# Tablets

- Tablets are solid dosage forms containing a single dose of one or more active ingredients and are usually prepared by compressing uniform volumes of particles (powders or granules).

- Tablets consist the most commonly used dosage form.

- They are used mainly for systemic use but some times for local (e.g. Antacids, antihelmentics).

1

# Tablets

**Tablets are popular for several reasons:**

- The oral route represents a convenient and safe way of drug administration
- Compared with liquid dosage forms tablets have general advantages in terms of chemical and physical stability
- The preparation procedure enables accurate dosing of drug.
- Tablets are convenient to handle by patient (Identification, swallowing)
- They provide an economical and suitable method to large scale production

2

# Tablets

**Main disadvantages:**

1. Some drugs (poorly water-soluble or poorly absorbable) have low bioavailability.

2. Some drugs may cause local irritant effects in the gastrointestinal mucosa.

3. Some drugs resist compression into dense compacts.

3

# Tablets

**Quality attributes of tablets**

1. They should contain a correct dose of the drug.
2. The appearance of tablets should be elegant and its weight, size, and appearance should be consistent.
3. The drug should be released from the tablets in a controlled and reproducible way.
4. The tablets should be biocompatible, i.e. not include excipients, contaminants, and microorganisms that cause harm to patients.

4

# Tablets

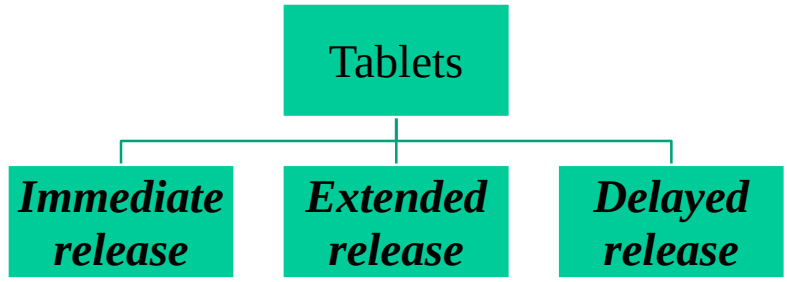
**Quality attributes of tablets**

5. The tablets should be of sufficient mechanical strength to withstand fracture and erosion during handling (the production, packaging, shipping and dispensing).
6. The tablets should be chemically, physically and microbiologically stable during the lifetime of the product.
7. The tablet should be acceptable by the patient.
8. The tablets should be packed in a safe manner.

- ❑ Tests and standards for some of these properties are found in the pharmacopoeias.

5

# Tablet Types




6

# Tablet Types

Tablets can be classified into three types based on their drug release characteristics:

- ***Immediate release tablets***: The tablets in which the drug is intended to be released rapidly after administration or the tablet is dissolved and administered as solution.
- This is the most common type of tablets and includes disintegrating, chewable, effervescent, sublingual and buccal tablets.

- ***Extended release tablets***: The drug is released from these tablets slowly and at nearly constant rate (Zero order kinetics). The formulation and the used excipients are usually different from those in conventional tablets.

- ***Delayed release tablets***: The drug is librated from these tablets sometime after administration. Example is enteric tablets, for which the tablet passes the stomach and the drug is released from in the upper small intestine.

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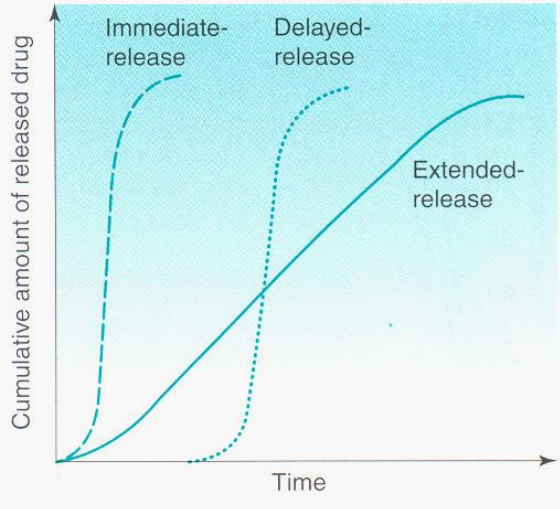


**Fig. 31.10** Schematic representation of the cumulative amount of drug released from immediate-, extended- and delayed-release tablets.

8

# Immediate release tablets

**Disintegrating tablets**

- This type of tablets is intended to be swallowed and to release the drug after disintegration and dissolution.
- They are often referred to as conventional or plain tablets.
- They should include disintegrant.

9

# Immediate release tablets

**Disintegrating tablets**

- Single disintegrating tablets can be formed as multilayer tablets, i.e the tablet consists of two or three layers cohered to each other.
- During the preparation of multilayer tablets the die is filled in two or three consecutive steps with different granules from separate feed stations.
- Disintegrating tablets also can be coated by different methods.

10

11

# Immediate release tablets

**Disintegrating tablets**

- The disintegration time of the tablet can be markedly affected by:
  - the choice of excipients, especially disintegrant
  - Granulation procedure
  - Mixing conditions during the addition of lubricants and antiadherents
  - The applied punch force

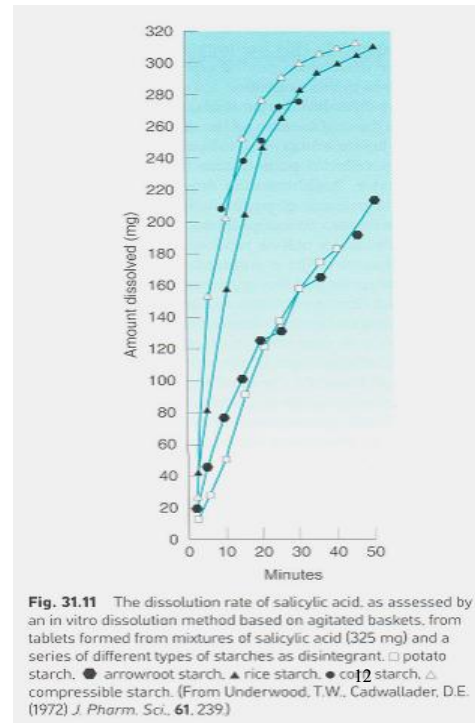


**Fig. 31.11** The dissolution rate of salicylic acid, as assessed by an in vitro dissolution method based on agitated baskets, from tablets formed from mixtures of salicylic acid (325 mg) and a series of different types of starches as disintegrant. □ potato starch, ● arrowroot starch, ▲ rice starch, ● corn starch, △ compressible starch. (From Underwood, T.W., Cadwallader, D.E. (1972) *J. Pharm. Sci.*, **61**, 239.)

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# Immediate release tablets

**Disintegrating tablets**

- The dissolution rate from a tablet is a function of:
  - the solubility (can be increased by salt formation).
  - the surface area (can be increased by particle size reduction and disintegration to primary particles).

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# Immediate release tablets

**Chewable tablets**

- These tablets disintegrate mechanically in the mouth by chewing it. The drug is normally swallowed and dissolves in the stomach or intestine.

- The aim of these tablets is to obtain rapid drug effect (e.g. Antacid tablets) or to facilitate the intake of the tablet (e.g. Aspirin and vitamins tablets for children).

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# Immediate release tablets

**Chewable tablets**

- They normally do not contain disintegrant.
- Flavors and colors are common
- Mannitol and sorbitol are common examples of fillers.

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# Immediate release tablets

***Effervescent tablets***

- These tablets are dropped into a glass of water before administration, during which carbon dioxide is librated facilitating tablet disintegration and drug dissolution.
- The effervescent carbon dioxide is is created by a reaction in water between a carbonate or bicarbonate and a weak acid such as citric or tartaric acid.

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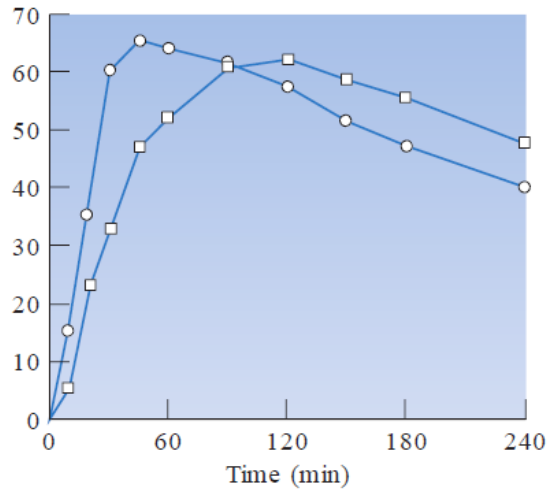


**Fig. 30.12** • Concentration of salicylates in plasma after administration of acetylsalicylic acid tablets (1 g). Circles, effervescent tablet; squares, conventional tablet. (Courtesy of Ekenved et al, 1975, with permission.)

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# Immediate release tablets

***Effervescent tablets***

- Effervescent tablets are used to obtain rapid drug action (e.g. analgesics) or to facilitate the intake of drug (e.g. vitamins).

- They often include a color and a flavor and do not contain a binder.

- Water soluble lubricants are preferred in order to avoid formation of a hydrophobic lubricant layer on the surface of the water after tablet dissolution.

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# Immediate release tablets

***Effervescent tablets***

- Humidity should be controlled during manufacturing.
- They should be packaged in a way that they are protected against moisture.
- Effervescent tablets are prepared by either direct compaction or by granulation (by fusion or using ethanol).

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# Immediate release tablets

***Lozenges***

- Lozenges are tablets that dissolve slowly and used for local treatment in the mouth.
- They are usually used to treat sore throat or to control coughing in the common cold.
- They may contain antiseptics, antibiotics, local anesthetics, demulcents, astringents and antitussives.
- They are normally prepared by compression under high pressure to have high mechanical strength and low porosity in order to dissolve slowly in the mouth.

20

# Immediate release tablets

***Lozenges***

- They do not contain disintegrants.
- The filler and binder should be water soluble.
- They often contain color, flavor and excipients which contribute to a pleasant taste or feeling during tablet dissolution.
- Common examples of fillers are glucose, sorbitol and mannitol.
- Common binder is gelatin.

