By:
Toleen
Alqasimi

* Demonstration example flowchart of tableting process

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).

no absorption

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

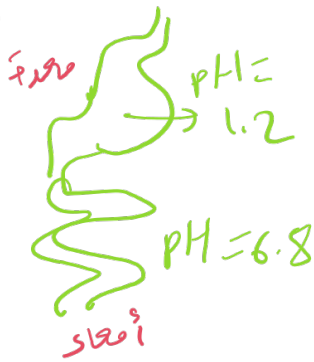
Tablets

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.



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.

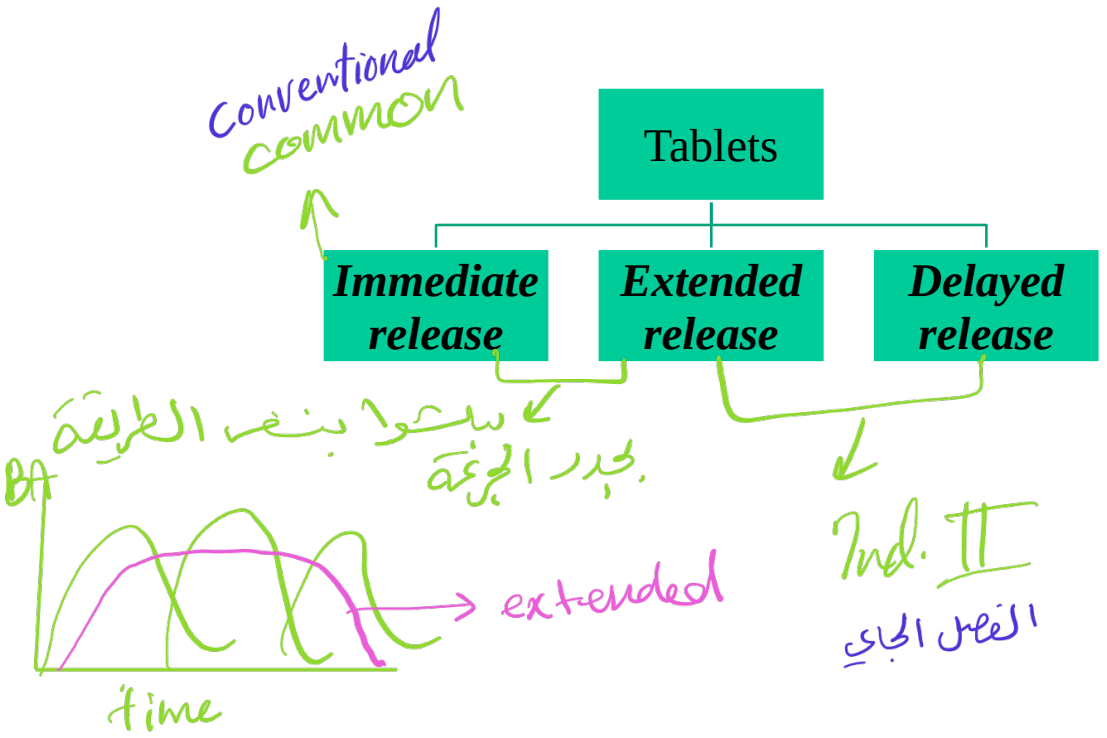
Tablets

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.

Tablet Types



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.

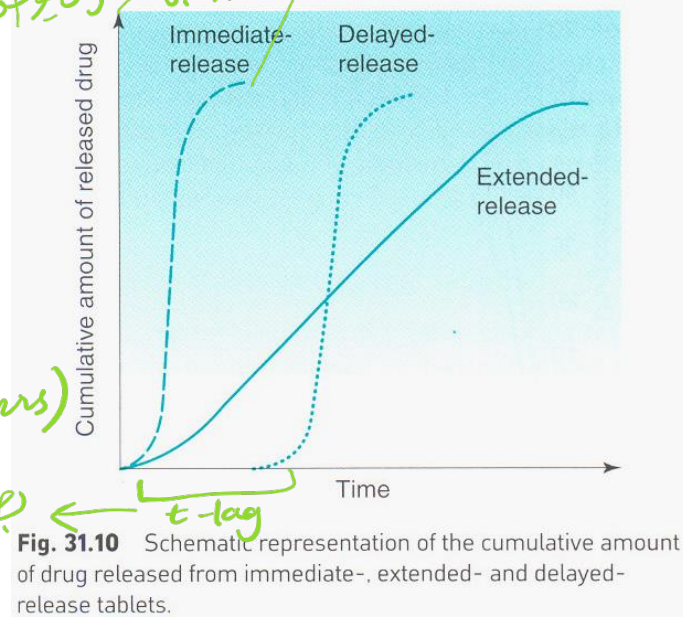


Fig. 31.10 Schematic representation of the cumulative amount of drug released from immediate-, extended- and delayed-release tablets.

