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Pellets

- production technology and use in pharmacotherapy

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Classification

- **geometrically defined, highly agglomerated units**
  - artificial fertilizers, pesticides, animal feeds, and semi-products in the metallurgical, ceramic, and polymer materials industries

- **drug microforms**
  - systems composed of particles, most often administered orally (or parenterally)
  - **pellets**, microcapsules, nanoparticles, liposomes, niosomes, pharmacosomes, CD complexes, etc.

- **2nd generation drugs** - controlled release (CR) - delayed, prolonged, pulsatile

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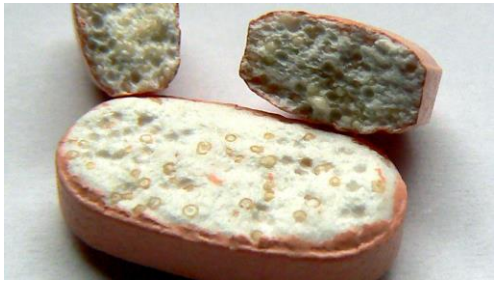
Pellets

- **spherical** or semispherical particles
- size usually ranges from **0.5 - 1.5 (2.0) mm**
- **free flowing**

- **semi-product** – final preparation:
  - **i.** **hard capsule** with uncoated or coated pellets (versatility x control of capsule integrity)

  - **ii.** **tablets** compressed from pellets (lower production costs x possibility of pellet damage during compression)



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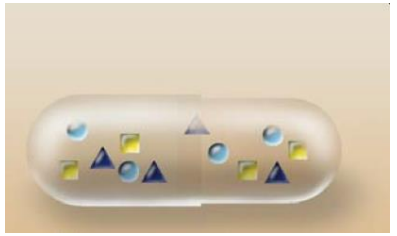
History of pellets as dosage form



- earlier pills – larger
- pellets were first introduced by the American pharma company "Smith, Kline & French" in 1952 under the name Spansules
  - the design of preparation of three types of pellets with different drug release rates, which were filled into gelatine capsules
- considerable development in the following period - number of patents granted
- in the 1960s - marumerizers (spheronizers) began to be used in Japan and the USA - producing pellets with up to 90% of API
- spray cooling of lipophilic particles (1962)

Advantages of pellet dosage

Technological

- excellent flow properties, narrow size distribution, and low abrasion - important for capsule filling (reproducible and uniform filling)
- high dosing accuracy
- spherical shape – optimal for film coating:
    i. production of pellets with controlled release
    ii. instability problems´ solutions
    iii. aesthetic intentions - visual attractiveness

- design flexibility in the development of new DF - possibility of combining pellets with different APIs that:
    i. can be mutually incompatible
    ii. may have different release rates

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Advantages of pellet dosage

Pharmacotherapeutic

- minimum irritation of GIT – after p.o. administration free dispersion in the GIT – irritation of the gastric and intestinal mucosa is reduced, and absorption of the drug substance is increased

- transport independent of gastric emptying - low dependence on food intake (passage through the closed pyloric sphincter)

- for controlled-release pellets
  i. Fluctuation of plasma drug levels is reduced (maintaining the therapeutic optimum for the required time interval)
  ii. Reducing side effects – increasing the safety of treatment
  iii. Simplification of the dosing regimen - improved patient compliance and adherence

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Disadvantages of pellets

- more complex and time-consuming production process
  - development of pellet DF
  - staff training and education
  - validation of technological process, equipment, and methods of evaluation of produced pellet DF
- specific expensive equipment

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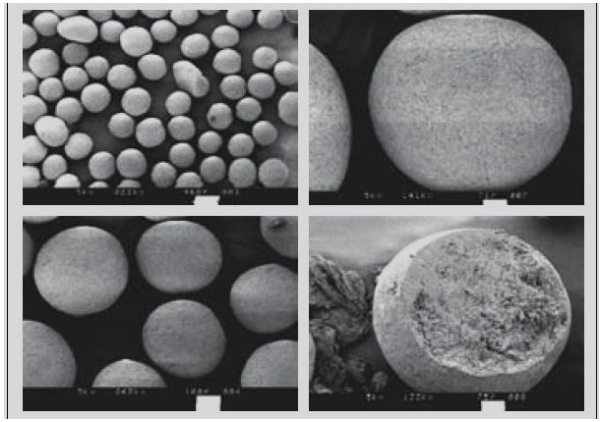
Types pellets

Coated

- polymeric coating - ensuring protection, CR, visual attractiveness
  - fluid-bed coating

