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YOUTH AND SPORTS

Engineering in Chemical and Pharmaceutical Processes

Properties of particulate solids

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced
  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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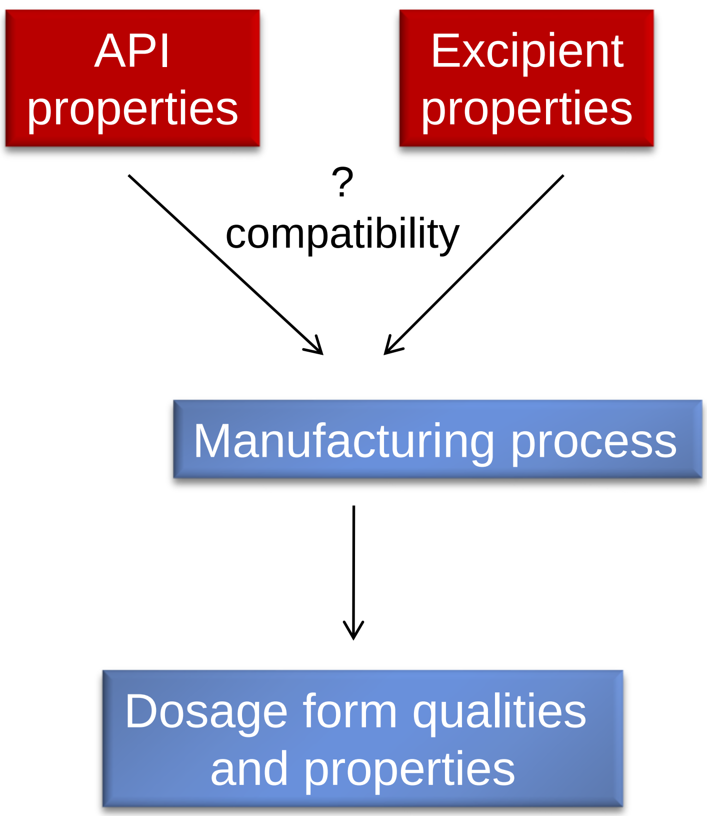
Particulate solids

- Stands at the origin of most solid dosage forms
  - Powders, granular powders (granulates), tablets, capsules and microforms
- Some properties and physical phenomena are different from known forms of matter (new states?)
  - as a result of transport, storage, etc. there are changes in some properties of bulk materials in time ...
- Loose bulk material
  - in various aspects behave similarly to liquids or solids
  - the bulk bed resists a certain shear stress (depending on the tightness of the arrangement)
  - negligible tensile strength of the bed
  - a number of characteristics do not have status behaviour (depends on the process)

Particulate solids in dosage form manufacturing process



- Dosage forms (Drugs) are disperse systems of APIs and excipients
- Particulate solids play many roles
  - Fillers, diluents
  - binders
  - disintegrants
  - lubricants
  - flowing agents
  - …

„Unusual“ behaviour of particulate solids

- Sand clock

Will the mass flow be steady in time?

$$G = const \cdot D_0^a h^b$$

- » G … mass flow through
- » D_0 … orifice diameter
- » h … height

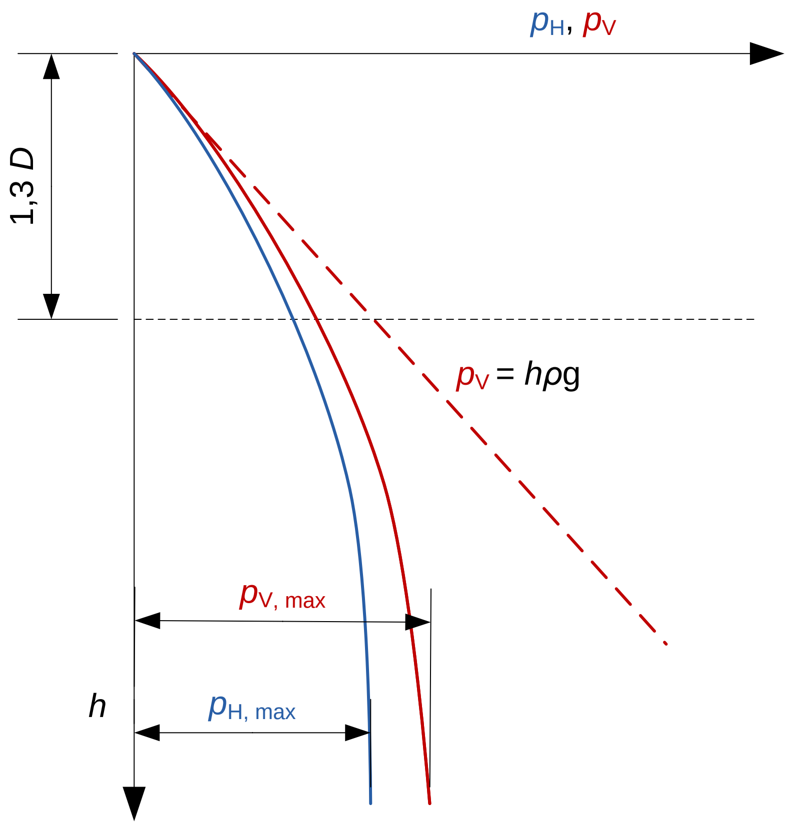
» Liquid

- » flow depends on the height of liquid column
- » b = ?

» Sand (particulate solid)

- » flow is nearly constant
- » b = 0 – 0,05

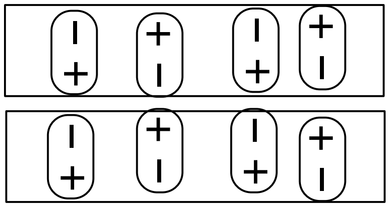
Explanation



- pressure in bulk solid is not proportional to depth (compare to liquids)
- the behaviour is due to the friction between particles

Friction

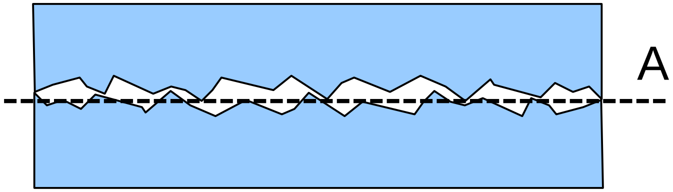
- Friction on ideally smooth surfaces



  - depends on material = density and strength of interactions (van der Waals)
  - depends on contact surface = total number of interactions
- Example
  - adhesive tape contact strength is proportional to its size

Friction

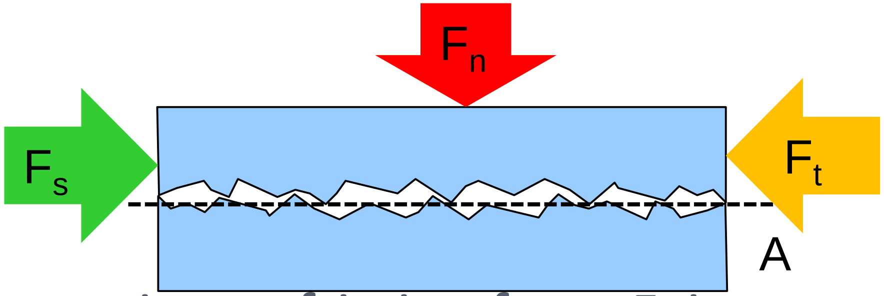
- Coulomb friction
  - corresponds to common solid materials
  - friction force independent of total apparent contact area(A)



  - real contact area is only small fraction of A (independent of total surface)

Friction

- Coulomb friction
  - net contact area increases according to acting normal force F_n



  - therefore, maximum friction force F_t increases

$$F_t \leq \mu F_n$$

  - friction force is up to external force F_s and of the opposite direction

Effects on particulate solids

- Friction between particles depends on
  - material
  - shape and size of grains
- Similar rules in effect for particle adhesion

- Mechanical properties of particulate solids depend on particle properties

Particle properties

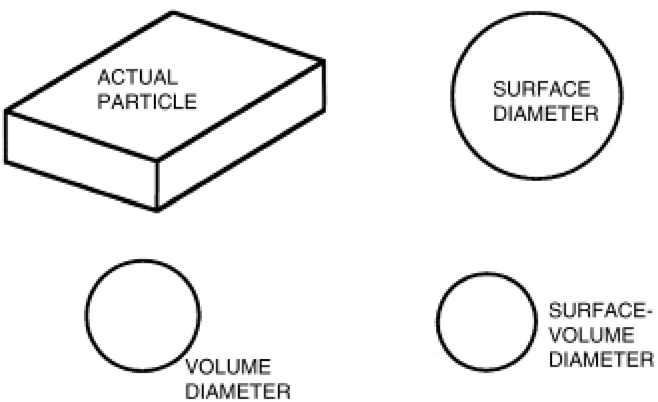
- Particle size distribution (PSD)
  - characteristic particle size
  - statistic variable
- Distribution of particle shape
  - sphericity, angularity, concavity/convexity
- Material properties
  - porosity, strength, ...
- Solid density ρ_s
  - Density of the material (single particle)

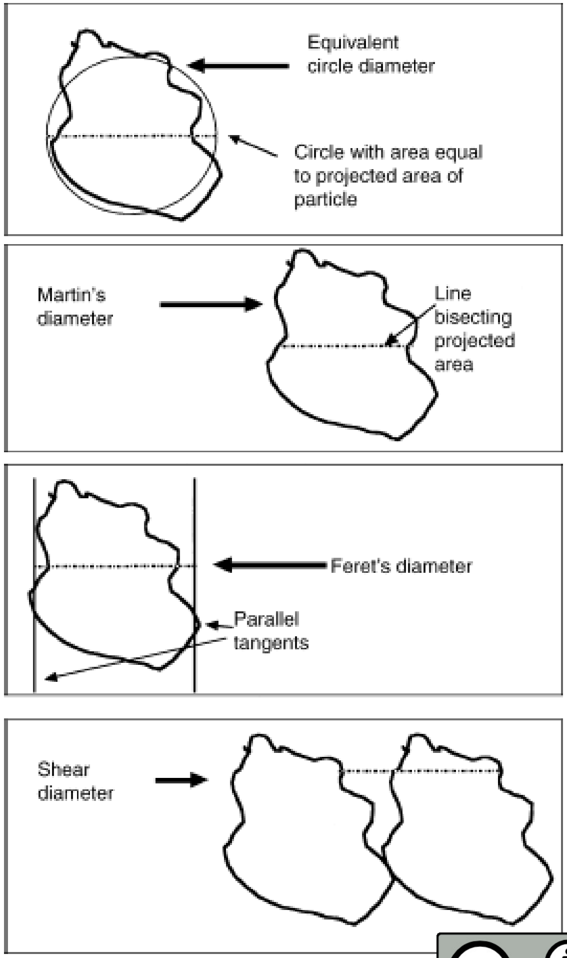
Particle size distribution

- How frequent are different particle sizes in our smaple
- Pharmacopeial property
- Many methods of measuring
  - different sensitivity and range of applicability
- Reported by distribution functions
  - cummulative
  - differential

Particle size

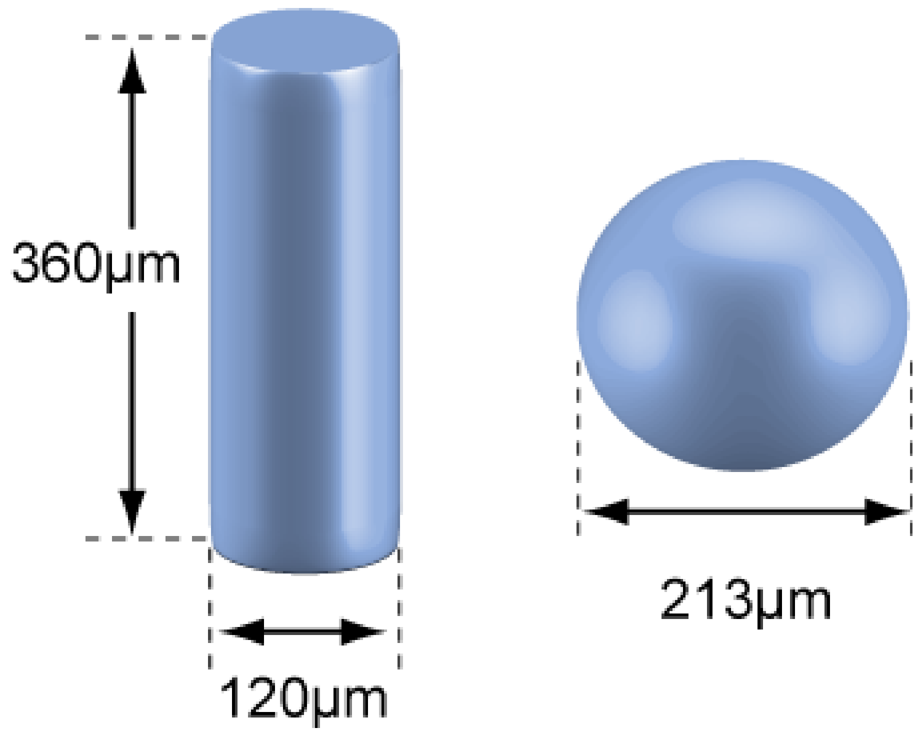
- Depends on shape
  - seldom ideal shape
- How to report size of irregular particle?



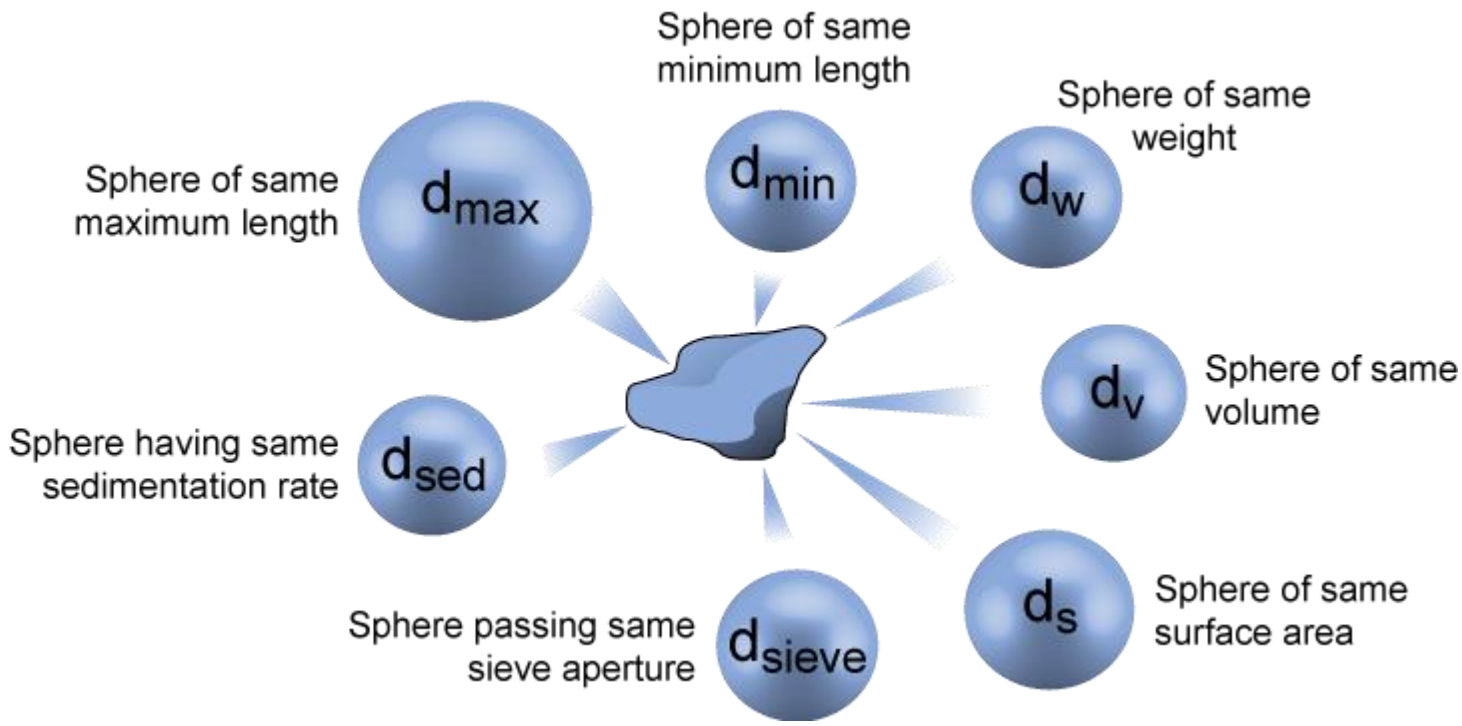


Particle size based on equivalent sphere

- Volume of cylinder = volume of eq. sphere =>
  - equivalent volume diameter

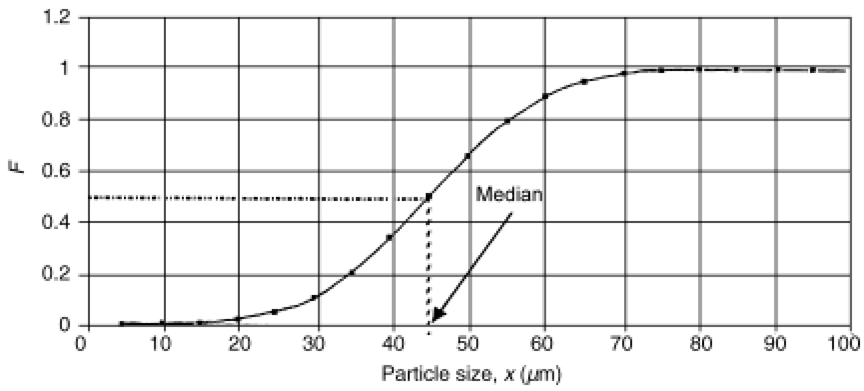


Equivalent diameters for various applications



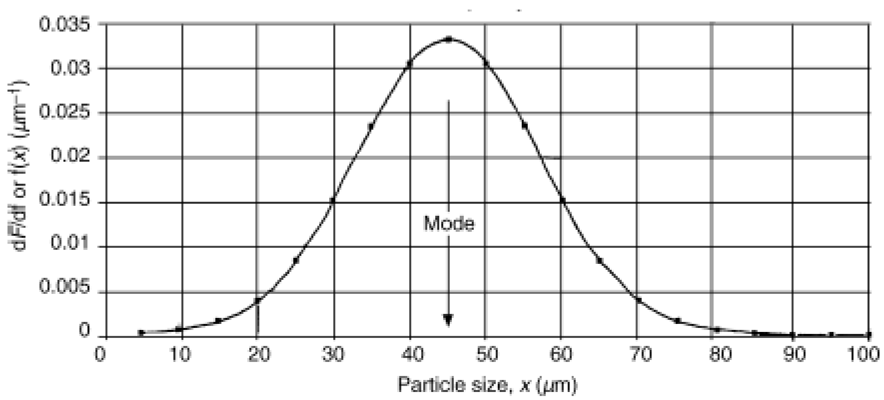
- Suitable diameter depends on usage
  - d_S – good for particle dissolution
  - d_V – good for representing mass content in mixture

F = Cumulative frequency distribution



- Meaning of $F(x)$
  - F % of particles are of size x or smaller
- Media
  - 50 % particles are smaller than median
  - 50 % particles are bigger than median

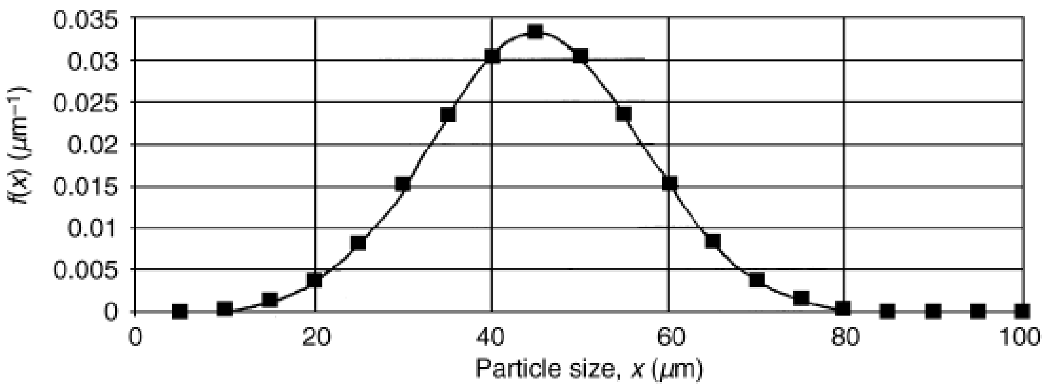
$dF/dx = f$ = Differental FD



- (or distribution density)
- $f(x)$
  - greater values = particles of that size are more frequent
- Mode
  - most frequent size
  - mode != median

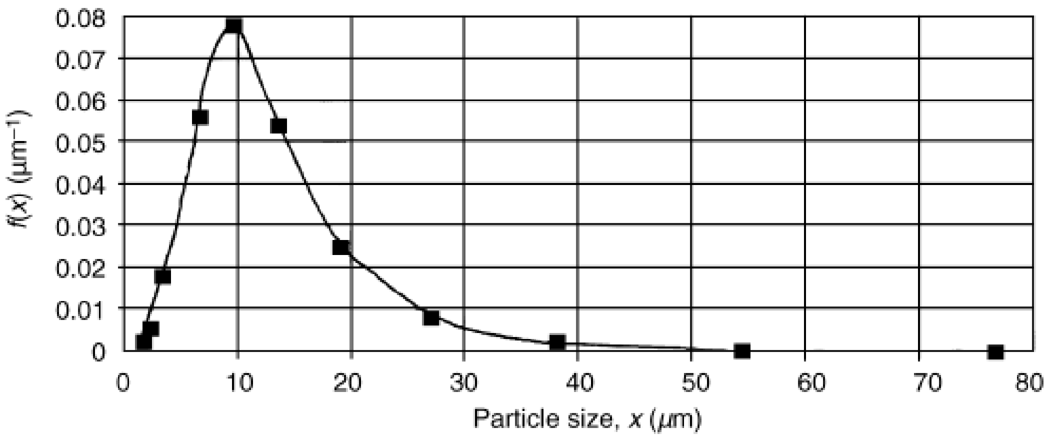
PSD of common bulk solids

- Arithmetic-normal distribution



$$f(x) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(x-\bar{x})^2}{2\sigma^2}\right]$$

- Log-normal distribution (typical)

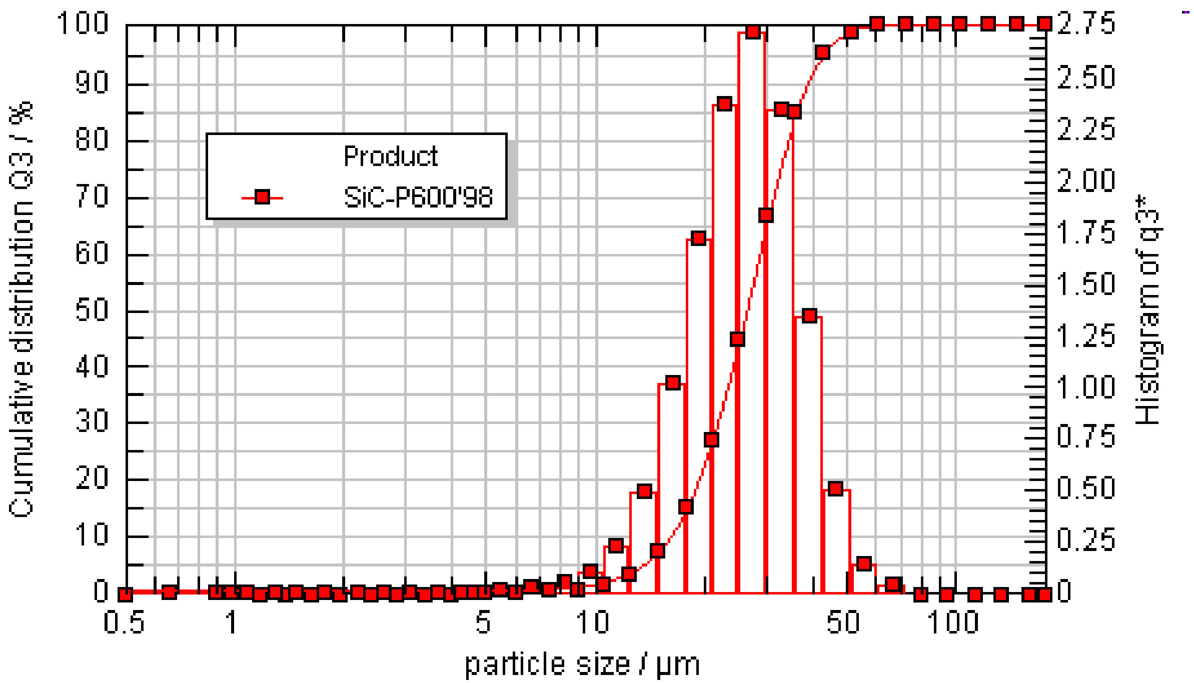


$$f(z) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left[-\frac{(z-\bar{z})^2}{2\sigma^2}\right]$$

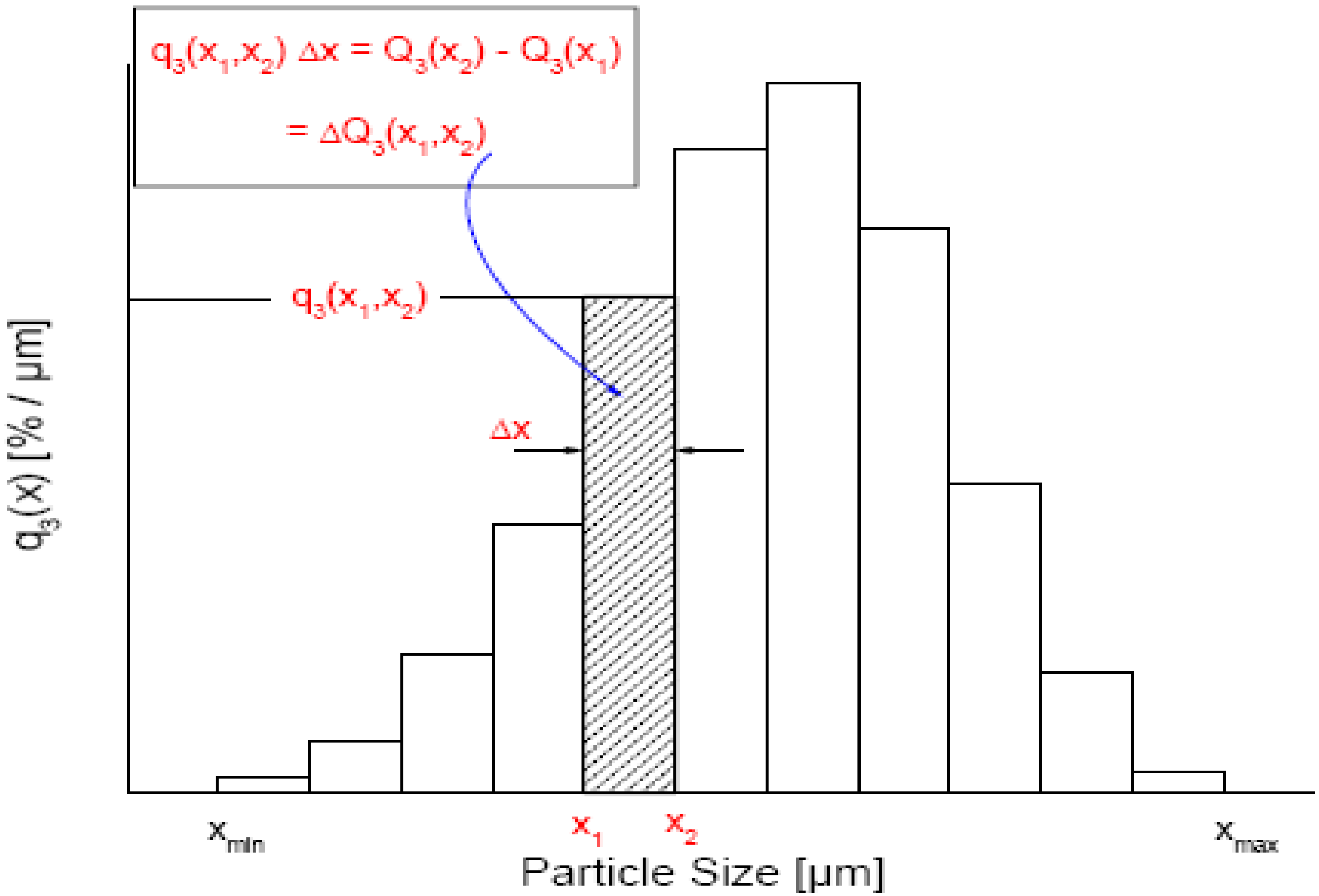
$$z = \log(x)$$

Reporting experimental results

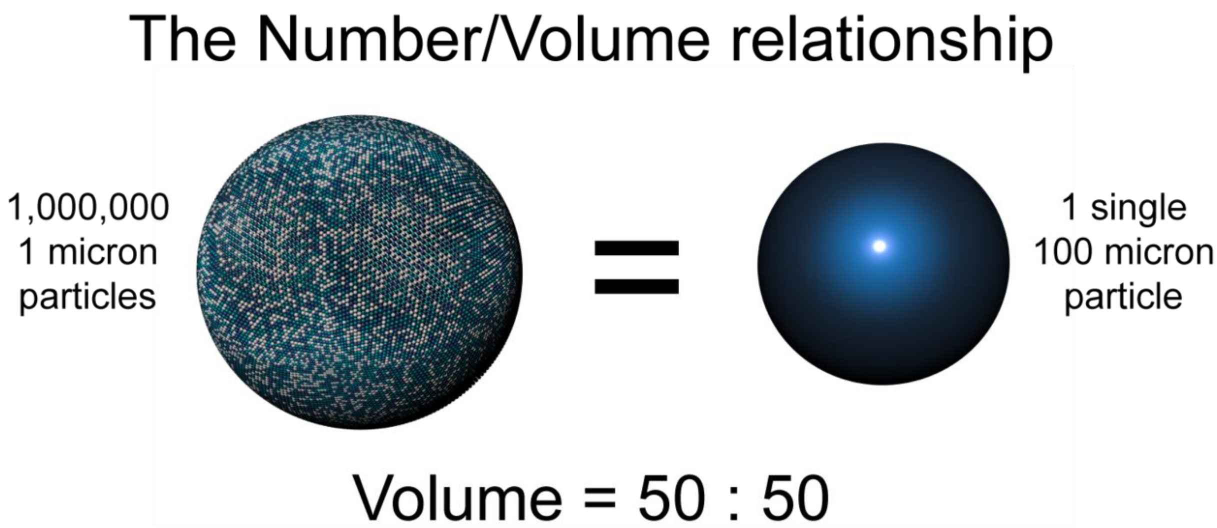
- Cumulative distribution
- Histogram

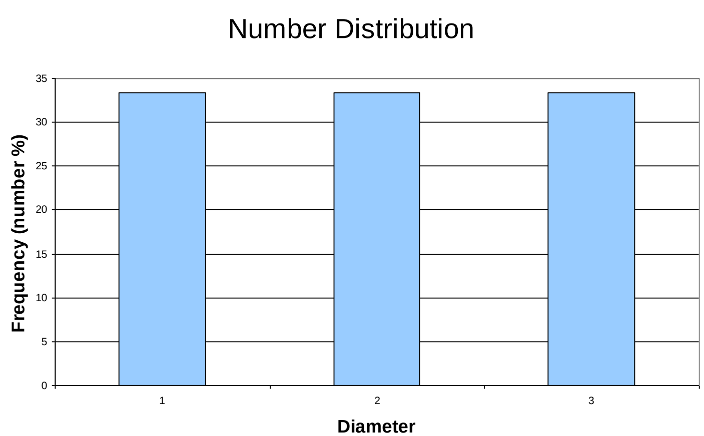


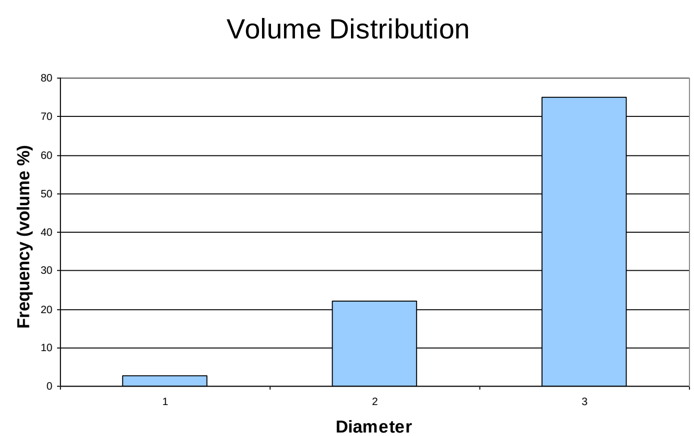
Reading histogram



Number/volume distributions







Distributions by number, surface, volume (mass)

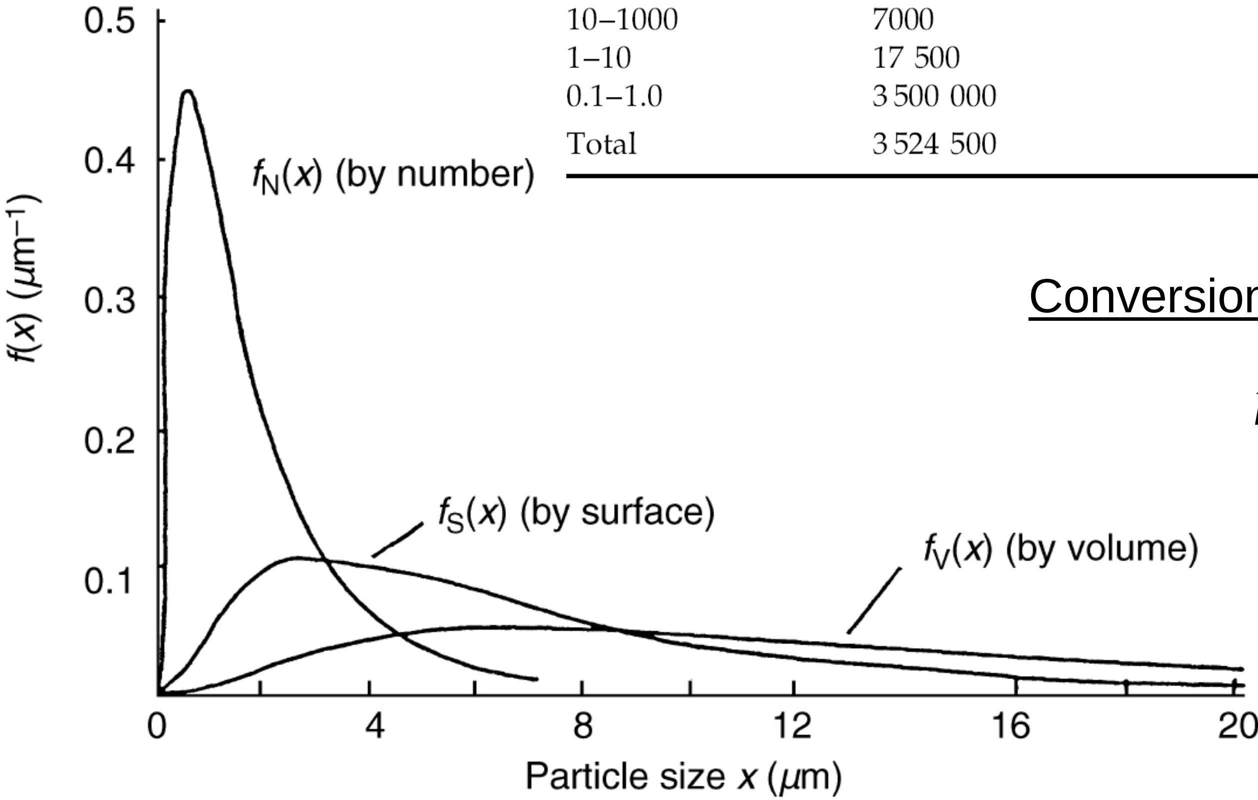


Table 1.3 Mass and number distributions for man-made objects orbiting the earth

Size (cm)	Number of objects	% by number	% by mass
10–1000	7000	0.2	99.96
1–10	17 500	0.5	0.03
0.1–1.0	3 500 000	99.3	0.01
Total	3 524 500	100.00	100.00

Conversion:

single particle volume — number of part. in fraction

$$f_V(x) = \frac{\alpha_V x^3 \, N f_N(x)}{V}$$

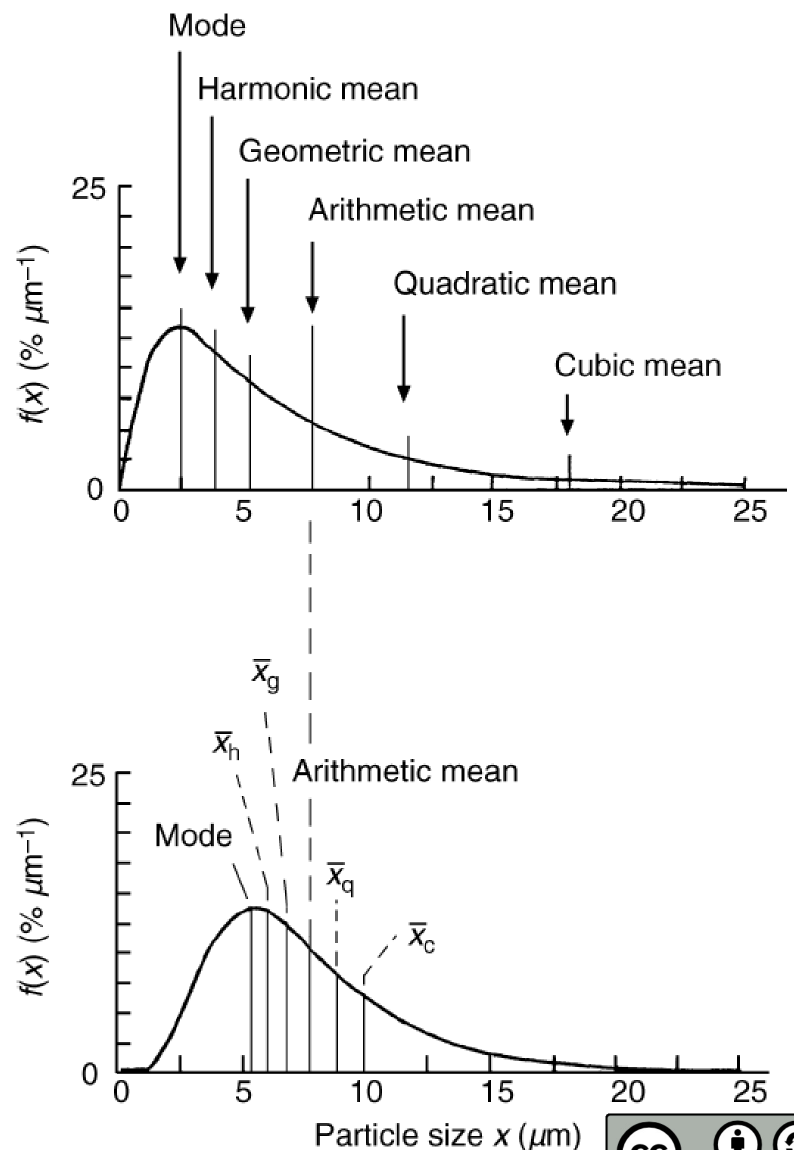
total volume

Mean particle size

Table 1.4 Definitions of means

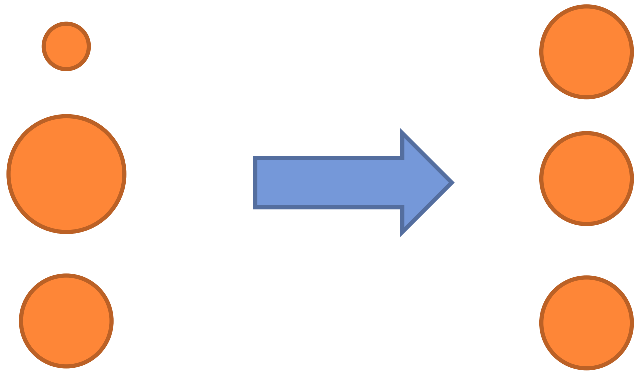
$g(x)$	Mean and notation
x	arithmetic mean, $\bar{x}_a$
x^2	quadratic mean, $\bar{x}_q$
x^3	cubic mean, $\bar{x}_c$
$\log x$	geometric mean, $\bar{x}_g$
$1/x$	harmonic mean, $\bar{x}_h$

- Different definitions of mean
  - Each definition conserve some property of the population (size, surface, volume)
  - Samples with same mean size can be different
  - Different applications will require different means



Mean particle size

- = replace real population by monodisperse population



- Monodisperse population
  - the same number of particles
  - sum of certain property of all particles
    - size
    - surface
    - volume

PSD measurement

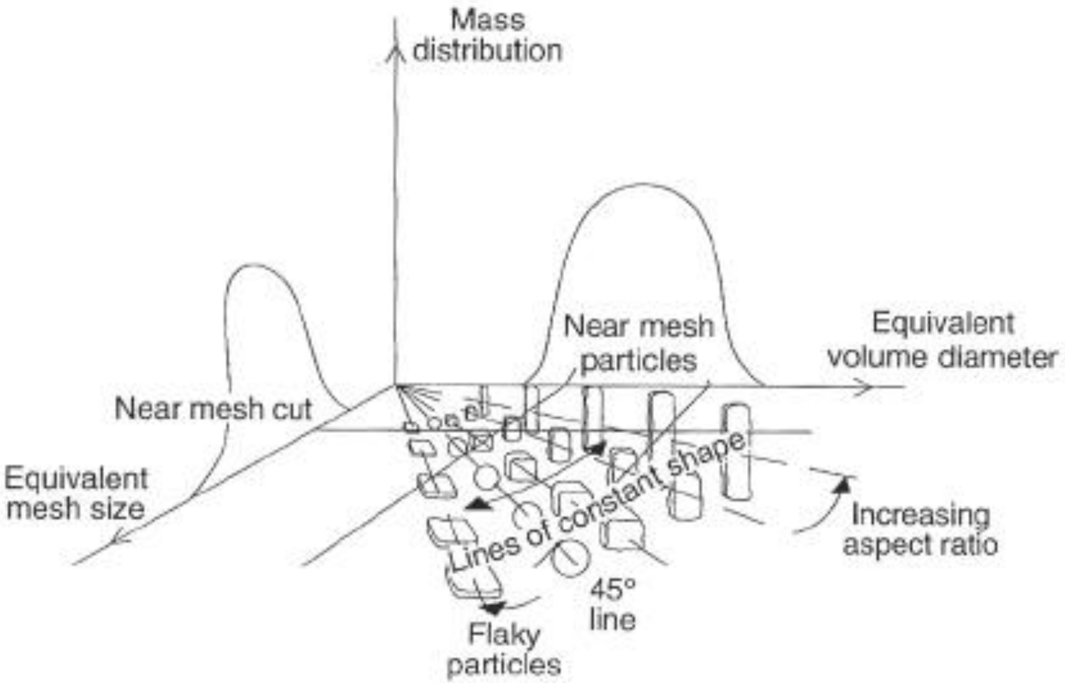
- Sieve analysis
  - splitting the sample to fractions in column of sieves with decreasing apertures

» Result

» mass distribution

PSD measurement

- Sieve analysis limitations
  - difficult interpretation for non-isometric particles ψ
  - < 150 µm (problems)
  - „wet sieving“ down to 30 µm)

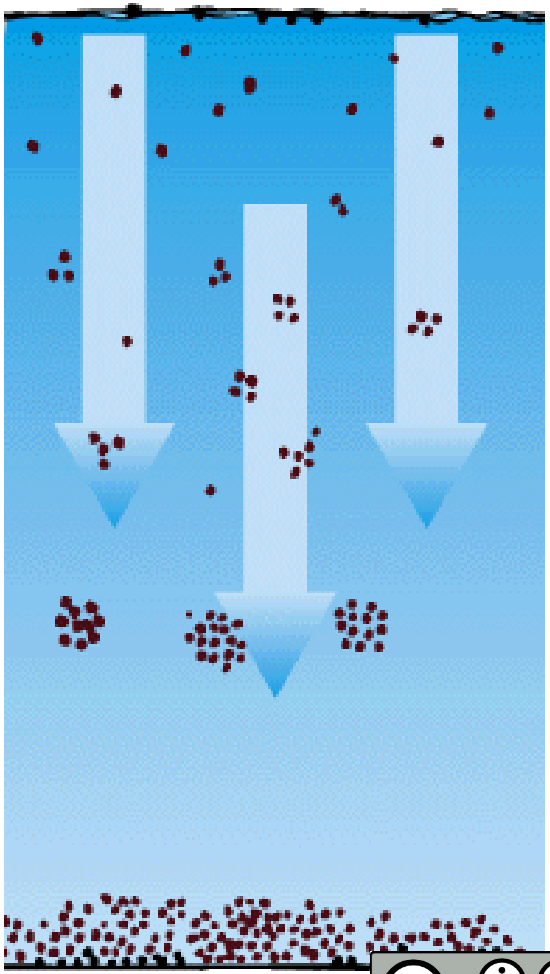


PSD measurement

- Microscopy
  - optical or SEM
  - direct observation of particle 2D projection
  - image analysis – evaluating PSD
  - limitations
    - image contrast
    - only 2D
    - 0.2 – 100 µm

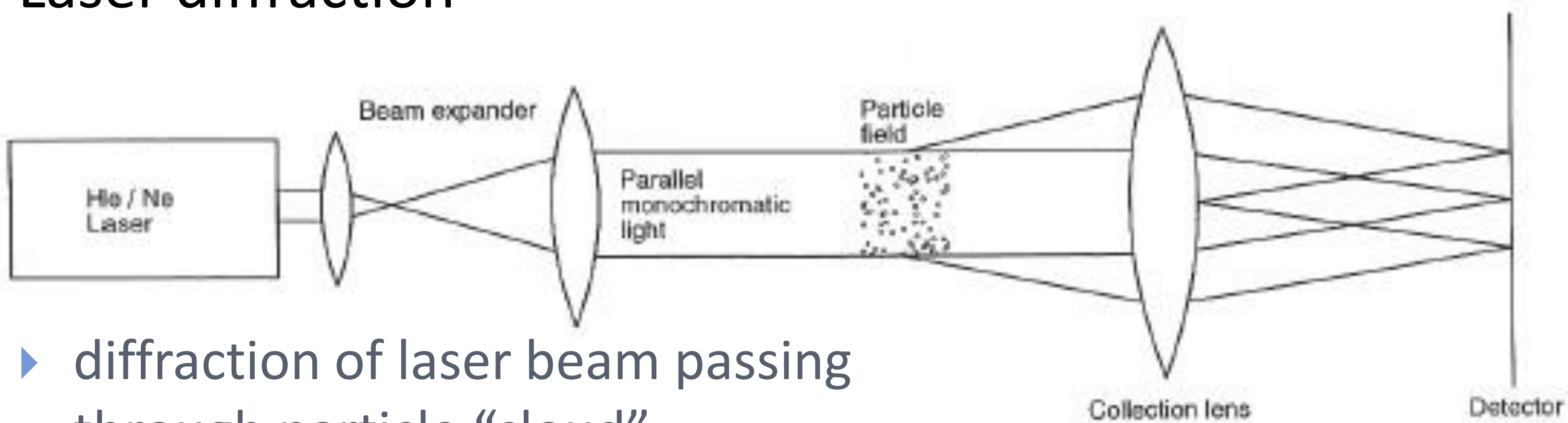
PSD measurement

- Sedimentation
  - differentiates particles according to settling velocity
  - 0,8 – 300 µm
- Elutriation



PSD measurement

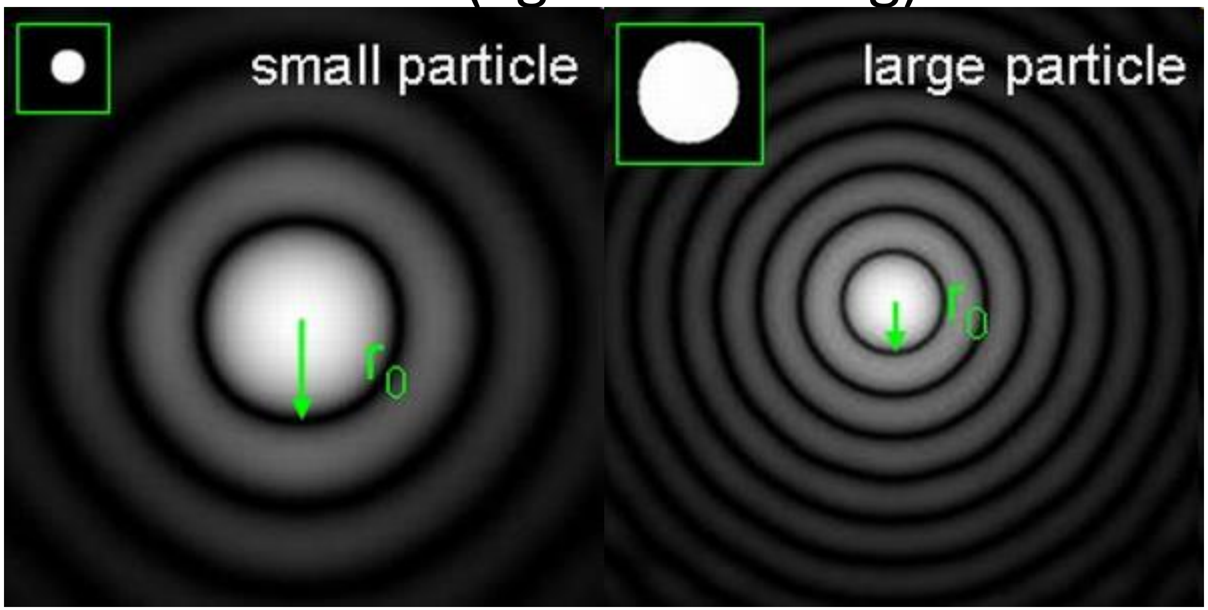
- Laser diffraction

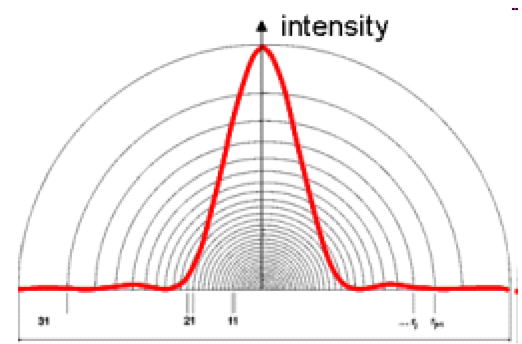


  - diffraction of laser beam passing through particle “cloud”
  - FT of diffraction patterns

PSD measurement

- Laser diffraction (light scattering)

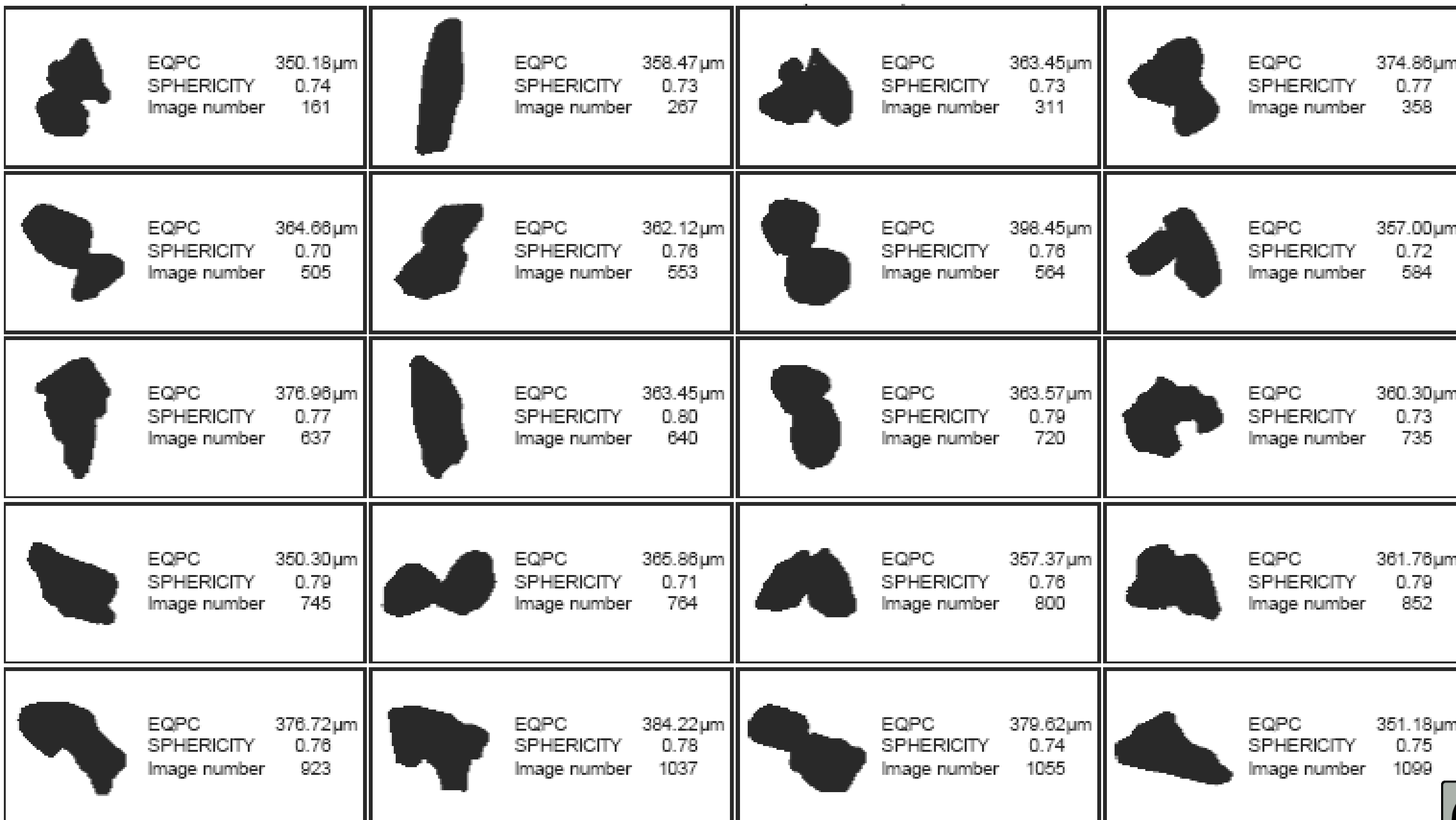




  - sensitive in 0.2 - 500 µm
    - (state-of-the-art equipment 0.02 – 2000 µm)
  - problems caused by transparent particles

Particle shape

- 2D or 3D image analysis

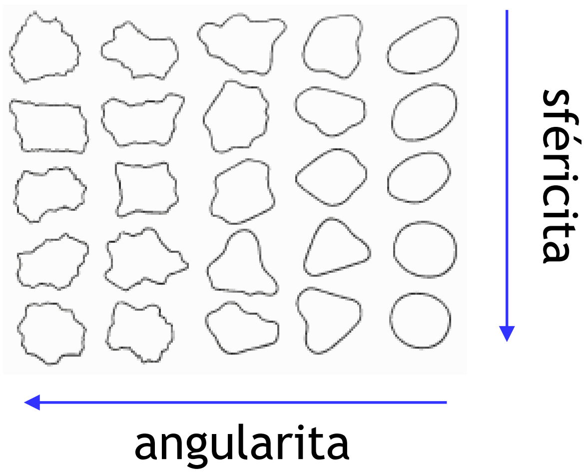


Particle shape

- Simple shape characteristics
  - sphericity
    - ratio of equivalent sphere surface to particle surface

$$\Psi = \frac{\pi^{\frac{1}{3}}\left(6V_p\right)^{\frac{2}{3}}}{A_p}$$

  - angularity (surface roughness)



Particle surface area

- Depends on particle size and shape
- Standard methods of measurement
  - Adsorption methods
  - Calculation using size and shape
  - Permeability measurements
- Reported as A_s
  - specific surface area m^2/g

Requirements for pharmaceutical bulk materials

- Must flow well (to pour)
  - so that the device can work with high performance and reliability
  - to ensure accurate volumetric metering
- Must be homogenous
  - so that the dose is constant
- Must have **sufficient surface**
  - to active substance dissolves well

Bulk particulate solid properties

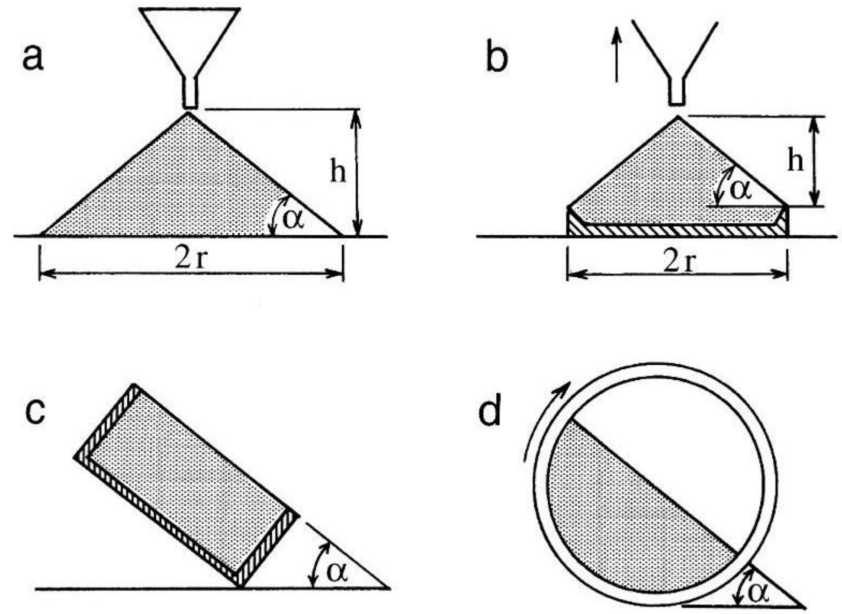
- Bulk density ρ_B
  - density of the particulate solid including the voids
  - not a state variable
- Tapped density ρ_T
  - bulk density after compacting the PS by tapping
- Packing fraction η
  - particle volume / bulk volume
- Void fraction $\varepsilon = 1 - \eta$
  - void volume / bulk volume

Flow properties

- Good flowability
  - larger particles
  - smooth particles
  - round, regular particles
- Poor flowability
  - fine particles
  - rough surfaces
  - irregular shape (flakes, needles)
- Particulate solid flow is determined by **stress state**

Brief methods for characterizing flowability

- Angle of repose
- „Flow“ rate through orifice (funnel)



a – kužel nasypaný na volnou podložku, b – kužel nasypaný na podložku s okrajem, c – stanovení v hranolovité nádobě, d – stanovení v otočném válci

Angle of repose

Brief methods for characterizing flowability

- Hausner ratio
  - tapped/bulk density ratio
  - measure of self-compressibility
  - poor flowability for H > 1,25
- Carr´s index
  - good flowability C < 15 %
  - poor flowability C > 25 %
  - common values 5 – 40 %

$$H = \frac{\rho_T}{\rho_B}$$

$$C = 100\frac{V_B - V_T}{V_B}$$

$$H = \frac{C}{100} + 1$$

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Engineering in Chemical and Pharmaceutical Processes

