Granulation

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Granulation

Granulation is the process in which the primary powder particles are made to adhere to form larger, multiparticulate entities called granules.

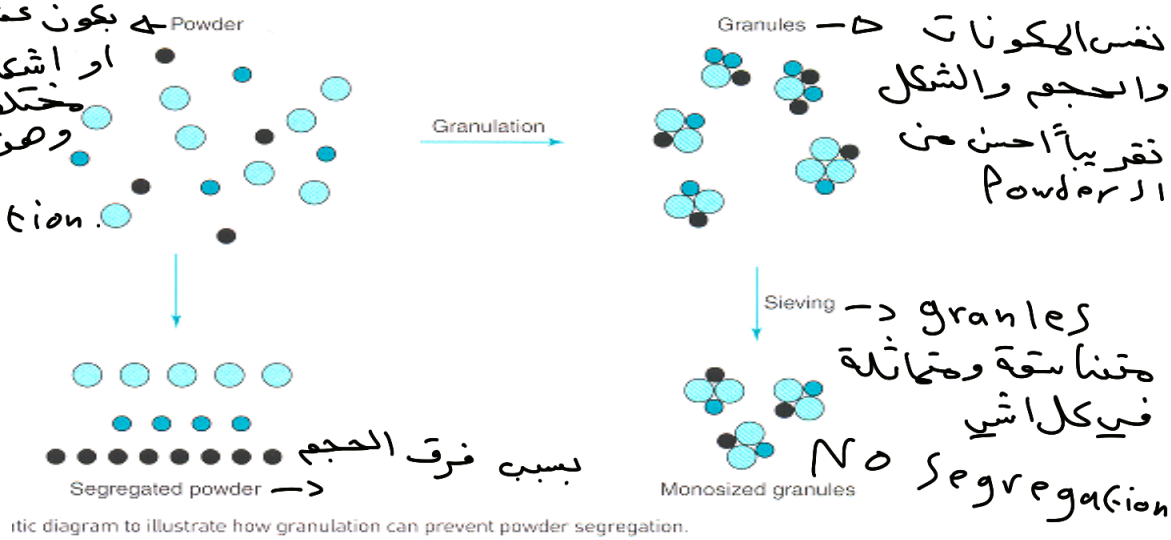
Granules are either used in their own right as a dosage form or as an intermediate product in the production of tablets or capsules.

Granulation

Reasons for granulation

The main aims of granulation are:

1. To prevent segregation and thereby improve homogeneity.
2. Improve the flowability of mix to ensure complete and uniform filling of tablet dies, capsules etc. This lead to less weight and dose variations.
   - Granules produced from cohesive materials will be larger and more isodiametric.
3. Improve the compactability of powder.
   - Some materials have bad flow and compression properties so that they can not be formed by direct compression and therefore need granulation.

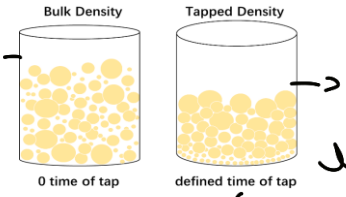


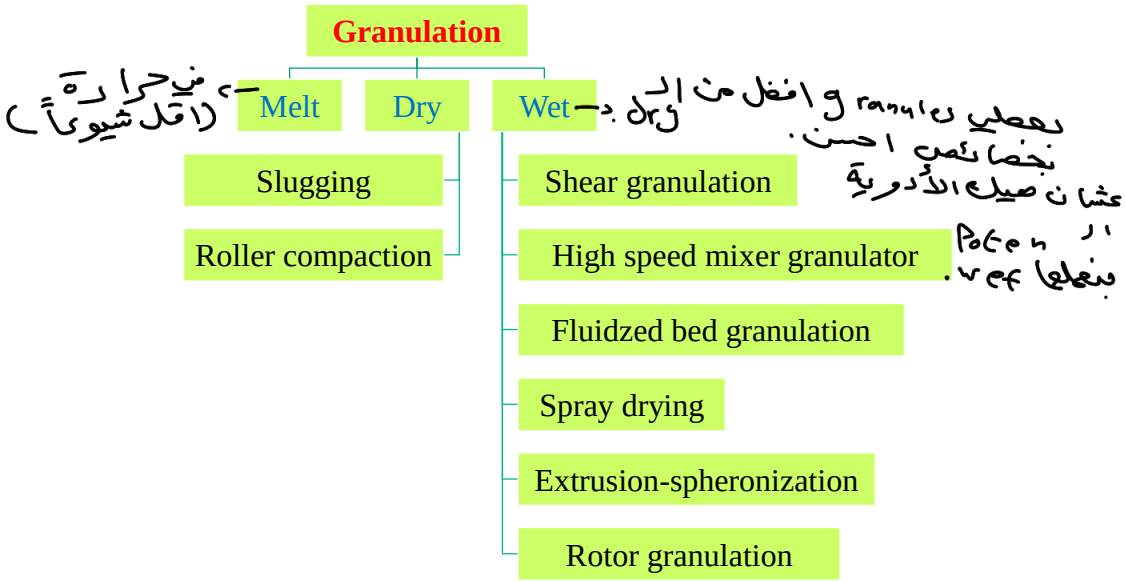
itic diagram to illustrate how granulation can prevent powder segregation.

Granulation

Reasons for granulation

4. Eliminate problems due to dust (e.g. toxic materials).
5. To reduce the problem of caking of hygroscopic materials.
6. Increase bulk density of the powder mixture making them more convenient for storage or shipment.





Granulation methods

Dry granulation:-

- Other term used to describe the process is compression granulation.
- It converts the powders into granules by application of pressure without the intermediate use of liquid.
- This method is used mainly with heat and moisture sensitive materials like aspirin and many vitamins.
- There are two main processes of dry granulation: **Slugging & Roller compaction**

Dry granulation methods

Slugging:-

Procedure:

- Powders (drug and additives like diluent, binder and disintegrant) are mixed and compressed on high capacity tableting machine.
- The compacted masses (slugs) are subsequently comminuted and screened into smaller granules.