من هون بتبلش خديرهات الفاينل ؛ سلايد 9-38

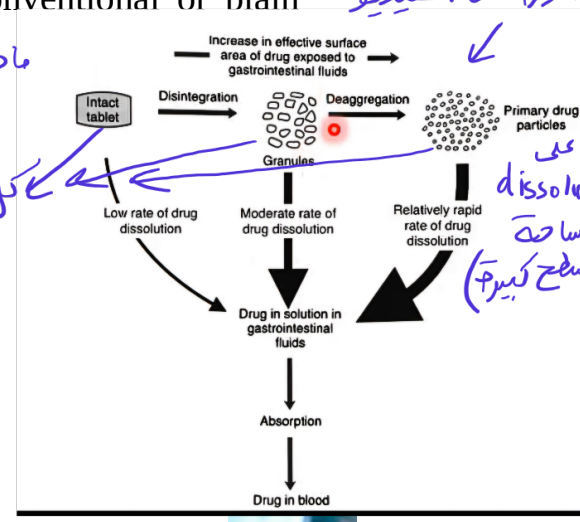
Immediate release tablets

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.



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.

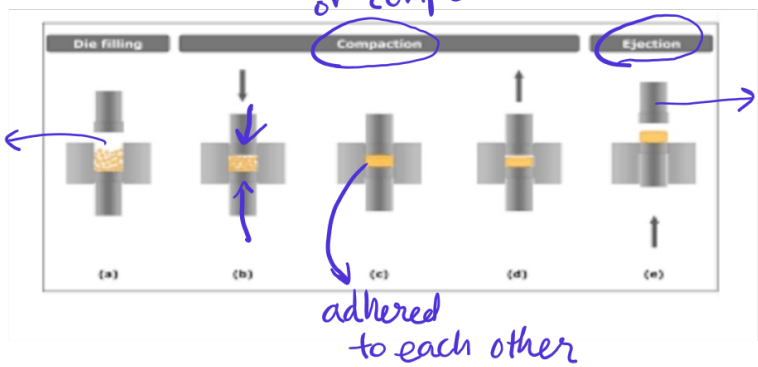
- During the preparation of multilayer tablets the die is filled in two or three consecutive steps with different granules from separate feed stations.

- Disintegrating tablets also can be coated by different methods.

first feed → slight compression
second feed → another compression
last compression → another compression (the strongest)

3 layers

2 layers



or compression

punch

die : القالب أو الفراغ اللي بتتعبى فيه الـ tablet

adhered to each other

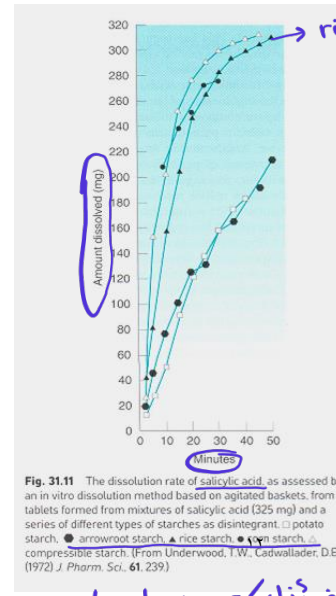
Immediate release tablets

Disintegrating tablets

- The disintegration time of the tablet can be markedly affected by:
  1 – the choice of excipients, especially disintegrant
  2 – Granulation procedure wet/dry
  3 – Mixing conditions during the addition of lubricants and antiadherents
  4 – The applied punch force

step آخر قبل compression

قوة الضغط من الـ punch (upper or lower or both)



rice starch

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.)

تعرض الفكرة منها في أنواع كتير من starch لها حسب نوعه ممكن يكون binder/disintegrant/filler وفي الوسيطة كل نوع أعطى dissolution rate مختلف

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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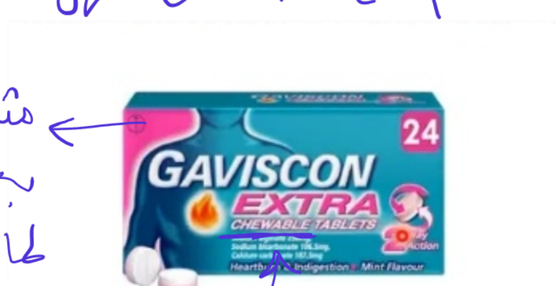
Immediate release tablets

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 خاصة للأطفال
- Mannitol and sorbitol are common examples of fillers.

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Immediate release tablets

CO_2 ↙ له أثر في زيادة absorption

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.

لازم المريض يشربه while bubbling ما يستنى الـ bubbles تروح

- 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.