Particle sizing and comminution processes

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Particle sizing

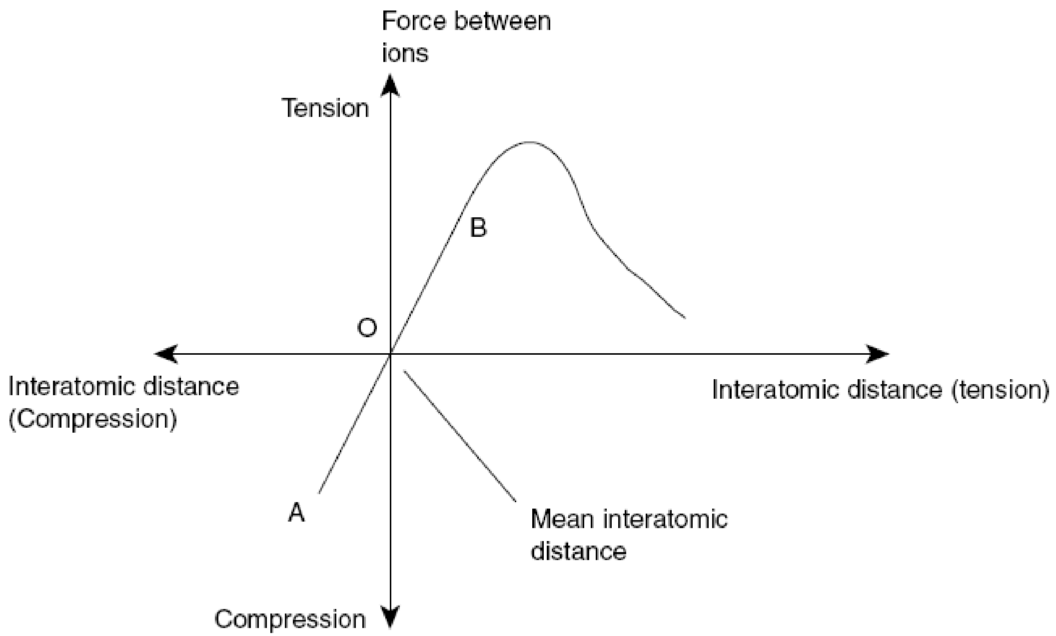
- Why make the particles smaller?
  - more precise dosage
  - increasing surface area
    - faster dissolution, drying
  - attain uniform size
  - better compressibility
- Why make the particles bigger?
  - decrease compressibility , improve flowability
  - fix homogeneity
  - improve particle shape

Decreasing particle size

- Comminution processes by input particle size
  - Coarse d = 20 – 100 cm (crushers, grinders, cutters)
  - Medium d = 2 – 20 cm (mills, raspers)
  - Fine d = 0.3 – 2 cm (mills)
  - Very fine (special mills)
- Comminution
  - very inefficient energy utilization

Fragmentation theory

- Solid (crystal)
  - Molecules arranged in a structure (crystal lattice)
  - Energy needed to break the structure

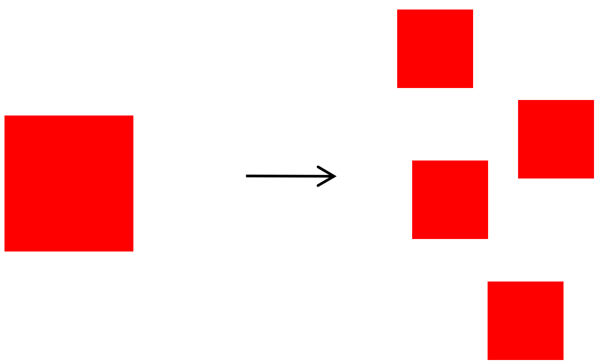


Energy consumption

- Fragmentation
  - energy consumption proportional to newly formed surface area
  - fragmentation occurs in structural defects
- Losses
  - elastic deformation of particles
  - powder bulk compaction
  - friction
  - plastic deformation of particles

Rittinger’s law (1867)

- Assumption
  - energy consumption proportional to newly formed surface area
- Based on balance of surface and volume of particles



$$V_1 = k_V d_1^3 \qquad V_2 = k_V d_2^3$$

$$S_1 = k_S d_1^2 \qquad S_2 = k_S d_2^2$$

$$N_{1\rightarrow 2} = \frac{V_1}{V_2}$$

Rittinger's law (1867)

- Newly formed surface

$$S_{1\to 2} = N_{1\to 2} S_2 - S_1 = \frac{V_1}{V_2} S_2 - S_1 = \frac{d_1^3}{d_2^3} k_S d_2^2 - k_S d_1^2$$

- Newly formed specific surface

$$S_{spec} = \frac{S_{1\to 2}}{m} = \frac{S_{1\to 2}}{V_1 \rho} = \frac{1}{\rho k_V d_1^3} \left(\frac{d_1^3}{d_2^3} k_S d_2^2 - k_S d_1^2 \right)$$

$$S_{spec} = \frac{k_s}{k_V} \frac{1}{\rho} \left(\frac{1}{d_2} - \frac{1}{d_1} \right)$$

Rittinger's law (1867)

- Integral form

$$E = C\left(\frac{1}{d_2} - \frac{1}{d_1}\right) = K_R f_c \left(\frac{1}{d_2} - \frac{1}{d_1}\right)$$

  - K_R ... Rittinger's constant
  - f_c ... material strength in compression [N.m^{-2}]
- Differential form

$$\frac{\mathrm{d}E}{\mathrm{d}d} = -C\frac{1}{d^2}$$

- Application
  - Suitable for very fine milling
  - $d_p < 0{,}05$ mm
  - Energy consumption overestimated for larger particles

Kick's law (1885)

- Assumption
  - Energy consumption proportional to comminution ratio
- Deriving differential form

$$\frac{d_1}{d_2}$$

$$\frac{d_2}{d_1} = \frac{d_1 - \Delta d_1}{d_1} = 1 - \frac{\Delta d_1}{d_1}$$

$$\Delta E = -C\frac{\Delta d}{d} \xrightarrow{\lim \Delta d \to 0} \frac{\mathrm{d}E}{\mathrm{d}d} = -C\frac{1}{d}$$

Kick's law (1885)

- Integral form

$$E = C \ln \frac{d_1}{d_2} = K_K f_c \ln \frac{d_1}{d_2}$$

- Symbols
  - K_K ... Kick's constant
- Application
  - underestimates energy needed to comminute smaller particles
  - good for coarse milling and crushing
  - $d_\mathrm{p} > 50$ mm

Griffith's theory

- Solid body under stress accumulates energy (deformation energy)
- Deformation energy (DE) is not distributed uniformly throughout the body
  - DE is concentrated on structural defects in material
  - Concentration factor

    $$K = \left(1 + 2\sqrt{\frac{L}{R}}\right)$$

    - L, R … longitudinal and lateral dimension of defect
- Fragmentation occurs by spreading the defects (failures) if
  - DE accumulated is greater than increase in surface energy by fragmentation
  - there is a defect within the material (most materials contain defects naturally)

Bond's law (1952)

- Semiempirical, validated by application on materials

$$E = C\left(\frac{1}{\sqrt{d_2}} - \frac{1}{\sqrt{d_1}}\right) = K_B f_c \left(\frac{1}{\sqrt{d_2}} - \frac{1}{\sqrt{d_1}}\right)$$

- Symbols
  - K_B ... Bond's constant
  - f_c ... material strength in compression [N.m^{-2}]
- Application
  - for common milling processes
  - 0.05 mm < d_p < 50 mm

Bond's law (1952)

- Integral form

$$E = C\left(\frac{1}{\sqrt{d_2}} - \frac{1}{\sqrt{d_1}}\right) = K_B f_c\left(\frac{1}{\sqrt{d_2}} - \frac{1}{\sqrt{d_1}}\right)$$

- Differential form

$$\frac{\mathrm{d}E}{\mathrm{d}d} = -C\frac{1}{d^{3/2}}$$

- "Practical" form
  - W_1 … work index
    - energy for comminution from infinity size to 100 µm
    - particle size approximated at F(d) = 80 %

$$E = W_1\left(\frac{10}{\sqrt{d_2}} - \frac{10}{\sqrt{d_1}}\right)$$

Energy consumption (generalization)

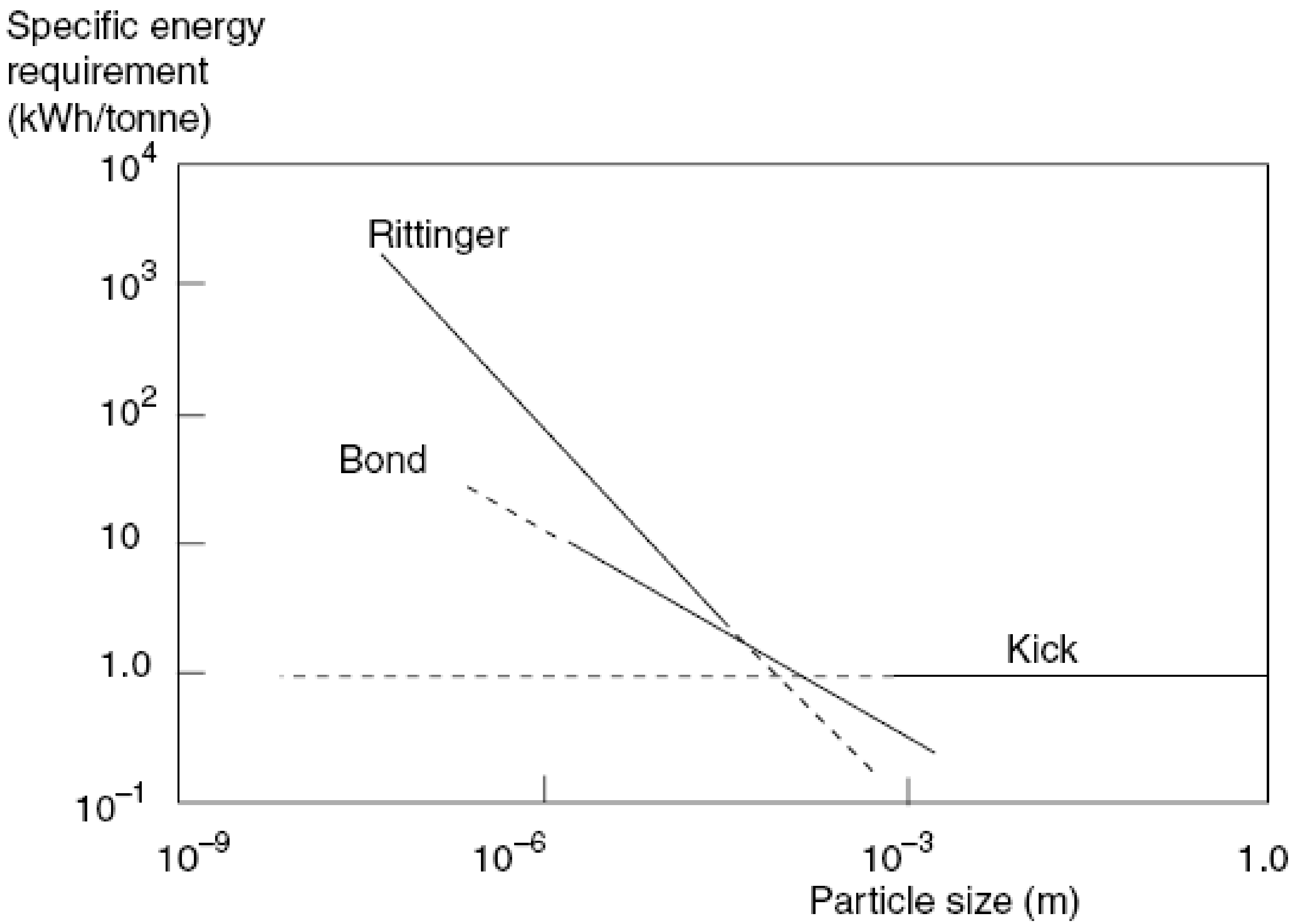
- General formula

$$\frac{\mathrm{d}E}{\mathrm{d}d} = -K f_c \frac{1}{d^n}$$

- Symbols
  - d ... particle size
  - E ... energy
  - K ... constant
  - n ... process order
  - f_c ... material strength

- Rittinger
  - n = 2, K = K_R
- Kick
  - n = 1, K = K_K
- Bond
  - n = 1,5, K = K_B

Comparison and validity of comminution laws



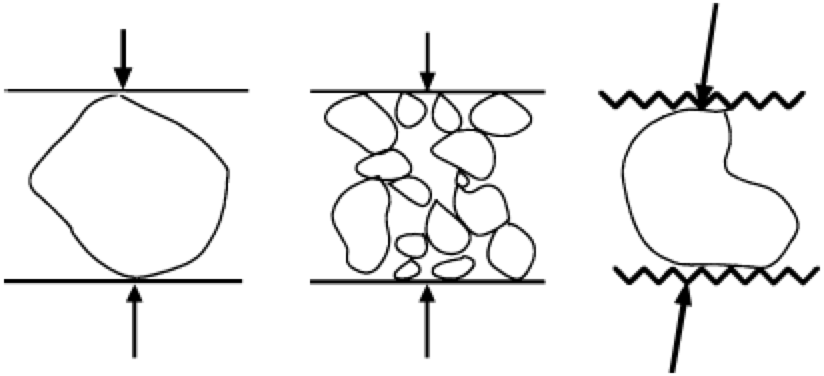
General comminution principles

- Degree of comminution, *s*
  - D … input size of coarse particles
  - d … output size of coarse particles
- Comminution energy
  - depends on particle size
- Comminution efficiency
  - low: 1 – 80 %
  - experiment needed to characterize the material in comminutor
  - then possible application of laws

$$s = \frac{D}{d}$$

Mechanisms of comminution

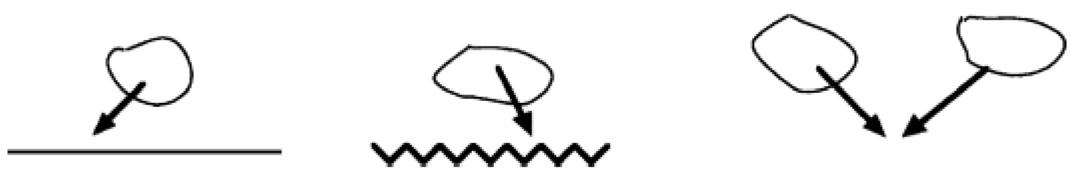
- Compression between surfaces
  - particle – particle or particle – equipment interaction
  - low speed 0.01 – 10 $m.s^{-1}$
  - crushing and shear



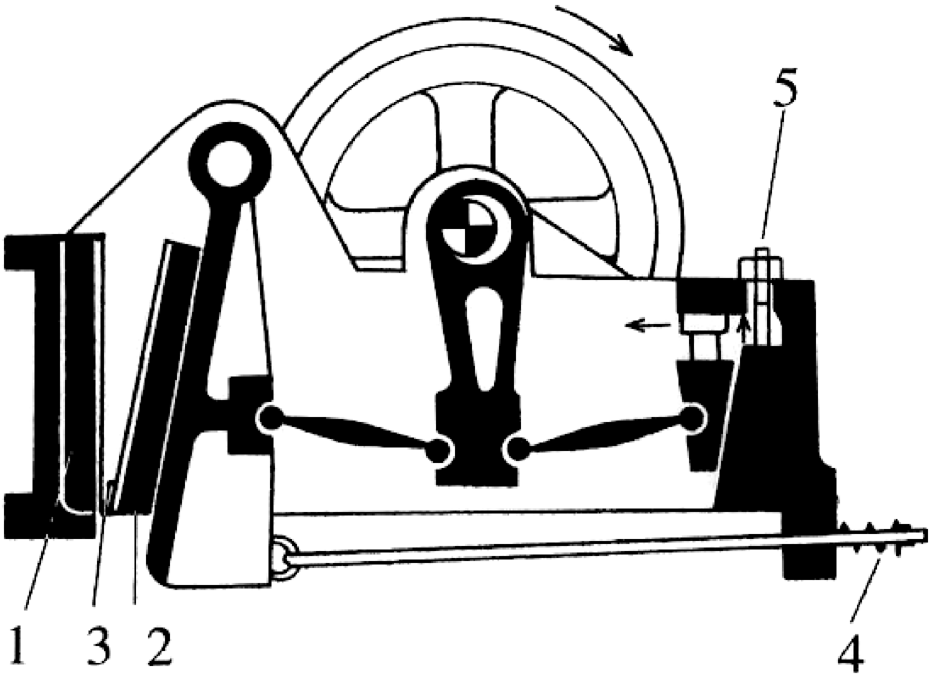
Mechanisms of comminution

- Impact on surface
  - particle – particle or particle – equipment interaction
  - high speed 10 – 2000 $m.s^{-1}$
  - impact and shear

- Shear applie

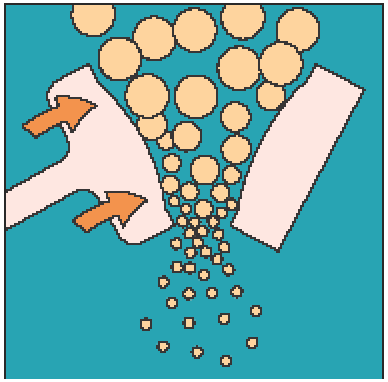


Jaw crusher

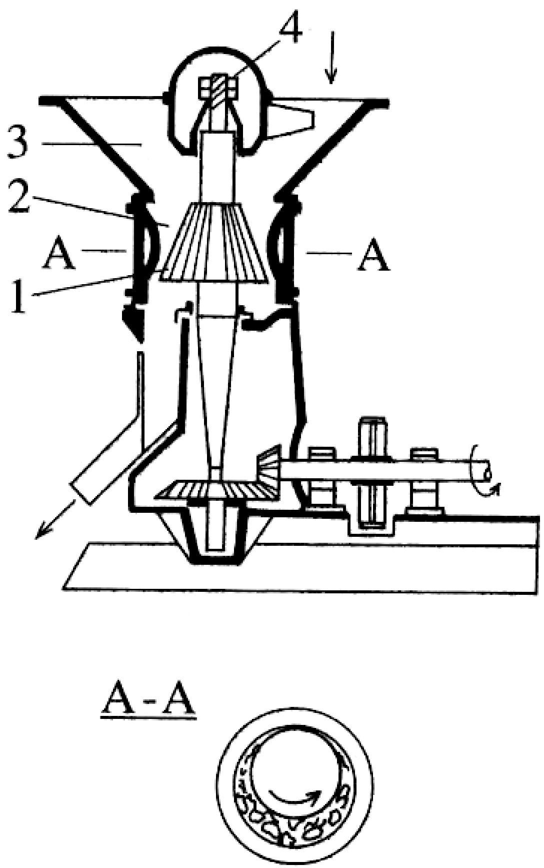


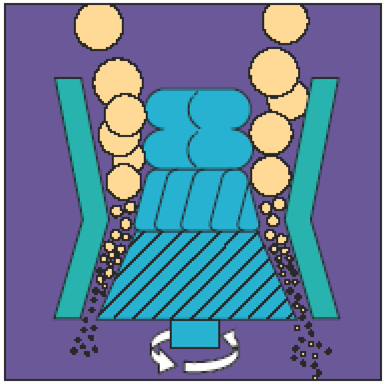
Čelisťový drtič

1 a 2 – čelisti, 3 – štěrbina, 4 – péro, 5 – stavěcí šroub



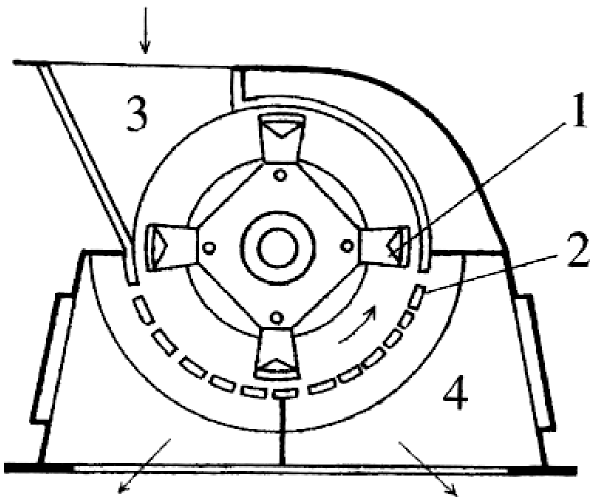
Cone crusher

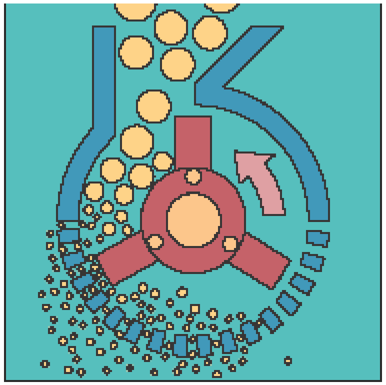




Kuželový drtič
1 – vnitřní kužel, 2 – vnější plášť, 3 – násypka, 4 – stavěcí šroub
A–A – řez vnitřním kuželem a vnějším pláštěm

Hammer mill

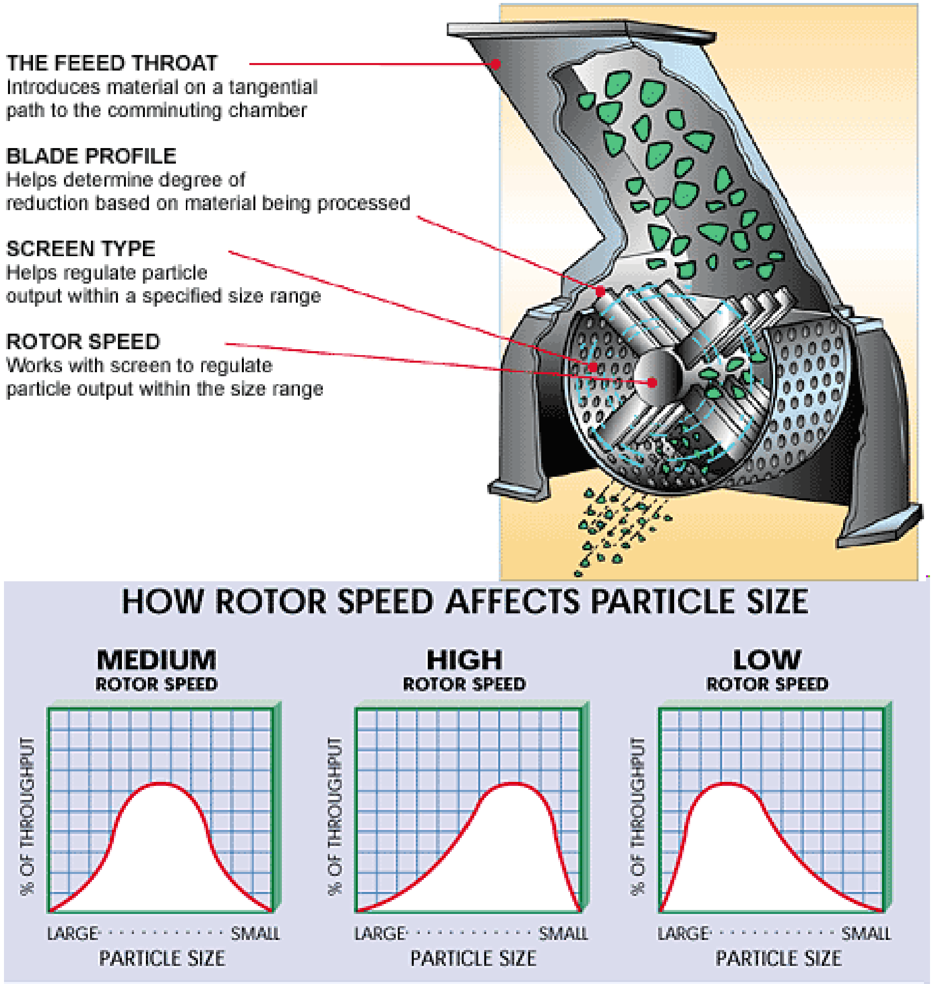


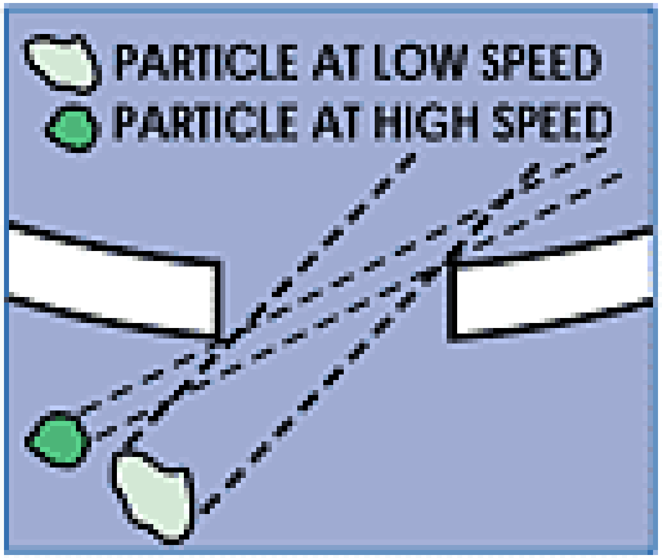


Kladivový mlýn
1 – kladiva, 2 – síto, rošty, 3 – násypka, 4 – zásobní komora

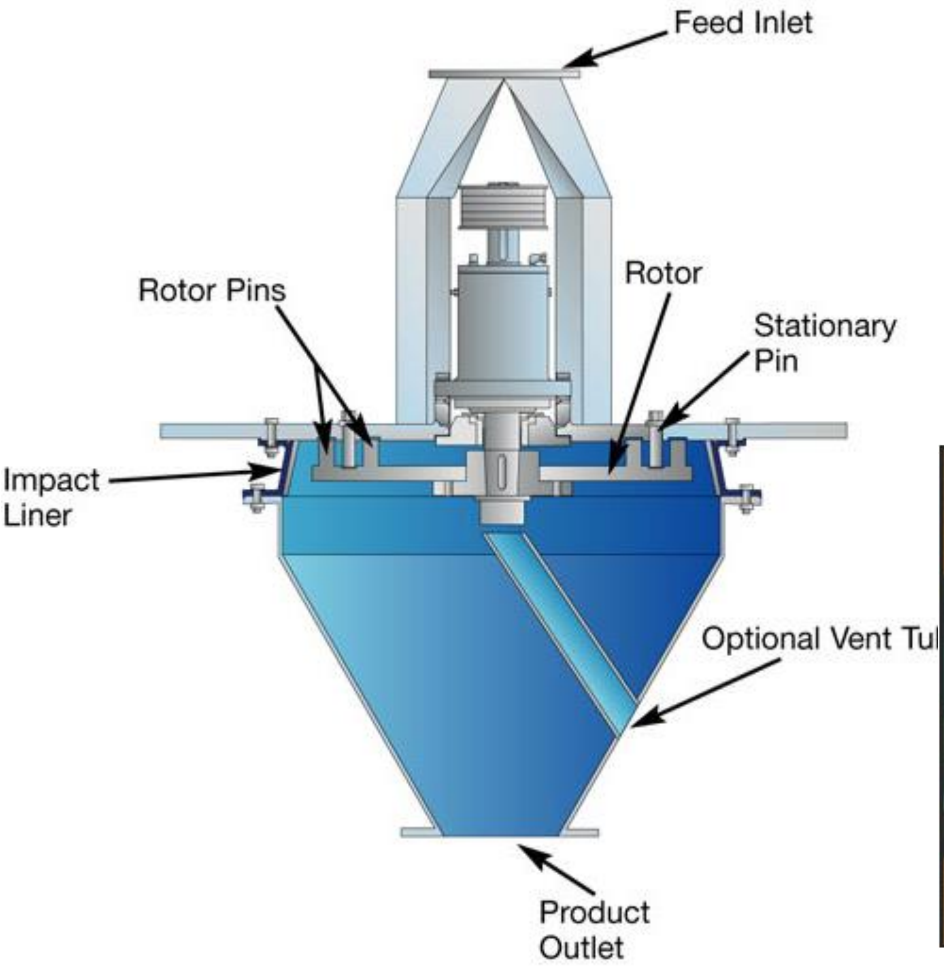
- Multi-purpose according to type of hammer
- Produces “sharp” particles (distinct edges)

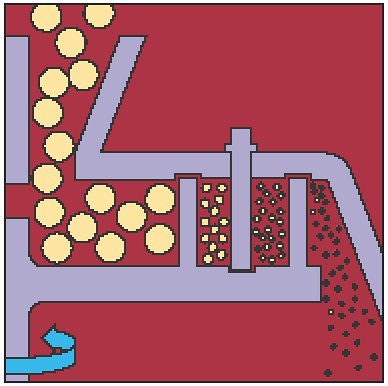
FitzMill® Comminutor

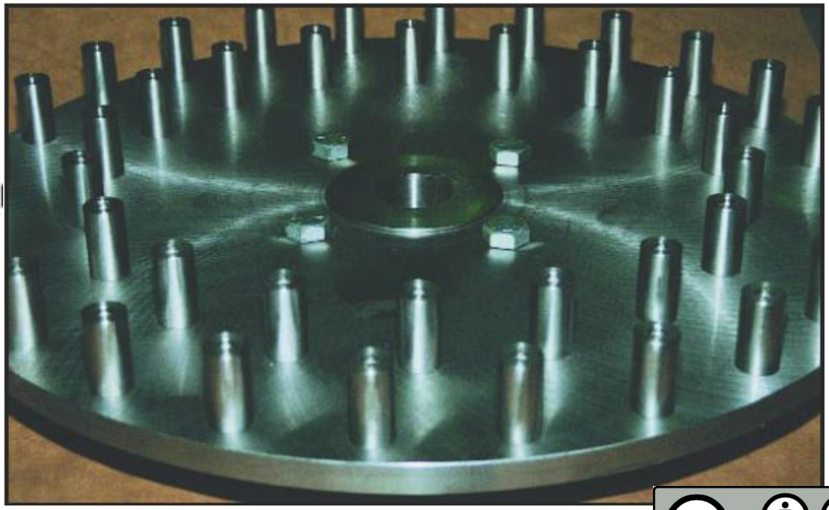




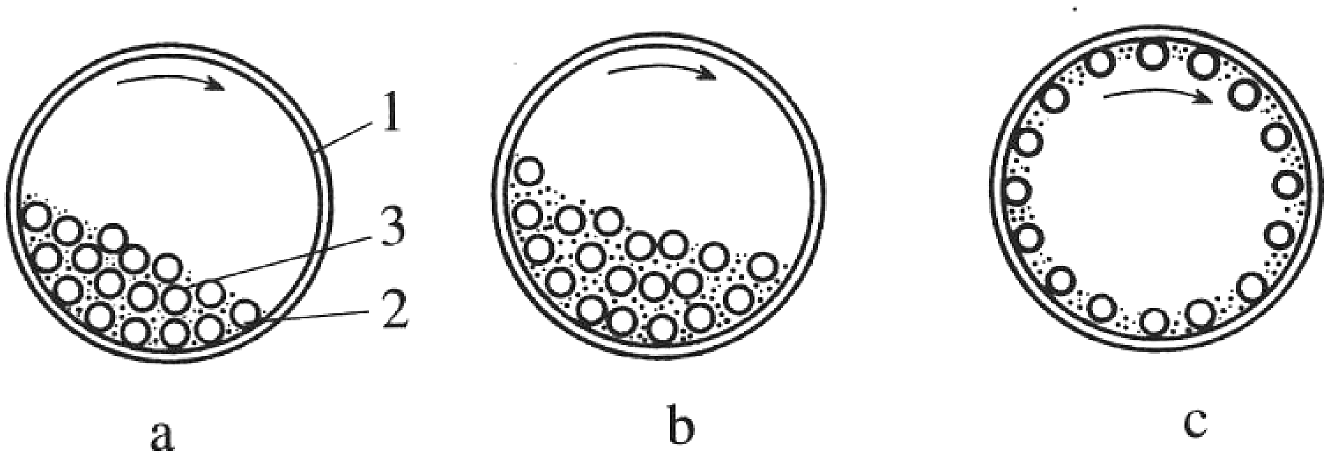
Vertical shaft mill







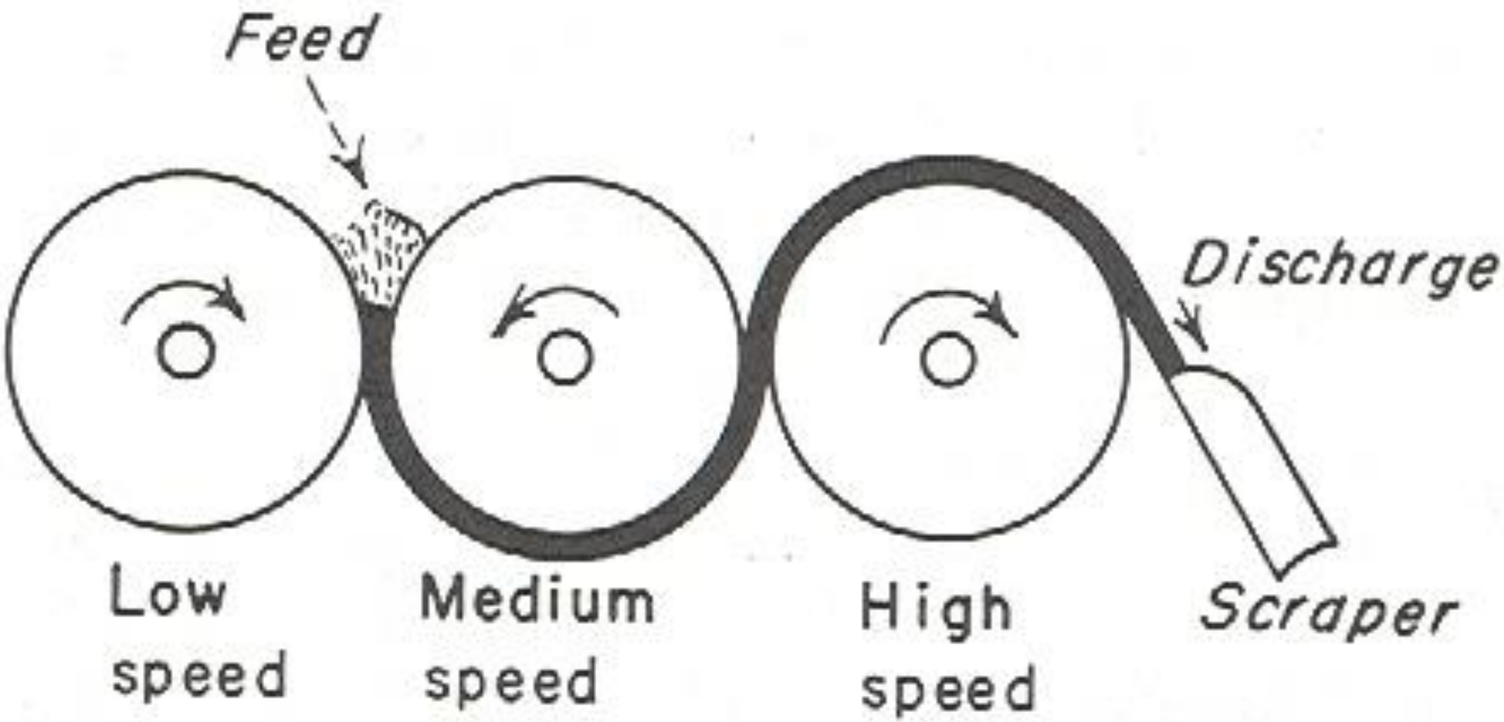
Ball mill



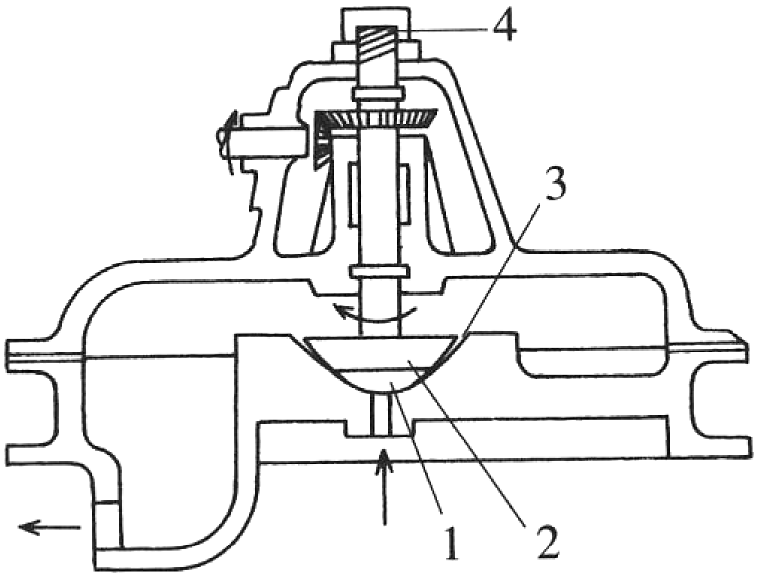
$$v_c = \sqrt{gr}$$

Obr. 3.5. Kulový mlýn
a – pomalá rotace bubnu, b – optimální počet otáček, c – příliš velký počet otáček;
1 – buben, 2 – koule, 3 – melivo

Roller mill



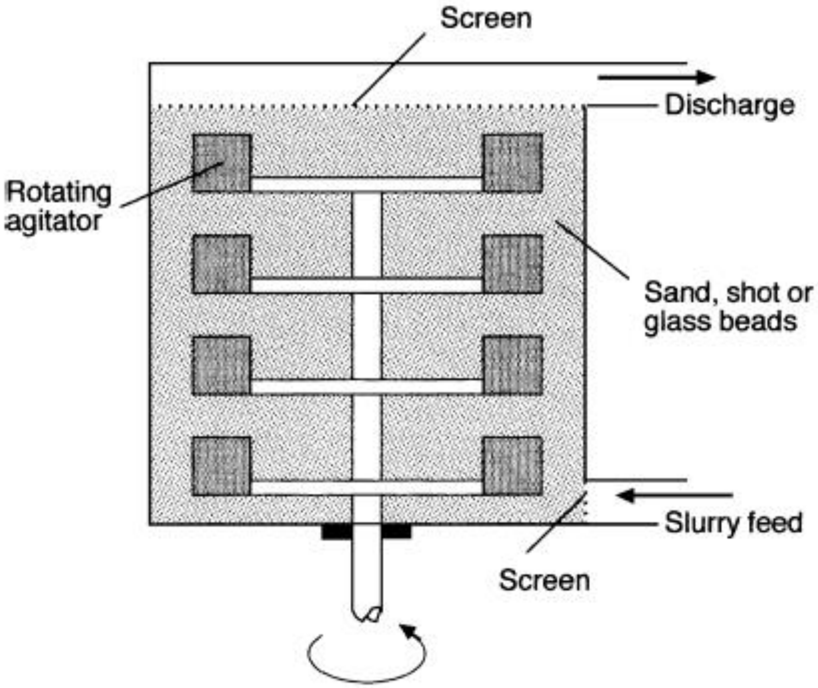
Colloidal mill



Obr. 3.6. Koloidní mlýn
1 – těleso mlýna, 2 – rotor, 3 – štěrbina, 4 – mikrometrický šroub

- Colloidal mill
  - wet operation
  - very fine milling
  - narrow PSD in product

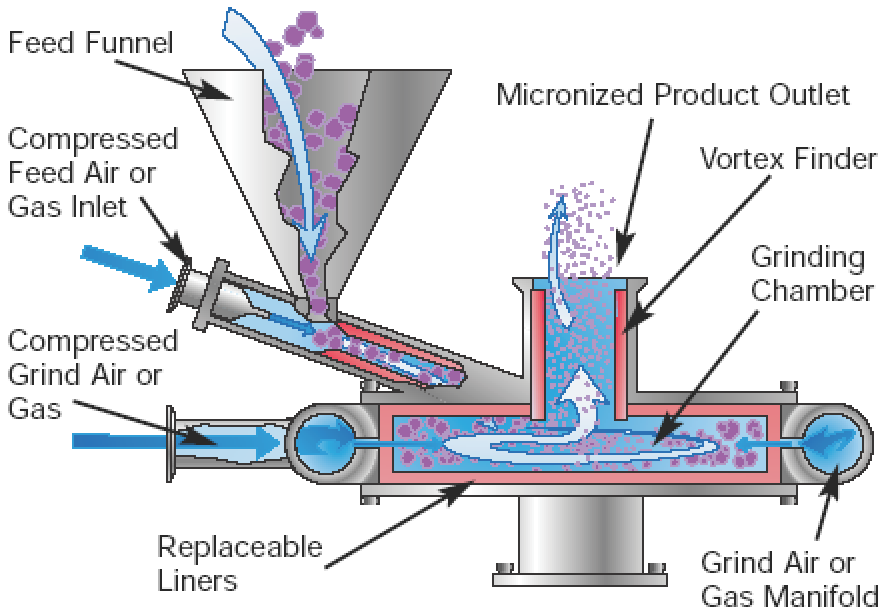
Bead mill

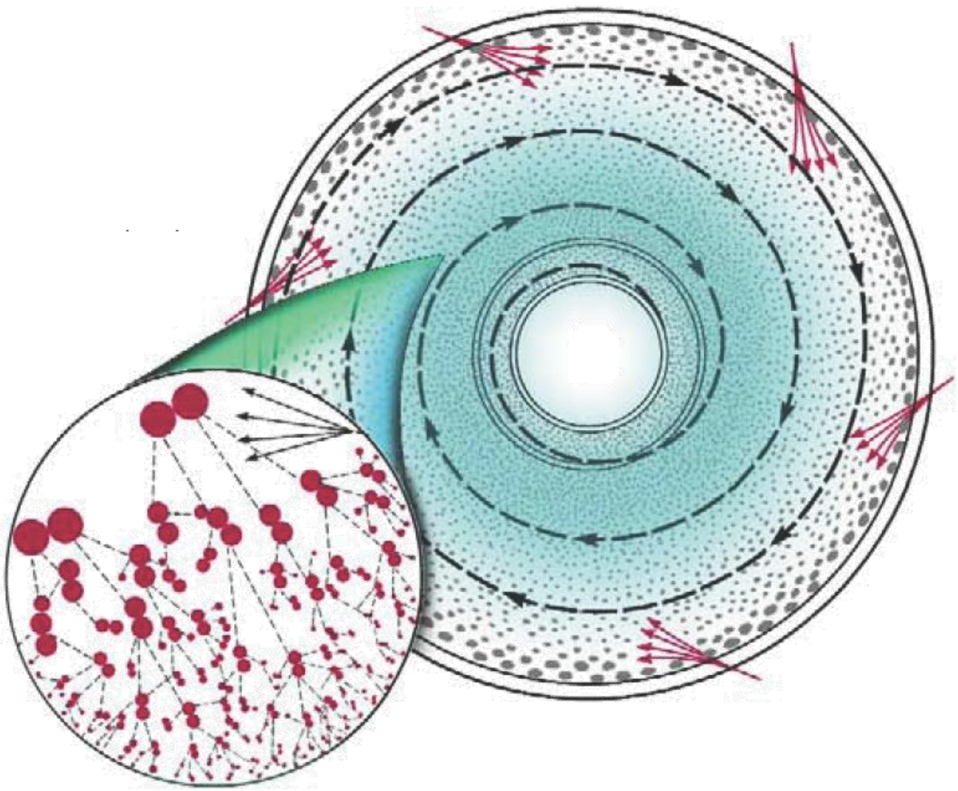


- slurry milling
- friction in milling media – spheres, beads, sand …

Micronizer

- Impacts of high velocity particles in gas stream

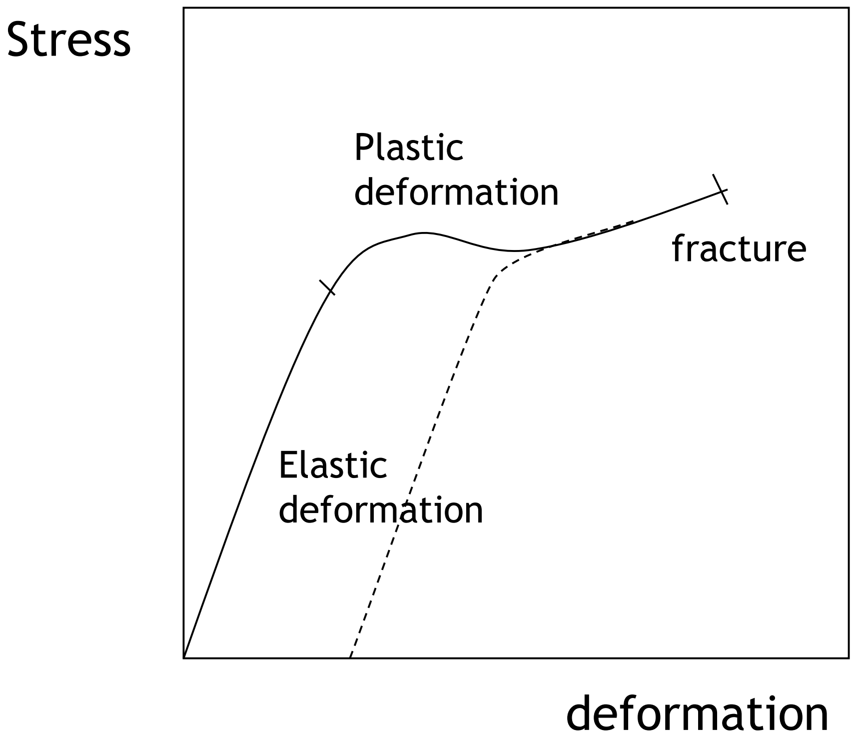




Mechanisms of comminution

- Direction of stress
  - Compression
  - Shear
  - (Tension)
- Application of force
  - direct (thin layer)
    - roller mill, colloidal mill
  - layer (lower efficiency – layer compression)
    - ball mill

Comminution affected by material properties



- Material properties
  - ductile x brittle
  - different properties in compression/shear
  - different behaviour in pressure/impact
  - different hardness

Specific requirements for equipment

- Due to the properties of comminuted material
  - hard (brittle and abrasive)
    - low speed, low contact equipment
  - plastic
    - ineffective compression, effective shear, cryoprocessing
  - wet, cohesive
    - poor flowability, possible wet operation (suspension)
  - temperature sensitivity
    - low shear, wet operation
  - sticky
    - simple equipment advantageous due to cleaning

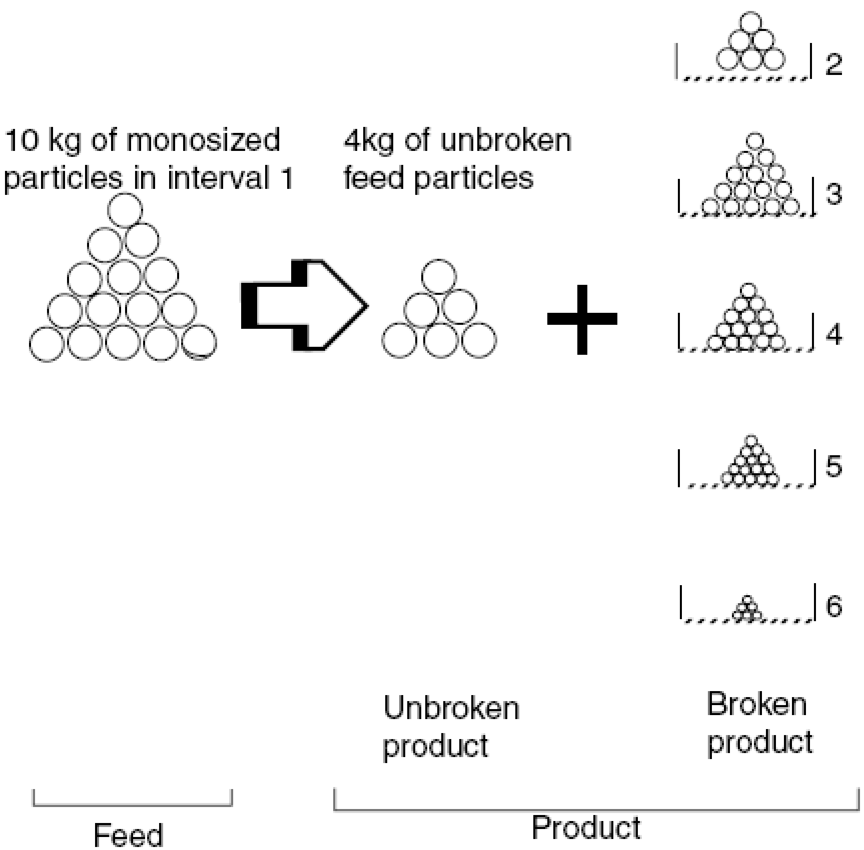
Specific requirements for equipment

- Due to the properties of comminuted material
  - slippery
    - inefficient compression
  - explosive
    - inert atmosphere, wet operation
  - toxic
    - process containments

Product particle size distribution

- Empirically determined for each apparatus
- Prediction
  - particle size classes
  - S_j … Specific rate of fragmentation for class j
    - determines fragmentation rate for each size class
    - similar to rate constant
    - [s^{-1}]
  - $b_{i,j}$ … Comminution distribution function
    - which particles will form by fragmentation of j-class particle
    - probability of formation i –class particle from j-class particle (percentage)

Product PSD



Size interval	Mass (kg)	$b\ (i, j)$	$B\ (i, j)$
2	0.9	0.15	1
3	1.8	0.3	0.85
4	1.5	0.25	0.55
5	1.2	0.2	0.3
6	0.6	0.1	0.1

Product PSD

$$\frac{\mathrm{d}m_\mathrm{i}}{\mathrm{d}t} = -S_i m_i + \sum_{i \neq j} b_{i,j} S_j m_j$$

Fragmentation of i-class particle

Formation of i-class particles from j-class particles

- S and b are mill properties
- Experimental estimation of S, b
- S, b may depend on operation (e.g. rotational speed)

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Flow Mechanics and Storage of Particulate Solids

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced
  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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Bulk particulate solid properties

- Bulk density ρ_B
  - density of the particulate solid including the voids
  - not a state variable
- Tapped density ρ_T
  - bulk density after compacting the PS by tapping
- Packing fraction η
  - particle volume / bulk volume
- Void fraction $\varepsilon = 1 - \eta$
  - void volume / bulk volume

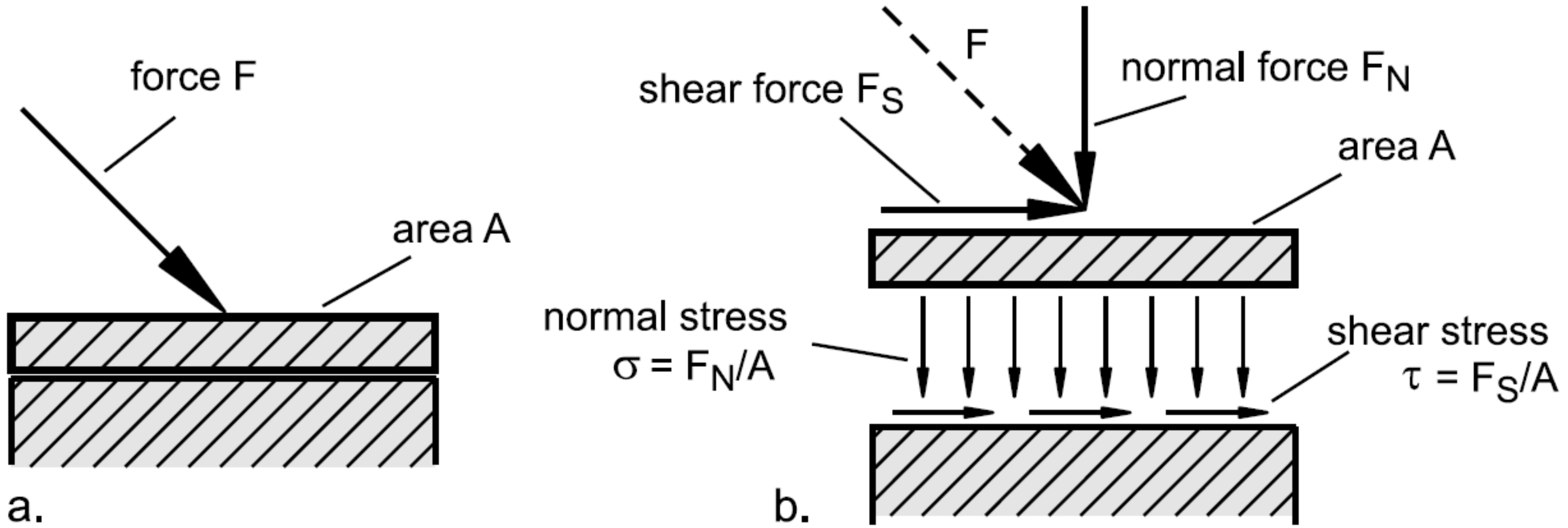
Flow properties

- Good flowability
  - larger particles
  - smooth particles
  - round, regular particles
- Poor flowability
  - fine particles
  - rough surfaces
  - irregular shape (flakes, needles)
- Particulate solid flow is determined by **stress state**

Particulate solids as continuum

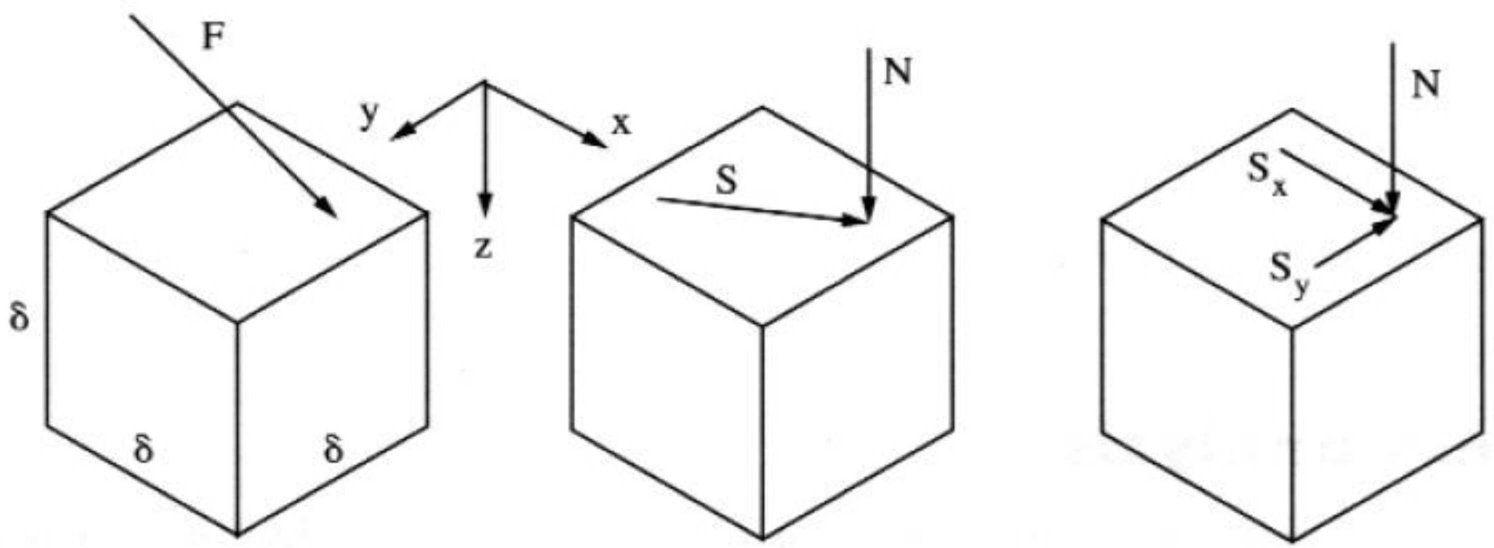
- Individual particles are not taken into account – description of volume elements

- stress state



Stress state 3D

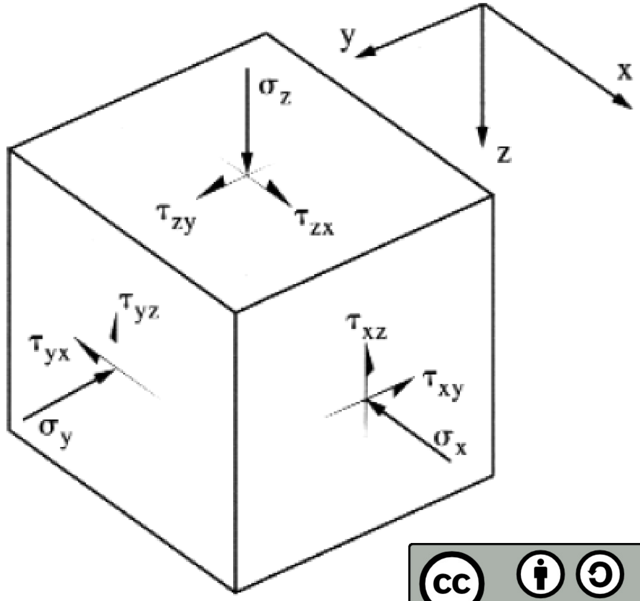
- **Stress = Force / Area [N.m^{-2}] [Pa]**
- Normal and shear stress
  - $\sigma = N / A$; $\tau = S / A$



3D stress state

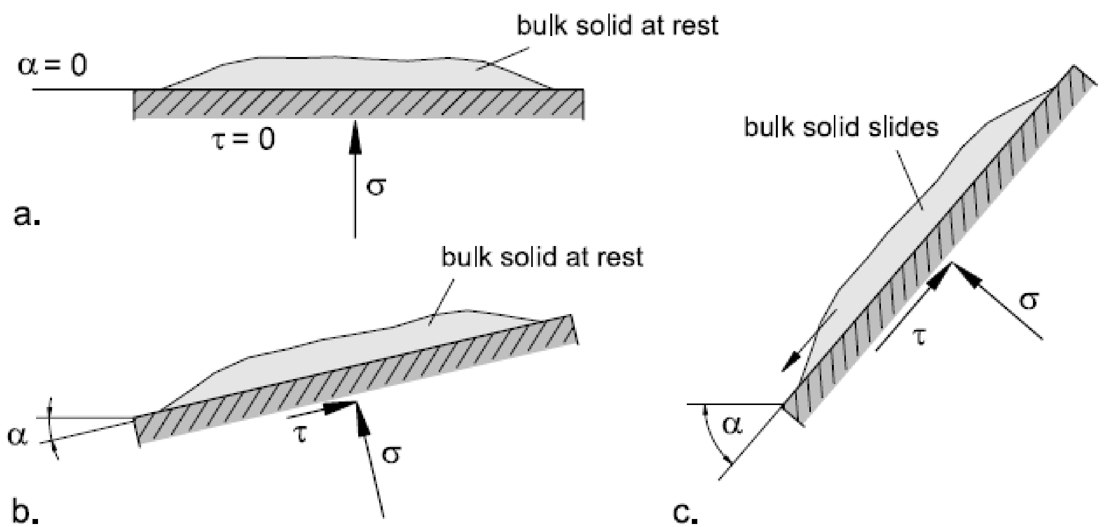
- Acting force can be decomposed to 3 dimensions → stresses can be defined on 3 perpendicular planes
  - Normal stresses σ_x, σ_y, σ_z,
  - Shear stresses τ_{xy}, τ_{yz}, τ_{zx}, τ_{yx}, τ_{zy}, τ_{xz}
  - $\tau_{zy} = -\tau_{yz}$ etc.
- Stress tensor

$$\begin{bmatrix} \sigma_x & \tau_{yx} & \tau_{zx} \\ \tau_{xy} & \sigma_y & \tau_{zy} \\ \tau_{xz} & \tau_{yz} & \sigma_z \end{bmatrix}$$



Shear stress

- Develops due to the friction between surfaces
- Exists in still or moving PS
- Depends on surface properties and acting force

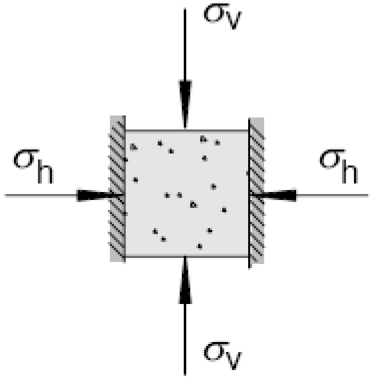


Stress in PS

- Pascal's law does not apply
  (equal pressure in all directions)
  - lateral stress ratio
  - λ ~ 0.3 .. 0.6

$$\sigma_V \neq \sigma_H$$

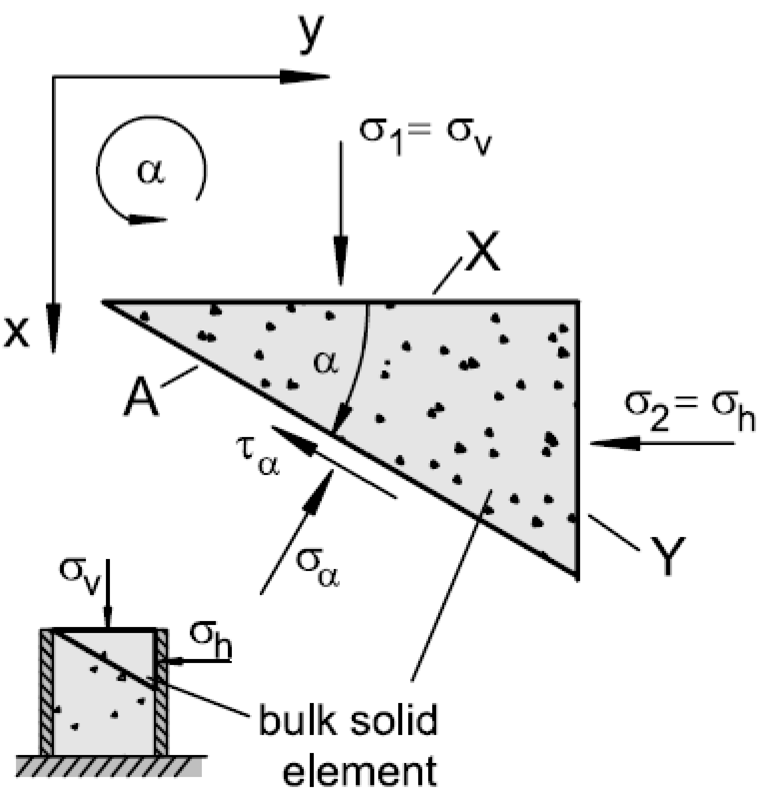
$$\lambda = \frac{\sigma_H}{\sigma_V}$$



- Shear stress in compressed element
  - zero on unconstrained planes (top, bottom)
  - non-zero on constrained planes (left, right)
    - (unless there is no friction)