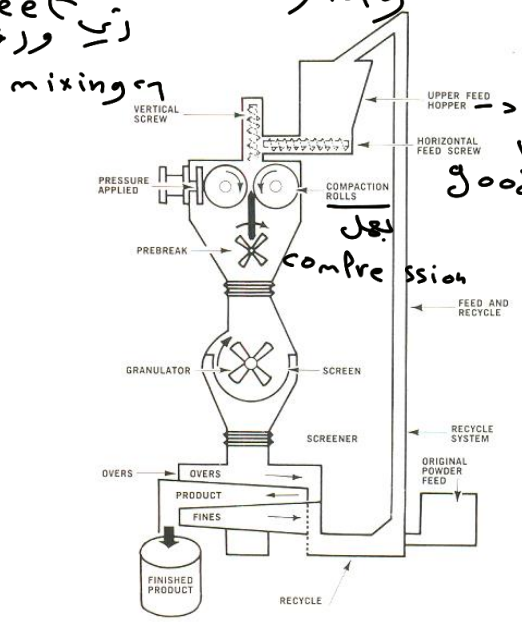
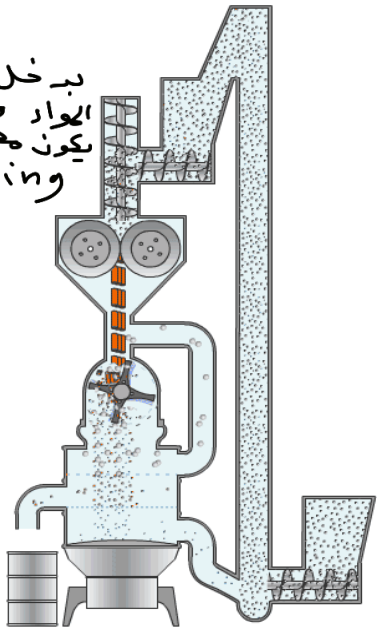


FIG. 11-13. *Schematic diagram of a Chilsonator roller compactor in a granulation production system. (Courtesy of the Fitzpatrick Company, Elmhurst, IL.)*



Dry granulation methods

Roller compaction

- On large scale, dry granulation can be performed on a specially designed machine called roller compactor.
- The powder is squeezed between two rollers to produce a sheet of material which is then comminuted and screened to small granules.

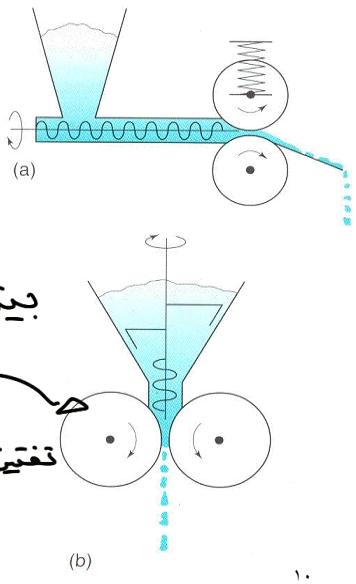


Fig. 29.12 Roller compaction: (a) Alexanderwerk and (b) Protec types.

اشكال الـ Compactor

Dry granulation methods

فوائد الـ dry:-

Advantages of the roller compaction process:

1. The process is economical.
2. There are relatively low investment costs compared with alternative granulation processes using multiple, and more expensive equipment.
3. It can cope with a wide range of materials, particle size, bulk density and flowability (But not all materials)
4. The process is easily scaled up.
5. The product has uniform properties with respect to its mechanical strength.
6. Additionally, the more gentle 'squeeze' of roller compactors leaves the resulting granules capable of further compaction into tablets without the work-hardening problems encountered with slugging.

١- عملية رخيصة وغير مكلفة مقارنة باد wet

٢- ممكن نستعملها مع مواد كثيرة بس مش كل المواد.

٣- بنقدر نستعملها للمختبرات نكبرها ونستعملها لمصنع.

٤- صفات الـ granule اللي بتطلع من ناحية قابلية الكبس (compactibility) لتعطينا tablet بتكون متشابهة.

٥- الـ roller compactor بعمل ضغط خفيف للمواد ويطلعها على شكل ورقة وبالتالي ممكن افتتتها بسهولة واضغطها بعدين عشان اعملها tablet بعكس الـ slugger اللي بطلع كتلة مضغوطة وقاسية كتير فبتكون عملية التفتيت والكبس اصعب لأنها بتكون (compact)

Dry granulation methods

Advantages of dry granulation:

- Utilizes less equipment and space than wet granulation.
- Eliminates the need for binder solution and drying process.

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Granulation methods

Wet granulation :-

- This is the main method for preparation of pharmaceutical granulation and the granules prepared are of good quality.

Disadvantages :-

A. High cost
B. Long operation procedure
C. The use of binding liquid and heat creates problem for heat and moisture sensitive drugs. Sometimes alcohol is used in binding liquid instead of water if the drug is sensitive to moisture.

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Granulation methods

Procedure :-

1. The ingredients to be granulated are mixed to achieve good homogeneity.
2. In addition to the active drug, the mixture may contain a diluent, disintegrant, binder.
3. The binder (adhesive) is either mixed with powders or dissolved in the granulation liquid.

Granulation methods

4. Granulation liquid is prepared (Volatile solvents are used such as water, ethanol and isopropanol, so that they can be removed by drying).
5. The granulation liquid is added to the powder mixture and mixing continues until uniform dispersion (wet mass) is obtained. This process is termed ***wet massing***.(Kneading :-
6. The wet mass is screened to obtain the desired coarse particle size and the particles are then tray - dried. Alternatively fluid-bed drying is applied.
7. Size reduction of granules may be done using a hammer mill.

Granulation mechanisms

Particle bonding mechanisms

There are five primary bonding mechanisms between particles:

1) Adhesion and cohesion forces in the immobile liquid films between individual primary powder particles.
   - An immobile layer (thin film) around particles will increase the diameter and decrease interparticulate distance, therefore it increases van der Waals forces.