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# Immediate release tablets

***Buccal and sublingual tablets***

- These tablets are intended to be held between the cheek and teeth (buccal) or under the tongue (sublingual) and to release their drug content for absorption directly through the oral mucosa (i.e. systemic drug effect).
- Advantages
  - More rapid onset of action (vasodilators)
  - Avoidance of gastric environment which cause decomposition for certain steroids and hormones.
  - Avoidance of first pass metabolism
  - Avoidance of nausea produced by swallowing certain drugs (e.g. methyltestosterone)

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# Immediate release tablets

***Fast dissolving tablets***

- These tablets that dissolve or disintegrate quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water.
- Rapidly dissolving tablets are also known as:
  - Melt in Mouth tablets
  - Mouth dissolving tablets (MDT)
  - Quick dissolving tablets
  - Rapid disintegrating tablets (RDT)
  - Fast disintegrating tablets (FDT)
  - Orally disintegrating tablets
  - Oro dispersible tablets (ODT)

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# Immediate release tablets

***Fast dissolving tablets***

Advantages

- Administration to patients who:
  - cannot swallow, such as: the elderly, stroke victims, bedridden patients;
  - should not swallow, such as those affected by renal failure;
  - refuse to swallow, such as pediatric, geriatric and psychiatric patients
- Rapid drug therapy intervention and more rapid drug absorption
- Convenience and patient compliance
- New business opportunities and patent-life extension

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# Immediate release tablets

**Vaginal tablets**

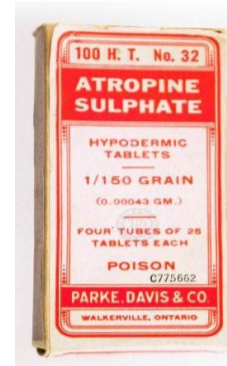
- Vaginal tablets, also called *vaginal inserts*, are uncoated, bullet-shaped or ovoid tablets inserted into the vagina for local effects.
- normal vaginal pH ranges **between 3.8 and 5.0**
- They are prepared by compression and shaped to fit snugly on plastic inserter devices that accompany the product.
- They contain antibacterials for the treatment of nonspecific vaginitis caused by *Haemophilus vaginalis* or antifungals for the treatment of vulvovaginitis candidiasis caused by *Candida albicans* and related species

25

# Immediate release tablets

**Dispensing tablets XXX**

- Dispensing tablets are intended to be added to a given volume of water by the pharmacist or the consumer.




**Hypodermic tablets XXX**

- Hypodermic tablets are no longer available.
- They were originally used by physicians in extemporaneous preparation of parenteral solutions.

26

# Tablet Manufacturing

Tablets are prepared by forcing particles into close proximity to each other by powder compression, which enables powders to cohere into a porous , solid specimen of defined geometry.

The compression takes place in a **die** by the action of two **punches**, the lower and the upper.

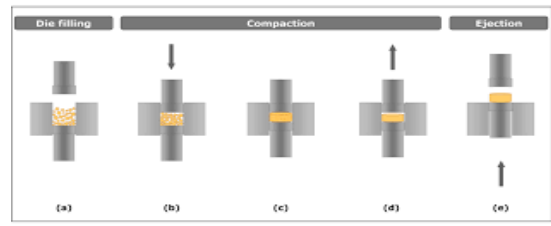
27

# Tablet Manufacturing

***Compression*** is defined as the reduction in volume of a powder owing to the application of pressure.

Because of the increased proximity of particle surfaces accomplished during compression, bonds are formed between particles which provides coherent to the powder, i. e. a compact is formed.

***Compaction*** is defined as the formation of a porous intact specimen of defined geometry by powder compression.




28

# Tablet Manufacturing

**Compaction cycle**:

**1. Die filling**

- This is normally accomplished by gravitational flow of the powder from a hopper via die table into the die.
- The die is closed at its lower end by the lower punch.

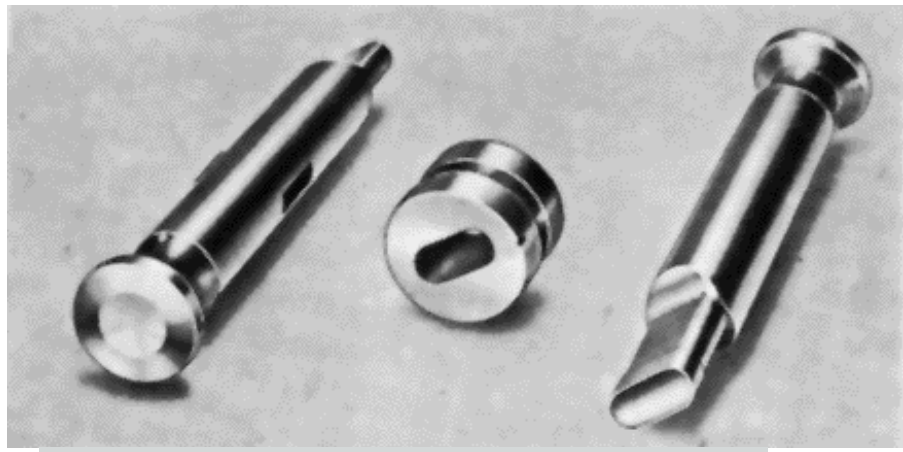
**2. Tablet formation**

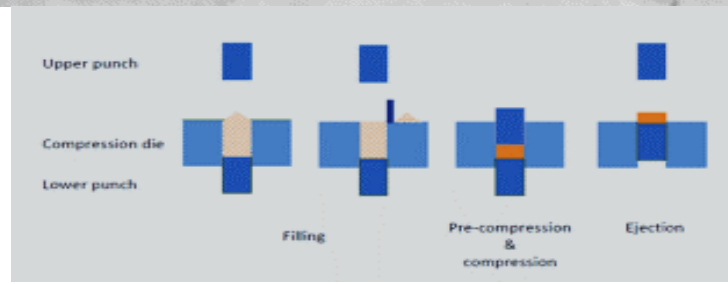
- The upper punch descends and enters the die and the powder is compressed until a tablet is formed.

**3. Tablet ejection**

- During this phase the lower punch rises until its tip reaches the level of the top of the die.

29



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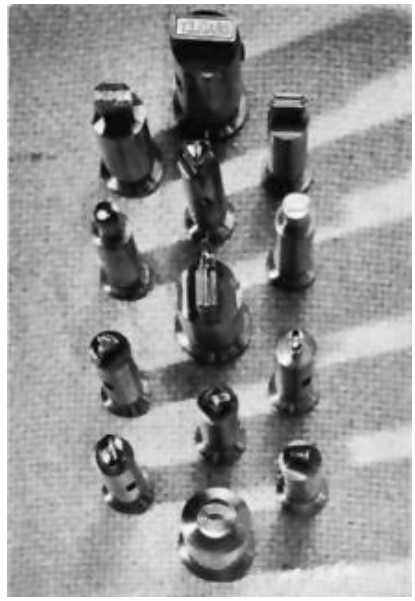
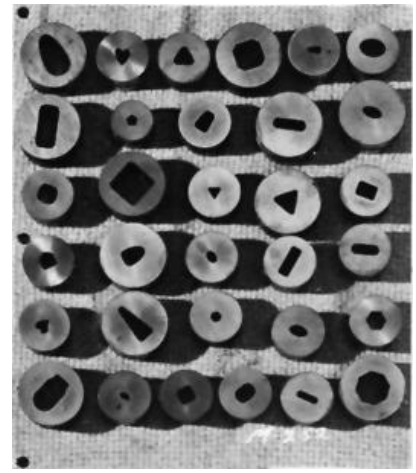




31

# Tablet presses

***single punch press (eccentric press)***

- A single-punch press possesses one die and one pair of punches.

- The output of tablets is about 200 tablets per min.

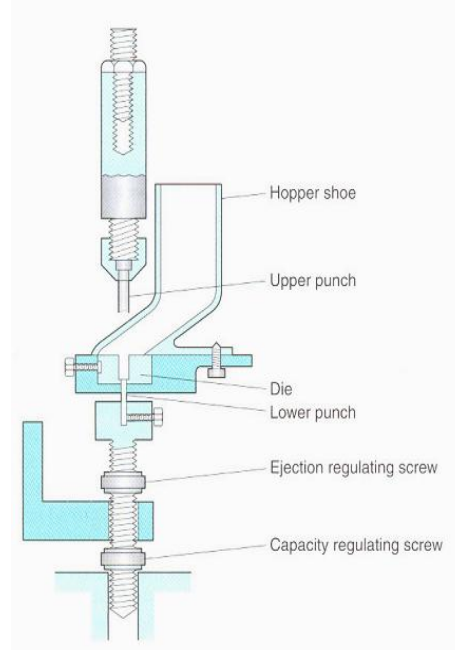



**Fig. 31.2** A single-punch tablet press.

32

# Tablet presses

***Single punch press (eccentric press)***

**Steps of compaction**

On turning the driving wheel:

1. Upper punch rises.
2. Feeder (hopper shoe) moves until becomes over the die.
3. The lower punch drops to a position controlled by the capacity regulating screw.
4. The hopper shoe moves aside leaving the die filled with powder.
5. Lower punch remains stationary while upper punch comes down compressing the powders into a tablet.
6. The upper punch rises out of the die and the lower punch rises also to eject the tablet.