Stress in PS

- Transformation of stress state to any plane



» can be expressed by formulae

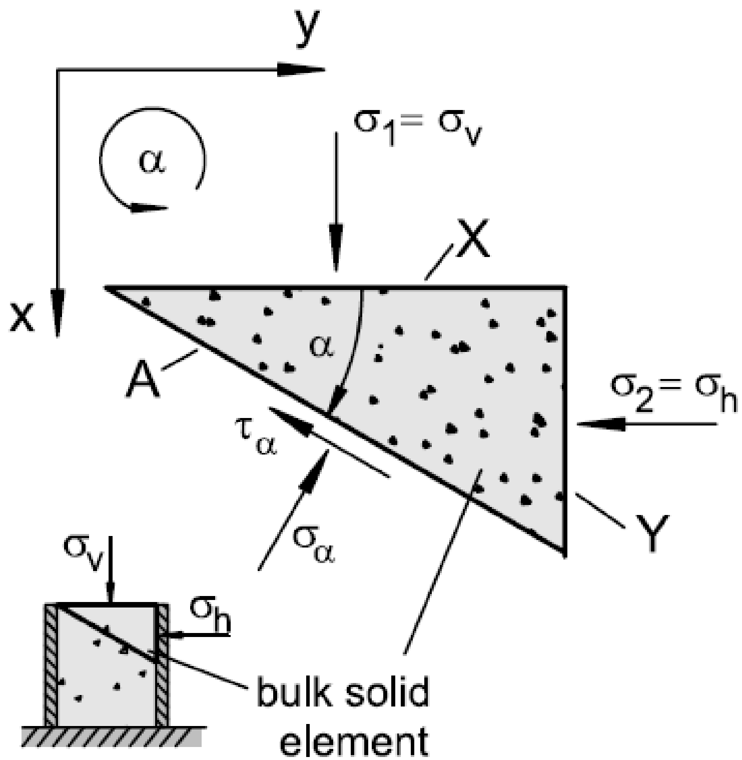
$$\sigma_\alpha = \frac{(\sigma_V + \sigma_H)}{2} + \frac{(\sigma_V - \sigma_H)}{2}\cos(2\alpha)$$

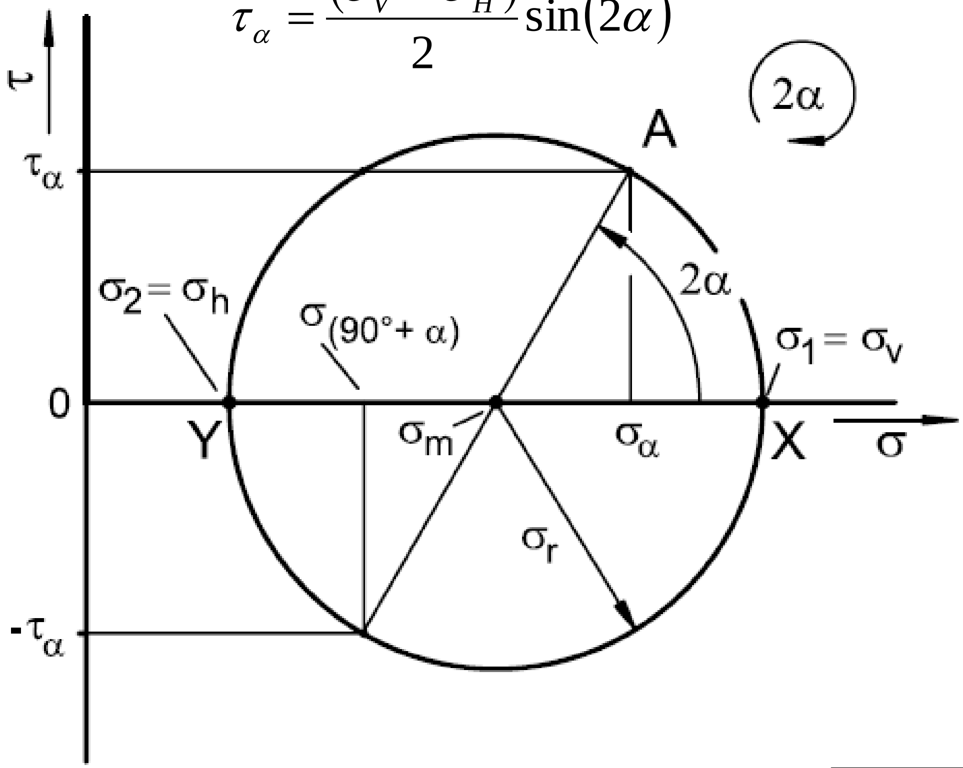
$$\tau_\alpha = \frac{(\sigma_V - \sigma_H)}{2}\sin(2\alpha)$$

Mohr's circle
graphical solution

$$\sigma_\alpha = \frac{(\sigma_V + \sigma_H)}{2} + \frac{(\sigma_V - \sigma_H)}{2}\cos(2\alpha)$$

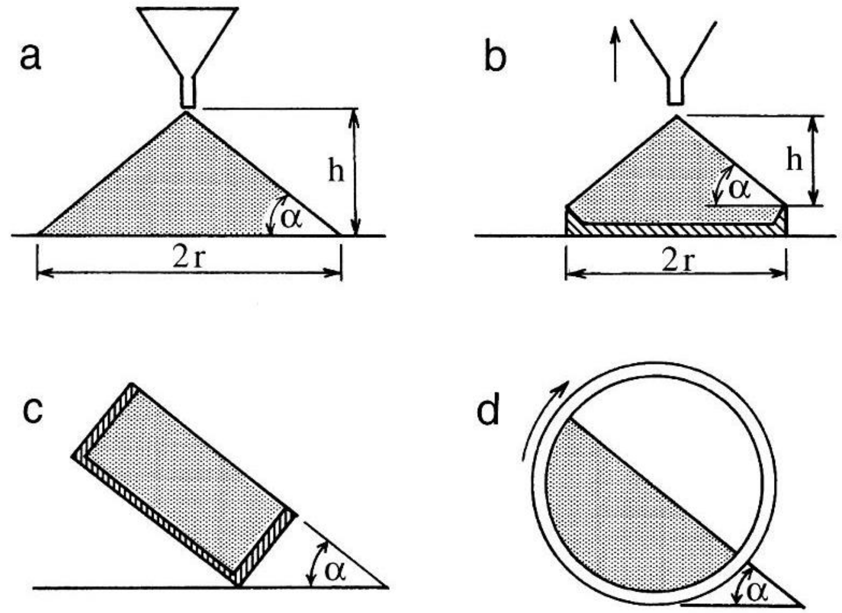
$$\tau_\alpha = \frac{(\sigma_V - \sigma_H)}{2}\sin(2\alpha)$$





Brief methods for characterizing flowability

- 1. Angle of repose
- 2. “Flow” rate through orifice (funnel)



a – kužel nasypaný na volnou podložku, b – kužel nasypaný na podložku s okrajem, c – stanovení v hranolovité nádobě, d – stanovení v otočném válci

Angle of repose

Brief methods for characterizing flowability

- 3. Hausner ratio
  - tapped/bulk density ratio
  - measure of self-compressibility
  - poor flowability for H > 1,25
- 3a. Carr´s index
  - good flowability C < 15 %
  - poor flowability C > 25 %
  - common values 5 – 40 %

$$H = \frac{\rho_T}{\rho_B}$$

$$C = 100\frac{V_B - V_T}{V_B}$$

$$H = \frac{C}{100} + 1$$

Powder properties and flow

- Powder flow depends on
  - adhesion to container
  - particle cohesion
  - often measures together as „flow properties“
- Adhesion and cohesion depend on
  - particle size and shape
  - texture of particle surface
  - dielectric properties
  - moisture

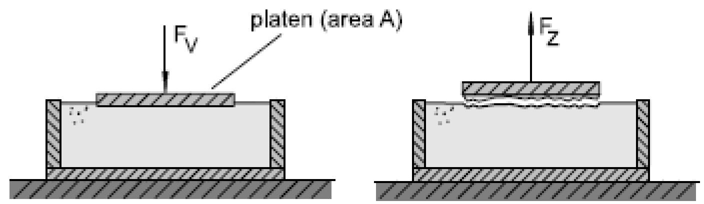
Powder flow

- Steps leading to powder flow
  - powder bed expansion
  - increasing interparticle distances
  - inertial forces break interparticle interactions
- Particulate solid flow
  - plastic solid flow
  - inertial flow
  - fluidized bed flow
  - suspension flow

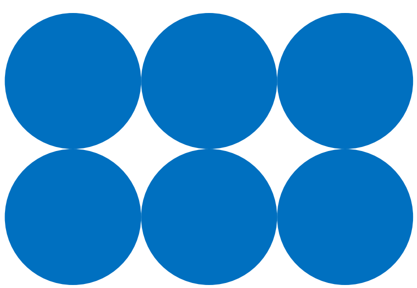
high dilution
low stress

Powder cohesion example

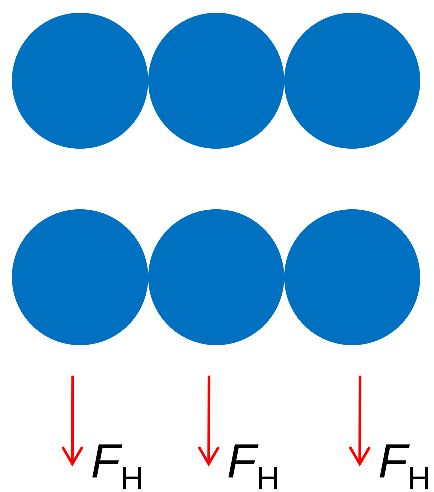
- 1. pressing glued platen
- 2. measuring tensile strength

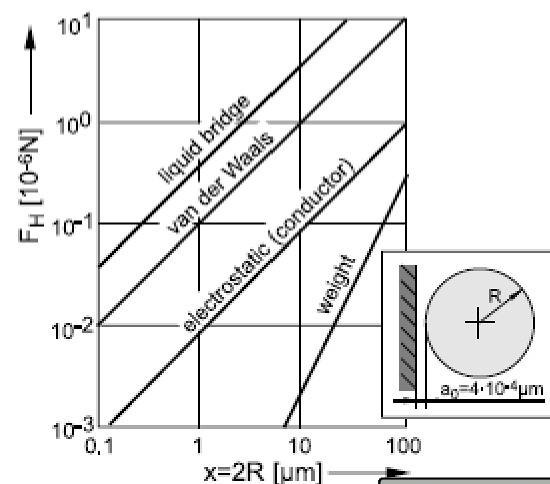


- Tensile strength depends on number of contacts between particles



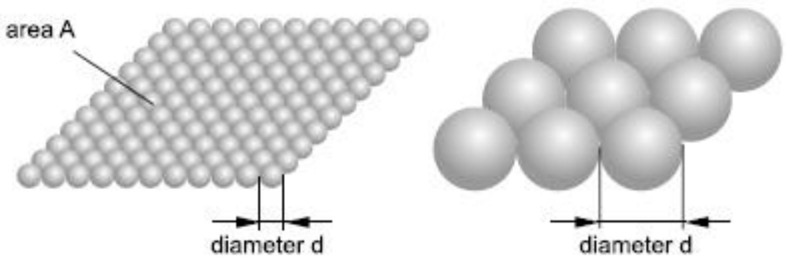
$$\sigma_t = \frac{F_Z}{A} \approx \frac{nF_H}{A}$$





Powder flow vs. particle size

- Number of contacts depends on particle size



- Tensile strength depends on the particle size

$$n \approx \frac{A}{d^2}$$

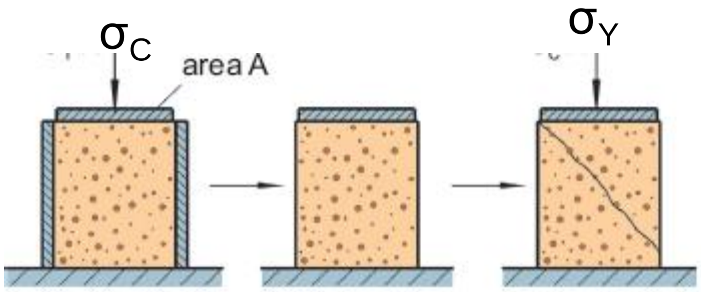
- Fine powder = poor flowability
- Particle shape effects the contact in similar manner

$$\sigma_t = \frac{F_Z}{A} \approx \frac{nF_H}{A} \approx \frac{nd}{A} \approx \frac{nd}{nd^2} \approx \frac{1}{d}$$

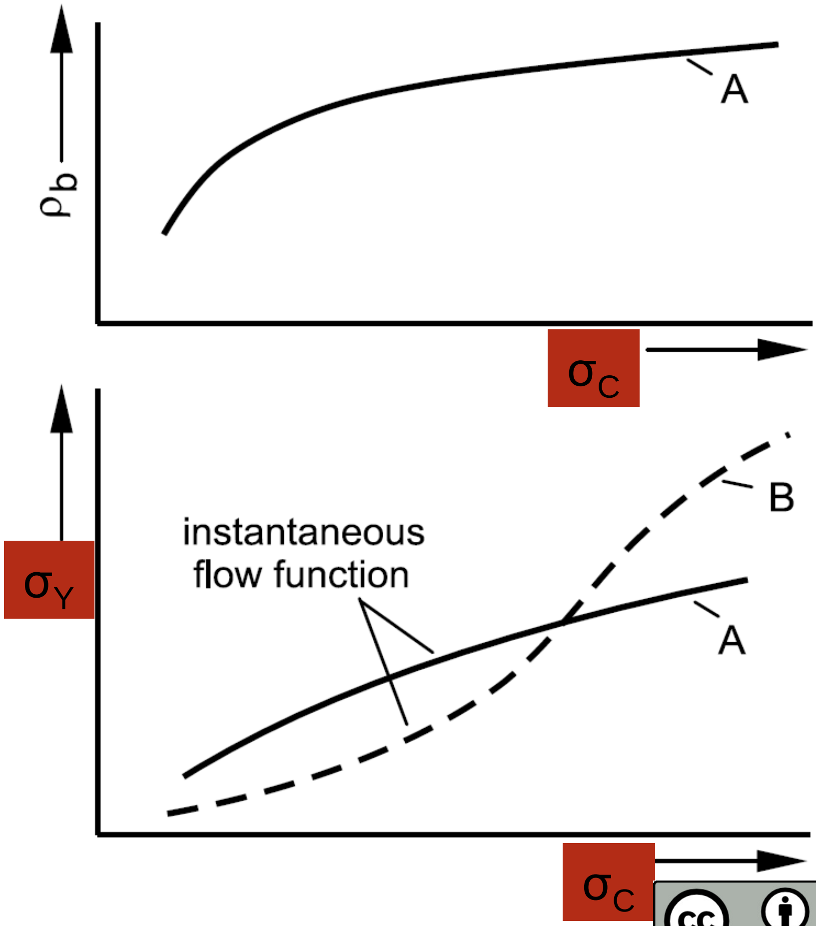
Flowability

- Good flowability (well flowing material)
  - consolidation does not occur
  - powder flows smoothly just due to gravitation
- Poor flowability (poorly flowing material)
  - consolidation by force or in time
  - non-steady flow, pulses, avalanches, etc.

Consolidation and strength of particulate solid

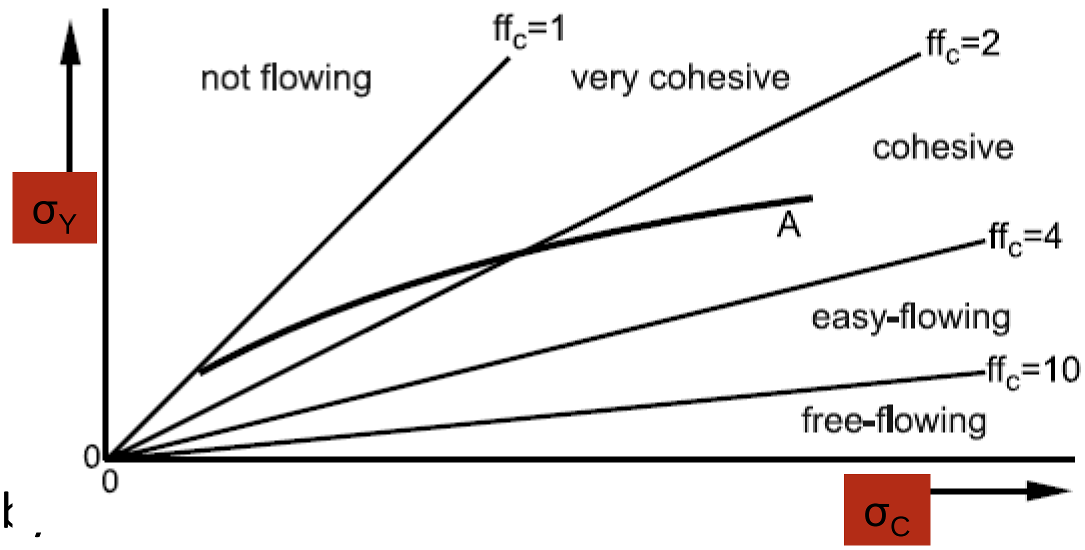


- σ_c … consolidating (compacting) stress
  - affects engineering ρ_B
- σ_y … unconfined yield strength
  - material property – how much force is necessary to start deformation



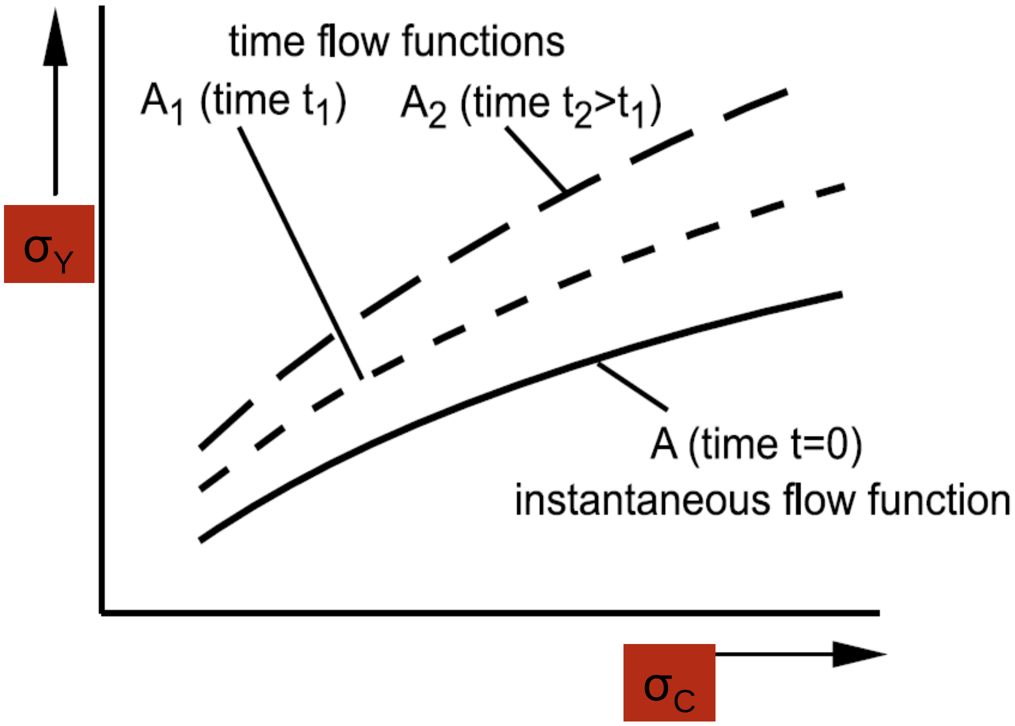
Expressing flowability numerically

- Flowability (as flow function coefficient)
  $$ff_C = \frac{\sigma_C}{\sigma_Y}$$
- higher = better
- Flowability cannot be universally characterized by a single number
- Flowability typically improves at increased consolidating stress



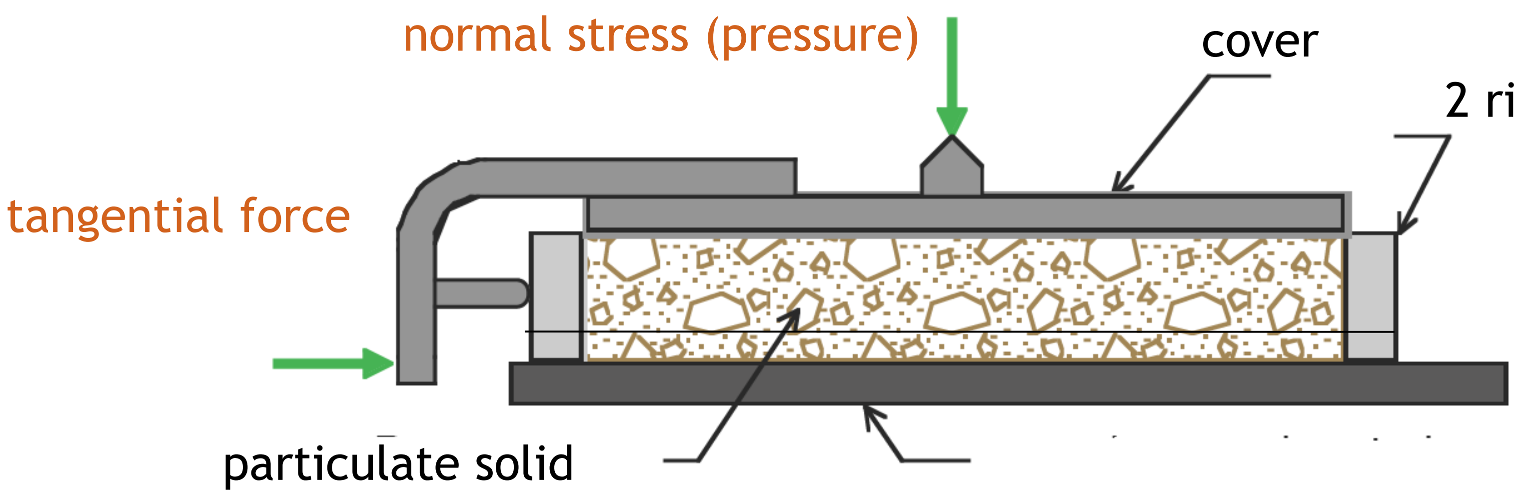
(Self)consolidation in time

- Some particulate solids
  - self-consolidation
  - change of flow function



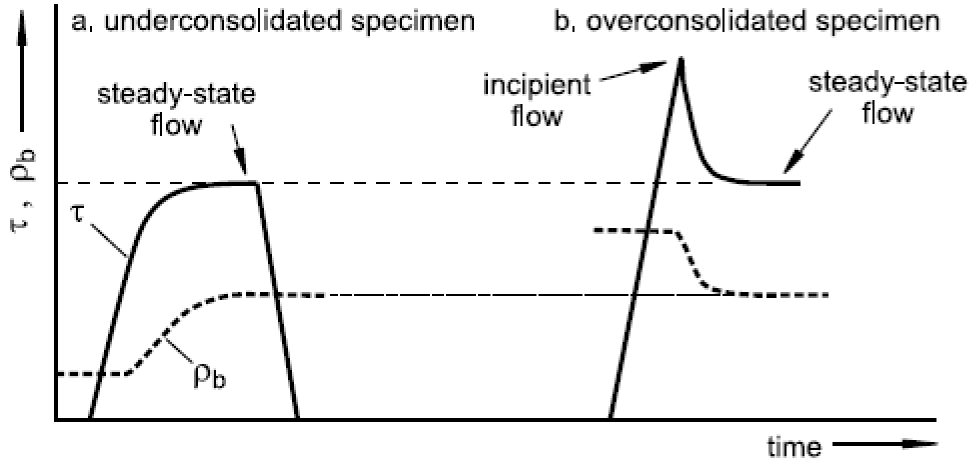
Measuring flow properties

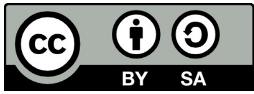
- Measuring shear stress



Stress development in consolidated powder

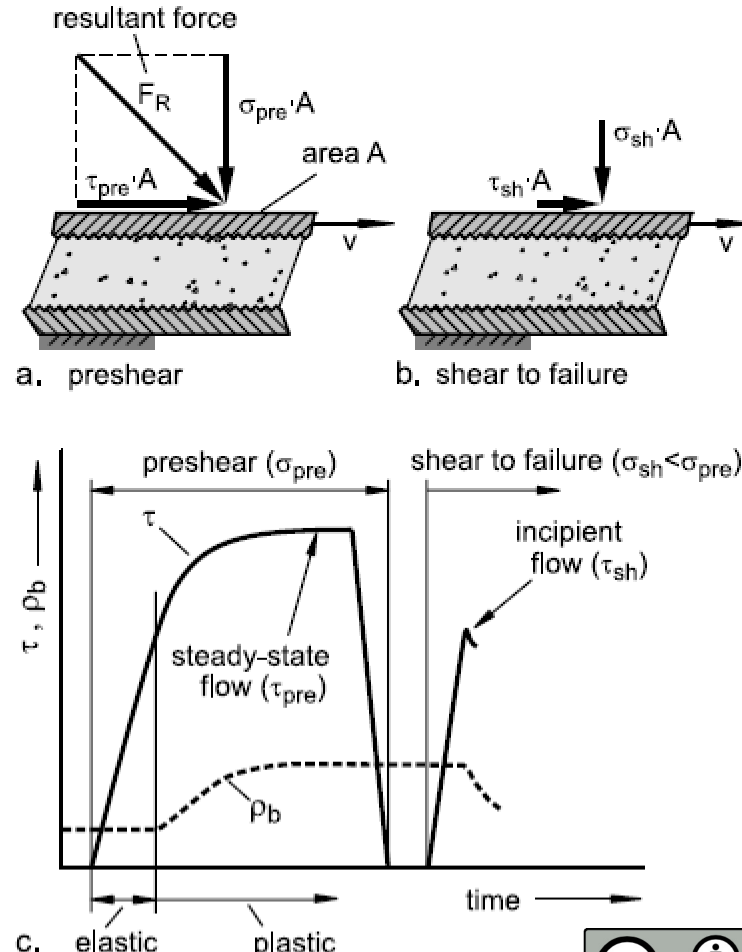
- Shear stress dependence on total shear distance (time) is affected by sample consolidation
- Bulk solid volume may change during the process of “beginning” flow



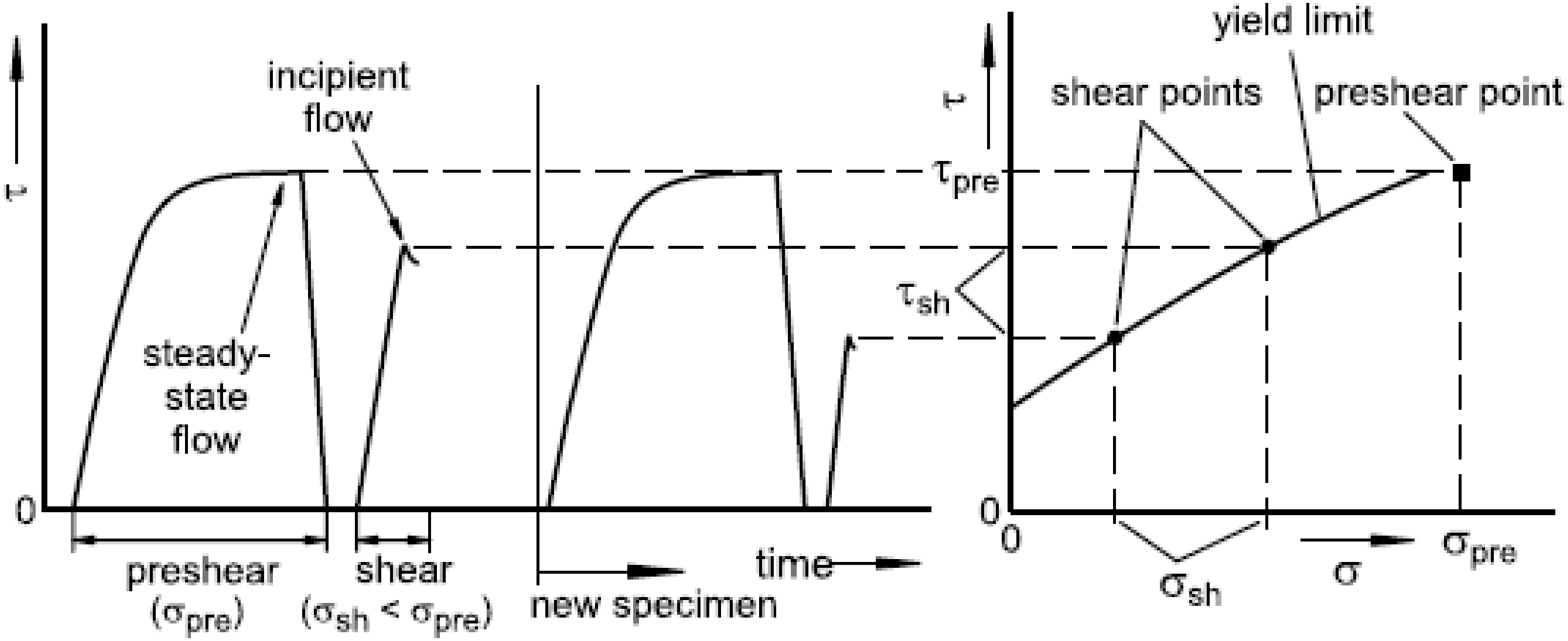


Shear cell measurement

- Bulk powder is consolidated undercritically
- Shear test is carried out (pre-shear) for σ_{pre}
- Repeated shear tests are carried out for $\sigma_{sh} < \sigma_{pre}$
  - shear stress is read at incipient flow conditions



Yield limit curve



Shear test results

- Yield limit (locus) is obtained on bulk solid sample at
  - the same pre-shear conditions
  - different normal stress levels
- Changing pre-shear may change yield limit, because of changed consolidation – family of yield limit curves

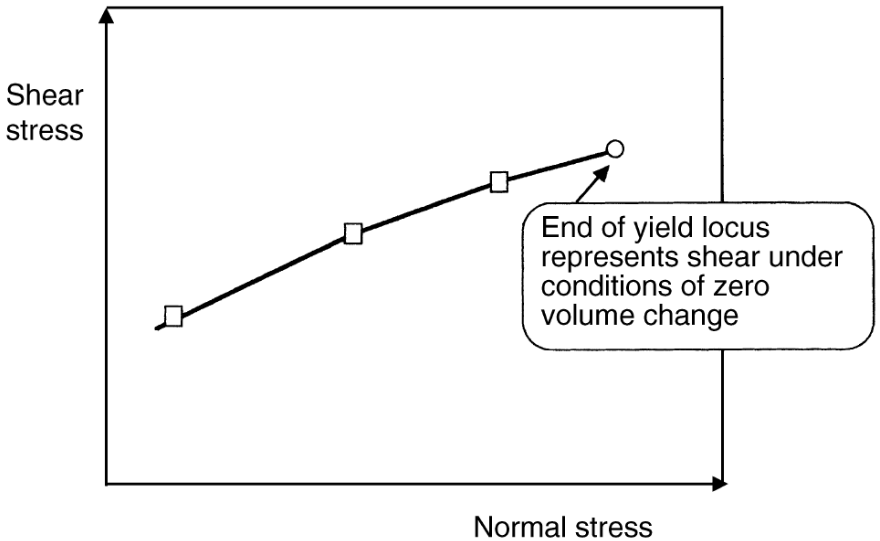
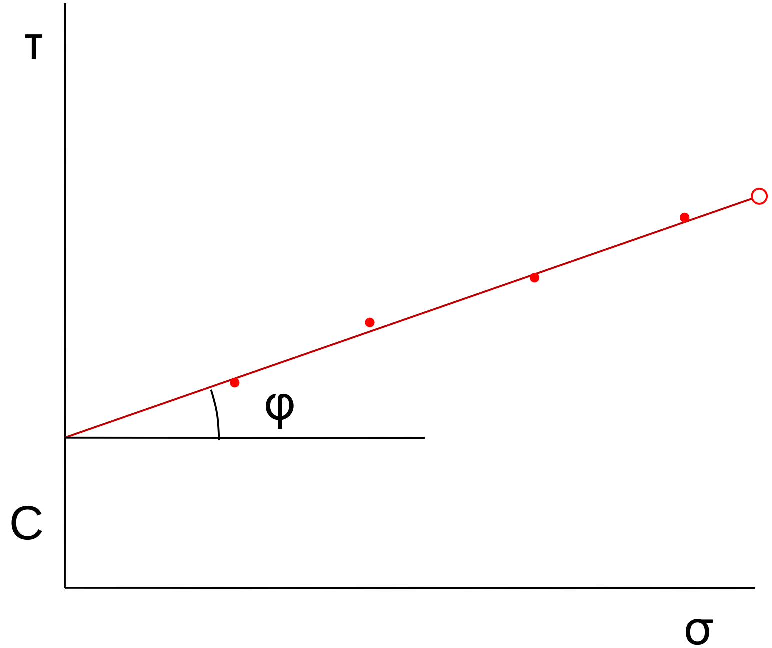


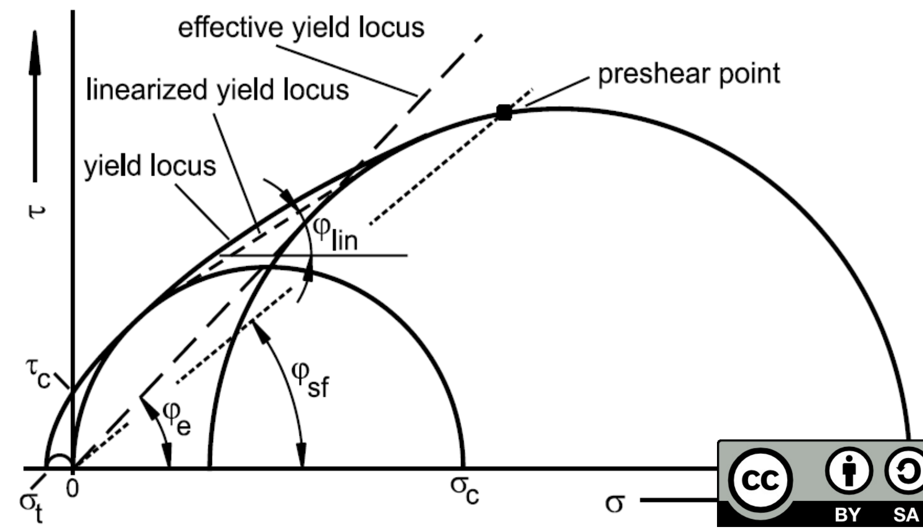
Figure 10.9 A single yield locus

Figure 10.10 A family of yield loci

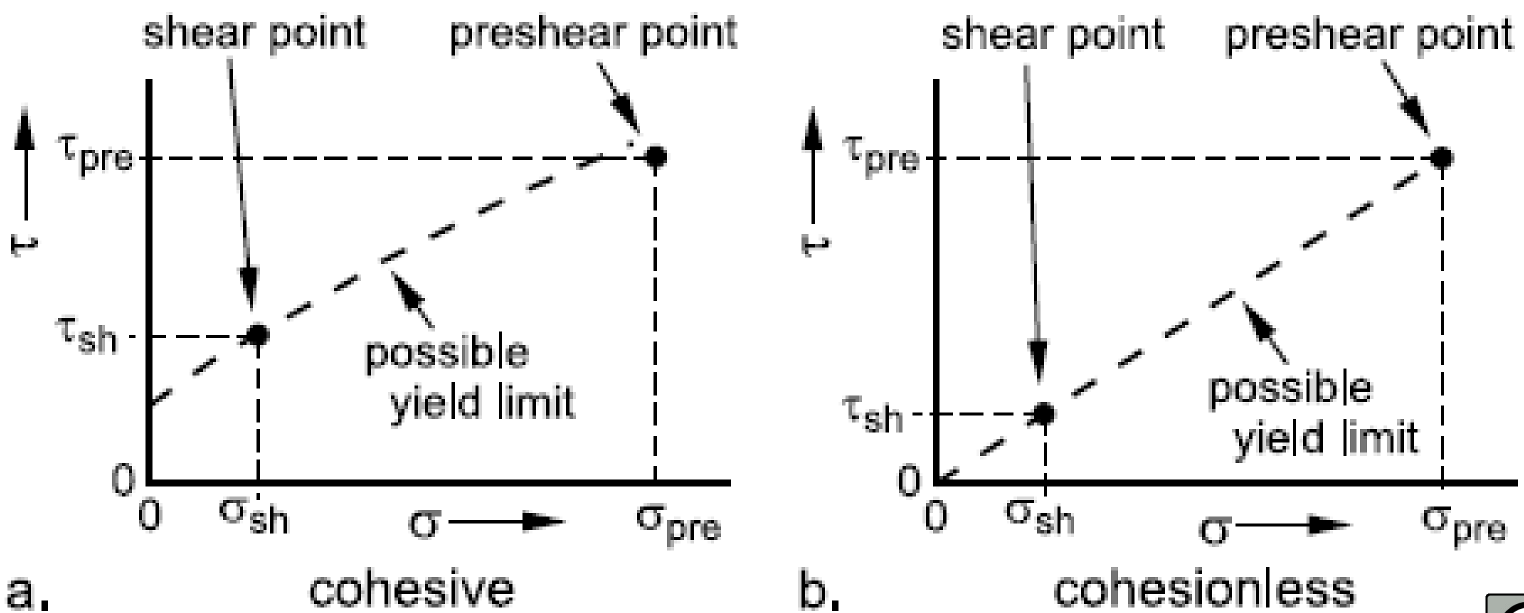
Linearized yield limit

- Angle of internal friction
- Cohesivity C = shear strength of powder at 0 normal pressure



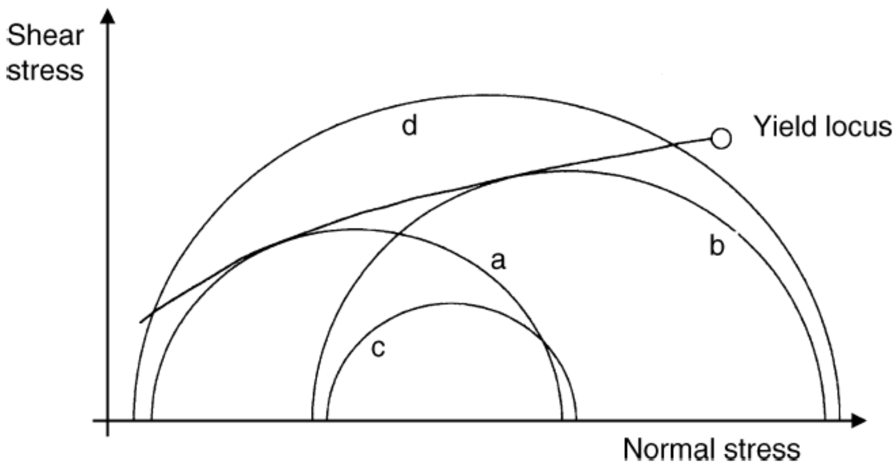


Yield limits of cohesive/cohesionless powders



Yield locus analysis using MC

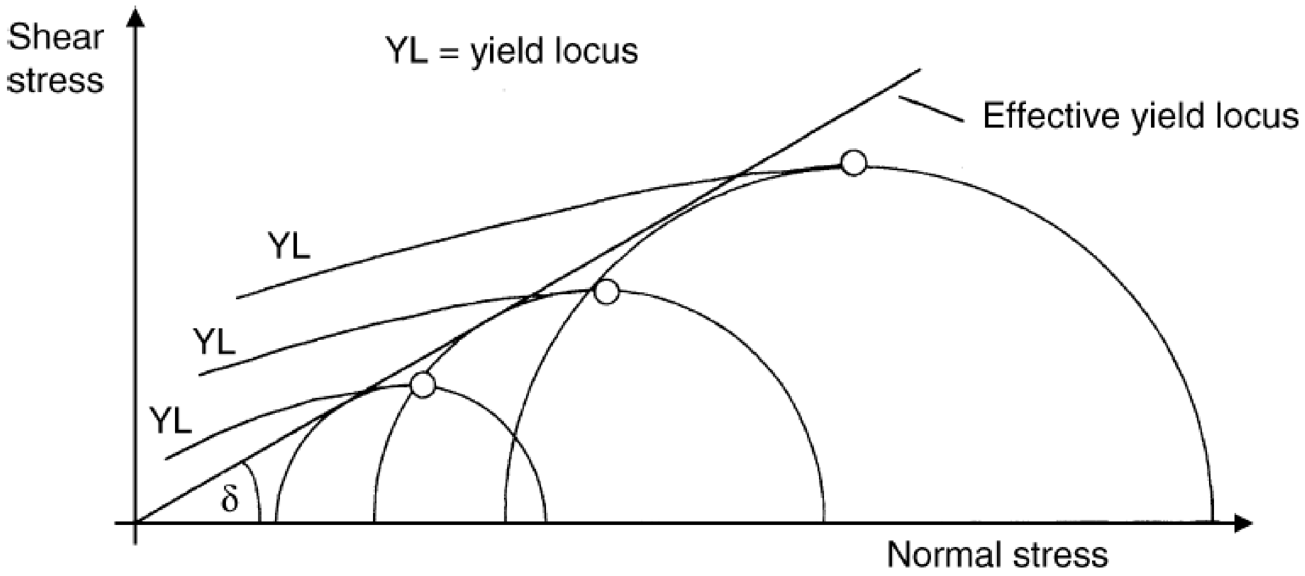
- Yield locus contains states of stress leading to deformation (flow)
- Mohr circles tangential to yield locus can be used to analyze state of stress at incipient flow



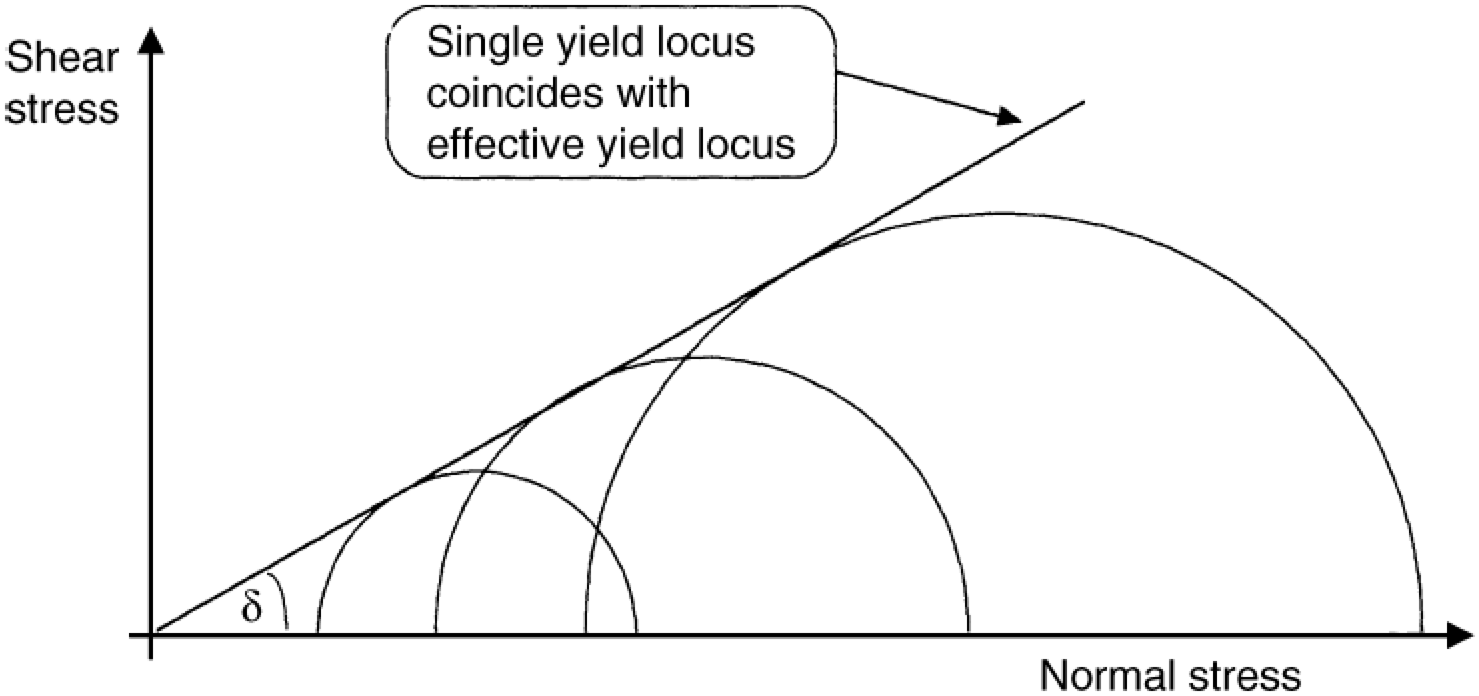
Effective angle of internal friction

- δ corresponds to stress at steady-state flow conditions

$$\frac{\sigma_1}{\sigma_2} = \frac{1 + \sin\delta}{1 - \sin\delta}$$

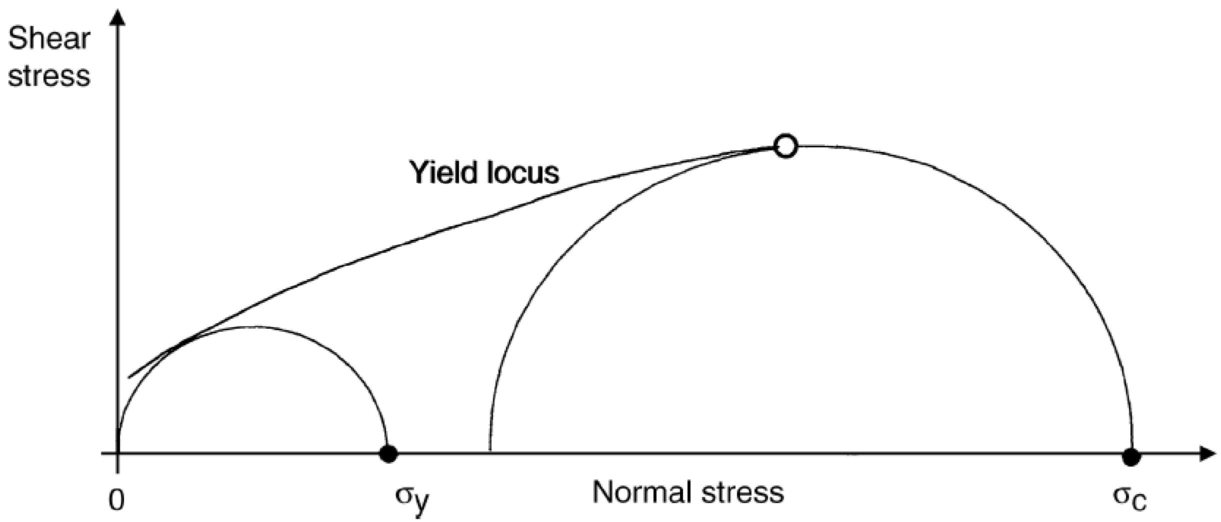


Yield locus for a free flowing powder

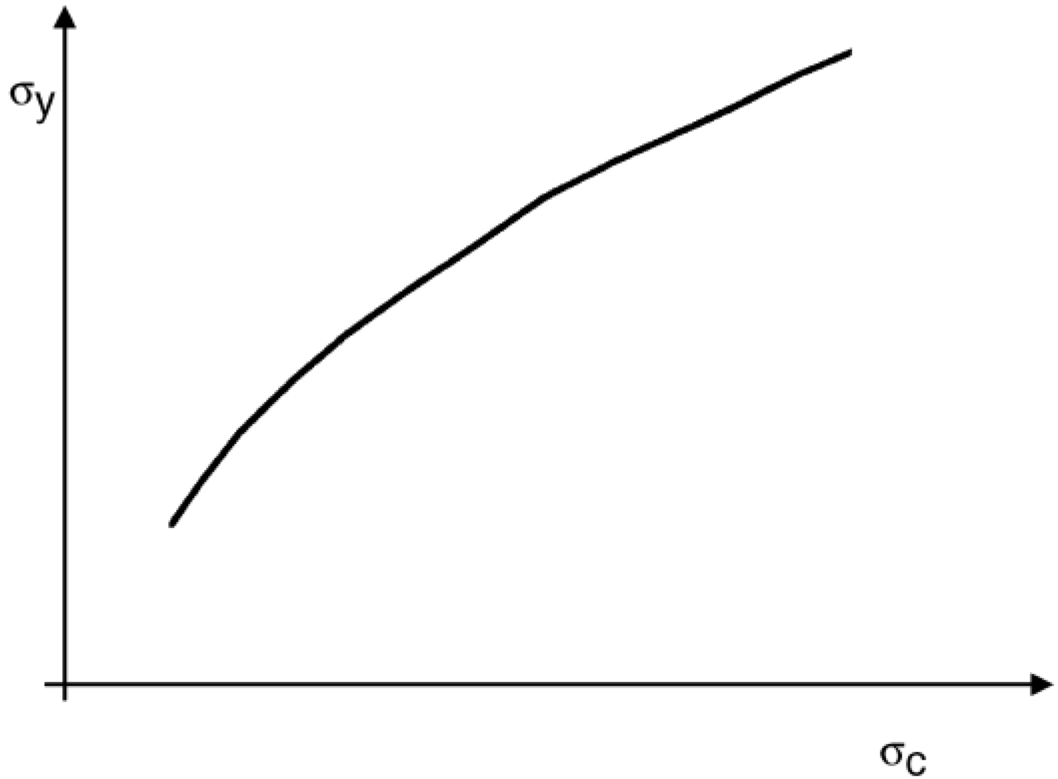


Yield limit vs flow function

- σ_c … compacting stress
  - maximum stress acting in powder

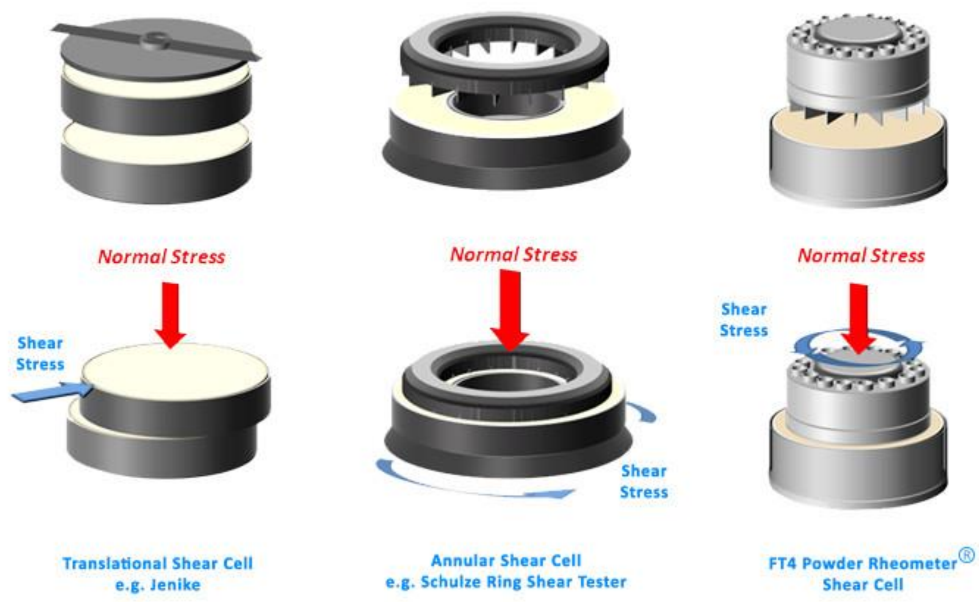


Powder flow function



Each point of flow function corresponds to one yield locus

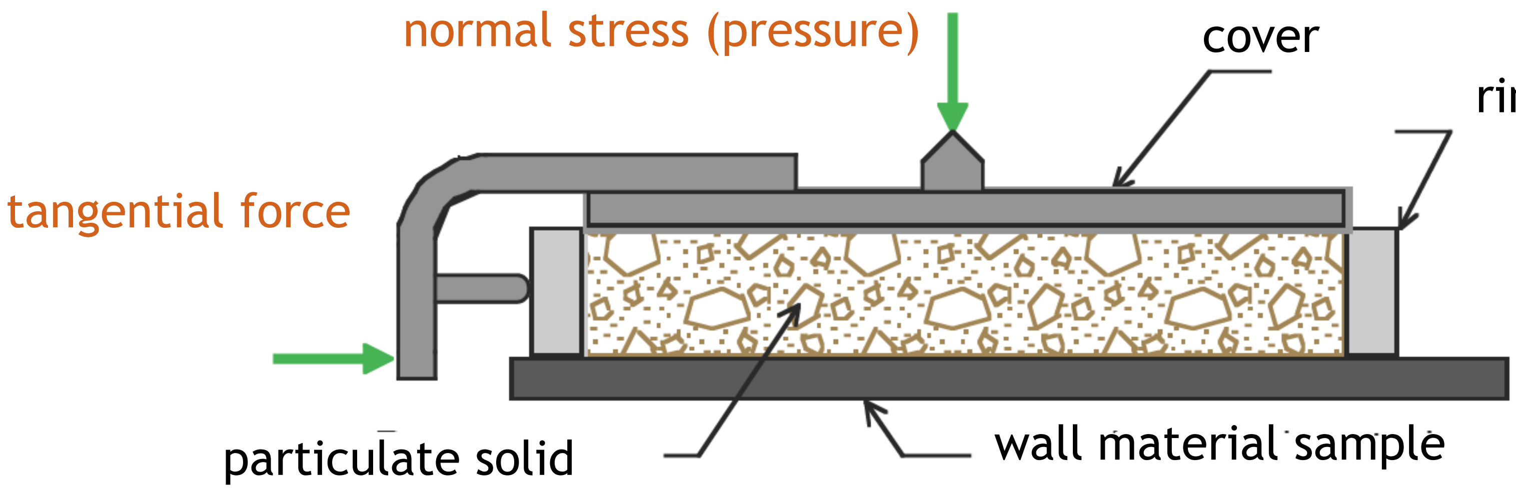
Other ways to measure flow properties



- see http://www.freemantech.co.uk/_powders/powder-testing-shear-cells

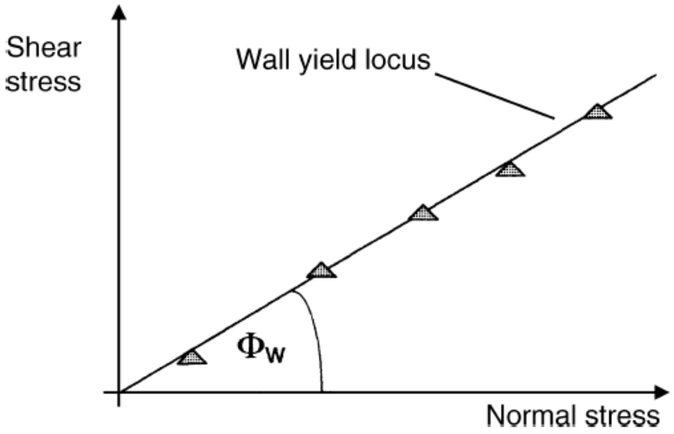
Measuring wall friction

- Measuring shear stress



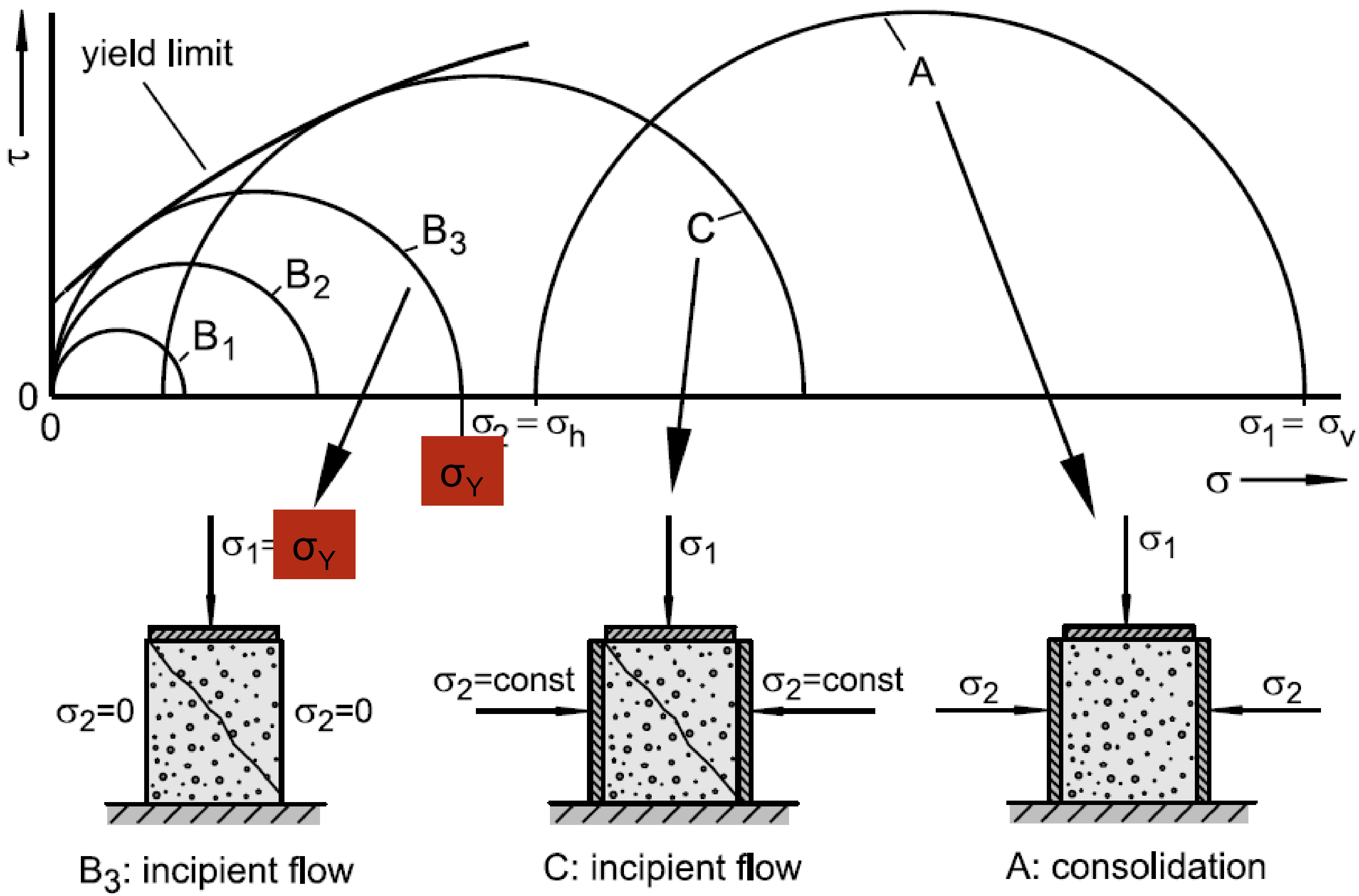
Friction on hopper wall

- (external) wall friction angle

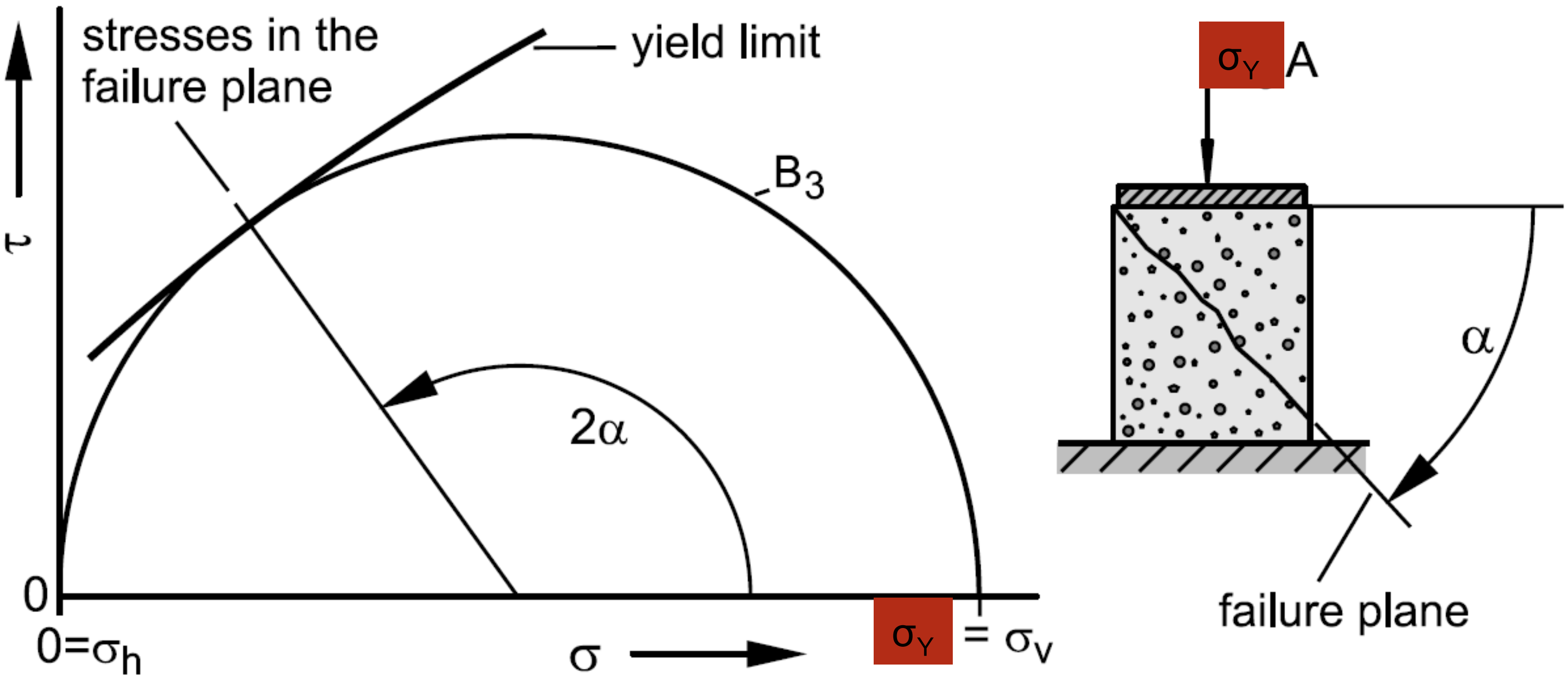


  - affected by
    - wall roughness
    - temperature
    - moisture
    - time of contact