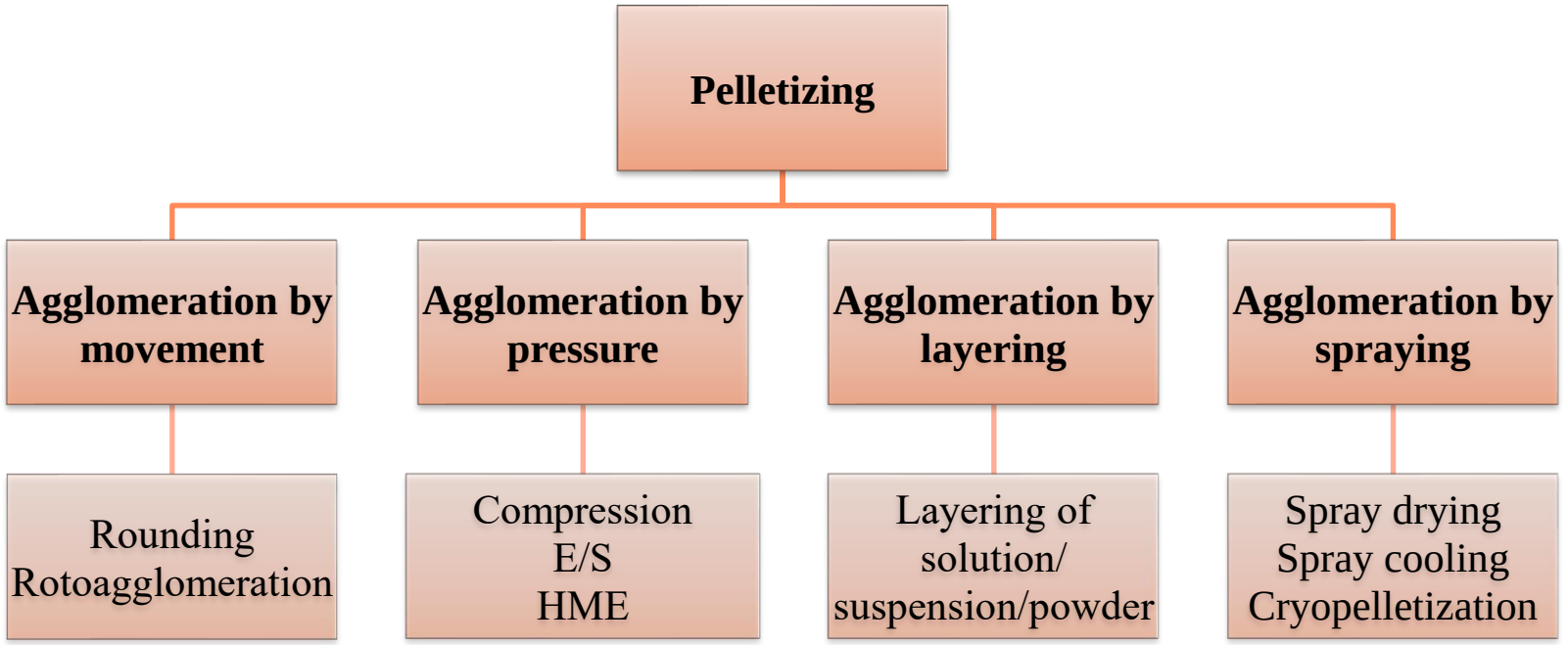
Matrix

- most often hydrophilic matrices, lipophilic, combined matrices also possible



Pellets preparation/manufacturing

- pelletization is the process of **agglomeration of** powdered material or granulate (API + excipients) into small, free-flowing, spherical particles - pellets
- several technologies/principles are used



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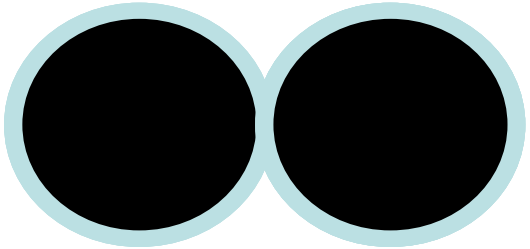
Pellets preparation/manufacturing

- binding mechanisms of particles during the pelletization process

Liquid bridges
(adhesive and cohesive forces during the process)



Solid bridges
(crystallization, binding, solidification, sintering)

Mechanical wedging

- industrial technologies:
  - Extrusion/spheronization
  - Layering on inactive cores
  - Rotoagglomeration

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Agglomeration by movement

- powder material changes into pellets with constant movement after moistening

- formation of a liquid film on the surface of particles - at the points of particles contact are formed **liquid bridges**
- there are air-filled spaces between individual grains – **capillary forces** are the cause of the cohesion of agglomerates
- by supplying energy, e.g., by impacting the walls and colliding with each other, the air is forced out of the agglomerates, and the liquid fills all the spaces between the particles
- capillary forces are during drying replaced by **permanent bonds**

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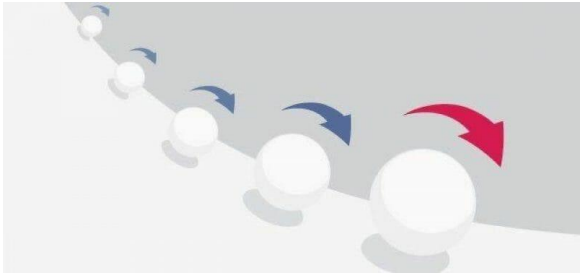
Agglomeration by movement - rounding

- in practice less used pelletizing process
- agglomeration of fine moistened particles by movement in the coating drum
- formation of nuclei/cores, which gradually enlarge and in the final step - drying, liquid bridges, and capillary forces are replaced by permanent bonds (solid bridges)

- wide size distribution
- low mechanical resistance of pellets



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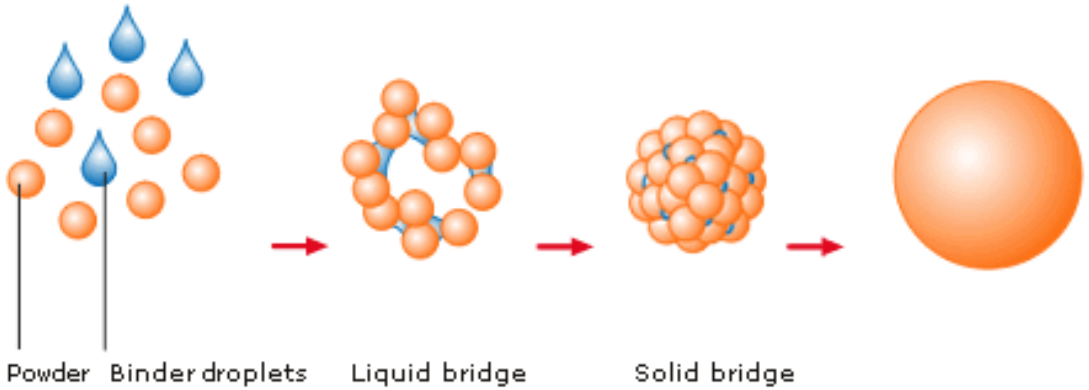
Agglomeration by movement - rotoagglomeration