2) Interfacial forces in mobile liquid films within the granule.
   - During wet granulation, sufficient liquid is added to produce a mobile film.
   - There are different states of liquid distribution between particles according to moisture content:
     - Pendular
     - Funicular
     - Capillary
     - Droplet (Suspension)

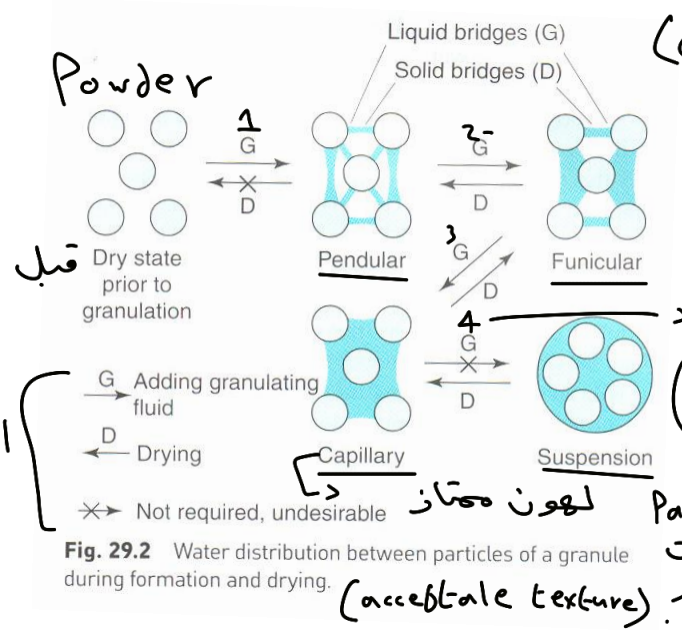


Fig. 29.2 Water distribution between particles of a granule during formation and drying.

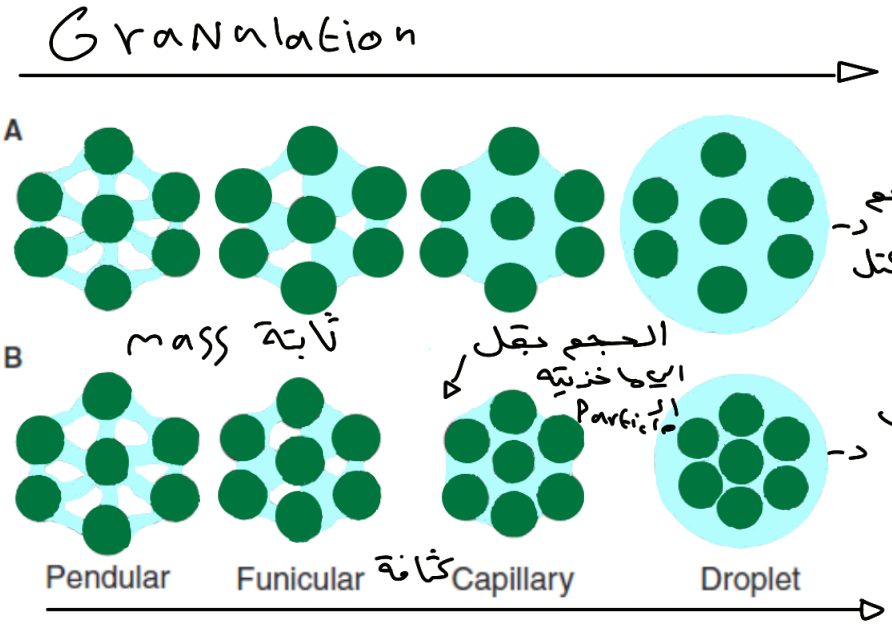


Fig. 2 Liquid-bridging state of agglomerates undergoing (A) binding liquid addition and (B) densification.

Particle bonding mechanisms

3) The formation of solid bridges after solvent evaporation(drying).
These can be formed by:
- Partial melting
- Hardening binders
- Crystallization of dissolved substances

4) Attractive forces between solid particles
- Electrostatic forces
- Van der Waal forces

5) Mechanical interlocking

اغلب اجهزة الصيدلة الصناعية التقليدية تم اخزصامن صناعة الحلويات

Pharmaceutical granulation equipment

Wet granulators

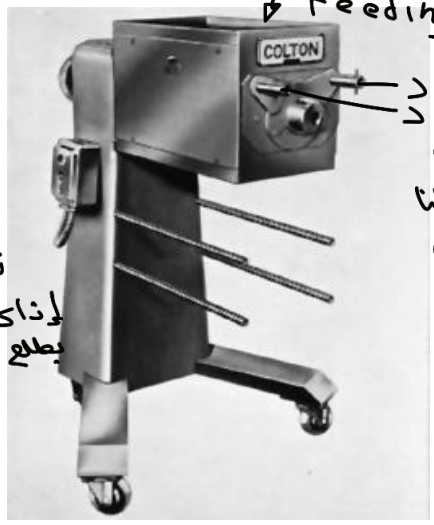
1) Shear granulators (جهاز بهللنا عجين)

- This is a traditional method of granulation. → تقليدي
- It often uses a ***planetary mixer*** for wet massing of the powders.
- Mixing of powders is either done in a separate mixers or in the same planetary mixer.
- The liquid is added as the paddles of mixer agitates the powder.
- The moist mass is then transferred to a granulator (such as ***oscillating granulator***)

الـ Planetary mixer صواني بنستعمله في صاير الحالة للـ mixing ولاضيف الـ binding agent بصير يعمل kneading (عجين) فيه نفسه وممكن نخلطهم بنفس الجهاز او كل powder لحال ولاضيف السائل بنفس قطعة بالجهاز لتصيرني Granulation وبنهللها العجينة و تتكون عنا الـ liquid مع الـ powder الكتلة و تخلطلنا الـ oscillating باستعمال granulator

Pharmaceutical granulation equipment

- The rotor bars of this granulator oscillate and force the moist mass through the sieve screen.
- The mass should be sufficiently moist to form discrete granules:
  - If excess liquid → strings of material will be formed زيادة سوائل بطلع خيوط
  - If too dry → the mass will be sieved to powders and not granules لو اكثير ناشف بطلع Powder برجع بتكسر
- The granules can then be collected on trays and transferred to a drying oven or dried using fluidized-bed drier.

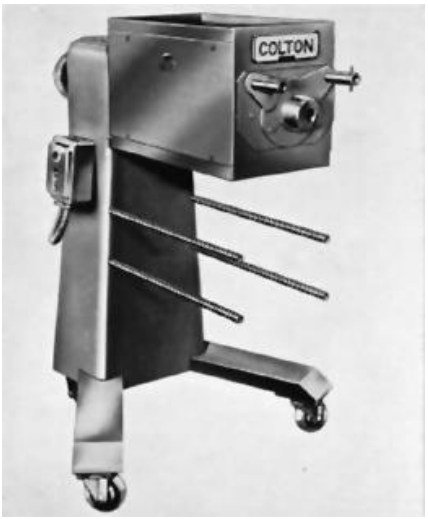


Feeding

عوامير متحركة صي اي بتحرك الـ sieve وبتطلعلنا Granules

oscillating granulator

بكون فيه مخل وبمرق العجينة منه عشان تطل wet granules وبعديها بنجمعهم وبنشفهم زي ما حكينا سابقاً.



planetary mixer ***oscillating granulator***

سموه صيلي عشان دا
بتحرك زي الكواكب

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دا
سموه صيلي عشان
بتحرك بشكل متذبذب
يعني بتروح الشمال
يمين يسار وهكذا .