Stress state during consolidation



Determining failure plane



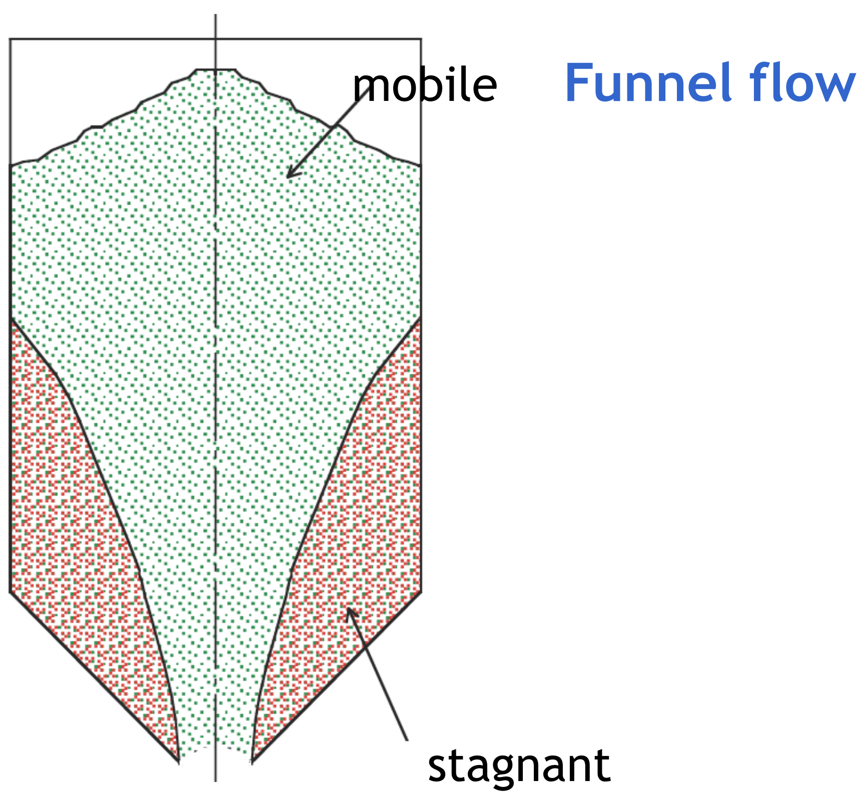
Particulate solids storage

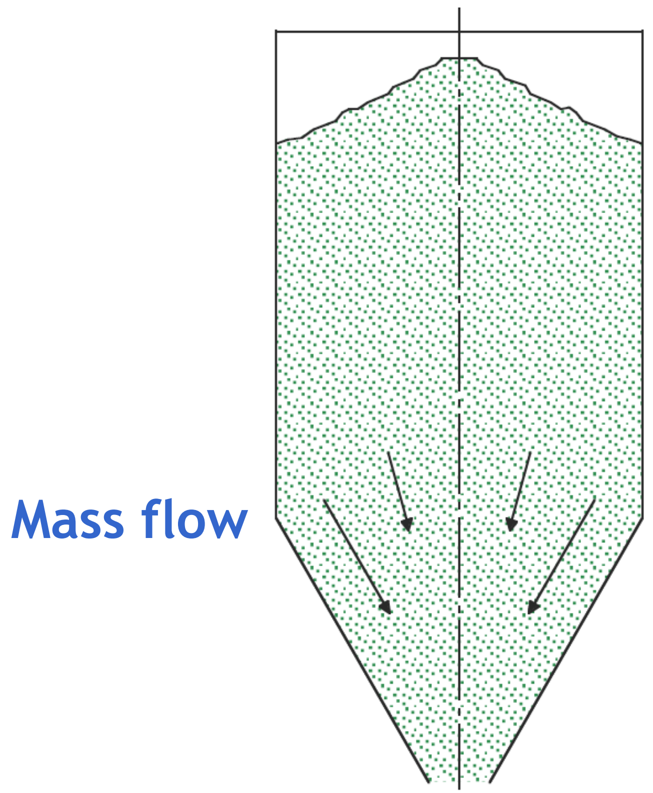
- Containers
  - smaller volumes
  - batch-oriented processing and logistics
  - long-term storage
- In hoppers (silos)
  - large volumes
  - input to continuous processes
  - interface between continuous and batch segment of the process
    - e.g. tabletting press reservoir

Storage consumption regime

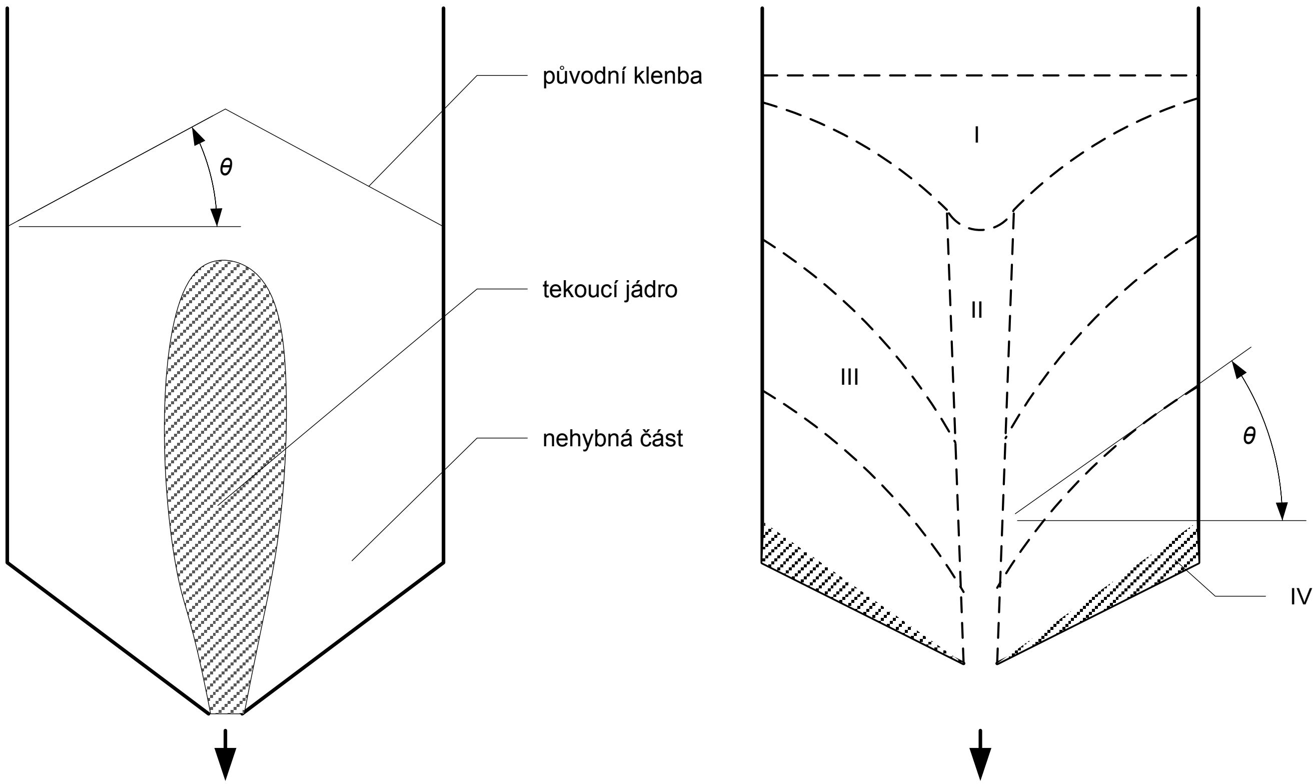
- Containers
  - governed by logistics
- Hoppers
  - consumption governed by flow regime
  - FIFO consumption
    - first in first out
    - desirable in pharma industry
  - LIFO consumption
    - last in first out
    - risk of degradation, residence time poorly defined

Particulate solid flow in silos



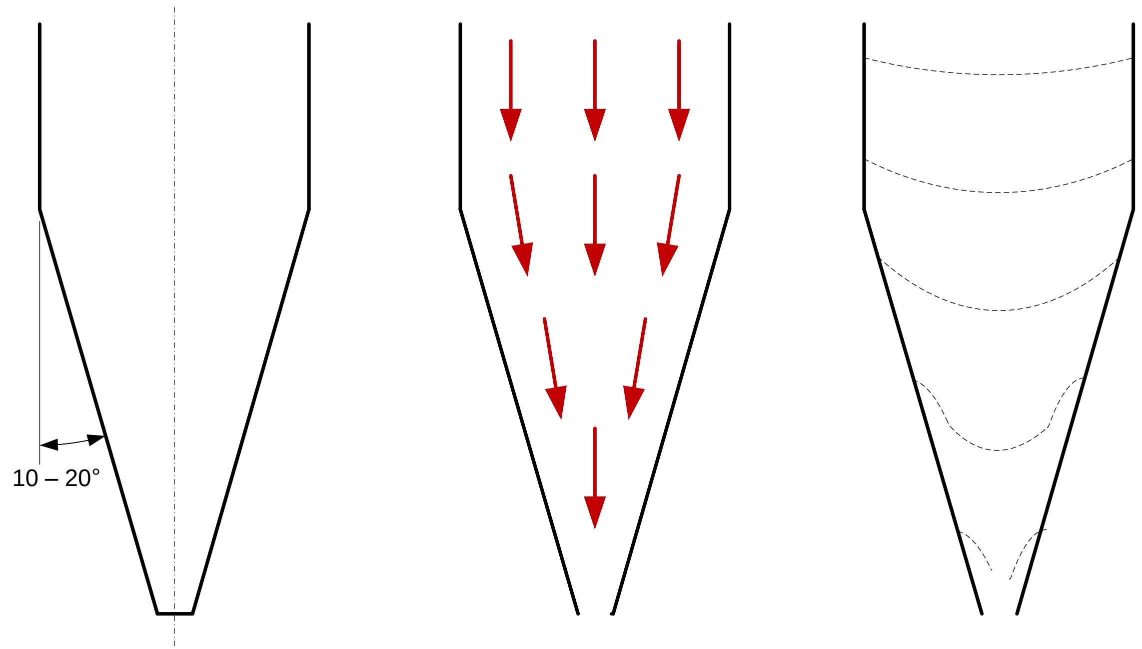


Funnel flow



- *Incipient funnel flow (left) and funnel flow regions (right)*
  I – plug-flow region, II - core, III –regions , discharging into core, IV – stagnant region

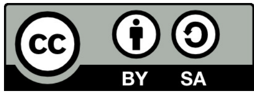
Mass flow



ideal shape

typical design

discharge progress

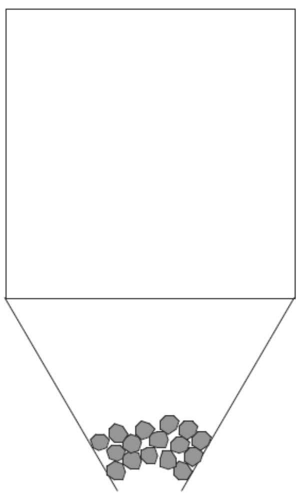


Flow problems

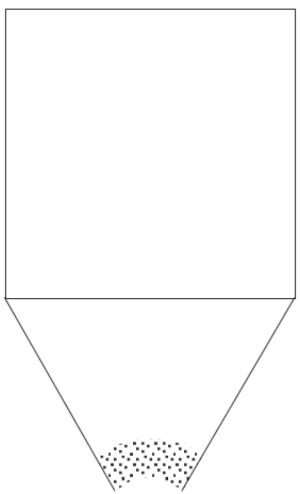
- Blocking the outlet opening(Arching)
- Uncontrolled flow (flooding)
- Consolidation of stagnant region
- Segregation
  - by particle size
  - of components of a mixture

Flow problems examples

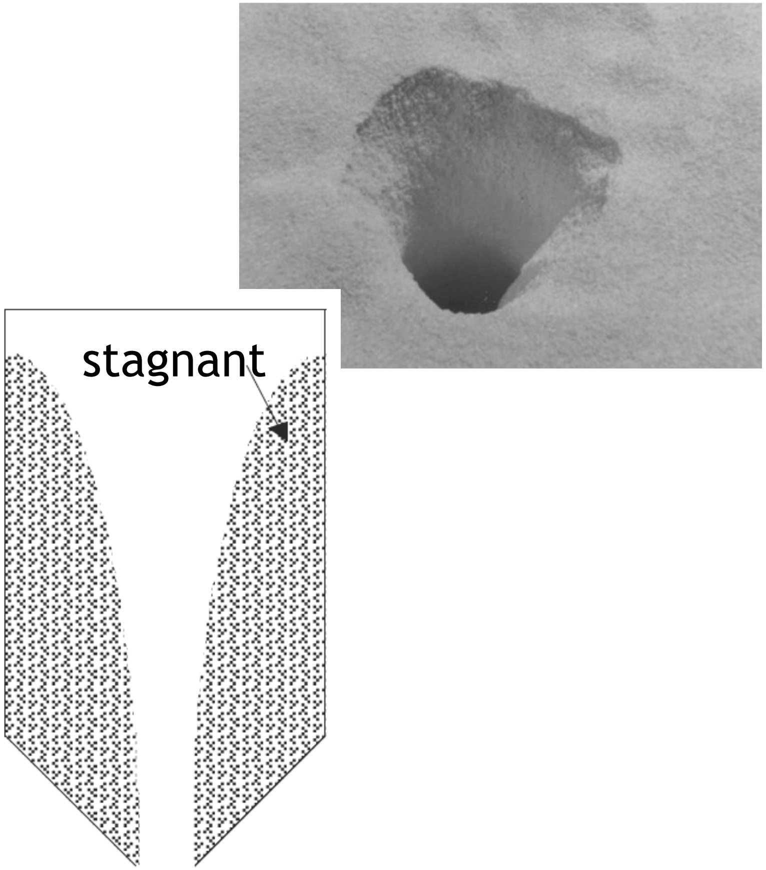
- bridging, arching



arch



cohesive bridge



» ratholing

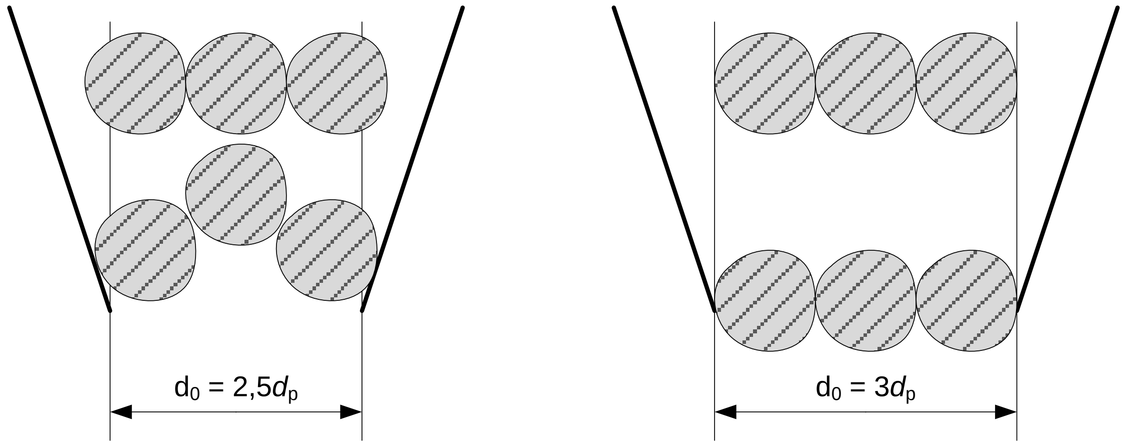
Flow regime and hopper design

- Funnel flow = economical solution
  - low slope in cone = space economy
  - low shear on the hopper wall = low abrasion
  - !!! safe only if the solid contains
    - coarse particles
    - non-sticky particles
    - non-segregating particles
    - non-degradable particles
- Pharmaceutical applications require mass flow

Hopper designs for mass flow

- Overcome friction in hopper
- Sufficient outlet opening
  - arching prevention
- Optimizing hopper shape
- Modification of powder properties by additives
  - lubricants – magnesium stearate
  - flowing agents – colloidal silicon dioxide– “Aerosil”

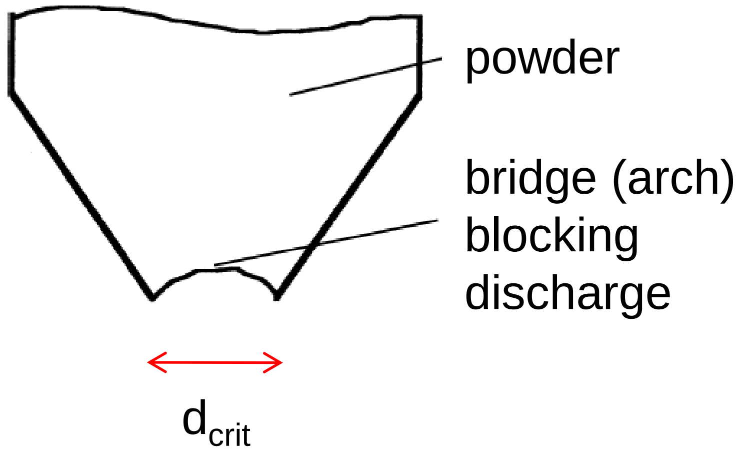
Mechanical arching



- Uncommon in pharma applications due to small particle size

Cohesive bridge

- Powder under pressure develops certain cohesion
- Cohesion may block the flow in silo
- σ_y … unconfined yield strength
  - free surface on arch = zero second principal stress
- σ_D … developed stress
  - depends on powder properties
  - wall properties
  - geometry



CONDITION OF FLOW

$$\sigma_D > \sigma_Y$$

Hopper flow factor *ff*

- Determines hopper's ability to induce flow

$$ff = \frac{\sigma_C}{\sigma_D}$$

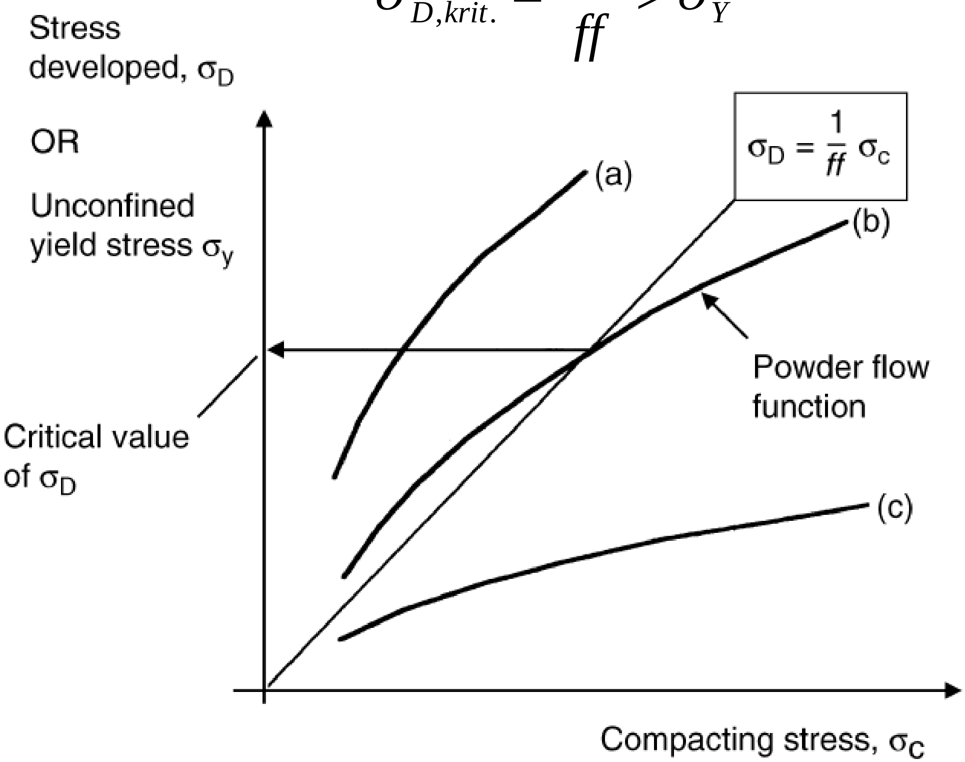
- σ_c … compacting stress in the hopper
- σ_D … developed stress in the arch
  - depends on powder properties
  - wall properties
  - geometry
- larger *ff* = worse flow conditions
- Critical conditions for flow

$$\sigma_{D,krit.} = \frac{\sigma_C}{ff} > \sigma_Y$$

Critical conditions for flow

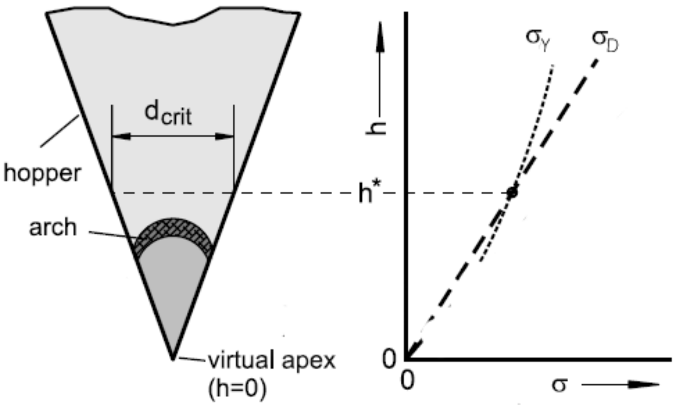
- Flow function and flow factor is needed

$$\sigma_{D,krit.} = \frac{\sigma_C}{ff} > \sigma_Y$$



Critical discharge opening

- On discharge, the principal stress in conus is proportional to diameter, i.e. the distance from apex
- Principal stress is the "developed stress" σ_D in the arch
- Flow occurs if the flow condition is met at the opening



$$d_{krit} = H(\theta)\frac{\sigma_{D,krit.}}{\rho_B g}$$

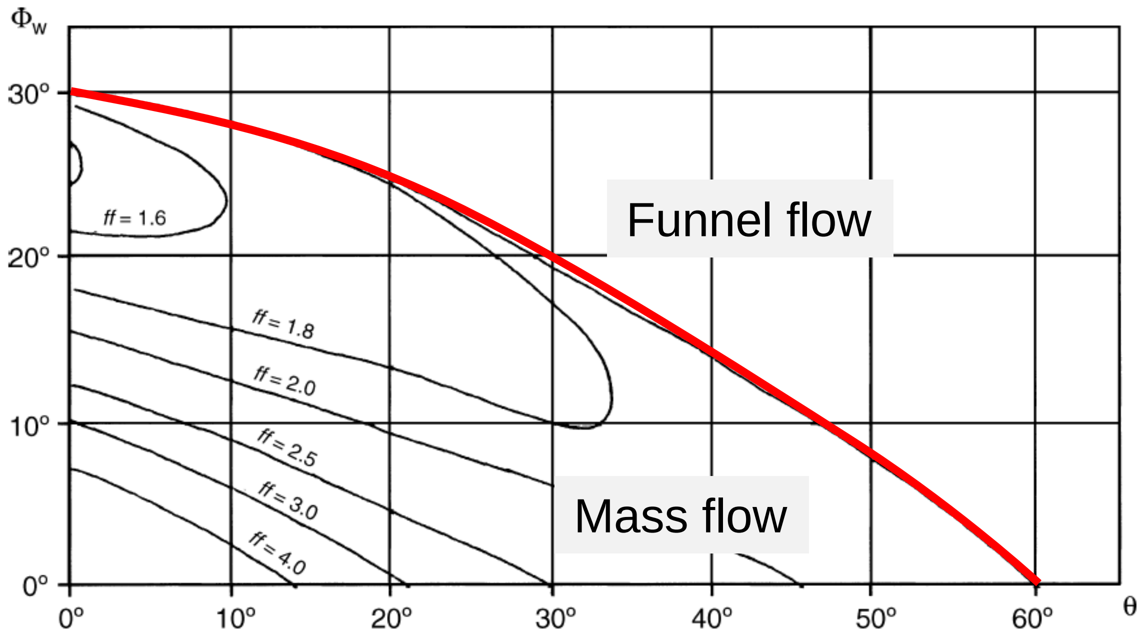
Critical opening diameter

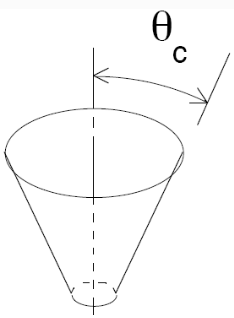
$$H(\theta_{conical}) = 2 + \frac{\theta}{60}$$

Determining hopper flow factor

- Determined by δ, θ, Φ_w

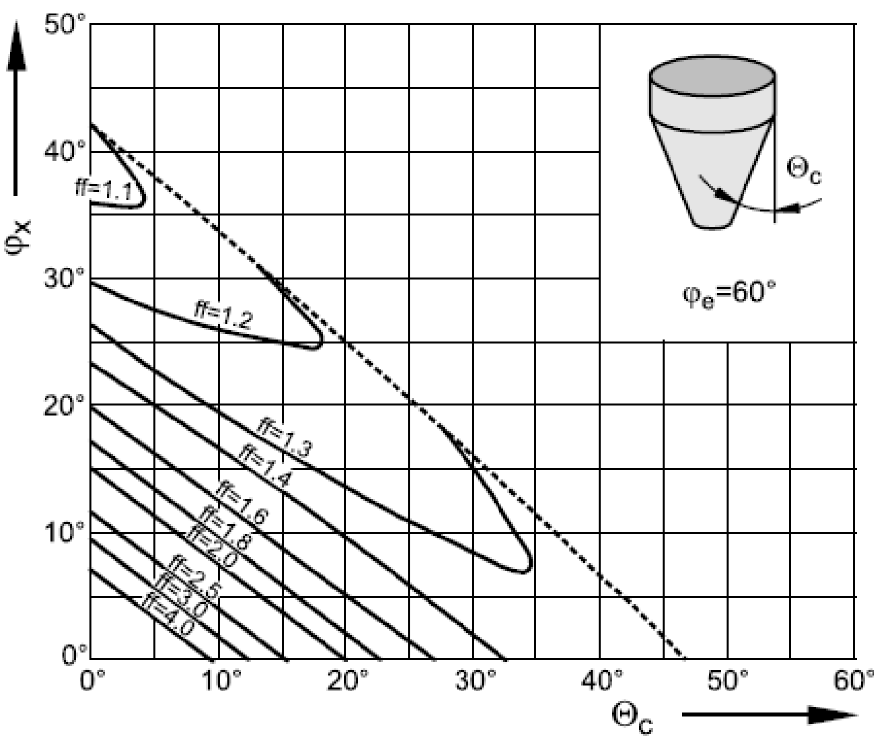
δ = 30°

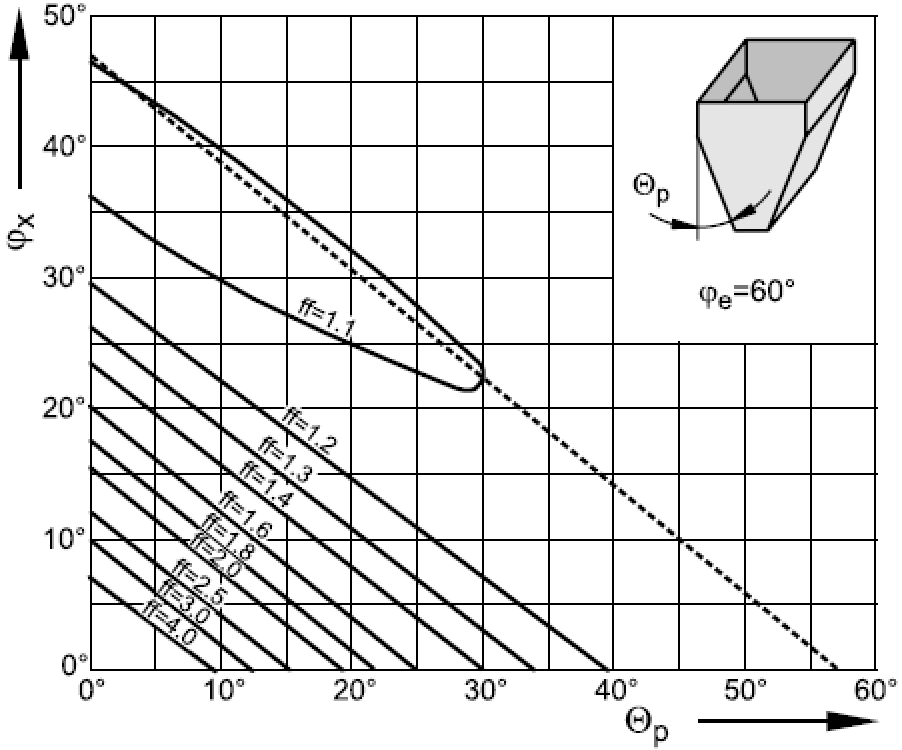




funnel flow is determined only by outlet opening diameter

Examples of other diagrams





Design procedure for mass flow

- Shear cell tests on powder give a family of yield loci.
- Mohr's circle stress analysis gives pairs of values of unconfined yield stress, and compacting stress, and the value of the effective angle of internal friction, δ.
- (iii) Pairs of values of σ_y and σ_C give the powder flow function.
- (iv) Shear cell tests on the powder and the material of the hopper wall give the kinematic angle of wall friction, Φ_w.
- (v) Φ_w and δ are used to obtain hopper flow factor, ff, and angle of conical hopper wall slope, θ.

Example

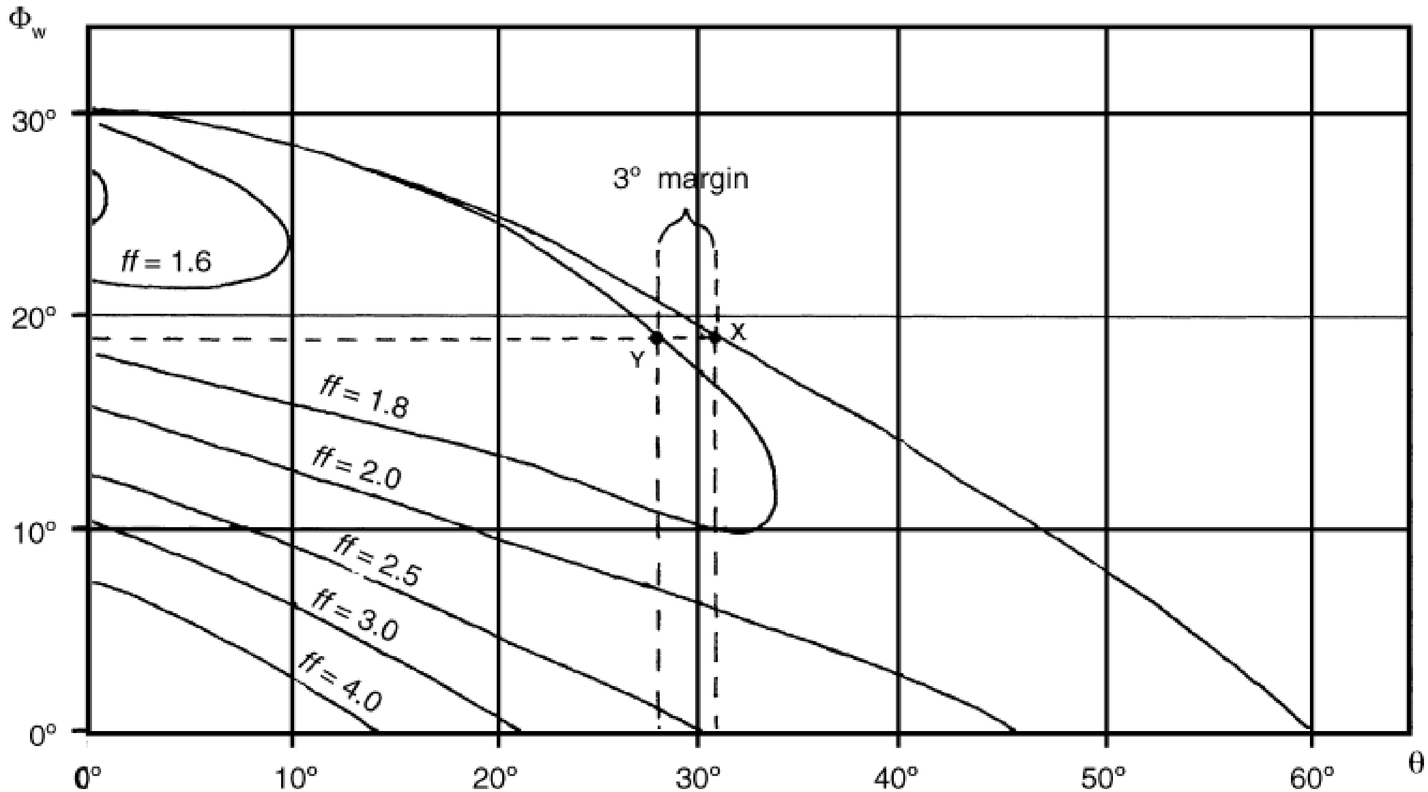


Figure 10.19 Worked example of the use of hopper flow factor charts. Hopper flow factor values for conical channels, $\delta = 30°$

Design procedure for mass flow

- (vi) Powder flow function and hopper flow factor are combined to give the stress corresponding to the critical flow – no flow condition, σ_{crit}.
- (vii) the minimum diameter of the conical hopper outlet is calculated

$$d_{krit} = H(\theta)\frac{\sigma_{D,krit.}}{\rho_B g}$$

$$H(\theta_{conical}) = 2 + \frac{\theta}{60}$$

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MINISTRY OF EDUCATION,
YOUTH AND SPORTS

Engineering in Chemical and Pharmaceutical Processes

Particle Agglomeration and Wet Granulation Techniques

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced

  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

Why make the particles bigger?

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

Increasing particle size

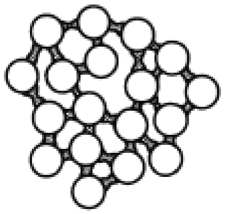
- Wet-granulation (in high-shear mixers)
  - High-shear (mixer) wet granulation
- Fluidized-bed granulation
- Compaction (dry granulation)

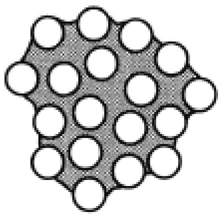
- (Extrusion)
- (Tablet compression)
- (Spheronisation)

SDF manufacturing

Interparticle forces

- Van der Waals
  - Attractive forces between molecules E ~ 0.1 eV
- Adsorbed liquid film interaction
  - Van der Waals interactions between liquid filmc condensing on particle surfaces
- Liquid bridges
  - Surface forces
  - Capillary forces





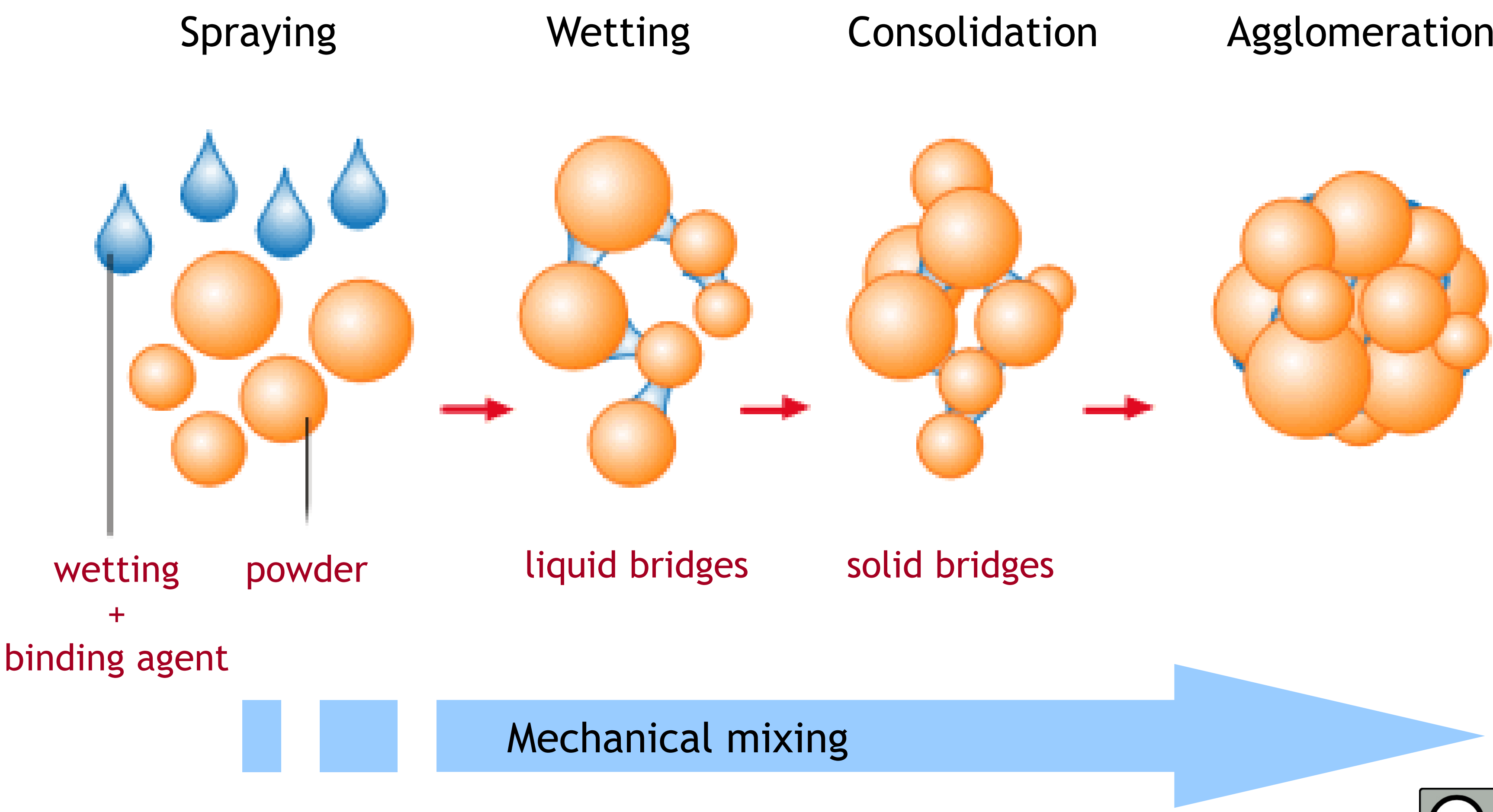
Cohesive forces in granules

- 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



Granule growth

Phases of wet granulation

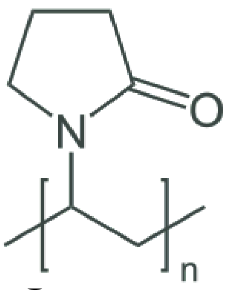
- Pre-homogenizing
  - dry premixing powders
- Spraying
  - spraying powder by binder solution
  - spraying powder – binder mixture by wetting agent
- Granulation
  - formation and growth of granules by intensive high-shear mixing
- Drying

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
  - Methylcelullose (MC, 1 – 5 %)
    - Swellable and soluble in cold water, similar to starch, higher stre
  - Hydroxypropylmethylcelullose (HPMC, 2 – 8 %)
  - Karboxymethylcelulose salts (CMC, 1 – 5 %)
  - Ethylcelullose (EC, 1 – 5 % in EtOH)
    - good disintegration, poor dissolution



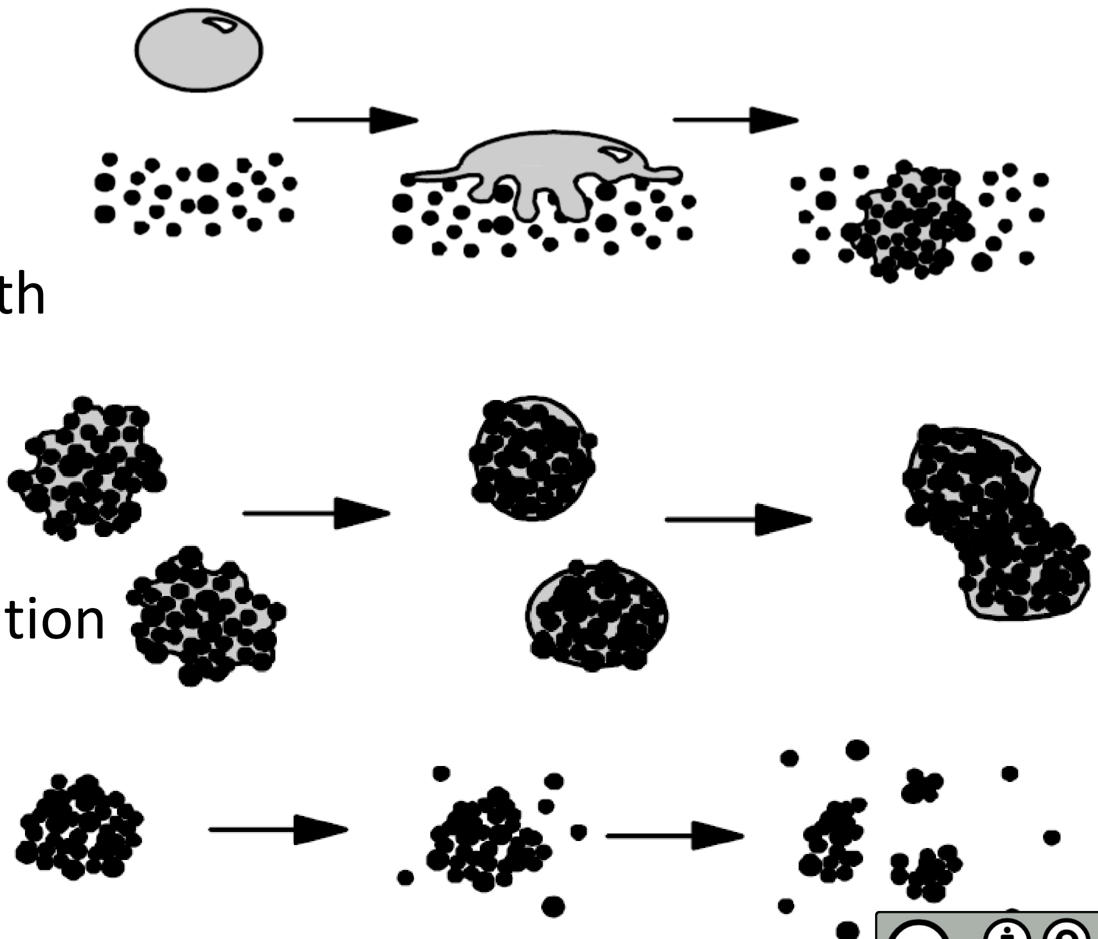
Selecting binder agent

- 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

$$\frac{dz}{dt} = \frac{r_{poru}\gamma\cos\Theta}{4\mu z}$$

  - Measuring penetration time t_p (simple)
    - time to soak single droplet of granulation liquid into the powder layer

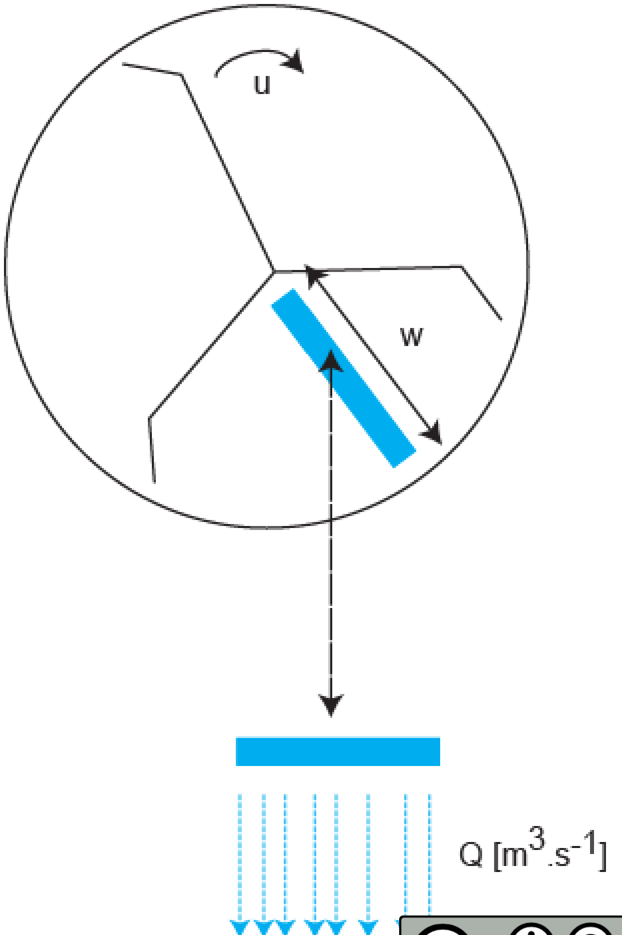
Spraying

- Droplets fall on the powder surface
  - separately

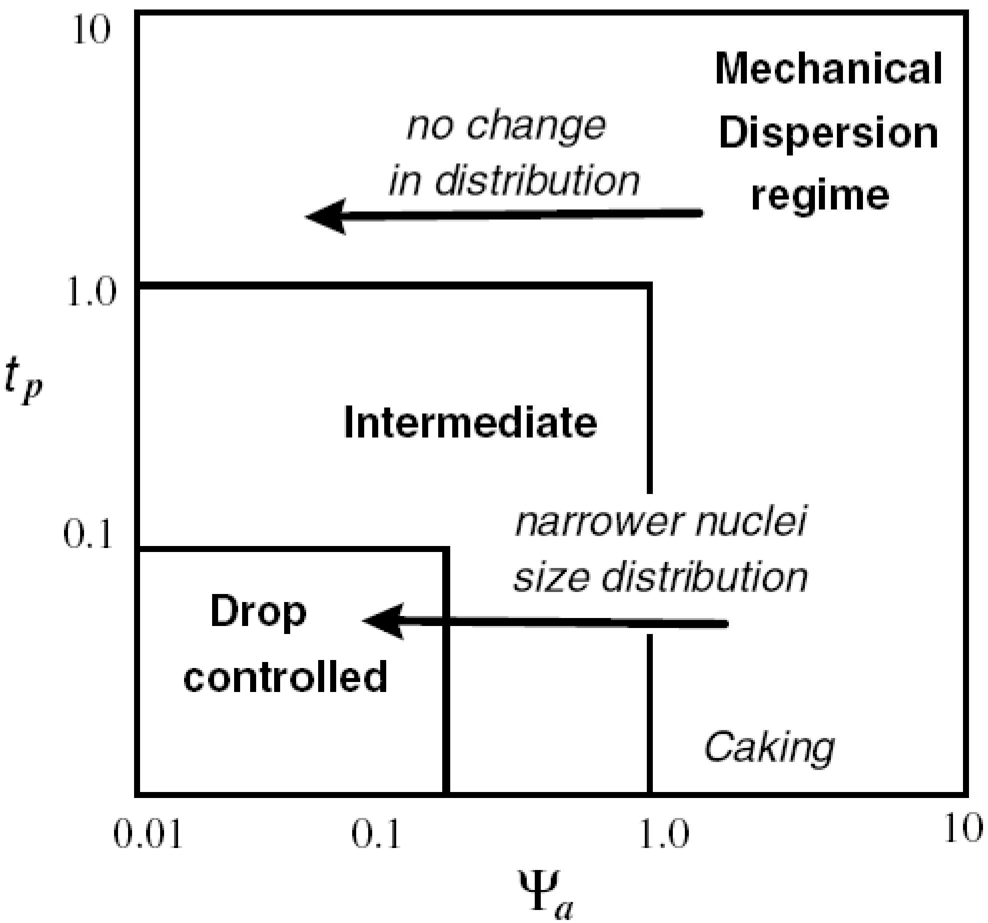
  - overlapping

- The spraying efficiency governed by
  - dimensionless factor of spray flow
  - (low value = separate droplets)

$$\psi = \frac{3Q}{2u_{surface}w_{spray}d_{droplet}}$$

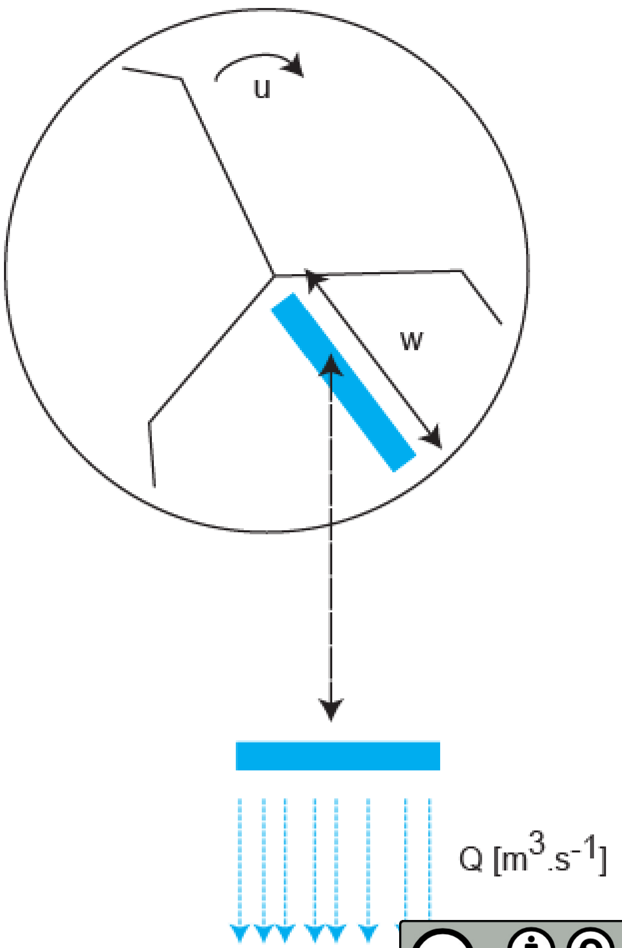


Nucleation regimes



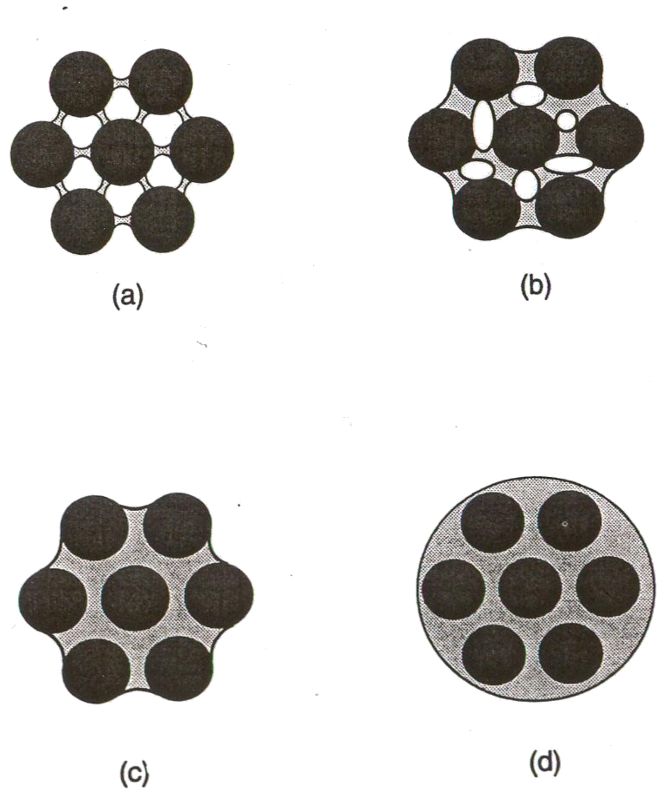
Ideal wetting conditions

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

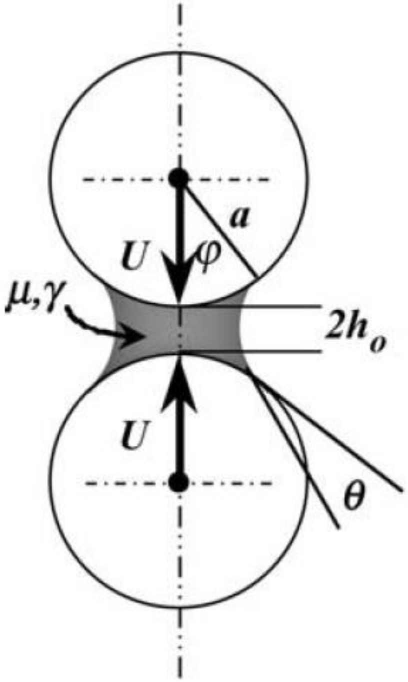


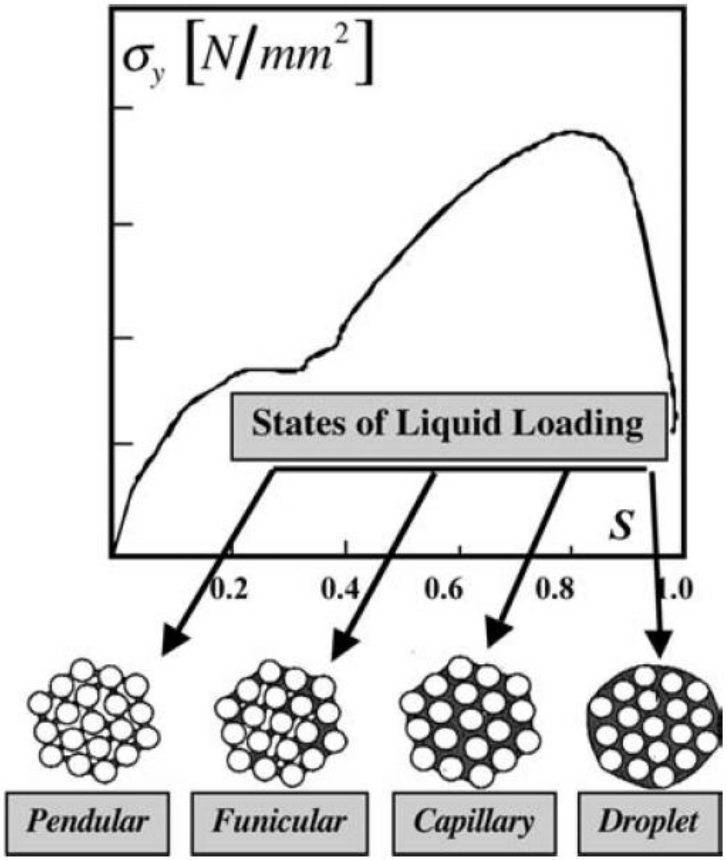
Amount of liquid and agglomerates

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



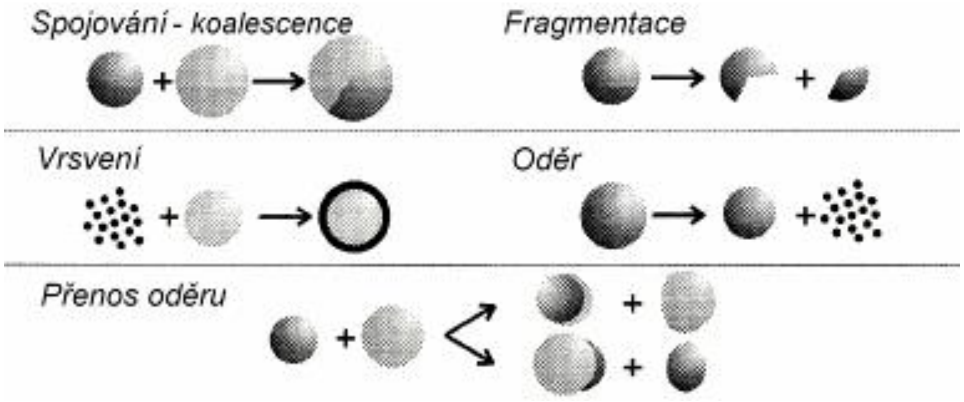
Cohesive forces



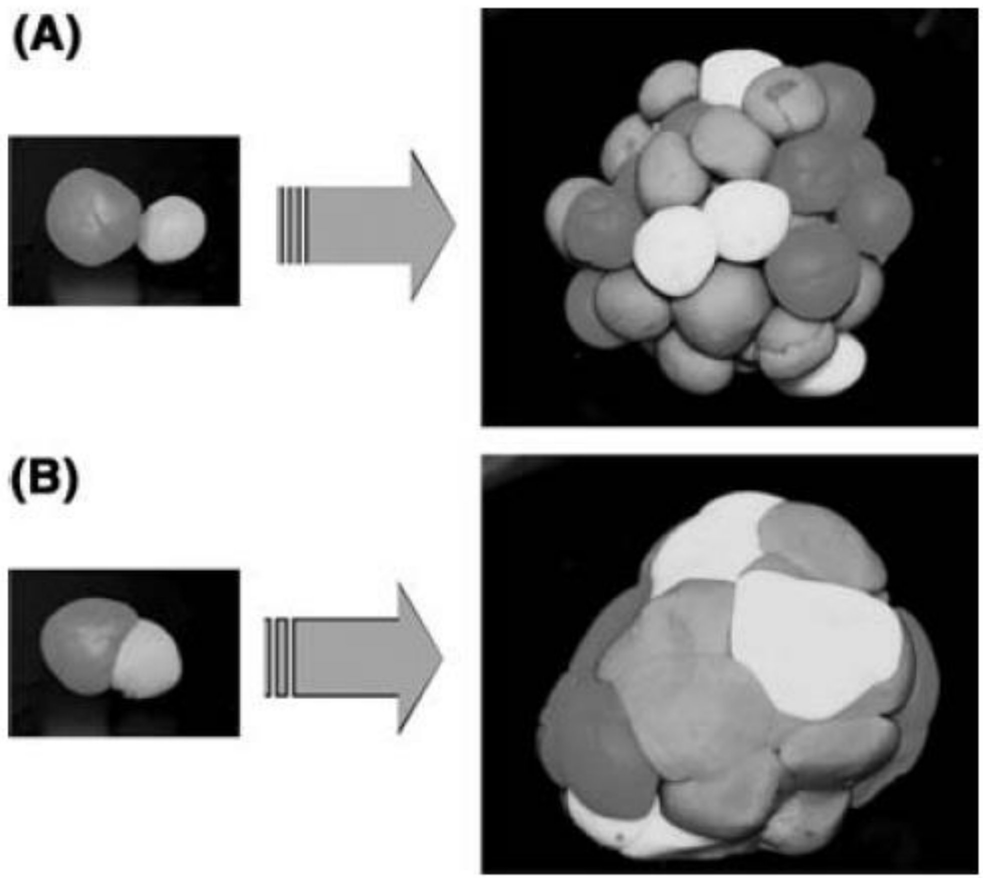


Consolidation and growth

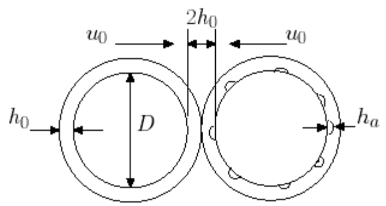
- mechanisms of granule growth
  - Coalescence
    - most important, fast
  - Coating
  - Transfer



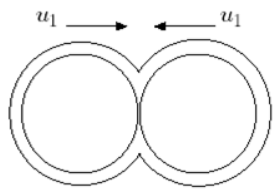
High- and low-deformability systems



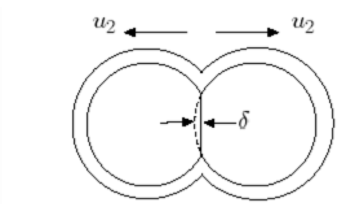
Granule impact and coalescence



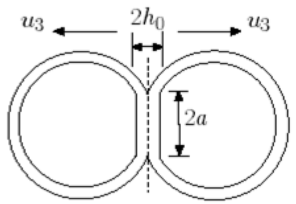
initial approach; c**oalescence of I.** type.