مصادر CO_2

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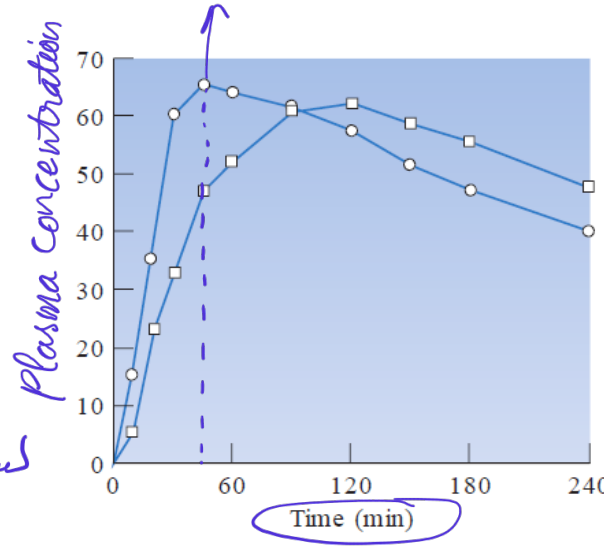

Fig. 30.12 • Concentration of salicylates in plasma after administration of acetylsalicylic acid tablets (1 g). Circles, effervescent tablet; squares, conventional tablet. (Courtesy of Ekenved et al, 1975, with permission.)

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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).

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.

Immediate release tablets

Lozenges

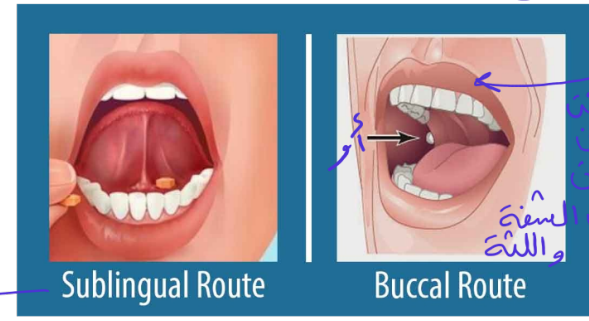
- They do not contain disintegrants.
- The filler and binder should be water soluble.
- They often contain color, flavor and excipients which contribute to a pleasant taste or feeling during tablet dissolution.
- Common examples of fillers are glucose, sorbitol and mannitol.
- Common binder is gelatin.

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
  1 – More rapid onset of action (vasodilators)
  2 – Avoidance of gastric environment which cause decomposition for certain steroids and hormones.
  3 – Avoidance of first pass metabolism
  4 – Avoidance of nausea produced by swallowing certain drugs (e.g. methyltestosterone)



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)
  - Fast disintegrating tablets (FDT)
  - Orally disintegrating tablets
  - Rapid disintegrating tablets (RDT)
  - Oro dispersible tablets (ODT)
  - Quick dissolving tablets

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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

٢٤

* all mucosal tissues have aquous media

for easy application

Immediate release tables

يتم تحضيرهم عن طريق compression

Vaginal tablets

مشابه لتبع ال oral tablets

- Vaginal tablets, also called *vaginal inserts*, are uncoated, bullet-shaped or ovoid tablets inserted into the vagina for local effects. بيضاوي
- normal vaginal pH ranges **between 3.8 and 5.0** (acidic)
- They are prepared by compression and shaped to fit snugly on plastic inserter devices that accompany the product. (applicator)
- 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

mostly used for fungal infections

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Immediate release tables

history of tablets

هدول النوعين مش موجودين حاليًا لكن حفظ

Dispensing tablets XXX

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

بتكون تابلت كبيرة بتسمها الصيدلاني بوزن معين وبعطيها للمريض

Hypodermic tablets XXX

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

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بذوبوا في الماء بعدين بحملوه filtration ، وبنعطى injection

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.

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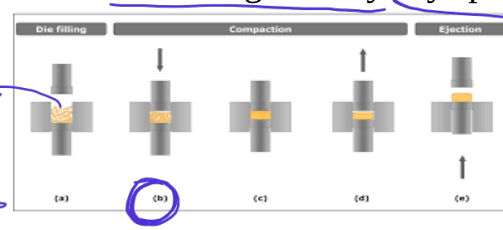
Tablet Manufacturing

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.



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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.

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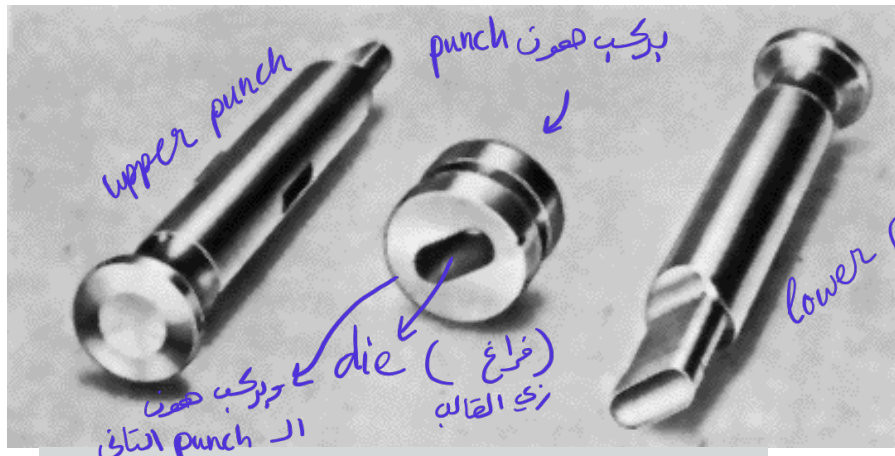