If excess liquid → strings of material will be formed
If too dry → the mass will be sieved to powders and not granules

ماي زيادة بعطيك خيوط .
ماي قليل بتتكسر الـ Granules وبتصير Powder .

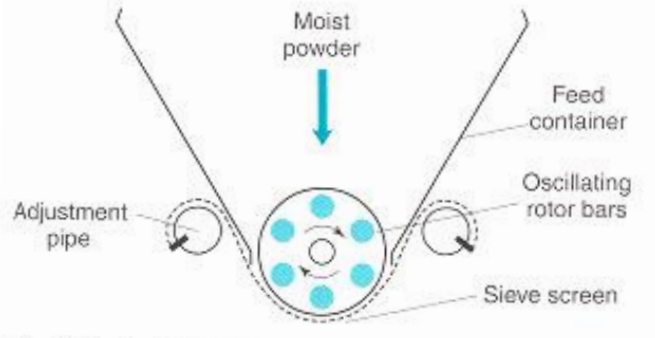

Fig. 29.6 Oscillating granulator.

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***Disadvantages of tray drying*:**

- The drying time is long
- Dissolved material may migrate to the upper surface of the bed on the tray
- Granules may aggregate due to bridge formation at the points of contact of granules

➢ To deaggregate the granules and remix them a **sieving** stage is necessary after drying

Advantages of the traditional method (shear granulation)

1. The process is not very sensitive to changes in the characteristics of the granule ingredients
2. The end-point can often be determined by inspection

Disadvantages of traditional granulation

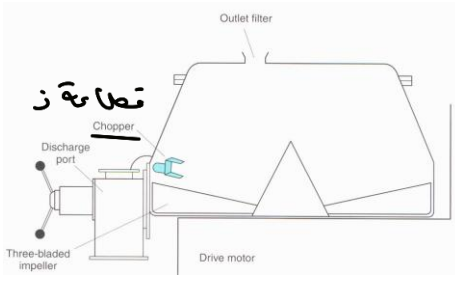
1. Too long duration
2. The need for several pieces of equipment
3. High material loss because of the transfer stages

Pharmaceutical granulation equipment

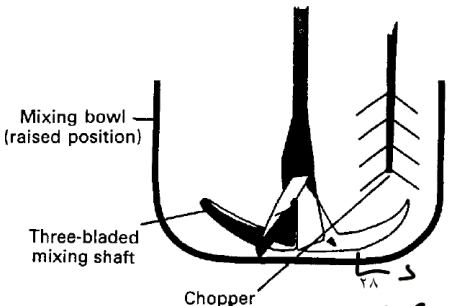
2) High-speed mixer/granulators (High shear granulators)

- This machine have a three-bladed main impeller, which revolves in the horizontal plane, and a three–bladed auxillary chopper which either revolves in the vertical or horizontal plane.
- The unmixed dry powders are placed in the bowl and mixed by the rotating impeller for a few minutes.
- The granulating liquid is then added via a port in the lid of the granulator while the impeller is turning.
- The chopper is usually switched on when the wet mass is formed to break up the wet mass to produce a bed of granular material.

Bottom-driven



Top-driven



Bottom-driven high shear granulators

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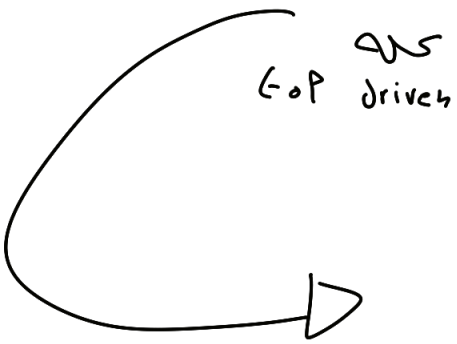


Top-driven high shear granulators

التكملة:- لما نعمل اد granules اي بدنا اياها بتوقف الجهاز وبتطلعها وبمررها على شبكة (sieving) عشان نكسر اي كتل متكونة وبنشفها بطريقة اد fluid bed dry ويعدين بنعملها sieving كمان مرة.

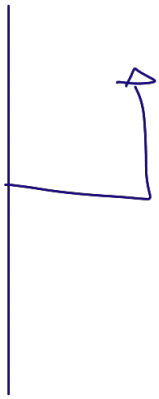
لأنها العملية كتير سريعة فممكن تصير عندنا الـ granules زي كرة الثلج وتبطل قابلة للاستعمال فلازم نعمل control لإضافة اد binder agent وما اضيفه بشكل كبير مرة وحدة عشان ما يصير عندنا over massing.

صاد الجهاز بتأثر بصفات المواد هو زي اللي قبليه.

فوائده:- سريع ما الخلط والعجين والـ granulation بصير بدقائق. وما عندي خسارة للمواد بسبب النقل.

High-speed mixer/granulators

- Once a satisfactory granules has been produced, the granular product is discharged , passing through a wire mesh that breaks up any large aggregates, into the bowl of a fluidized-bed drier.
- Granulation proceeds rapidly and controlling with care is necessary as granules can proceed very rapidly to unusable, overmassed system.
- The process is sensitive to variations in raw material.
- ***Advantage***: Mixing, wet massing and granulation are done in few minutes.



