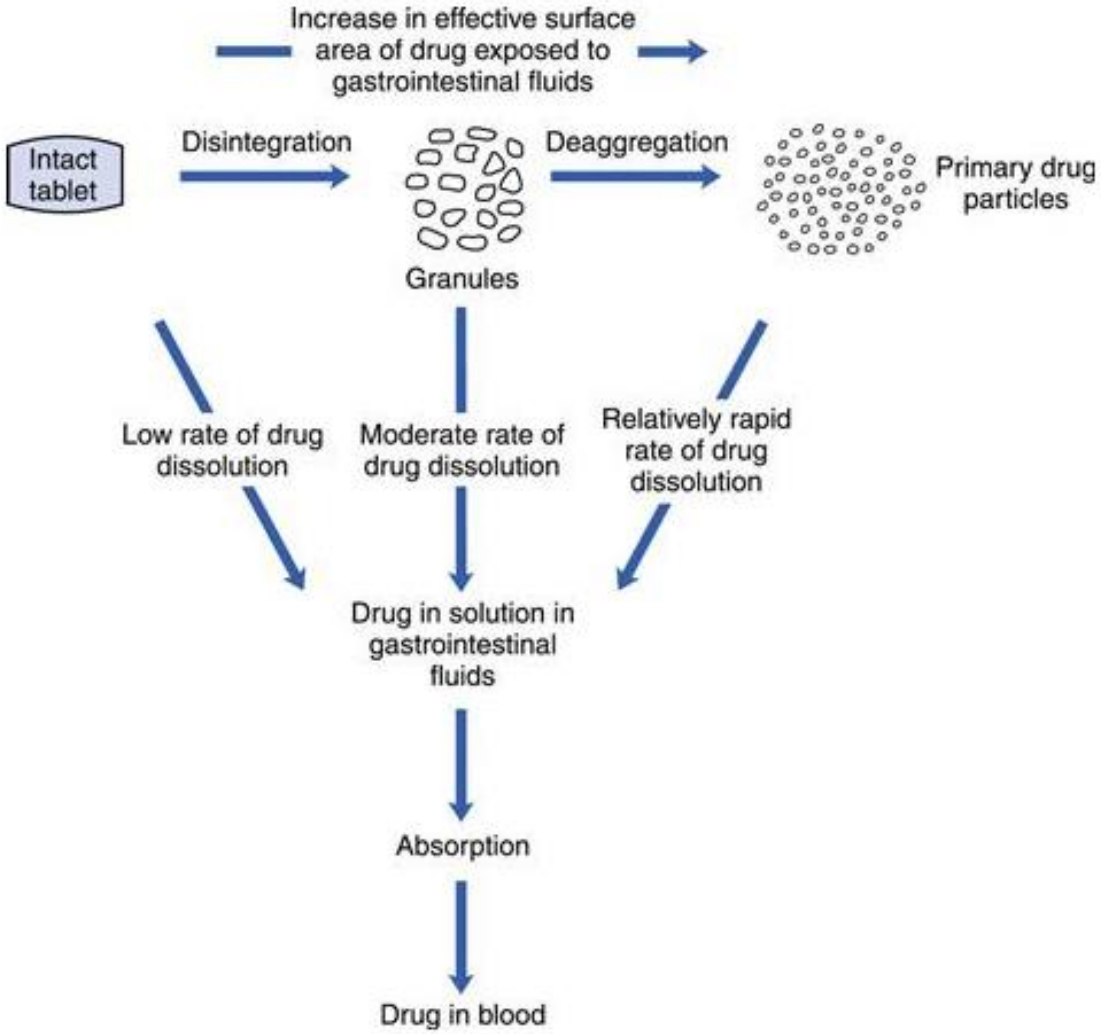
Binders / Adhesives

Binder	Method of incorporation	Percentage used in formula	Solvent	Percentage used in granulating system
Natural polymers				
Starch	Wet mixing	2–5	Water	5–25
Pregelatinized starch	Wet mixing	2–5	Water	10–15
	Dry mixing	5–10	Water	
Gelatin	Wet mixing	1–3	Water	5–10
Acacia	Wet mixing	3–5	Water	10–15
Alginic acid	Dry mixing	1–5	Water	
Sodium alginate	Wet mixing	1–3	Water	3–5
Synthetic polymers				
PVP	Wet mixing	0.5–5	Water or hydroalcoholic solution	5–10
	Dry mixing	5–10		
Methyl cellulose	Wet mixing	1–5	Water	2–15
	Dry mixing	5–10		
HPMC	Wet mixing	2–5	Water or hydroalcoholic solution	5–10
	Dry mixing	5–10		
Na-CMC	Wet mixing	1–5	Water	5–15
	Dry mixing	5–10		
Ethyl cellulose	Wet mixing	1–5	Ethanol	2–10
	Dry mixing	5–10		
Sugars				
Glucose	Wet mixing	2–25	Water	25–50
Sucrose	Wet mixing	2–25	Water	50–67
Sorbitol	Wet mixing	2–10	Water	2–25

MW

PEG 6000

Disintegrants



Disintegrant	Concentration in granulation (% w/w)	Disintegration mechanism
Starch	5-20	Wicking and deformation
Pregelatinized starch	5-10	Swelling
Avicel PH 101 ve PH102 (YG)	5-20	Wicking
Solka floc	5-15	Wicking
Kaolin (eksternal)	5-15	Swelling
Bentonit (eksternal)	5-15	Swelling
Alginic acid	5-10	Swelling
Veegum (YG)	5-15	Swelling

Superdisintegrants

Superdisintegrant	Examples	Effect	Comments
Crosslinked cellulose	Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol®	- Swells 4-8 folds in <10 s - Swelling and wicking effect both Deformation	-Direct tableting or wet granulation