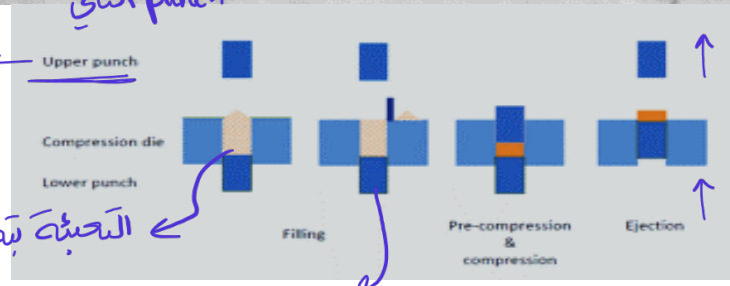

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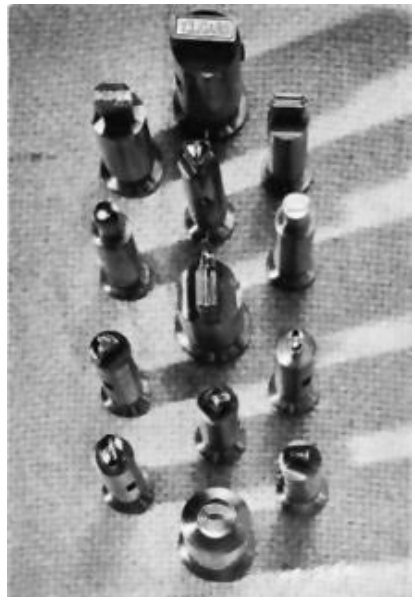
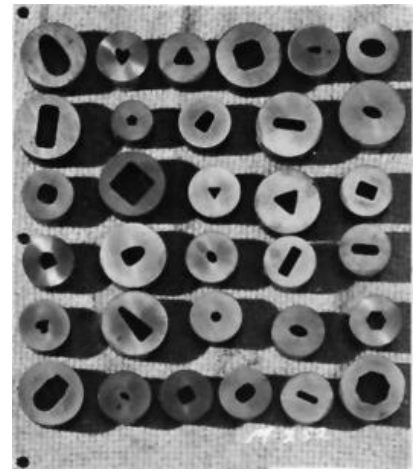
punch ← dies وحسب شكله بكون شكل ال





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نوعين حسب حجم ال batch

Tablet presses

① ***single punch press (eccentric press)***

زي مبدأ ماكنة الخياطة الجزء العلوي بطلع وبنزل

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

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

small scale

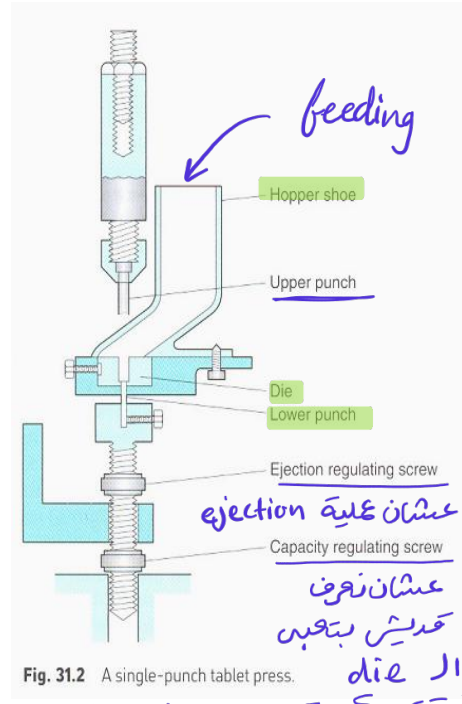


Fig. 31.2 A single-punch tablet press.

عشان عملية ejection

عشان نعرف قديش بتعبي ال die

(بتتحكم قديش رح ينزل الlower punch)

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.

أو برتفع كمان وقت الكبس ← وقت الكبس

large scale وهو نفس المبدأ

how much filling? حسب
- die size
- lower punch distance كم الـ اللي فوقه (كلما نزلته أكتر بقدر أعبيه أكتر)