Pharmaceutical granulation equipment

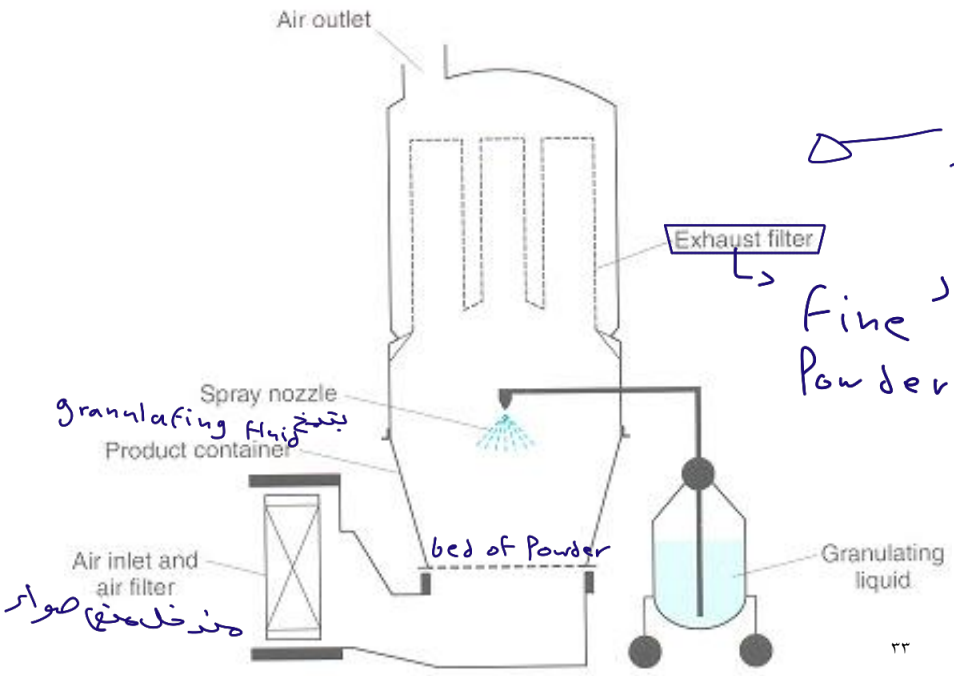
يعتبر من الأجهزة المتقدمة (All in one):

3) Fluidized-bed granulators :

- Fluid-bed granulators are similar in design and operation to fluid bed dryers, but in addition fluid is sprayed from a nozzle on to the bed of powder.
- Heated and filtered air is blown through the bed of unmixed powders to fluidize the particles and mix the powder.
- Exhaust filters allow the prevent the escape of powders.
- Granulating fluid is pumped over the bed of powder which cause particles to adhere and form granules.
- After formation of granules, the spraying is stopped and the fluidizing hot air continues to dry them.

Powder حنرخل وبتطلعها fluidization حنرخل هواء وعند التنشيف حنرخل هواء ساخن

الشرح:- تصميمه بشبه تصميم جهاز اد drying ولكن في عندي اضافة بخاخ بطلع منه الـ binder agent، بدخل الهواء الساخن والفلتر من خلال bed of powder بتصير كل ذرة تتحرك لحالها وبتخلطهم مع بعض ولكن الهواء oxidizable بدخل CO_2 او N_2 وعندنا fine powder حكينا بجمع اد filter وبمنع خروج البودرة بشكل عام" اما البخاخ فبعد الخلط بصير يبخ اد binder ويكون عندنا wet granules بس تتكون عنا بوقف البخاخ والهواء الساخن بنشف اد granules لحالها وبصير عندنا dry granules.



الشرح عكاي ←

تمتص ال Fine Powder

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Fluidization: راح تتحرك Particle يعني كل
لحال وصار ميزة بتغيير بعملية التنشيف منع التكتلات بسبب الهواء.
فيه فلتر بمنع ال (loss and ignition).

← فيه كل الخلطة

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Fluidized-bed granulators

Advantages

1. The performance of many steps (mixing, granulation and drying) in one equipment.
2. The Process can be automated once the conditions affecting the granulation have been optimized.

Disadvantages

A. Expensive instrument

B. Optimization needs extensive work

Apparatus, process and product variables influencing fluidized-bed granulation

Apparatus parameters	Process parameters	Product parameters
Air distribution place	Bed load	Type of binder
Shape of granulator body	Fluidizing air flow rate	Quantity of binder
Nozzle height	Fluidizing air temperature	Binder solvent
Positive or negative pressure operation	Fluidizing air humidity	Concentration of granulating solution
	Atomization • Nozzle type • Spray angle • Spraying regime • Liquid flow rate • Atomizing air flow rate • Atomizing air pressure • Droplet size	Temperature of granulating solution
		Starting materials • Fluidization • Powder hydrophobicity

أشهر مثال على حليب الأطفال بتسوي بهاي الطريقة وصاي الطريقة بعطينا amorphous وصورشكل سريع الذوبان مع انه فيه صون ولكن سريع الذوبان بالماي.

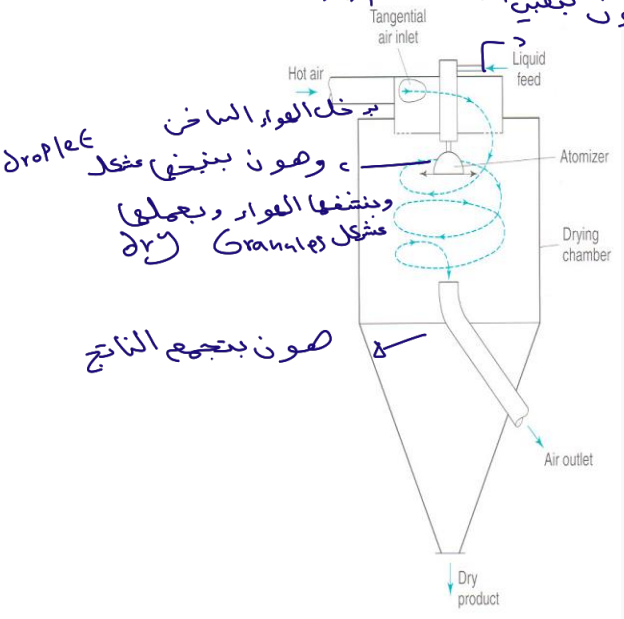
Pharmaceutical granulation equipment

4) Spray driers :- جفرق عن الـ fluid bed

- This differs from other methods of granulation in that granules are formed from a solution or a suspension rather than initially dry powder particles. suspension لازم احضر المادة عشكل واضل احركها عشان ما يصير عندي تكتلات
- The components (drug, diluent) are suspended in a liquid that may contain a dissolved binder. suspension بالliquid لازم نسبة الـ solid اعلى من الـ liquid
- The solid percentage should be relatively high. — د
- The suspension is pumped under continuous agitation in a stream of hot air. — د وحكينا لازم يضل متحرك وبنضخه لجوا وبنعرضه للهوا الساخن
- The liquid evaporates leaving the solid in form of free-flowing hollow spherical granules with uniform size. — د يتبخر السائل بثواني لإنه يشتغل بكل droplet لحاله وبعطيك spherical granule بحجم متناسق