Deformation, cores in contact.



Elastic deformation, springback.



Separating; c**oalescence of II. type** or bounce.

Coalescence in non-deforming systems

- Kinetic energy of impact

$$E_k \approx m u_c^2 \approx \rho d_p^3 u_c^2$$

  - u_c … characteristic collision velocity
- Energy losses by friction in liquid film
  - Stokes viscosity force

$$F_{St} \approx \eta d_p u_c$$

  - Energy losses

$$E_{St} \approx F_{St} d_p \approx \eta d_p^2 u_c$$

- Kinetic energy to losses ratio
  - Stokes number

$$St \approx \frac{\rho_g u_c d_p}{\eta}$$

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
  - high value
    - too high impact energy to dissipate = bouncing

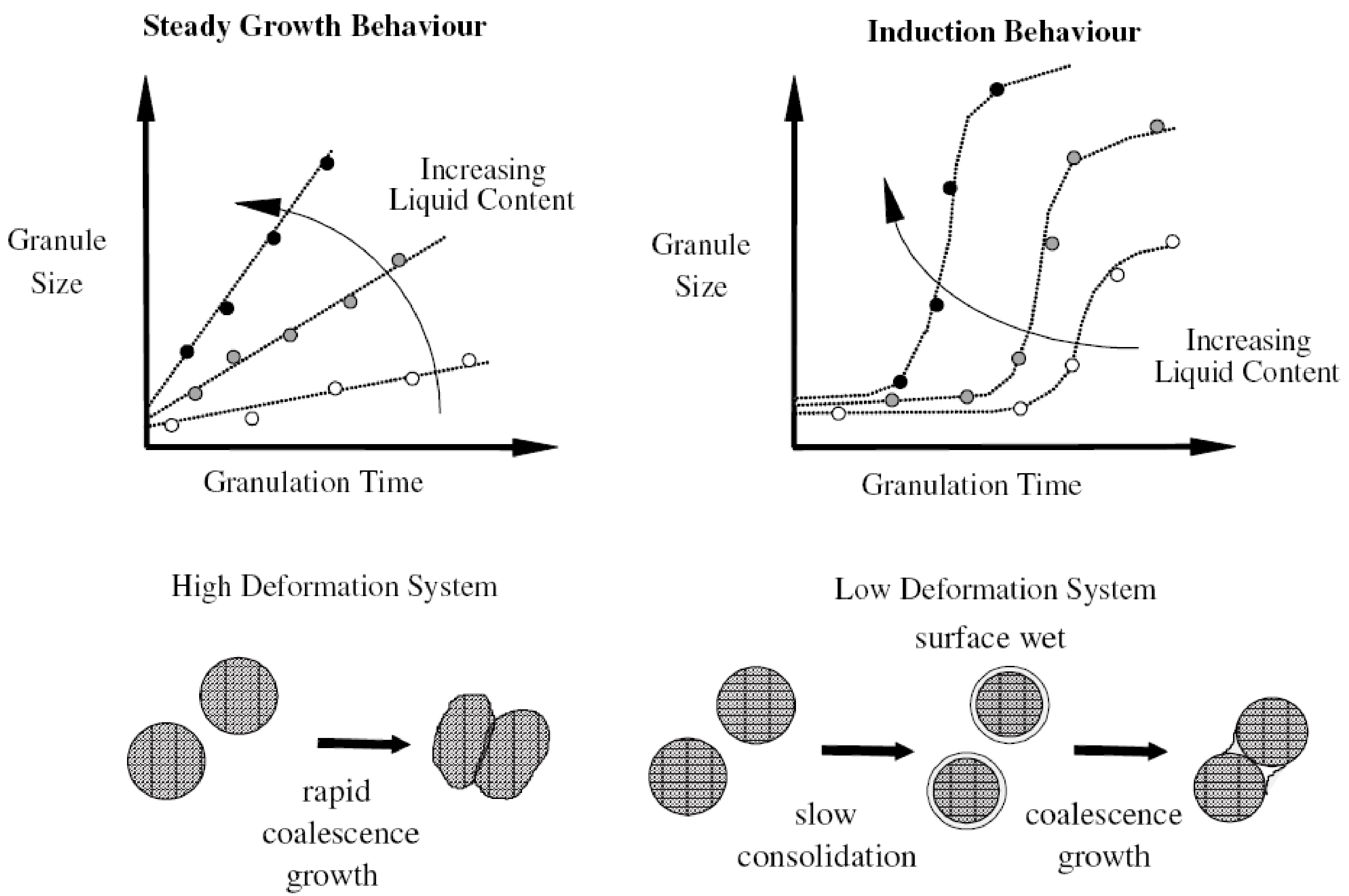
$$St \approx \frac{\rho_g u_c d_p}{\eta}$$

Coalescence regimes in non-deforming systems

- d_p distribution → St distribution
- Modes
  - non-inertial
    - St is low for all particles
    - all impacts lead to coalescence
    - insensitive to fluctuations of properties, velocity, …
  - inertial
    - St is about the critical value
    - only some impacts lead to coalescence
    - coalescence rate is sensitive to fluctuations of properties, velocity
  - coating
    - St is over critical value for more than 50 % of particles
    - coalescence is compensated by disintegration
    - net growth only by coating

$$St \approx \frac{\rho_g u_c d_p}{\eta}$$

Deformability effects



Deformation behaviour of granules

- Given by ratio
  - acting impact forces σ_{impact} [Pa]

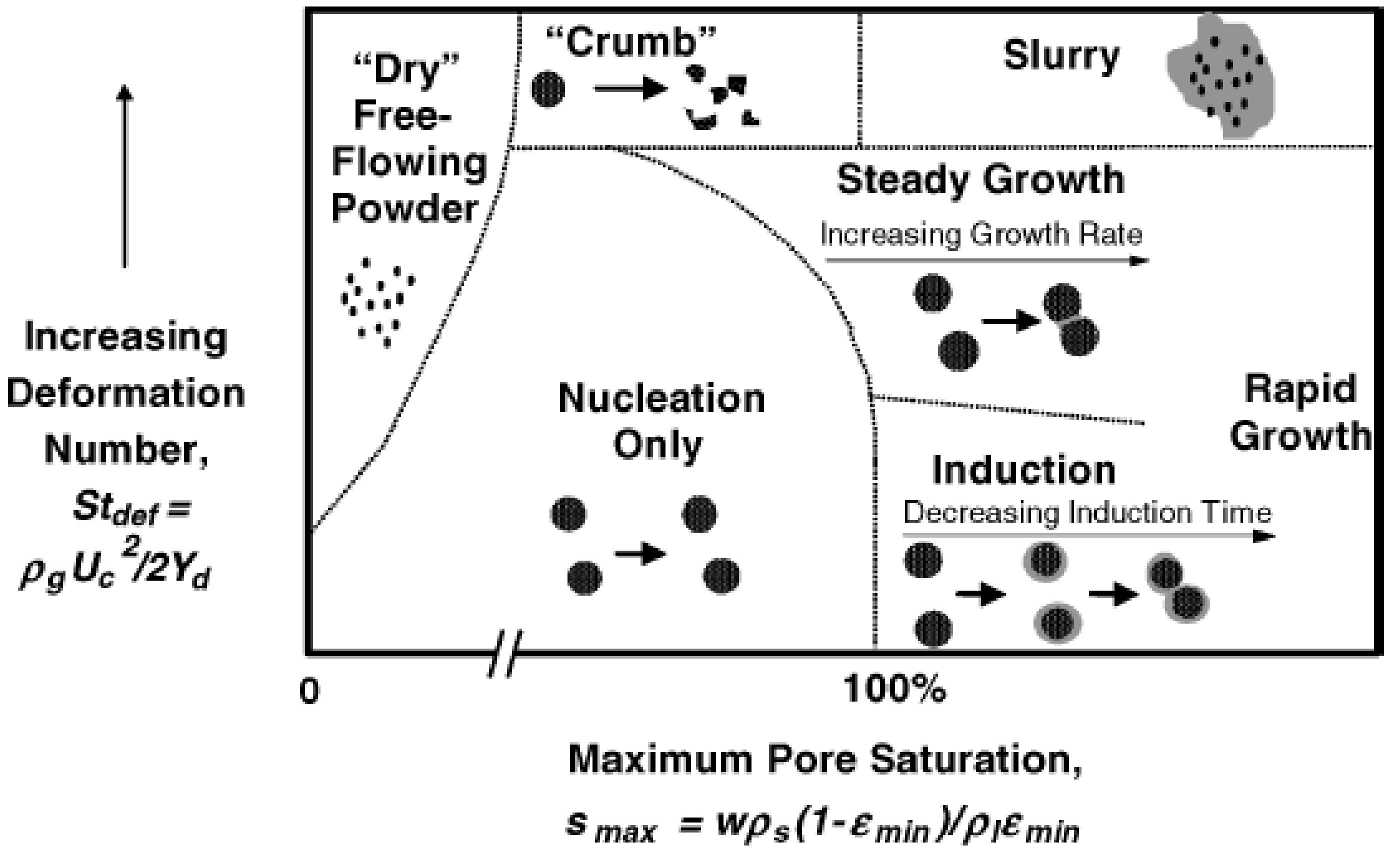
$$\sigma_{impact} = \frac{1}{2}\rho_g u_c^2$$

    - u_c … characteristic collision velocity
  - granule strength σ [Pa]
- Stokes deformation number

$$St_{def} = \frac{\rho_g u_c^2}{2Y_d}$$

    - Y_d … dynamic strength of granules

Growth map



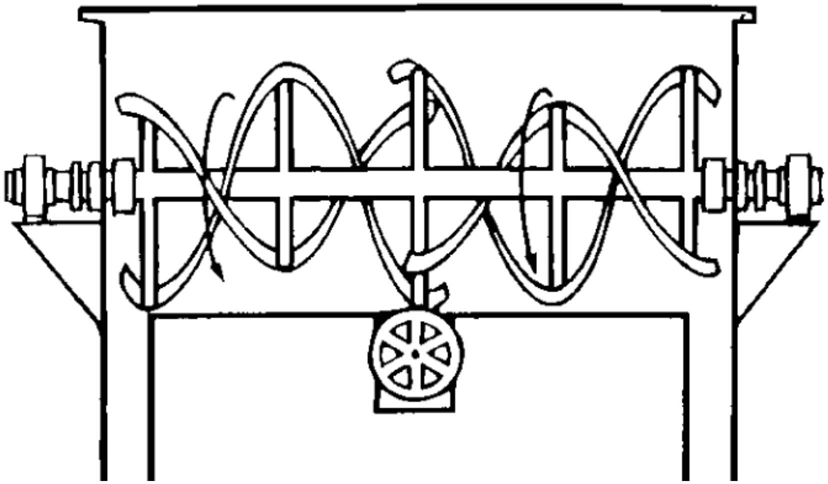
Increasing
Deformation
Number,
$St_{def} = \rho_g U_c^2 / 2Y_d$
"Dry" Free-Flowing Powder
"Crumb"
Slurry
Steady Growth
Increasing Growth Rate
Nucleation Only
Rapid Growth
Induction
Decreasing Induction Time
0
100%
Maximum Pore Saturation,
$s_{max} = w\rho_s(1-\varepsilon_{min})/\rho_l\varepsilon_{min}$

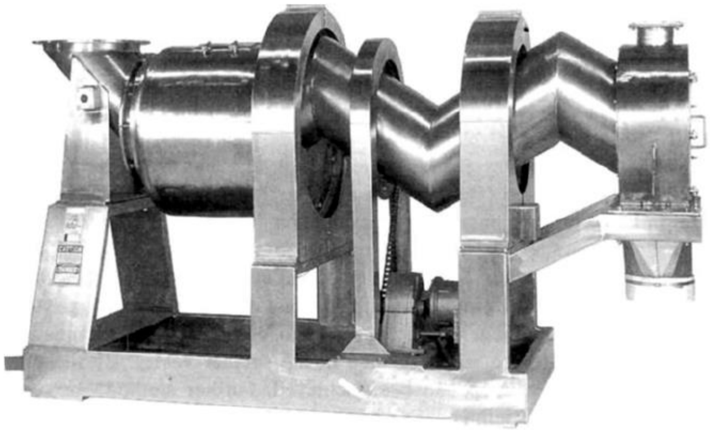
Wet granulation equipment

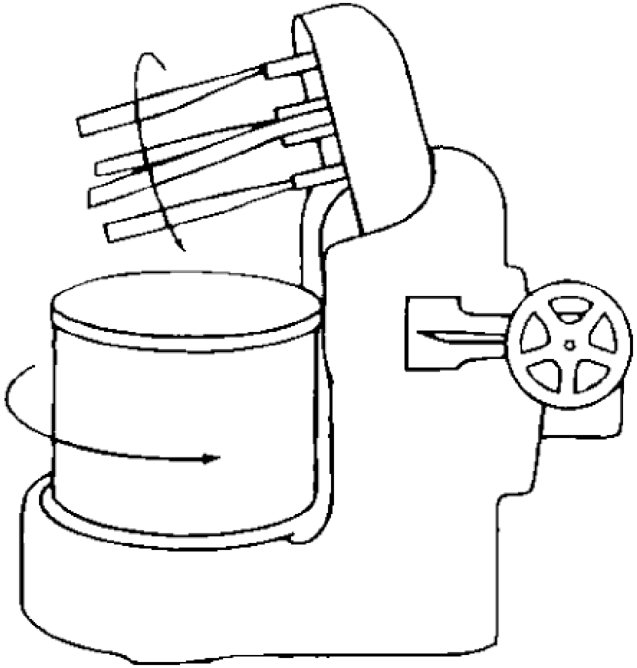
- High-shear wet granulation
  - common granulation in mixers
  - high energy, high shear, dense granules
- Low-shear wet granulation
  - similar to blenders
  - lower density granules, similar to fluidized bed
- Fluidized bed granulators
  - granulation in fluidized bed

High-shear wet granulators

Low-shear wet granulators

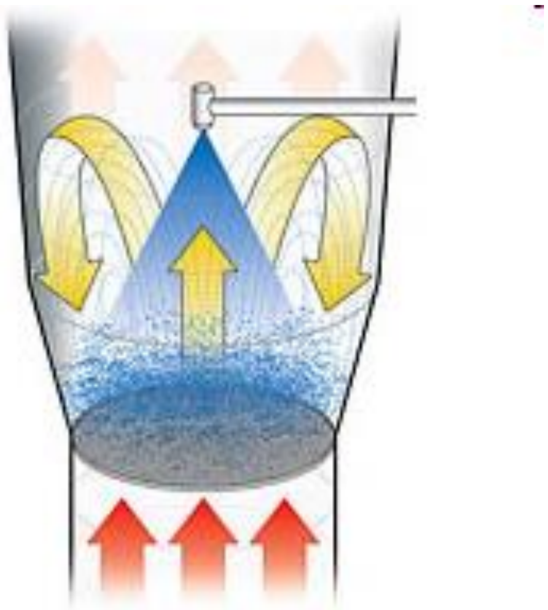


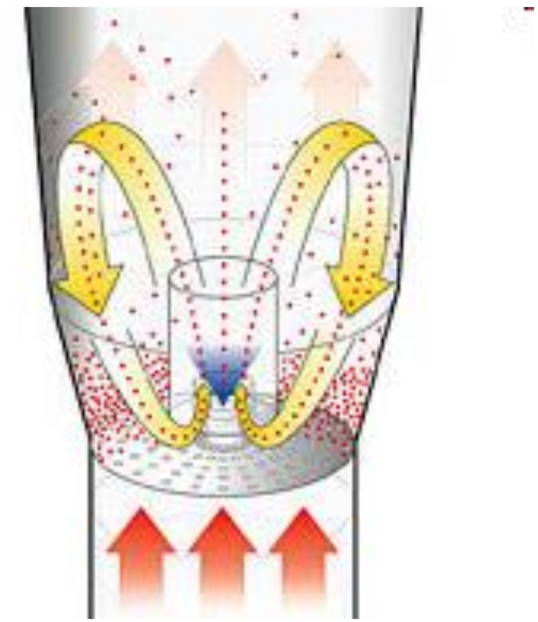




Fluidized bed granulators

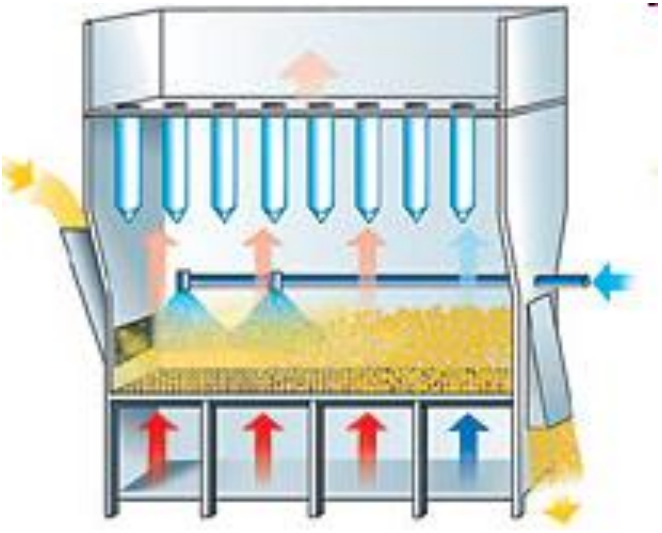
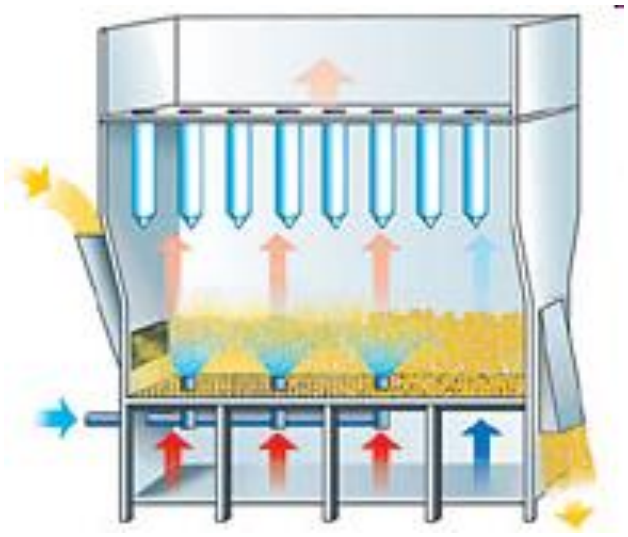
- Batch fluidized bed granulators
  - top spraying
  - bottom spraying





Fluidized bed granulators

- Continuous fluidized bed granulators
  - top spraying
  - bottom spraying

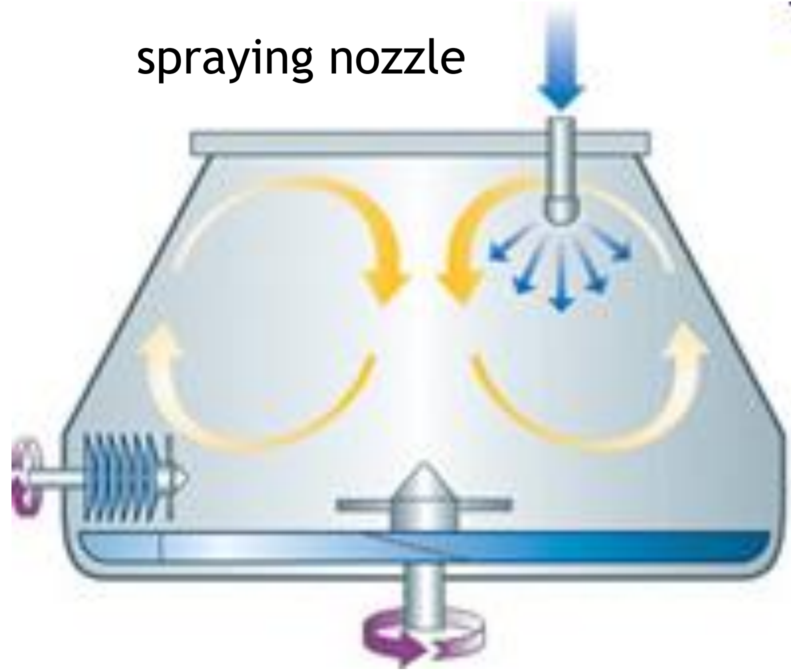
Comparing granules by process

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

- Fluidized bed
  - Better solubility
  - low density
  - adjustable PSD

Granulator

spraying nozzle

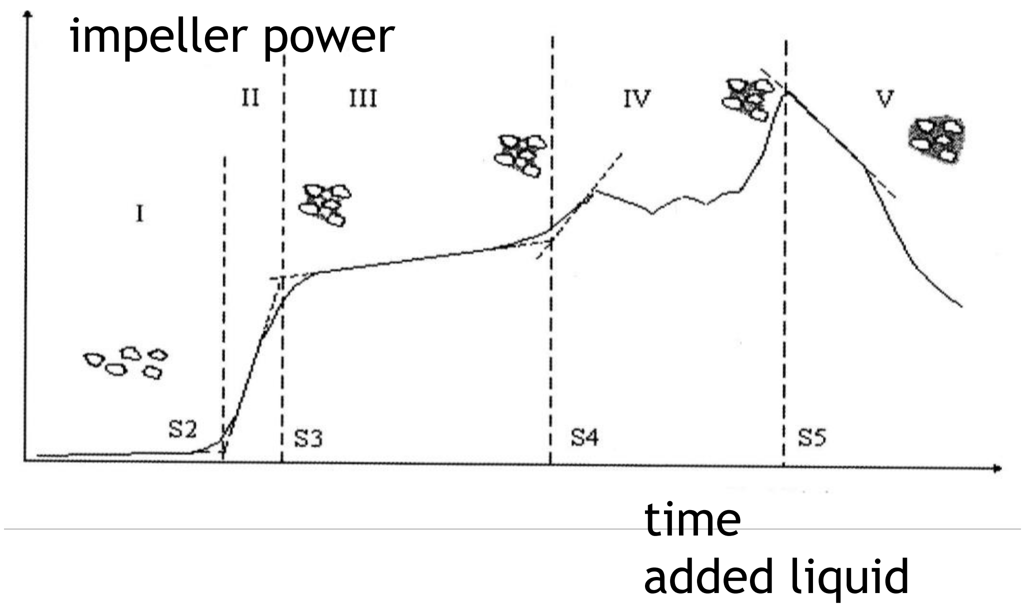


chopper

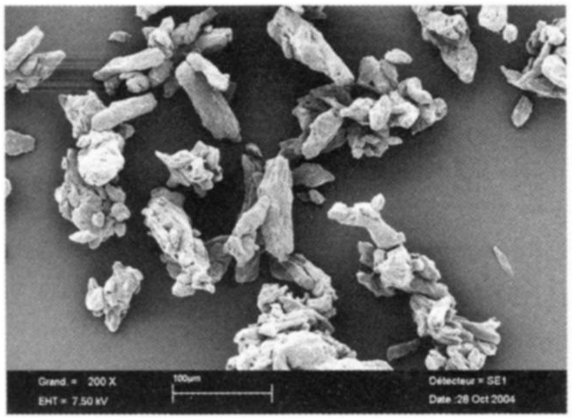
impeller

Process monitoring

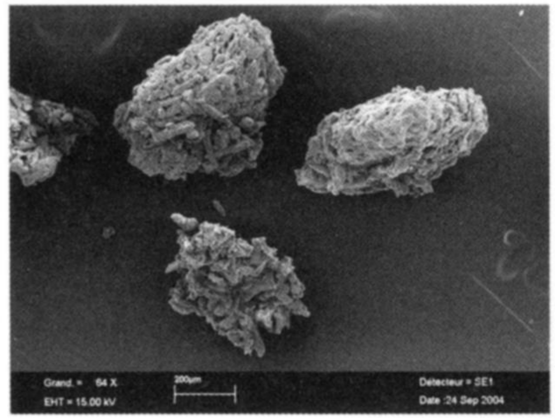
- I Wetting
  - low liquid content
  - no agglomeration
- II formation of liquid bridges
- III – IV granule consolidation and growth
- V Too much liquid - suspension



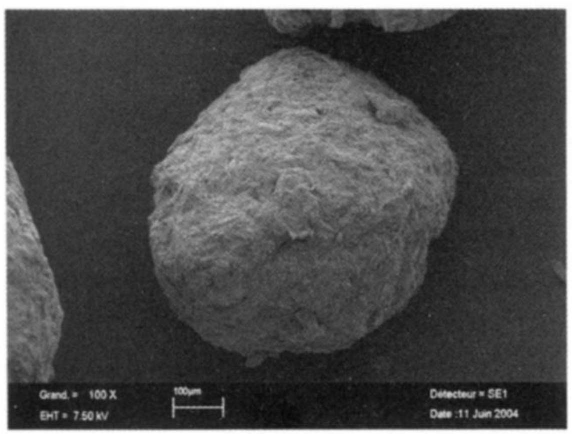
Liquid amount and agglomeration



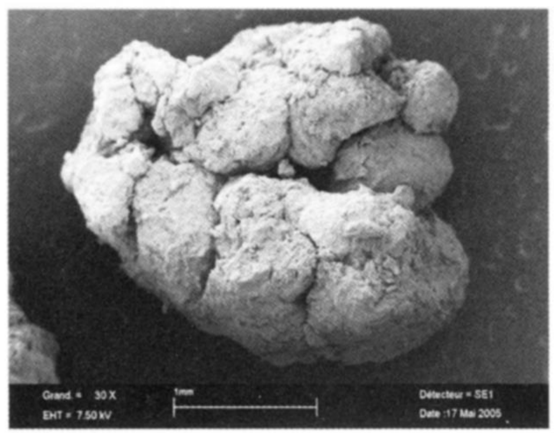
Regime I (L/S<33.3%)



Regime II (33.3<L/S<83.3%)



Regime III (L/S= 100%)



Regime III (L/S=108%)

Controlling the process

- Setpoint
  - optimal granules PSD
- Avoid
  - overgranulation
- Measured variable
  - impeller power
- Conditions
  - propper amount of liquid

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Engineering in Chemical and Pharmaceutical Processes

Compaction

References and study material

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  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
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  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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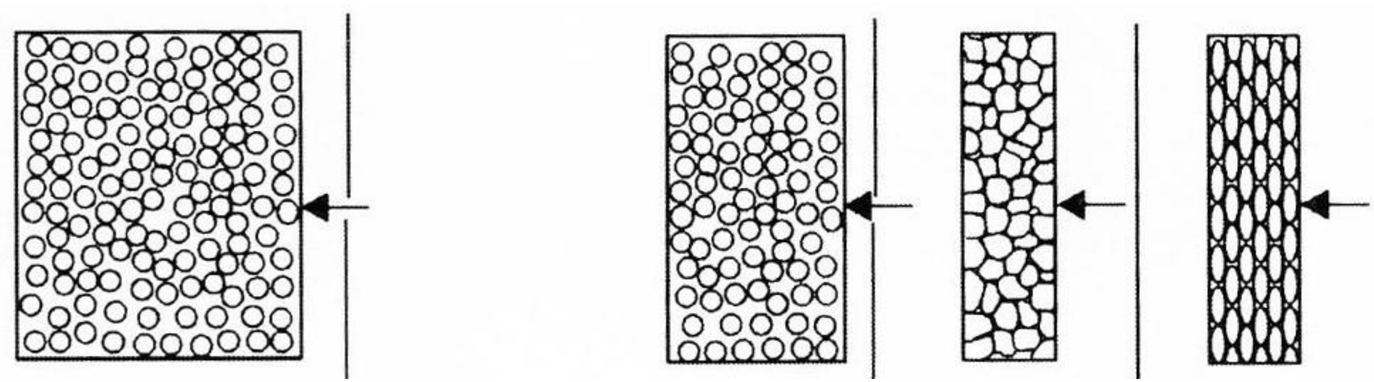
Compaction

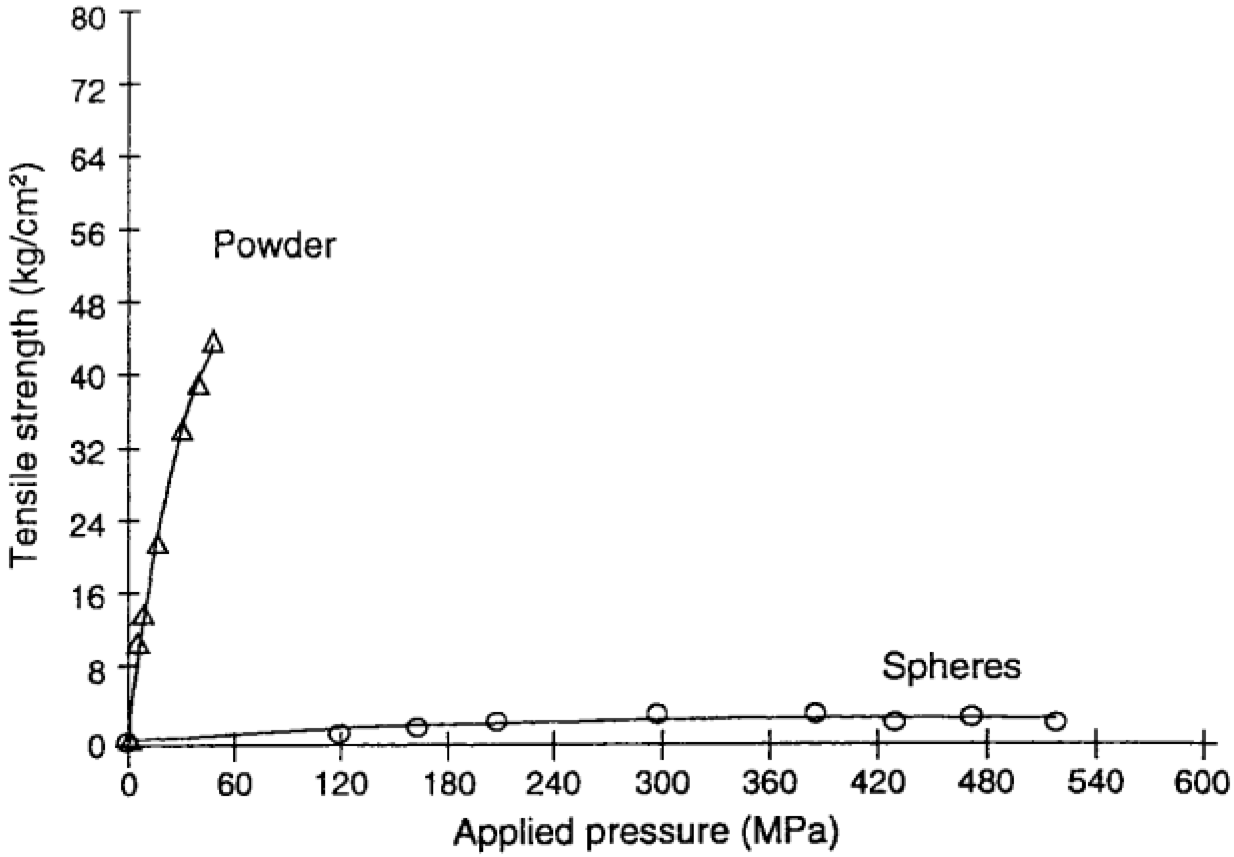
- „Dry-granulation“
- Principle
  - Compressing the powder between two surfaces
- Cohesive forces
  - van der Waals
  - mechanical interlocking
  - solid bridges (instantneous melting of the particles’ surfaces)

Compaction

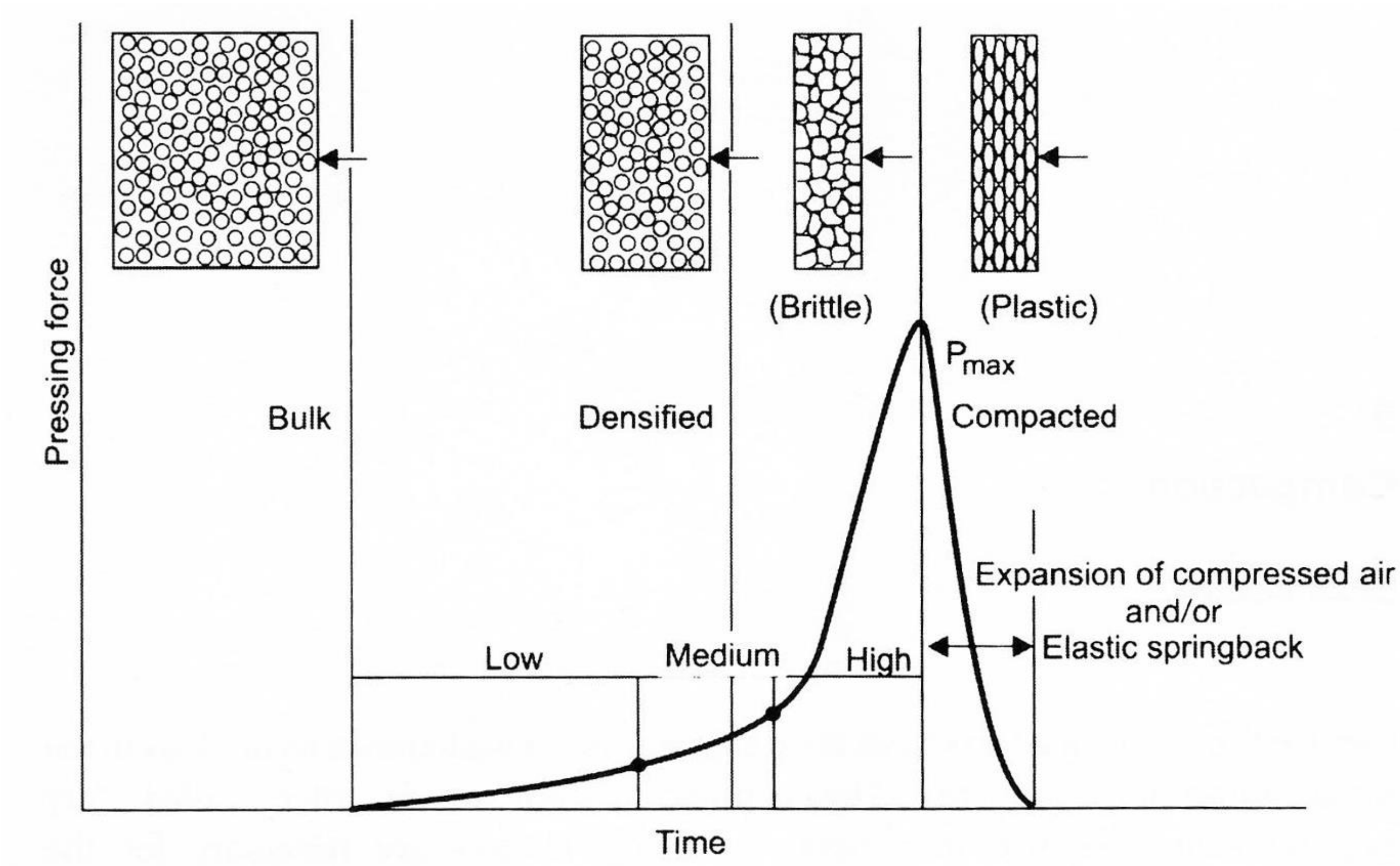
- Categories of materials
  - compactable
  - compactable with fragmentation
  - non-formable (glass, sand)



Materials compactability

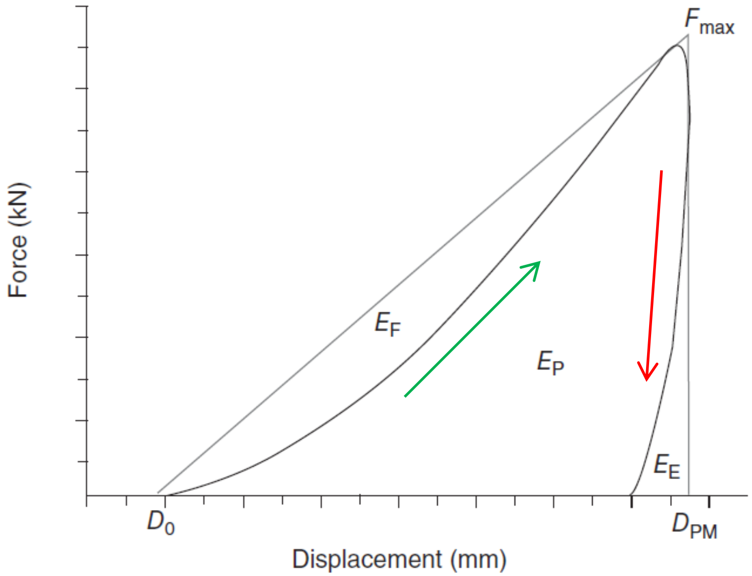


Mechanism of compaction



Energy analysis of compaction

- Analysis of force required per displacement during compression and decompression
- Energy = force * length
- Energy = area under curve
  - E_P = plastic deformation
  - E_E = elastic deformation
  - E_F = rearrangement /friction



Mathematical model of compaction

- Heckel equation
  - one of many equations
  - assumes the compaction takes place by reducing porosity as the first order process

$$\frac{\mathrm{d}\rho_{rel}}{\mathrm{d}p} = k\varepsilon \qquad \frac{\rho_B}{\rho_{solid}} = \rho_{rel} \qquad \varepsilon = \frac{V_B - V_{solid}}{V_B} = 1 - \frac{V_{solid}}{V_B} = 1 - \rho_{rel}$$

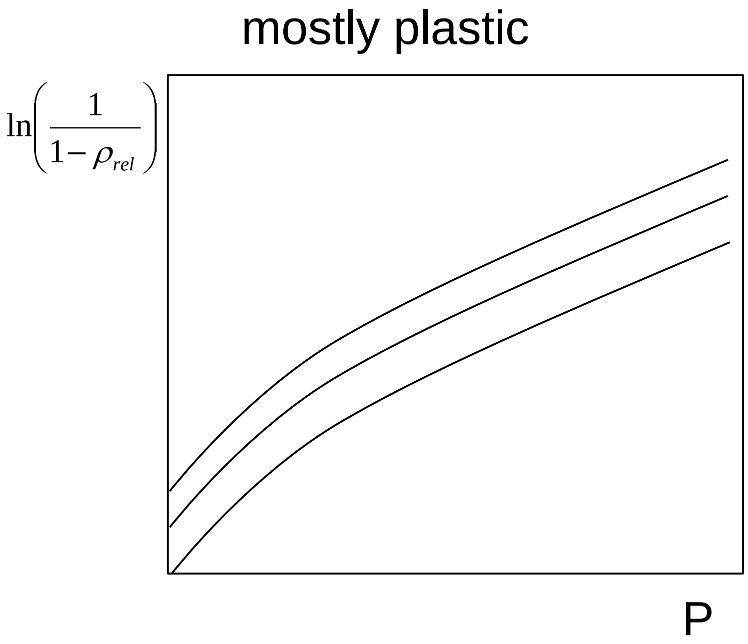
$$\frac{\mathrm{d}\rho_{rel}}{\mathrm{d}P} = k\left(1 - \rho_{rel}\right)$$

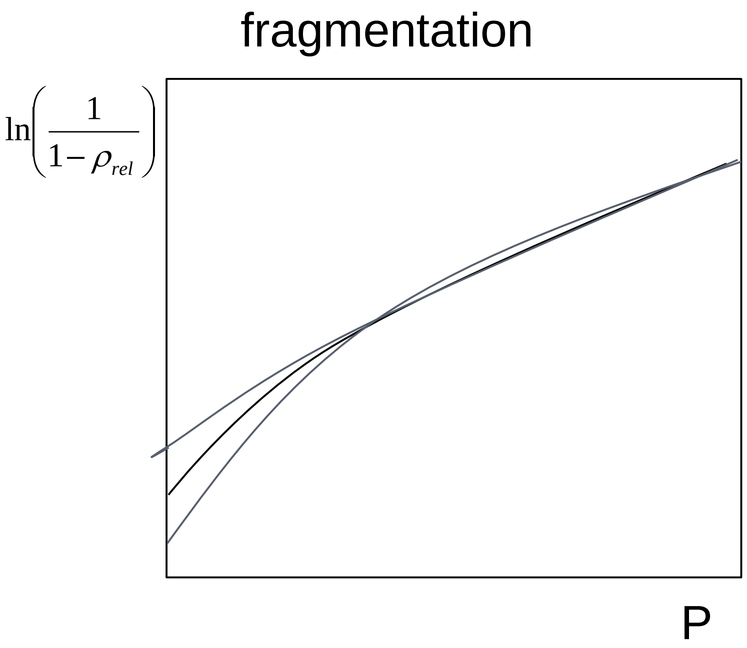
$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = kp + A \qquad \ln\left(\frac{1}{1-\rho_0}\right) = A$$

ρ_0 = rel. density at low pressure

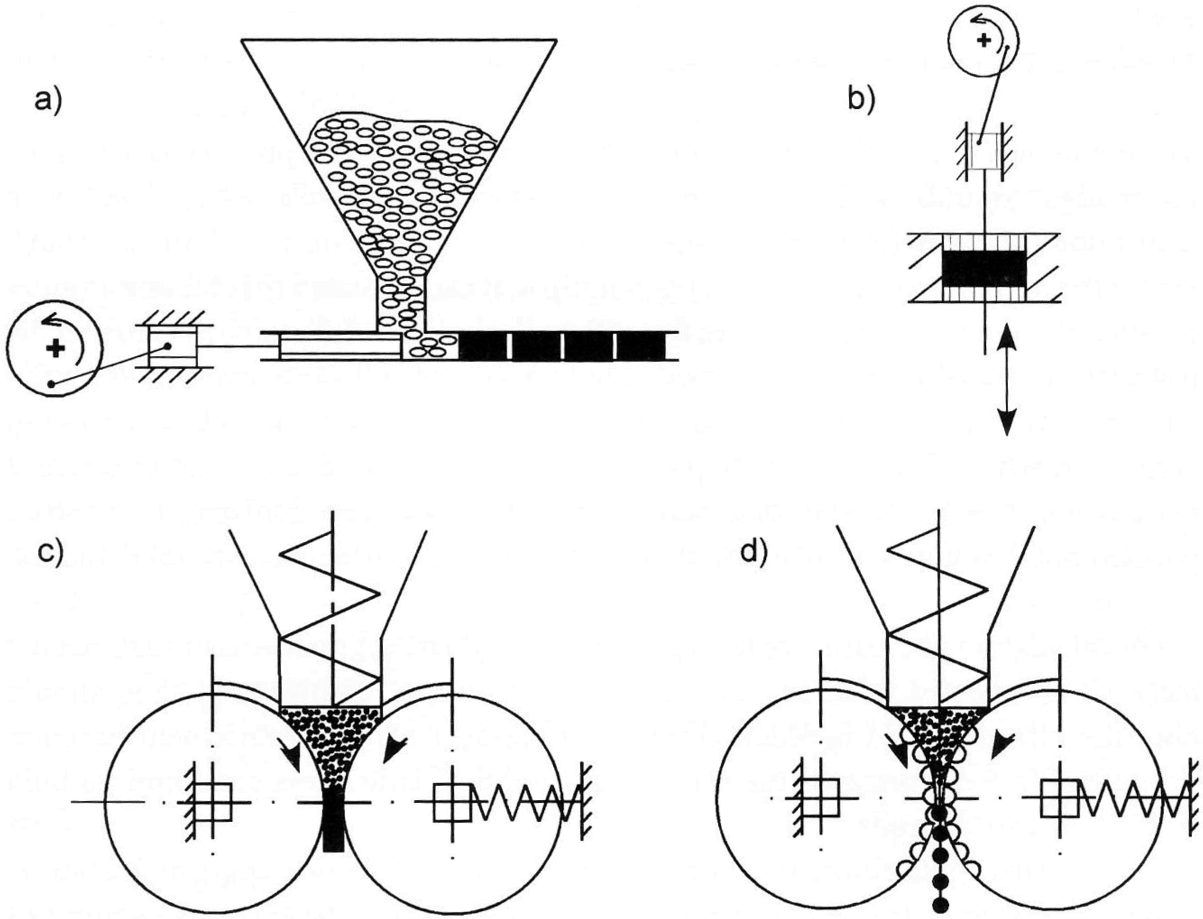
Types of compaction behaviour

- Compacting different size fractions of the same material

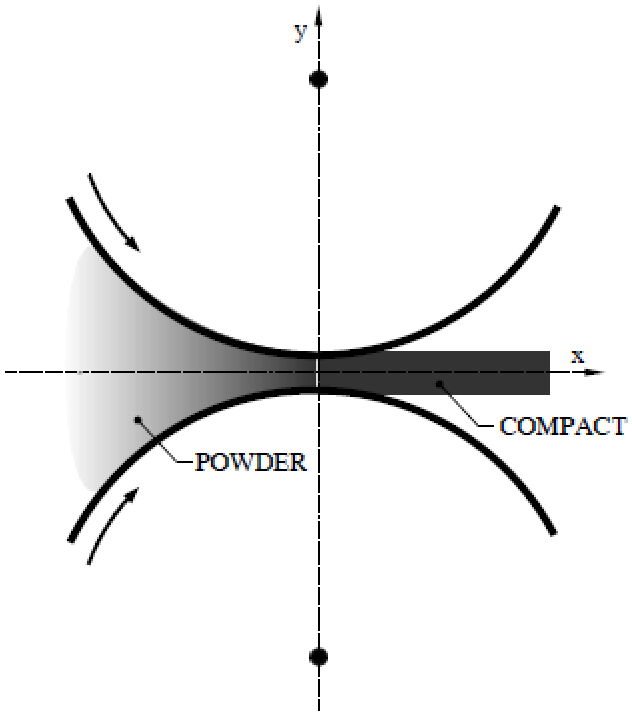




Compaction equipment

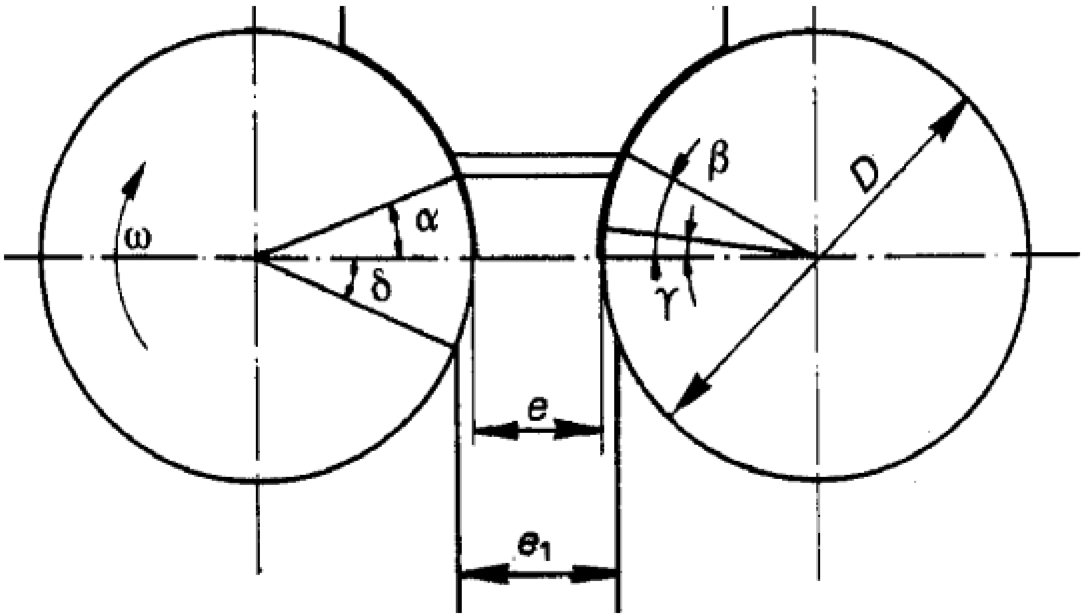


Roller compaction



- Compacting powder between rollers
- Powder is fed by gravitation or using screw conveyor
- Powder is pulled into the gap by action of friction force between the roller surface and the powder

Critical parameters of roller compaction



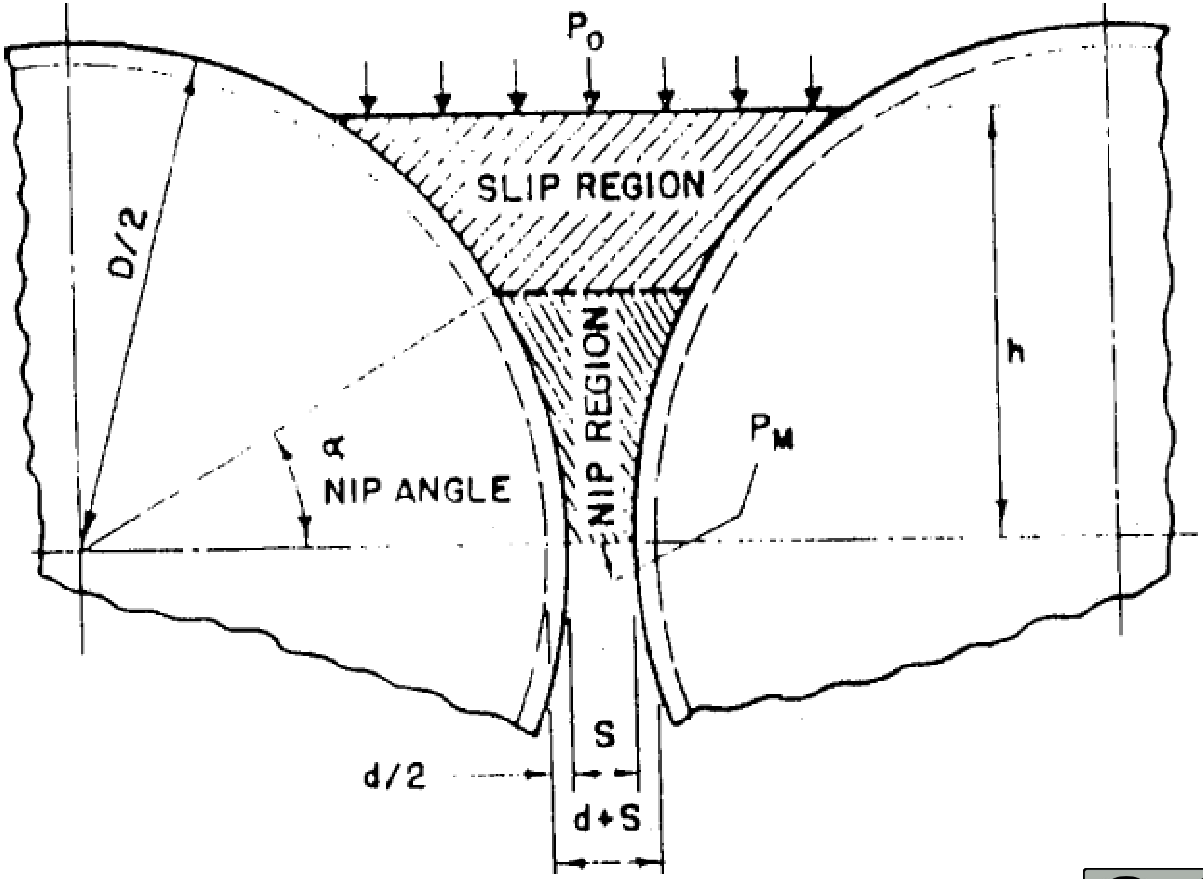
- ω … angular speed
- α … nip angle
- γ … angle of max pressure p_{max}
- δ … elastic expansion angle
- e … gap size
- e_1 … size of product ribbon

Zones between the rollers

- Entry zone
  - powder is not entrained by the rollers
- Slip zone
  - powder is pulled into the gap, but moving more slowly than roller surface
- Nip zone
  - powder is pulled into the gap at the roller surface velocity

Regions of different material motion

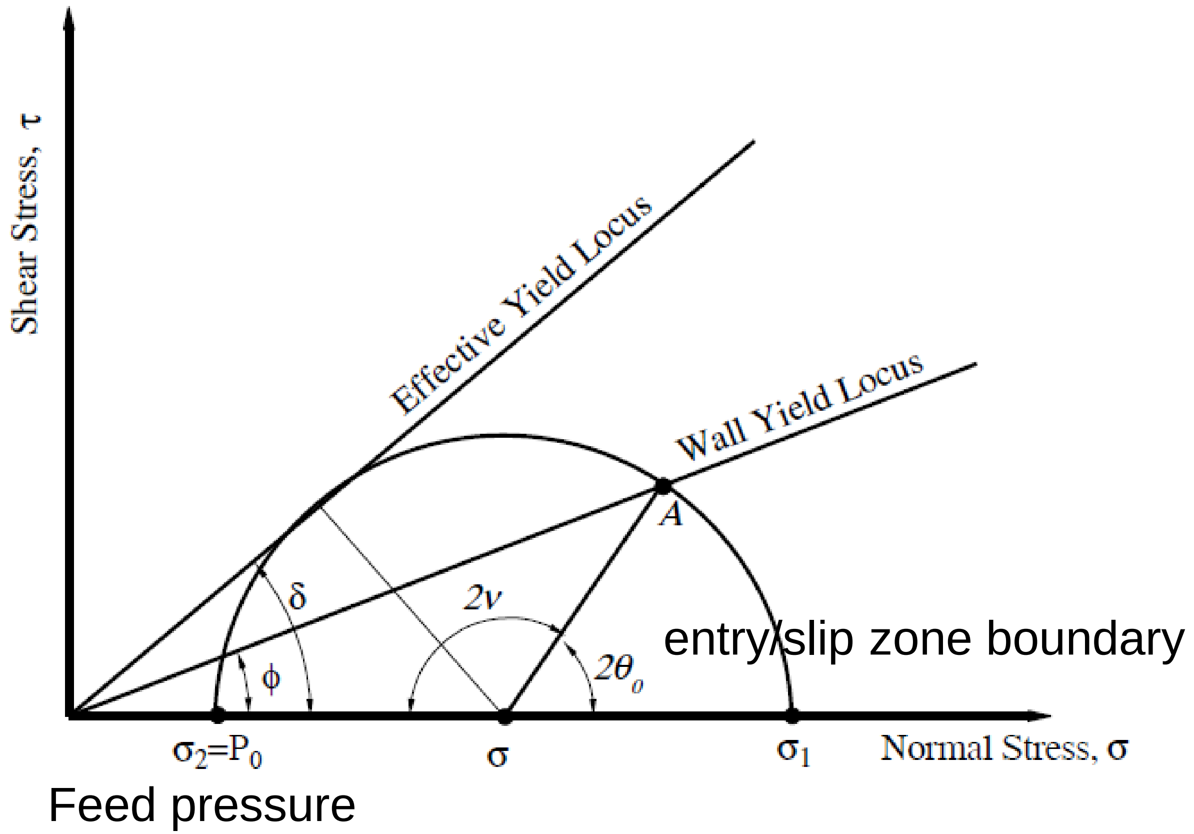
α given by pressure, layer height and material properties



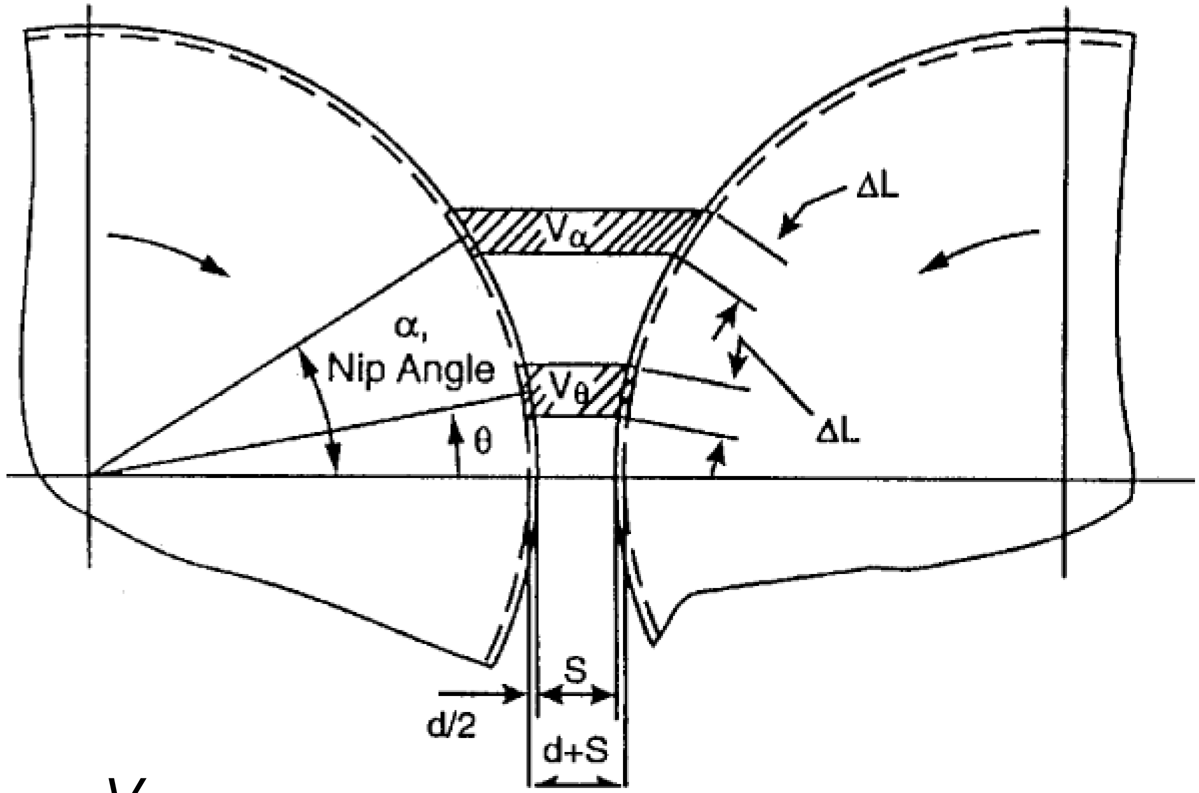
Parametes affecting roller compaction

- Geometric
  - roller diameter, gap size
- Operation
  - Feed pressure, angular velocity
- Powder
  - internal friction angle, bulk density, compressibility
- Interface
  - wall friction angle