Crosslinked PVP	Crosspovidone Crosspovidon M® Kollidon® Polyplasdone®	- Swells very little and returns to original size after compression - Wicking	- Insoluble in water - Spongy in nature so get porous tablet
Crosslinked starch Sodium starch glycolate	Explotab® Primogel®	- Swell 7-12 folds in <30 s	- Swells in three dimensions and high level serves as sustained release matrix.

Superdisintegrant	Examples	Effect	Comments
Crosslinked alginic acid	Alginic acid NF Satialgine®	- Rapid swelling in aqueous medium or wicking action	-Promotes disintegration in both dry or wet granulation
Natural super disintegrant	Soy polysaccharides Emcosoy®	-Kapiler etki olabilir.	-Does not contain any starch or sugar. Used in nutritional products
Ion exchange resin	Amberlite® (IPR 88)	- Swelling	- Dry or wet granulation

Lubricants

Lubricants:

- Prevent tablets from sticking to punch surfaces.
- Provide the ease of removal of the tablet from the die or matrix.
- Prevent friction between the punches and the die wall, thus preventing wear of the tools.
- Provide equal distribution of the punch pressure into the tablet.

Their effectiveness depends on:

- Surface area,
- Form and order to be added to the formulation,
- Mixing time
- Amount

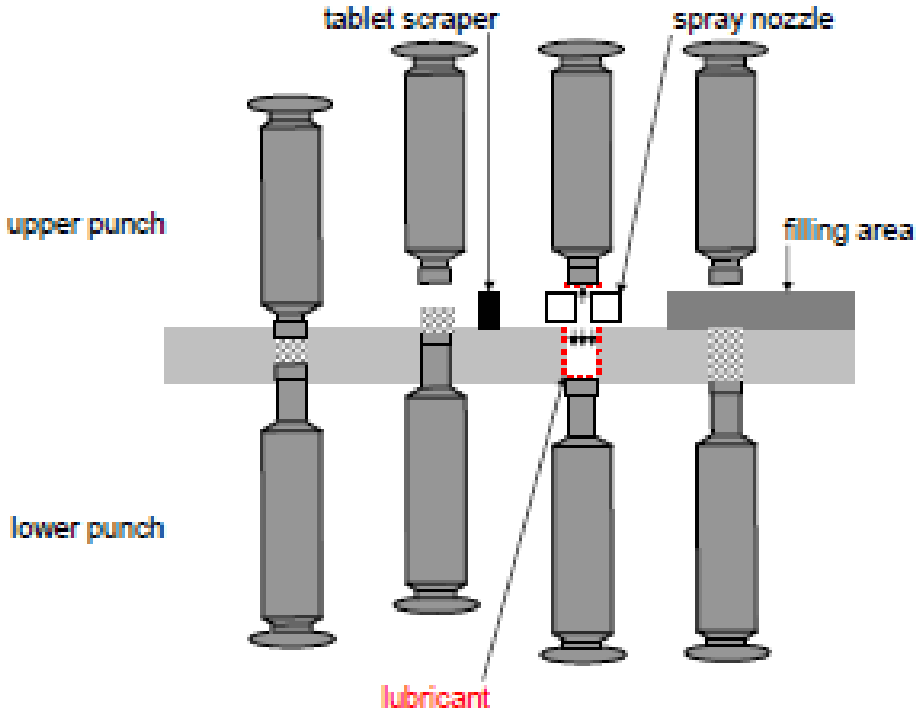
The disadvantages of long-term mixing of lubricants and other tablet components:

1. The hardness of the tablet decreases as the surface of the particles forms a thick layer rather than a monomolecular film layer.
2. Friability of tablets increases.
3. The ejection of the tablet from punch and die can be difficult.
4. Hydrophobicity of tablets increases.
5. Physical and chemical stability problems may occur.

Water-insoluble lubricants	% w/w
Metallic stearates (Mg-, Al-, Ca-, Na-, Zn-)	0.25 -1
Stearic acid	
Hidrojenated vegetable oils (Sterotex®, Lubritab®, Cutina® HR)	0.5-2
Fatty acid esters Na-stearyl fumarate (Pruv®) Gliceryl behenate (Compritol® 888) Gliseryl palmito-stearate (Precirol® ATO) Sucrose mono-palmitate and –laurate	 1-3 1.5-3 0.5 12
PTFE (Fluon L 169)	0.5
Talc	0.5-5

Water-soluble lubricants	% w/w
Sodium lauryl sulfate	1-5
Magnesium lauryl sulfate	1-2
Polymers PEG 4000 and 6000 (Carbowax) POE-POP copolymer (Lutrol F68)	1-5
Sodium benzoate	5
Adipic and fumaric acids	
DL-Leucin	1-5

External lubrication



Glidants

The mechanisms of action are:

- They control the electrostatic charge distribution on the granule surface.
- By taking place between granules / particles, they reduce the effectiveness of static forces.
- It adheres to the surfaces of particles / granules and reduces their surface roughness and friction between them.
- They can inhibit the adsorption of gas / air to the surfaces of particles / granules by adsorbing themselves.

Type	% w/w
Starch*	2 – 5
Talc*	0.3 – 10
Metallic stearates	0.2 – 3
Dibasic calcium phosphate	1-3
Magnesiuum carbonate	0.5-2
Magnesiumum oxide	0.5-2.5
Calcium silicate	0.5-1
Silica aerogels (SiO_2)* Cab-O-Sil, Aerosil	0.1-0.5