- use of equipment (rotoprocessor, rotary granulator, spir-a-flow system, etc.)
- combination of fluid-bed device and spheronizer
- based on the effect of centrifugal, fluidizing, and gravitational forces
    i. source of centrifugal force - a rotating disc that directs the pellets to the chamber walls
    ii. fluidizing force - airflow through the slit pushes particles upwards
    iii. with height, the fluidization force weakens, and particles fall back to the rotating disc due to gravitational force
    iv. the combination of these forces results in the spiral movement of the material
- production flexibility, automation, process control x cost of equipment

Agglomeration by movement - rotoagglomeration

- during wetting, a thin film of liquid forms on the surface of the particles; liquid bridges are formed at the points of contact
- in rotation movement, particles agglomerate
- capillary forces and cohesive bonds are during drying replaced by solid bonds (solid bridges, VdW, mechanical bonds)



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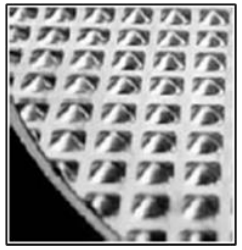
Agglomeration by movement - rotoagglomeration - factors influencing the process

- **wetting**
  - the quantity and physical properties of the mixture of powder materials
  - type and quantity of liquid
  - speed of adding liquid
  - rotation speed and disc type
  - fluidization pressure
  - nozzle type and nozzle pressure



- **agglomeration**
  - the quantity and physical properties of the mixture of powdered materials
  - rotation speed and disc type
  - fluidization pressure
- **drying**
  - the quantity and physical properties of the material
  - disc type and rotation speed
  - temperature and drying time

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Agglomeration by pressure

- use of mechanical force
- **compression**
- **extrusion/spheronization** - extrusion of moistened plastic material with the drug through a perforated extrusion membrane/die and subsequent rounding of cylindrical semi-products to pellets in spheronizer
- process enables the preparation of pellets with up to 90% drug content with suitable physico-chemical properties
- introduced 1960s

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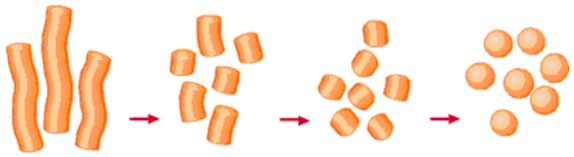
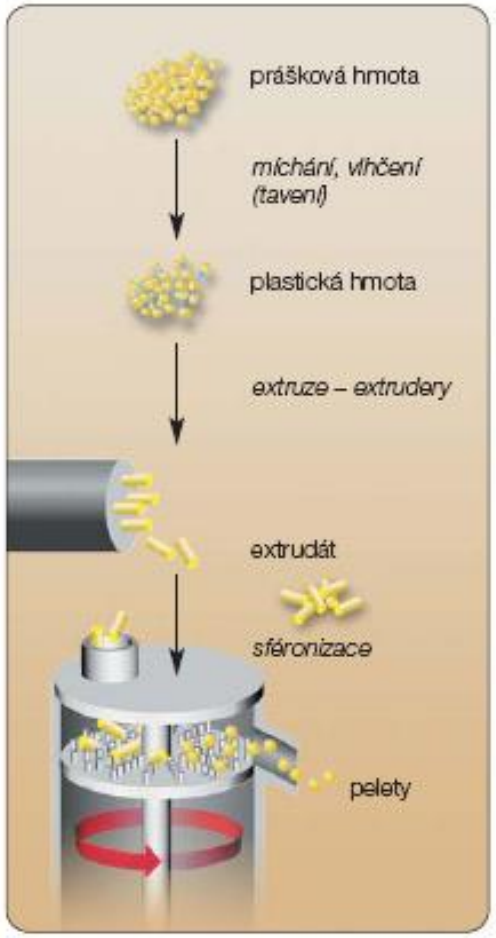
Agglomeration by pressure - extrusion/spheronization – 5 steps

- **homogenization**
- **wetting** - preparation of a wet granulate-like mass
- **extrusion** - formation of ropes/cylinders from moistened material
- **spheronization** - breaking the extrudate and rounding the product
- **drying** – a gain of dry solid pellets

- into the device are inserted moistened powders containing drug and binders
- as it moves forward, the mass compresses, plasticizes, and emerges in the form of ropes with homogeneous shapes and density
- extrudate is rounded in the spheronizer



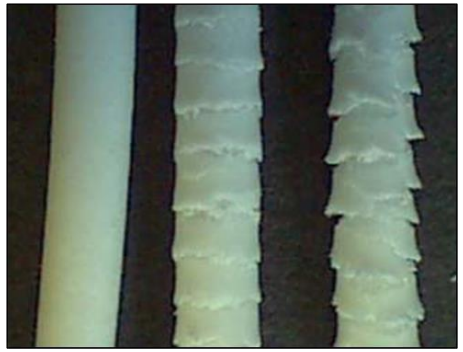


Agglomeration by pressure - extrusion/spheronization – mixing + wetting

- critical step affecting pellet properties (hardness, size, homogeneity, etc.)
- product - extrudable material - plasticity, cohesion, non-sticky
- planetary or high-shear mixers, sigma blenders, granulators
- wetting liquids: water, ethanol - usually tens of %
  - lack of liquid: dusty, incoherent product, high friction
  - excess of liquid: sticking, large product
    - the solubility of the ingredients is important
    - correct wetting – experience/skill, rheometers

Agglomeration by pressure - extrusion/spheronization – extrusion

- pressure causes the movement and extrusion of the wet plastic material through the perforated membrane/die, resulting in the formation of 2 - 20 cm long cylindrical "ropes"
- important is deformability, plasticity, degree of wetting
- pellet size, shape, density, etc., influenced by:
  - extrusion rate, membrane thickness + hole diameter, temperature
- **screw extruder** (allowing continuous extrusion)
- used are also extruders:
  - **piston, cylindrical, basket, sieve**