❖ Used mainly for the preparation of direct compression diluents. بنستعمله بشكل عام د للمواد المخففة اللي بتنضغط بشكل مباشر.

suspension صون بنفس الـ



داخل الهوا الساخن
droplet وصون بتبخر عشكل
وبتنشفها الهوا وبعطيك dry granules عشكل
صون بتجمع الناتج

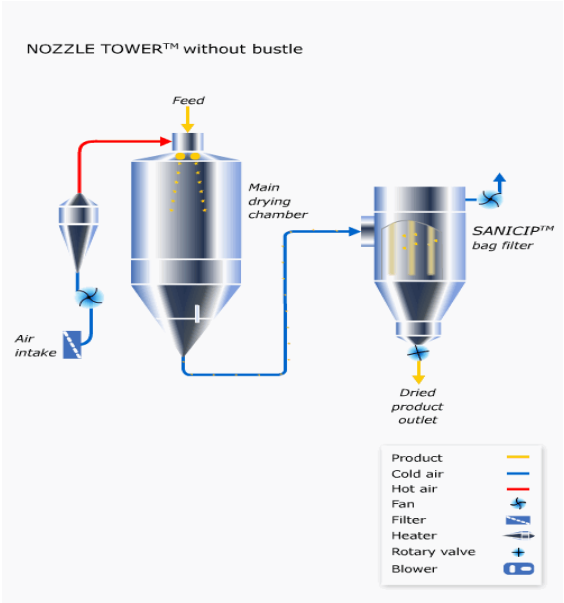


Fig. 30.7 Spray dryer.

الشرح :- القطرة مع التنشيف بصير الماي اللي فيها تطلع عالسطح وتتبخر فيتسحب معها الـ Solute وبزيد تركيزه عالسطح وبصير فراغ بنص القطرة يكون فيه هواء وبصير بشكل Hollow وهاذ اللي بدنا اياه اي drying بعد صيك بخار القطرة وبصير فيها تهريب وبتنكمش وبتخرب وهاذ ما بدنا اياه. Sphere

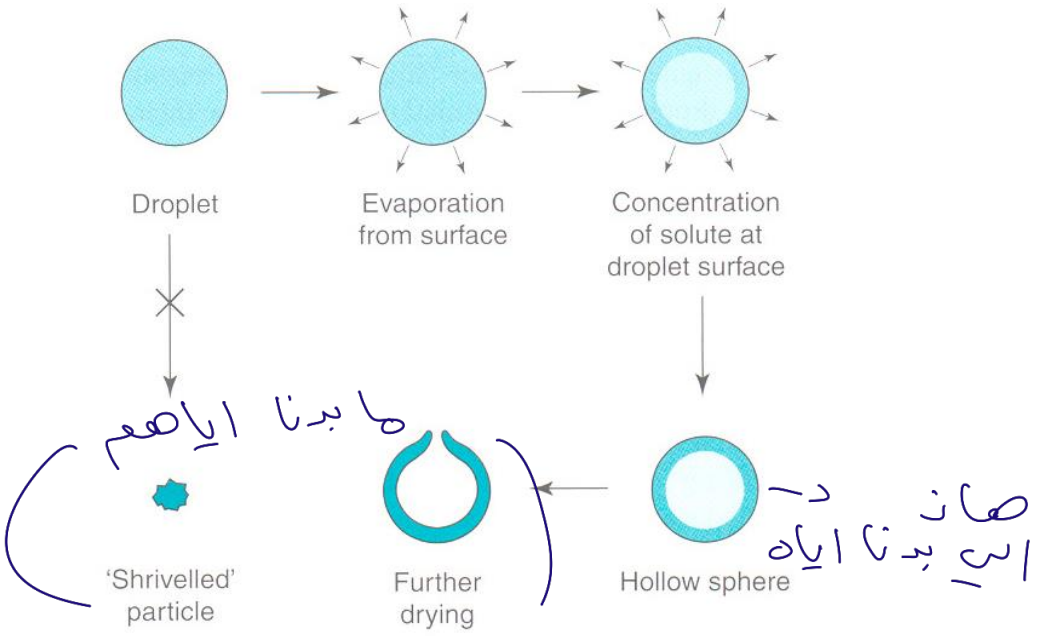


Fig. 30.9 Formation of product in spray drying.

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١- وقت تنشيف سريع (بض كيلو بدقيقة)
٢- الهوا اللي بتخرب بالحرارة ما بتاثر زي البروتين اللي بالحليب لأنه وقت تعرض القطرة للحرارة قصير.
٣- الـ Granules تطلع Spherical و amorphous وبالتالي اعلى Surface area و ذوبان سريع
٤- الحجم بطلع نفسه للكل
٥- الـ flow وقابلية الكبس بتكون ممتازة للمنتج
٦- اجور الماكنة قليلة

Spray driers

Advantages :- امزايا

A. Short drying time
B. Minimal exposure of the product to heat → little deterioration of heat-sensitive materials.
C. The characteristic particles have large surface area and so rapid dissolution.
D. The powder has a uniform and controllable particle size.
E. The product formed has excellent flow and compaction properties.
F. Labor costs are low.

Disadvantages :- عيوب

A. It is costly process and the machine is expensive.
B. The overall thermal efficiency is low.

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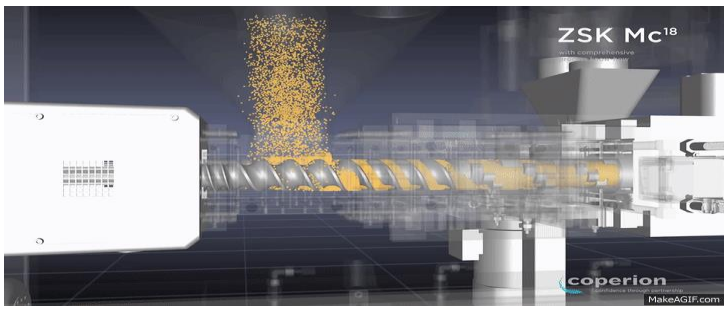
١- عملية التصنيع غالية والماكينة غالية كمان.
٢- توزيع الحرارة لكل الجهات
٣- overall thermal efficiency :- هاذ شيء بهاذ الجهاز كانتقال للحرارة بشكل كامل شيء.
٤- thermal efficiency :- توزيع الحرارة

Pharmaceutical granulation equipment

5) Extruders/Spheronizers:-

- Extrusion/spheronization is a multistep process used to make uniformly sized spherical particles.