33

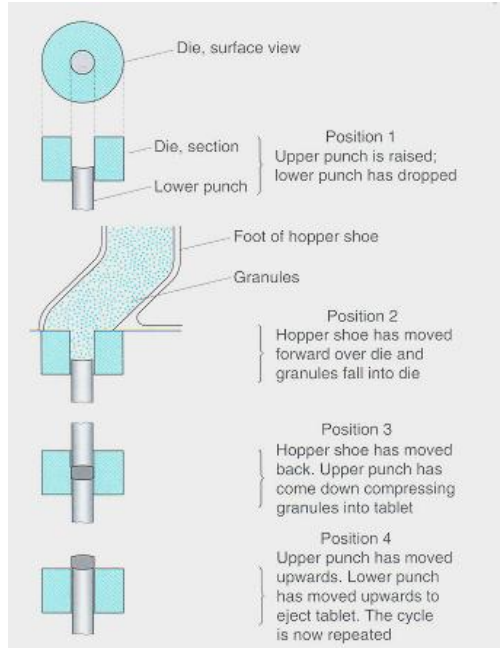
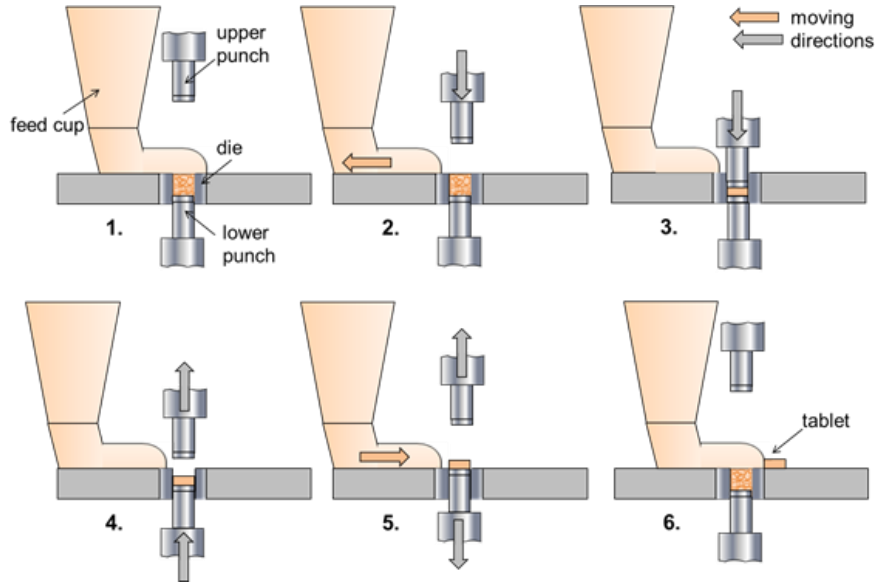



**Fig. 31.1** The sequence of events involved in the formation of tablets.

34




35

# Tablet presses

***Rotary press (multistation press)***

- The rotary tablet machine consists of three parts:
  - An upper part carrying the upper punches
  - Lower part carrying the lower punches
  - Central part carrying the dies
- Both the die table and punches rotate together during operation
- It can press tablets in a rate higher than 10 000 tablet/min.
- Number of dies and sets of punches can vary considerably from 3 to 60.

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# Tablet presses

***Rotary press (multistation press)***

The process can be summarized by the following steps:

- When the lower punches pass below the feed frame they will be in their lowest point.
- The powder from the hopper is fed continuously to the feed frame so the dies will be filled with powder.
- Then the dies will pass over the powder volume adjuster to expel the excess of the powder.
- The lower and upper punches move towards each other to compress the powder.
- Both the upper and lower punches rise to eject the tablet.

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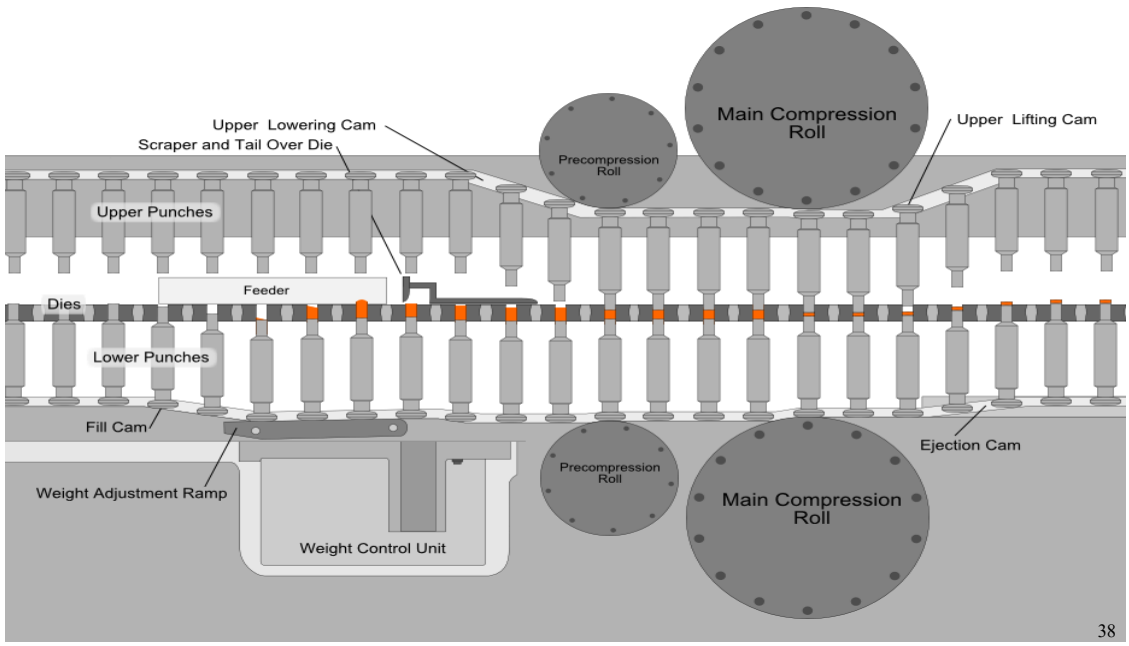


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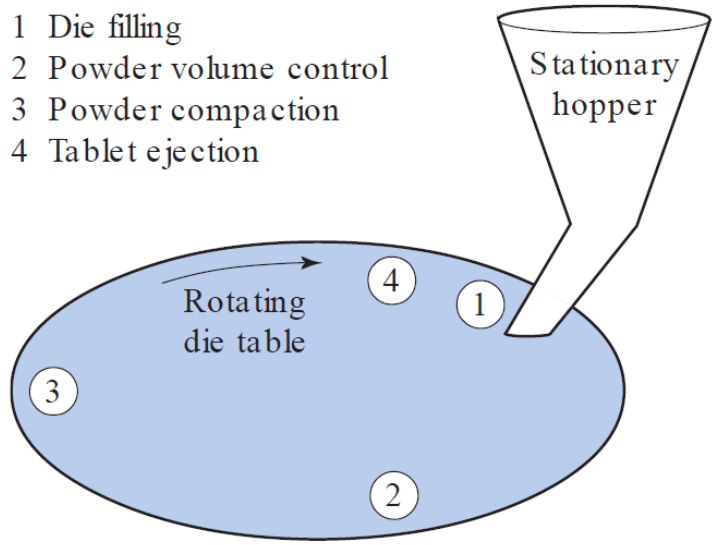
1 Die filling
2 Powder volume control
3 Powder compaction
4 Tablet ejection
Stationary hopper
Rotating die table
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2
3
4

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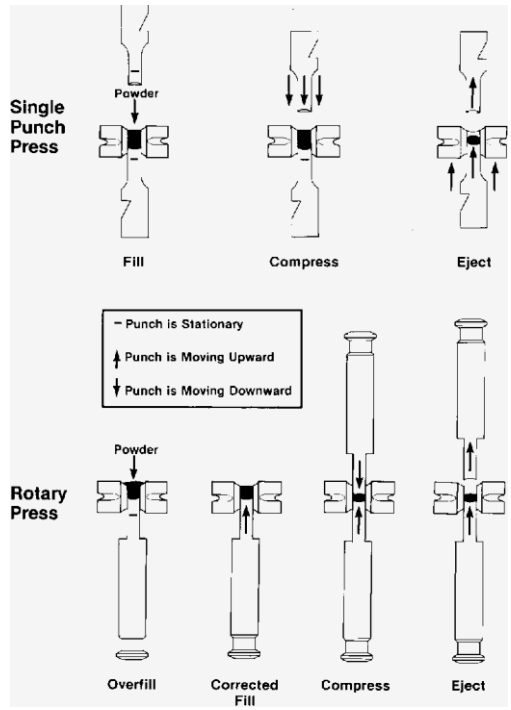


41

# Tablet presses

***Computerized hydraulic press (simulators)***

- For computerized hydraulic presses the movement of the punches can be controlled and varied considerably.

- Tablets can be prepared under controlled conditions with respect to the loading pattern and loading rate.

- Possible applications are the investigation of the sensitivity of a drug to such variations or to mimic the loading pattern of production presses to predict scale-up problems.

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# Tablet production via granulation

The main aims of granulation before tabletting are:

1. to increase bulk density of the powder mixture and thus ensure that the required volume of powder can be filled into the die.

2. to improve mixing homogeneity and reduce segregation.

3. to improve the flowability of powder to ensure complete and uniform filling of dies and therefore less weight and dose variation in the tablets.

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# Tablet production via granulation

The main aims of granulation before tableting are:

4. to improve the compactability of powder by adding a solution binder, which is effectively distributed on the particle surfaces.

5. to ensure a homogenous color in a tablet by adding the color so that it is distributed effectively over the tablet surface.

6. to affect the dissolution process for hydrophobic poorly soluble particles by using fine particles and mixing them with a hydrophilic filler and a hydrophilic binder.

- Granulation methods are either ***dry*** or ***wet***

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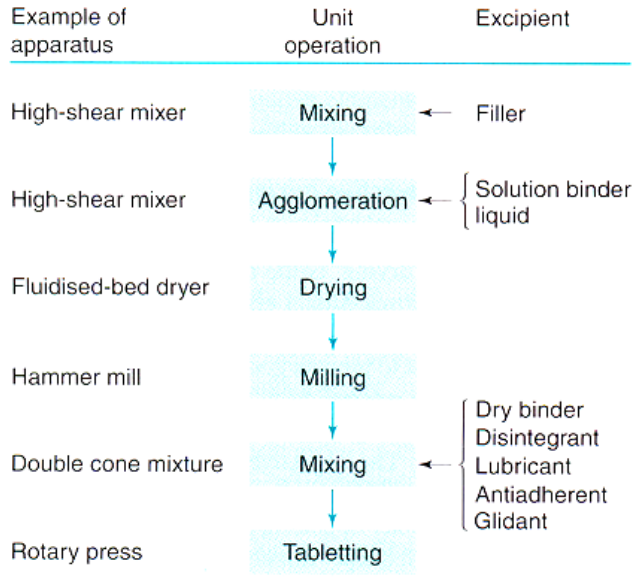


**Fig. 31.5** Overview of the sequence of unit operations used in the production of tablets with precompaction treatment by granulation.