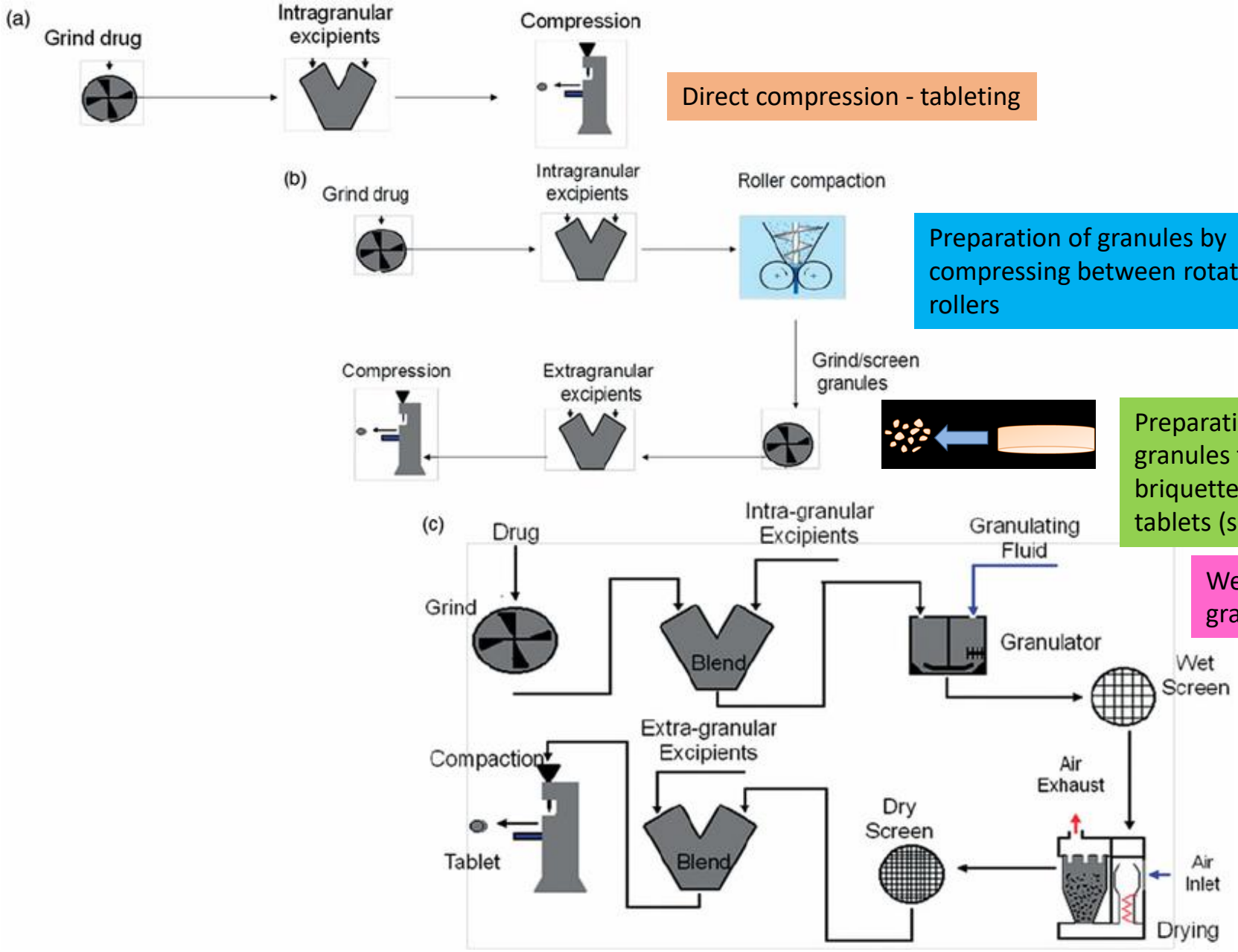
TABLET PREPARATION METHODS

Methods used in tablet manufacturing are mainly classified in two classes:

1- Granulation method

- **a. Wet granulation**
- **b. Dry granulation**
  - **i. Preparation of granules from briquette / slug tablets (slugging)**
  - **ii. Preparation of granules by compressing between rotating rollers**

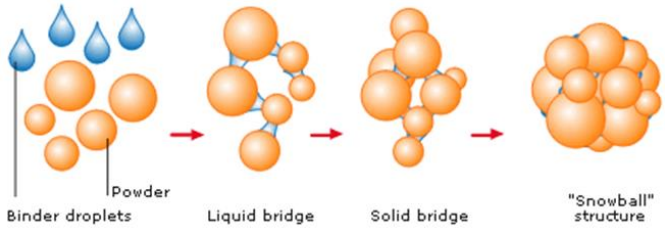
2- Direct Tableting


(a)
Grind drug
Intragranular excipients
Compression
Direct compression - tableting
(b)
Grind drug
Intragranular excipients
Roller compaction
Preparation of granules by compressing between rotating rollers
Compression
Extragranular excipients
Grind/screen granules
Preparation of granules from briquette / slug tablets (slugging)
(c)
Drug
Intra-granular Excipients
Granulating Fluid
Grind
Blend
Granulator
Wet Screen
Wet granulation
Extra-granular Excipients
Compaction
Air Exhaust
Dry Screen
Tablet
Blend
Air Inlet
Drying