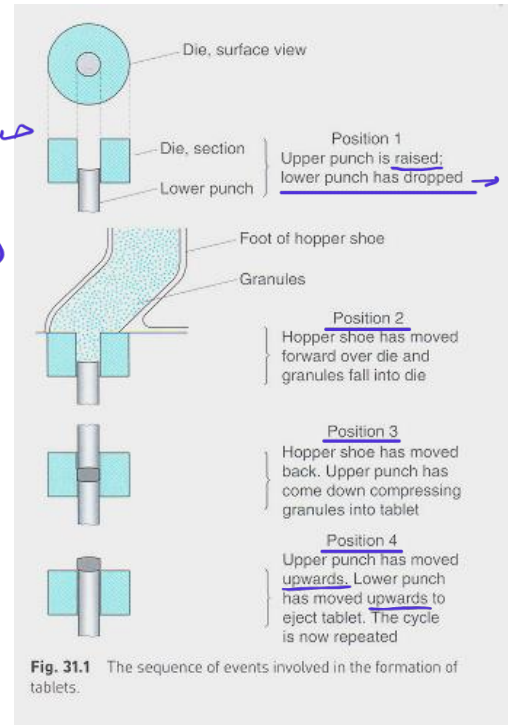
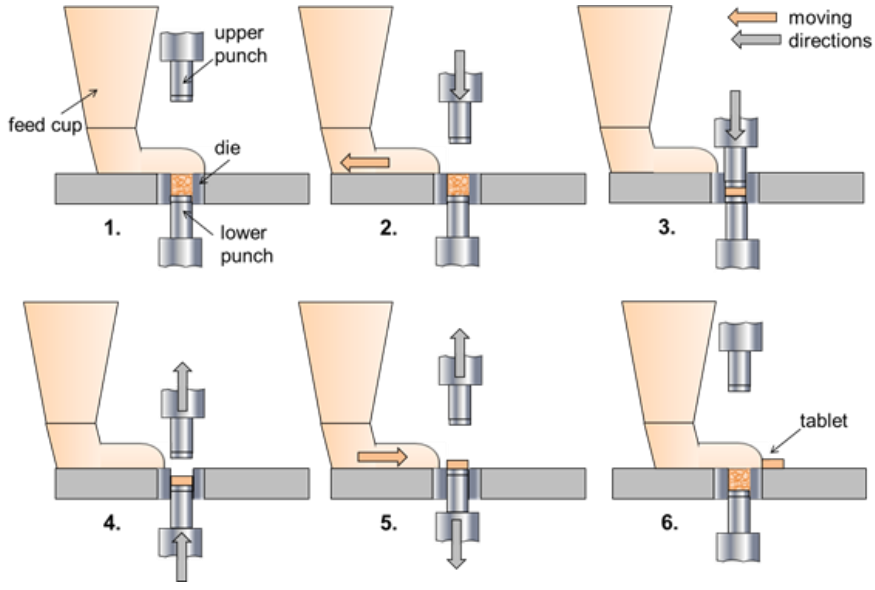


Fig. 31.1 The sequence of events involved in the formation of tablets.

عشان نعبي بودرة فوقه

* زي اللي شفناها في اللاب



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Tablet presses

② ***Rotary press (multistation press)***

نفس الطريقة بس عندنا many dies (12 or more & their punches)

- 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. production scale (large scale)
- Number of dies and sets of punches can vary considerably from 3 to 60.