45

# Tablet production by direct compaction

- This process involves mixing of the active ingredients and additives and compression directly in the tableting machine.

***Advantages:***

1. Simple process
2. Reduced production time and operation cost
3. Improved product stability by avoidance of moisture and heat.

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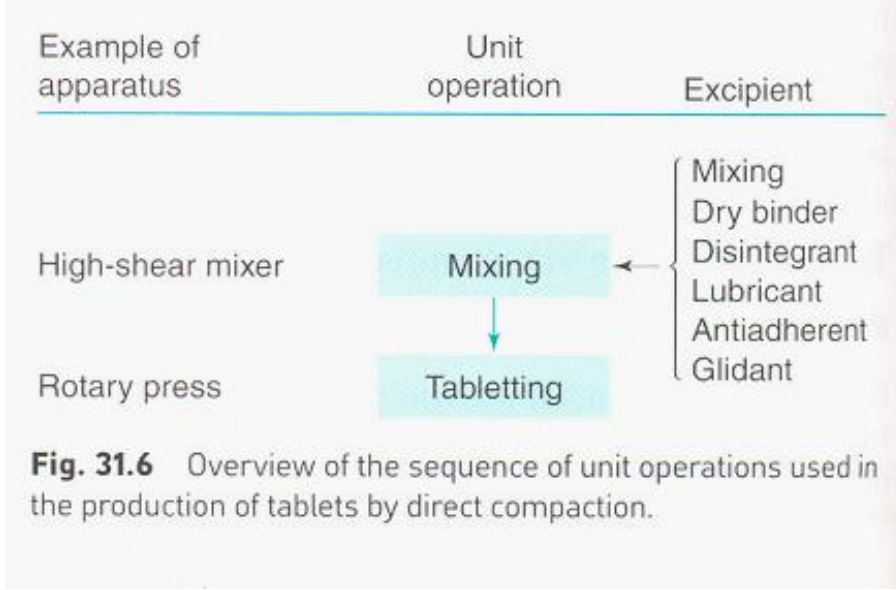


**Fig. 31.6** Overview of the sequence of unit operations used in the production of tablets by direct compaction.

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# Tablet production by direct compaction

***Limitations:***

- Relatively large particle size must be used to have acceptable flowability and bulk density which:
  - may affect degree of mixing
  - Segregation may occur.
- It needs specially designed fillers which are usually more expensive than traditional ones.
- If the drug is the major component the application of direct compression depends mainly on the properties of drug.

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# Molded Tablets

- Molded tablets are usually prepared from soluble ingredients so that the tablets are completely and rapidly soluble.
- After the excipient is blended with the drug, the powder mix is dampened with solutions containing high percentages of alcohol.
- The dampened powders are pressed into molds, removed, and allowed to dry.

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# Molded Tablets

- Solidification depends upon crystal bridges built up during the subsequent drying process and not upon the compaction force.
- They can be prepared in small or large scale.
- They are not common nowadays.

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# Tablet excipients

**Diluents (Fillers)**

- Materials used to increase the bulk volume of powder and hence the size of the tablet.
- Tablets weigh at least 50 mg.
- They are not necessary if the dose of drug per tablet is high.

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# Tablet excipients

**Diluents (Fillers)**

- The ideal diluent should fulfill a series of requirements such as:
  1. be chemically inert
  2. be non-hygroscopic
  3. be biocompatible
  4. be color compatible
  5. possess good biopharmaceutical properties (e.g. water soluble or hydrophilic)
  6. possess good technical properties (such as compactability and flowability)
  7. no chemical or physical changes on aging
  8. acceptable taste
  9. be cheap

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# Tablet excipients

Examples on diluents:

- Lactose
  - The most commonly used because of good properties (dissolves readily in water, has a pleasant taste, non-reactive, non-hygroscopic, has good compactability)
  - Its main limitation is that some people have intolerance to lactose.
  - In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions. It is found as:
    - monohydrate
    - anhydrous
    - amorphous (spray dried lactose)

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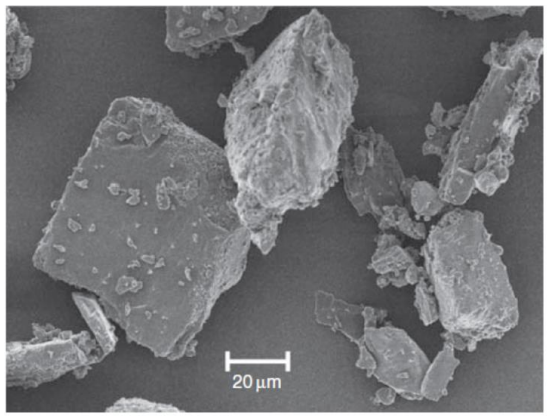
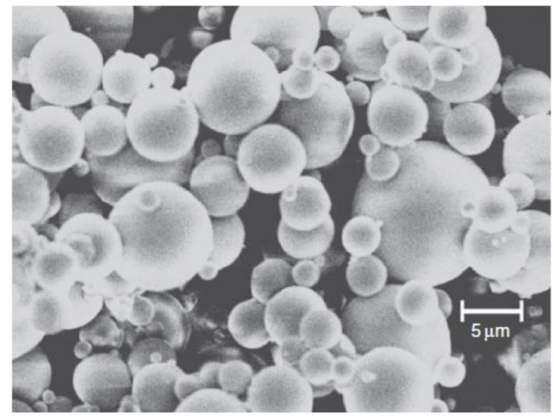



crystalline lactose




spray-dried lactose

55

# Tablet excipients

Examples on diluents:

- **Celluloses**
  - Advantages
    - Biocompatible
    - Chemically inert
    - Have good tablet-forming and disintegration properties
  - They are used also as dry binders and disintegrants in tablets.
  - They are compatible with many drugs but, owing to their hygroscopicity, may be incompatible with drugs prone to hydrolysis in solid state.
  - The most common type of cellulose powder used in tablet formulation is microcrystalline cellulose (Avicel®).

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# Tablet excipients

- Dicalcium phosphate dihydrate (Emcompress®)
  - Insoluble in water and nonhygroscopic but is hydrophilic, i.e. easily wetted by water.
  - It is slightly alkaline and thus may be incompatible with drugs sensitive to alkaline conditions.
  - It can be obtained both in a fine particulate form, mainly used in granulation, and in an aggregated form, used in direct compression.

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# Tablet excipients

- Sucrose (serves also as binder)
  - Sucrose-based tablet diluent-binders are available under a number of trade names which include:
    - Sugartab® (90 to 93% sucrose plus 7 to 10% invert sugar).
    - Di-Pac® (97% sucrose plus 3% modified dextrins),
    - NuTab® (95% sucrose, 4% invert sugar, and 0.1 to 0.2% each of cornstarch and magnesium stearate).
  - Confectioner's sugar is a mixture of sucrose (not less than 95.0%) and corn starch.

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# Tablet excipients

Other examples on diluents:

- Glucose
- Sorbitol, Mannitol
  - They are optical isomers.
  - Used in chewable tablets since they have negative heat of dissolution
- Calcium carbonate
- Calcium sulphate dihydrate

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# Tablet excipients

- Direct compression diluents:
  - Examples on diluents:
    - Spray dried lactose, Anhydrous lactose
    - Sucrose based excipients (Di-Pac®)
    - Sorbitol, mannitol
    - microcrystalline cellulose (Avicel®)
    - Dicalcium phosphate (anhydrous, dihydrate)
    - Spray crystallized maltose dextrose
    - hydrolized starches (like Emdex®)
    - Pregelatinized starch (e.g. Starch 1500®)
    - Ludipress® (93.4% a-lactose monohydrate, 3.2% polyvinylpyrrolidone and 3.4% crospovidone)

60

# Tablet excipients

- ***Coprocessed Excipient Products*:**
  - Ludipress® (93.4% a-lactose monohydrate, 3.2% polyvinylpyrrolidone and 3.4% crospovidone)
  - Cellactose 80™ contains α-lactose monohydrate and cellulose powder
  - Prosolv SMCC, silicified MCC, contains 98% MCC and 2% colloidal silicon dioxide, which provides a better granule flow and an opportunity for smaller and denser tablets upon direct compression.
  - MCC microcrystalline Cellulose

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# Tablet excipients

**Binders (Adhesives)**

- A binder is added to ensure that granules and tablets can be formed with the required mechanical strength.
- Typical concentration 2 – 10 % by weight.
- Binders can be added to a powder in different ways
  - As a solution which is used in wet granulation (***solution binder***)
  - As dry powder which is mixed with the other ingredients before wet granulation
  - As a dry powder which is mixed with other ingredients (powders or granules) before compaction (***dry binder***)

- Solution binders are generally considered the most effective

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# Tablet excipients

**Binders (Adhesives)**

- Examples:
  - Common traditional solution binders (starch, sucrose and gelatin)
  - Acacia, sodium alginate, tragacanth.
  - Synthetic polymers used as solution binders (Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and methyl cellulose, polyethylene glycol )
  - Dry binders include: microcrystalline cellulose(MCC), methylcellulose, polyethylene glycol and crosslinked PVP).

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# Tablet excipients

**Disintegrants**

- A disintegrant is added to most tablet formulations to facilitate the breakup (disintegration) of the tablet when it contacts water in the GIT, which promotes rapid drug dissolution.
- The disintegration process for tablets occurs in two steps: First, the liquid wets the solid and penetrates the pores of the tablet. Then, the tablet breaks into smaller fragments.