Granulation methods: Benefits:

- Improvement in powder flow
- Increase in bulk density (due to densification = compaction of particles)
- Uniform size distribution and uniform shape
- Decrease in sticking to punch surfaces
- Decreased tendency to capping
- Increased employee safety
- Homogeneous mixture formation by preventing segregation

The advantages of the WG method are as follows:



1. The cohesiveness and compressibility of the powders are enhanced by the addition of the binder solution covering each powder particle.
2. By this method, the active substances with high doses, poor flowability and poor compressibility are converted to granules with suitable flow and cohesion for compression by this method.
3. The amount of binder used is less than the amount of dry binder used in DT.
4. Soluble low-dose active substances and color additives can be incorporated into the binder solution. This ensures a good distribution and uniformity of content.
5. Various powders can be combined in this process and their individual properties can be changed to be useful for tableting.
6. Voluminous and dusting powders can be easily processed without contamination.
7. WG prevents the segregation of the components during the tableting process.
8. Depending on the choice of solvent and binder, the dissolution rate of an insoluble active agent may be increased or a controlled release of the active substance can be achieved.

WG process has limitations / disadvantages:

1. Due to the large number of process steps, there is a need for a space where temperature and humidity are controlled.
2. It requires a large number of equipment.
3. It is especially time consuming due to wetting and drying steps.
4. There is a possibility of loss of material during transportation of the material from one process to another. (Especially during the transfer of wet mass)
5. There is a higher risk of cross contamination than DT.
6. Sometimes the dissolution of the active substance from the inner side of the granule can be slow.

Dry granulation

It is preferred:

1- When the dose of the active substance is too high,
2- If the compressibility of the active substance is not appropriate,
3- In case of active substances sensitive to moisture and / or temperature,
4- In cases where powder particles cannot be combined with binding agent,
5- In case the active substance is migrated and could not be distributed homogeneously during the drying of wet granules.
6- For the improvement of disintegration and dissolution since a binder is not used.

Farmasötik birim işlem	Proses parametresi	Potansiyel kalite özellikleri
Silindirler arasında sıkıştırma ile granülasyon (roller compaction)	Silindir dönü hızı Silindirlerarası boşluk Silindir basıncı Burgu hızı Silindir tipi	Görünüm Şerit/partikül büyüklüğü ve şekli Şerit dansitesi, direnci ve kalınlığı Katı form

ROLLER COMPACTOR

https://youtu.be/HzvKzTOleGs

Direct (Compression) Tableting

The advantages of this process

1. The first and obvious advantage is that it is economical.
2. Unlike WG, it is not necessary to wet and heat powder mix and high pressure application is not mandatory as compared with the DG.
3. Moisture and heat applied in tableting with WGmay not be suitable for stability of active substances.
4. Granulation process parameters in WG affect granule properties; the drying process may cause the migration of soluble active agents.
5. The high number of unit operations in the granulation methods, can increase the probability of changing the properties of tablets between batches.
6. It has no negative effect on disintegration of the tablets and the rate of dissolution of the active substance.
7. The effect of disintegrants in direct compression is optimum. (no change by internal or external addition)

Then why isn't all the tablets prepared by this method?

1. Many active substances are used micronized in terms of dissolution and BA. Micronisation inevitably leads to increased interparticle friction and reduced powder flowability.
2. In the DT process, there is a need for direct tableting agents (DTA) with suitable flow properties and compressibility which have two functions as both filler and binder.
3. The dilution potential of DTAs is important.
4. Another limitation is the content uniformity.
5. Colorants may not be distributed uniformly.
6. Lubrication is more important and complex in DT.

Properties of DTAs:

- Good flowability.
- Compressibility.
- Having a good pressure-hardness profile.
- High dilution potential.
- Can be colored uniformly
- No interference with BA of the active substance.
- The particle size range identical to that of the active substances.
- Bulk density.
- Moisture content. When it is high, it reduces the hardness of the tablet.
- Re-usability without losing flowability and compressibility properties.
- Physiological inertness, compatibility, stability.
- Colorless and odorless.