- It is used mainly to produce multiparticulates for controlled drug release applications.



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Extruders/Spheronizers

- The main steps of the process are:

1. Dry mixing of ingredients

2. Wet massing

- More amount of liquid is used than other methods.
- Uniform dispersion of liquid is necessary

3. Extrusion

- The wet mass is forced through dies to form rod-shaped particles of uniform diameter.

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زي البرغي بتحرك

بلف حول المحور

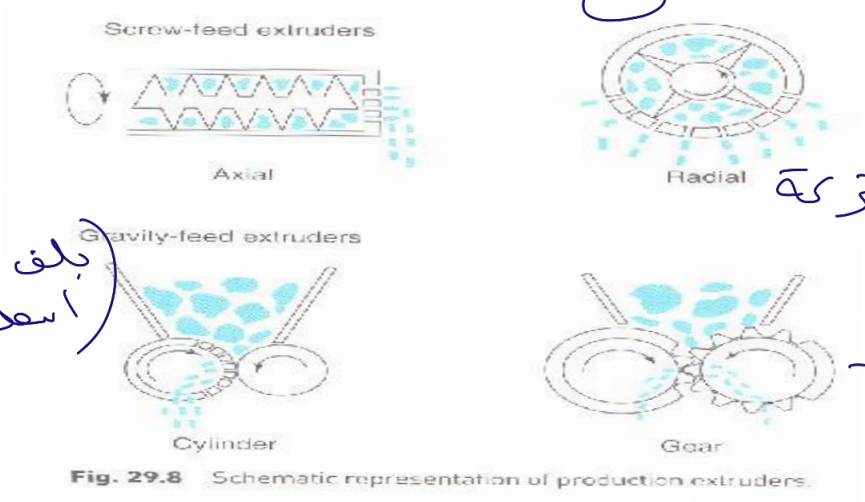
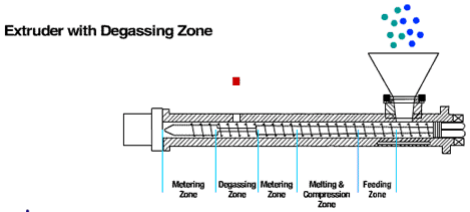


Fig. 29.8 Schematic representation of production extruders.

حسب اتجاه الحركة بنسمي

بلف بيشكل اسطواني

د- زي المسننات بلف



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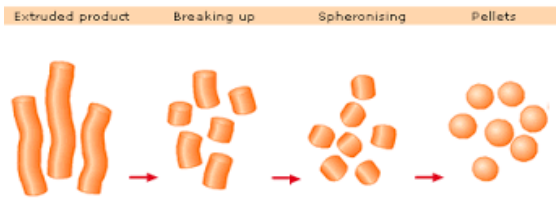
ج- بنحطها بإش اسمه Spinning friction wheel بصير يتحرك وبعملها Sphere عن طريق الـ Attrition.

4. *Spheronization* (انه اعمل الخيوط عشكل دوائر)

- To round off the rods into spherical particles
- This is done in a simple apparatus with fixed side walls and rapidly rotating bottom plate with grooved surface.
- The rounding is done by particle-particle and particle-surface frictions.



شكل الخيوط هم الوقت في عملية رقم ٤ كيف بتحول لـ Sphere

٥- تنشيف

5. *Drying*: Either fluidized-bed or tray drying.

٦- بنعملها Screening

6. *Screening:* To obtain suitable narrow particle size

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عشان نطلع الحجم المناسب.

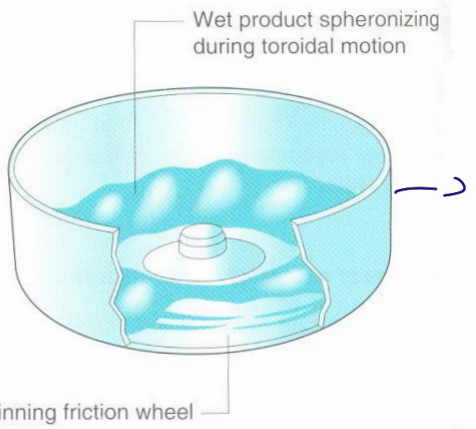


Fig. 29.9 A spheronizer showing the characteristic toroidal (rope-like) movement of the forming pellets in the spheronizer bowl during operation.

بنعمل فيها spheronizing

بتحرك بشكل تورويد (حركة دائرية)

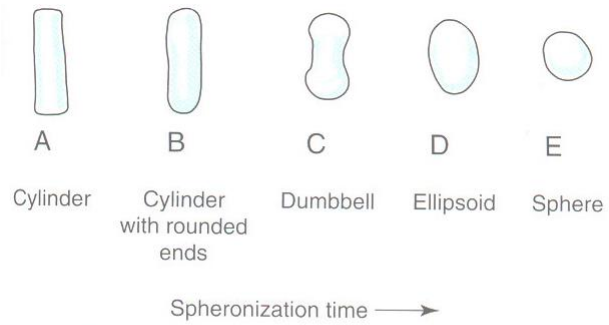


Fig. 29.10 Representation of a mechanism of spheronization. The diagram shows a transition from cylindrical particles (a) into cylindrical particles with rounded edges (b), then dumbbells (c), to ellipsoids (d) and finally spheres (e).

Pharmaceutical granulation equipment

6) Rotor granulation

- This process allows the direct manufacture of spheres from dry powder.

يصنع Sphere بشكل مباشر من البودرة

- In the Freund granulator, the powder mix is added to the bowl and wetted with granulation liquid from a spray.

البودرة جوا الجهاز بنحطها داخل الوعاء ونبخ عليها السائل اللي بعمل Granulation.

- The baseplate rotates at high speed and centrifugal force keeps the moist mass at the edges of the rotor.

القاعدة بتلف بشكل دائري فبالتالي المجينة بتضل على حواف الوعاء بفعل قوة الطرد المركزي (جدار).