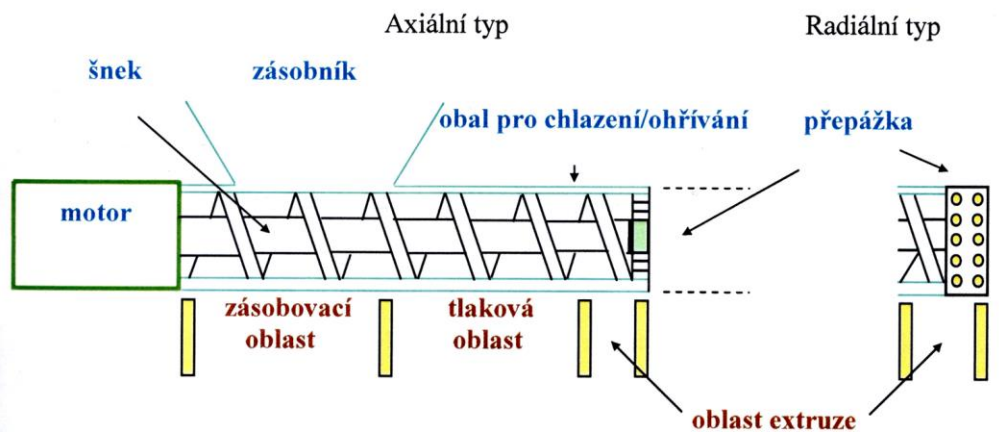


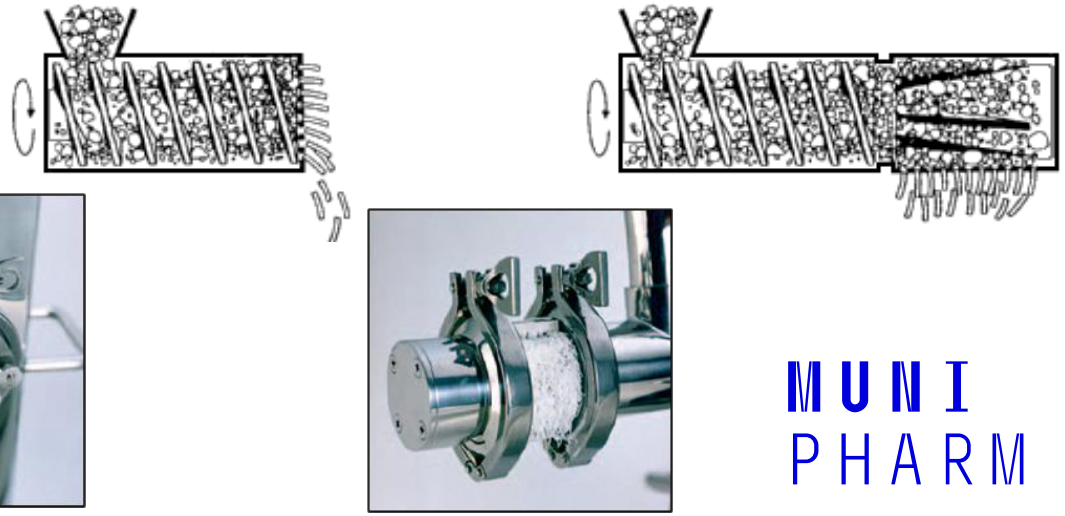
Agglomeration by pressure - extrusion/spheronization – extrusion

- **screw extruders** - differ in location of extrusion membrane and number of screws
- wet mass is fed through the hopper to the screw part, which transports it through the supply area to the pressure area, where it is compressed and from where it is further pushed out through the extrusion membrane/die

radial – membrane around the screw axis, extrudate escapes perpendicular to the axis (higher volume, lower t)

axial – membrane perpendicular to the axis, the material comes out in the same direction as it is transported (higher pressure – higher density)





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Agglomeration by pressure - extrusion/spheronization – extrusion

- **basket**, **sieve** – wet mass fed into the extrusion chamber by force or by its own weight. The plastic material is forced by rotation or oscillation through a membrane that forms the wall of the cylinder (basket extruder) or is placed underneath the device (sieve extruder).

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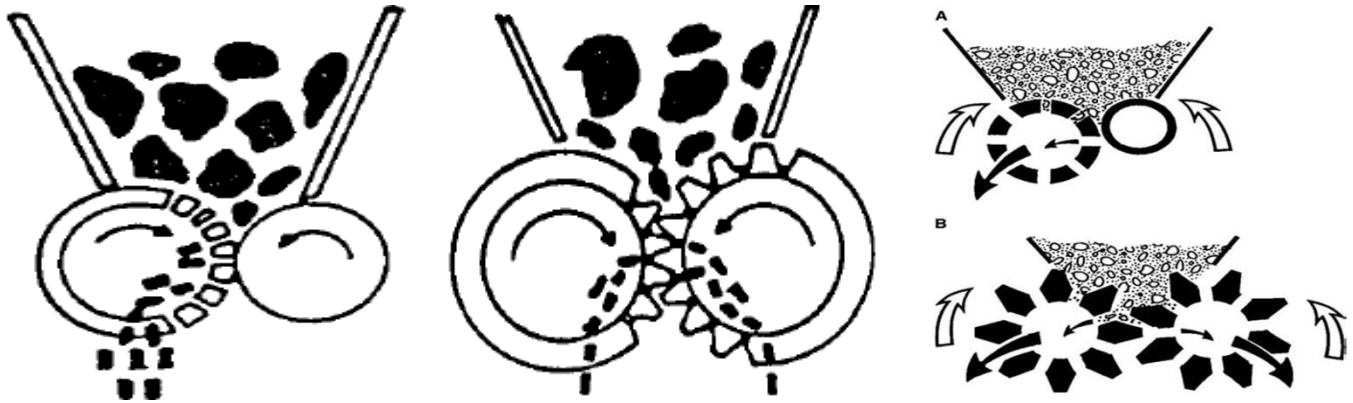
Agglomeration by pressure - extrusion/spheronization – extrusion