VARIOUS CO-PROCESSED EXCIPIENTS

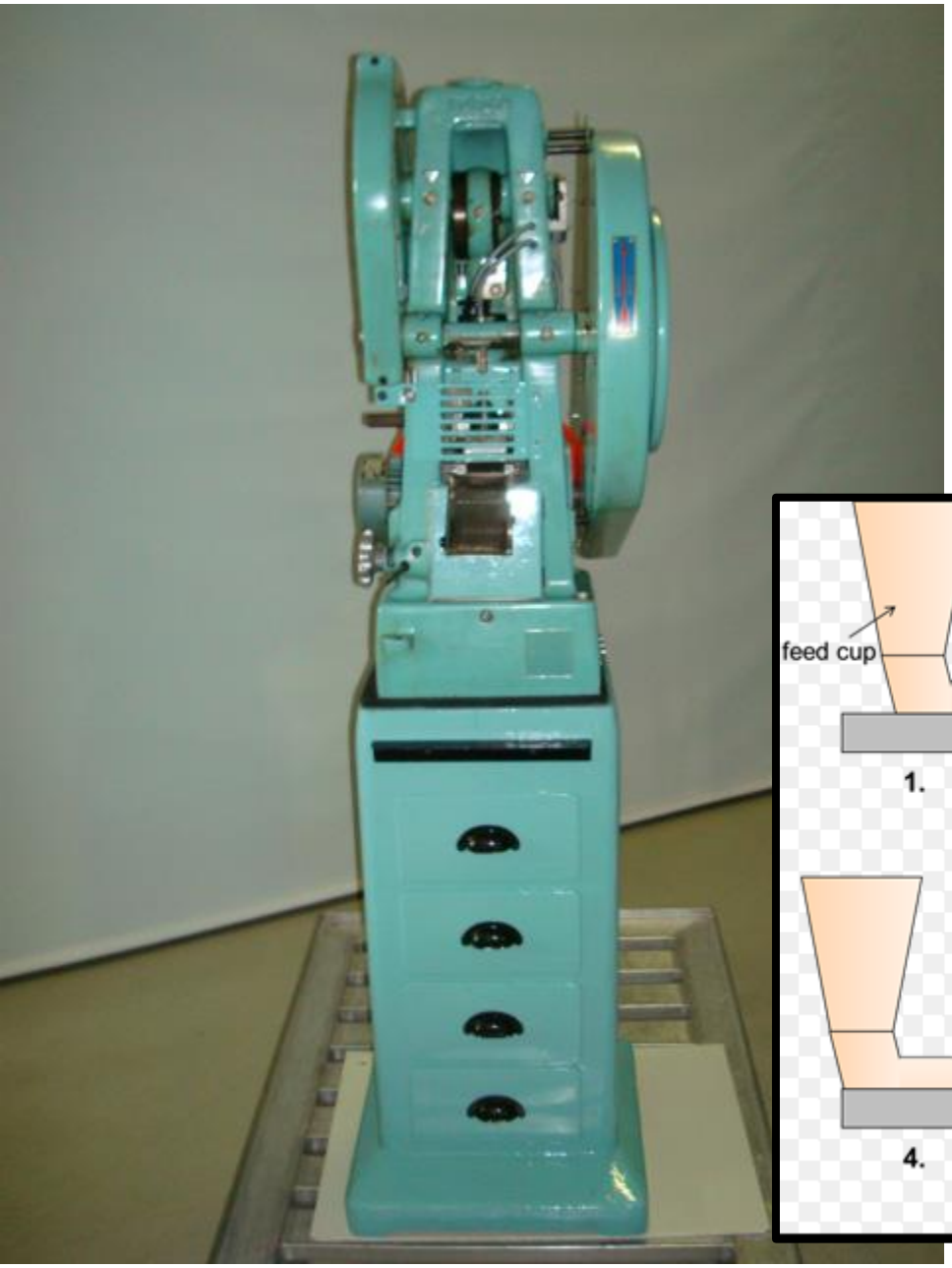
Trade Name	Composition	Manufacturer	Advantages
Advantose FS 95®	Fructose, starch	SPI Pharma	Good flow, high compressibility and taste-masking due to the inherent sweetness of fructose
Avicel CE-15®	MCC, Guar gum	FMC Corp.	Less grittiness, reduced tooth packing and creamier mouthfeel
Cellactose®	Lactose, Cellulose	Meggle	High compressibility and good mouthfeel
F-MELT®	–	Fuji Chemicals	High compressibility, good flow and tailor-made for ODTs
Formaxx®	Calcium carbonate, Sorbitol	Merck	High compressibility, good flow, superior compaction at low compression force

