Why make the particles bigger?

- decrease compressibility, improve flowability
- fix homogeneity
- improve particle shape
- improve tablet compression compatibility
Increasing particle size

- Wet-granulation (in high-shear mixers)
  - High-shear (mixer) wet granulation
- Fluidized-bed granulation
- Compaction (dry granulation)

- (Extrudation)
- (Tablet compression)
- (Spheronisation)

Interparticle forces

- Van der Waals
  - Attractive forces between molecules $E \sim 0.1$ eV
- Adsorbed liquid films interaction
  - Van der Waals interactions between liquid film condensing on particle surfaces
- Liquid bridges
  - Surface forces
  - Capillary forces
Cohesive forces in granules

- **Electrostatic forces**
  - Caused by electron transfer between surfaces

- **Solid bridges**
  - **Crystal bridges**
    - formed by wetting, partial dissolution and recrystallization of original particles
  - **Binder bridges**
    - formed by evaporating the solvent from binder solution

Granulation

- **Granulated product advantages**
  - no dust particles
  - good flowability
  - stable bulk density
  - better compressibility (porous)
  - good solubility
  - higher bulk density
Wet granulation: principle

Spraying  →  Wetting  →  Consolidation  →  Agglomeration

binding agent

Mechanical mixing

Granule growth
Phases of wet granulation

- Pre-homogenizing
  - dry premixing powders
- Spraying
  - spraying powder by binder solution
  - spraying powder – binder mixture by wetting agent
- Granulation
  - formation and growth of granules by intensive high-shear mixing
- Drying

Binding agents, Granulating agents

- Starch (5 – 25 %)
  - Traditional, difficult for process control
- Pre-gelatinized starch (0,1 – 0,5 %)
  - soluble in cold water
  - possible mixing into dry powder
- Other natural binders
  - acacia gum, alginic acid, alginates
  - gelatin
  - saccharides
Binding agents, Granulating agents

- **Synthetic binders**
  - Polyvinylpyrrolidone (PVP, 2 – 8 %)
    - Hygroscopic, high polymer degree = dissolution problems
  - Methylcelulose (MC, 1 – 5 %)
    - Swellable and soluble in cold water, similar to starch, higher strength
  - Hydroxypropylmethylcelulose (HPMC, 2 – 8 %)
  - Karboxymethylcelulose salts (CMC, 1 – 5 %)
  - Ethylcelulose (EC, 1 – 5 % in EtOH)
    - good disintegration, poor dissolution

Selecting binder agent

- **Powder and binder properties**
  - powder wettability and penetration
  - solvent
  - binder x substrate compatibility

- **Binder amount**
  - aids granulation, increased granule strength
  - can hydrophilize hydrophobic surface
  - worsens disintegration of tablets
  - slows down the dissolution
Mechanism of wet granulation

- Nucleation and binder distribution
- Consolidation and growth
  - Coalescence
  - Coating
  - Transfer
- Abrasion and fragmentation
  - Fragmentation
  - Abrasion

Wetting and nucleation

- Wetting and uniform distribution of liquid
  - effects the size and formation of granules
  - effects the granules uniformity
- Measuring liquid penetration
  - Washburn test (calculating penetrating rate from physical chemistry) experimentally difficult
  \[
  \frac{dz}{dt} = \frac{r_{\text{penet}} \cos \Theta}{4 \mu z}
  \]
  - Measuring penetration time \( t_p \) (simple)
  - time to soak single droplet of granulation liquid into the powder layer
Spraying

- Droplets fall on the powder surface
  - separately
  - overlapping

- The spraying efficiency governed by
  - dimensionless factor of spray flow
  - \( \psi = \frac{3Q}{2u_{\text{surface}} w_{\text{spray}} d_{\text{droplet}}} \)

Nucleation regimes
Ideal wetting conditions

- Droplet controlled nucleation regime
  - low spraying factor
    - droplet fall on the powder surface creating a new nucleum
  - sufficient penetration rate
    - droplet must soak into the powder until next droplet comes in

Amount of liquid and agglomerates

- a) pendular bridges
- b) funicular bridges
- c) capillary bridges
- d) droplet / suspension
Cohesive forces

Consolidation and growth

- mechanisms of granule growth
  - Coalescence
    - most important, fast
  - Coating
  - Transfer
High- and low-deformability systems

(A) 

(B) 

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Granule impact and coalescence

initial approach; coalescence of I. type.

Deformation, cores in contact.

Elastic deformation, springback.

Separating; coalescence of II. type or bounce.

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Coalescence in non-deforming systems

- Kinetic energy of impact
  - $u_c$ ... characteristic collision velocity

- Energy losses by friction in liquid film
  - Stokes viscosity force

- Energy losses
  - $F_{si} \approx \eta d_p u_c$

- Kinetic energy to losses ratio
  - Stokes number
    - $E_{si} \approx F_{si} d_p \approx \eta d_p u_c$
    - $St \approx \frac{\rho u_c d_p}{\eta}$

Coalescence in non-deforming systems

- Coalescence of I. type can occur if there is a liquid film on granule surface
- Stokes number determines the coalescence of II. type

- low value
  - impact energy dissipates in a surface liquid film
  - coalescence of II. type occurs

- critical value
  - $St \approx \frac{\rho u_c d_p}{\eta}$

- high value
  - too high impact energy to dissipate = bouncing
Coalescence regimes in non-deforming systems