- **cylindrical extruders** (pellet mills)
  i. the first type has two rotating cylinders facing each other, which are perforated (both or only one), and the mass is pushed into the cylinders
  ii. the second type has a perforated drum rotating around one or more rollers that push the mass outside the drum



- **piston extruders** - piston moving inside the working cylinder that compresses the material and pushes it through the holes in the membrane

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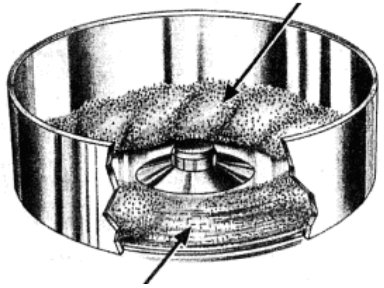
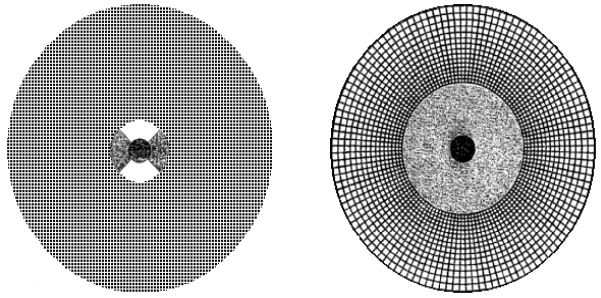
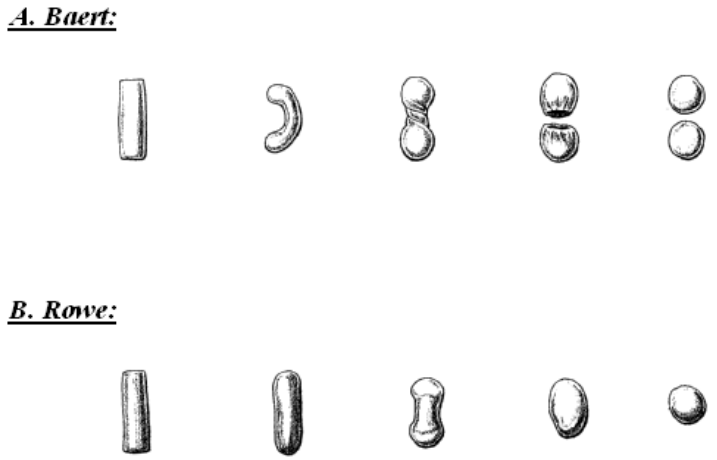
Agglomeration by pressure - extrusion/spheronization – spheronization

- vertically positioned cylinder with smooth inner walls (diameter 20-100 cm)
- rotational plate on the bottom with scalloped or hatched surface, which multiply the friction force required to form pellets
- extrudate is broken into smaller particles, which are further formed into spherical pellets by the rotational movement of the plate and centrifugal force
- rotation speed of the spheronization plate, extrudate load, spheronization time







(a) Baert – I. Cylinder; II. Rope; III. Dumb-bell; IV. Sphere with a cavity outside; V. Sphere.
(b) Rowe – I. Cylinder; II. Cylinder with rounded edges; III. Dumb-bell; IV. Ellipse; V. Sphere.

Agglomeration by pressure - extrusion/spheronization – drying

- the size of the pellets decreases

microwave oven

- faster - most of the wetting liquid evaporates at the beginning - the pellet structure remains almost unchanged - slight shrinkage
- less smooth surface with higher porosity and lower strength
- drying time in minutes (max 10)

fluid-bed dryer

- smaller pellets are produced than in a hot air dryer - abrasion of dried particles due to movement
- fast evaporation of liquid - dried pellets have higher porosity
- drying time 5-30 minutes

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Agglomeration by pressure - extrusion/spheronization – drying

hot air (cabinet) dryer

- the liquid evaporates gradually in layers, reaching the surface through a capillary system of particles
- slow - compared to the microwave
- drying time - hours

freeze-drying (lyophilization)

- sublimation of ice after freezing of wet pellets under low pressure - suppression of shrinkage of pellets - coarser surface and more porosity

silica gel drying

- pellets with water content up to max. 5 %
- slow process - more significant particle reduction - less porosity

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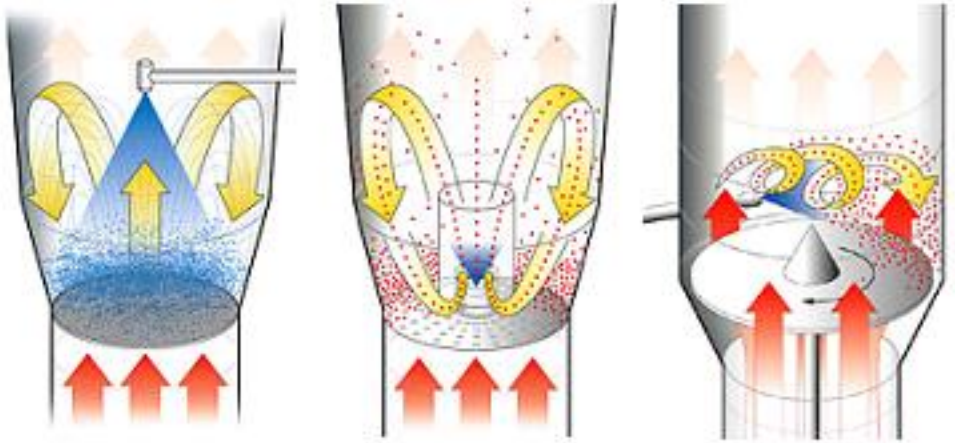
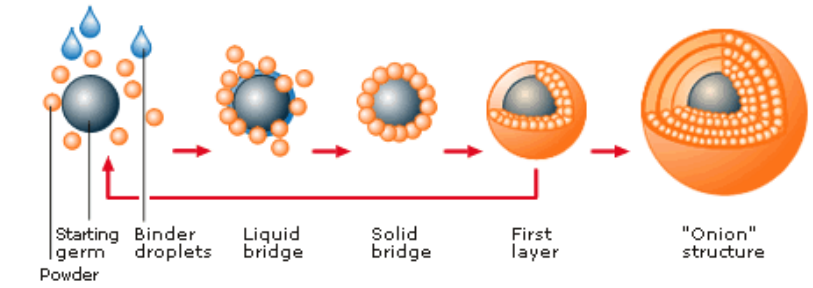
Agglomeration by layering