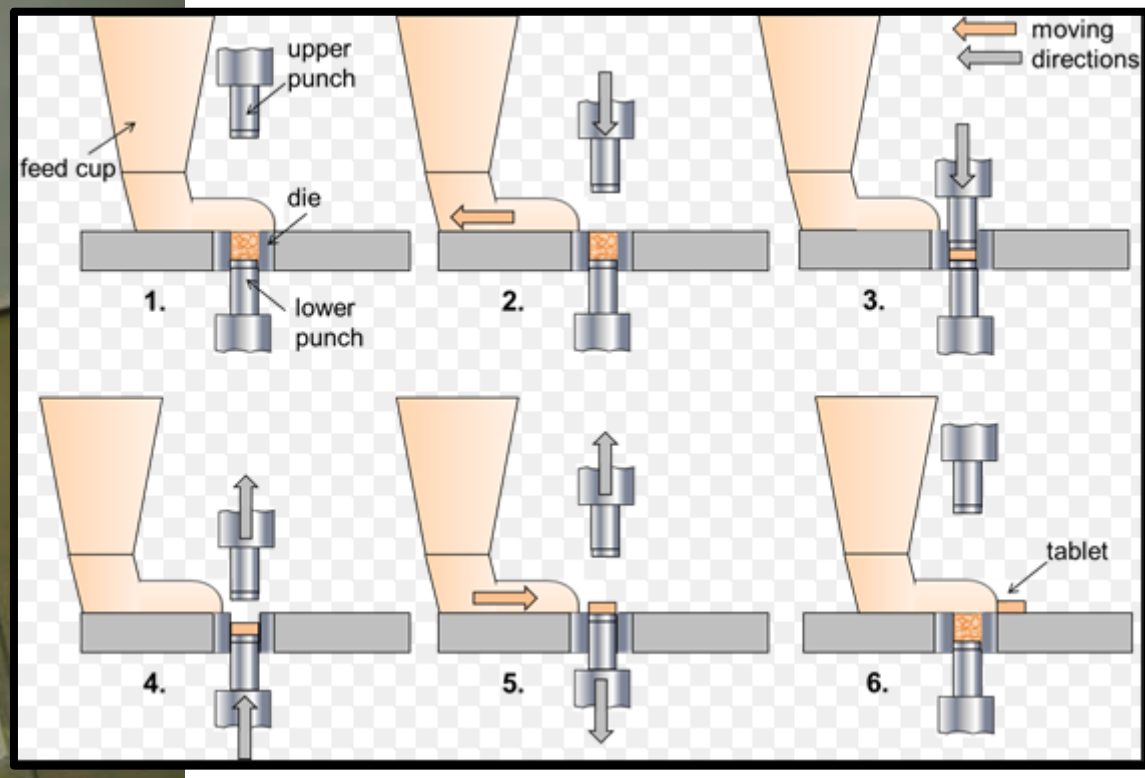
Ludipress®	Lactose, Kollidon 30, Kollidon CL	BASF	Low hygroscopicity, good flowability, disintegrant functionality
MicroceLac®	MCC, Lactose	Meggle	Excellent compressibility for high dose formulations, good flow
Prosolv®	MCC, Colloidal silicon dioxide	Penwest	Good flow, reduced sensitivity to wet granulation, hard tablets with low friability
Star Lac®	Lactose, Maize starch	Roquette	Good flow with disintegration functionality; ideal for ODTs
Xylitab 100®	Xylitol, Polydextrose	Danisco sugars	Directly compressible sugar with improved mouthfeel