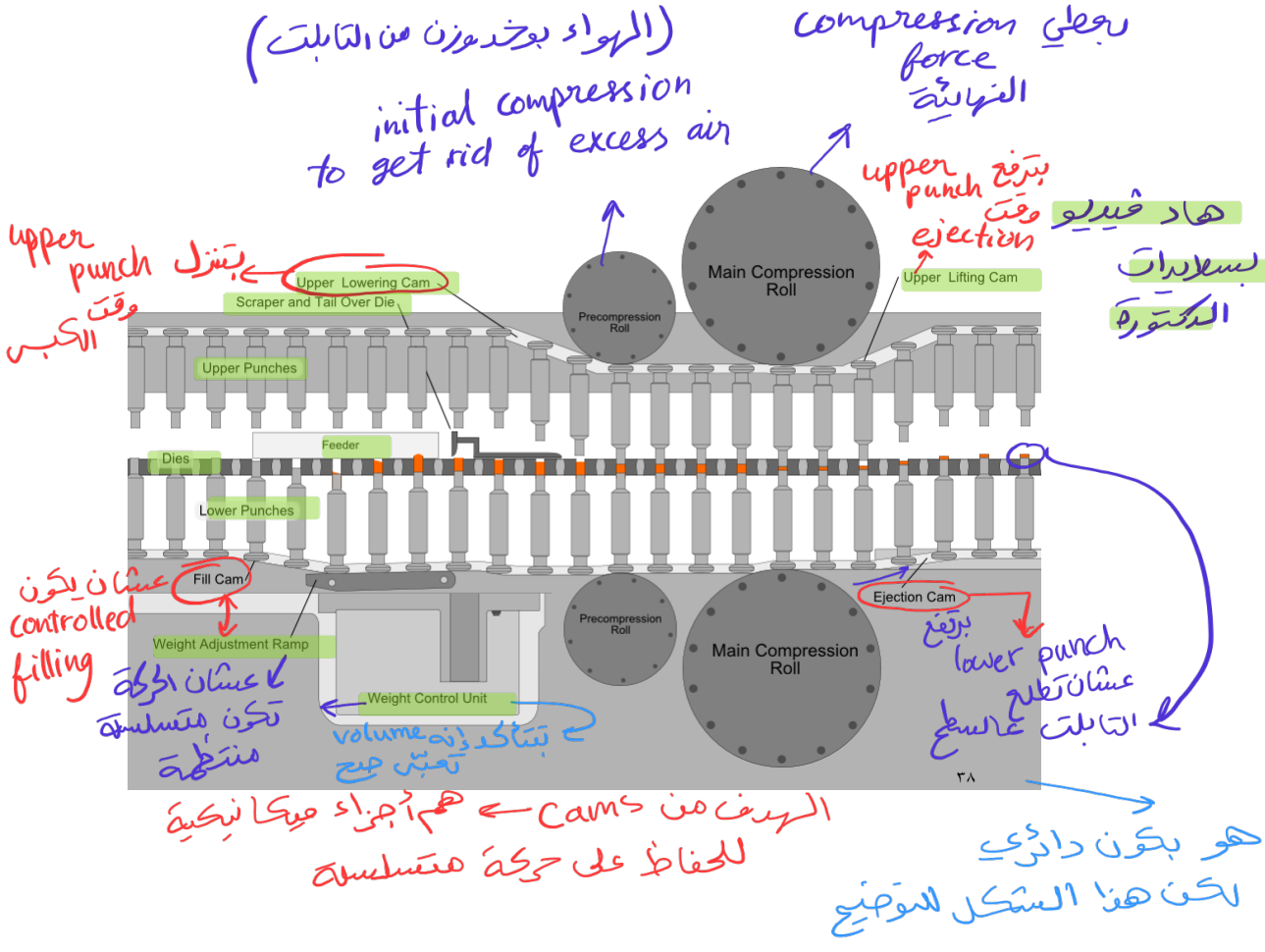
٣٦

Tablet presses

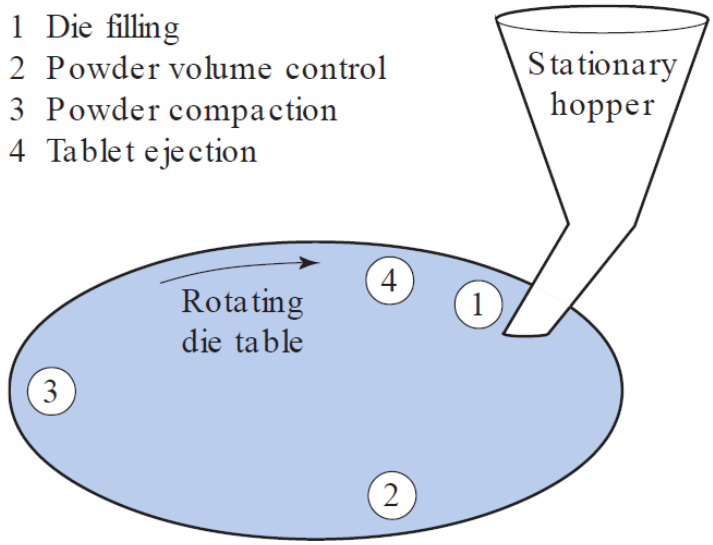
Rotary press (multistation press)

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.



* الفيديو الثاني (سلايدات 39-70)



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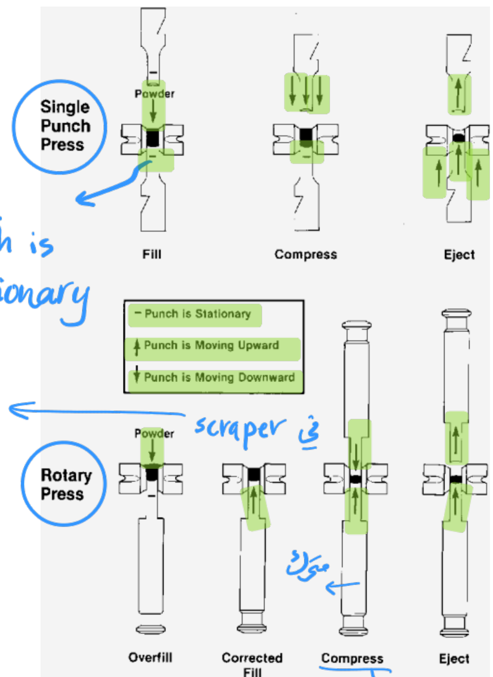

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Tablet presses

<u>Computerized hydraulic press (simulators)</u>

- 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.

٤٢

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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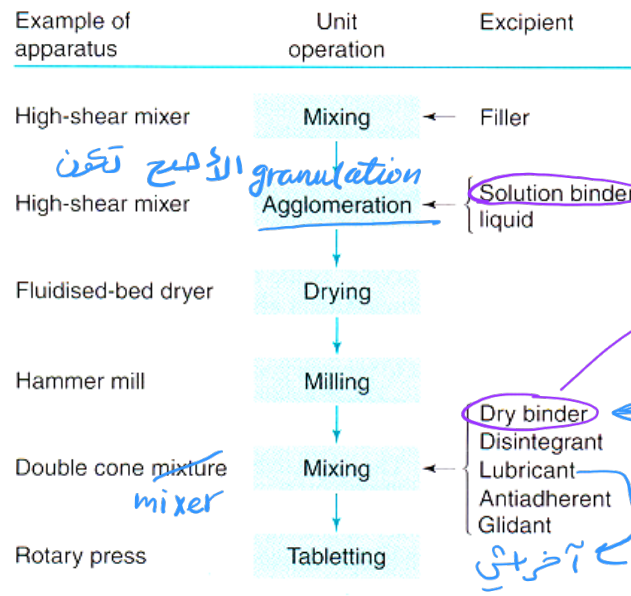

Fig. 31.5 Overview of the sequence of unit operations used in the production of tablets with precompaction treatment by granulation.