Stress state in the slip zone

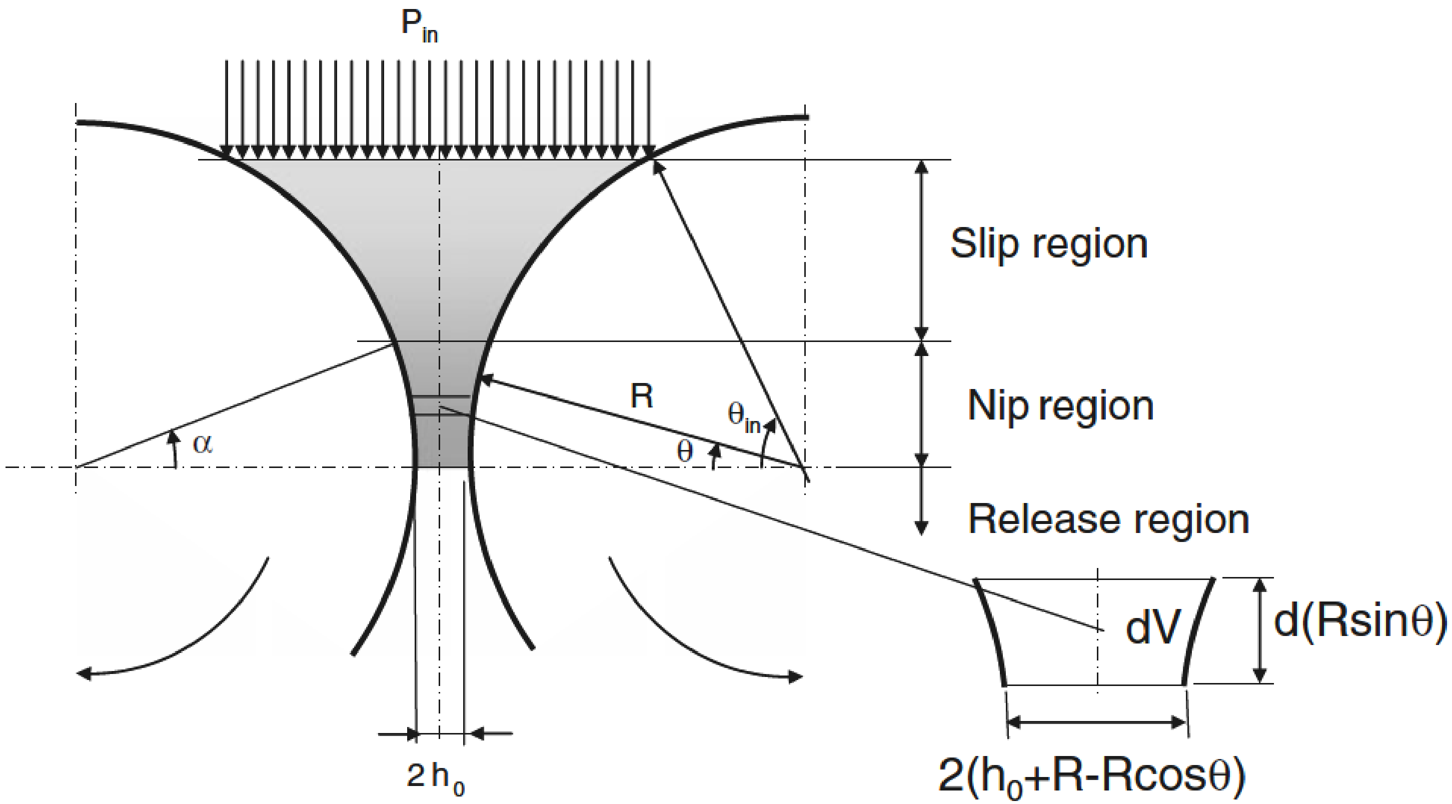


Geometry-compression relationship



$$\frac{\rho_{B,\alpha}}{\rho_{B,\theta}} = \frac{V_\theta}{V_\alpha}$$

Geometry-compression relationship



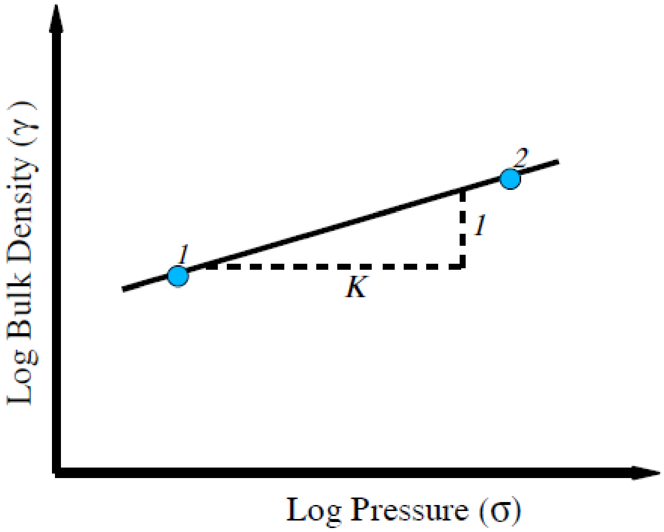
$$\mathrm{d}V = 2\left(h_0 + R - R\cos\theta\right)\cdot \mathrm{d}\left(R\sin\theta\right) \qquad V = 2\left(h_0 + R - R\cos\theta\right)\cdot\left(R\cos\theta\right)$$

Stress in nip zone

- Empirical relationship

$$\frac{\sigma_1}{\sigma_2} = \left(\frac{\rho_1}{\rho_2}\right)^K$$

  - K .. compressibility



$$\sigma_\theta = \sigma_\alpha \left[\frac{(1 + S/D - \cos\alpha)\cos\alpha}{(1 + S/D - \cos\theta)\cos\theta} \right]^K$$

Nip angle

- Slip zone
  - stress gradient = function (D, S, θ, δ, ϕ)

$$\frac{d\sigma}{dx} = \frac{4\sigma\left(\pi/2-\theta-\nu\right)\tan\delta}{\frac{D}{2}\left[\left(1+S/D-\cos\theta\right)\right]\left[\cot\left(A-U\right)-\cot\left(A+U\right)\right]}$$

- Nip zóne
  - stress gradient = function (D, S, K)

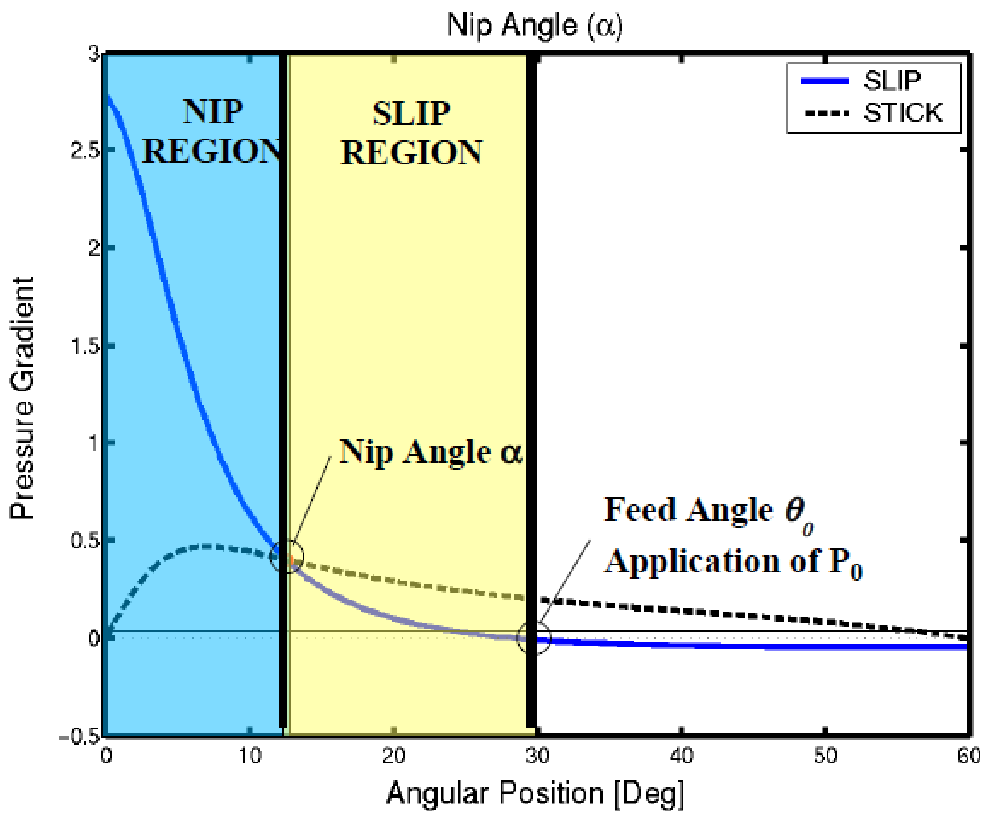
(for illustration only)

$$\frac{d\sigma}{dx} = \frac{K\sigma_\theta\left(2\cos\theta-1-S/D\right)\tan\theta}{\frac{D}{2}\left(1+S/D-\cos\theta\right)\cos\theta}$$

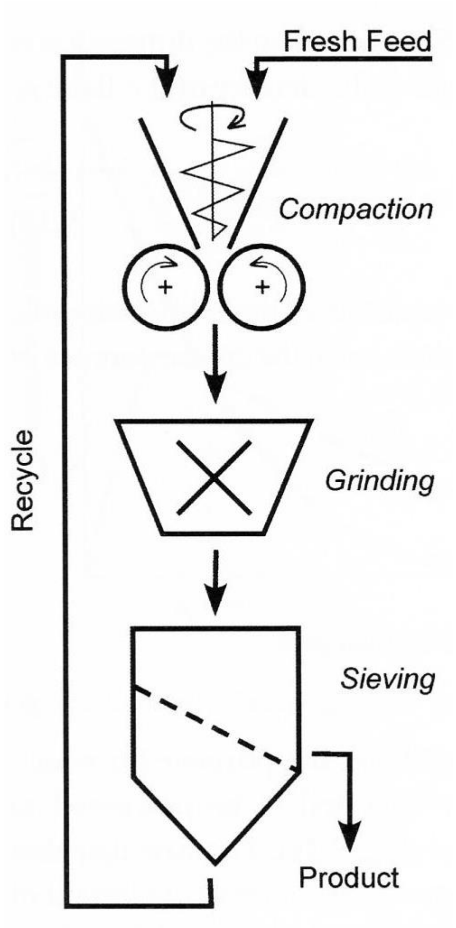
(for illustration only)

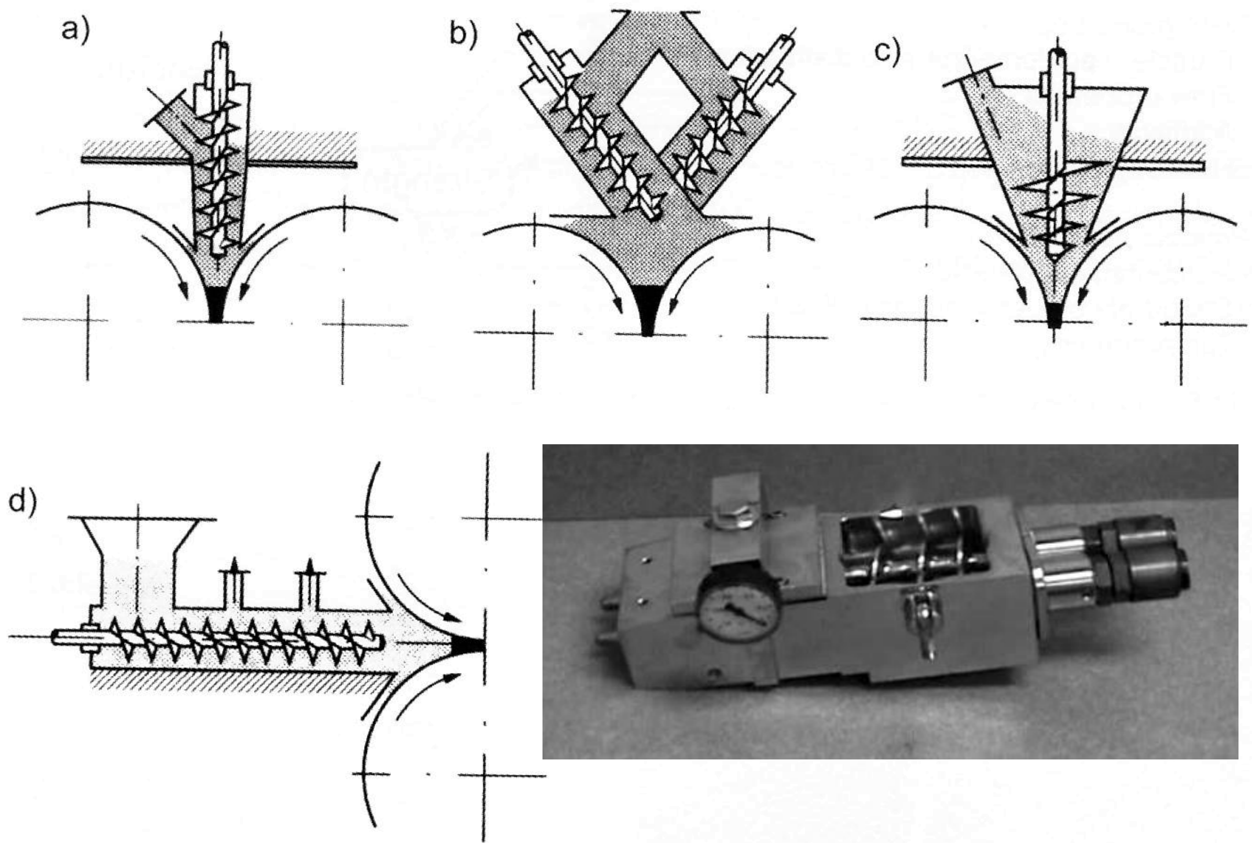
Nip angle

- Nip angle belongs to both zones

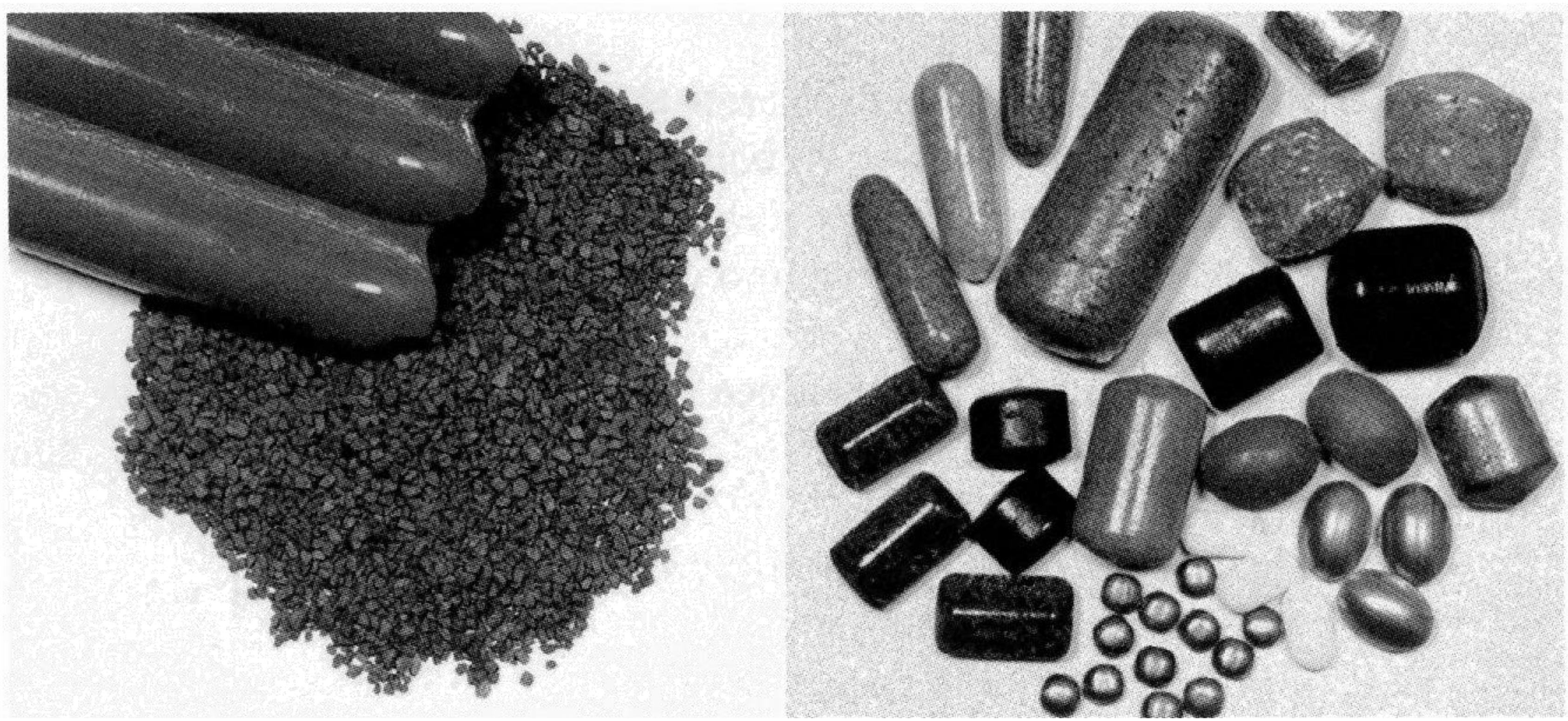


Application of compaction in pharma processes – feed screw designs





Compacted products



Compacted product usage

- Intermediate product with better flowability
- Content of
  - hard gelatin capsules
  - sachets
  - effervescent drugs

Factors affecting compacts strength

- Raw material
  - particle size distribution
  - flowability
  - additives (eg. hydroxypropylcellulose)
  - moisture
- Process parameters
  - recycle
  - process speed / time-under-pressure
  - temperature

Compacted vs. granulated product

- Specific properties
  - lower porosity
  - smoother surface
- No binder necessary
- Dry-processing (no moisture)
- No drying necessary
  - thermal stability issues

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Engineering in Chemical and Pharmaceutical Processes

Extrusion and Postprocessing of Agglomerated Products

References and study material

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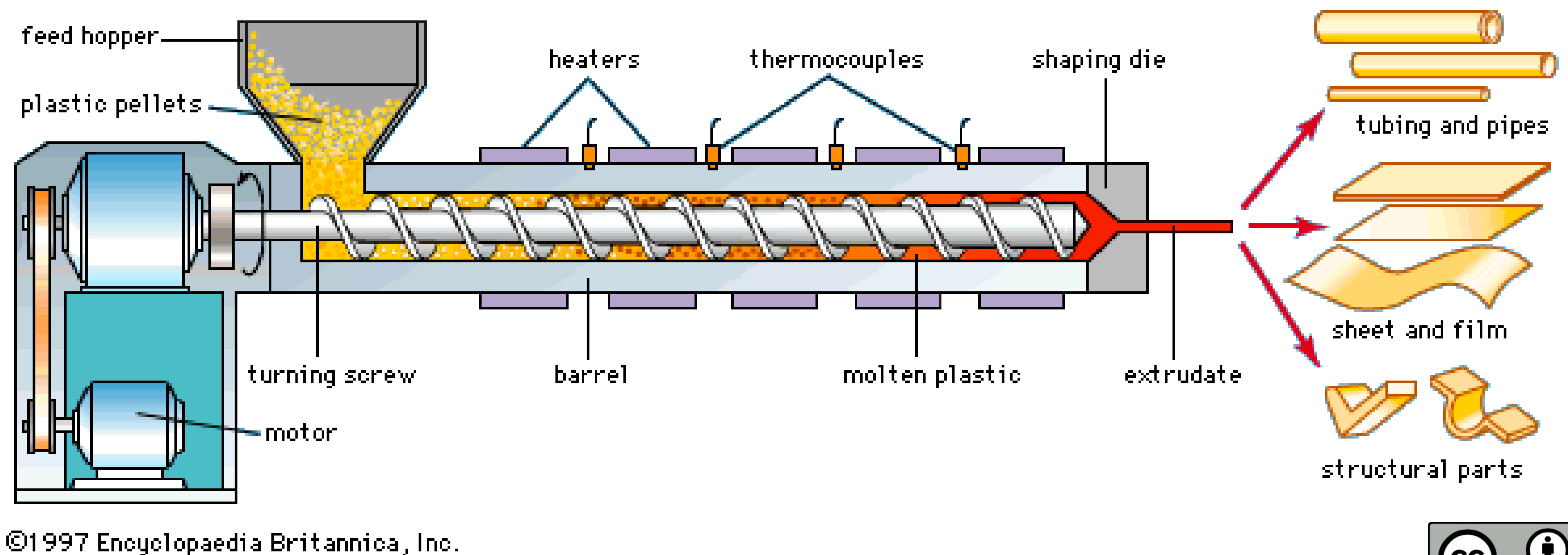
Extrusion (Hot-melt extrusion)

- History
  - 18th century – lead pipes
  - 19th century – insulated cables
- Nowadays
  - Polymer and food processing
  - Pharmaceutical industry
    - Granules, tablets/capsules with modified release, implants, Transdermal Therapeutic Systems (TTSs)
- Advantages and disadvantages
  + Simple and continuous process
  + Leads to homogeneous dispersion
  + Can be done without solvent (melt extrusion) -> eliminates drying
  - Processing temperature

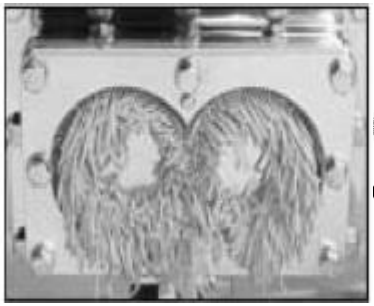
Extrusion

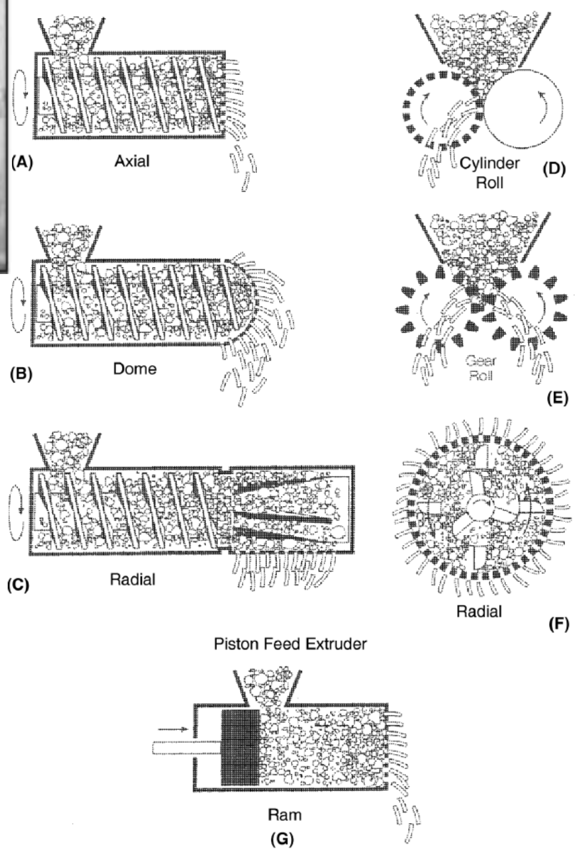
- Pushing the paste-like material through orifice
  - melt
  - powder + liquid

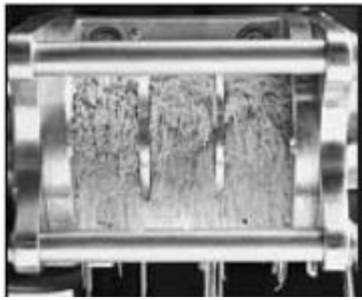


Extruders

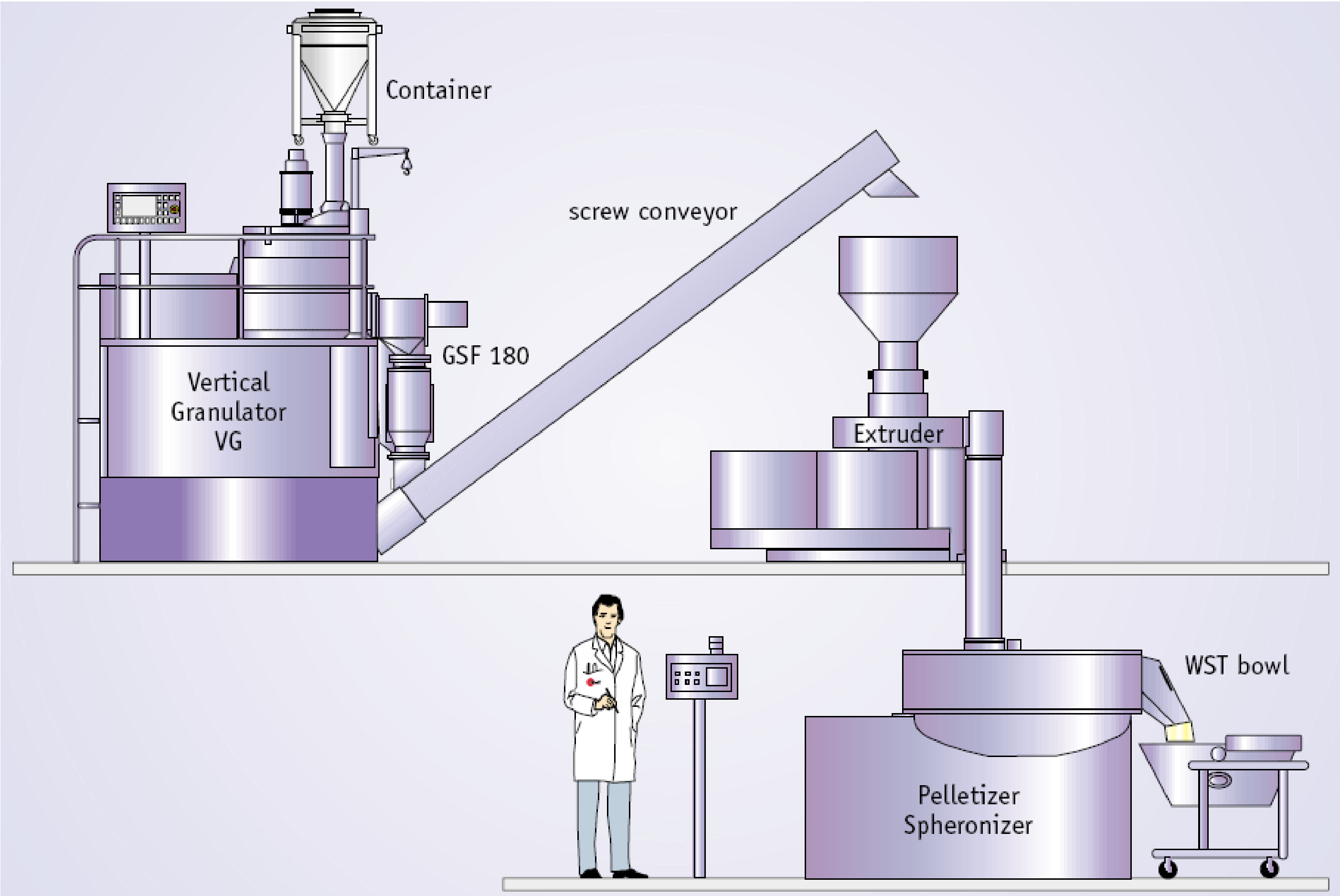
- Cylinder rolls
- Radial
- Piston feed
- Axial screw
- Double-screw



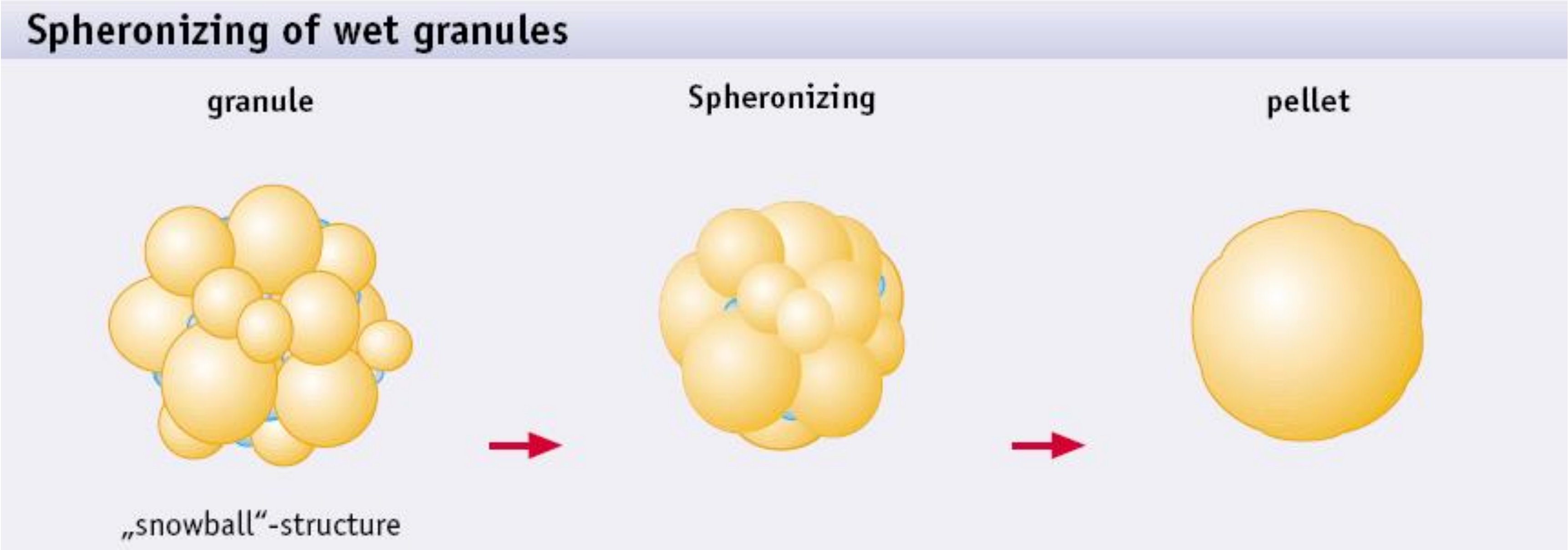




(Granulation) / Extrusion / Spheronization (Glatt process)

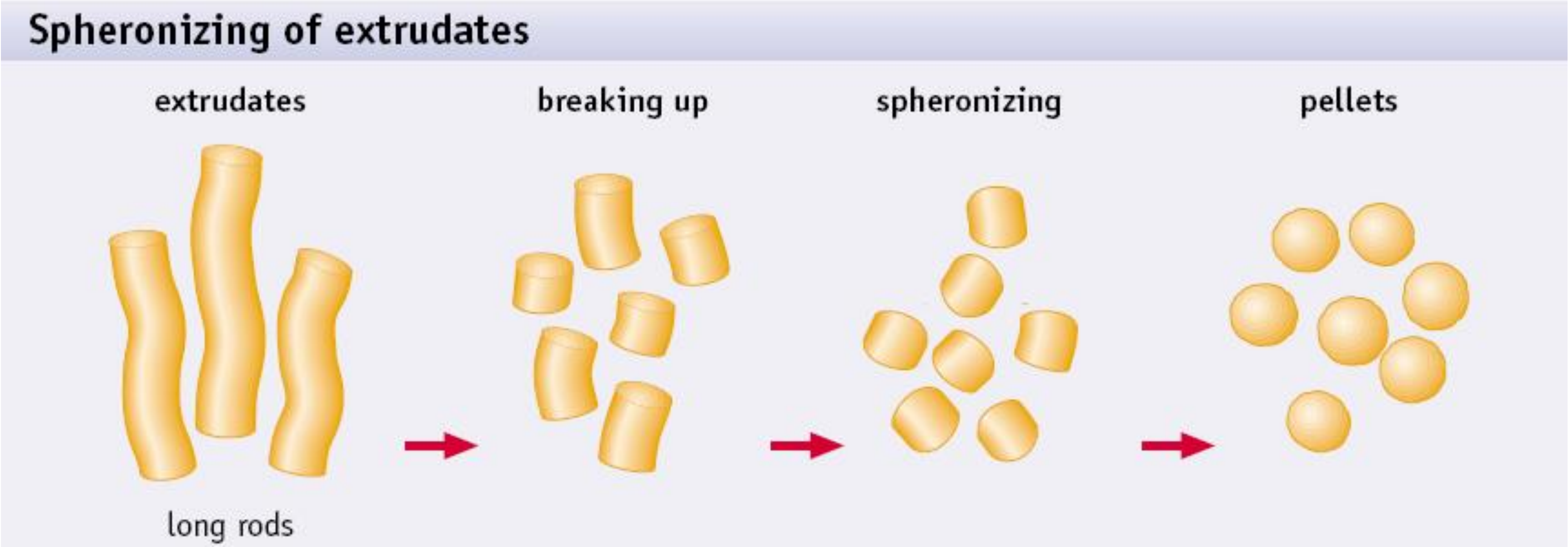


Spheronization



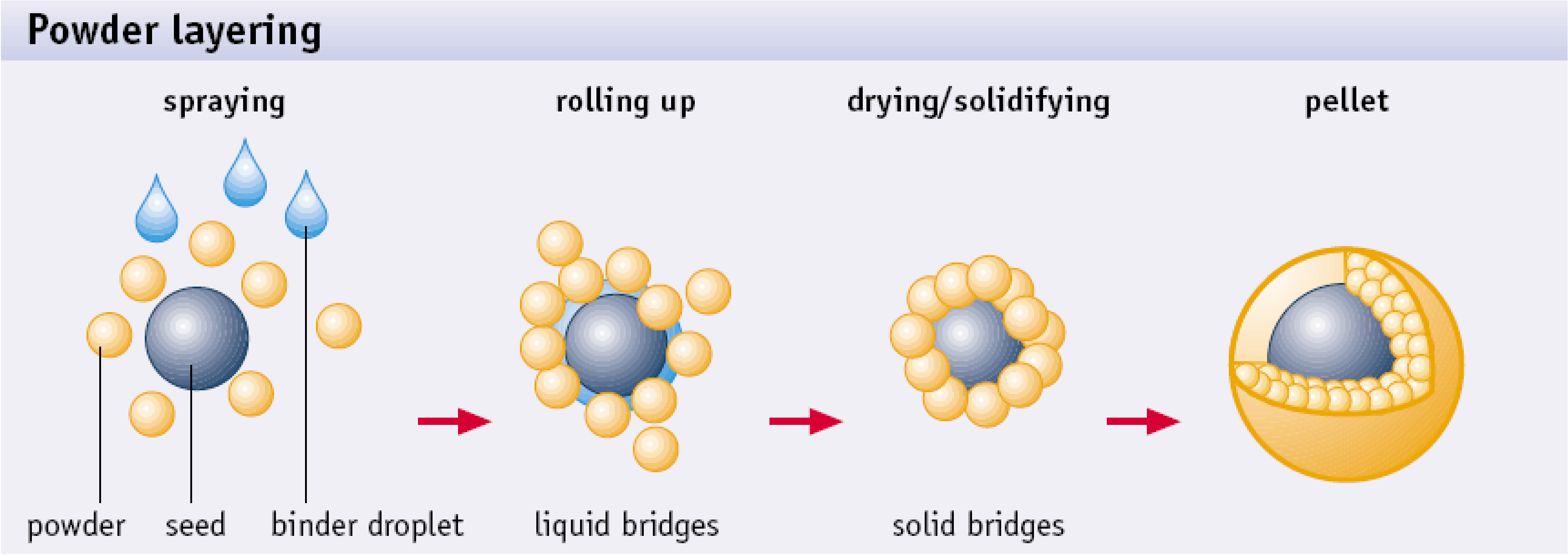
- Smooth surface = further improvement of the flowability
- Low dust, better coating

Spheronizing extrudates

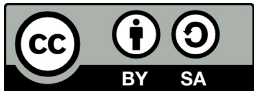


- Uniform particles
- Good dissolution and dispergation
- Attractive design

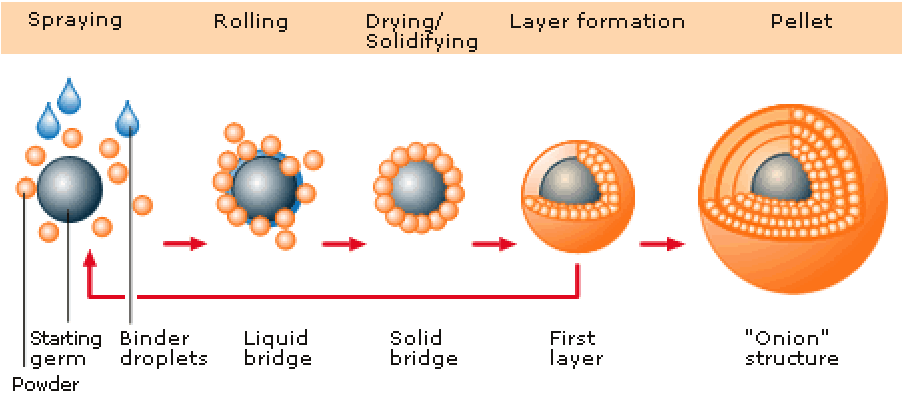
Powder coating

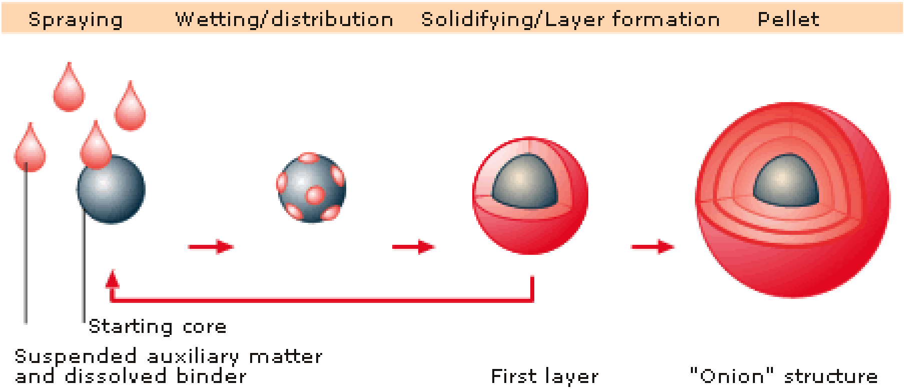


- Creating layered structure

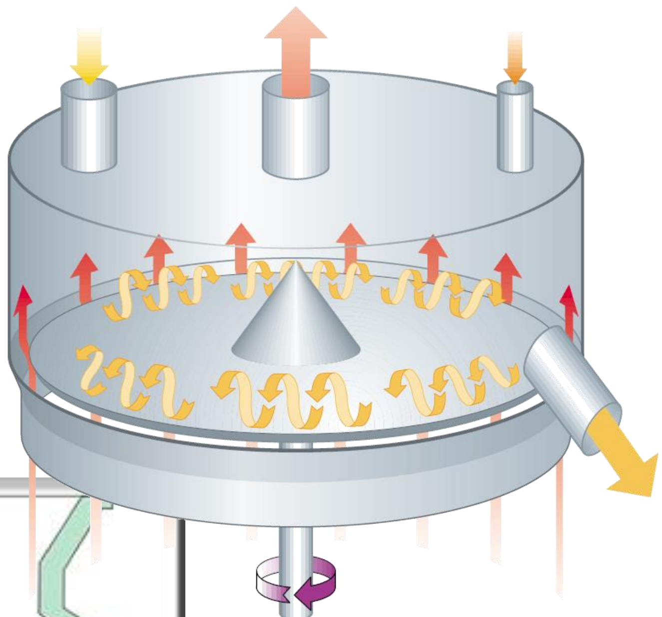


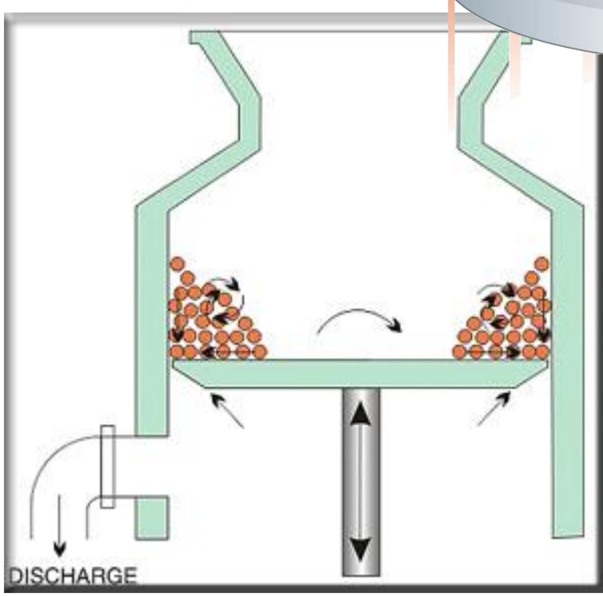
Controlled Release for powder coating



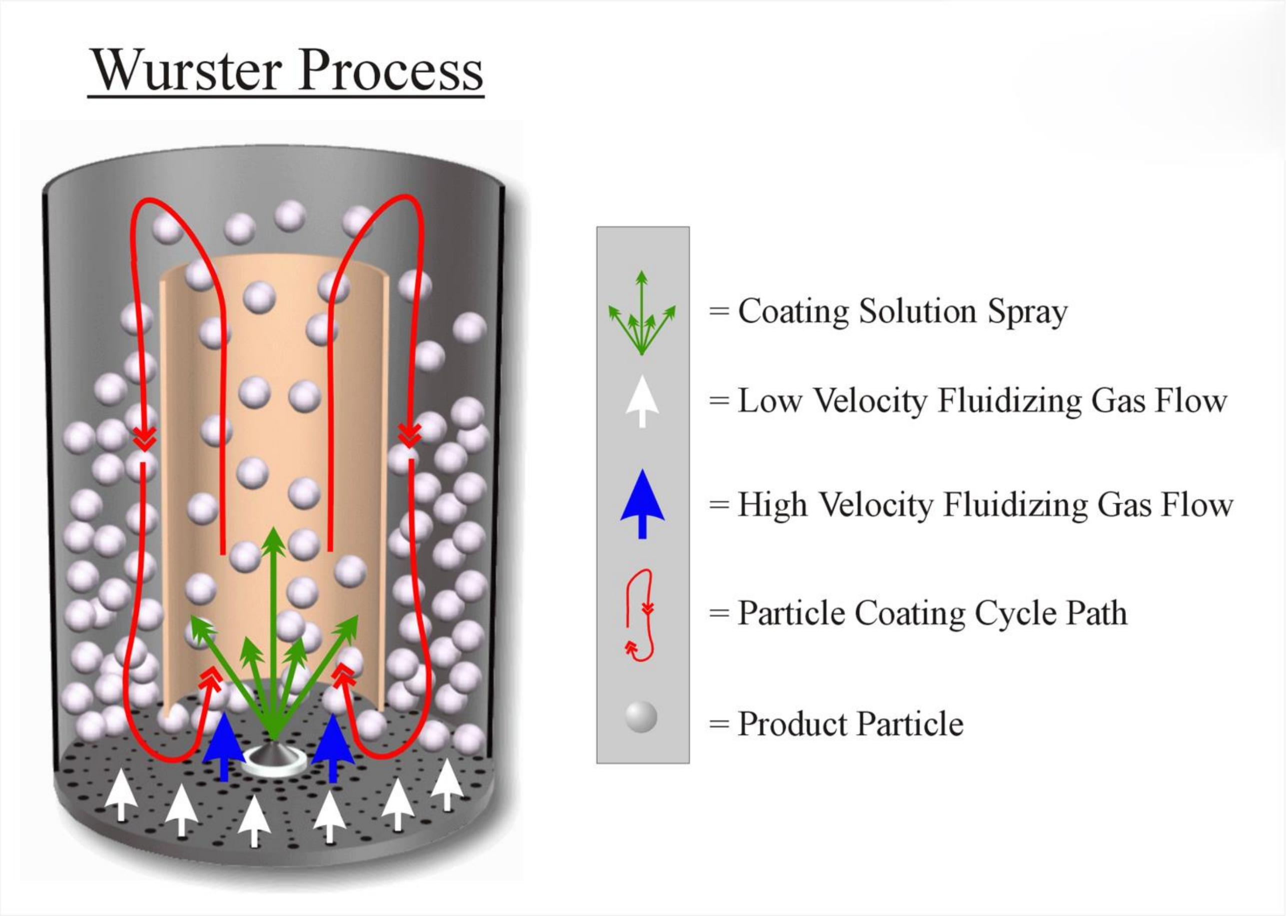


Spheronization

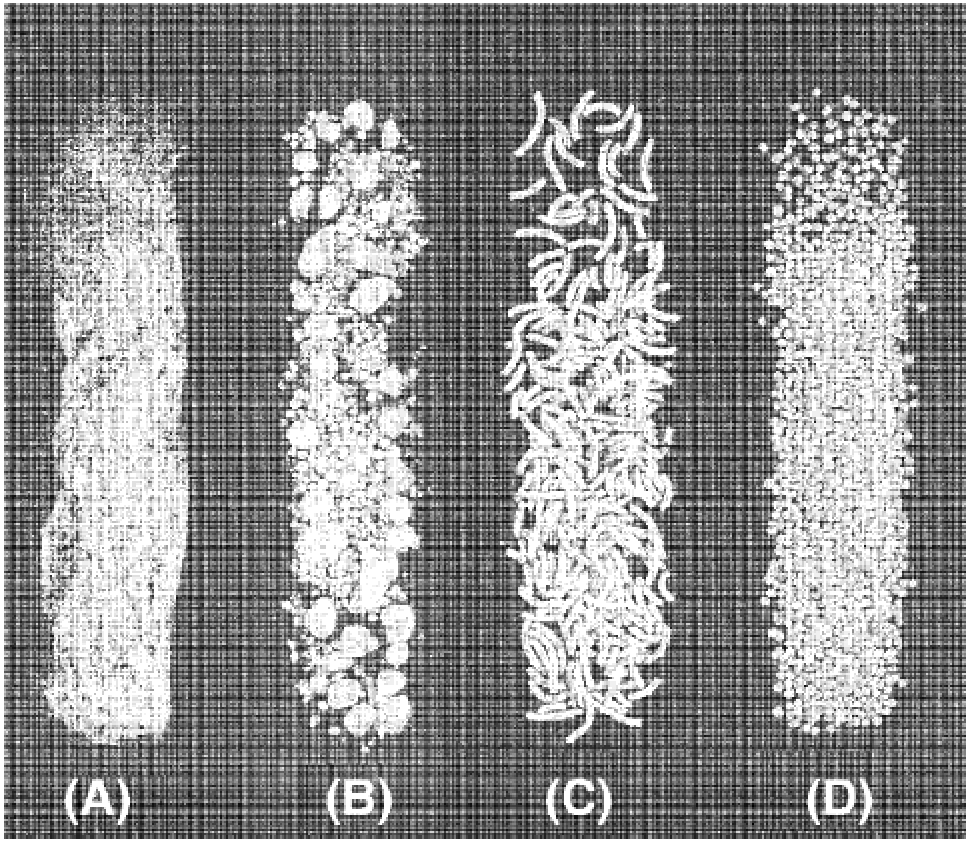




Spheronization / coating process



Products

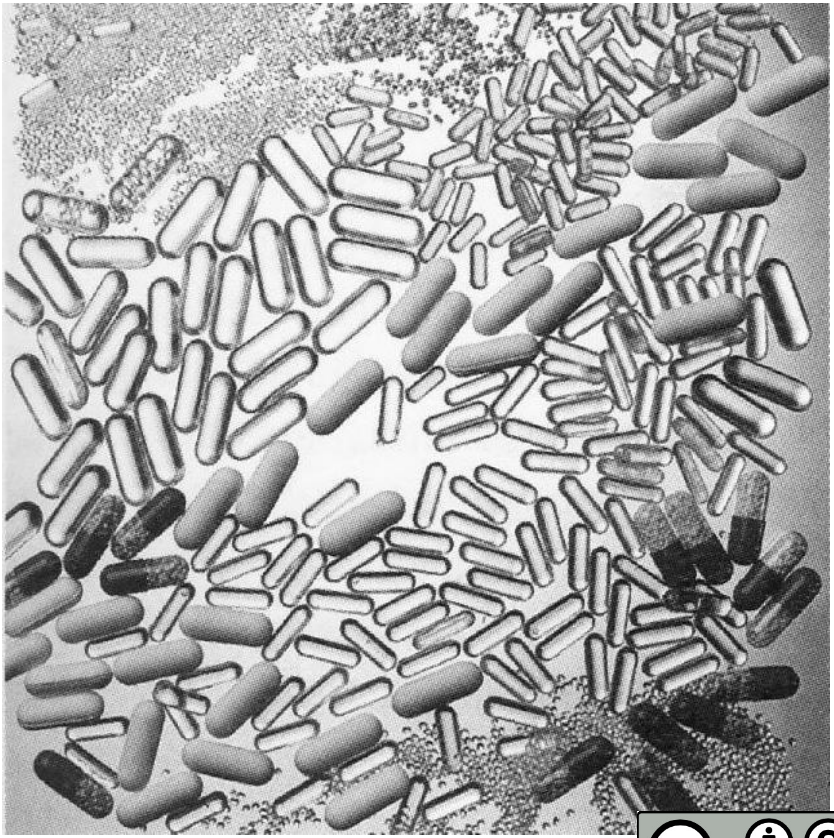


powder granulate extrudate spherules/pellets

Pharmaceutical extrusion

Melt-extrusion process

- Alternative to tablet compression
- Advantages
  - no granulation, drying
  - special properties
  - appearance
- Disadvantages
  - processing temperature
  - special excipients
    - solubility
    - thermoplasticity



Melt-extrusion excipients

- Carriers
  - Compound in which API is dispersed
  - Easy melting compounds or mixtures of compounds
    - Polymers or waxes with low melting point
      - Methacrylate copolymers
      - Polyethylenglykol
      - Polyvinylpyrrolidone
      - Polyvinylacetate
      - Carnauba wax, etc.

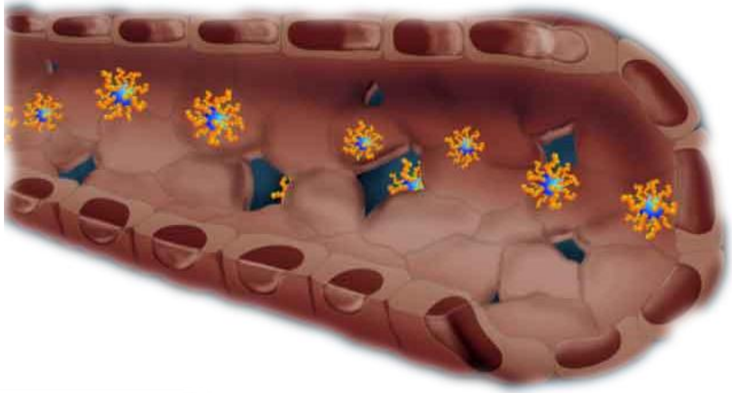
- Plasticizers
  - Low molecular weight compounds capable of softening polymers
  - Improve the processing conditions (temperature, torque)
    - Mostly esters (citrate esters, fatty acid, sebacate)
    - Glycol derivatives

Melt-extrusion excipients

- Low melting point
  - Polyethylenglykol
    - mp. ~ 35 – 60 °C
    - drug form thermal stability problems
- Acceptable melting point
  - Polyvinylpyrrolidon
    - mp. ~ 90 – 180 °C
    - API thermal stability problems

Melt extrusion for improving bioavailability

- Dispersion of drug in melted water-soluble polymer



Hot melt extrusion - Essential in the manufacture of solid dosage forms

- **significant increase in the bioavailability of poorly soluble API**

water-poorly soluble / insoluble API

↓

soluble or melt in a melt of a suitable polymer / dispersion in the polymer matrix

↓

dosage form

↓

after administration - dissolution of the polymer matrix and release of the API

Example – Base Case

Aims of the work

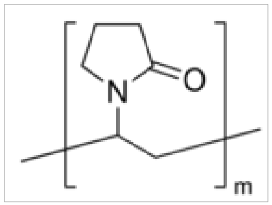
- Monitoring the rheological properties of melts containing API in extrusion by one screw extruder

  ➡ rheometer AR G2

- Evaluation of the impact of material composition and extrusion conditions at the phase change

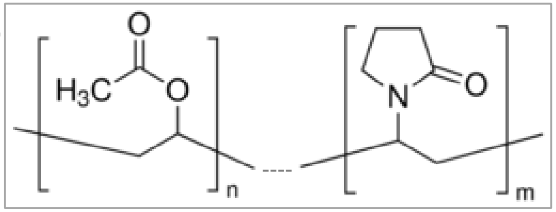
  ➡ DSC, XRD

Materials



Kollidon® 30
PVP
50 000 g.mol^{-1}
T_g = 150 °C
T_{deg} = 175 °C

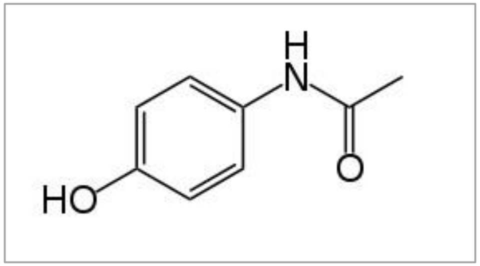
Kollidon® VA 64
PVP/PVAC copolymer
45 000 g.mol^{-1}
T_g = 77 °C
T_{deg} = 230 °C



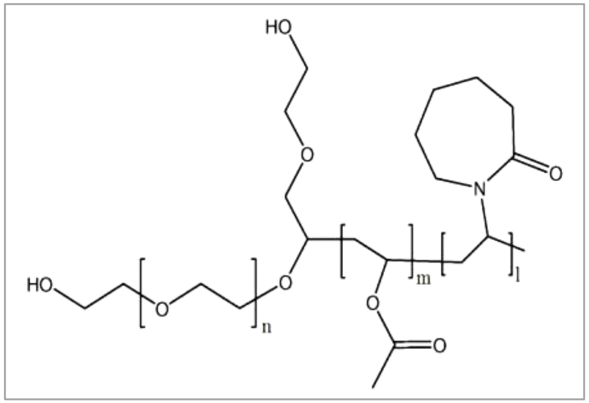
matrix

Model API

Paracetamol



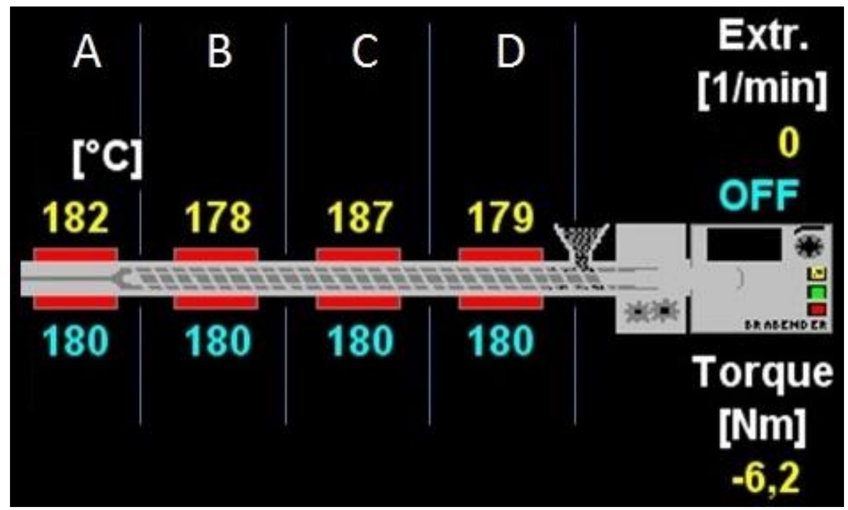
Soluplus®
PVCL/PVAC/PEG
graft copolymer
118 000 g.mol^{-1}
T_g = 62 °C
T_{deg} = 250 °C



Extruder with rheological capillary head

Experimental conditions of extrusion:

- 10 min^{-1}
- Capillary Roundcap 20/1
- T_{min} ~ 400 bar
- T_{max} ~ viscosity of extrudates

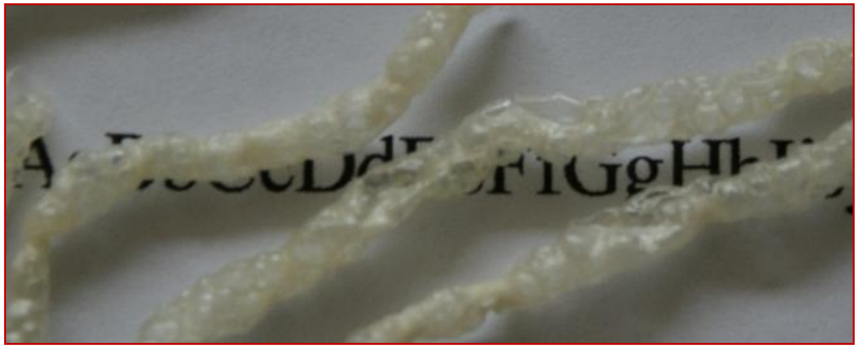


Extrusion of polymers

Kollidon® 30

Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
180/65	180	185	180	175

Soft, foamy => unsuitable



Kollidon® VA 64

Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
160/100	160	165	160	155

Transparent, hard, easily collectable => suitable

Soluplus®

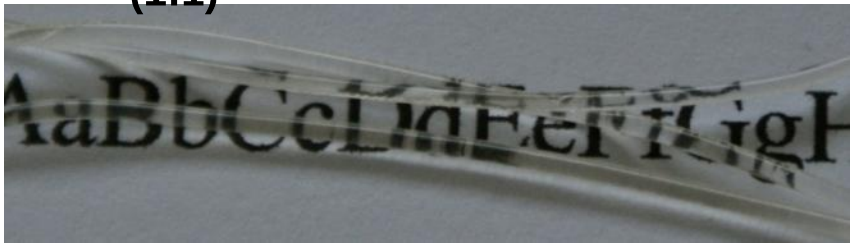
Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
150/80	150	155	150	145

Transparent, hard, easily collectable => suitable

Extrusion of mixtures with API (1)

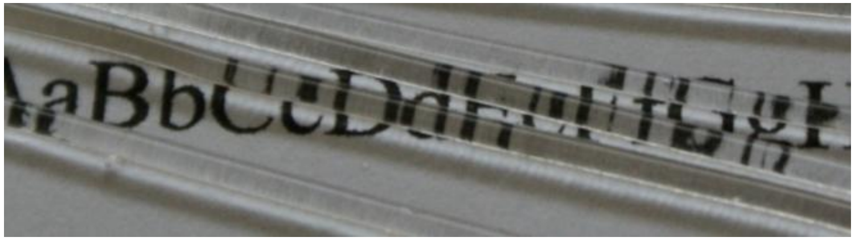
Temperature and pressure of melt in the head [°C/bar]	Zone A	Zone B	Zone C	Zone D
	[°C]			
90/350	90	95	90	85
105/45	105	110	105	100
120/7	**120**	**125**	**120**	**115**

Kollidon VA 64:paracetamol (1:1)



Temperature and pressure of melt in the head [°C/bar]	Zone A	Zone B	Zone C	Zone D
	[°C]			
105/210	105	110	105	100
120/45	**120**	**125**	**120**	**115**
135/13	135	140	135	130

Kollidon VA 64:paracetamol (2:1)



Temperature and pressure of melt in the head [°C/bar]	Zone A	Zone B	Zone C	Zone D
	[°C]			
115/255	115	120	115	110
120/140	**120**	**125**	**120**	**115**
135/43	135	140	135	130
150/5	150	155	150	145

Kollidon VA 64:paracetamol (3:1)

Extrusion of mixtures with API (2)

Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
105/330	105	110	105	100
120/42	**120**	**125**	**120**	**115**
135/18	135	140	135	130

Soluplus:paracetamol (1:1)

Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
110/385	110	115	110	105
120/130	120	125	120	115
135/60	**135**	**140**	**135**	**130**
150/14	150	155	150	145