Tablet compression

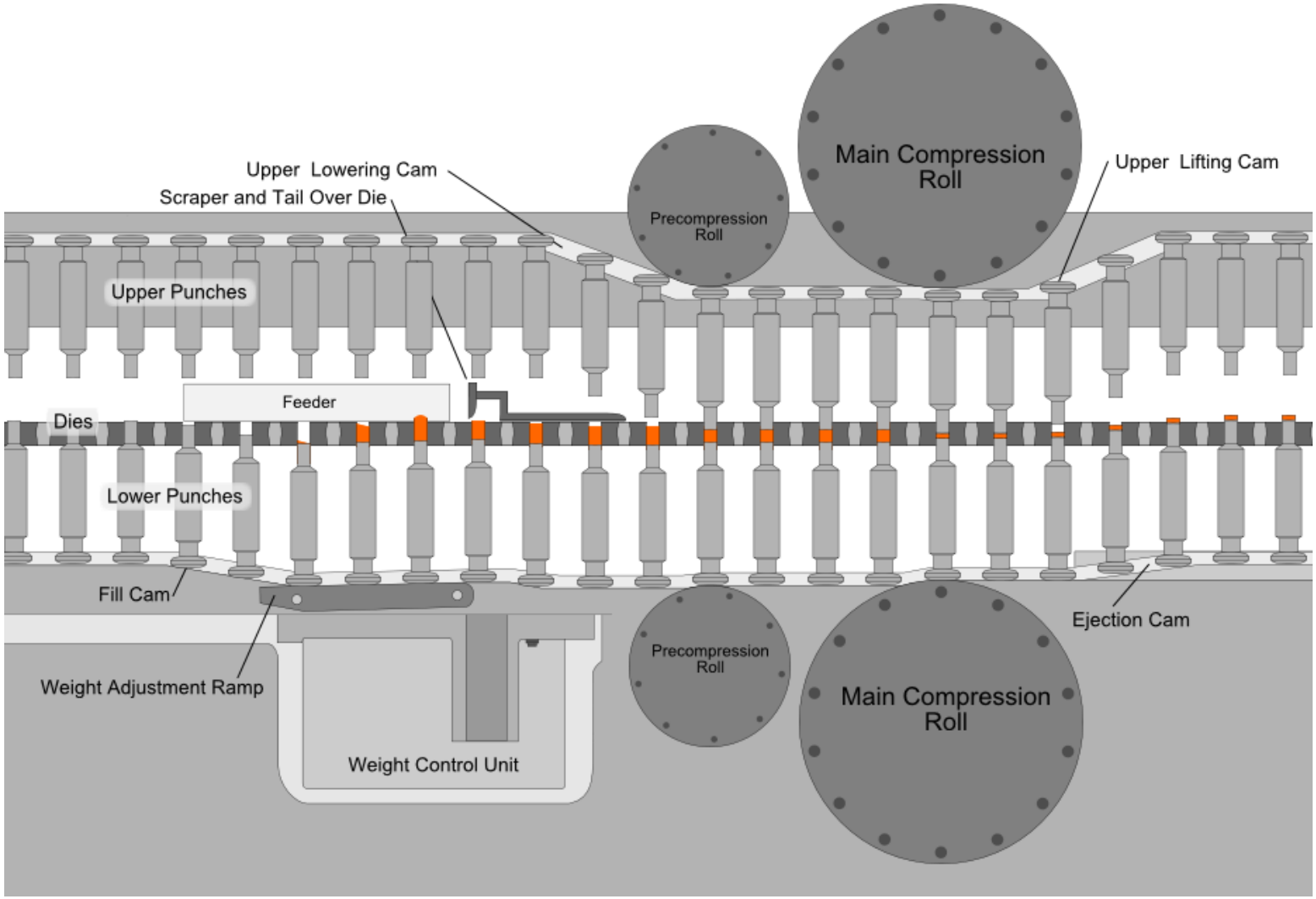
Maintenance of punches and dies: They are washed with soapy water, dried and liquid paraffin is applied to their surfaces for protecting from air oxygene and they are stored in separate boxes.

Eccentric tablet machine





Rotary tablet machine



The tail over die is an essential feature of the high-speed tablet press. The function of the tail over die is to keep the filled die covered until the last moment before the upper punch enters the die.