- deposition of the drug from solution, suspension, or powder onto nuclei/cores - usually inactive (nonpareil)
- historically, coating drums were used, today fluid-bed equipment is preferred - deposition of API and drying at the same time
- layering in the form of powder (necessary to moisten the cores) x in the form of a solution or suspension (direct spraying)



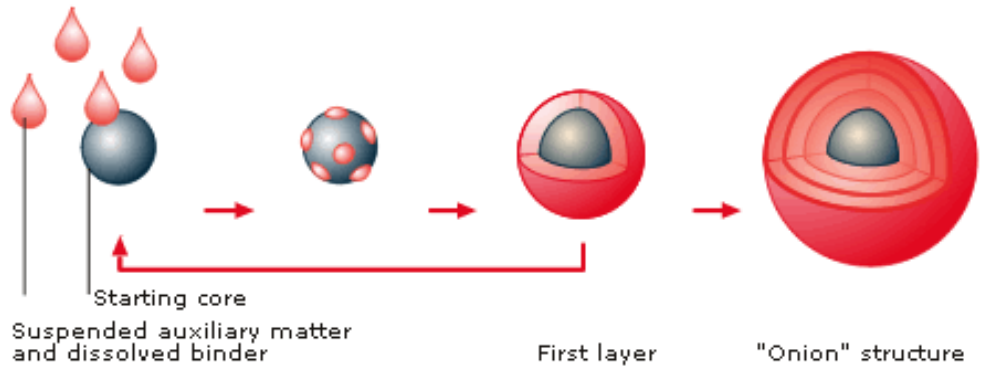
Agglomeration by layering - powder

- solution of binder and powder filler + API is applied to the cores until the pellets of the desired size and API content are formed
- layers are dried by hot air
- powdered drug adheres to the surface of wetted cores by capillary forces; during drying, substances dissolved in the binder solution crystallize, and solid bridges replace liquid bridges
- overwetting of the cores causes forming of large agglomerates and sticking to the equipment
- unmoistened cores – pellets with irregular shape, formation of dust, which receives moisture during further spraying - formation of new unwanted cores (unsatisfactory content uniformity)



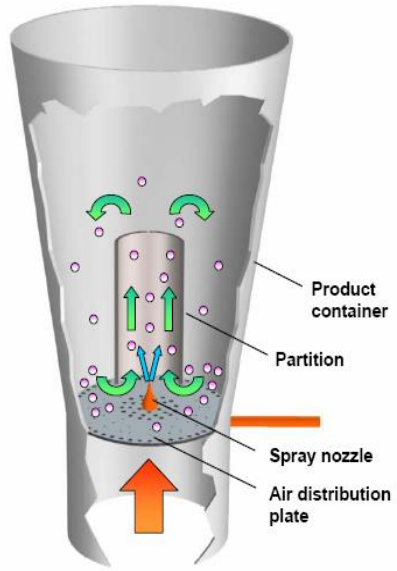
Agglomeration by layering - solution or suspension

- solution or suspension of the drug and binder is directly sprayed using a nozzle
- droplets hitting the surface of nuclei spread out on it, liquid evaporates, and solutes crystallize on the surface of nuclei (formation of solid bridges)
- cycle is repeated until the desired pellets (size, content) are produced
- due to abrasion or premature drying of droplets (before reaching the surface of the cores), fine dust may be produced - the layering rate decreases or stops completely, and dust particles may stick to the surface of the pellets - easier abrasion and brittleness



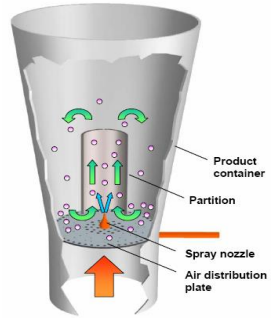
Agglomeration by layering - solution or suspension – Wurster method

- inside the working chamber is inserted a cylinder (Wurster column) of approx. half diameter
- there is a slit between the cylinder and the bottom
- the bottom of the working chamber is made of a perforated plate with different size of holes:
  - larger openings in the center - help the particles to move in a directed manner - fluidizing air flows faster, outwards the openings become smaller
- nozzle goes through the center of the perforated bottom
- suspension of nuclei in air is formed by two fluid layers – one layer moves upwards in the center of the chamber, and the other layer moves downwards around the perimeter of the chamber



Agglomeration by layering - solution or suspension – Wurster method

- air flow is faster in the center of the working chamber - particles are carried upwards through the center of the inner cylinder (WC) around the nozzle where layering occurs
- in the expansion chamber is material dried
- pellets fall back into the working chamber through the space between the outer and inner cylinder
- by passing through the gap between the inner cylinder and the bottom, the particles are "sucked" back into the rising air stream, and the process is repeated
- it is necessary that the concentration of particles in the spray zone is sufficient (each drop of liquid is applied onto the core)



Agglomeration by layering – factors affecting the process

- **nozzle type and location, nozzle pressure**
  - the nozzle should be as close as possible to the moving nuclei, the droplet should hit the surface of the cores as soon as possible, and the liquid must not evaporate prematurely
- **speed of application of solution, suspension, or powder**
- **temperature, humidity, and velocity of the fluidizing air**
- **product temperature**
- **drying time**
- **type of perforated bottom plate, pressure in the gap/slit between the plate and the wall**

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Spray agglomeration - spray drying, cooling, cryopelletization