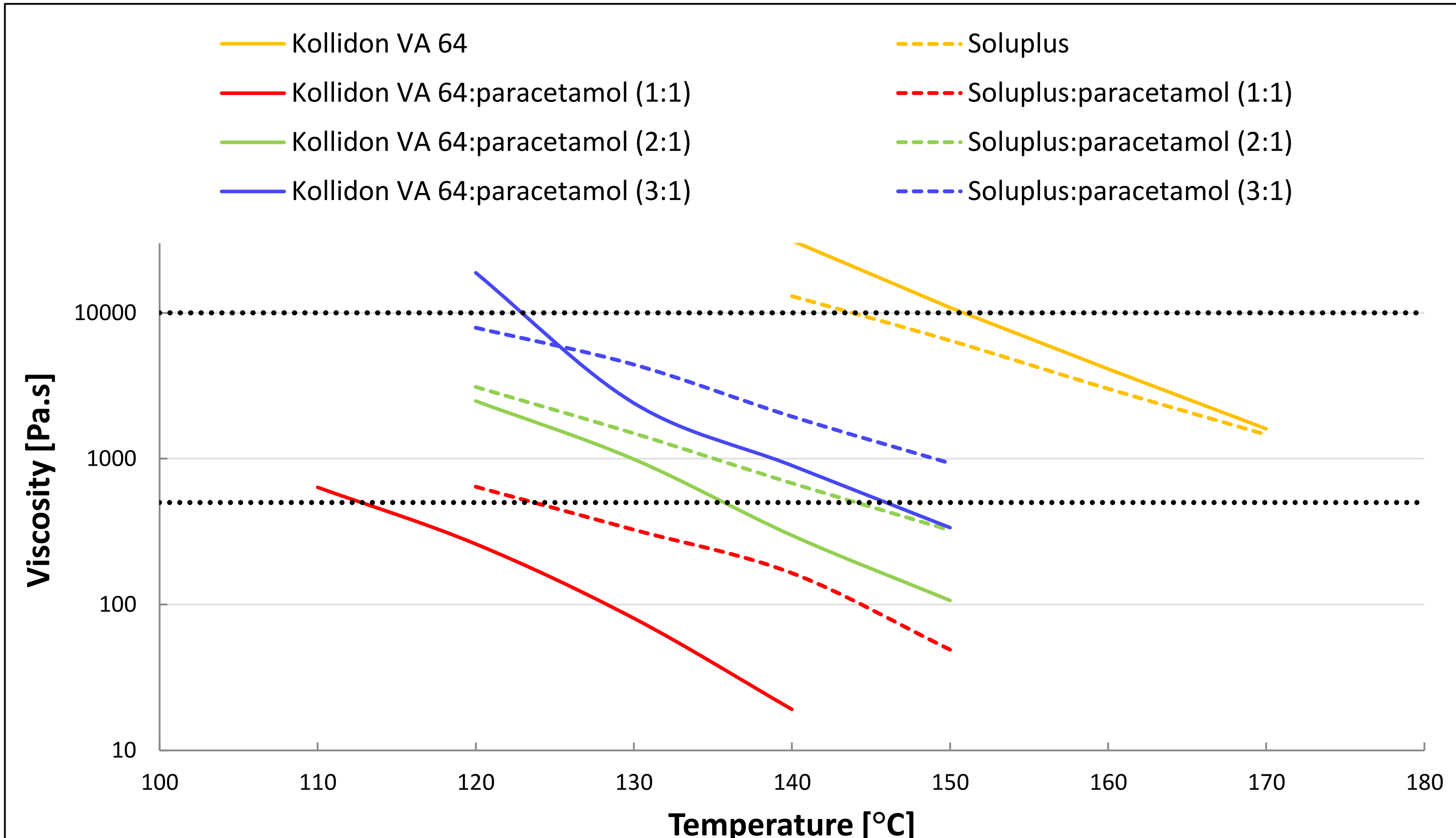
Soluplus:paracetamol (2:1)

Temperature and pressure of melt in the head [°C/bar]	Zone A [°C]	Zone B [°C]	Zone C [°C]	Zone D [°C]
120/360	120	125	120	115
135/150	**135**	**140**	**135**	**130**
150/60	150	155	150	145

Soluplus:paracetamol (3:1)

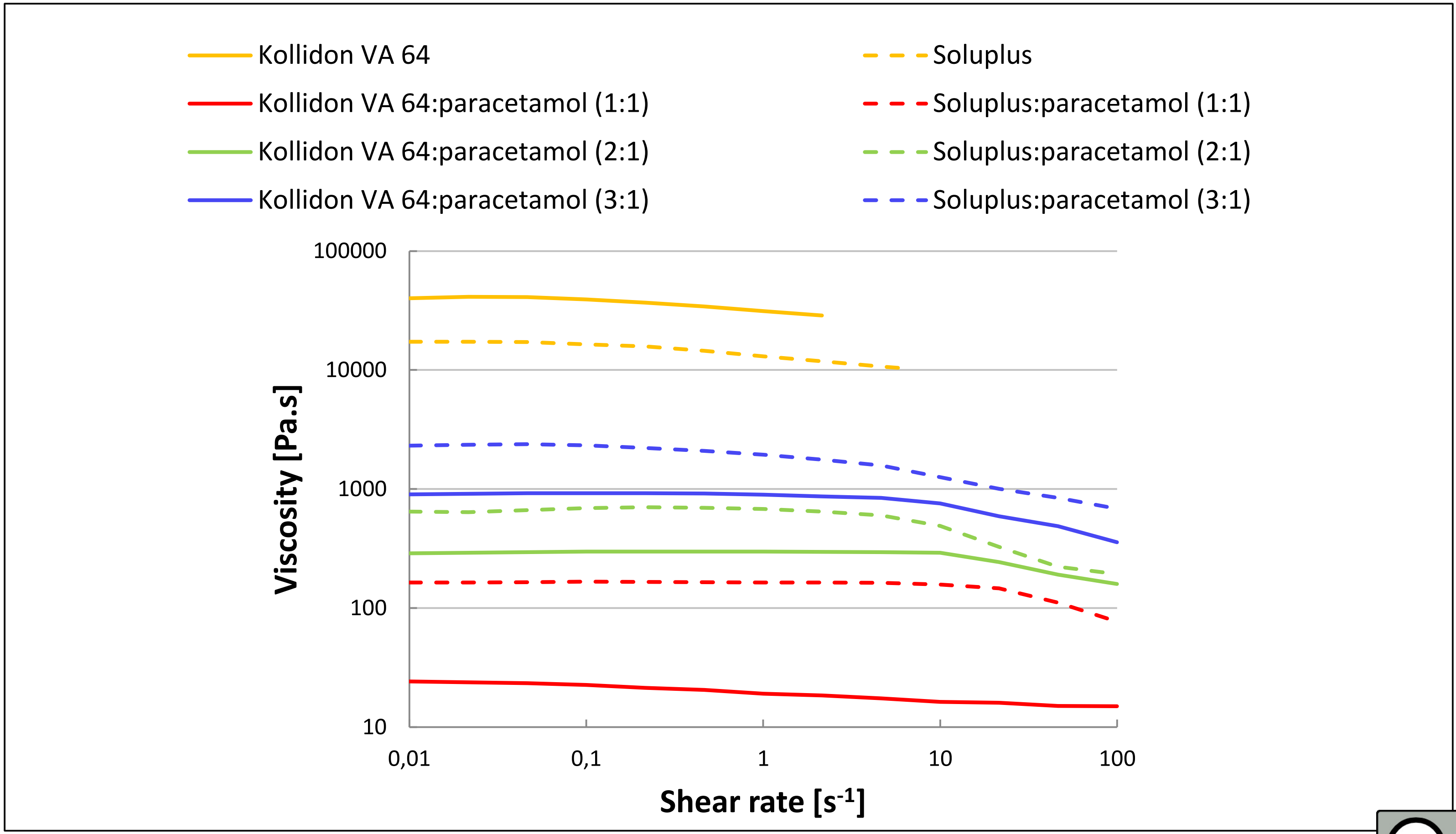
Evaluation of flow properties – rheometer AR G2

- Dependence of viscosity on temperature - shear rate $\dot{\gamma} = 1\ s^{-1}$

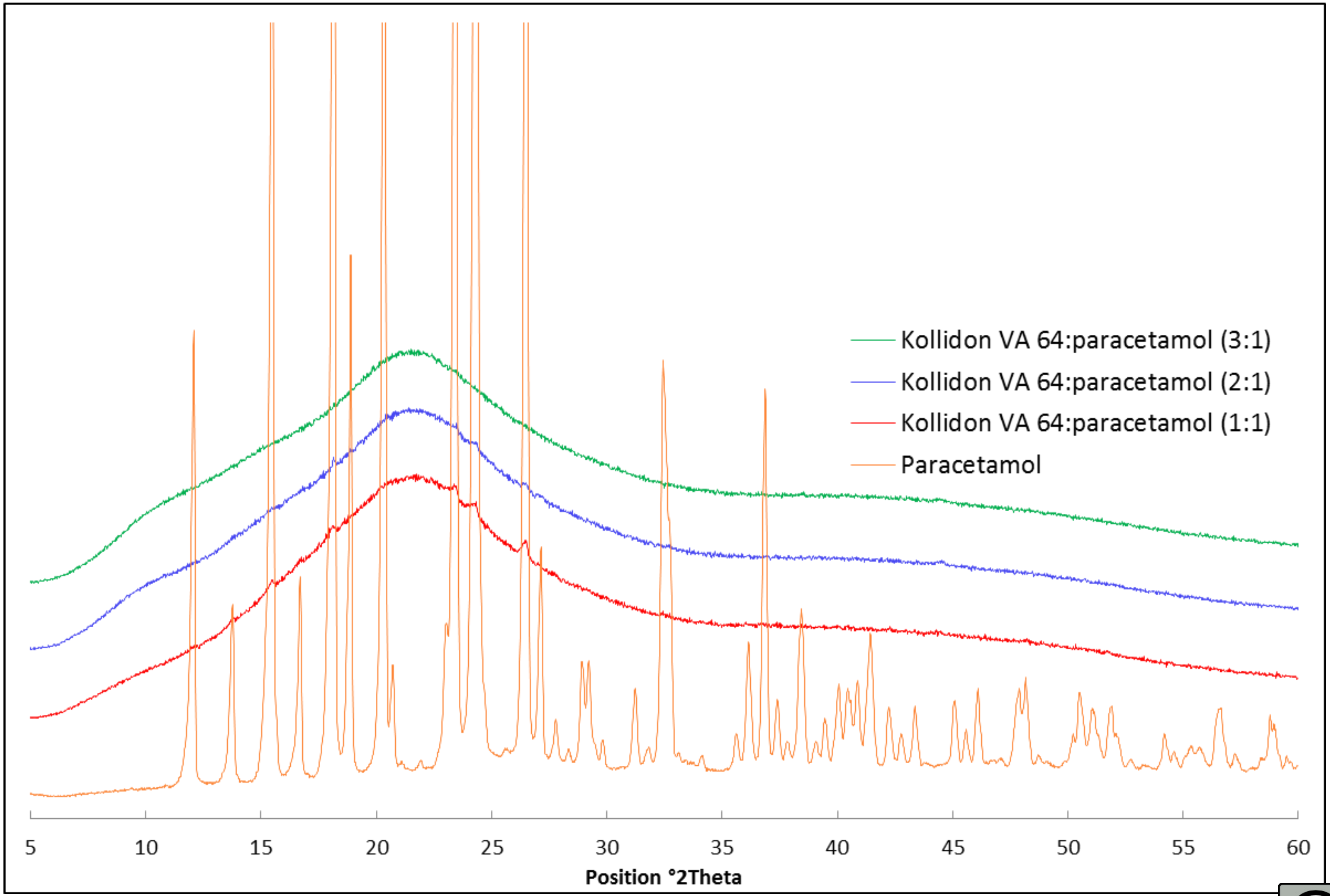


Evaluation of flow properties – rheometer AR G2

- Dependence of viscosity on shear rate - temperature 140 °C



Evaluation of the phase changes– XRD



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Development and Education

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YOUTH AND SPORTS

Engineering in Chemical and Pharmaceutical Processes

Tablet Compression

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced
  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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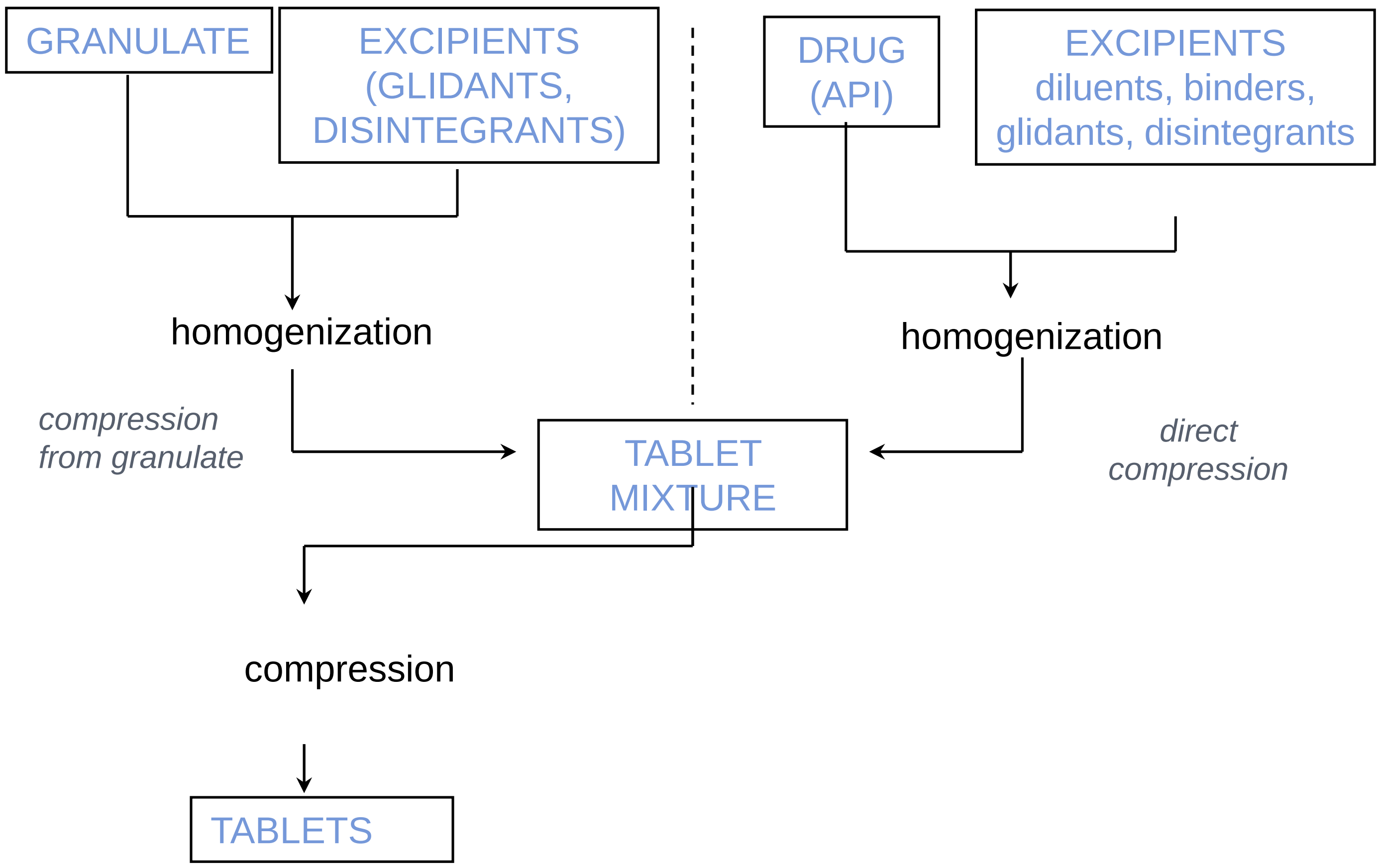
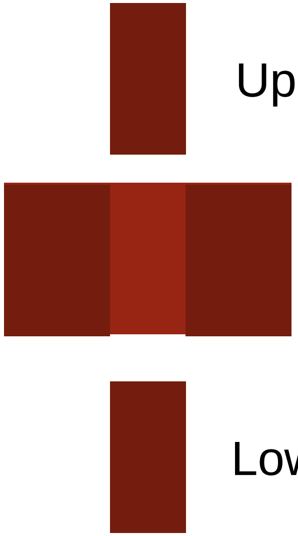
Tablet compression



Tablet-press tooling

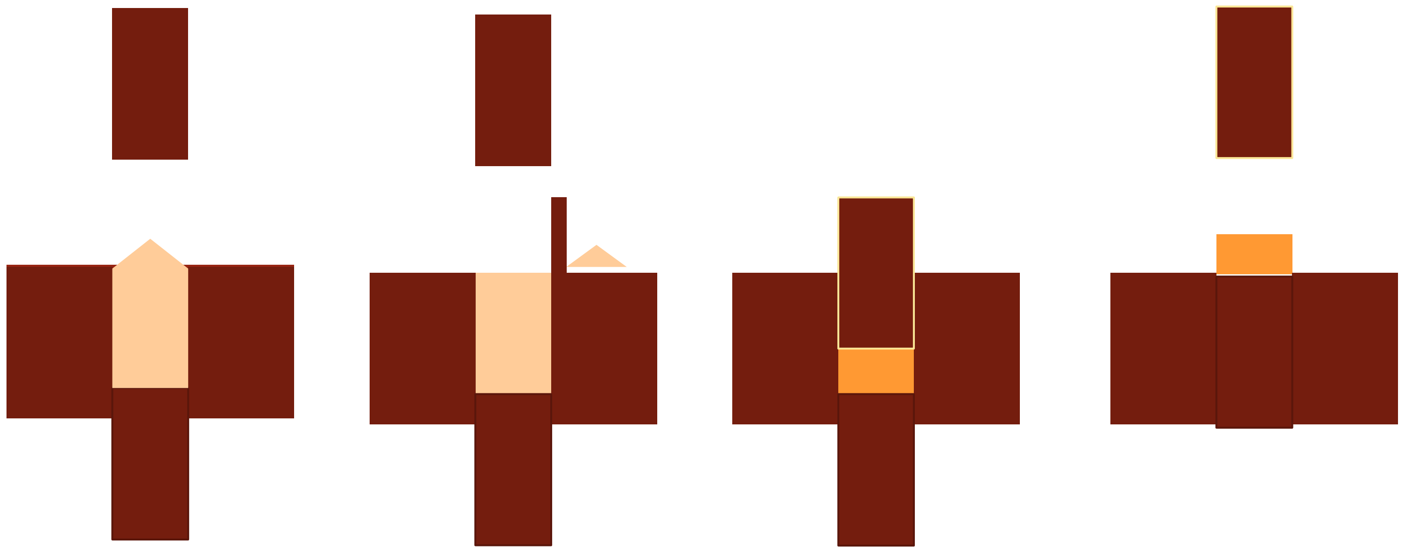


Upper punch

Compression die

Lower punch

Steps in tablet compression



Filling

excess powder
removal

pre-compression
compression

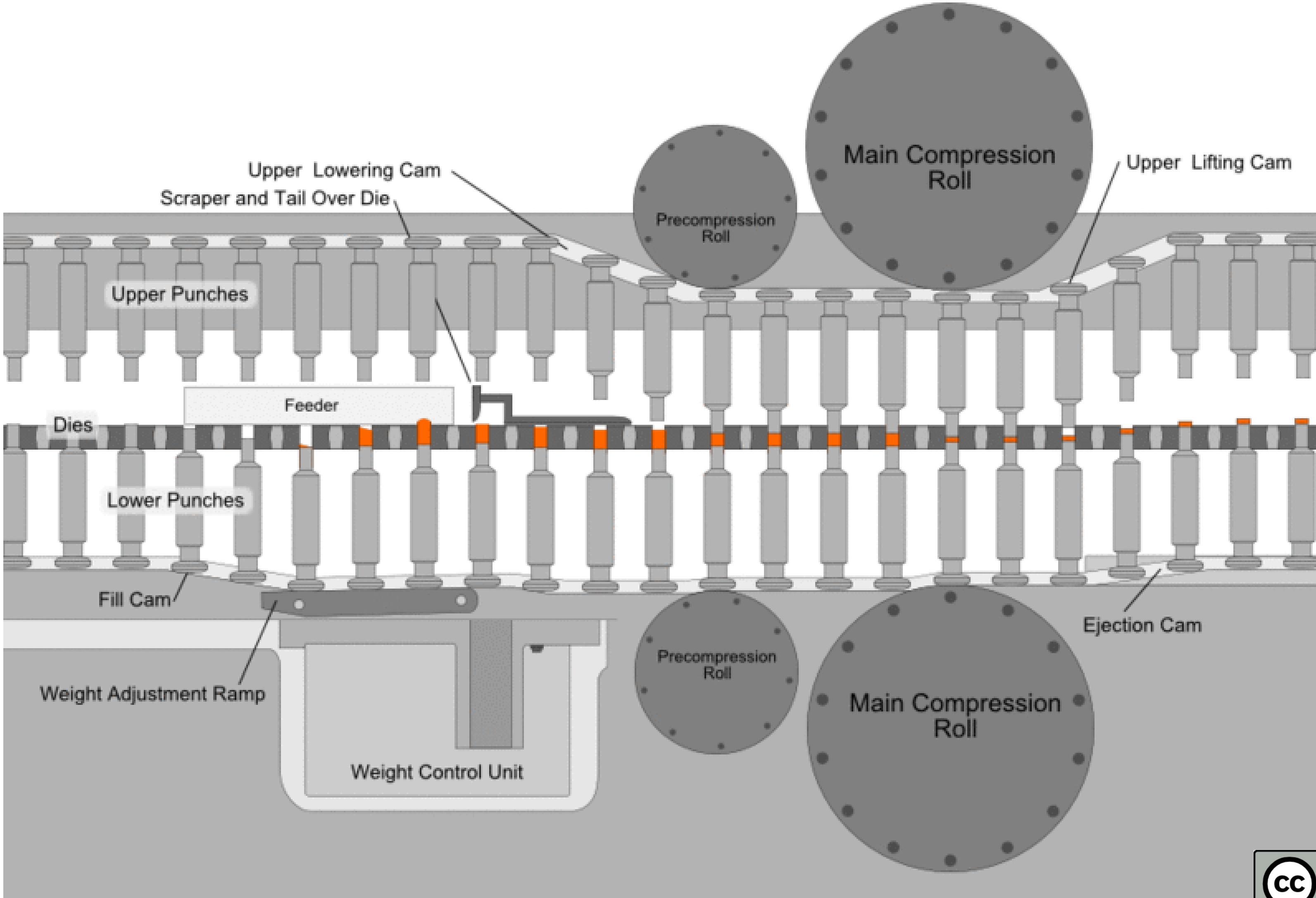
ejection

Tablet press

- Rotary
  - several dies

- Single-punch
  - one die

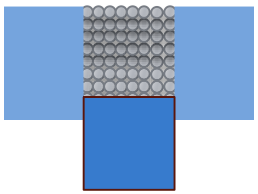
Tablet compression

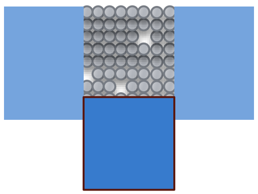


Die filling – requirements and problems

- The die must be filled without any cavities

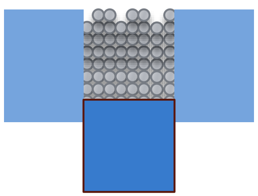
YES





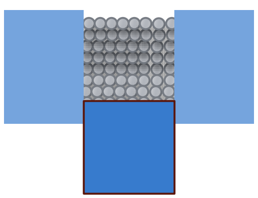
NO

- The filling surface must be smooth



NO

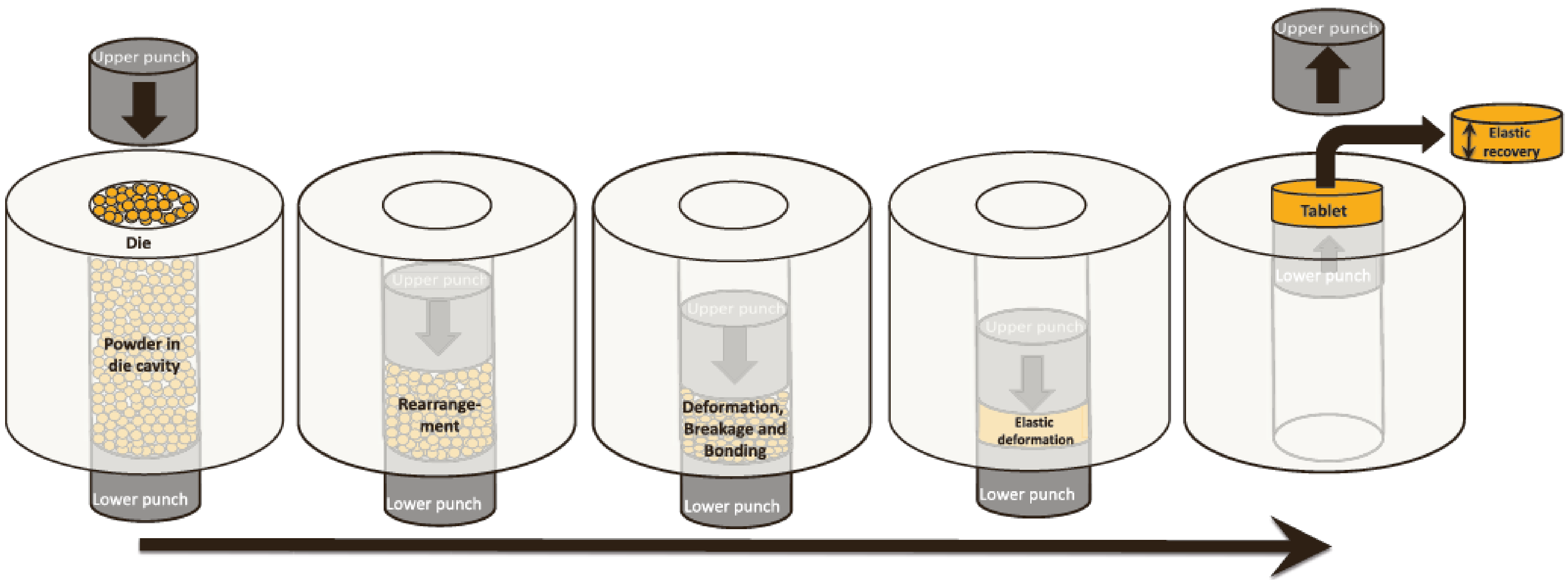
- The material should not reduce volume due to vibrations



NO

- Good flow properties are key to eliminate those problems
- Common methods
  - Angle of repose
  - Hausner ratio
  - They can be used to evaluate overall mixture performance
- Advanced methods like POWDER RHEOMETRY can provide detailed info about
  - the properties of the components of the mixture
  - compare the effects of adhesion/cohesion
  - determine the flow properties at state most relevant to situation of die filling
  - examine the effects of previous blend treatment
  - examine flow patterns

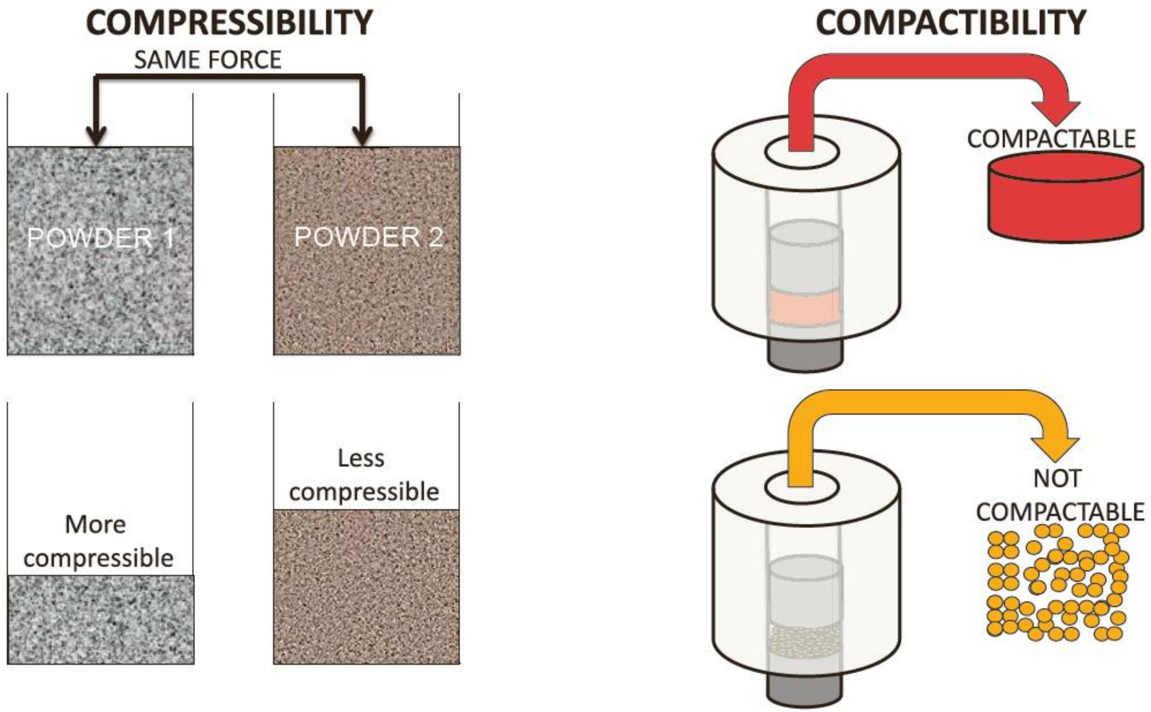
Powder compaction during compressing the tablets



Mahmoodi F.: Compression properties of powders ..

Material properties

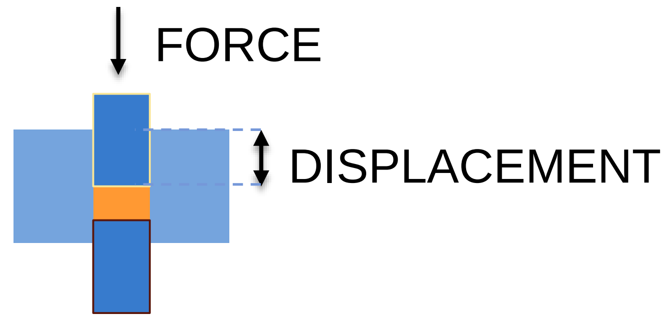
- Compressibility = ability to reduce volume
- Compactibility = ability to form strong compacts

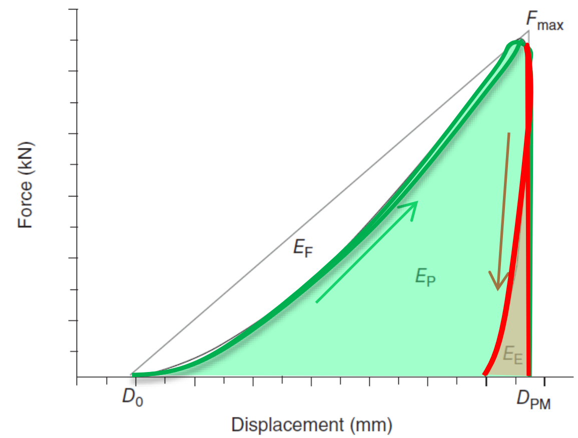


Mahmoodi F.: Compression properties of powders …, Uppsala 2012

Energy analysis of compaction: Force - displacement

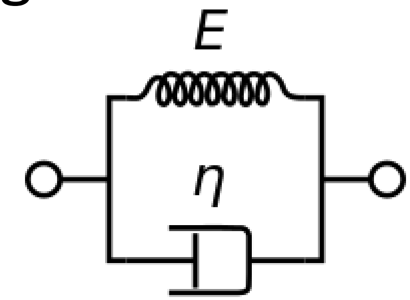
- Analysis of force required per displacement during compression and decompression
- Work = force * length
- Work = area under curve
  - gross work of compression includes
    - work of friction
    - work of plastic deformation
    - work of elastic deformation
    - work of friction
  - work of elastic relaxation
- Alternative explanation (empirical/inaccurate)
  - E_P = plastic deformation
  - E_E = elastic deformation
  - E_F = rearrangement /friction





Model of viscous-elastic deformation

- Kelvin-Voigt model



$$\sigma = F\varepsilon + \eta \frac{d\varepsilon}{dt}$$

- elastic component (spring) – Hooke body
  - instantaneous elastic deformation
  - reversible

$$\sigma = F\varepsilon$$

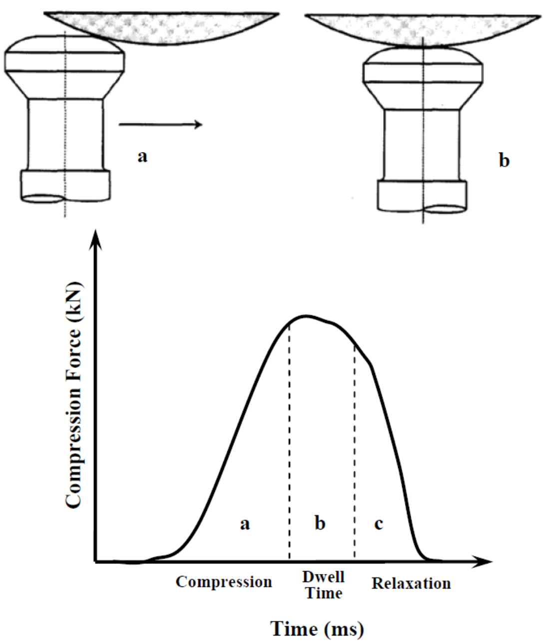
σ … stress
ε … relat. deformation
F… Young module
η … viscosity coefficient

- plastic component (“damper”)
  - rate is proportional to acting stress
  - irreversible

$$\sigma = \eta \frac{d\varepsilon}{dt}$$

Force - time relationship

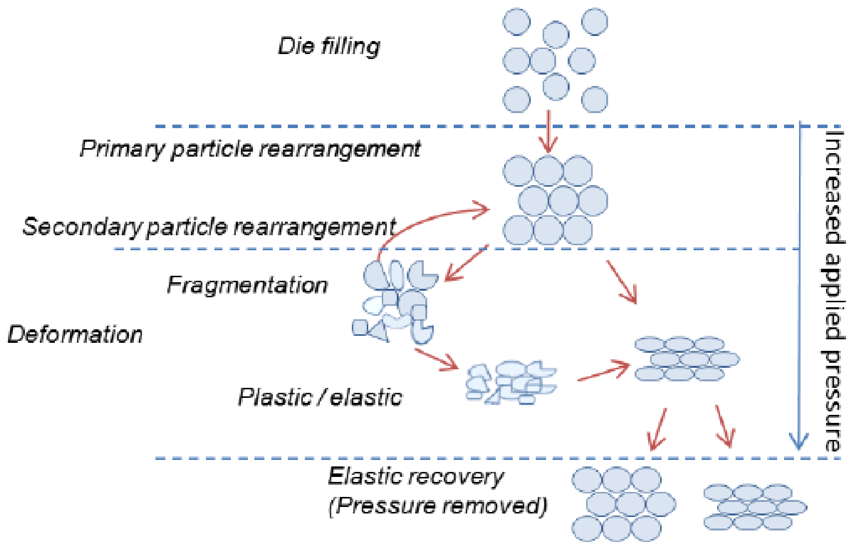
- Joint effect of the machine speed and the rate of plastic deformation
- More difficult to measure, but may be simulated by advanced compaction analyzer
- Compression
  - increasing displacement
- Dwell time
  - constant displacement (flat part of the punch head under the roll)
- Relaxation
  - decreasing displacement



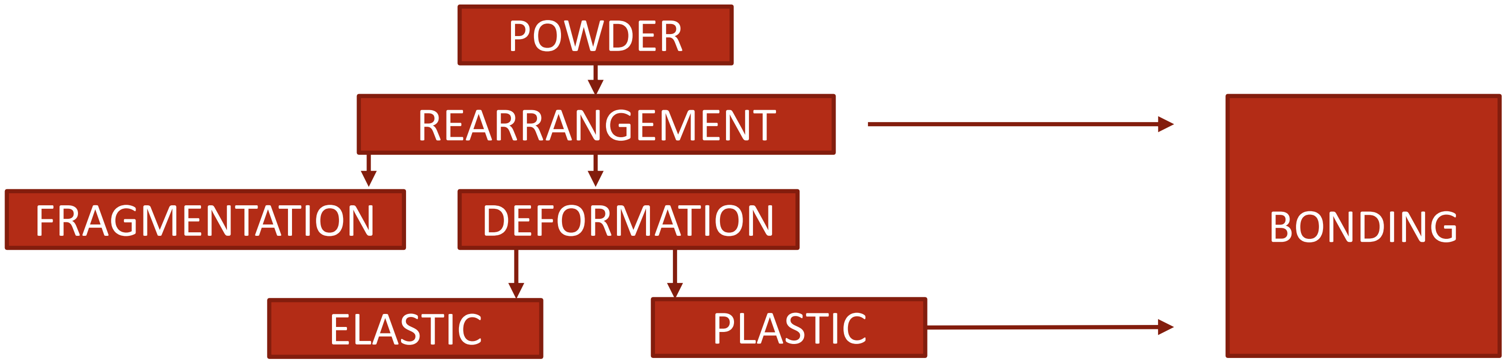
Schmidt PC, Leitritz M.: Eur J Pharm Biopharm. 1997;44:303–

Compression phases

- Particle rearrangement
- Deformation on contact points
- Fragmentation
- Bonding
- Deformation of solid body
- Decompression
- Ejection

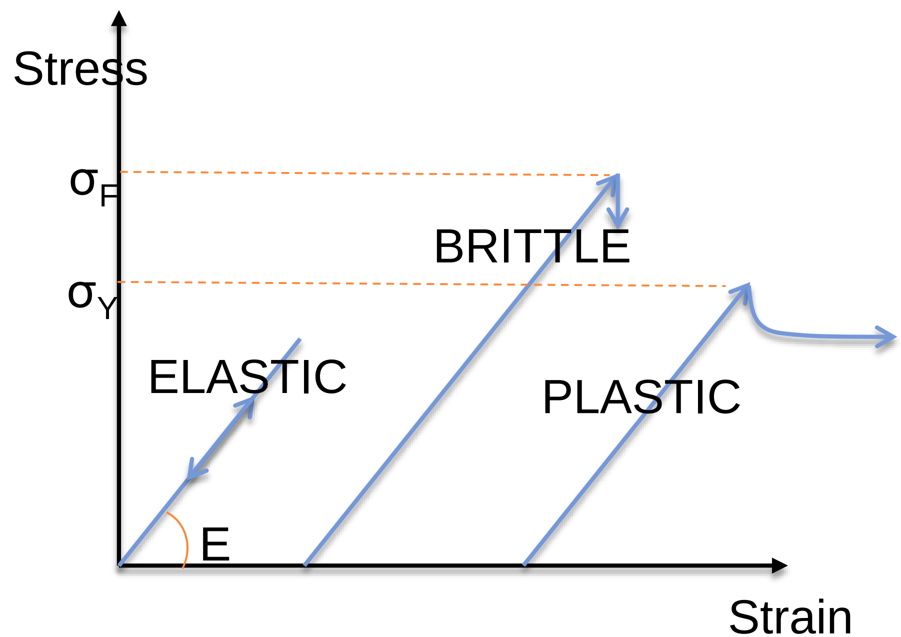


Compression



Particle deformation

- Elastic
  - reversible
  - E … (elastic) Young's module
- Brittle fracture
  - irreversible
  - σ_F … fracture strength
- Plastic (ductile)
  - irreversible
  - σ_Y … yield strength

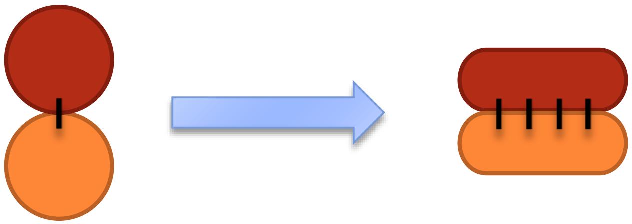


Particle rearrangements

- Low pressure – big volume reduction
- Particles changing orientation, move, fill void spaces, percolate
- Better flowability means less rearrangement

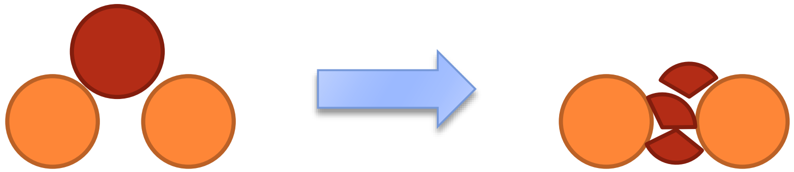
Deformation

- Deformation occurs under pressure
  - elastic
  - plastic
  - breakage
- Plastic deformation occurs at yield pressure
- Deformation develops increased contact area – therefore new bonds



Fragmentation

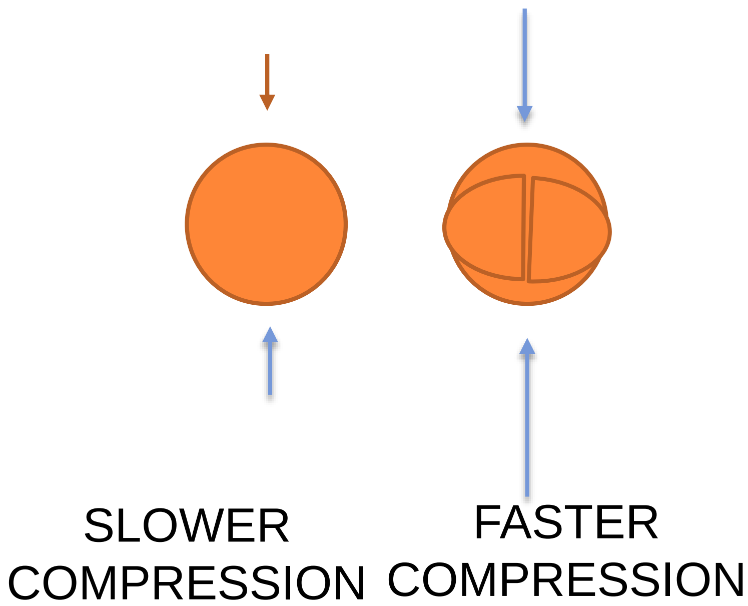
- Exceeding the material strength cause fragmentation of original particles
- Fragmentations enables further compression and develops new surface for bonding



- Fragmentation is typical for less plastic materials

Time dependency of the deformation

- Elastic deformation
  - instantaneous
  - strain is proportional to immediate stress
- Plastic deformation
  - proceeds at rate proportional to immediate stress
- Brittle Fracture
  - occurs if the stress exceeds the fracture strength



- Too fast compression may
  - break the particles
  - provide less plastic deformation

Force balance in die

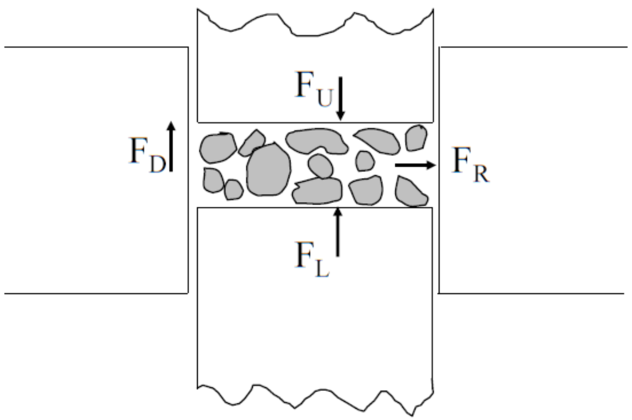
- Pressure developed by upper punch F_U, lower punch force F_L is different
- axial profile of strength

$$F_L = F_U e^{-k\frac{H}{D}}$$

  - k … material constant
- Force balance

$$F_L + F_D = F_U$$

  - F_D … friction force
- Mean force provides better information than F_U



Mean compression force

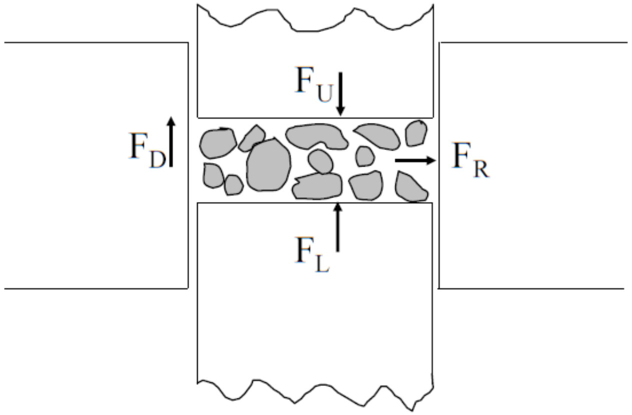
- arithmetic

$$F_A = \frac{F_L + F_U}{2}$$

- geometric

$$F_G = \sqrt{F_L F_U}$$

Force balance in die



- Radial force

$$F_R = \lambda F_U$$

  - λ … lateral stress ratio

$$\lambda \approx \frac{\Delta D}{\Delta H}$$

- Friction on die wall

$$F_D = F_R tg\varphi_W$$

- Lubrication ratio R (R = 1 for zero friction)

$$R = \frac{F_L}{F_U}$$

Compression equations

- Heckel equation

$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = kp + A \qquad \frac{\rho_B}{\rho_{solid}} = \rho_{rel}$$

$$\ln\left(\frac{1}{1-\rho_0}\right) = A$$

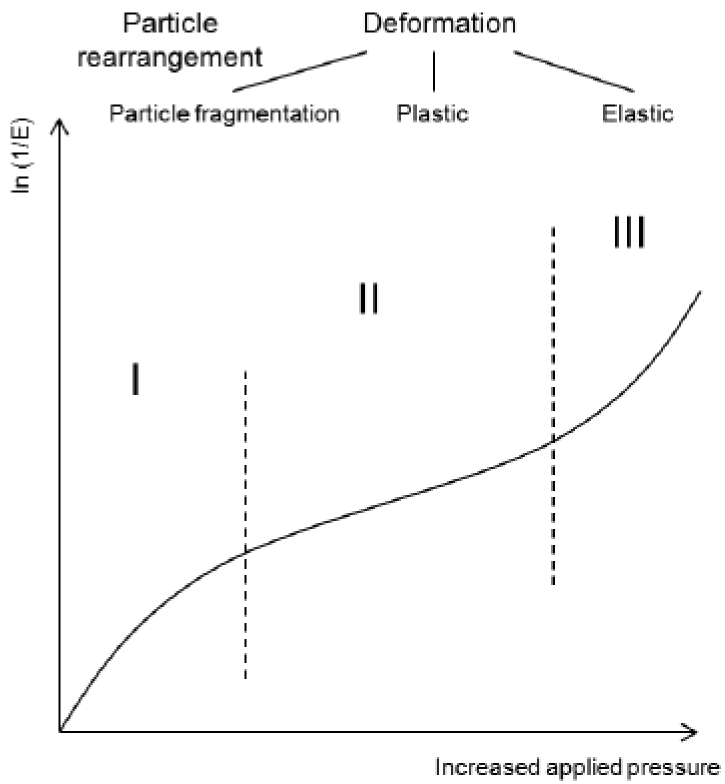
ρ_0 = projected rel. density at zero pressure

$$\ln\left(\frac{1}{1-\rho_{rel}}\right) = kp + \ln\left(\frac{1}{1-\rho_0}\right) \qquad \frac{1}{k} = p_y$$

yield pressure
initial plast. def.

Heckel plot

- Heckel equation fits only the linear section II

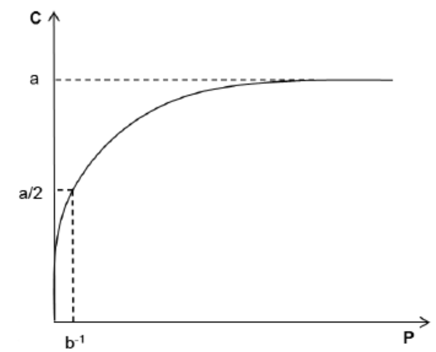


Compression equations

- Kawakita equations
  - compression ratio at given pressure

$$C = \frac{V_0 - V}{V_0} = a\frac{bp}{1+bp}$$

C … compression
V_0 … initial volume
V … current volume
a, b … parameters



  - a = maximum compression

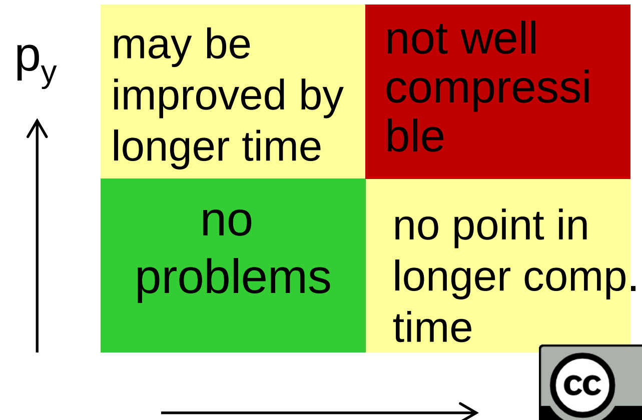
$$\frac{p}{C} = \frac{p}{a} + \frac{1}{ab}$$

$$\frac{1}{b} = p_k$$

pressure required to reduce volume by 50 %
- low value = more plastic deformation

Heckel-Kawakita analysis

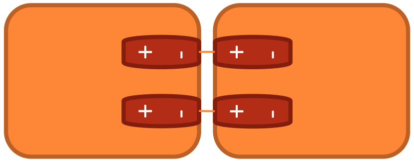
- Heckel equation – linear relationship at high pressure
- Kawakita equation - linear relationship at lower pressure
- different meaning of p_y and p_k
  - p_y onset of plastic deformation
  - p_k measure of plastic deformation (time dependent)
- p_y a p_k differ at longer residence time
- common interpretation of
  Heckel and Kawakita parameters



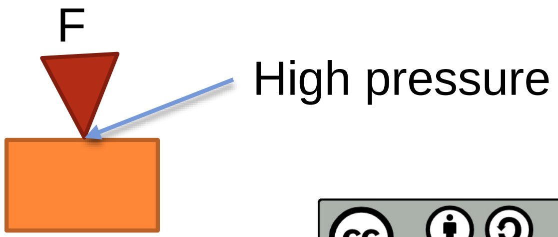
Bonding

- Different mechanisms
  - Mechanic theory – mechanic interlocking of particles

  - Intermolecular theory – interactions between molecules at surface of particles (e.g. van der Waals)

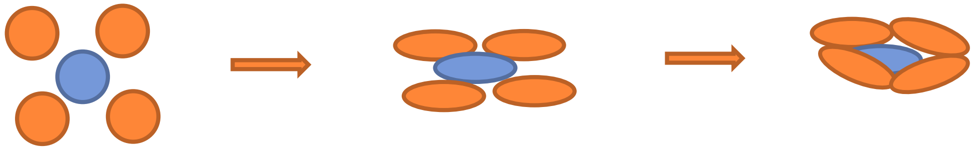


  - Liquid film theory – high pressure at contact edges aids dissolution/metling
    - most insoluble materials have poor compactibility
    - dry powders are poorly compactable



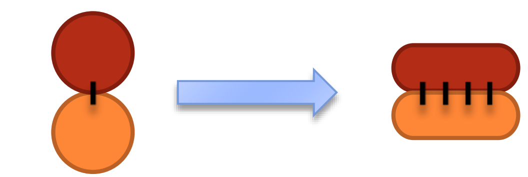
Bonding in binary mixture

- Percolation threshold
  - increased consolidation may cause rapid change of properties = percolation threshold
  - Threshold is determined by connected structure of one of the phases

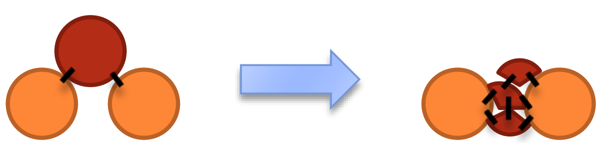


Contact area and microstructure effect on bonding

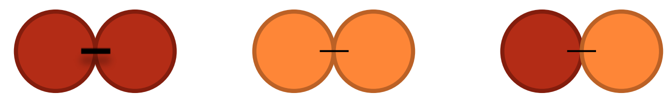
- Contact area affects the number of interparticle interactions



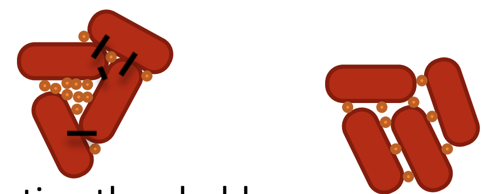
- Plastic deformation and brittle fracture may increase the contact area



- Different materials may have bonds of different strength



- Microstructure is essential for overall strength



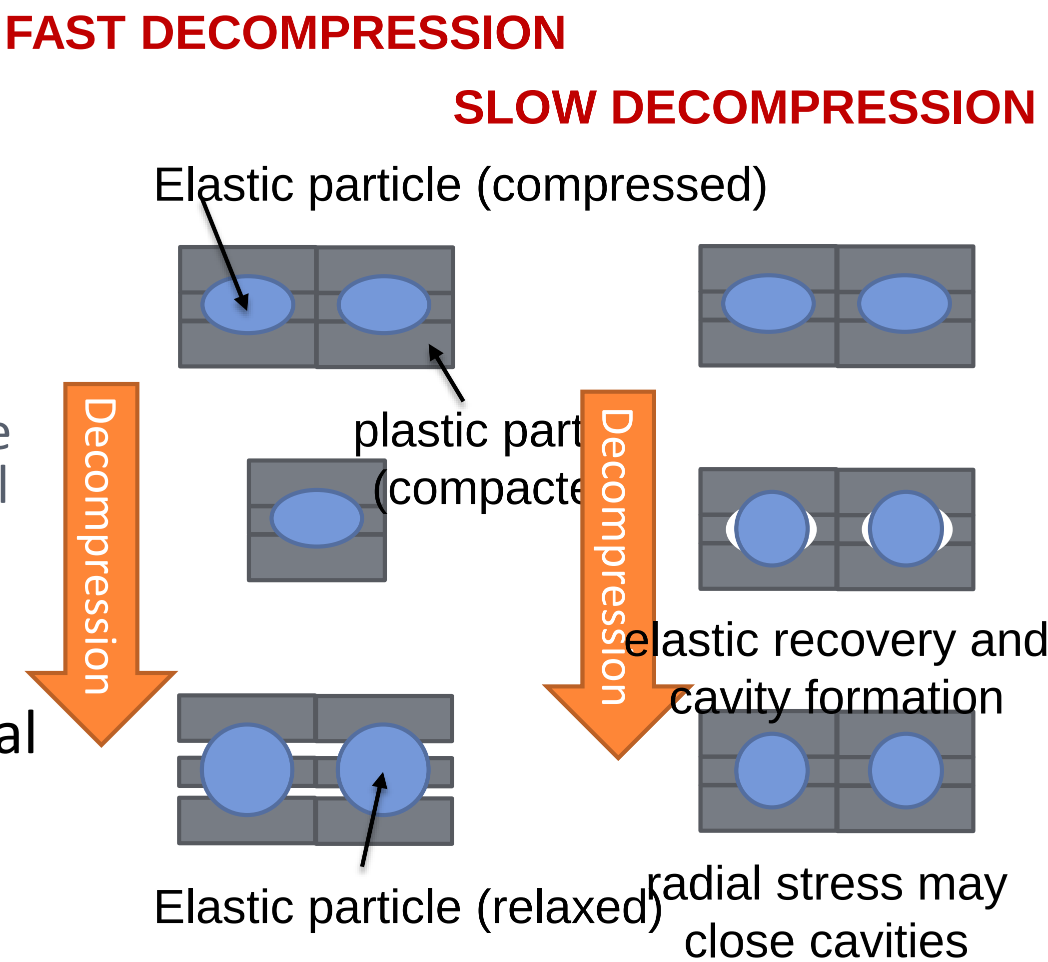
- Percolation threshold
  - small amount of component has crucial effect on strength
  - Positive: binder in granules
  - Negative: lubricant mixed for too long

Decompression

- On decompression – elastic springback – develops stress in the tablet
- Tablet must withstand this stress
- Stress released by
  - plastic deformation of tablet
  - fragmentation of the tablet
- Effect of tablet press speed – decompression rate
  - rate determines residence time – rate of crystallization (liquid film theory) – crystal strength

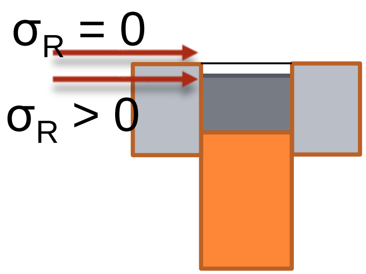
Decompression

- Releasing pressure by upper punch
  - elastic recovery of the axial stress
  - some residual radial stress persists
- Elastic particle relaxation
  - FAST – accommodated by brittle fracture of surrounding material
  - SLOW – accommodated by plastic deformation of surrounding material
- Cavity closure by residual radial stress
  - may depend on lubrication
  - may form secondary pore structure



Tablet ejection

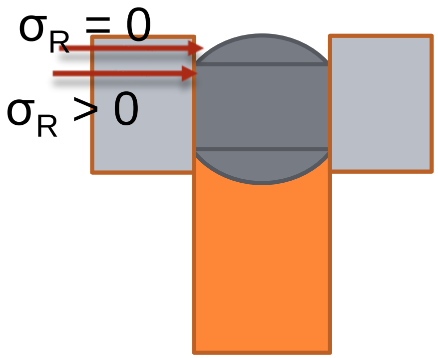
- Tablet expands only axially during decompression
- There is still radial stress in the tablet while contained in the die
  - Radial expansion after leaving die (2 – 10 %)
- Tablet may fracture
  - lamination
  - capping



Further problems during decompression/ejection

- Capping
  - Deep concave punches may expand radially, while the cylindrical part cannot
- Lamination
  - Elastic expansion of some particles
  - Expansion of entrained air
- Sticking
  - Too much adhesion on the punch
    - intrinsic
    - due to punch wear

Capping



Lamination

Sticking

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Engineering in Chemical and Pharmaceutical Processes

Mixing and Segregation

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced

  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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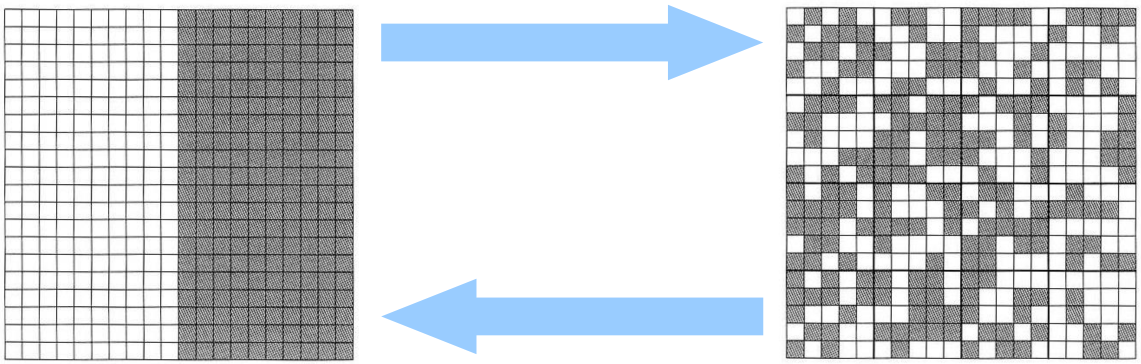
Blending

- Definitions
  - Operation aimed at processing two or more separate components so as to achieve a situation when each particle of any component is as close as possible to a particle of the other component
- Objectives
  - Achieve the mixture uniformity
    - uniformity of final products
  - Maximize the contact surface area of components
    - promote interfacial physical and chemical processes

Mixing is reversible process

mixing, blending
(mixing, blending)