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# Tablet excipients

**Disintegrants**

- Several mechanisms of action have been suggested.
- The most common and effective disintegrants act via a swelling mechanism.
- Disintegrant can be added to the granules just before compaction (extragranular) or to the powder before granulation (intragranular) or part of the amount is added intragranularly and the other part extragranularly.

65

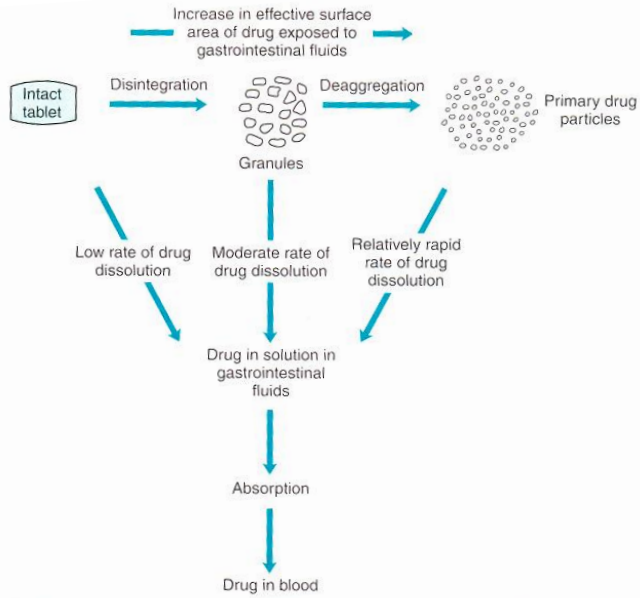


**Fig. 31.7** Mechanistic representation of the drug release process from a tablet by disintegration and dissolution. (From Wells, J.I., Rubinstein, M.W. (1976) *Pharm. J.*, **217**, 629.)

66

# Tablet excipients

**Disintegrants**

Examples:

- **Starches (up to 10 %)**
  - Most commonly used
  - Include corn starch, potato starch and rice starch, wheat starch.
  - Advantages
    - Safe (used as food)
    - Low cost
    - efficient
  - Disadvantages
    - Poor flowability and compressibility
    - hygroscopicity
  - Some new modified forms of starch have been developed like pregelatinized starches (about 5 % conc. Used).

67

# Tablet excipients

**Disintegrants**

Examples:

- **Sodium starch glycolate (Primogel®, Explotab®)**
- **Alginates**
- **Crosslinked polyvinylpyrrolidone (CROSS PVP)**
- **Cellulose and Cellulose derivatives**
  - Include microcrystalline cellulose and carboxymethyl cellulose.
- **Effervescence inducing disintegrants**
  - Used in effervescent tablets
  - Composed of Citric or tartaric acid with a source of $CO_2$ (like bicarbonates or carbonates)

68

# Tablet excipients

**Glidants**

- These are materials intended to promote the flow of powders or granules.

- Examples:
  - Colloidal silica (0.2 %)
  - Talc (1 -2 %)
  - Mg stearate (< 1 %)
  - Maize starch

69

# Tablet excipients

**Lubricants**

- These are materials intended to reduce friction during table ejection between tablet and the walls of the die.

- High friction during tableting may cause a series of problems (capping, fragmentation of tablet, vertical scratches on tablet edges) and may even stop production.

70

# Tablet excipients

**Lubricants**

- Besides reducing friction lubricants may cause undesirable changes in the properties of tablets:
  - The presence of a lubricant in a powder is thought to interfere negatively with the **bonding** between the particles during compaction, and thus reduce tablet strength.
  - Because many lubricants are hydrophobic, tablet disintegration and dissolution are often retarded by the addition of a lubricant (Mixing time and mixing intensity and the amount of lubricant are important in this context) Stearate derivatives

71

# Tablet excipients

- Lubrication is achieved by mainly two mechanisms:

***a) fluid lubrication***

- A layer of fluid is located between and separates moving surfaces from each other.
- Fluid lubricants are **seldom** used in tablet formulation
- Example is paraffin oil.

72

# Tablet excipients

***b) boundary lubrication***

– A thin film of powder separates moving surfaces from each other.

– A number of mechanisms have been discussed including that lubricants are substances showing a low resistance towards shearing.

- Examples: Stearic acid and its salts (e.g. Mg stearate is the most widely used lubricant), sodium lauryl sulphate, sodium stearyl fumarate. glyceryl behenate, sodium benzoate and PEG.

73

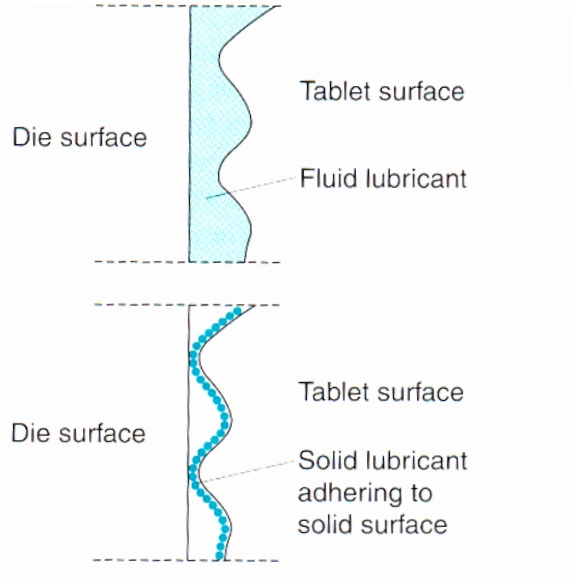


**Fig. 31.8** Schematic illustration of lubrication mechanisms by fluid and boundary lubrication.

74

# Tablet excipients


**Anti-adherent**

- These are materials intended to reduce sticking or adhesion of the powder to the punches or die wall.
- Many lubricants such as magnesium stearate have also anti adherent properties.
- However, other substances with limited ability to reduce friction can also act as antiadherents such as talc and starch.

75

# Tablet excipients

**Sorbents**

- These are substances that are capable of sorbing some quantities of fluids in apparently dry state.
- They are used for incorporation of oils or fluid extracts into the tablets.
- Examples: Microcrystalline cellulose, silica, kaolin, bentonite and magnesium carbonate

76

# Tablet excipients

**Colors**

- Colors are added to the tablets for the following reasons:
  - Elegancy
  - To help the patient to distinguish the product
  - To provide control during manufacturing
  - To help in hiding color differences between drug and additives

- Colorants are added to uncoated tablets either as an insoluble powder or dissolved in the granulation liquid in case of wet granulation.

- Care should be taken in wet granulation as migration of soluble color may occur during drying.

77

# Tablet excipients

**Colors**

- Many synthetic dyes were decertificated because of their carcinogenic effect.
- Natural vegetable colors are limited and they are often unstable.
- In the United States, FD&C numbers (which indicate that the FDA has approved the colorant for use in foods, drugs and cosmetics) are given to approved synthetic food dyes that do not exist in nature, while in the European Union, E numbers are used for all additives, both synthetic and natural, that are approved in food applications.
- Lakes are dyes that have been absorbed on a hydrous oxide and usually are employed as dry powders

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# Tablet excipients

**Flavors and sweeteners**

- Flavors are incorporated in a formula to give a tablet a better taste or to mask unpleasant taste.
- Flavors are often thermolabile and so cannot be added prior to operations involving heat.
- Flavors are usually used in effervescent, chewable tablets and other tablets intended to dissolve in the mouth.

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# Tablet testing

***Uniformity of content of active ingredient***

- In practice, small variations between individual preparations are accepted and the limits for this variation are defined as standards in the pharmacopoeias.
- Uniformity of dose is tested in two separate tests: uniformity of weight and uniformity of content of active ingredient.

80

# Tablet testing

***Uniformity of content of active ingredient***

- The test for uniformity of weight is carried out by collecting a sample of tablets, normally 20, from a batch and determining their individual weights.

- First: The average weight is calculated.
- Calculate average and SD
- The samples complies with the standards if the individual weights do not deviate from the mean more than is permitted in terms of percentage.
- Second: Check content uniformity

81

# Tablet testing

***Uniformity of content of active ingredient***

- The test for uniformity of drug content is carried out by collecting a sample of tablets , normally 10, and determination of the amount of drug in each.

- The average drug content is calculated and the content of the individual tablets should fall within a specific limits in terms of percentage deviation from mean.

82

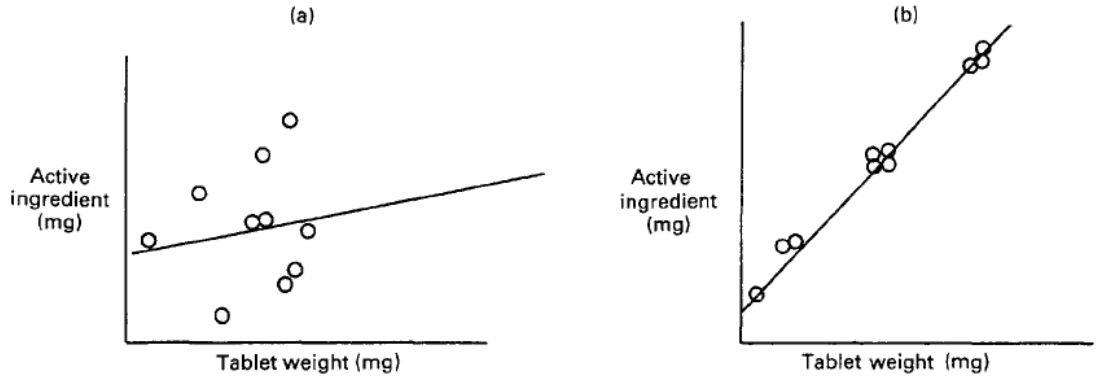



**Fig. 27.18** Correlation between amount of active ingredient and tablet weight for (a) a low dose (drug content 23% of tablet weight) and (b) a high dose (drug content 90% of tablet weight) tablet. (From Airth, J.M., Bray, D.F., and Radecka, C. (1967). J. Pharm. Sci., 56, 233–235.