- The velocity difference between the rotor and the static walls, combined with the upward flow of air around rotor plate, causes the mass to move in a toroidal motion, resulting in the formation of discrete spherical pellets.

فرق السرعة بين الجزء اللي بلف والجدار الثابت مع حركة الهواء اللي طالع لفوق بتخلي المجينة[٤٧] تتحرك بشكل دائري وتتحول بالنهاية Spheres

Pharmaceutical granulation equipment

6) Rotor granulation

- These spheres are dried by the heated inlet air from the air chamber, which acts also as a positive pressure seal during granulation.

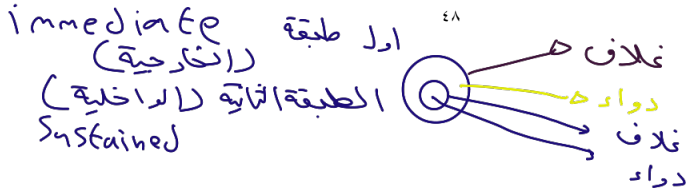
الهواء الساخن بنشف الـ Granules وبعطينا (Positive Pressure)

- Using this technique, it is possible to continue the process and coat the pellets by subsequently spraying coating solution on the rotating dried pellets.

ممكن أغلف المنتج واستعمله كدواء معطول بحيث انه يعطي الغلاف Immediate release جوا Sustained عن طريق أبخ عليها سائل التغليف على الـ Granules

- In addition, layered pellets can be formed by using uncoated pellets as nuclei in a second granulation with a powder mix of a second ingredient.

أو بغلفها على شكل طبقات



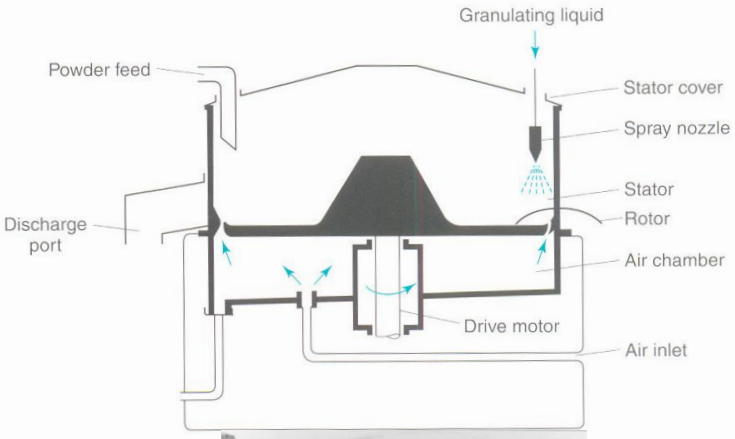


Fig. 29.11 Rotorgranulator.

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Melt granulation

- Melt granulation and melt pelletization processes that have gathered increasing interest in the pharmaceutical industry.
- Unlike the conventional use of aqueous or organic solutions of binders, a molten liquid which remains as a constituent of the formulation is utilized as a binder.
- However, the basic principles in melt granulation processes are relatively similar to those of wet granulation processes with solvents except that the interpretation of the melt agglomeration processes is not complicated by an evaporation of the molten binding liquid.

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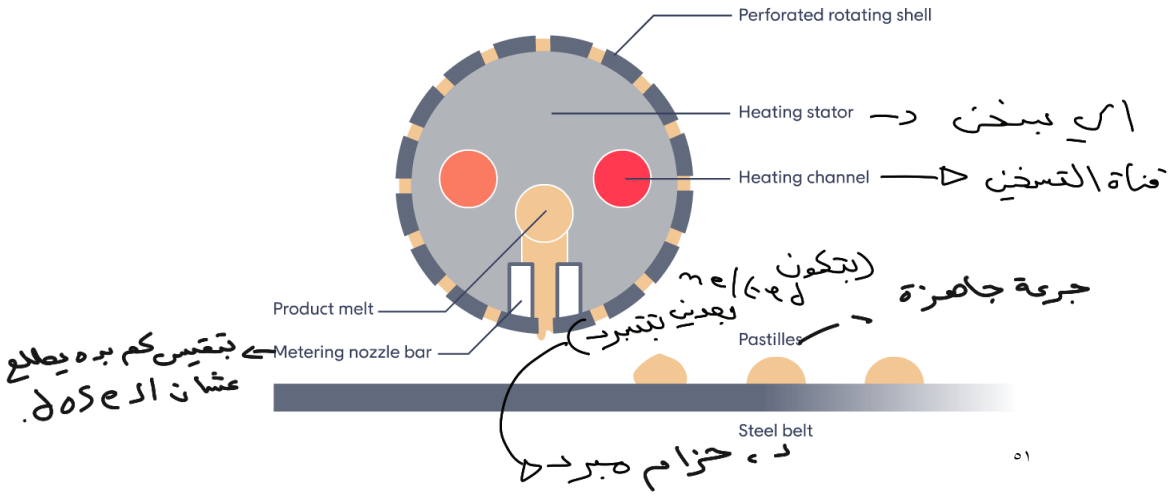
Melt granulation and melt pelletization



Melt granulation

Hot melt binders

- Hydrophilic:
  - Polyethylene glycols (PEGs): Grades between 2000 - 6000
- Hydrophobic (water insoluble)
  - Carnauba wax
  - Hydrogenated castor oil
  - Hydrogenated cotton-seed oil
  - Stearic acid
  - Fatty acids derivatives (glyceryl behanate, glyceryl monostaearate, glyceryl trilaurate, glyceryl tripalmitate, glyceryl tristearate, hexadecyl palmitate)

Melt granulation

Hot melt processes

- The following methods (machines) have been adapted for melt granulation:
  1. Shear granulation
  2. High speed mixer granulators
  3. Spray drying
  4. Spray congealing is similar to spray drying. However a molten sample is sprayed and subjected to cold air for congealing.
  5. Fluidized bed granulation
  6. Extrusion/spheronization

Preparation of effervescent granules

Wet Granulation Methods

- The acid and carbonate parts of the effervescent formulation can be granulated either separately or as a mixture with water (crystal water of citric acid, liquid water, or water vapor), ethanol (possibly diluted with water), isopropanol, or other solvents.

Dry Granulation

- Granulation by slugging or roller compaction is suitable for active ingredients that cannot be wet granulated.