- surface activity of liquids - trying to form **the smallest possible surface**

spray drying

- solution or suspension of the drug is sprayed into a stream of hot air - the liquid evaporates quickly - solid particles are formed
- dry spherical particles (often hollow) are formed

spray cooling

- drug is mixed with a hot meltable material (resins, waxes, fatty acids), and the melt is injected into a chamber with temperature below the melting point of the product components
- spherical particles are formed, long exposure to a higher temperature

spray lyophilization (cryopelletization)

- solution or suspension of the drug and excipients is injected into a chambre with liquid nitrogen (-196 °C), and the product is subsequently lyophilized
- highly porous product, sensitive/gentle method

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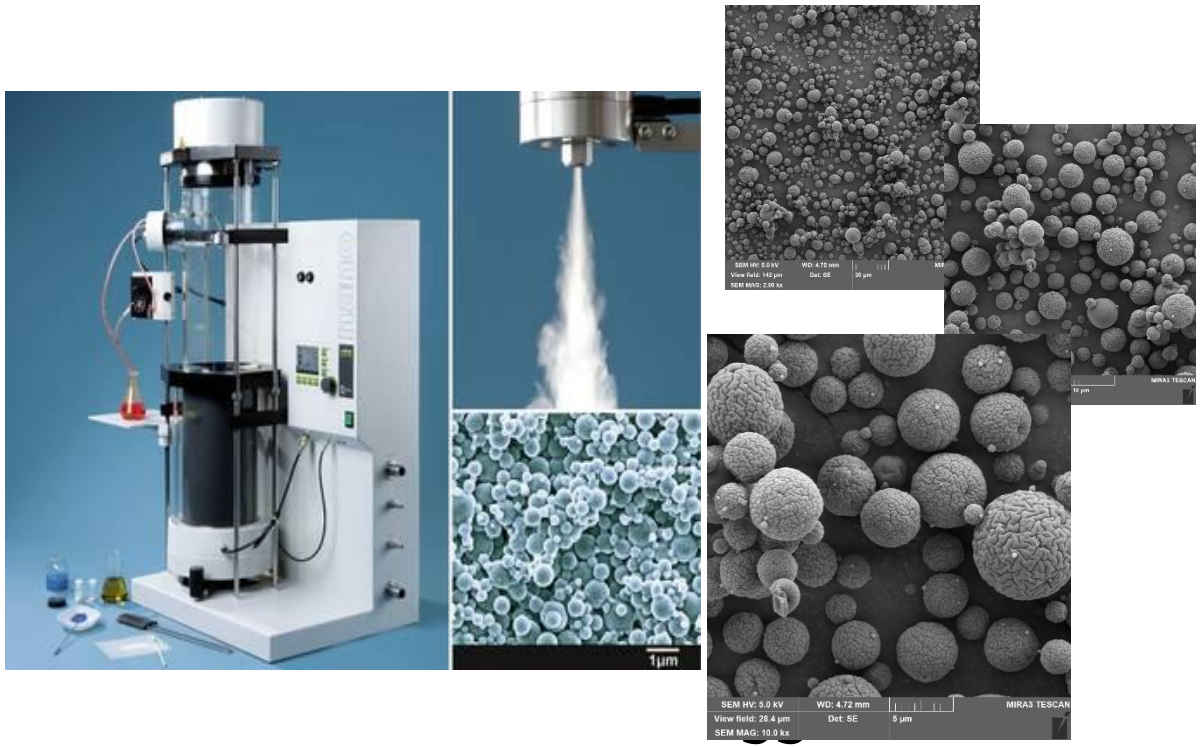
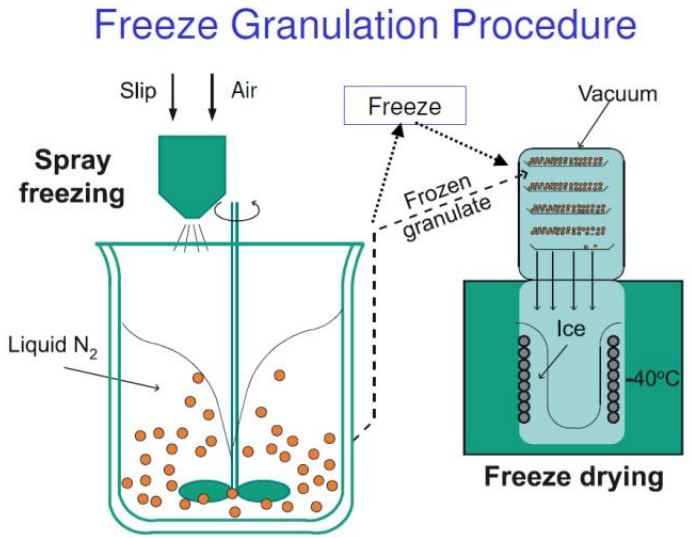
Spray agglomeration - spray drying, cooling, cryopelletization





Innovative pelletizing techniques - pelletization of melts and liquids

hot melt extrusion - formation of plastic material by melting (heated extruder)

melt pelletization in fluid-bed devices - agglomeration of undissolved particles of powder mixture by the molten liquid binder to form liquid bridges that solidify at room temperature

melt cooling pelletization - API melt is applied in the form of droplets into a column with an immiscible liquid

pelletization of liquid - a stream of liquid is forced through a nozzle and cut off by a string or disc or blown off or separated by vibration; the resulting rollers are transformed into spheres in the hardening bath due to surface tension

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Comparison of the most used pelletizing technologies

layering

+ pellets of uniform size thanks to uniform starting cores (suitable for packaging), closed system in one device (suitable for GMP)

- need for inactive nuclei, drug content up to 50%, long process

extrusion and spheronization

+ drug content up to 90%, narrow size distribution, mechanical resistance

- open, multi-step system

rotoagglomeration

+ fast process in one enclosed facility

- drug content up to 65%, wider size distribution

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Excipients for pellets

- significantly influence morphological, flow, mechanical properties, and API release rate

Fillers - indifferent substances, replenishing the volume of the drug to a processable level

- MCC - controls the movement of water in the moistened mass and modifies the rheological properties of other components. Further gives the material a certain degree of plasticity, which allows easy pelletization. It improves the flow properties of pellets, increases hardness, and reduces abrasion.