83

# Tablet testing

## Solid oral drug products:

***d) Uniformity of dosage units:***

<905> UNIFORMITY OF DOSAGE UNITS (USP monograph)

**Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms**

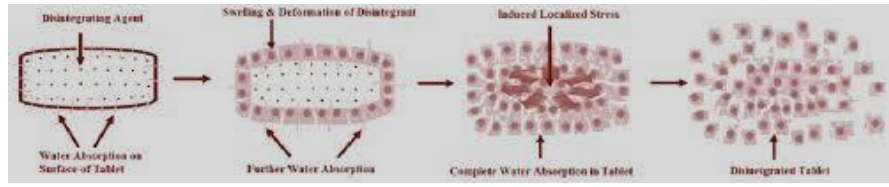
| Dosage Form | Type | Subtype | Dose & Ratio of Drug Substance: ≥25 mg and ≥25% | Dose & Ratio of Drug Substance: <25 mg or <25% |
|---|---|---|---|---|
| Tablets | Uncoated | | WV | CU |
| | Coated | Film | WV | CU |
| | | Others | CU | CU |
| Capsules | Hard | | WV | CU |
| | Soft | Suspension, emulsion, or gel | CU | CU |
| | | Solutions | WV | WV |
| Solids in single-unit containers | Single compo-nent | | WV | WV |
| | Multiple compo-nents | Solution freeze-dried in final con-tainer | WV | WV |
| | | Others | CU | CU |
| Solutions in unit-dose containers and into soft cap-sules | | | WV | WV |
| Others | | | CU | CU |

84

# Tablet testing

***Disintegration***

- The drug release process from immediate release tablets often includes a step at which the tablet disintegrates into smaller fragments.
- In order to assess this, disintegration test methods have been developed and examples are described as official standards in the pharmacopeias.
- The test is carried out by agitating, in a disintegration apparatus, a given number of tablets in an aqueous medium at a defined temperature.
- Disintegration test gives an idea but does not necessarily guarantee acceptable drug release.




85

**Fig. 31.19** Diagram of a disintegration instrument for the testing of tablet disintegration time.

86

# Tablet testing

***Disintegration***

- The disintegration apparatus consists normally of six tubes open at the upper end and closed by a screen at the lower.

- One tablet is placed in each and normally a plastic disc is placed on it. Then the tubes are placed in a water bath and raised and lowered at certain rate in the water in a way that the screen remains below the surface of water.

- The time to reach the end point (at which all visible parts have been eliminated from all the tubes) is recorded and the preparation complies with the test if this time is below a given limit.

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# Tablet testing

***Dissolution test***

- Dissolution test is the most important way to study the release of a drug from a solid dosage form under in vitro conditions.

- During the dissolution study the cumulative amount of drug that passes into solution is studied as a function of time.

- Aims of dissolution studies:
  - To indicate the performance of a formulation under in vivo conditions.
  - To evaluate the effect of formulation and process variables on the bioavailability.
  - To ensure that preparations comply with product specifications.

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# Tablet testing

***Dissolution test***

- Dissolution is accomplished by locating the tablet in a chamber containing a flowing dissolution medium. The factors affecting the dissolution process (such as composition and temperature of dissolution medium, flow or agitation rate) must be standardized.

- Normally, the concentration of the drug substance in the bulk of the dissolution medium shall not exceed 10 % of the solubility of the drug to be near to sink conditions.

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# Tablet testing

***Dissolution test***

- The amount of drug dissolved is analyzed once or at a series of consecutive times.

- The composition and pH of the dissolution medium may vary between different test situations.

- A number of official and nonofficial methods exist for dissolution testing, which can be applied for both drug substances and formulated preparations.

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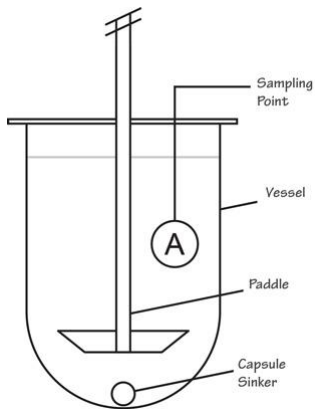
# Tablet testing

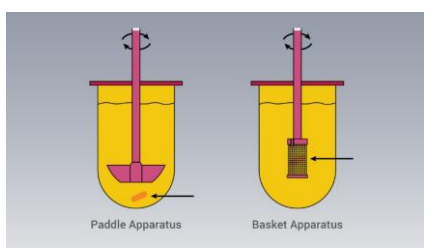
***Dissolution test***

Stirred vessel methods

- The most important stirred vessel methods are the *rotating-basket* and the *paddle* methods.
- Both use the same type of vessel, which is filled with certain volume of a dissolution medium of certain temperature.
- In the paddle method, the tablet is placed in the vessel and the dissolution medium is agitated by rotating the paddle.
- In the basket method, the tablet is placed in a small basket formed from a screen, which is then inserted in the dissolution medium and rotated.

91

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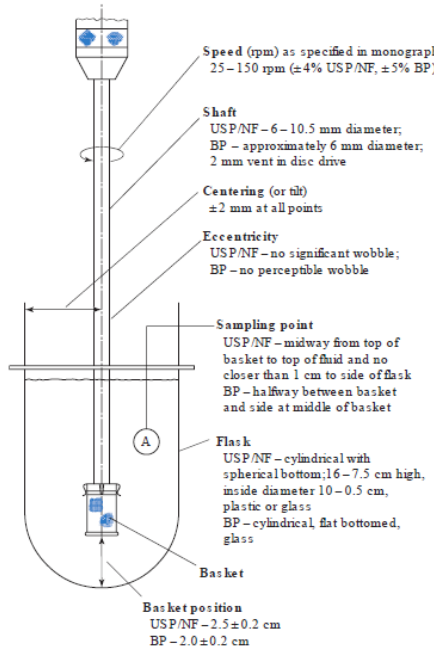


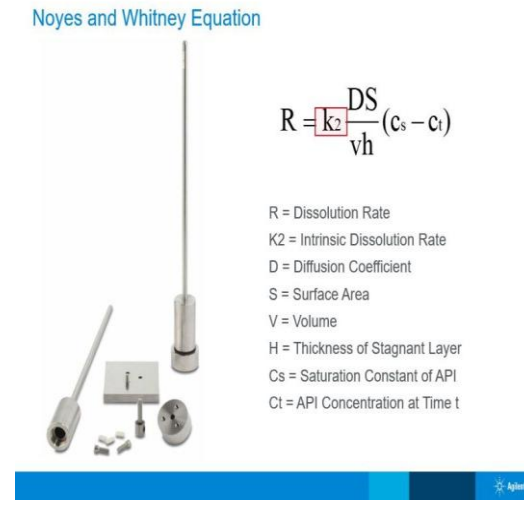


**Fig. 30.20** • Diagram of a dissolution instrument based on the rotating-basket method for the testing of tablet dissolution rate. (Courtesy of Banakar, 1992, with permission.)

93

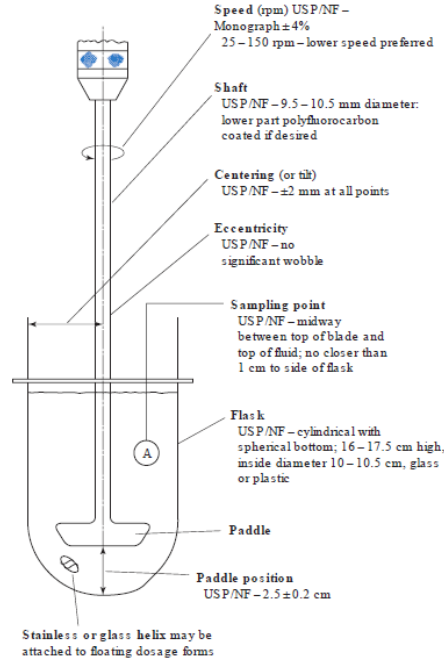


**Fig. 30.21** • Diagram of a dissolution instrument based on the rotating paddle method for the testing of tablet dissolution rate. (Courtesy of Banakar, 1992, with permission.)

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# Tablet testing

***Dissolution test***

Continuous flow method

- In the Continuous flow method the preparation is held within a flow cell, through which the dissolution medium is pumped at a controlled rate from a large reservoir.

- The liquid which has passed the flow cell is collected for analysis of drug content.

- Advantages
  - Maintain sink conditions throughout the experiment
  - Avoid floating of the preparation.

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# Tablet testing

***Mechanical strength***

- An acceptable tablet must remain intact during handling between production and administration.

- An integrated part of the formulation and production of tablets is the assessing of their mechanical strength.

- Aims of mechanical strength testing:
  - To assess the effect of formulation and production variables on their resistance towards fracturing and attrition.
  - To characterize the fundamental mechanical properties of materials used in tablet formulation.
  - To control the quality of tablets during production (in-process control).

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# Tablet testing

***Mechanical strength***

- The most commonly used methods for strength testing are the resistance to abrasion test (friability test) and the crushing strength (fracture resistance).

<u>Attrition- resistance methods</u>

- The most common method to determine attrition (abrasion) resistance involves the rotation of tablets in a cylinder followed by the determination of weight loss after a given number of rotations.

- Normally, weight loss of less than 1% of tablet weight is required.

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# Tablet testing

***Mechanical strength***

Crushing (Fracture) resistance methods

- In this test, the tablet is usually placed against a platen and the load is applied along its diameter by a movable platen. The force needed to fracture the tablet is recorded.

- The force needed to fracture a tablet depends on the tablets dimensions.