- Distribuce $d_p \rightarrow$ distribuce $St$
- Režimy
  - nesetrvačný (nesetřivačný)
    - $St$ je nízké pro malé i velké částice
    - téměř všechny srážky vedou ke koalescenci
    - necitlivý na malé změny viskozity, velikosti částic, rychlosti
  - setrvačný
    - $St$ je pro některé částice podkritické a pro jiné nadkritické
    - pouze některé srážky vedou ke koalescenci
    - rychlost koalescence je citlivá na malé změny viskozity, velikosti částic, rychlosti
  - obalovací
    - $St$ je pro polovinu částic nadkritické
    - koalescence je vyvážena rozpadem

\[ St \approx \frac{\rho d_p u d_p}{\eta} \]

Deformability effects

Steady Growth Behaviour
- Granule Size vs. Granulation Time
- Increasing Liquid Content
- High Deformation System
  - rapid coalescence growth

Induction Behaviour
- Granule Size vs. Granulation Time
- Increasing Liquid Content
- Low Deformation System
  - slow consolidation
  - coalescence growth
  - surface wet
Deformation behavior of granules

- Given by ratio
  - acting impact forces $\sigma_{\text{impact}} \, [\text{Pa}]$
    
    \[ \sigma_{\text{impact}} = \frac{1}{2} \rho_g u_c^2 \]
  - $u_c$ ... characteristic collision velocity
  - granule strength $\sigma \, [\text{Pa}]$
- Stokes deformation number
  
  \[ S_{\text{def}} = \frac{\rho_g u_c^2}{2Y_d} \]
  - $Y_d$ ... dynamic strength of granules

---

**Growth map**

- “Dry” Free-Flowing Powder
- “Crumb”
- Slurry
- Nucleation Only
- Steady Growth
- Rapid Growth
- Induction

Maximum Pore Saturation,

\[ s_{\text{max}} = w \rho_c (1 - \epsilon_{\text{min}}) \rho \epsilon_{\text{min}} \]
Wet granulation equipment

- High-shear wet granulation
  - common granulation in mixers
  - high energy, high shear, dense granules
- Low-shear wet granulation
  - similar to blenders
  - lower density granules, similar to fluidized bed
- Fluidized bed granulators
  - granulation in fluidized bed

High-shear wet granulators
Low-shear wet granulators

Fluidized bed granulators

- Batch fluidized bed granulators
  - top spraying
  - bottom spraying
Fluidized bed granulators

- Continuous fluidized bed granulators
  - top spraying
  - bottom spraying

Comparing granules by process

- High-shear
  - Compact
  - high density
  - low hygroscopicity
  - broad PSD

- Fluidized bed
  - Better solubility
  - low density
  - adjustable PSD
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Particle Sizing - Agglomeration

Granulator

Process monitoring

- I Wetting
  - low liquid content
  - no agglomeration
- II formation of liquid bridges
- III – IV granule consolidation and growth
- V Too much liquid - suspension

![Diagram of Granulator with spraying nozzle, chopper, and impeller]

![Graph showing impeller power over time added liquid]
Liquid amount and agglomeration

Controlling the process

- **Setpoint**
  - optimal granules PSD
- **Avoid**
  - overgranulation
- **Measured variable**
  - impeller power
- **Conditions**
  - proper amount of liquid
Critical process parameters

- **Amount of liquid**
  - granulation rate, size and properties of granules
  - experimental setup
  - transfer to different material
    - $\pi$ ... dimensionless amount of granulating liquid
    - $V$ ... added liquid
    - $V_M$ ... (moisture) max. amount of liquid not creating granules
    - $V_S$ ... (saturation) amount of liquid to fill all interparticle gaps

\[
\pi = \frac{V - V_M}{V_S - V_M}
\]

- **Geometry**
- **Powder properties**
- **Liquid amount and spraying quality**
- **Impeller frequency**
  - decrease number of lumps (extremely large granules)
  - increasing mean granule size (s výjimkou hrudek)
  - eliminating fines
Impeller frequency effect

- Scale up (simplified)
  - impeller tip velocity is crucial for achieving similarity

\[ S, N \]

\[ \omega, \text{s}^{-1} \]

\[ V \approx 10^2 \text{l} \]

\[ V \approx 10^1 \text{l} \]

\[ V \approx 10^0 \text{l} \]

Granulating process similarity

- Important variables and constants (7)
  - \( \Delta P \) ... net impeller power, \( W \), kg.m\(^2\).s\(^{-3}\)
  - \( D \) ... impeller diameter, m
  - \( N \) ... impeller rotating frequency, s\(^{-1}\)
  - \( h \) ... powder layer height, m
  - \( r \) ... bulk density, kg.m\(^{-3}\)
  - \( \eta \) ... dynamic viscosity of granulated material, Pa.s, kg.m\(^{-1}\).s\(^{-1}\)
  - \( g \) ... gravitational acceleration, m.s\(^{-2}\)

- Basic properties (3)
  - mass, length, time
Granulating process similarity

- **Buckingham theorem**
  - Similarity can be evaluated by $7 - 3 = 4$ dimensionless numbers
  - Newton’s power number

- Reynolds’ number
  - $N_r = \frac{\Delta P}{\rho N^L D^4}$

- Froude number
  - $Re = \frac{\rho N^L D^2}{\eta}$

- Geometric number
  - $Fr = \frac{DN^2}{g}$
    
    $$\frac{h}{D}$$