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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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have adhesiveness & cohesiveness properties

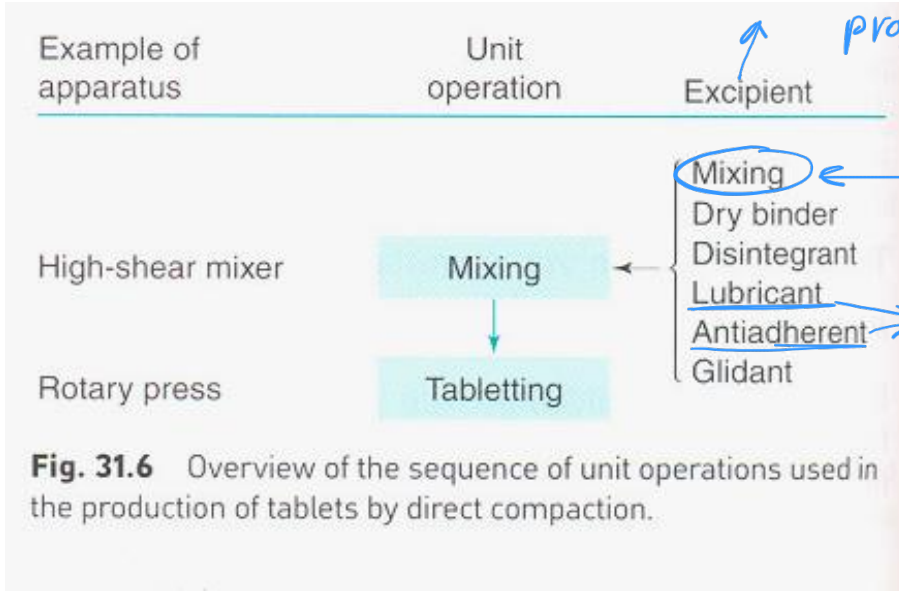

Fig. 31.6 Overview of the sequence of unit operations used in the production of tablets by direct compaction.

عالأغلب بيتم على مراحل

آخر اشي بنضيفهم

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Tablet production by direct compaction

granules زي كأني بحكي عن granules بس ما في

Limitations:

1. Relatively large particle size must be used to have acceptable flowability and bulk density which:
   - may affect degree of mixing
   - Segregation may occur.

حتى granules أفضل عشان good mixing أحصل على

2. It needs specially designed fillers which are usually more expensive than traditional ones.

يكون اسمه direct compression filler

ex: panadol 500mg, antacids

3. If the drug is the major component the application of direct compression depends mainly on the properties of drug.

٤٨

potent drug أحيانا ما بيكون بتكون كمية قليلة ضريبة excipients مواصفات ال

particle size
flowability
bulk density

ما عادت تستخدم حالياً

Molded Tablets

- Molded tablets are usually prepared from soluble ingredients so that the tablets are completely and rapidly soluble.

شرط

- After the excipient is blended with the drug, the powder mix is dampened with solutions containing high percentages of alcohol.

wetting

زي العجينة

بنضغطهم مش بنكبسهم

- The dampened powders are pressed into molds, removed, and allowed to dry.

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mold

suppositories زي مبدأ عمل

بنظغطهم وبنشغرهم wet granules ← ممكن تكون

compressable ← ممكن تكون

granulation بدون

بس بنظلها mold من اد

٥٠

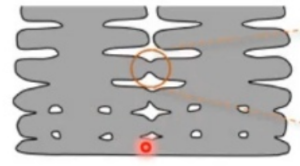
* بنعرف إنه خصائص ال solid بتختلف حسب ال solvent

Molded Tablets

- Solidification depends upon crystal bridges built up during the subsequent drying process and not upon the compaction force.

evaporation خلال عملية ← فبتتكون وبصير في adhesiveness

- They can be prepared in small or large scale.
- They are not common nowadays.



bridgeng

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الأسماء الموجودة في كل نوع excipient معلومة

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.

not dose بتحكي عن كتلة الحبة ككل

- They are not necessary if the dose of drug per tablet is high.

ex: amoclan 1g
paracetamol 500mg ← أغلب الحبة active ingredient

diluent مادة مالية أو غير موجودة

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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

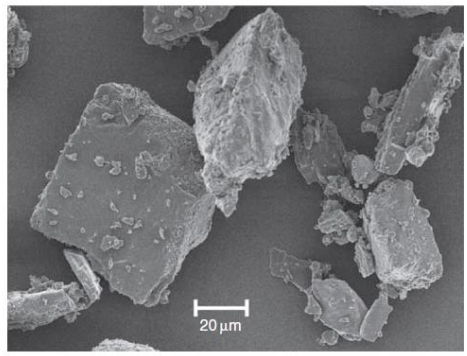
Tablet excipients

Examples on diluents:

1 • Lactose

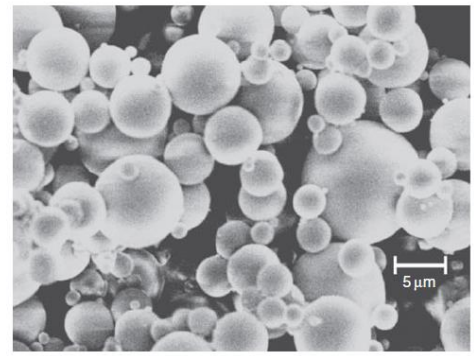
– The most commonly used because of good properties (dissolves readily in water, has a pleasant taste, non-reactive, non-hygroscopic, has good compactability)
– Its main limitation is that some people have intolerance to lactose.
– In the solid state, lactose appears as various isomeric forms, depending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

A • monohydrate
B • anhydrous
C • amorphous (spray dried lactose)



crystalline lactose

normal crystallization process



spray-dried lactose

amorphous
better flowability

spheres

Tablet excipients

Examples on diluents:

2. **Celluloses** → Cellulose derivatives *

لأنه cellulose نفسه لا يستعمل

- 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®).

مثلاً لو دواء زي aspirin بصيره hydrolysis في الماء

بتكون هاي أنواع الـ cellulose

incompatible مع

(MCC) cellulose معدّل كيميائياً

حفظ

* Lactose & cellulose derivatives ⇒ organic

Tablet excipients

inorganic

3 • 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

organic?

4 • Sucrose (serves also as binder)

– Sucrose-based tablet diluent-binders are available under a number of trade names which include:

1. • Sugartab® (90 to 93% sucrose plus 7 to 10% invert sugar).
2. • Di-Pac® (97% sucrose plus 3% modified dextrins),
3. • 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)

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Tablet excipients

2 excipients or more بعطوني خصائص معينة

- ***Coprocessed Excipient Products*:**
  1. – Ludipress® (93.4% a-lactose monohydrate, 3.2% polyvinylpyrrolidone and 3.4% crospovidone) filler + binder
  2. – Cellactose 80™ contains α-lactose monohydrate and cellulose powder
  3. – 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. → contains silica → has anti adherant properties
  4. – MCC microcrystalline Cellulose

* الأرقام برای السلاید مش مطلوبة *

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Tablet excipients

نوع excipients جديد

Binders (Adhesives)

- A binder is added to ensure that granules and tablets can be formed with the required mechanical strength → زي لما نطلع الحبة من tableting machine لطلعوا كتير حبات مع بعض بعدين coating shipping إلخ
- 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)

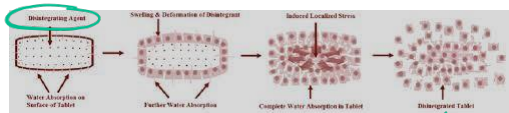
- Examples:
  - Common traditional solution binders (starch, sucrose and gelatin)
  - Acacia, sodium alginate, tragacanth.
  - Synthetic polymers used as solution binders (Polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC) and methyl cellulose, polyethylene glycol)
  - Dry binders include: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

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.



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.

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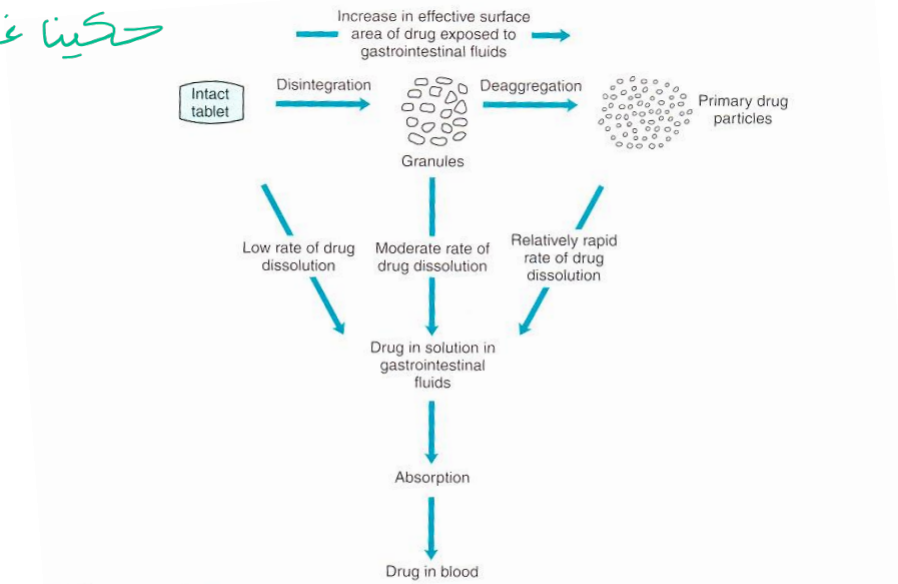

Fig. 31.7 Mechanistic representation of the drug release process from a tablet by disintegration and dissolution. (From Wells, J.I., Rubinstein, M.W. (1976) *Pharm. J.*, **217**, 629.)

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Tablet excipients

Disintegrants → indirectly affects dissolution

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).

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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)

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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

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Tablet excipients

Lubricants

- These are materials intended to reduce friction during tablet 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.

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