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# Tablet testing

***Mechanical strength***

Crushing (Fracture) resistance methods

- An ideal test, however, should allow comparison of tablets of different sizes or even shapes.
- This can be accomplished by assessing the strength of the tablet, i.e. the force needed to fracture the tablet per unit fracture area.
- For a cylindrical flat-faced tablet the tensile strength can be calculated by the following Eqn provided that the tablet fails in a tensile fracture mode:

$$\sigma_t = 2F/\pi Dt$$

- F: the force needed to fracture the tablet, D and t are the diameter and thickness of tablet

100

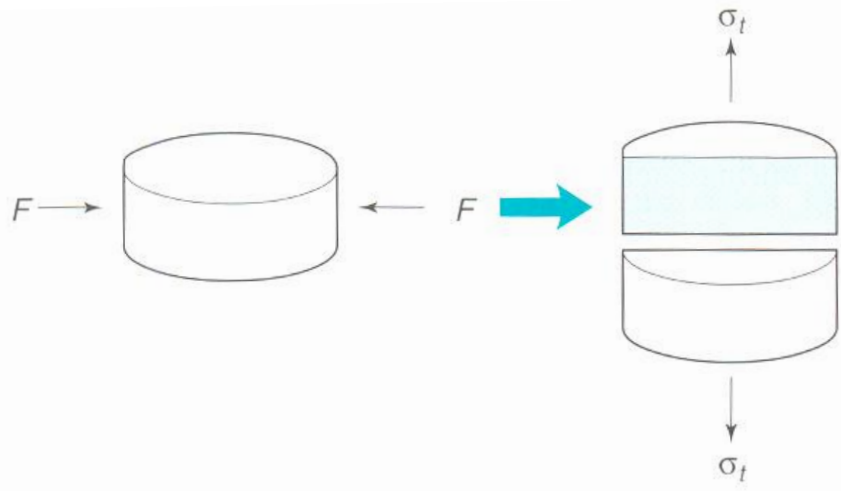



**Fig. 31.22** Illustration of the tensile failure of a tablet during diametral compression.

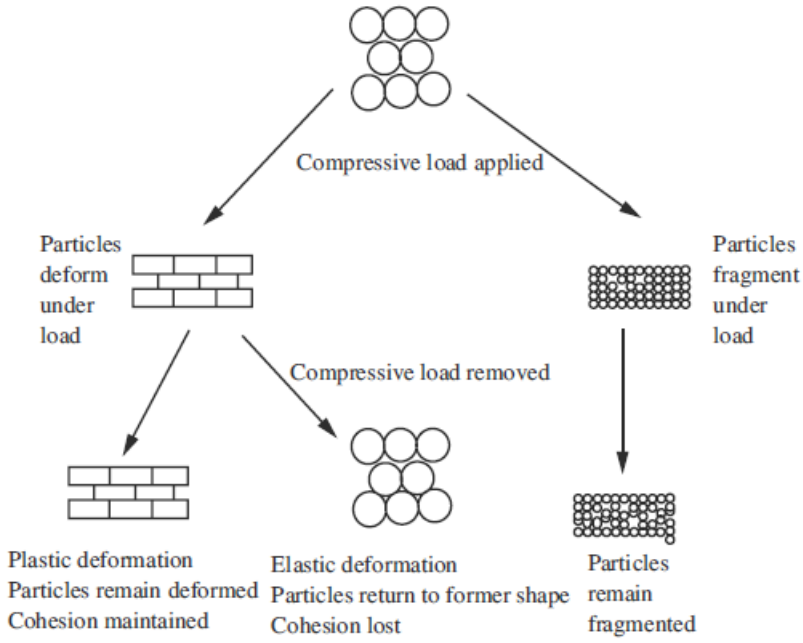
101

## Fundamental aspects of compression of powders

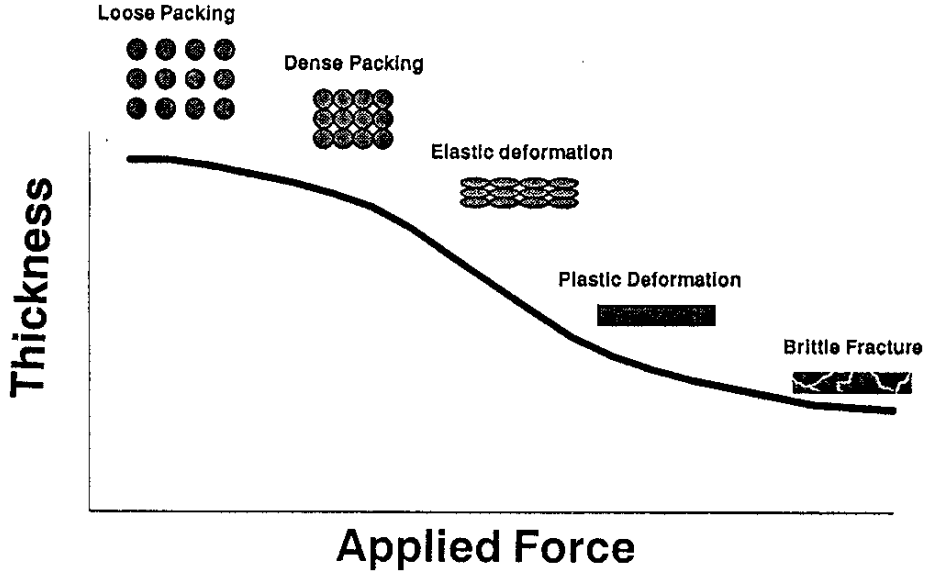
**Compressibility**: the propensity of a powder to reduce in volume while loaded.

- The compression of a powder bed is started by rearrangement of particles in the die, resulting in reduced porosity (closer packing).
- At a certain load the reduced space and friction between particles prevent further movement of particles.
- The subsequent decrease in tablet volume is therefore associated with changes in the dimensions of particles (fragmentation or deformation).
  - Elastic deformation: reversible on removal of the load
  - Plastic deformation: Irreversible
  - Fragmentation: particles are fractured to smaller size
- Sometimes the degree of deformation is time-dependent and is referred to as viscous deformation and viscoelastic deformation.

102


Compressive load applied
Particles deform under load
Particles fragment under load
Compressive load removed
Plastic deformation
Particles remain deformed
Cohesion maintained
Elastic deformation
Particles return to former shape
Cohesion lost
Particles remain fragmented

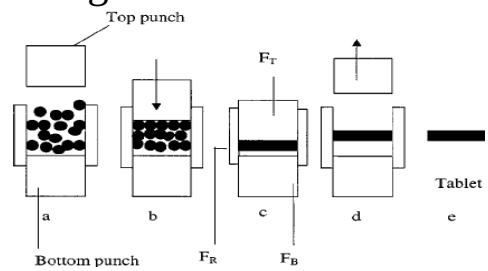
103


Loose Packing
Dense Packing
Elastic deformation
Plastic Deformation
Brittle Fracture
Thickness
Applied Force

104

## Fundamental aspects of compression of granules

- For granules processes involved in their compaction can be classified into two groups:
  - Physical changes in the granules
  - Physical changes in the primary particles from which the granules are formed
- At low compression forces the reduction in volume of the bed of granules can occur by a rearrangement within the die.




105

## Fundamental aspects of compression of granules

- With increased loading the granules can:
  - Deform elastically
  - Deform plastically
  - Densify (i.e. reduce their intragranular porosity)
  - Broken into smaller units by different mechanisms
    - Primary particles might be removed from the surface of granules when they slide against each other or against the die wall (granule attrition).
    - Granules can fracture into a number of smaller ones (granule fragmentation)

106

## Fundamental aspects of compaction of powders

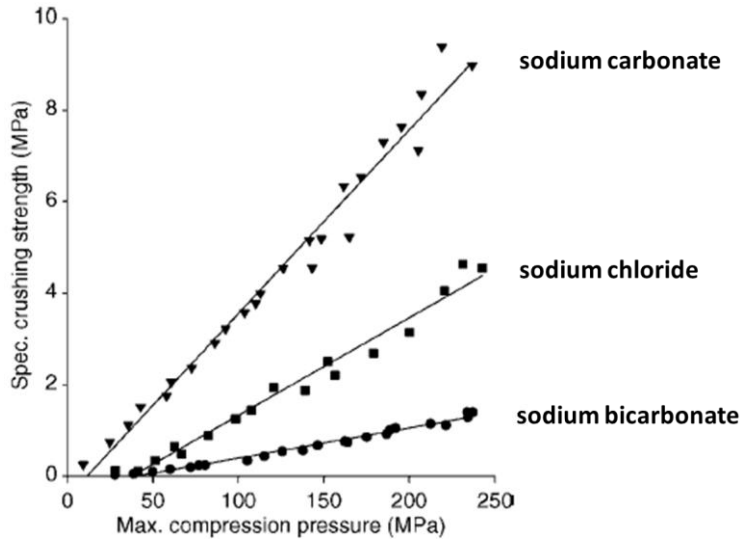
**Compactability**: The propensity of powder to form a coherent tablet.

- Factors affecting compactability could be related to material and formulation or processing conditions or environmental conditions.

- In practice, the most common way to assess powder compactability is to study the effect of compaction pressure on the strength of resulting tablet.

107

## Fundamental aspects of compaction of powders




108

## Fundamental aspects of compaction of powders

- Mechanisms of bonding in tablets include:
  - Solid bridges
  - Bonding by liquid (surface tension forces)
  - Binder bridges
  - Intermolecular and electrostatic bonding
  - Mechanical interlocking

109

## Relationships between material properties and tablet strength

**Role of moisture**

- Small percentage of moisture in tablet formulas can dramatically affect the behavior of these feed materials and that of finished products.
- Moisture is also important in wet granulation process.
- Water may be squeezed out during compaction and the expelled moisture may act as lubricant at the die wall but it can also cause sticking to the punch faces.

110

# Relationships between material properties and tablet strength

**The compaction of granules**

- The compactability of granules is affected by:
  - the mechanical properties of the primary components (i.e. particles before granulation)
  - the design of the granulation process

- Granules may deform or fragment into smaller components during compression.

111

# Relationships between material properties and tablet strength

**Post compaction tablet strength changes**

- The mechanical strength of powder can change with time.

- The underlying mechanisms for such change are complex.

112

# Problems and difficulties in tableting

- A number of technical problems can arise during the tabletting procedure.

- Such problems are related to:
  - the properties of the powder intended to be formed into tablets, and
  - the design and conditions of the press.