Binders - usually 2-10 %, they allow the agglomeration of particles

- water-soluble x organic x meltable - starches, gelatine, PVP,

cellulose derivatives, waxes, higher fatty alcohols

Wetting agents - water, EtOH

Release modifiers; Lubricants and anti-adhesive agents; Disintegrants

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Evaluation of pellets

$$d = \frac{\sum_{i=1}^{n} x_i \cdot d_i}{100} \; [mm]$$

d - mean diameter of pellets [mm]

x_i **- arithmetic mean of the mesh size upper and lower sieve fraction i** [mm]

d_i **- mass fraction of fraction i** [%]

size, shape, particle surface, porosity

- sieve analysis - size distribution
- optical analysis - light vs. electron microscope
- mercury porosimeter, BET

$$SF = \frac{4\pi \cdot A}{P^2}$$

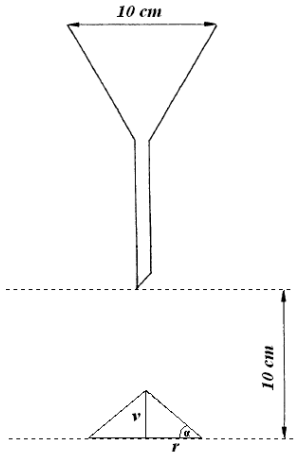
SF - roundness factor
A - displayed area of the pellet [µm2]
P - circumference of the particle [µm]

densities, Hausner ratio, compressibility index

- helium pycnometer
- bulk and tapped volumes/densities

$\rho_0 = m/V_0$ $\rho_{1250} = m/V_{1250}$ $H_f = \frac{\rho_{1250}}{\rho_0}$ $CI = 100 \cdot \frac{\rho_{1250} - \rho_0}{\rho_{1250}}$

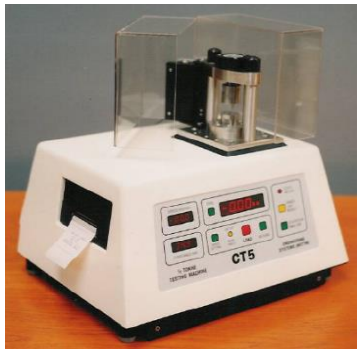
Evaluation of pellets



$$\mathrm{tg}\ \alpha = \frac{v}{r}$$

pellet flow

- angle of repose
- flowability (9.5-10.5 g/s)



mechanical resistance

- hardness
- abrasion (10 g sample, 20 rpm, 10 min, 200 glass beads Ø 4 mm) - 1.7%

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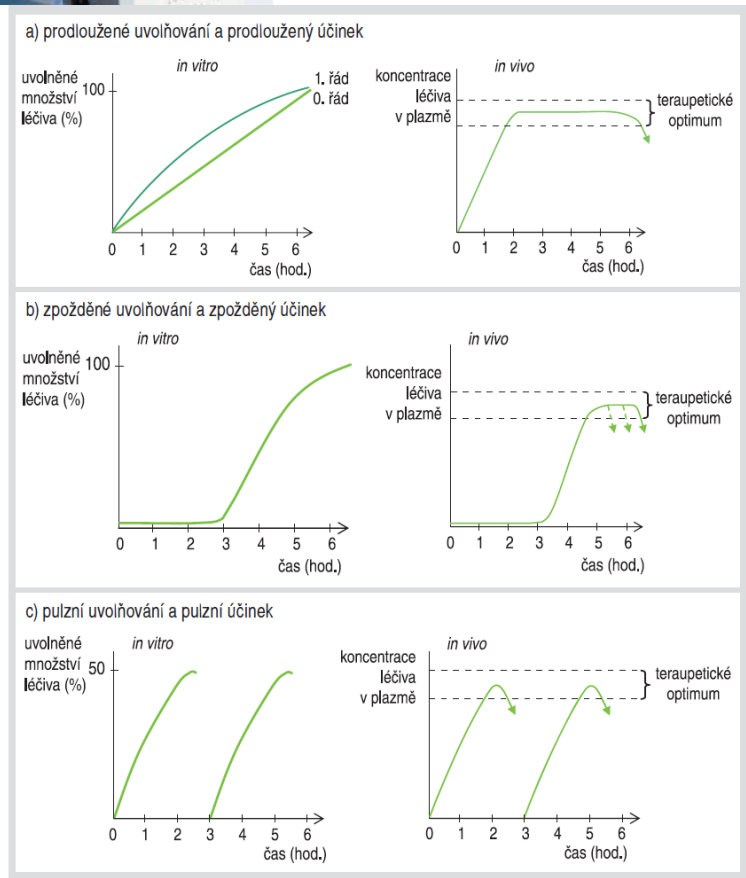
Evaluation of pellets

determination of content

- spectrophotometry, HPLC

dissolution test

- basket apparatus
- paddle app.
- apparatus with reciprocating cylinder
- flow-through cell method
- true dissolution



Examples of clinical use of pellets

- **Fokusin** (tamsulosin) - benign prostatic hyperplasia, cps with pellets
  - Eudragit coating - extended release
- **Helicid** (omeprazole) - reflux, ulcer disease - cps with pellets - delayed release - API stability
  - sucrose cores, Eudragit acid-resistant coating
- **Kreon** (pancreatin) - substitution of digestive enzymes (e.g. CF) - cps with enterosolvent pellets
  - HPMC phthalate coating
- **Euphyllin** (theofiline) - nocturnal asthma attacks, cps with sustained release pellets
  - coating made of cellulose derivatives
- **Diclofenac DUO** - cps with two types of pellets - 1/3 dose released in duodenum, 2/3 prolonged
  - 2 types of polyacrylate coating

- IBD, pain…

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Thank you for your attention.

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