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# Problems and difficulties in tableting

## Capping and lamination

- **Capping**: Partial or complete separation of the top or bottom of a tablet from the main body
- **Lamination**: The separation of the tablet into two or more distinct layers
- Usually these problems appear immediately after compression but may occur after hours or days.
- **Causes of capping and lamination:**
  - Rapid speed of compression: air is not given enough time to escape.
  - Presence of excessive fines
  - Over drying of granules
  - Incorrect setup at the press

114

Capping

Lamination

115

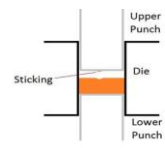
# Problems and difficulties in tableting

## Picking and sticking

- Picking: The removal of the surface material of tablet by sticking to punches.
- Picking is of particular concern in case of engraved punches, especially with letters of small enclosed areas like “B” and “A”, which are difficult to manufacture cleanly.
- Sticking: The adhesion of tablet material to the die walls.
- Sticking can cause chipping of edges of tablet and does not allow free movement of lower punch (may cause machine damages).

Sticking

Picking




Sticking to punch and picking from tablet

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# Problems and difficulties in tableting


## Picking and sticking

- Solving of picking and sticking:
  - Engraved letters should be designed as large as possible
  - Addition of lubricants and ant-adherents.
  - Additional binder or change of binder may may the granules more cohesive and therefore less adhesive to the punches and die.
  - Low melting materials (such as stearic acid and PEG) which may soften from the heat of compression causing sticking may be replaced by higher melting point additives.
  - High moisture content may cause sticking and this is solved by further drying

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# Problems and difficulties in tableting

## Mottling

- It is unequal distribution of color on tablets

- Reasons:
  - Difference in color between drug and excipients
  - Colored degradation products
  - Migration of color during drying of granules (May be solved by changing solvent system, changing the binder system, reducing temperature or grinding granules to smaller particle size).
  - In direct compression formulations, uneven distribution of dye or large particle size may cause mottling

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# Problems and difficulties in tableting

## Weight variation

- Reasons
  - bad flowability of powder
  - Variation in size and size distribution of granules
  - Poor mixing with glidants and lubricants.
  - Punch variation (lower punches are unequal in lengths)

## Hardness variation

- It has the same causes as weight variation because hardness depends on the weight of material forming the tablet

119

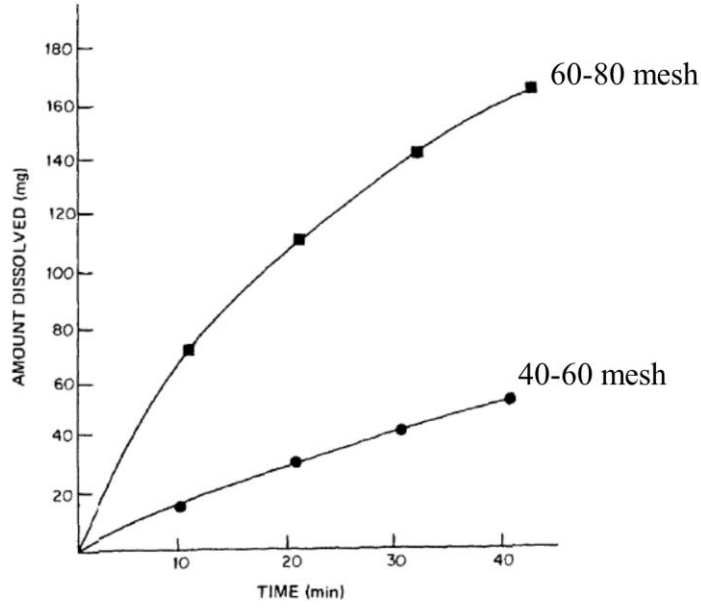



Figure 2 Effect of granule size on the dissolution rate of salicylic acid contained in compressed tablets. Key: ● 40- to 60-mesh granules; ■ 60- to 80-mesh granules.

120

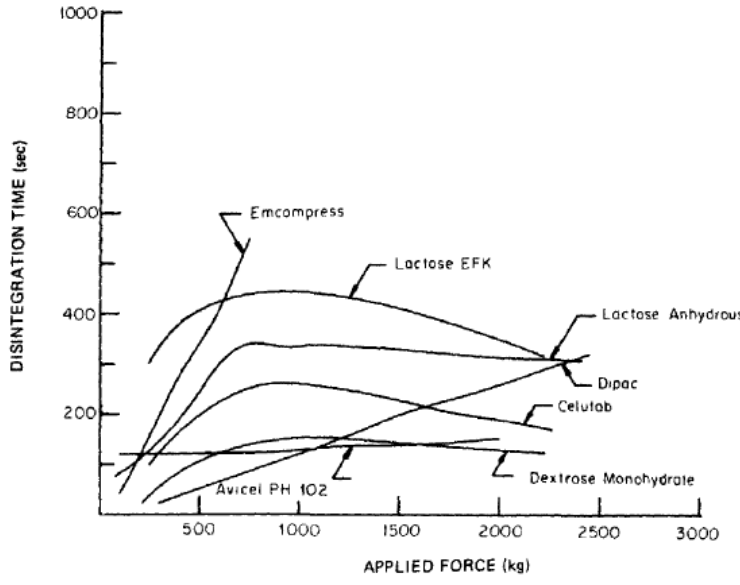



**Figure 4** Disintegration time versus applied force for compacts of various materials.

121

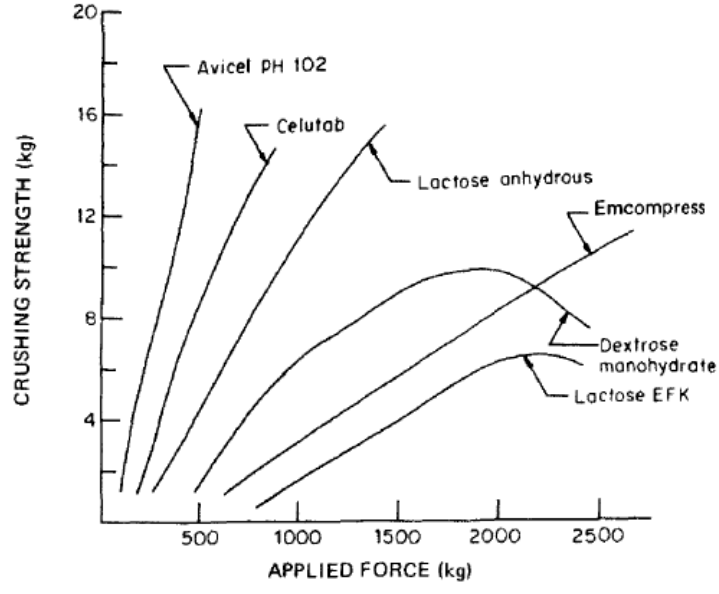



**Figure 5** Crushing strength versus applied force for compacts of various materials.

122

## Effect of diluent and diluent proportions

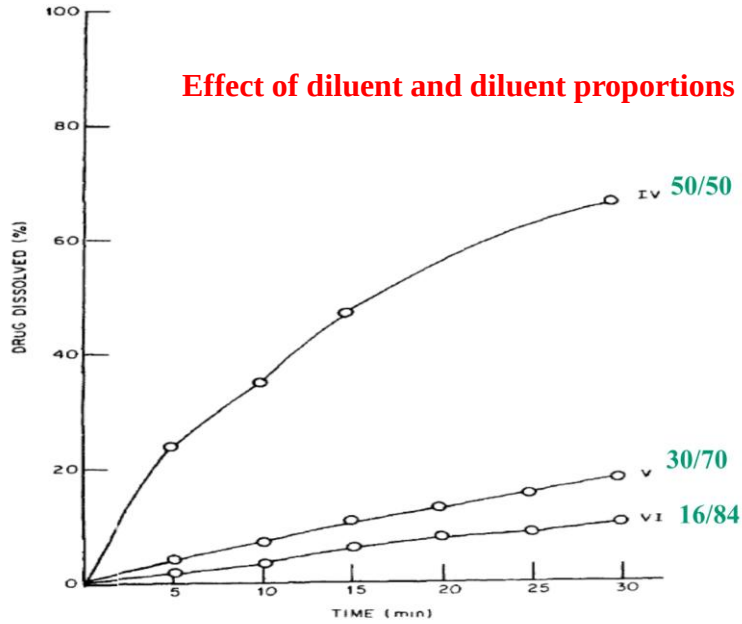
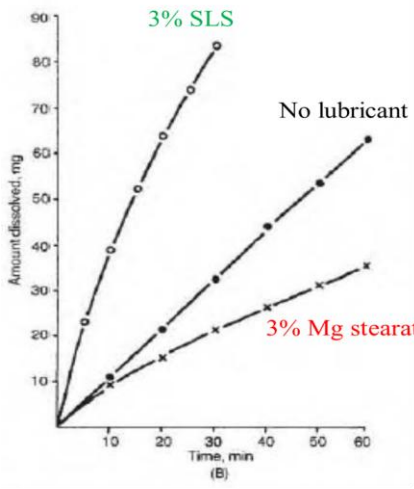
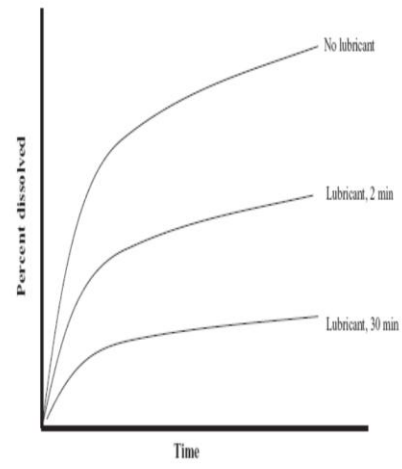



**Figure 7** Drug release of an insoluble drug from direct-compression diluents diluents (see text). IV = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 50:50. V = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 30:70. VI = microcrystalline cellulose N.F./dibasic calcium phosphate N.F., 16:84.

123




Effect of **lubricant** type on dissolution of salicylic acid from compressed tablets




Effect of **lubricant** and its mixing time on dissolution rate of drugs

124