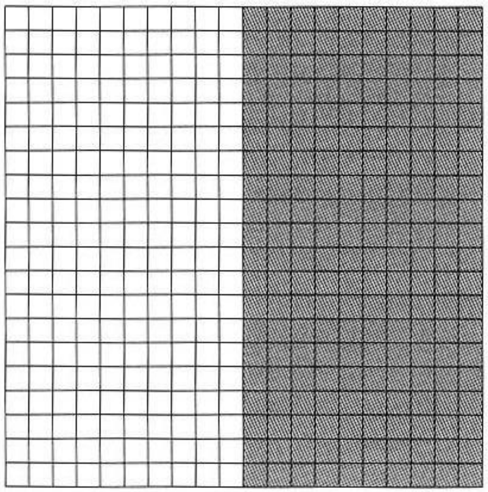


demixing, segregation
(demixing, segregation)

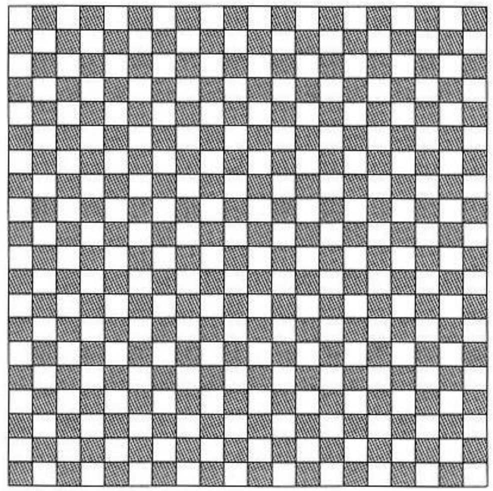
Spontaneity of mixing

- Positive
  - proceeds spontaneously without external action
  - e.g. diffusive mixing of gases in a vessel
- Negative
  - segregation proceeds spontaneously, without external action the components will separate
  - e.g. suspension settling
- Neutral
  - nothing happens without external action
  - e.g. powder mixture

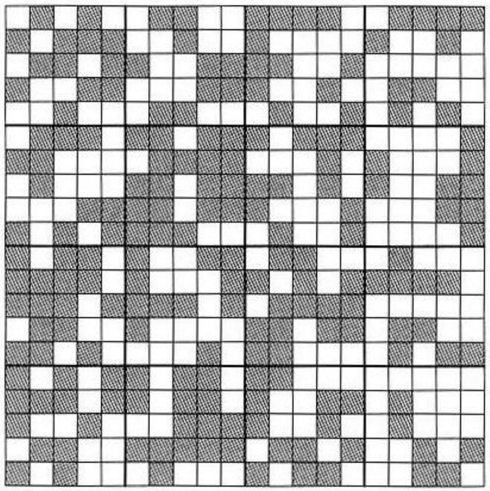
Types of mixtures



perfectly separated
mixture



perfectly mixed
(ordered)
mixture

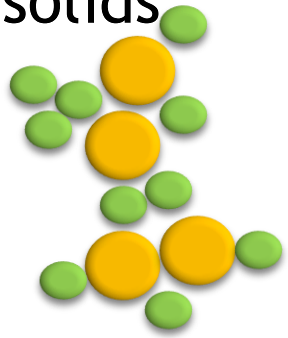


random
mixture

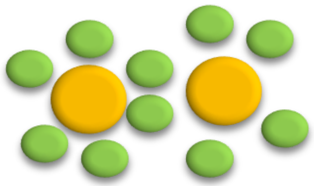
probability of occurence of a specific component in any position in the mixture is equal to the content of that component in the r

Real mixture

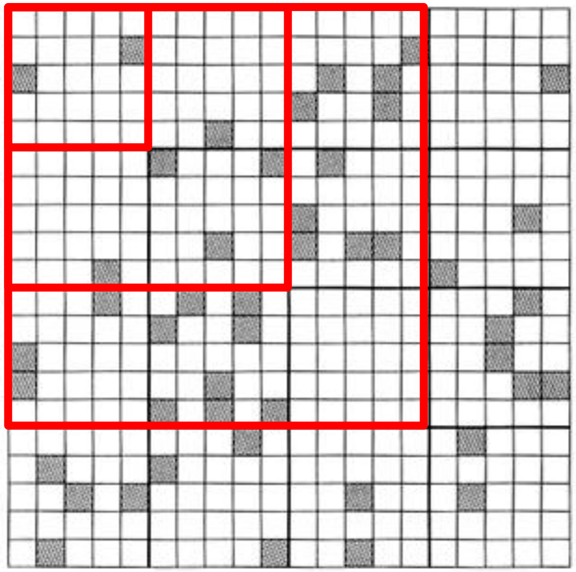
- Random
  - well flowing particulate solids



- Ordered
  - cohesive materials
  - interaction between components



Scale of scrutiny



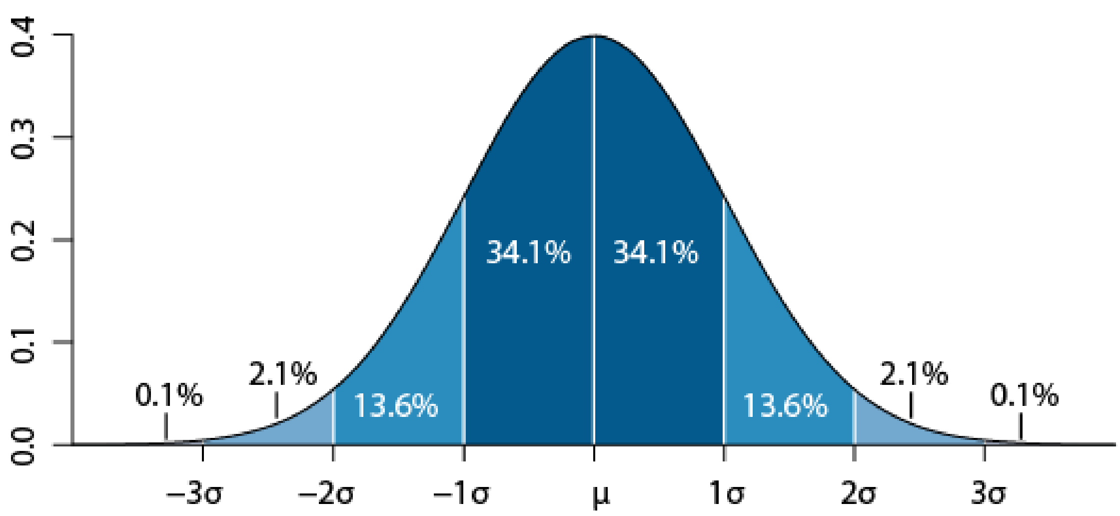
- Homogeneous mixture = samples taken from the mixture have equal properties
- Homogeneity depends on the sample size
  - all mixtures seem being uniform at sufficiently large sample size
- Scale of scrutiny
  - Minimum sample size to be used to achieve the variance of samples below desired limit

Practical homogeneity in pharmaceutical production

- Character of mixtures
  - probability of achieving ordered mixtures is small
  - most mixtures are random (especially for powder-powder) - random nature of mixtures
- Multi-component mixtures
  - API homogeneity is important
  - pseudo-binary approach to mixtures, API + excipients
- Scale of scrutiny
  - corresponds to the size of final dosage form

Statistics tutorial

- Standard error of a random variable
  - measure of variability of random variable
    - random variable result will be within +- standard deviation from average with approximately 2/3 probability
    - random variable result will be within +- 2 x standard deviation from average with very high probability



$$\sigma_X = \sqrt{\frac{\sum_{i=1}^{N}\left(X_i - \overline{X}\right)^2}{N}}$$

Statistics tutorial

- Selective standard error
  - measure of random events variability
    - API content variability in taken samples

$$s_x = \sqrt{\frac{\sum_{i=1}^{N}\left(x_i - \bar{x}\right)}{N-1}}$$

- Relative (selective) standard error, RSD %
  - measure of variability related to mean value
    - e.g. comparable for two drug potencies (2 mg and 4 mg of API content)

$$RSD = \frac{s_X}{\bar{X}} \cdot 100\% = \frac{1}{\bar{X}}\sqrt{\frac{\sum_{i=1}^{N}\left(x_i - \bar{x}\right)}{N-1}} \cdot 100\%$$

Evaluating homogeneity

- Relative selective standard error of taken samples
  - simple
  - frequently used
  - not in 0 - 100 % range
- Mixing index $$M = \frac{\sigma^2 - \sigma_{MIN}^2}{\sigma_{MAX}^2 - \sigma_{MIN}^2}$$
  - multiple definitions
  - 0 - 100 % range
  - σ_{MAX} … completely segregated state $\sigma_{MAX}^2 = w_{API}(1 - w_{API})$
  - σ_{MIN} … minimum achievable non-homogeneity (analytical error)

W(API)		sigmaMAX	RSD_MAX
0,001	0,000999	0,03	31,61
0,01	0,0099	0,10	9,95
0,1	0,09	0,30	3,00
0,2	0,16	0,40	2,00
0,3	0,21	0,46	1,53
0,4	0,24	0,49	1,22
0,5	0,25	0,50	1,00
0,6	0,24	0,49	0,82
0,7	0,21	0,46	0,65
0,8	0,16	0,40	0,50
0,9	0,09	0,30	0,33
1	0	0,00	

Random mixture properties

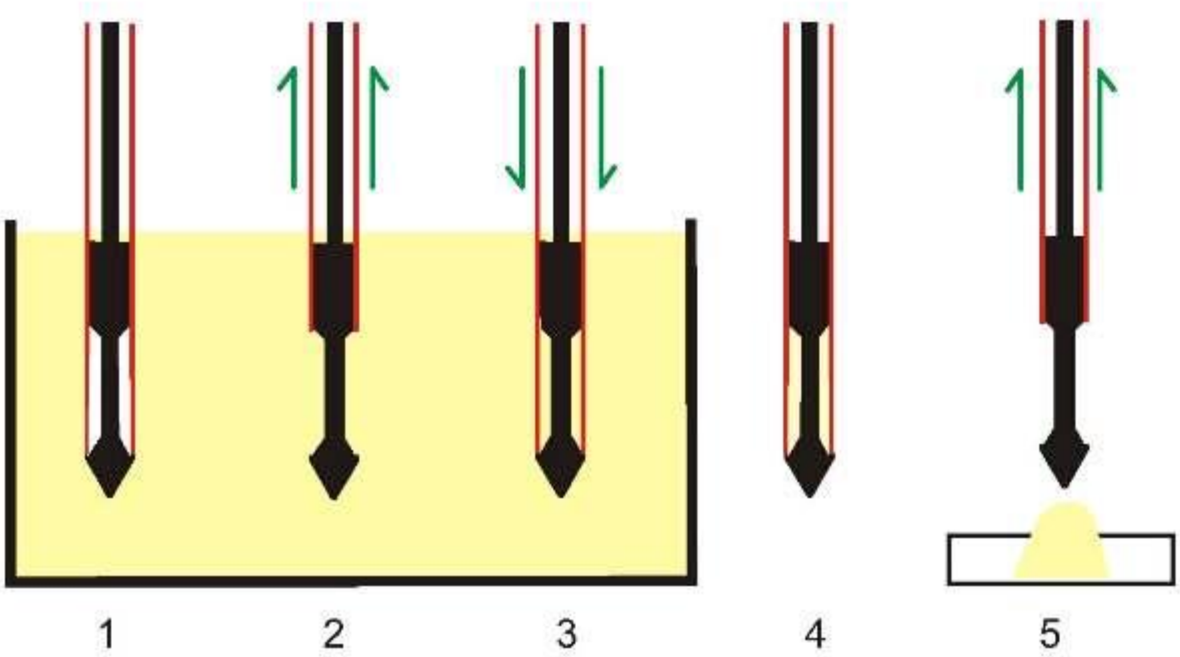
- Variability of taken samples
  - Assumption of (pseudo) binary mixture of similar components

$$\sigma = \sqrt{\frac{w_{API}(1-w_{API})}{n}}$$

    - w_{API} … single component conteny in mixture (API)
    - s … standard error of API content
    - n … number of particles in the sample
  - Defines the number of particles needed in dosage form to achieve desired uniformity

WAPI =	0,01	
n	sigma_min	RSD_min, %
1	0,099499	995,0
10	0,031464	314,6
100	0,00995	99,5
1000	0,003146	31,5
10000	0,000995	9,9
100000	0,000315	3,1
1000000	9,95E-05	1,0
10000000	3,15E-05	0,3

Sampling



Mixing particulate solids

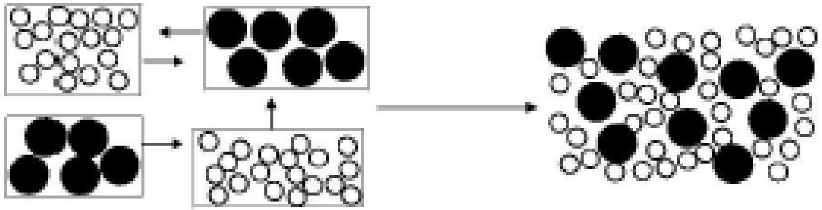
Mechanisms of mixing

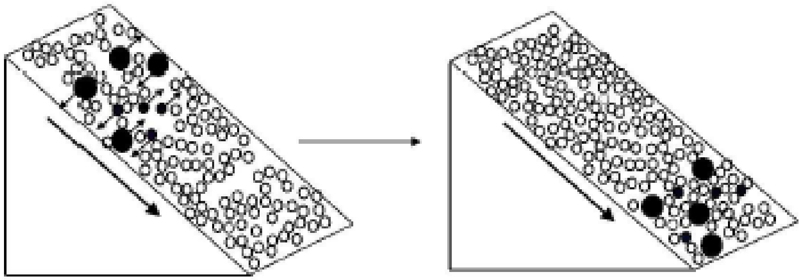
- convection
  - movement of particle groups relative to other groups
  - macroscopic mixing,
- dispersion
  - movement of individual particles among other particles
  - micro-mixing
- shear
  - movement of powder layers
  - disruption of agglomerates

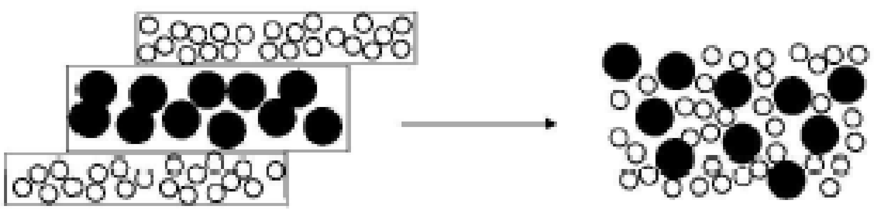
Mixing particulate solids

» Mechanisms of mixing

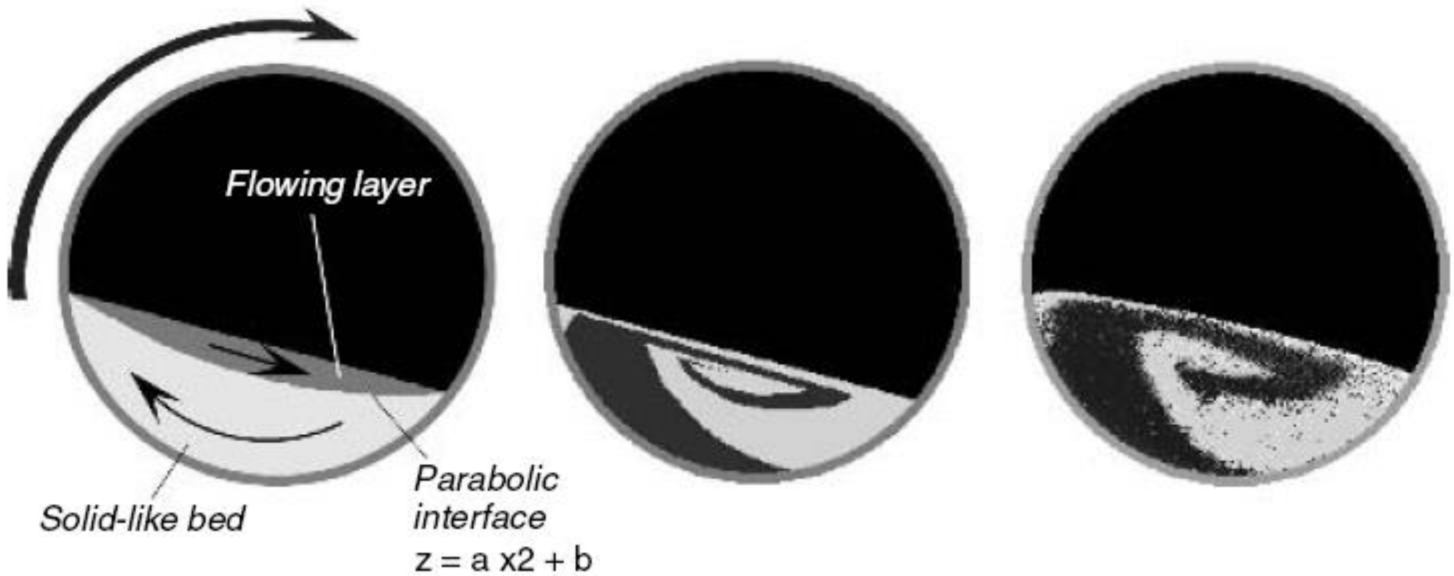
- » convection
- » dispersion
- » shear





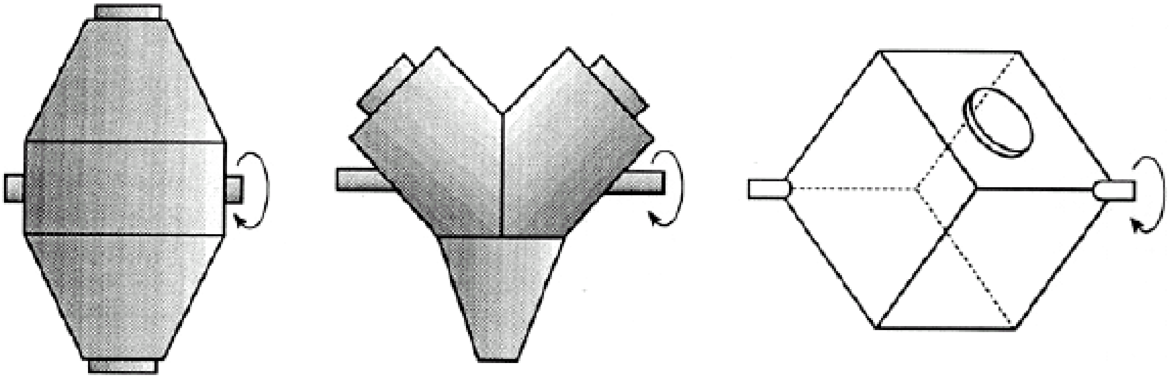


Convective and dispersion mixing



Mixing particulate solids

» Tumbling blenders



» r

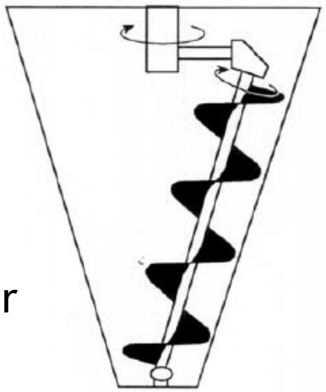
» convection and diffusion

» rotating frequency 5 – 30 min^{-1}

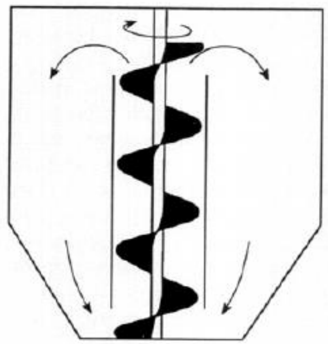
Mixing particulate solids

Convective blenders

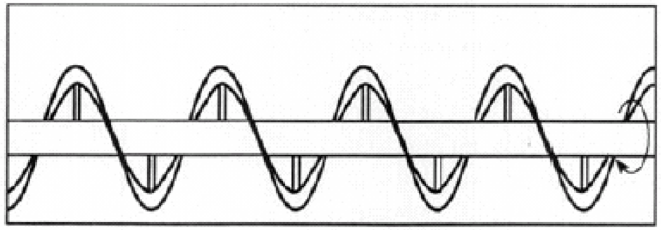
orbital agitator

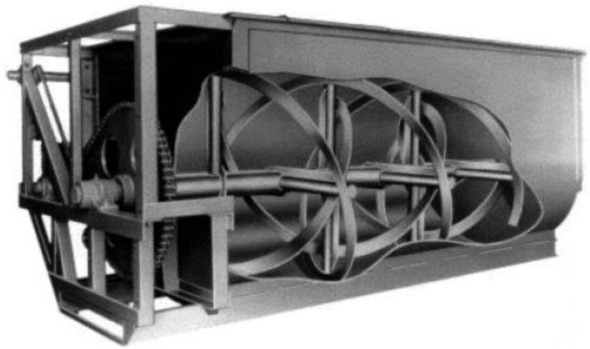


vertical agitator



horizontal agitator



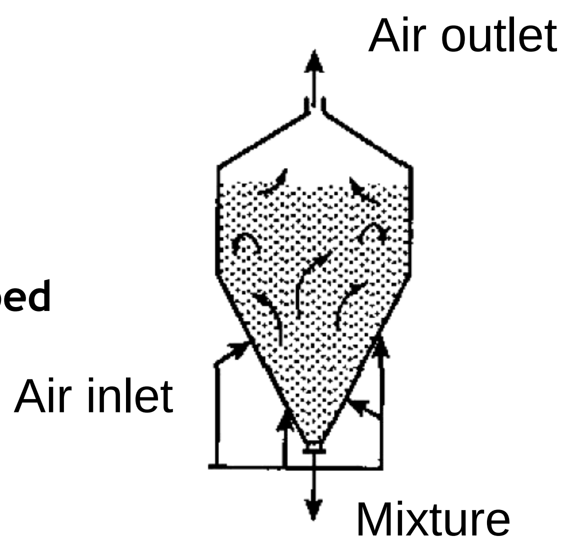


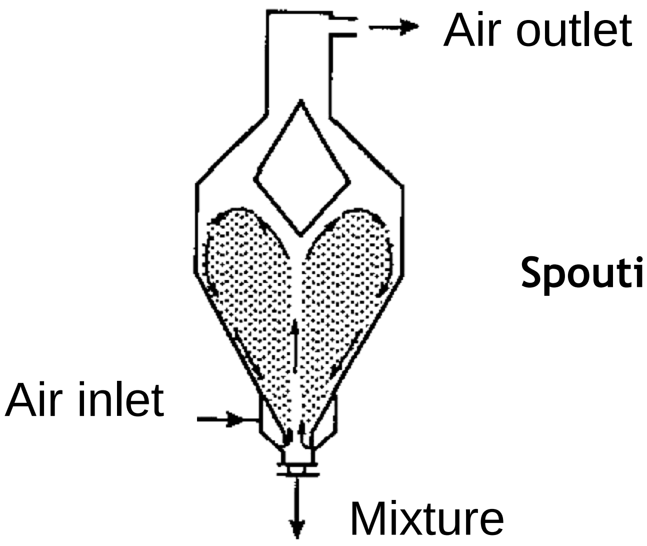
- static vessel equipped with conveyor
- convection, shear
- good for agglomerating mixtures
- difficult cleaning

Mixing particulate solids

Fluidized bed mixers

Bubbling fluidized bed





Spouting fluidized bed

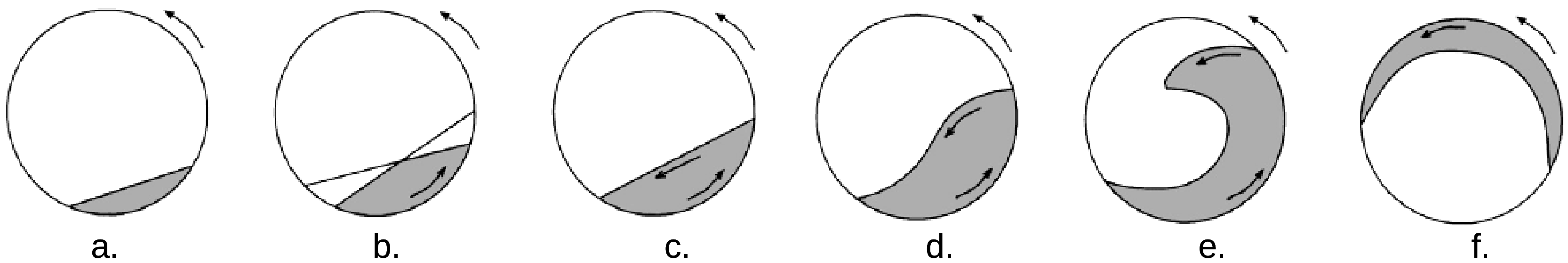
- Very fast mixing
- Multiple operations in single unit
  - drying, granulation
- suitable for free flowing and mildly cohesive materials

Process parameters of tumbling blenders

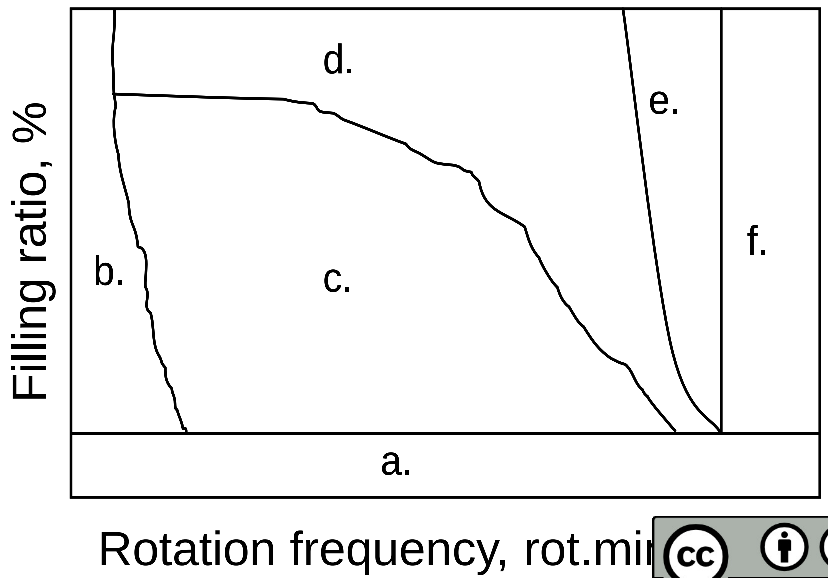
- Key parameters
  - rotating frequency … f [s^{-1}]
  - filling ratio … φ [%]
  - equipment size
- Critical rotating speed
  - causes centrifugal movement of particles = no mixing

$$f_c = \frac{1}{2\pi}\sqrt{\frac{g}{R}}$$

Powder movement in blender

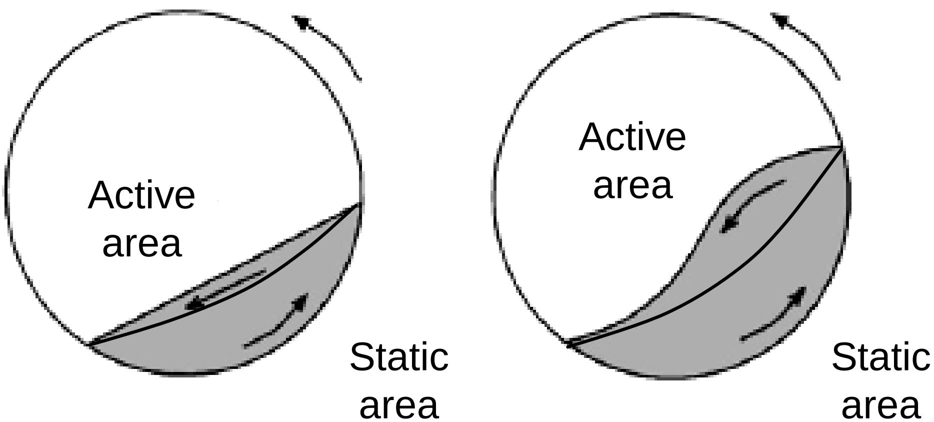


- Powder movement regimes
  - a. sliding
  - b. slumping (0 – 3 % f_c)
  - c. rolling (3 – 30 % f_c)
  - d. cascading (3 – 30 % f_c)
  - e. cataracting (30 – 100 % f_c)
  - f. centrifuging



Powder movement in blender

» Rolling and cascading motion



Rolling motion

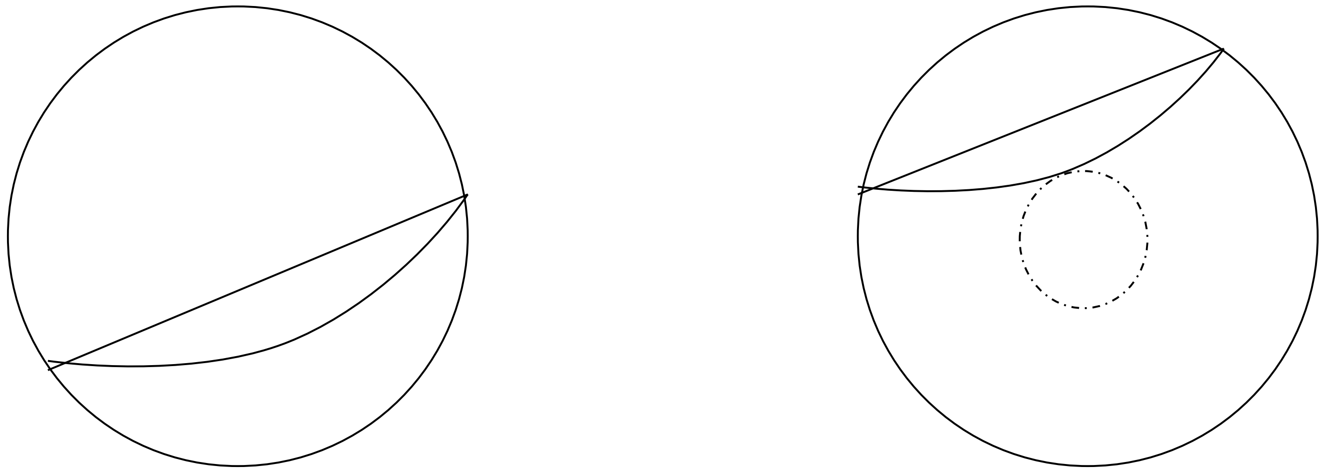
Cascading motion

» Depends on the filling ratio

» Mixing proceeds only in the active zone

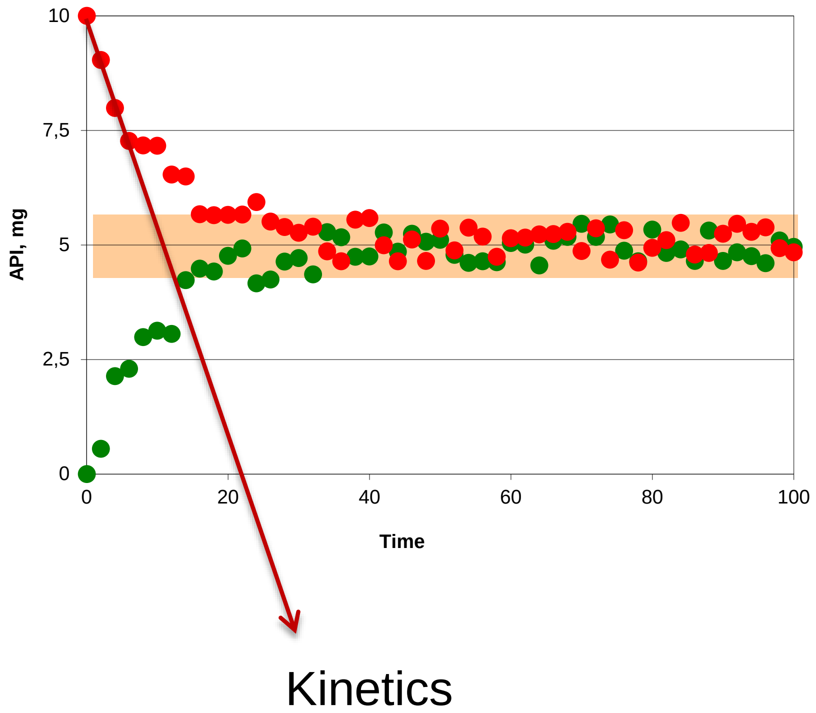
Filling ratio

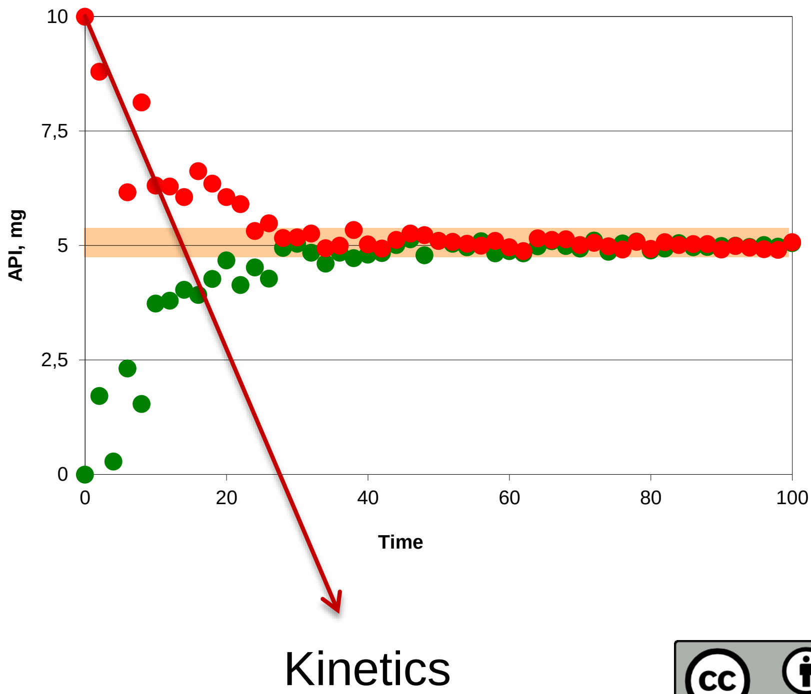
- Filling ratio > 50 %
  - non-mixed core may develop



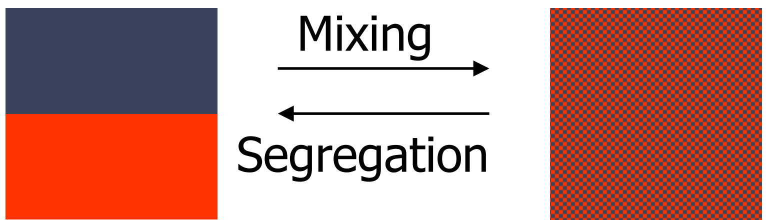
Kinetics and eqiuilibrium of blending

- Kinetics – **How long to mix ?**
- Equilibrium – **How well mixed it can become ?**

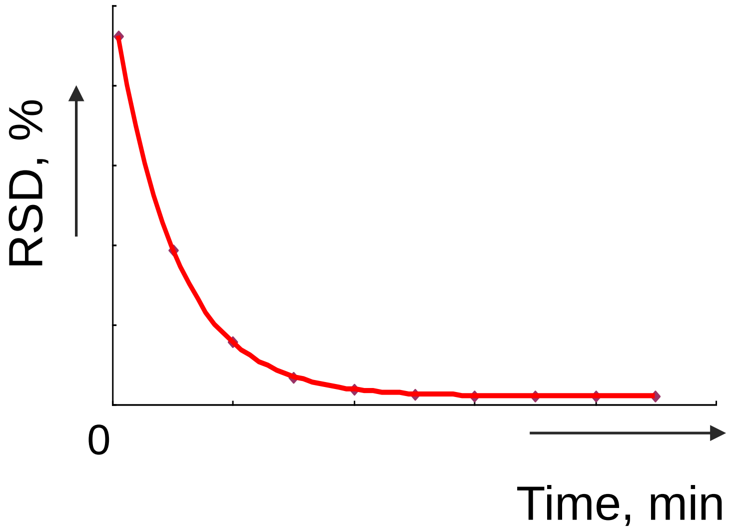




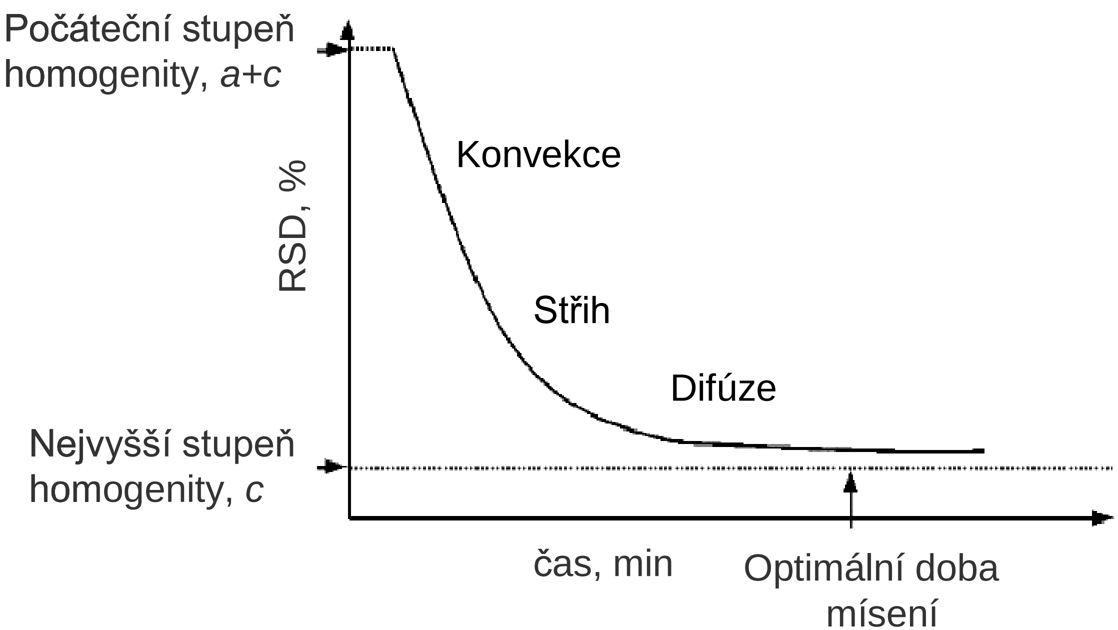
Processes taking place in powder homogenization



Mixing is a reversible process



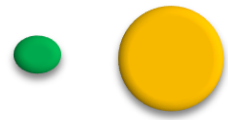
Mixing kinetics



$$RSD = a.e^{-bt} + c \qquad \frac{dRSD}{dt} = -k_M RSD + k_S \left(RSD_0 - RSD\right)$$

Causes for segregation

- Differences in particle size
- Differences in morphology



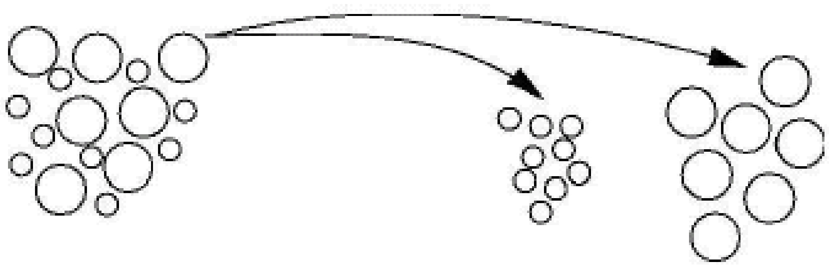
- Differences in density

- Components ratio

- Cohesive interactions
  - moisture
  - static charge

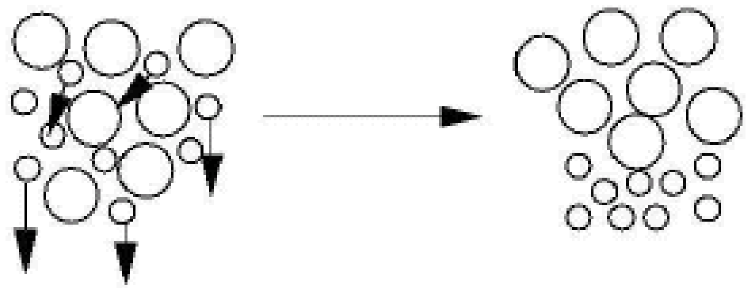
Segregation mechanisms

» Trajectory



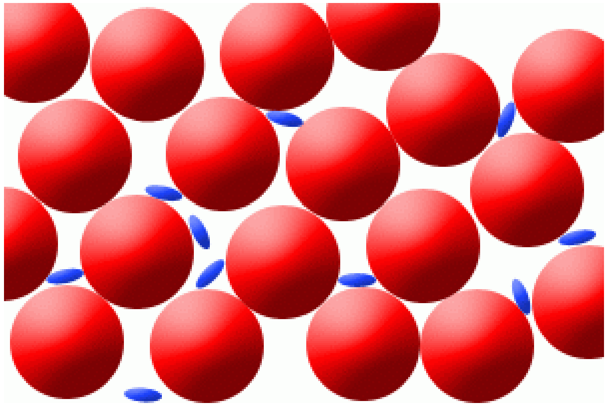
» Percolation

» Fluidization

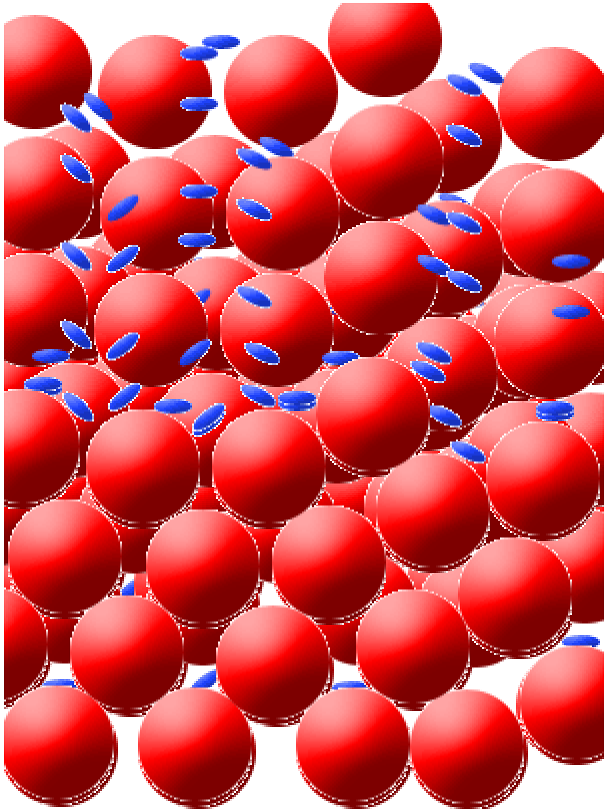


Segregation mechanisms

- Sifting

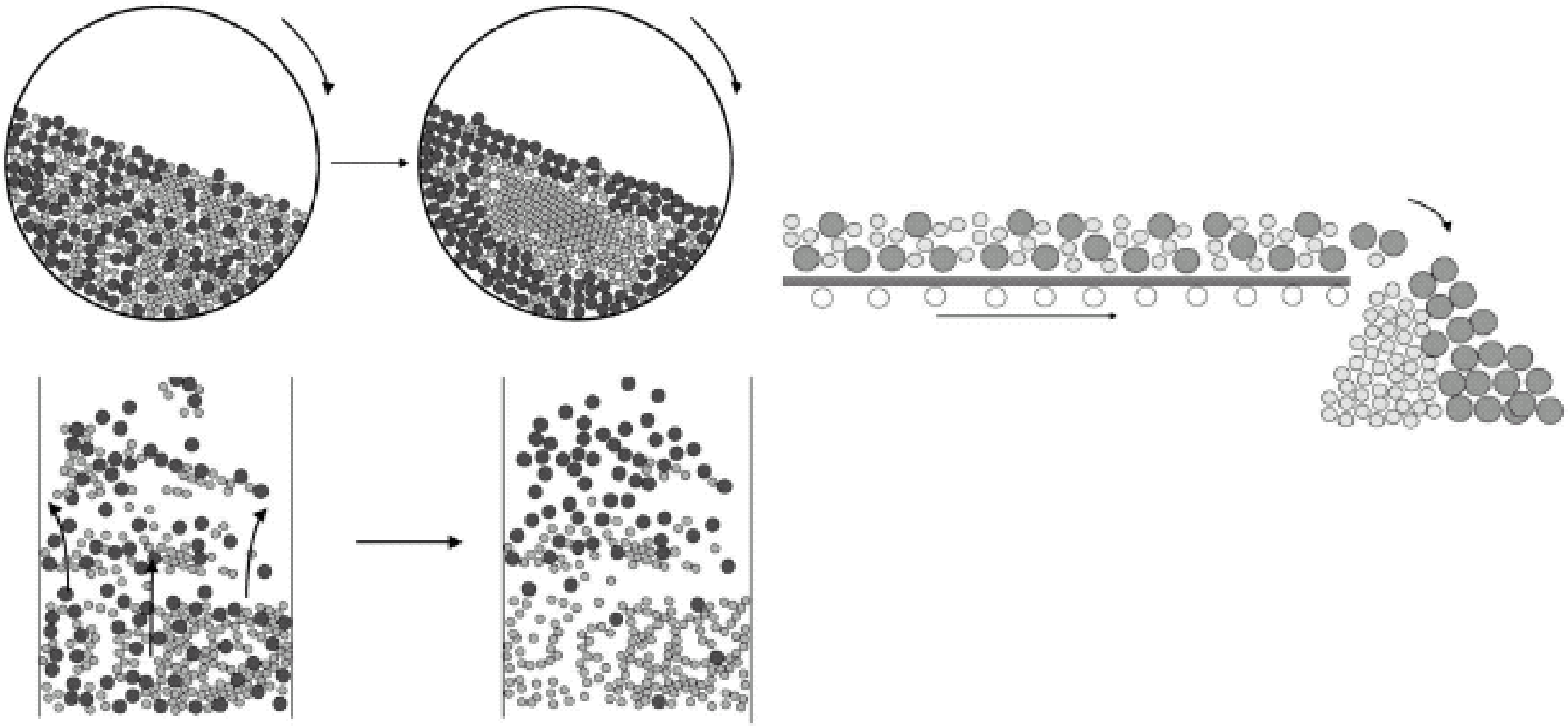


- Fluidization



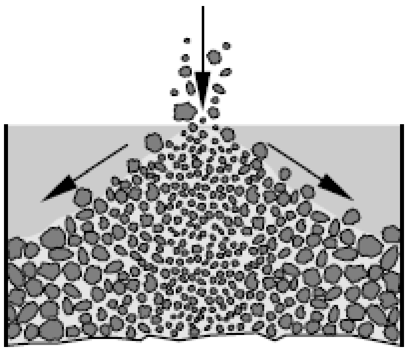
Segregation

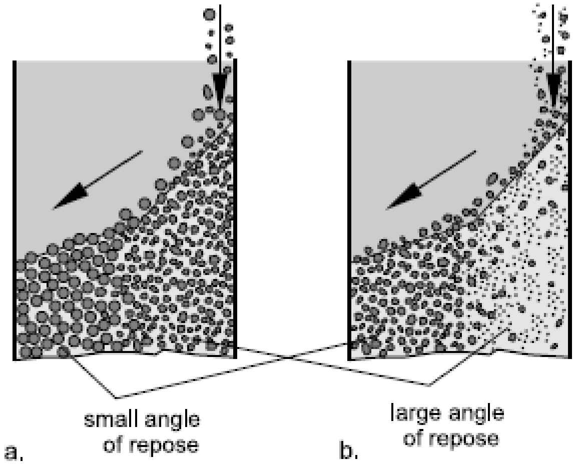
» Segregation in different blenders



Segregation examples

- Larger particles are heavier and are subjected to higher inertial forces
- Different angle of repose

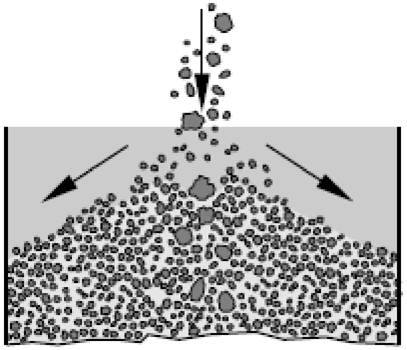


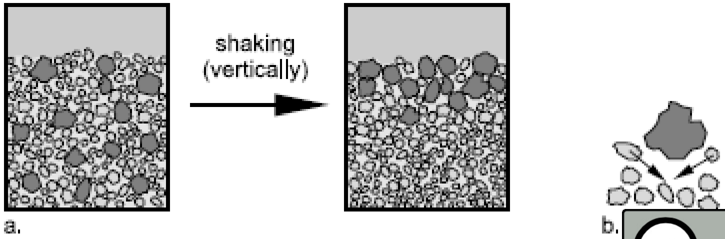


Segregation examples

- Larger particles are heavier and fall into the "crater"

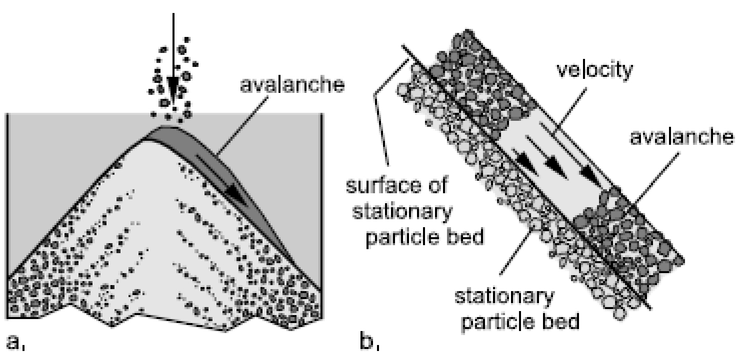
- Sifting - large particles cannot pass through the small ones, but the opposite is possible

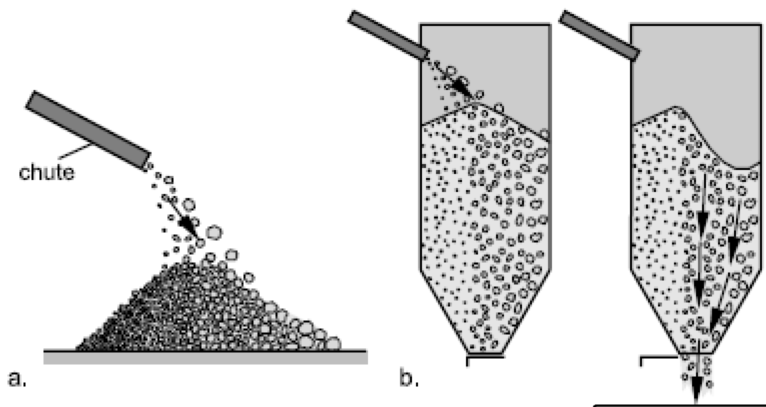




Segregation examples

- Larger particles may trigger an avalanche
- Trajectory segregation in aerodynamic conditions

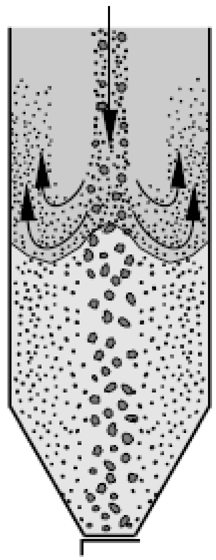


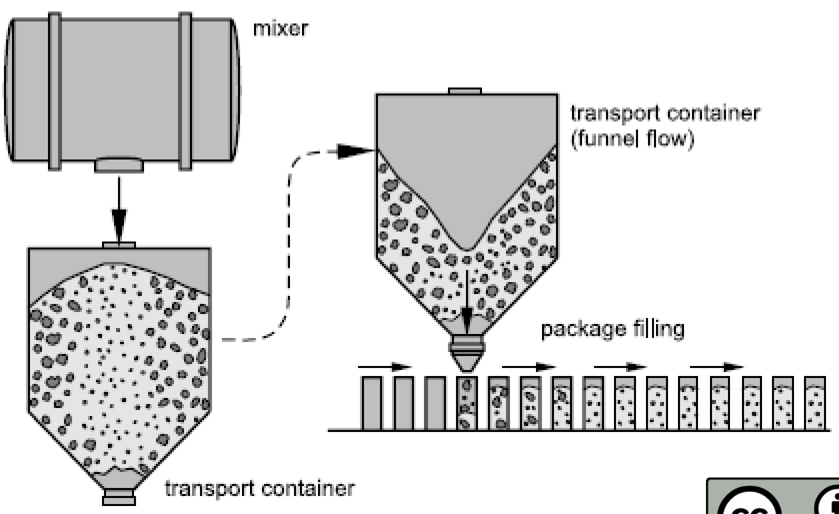


Segregation examples

» Fluidizing at silo filling

» Discharging segregated mixture by funnel flow





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Engineering in Chemical and Pharmaceutical Processes

Pharmaceutical Process Scale-up

References and study material

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  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
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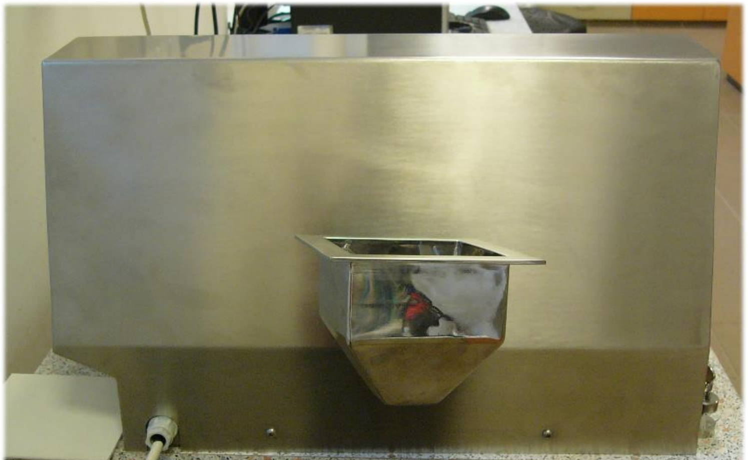
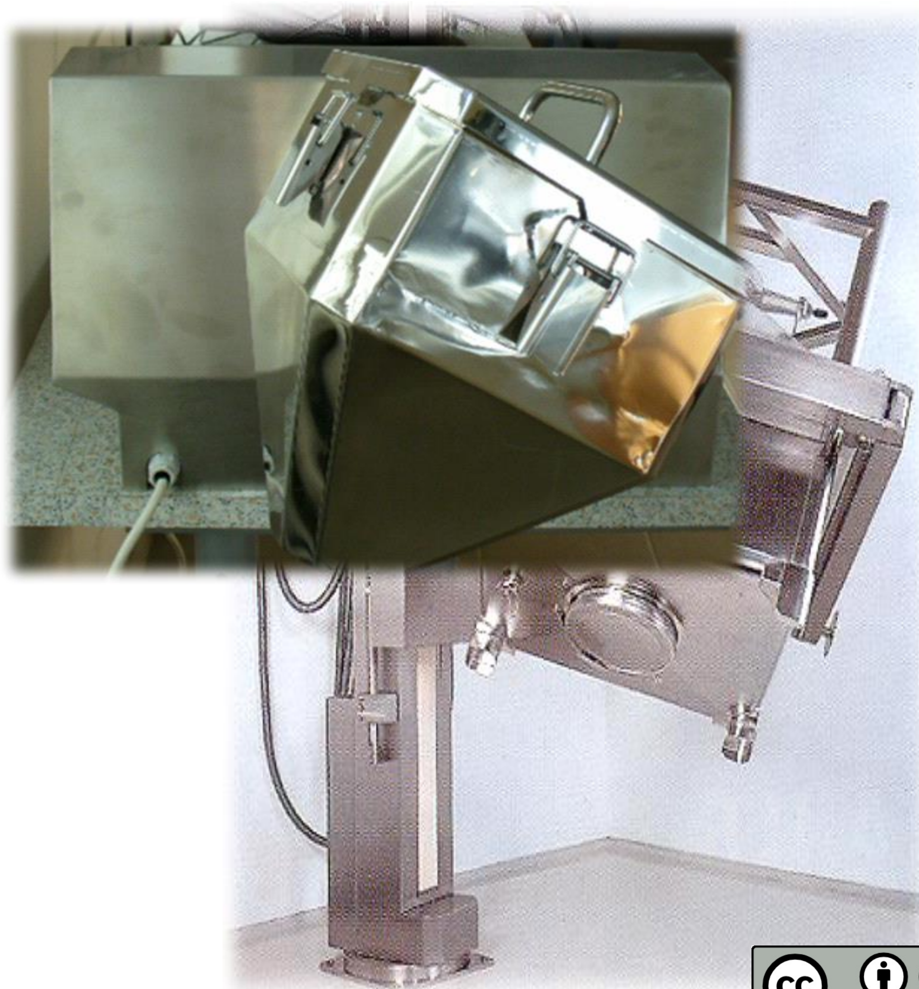
Scale change...

... small processes differ from the great ones



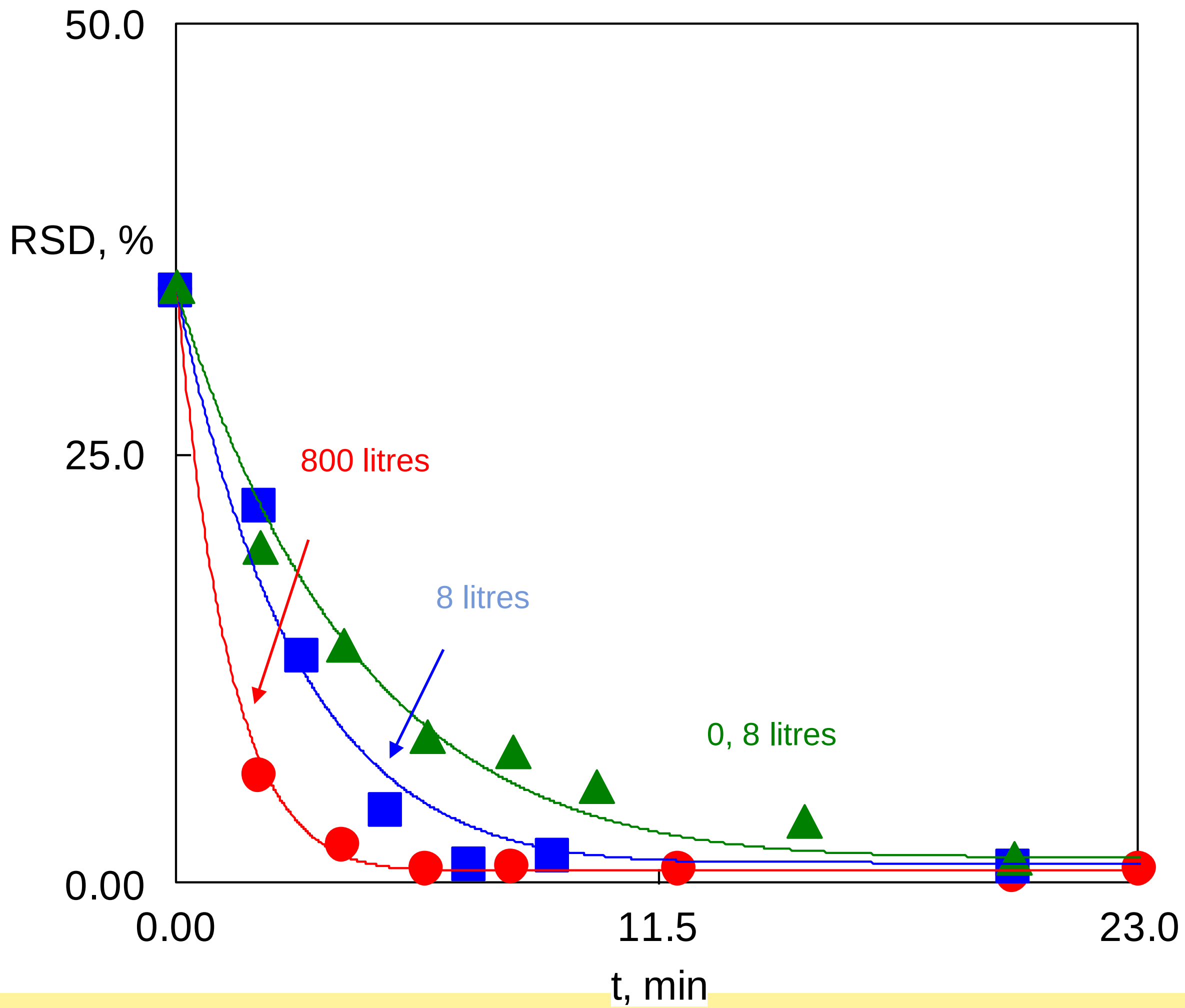
0.8 litres 8 litres



800 litres

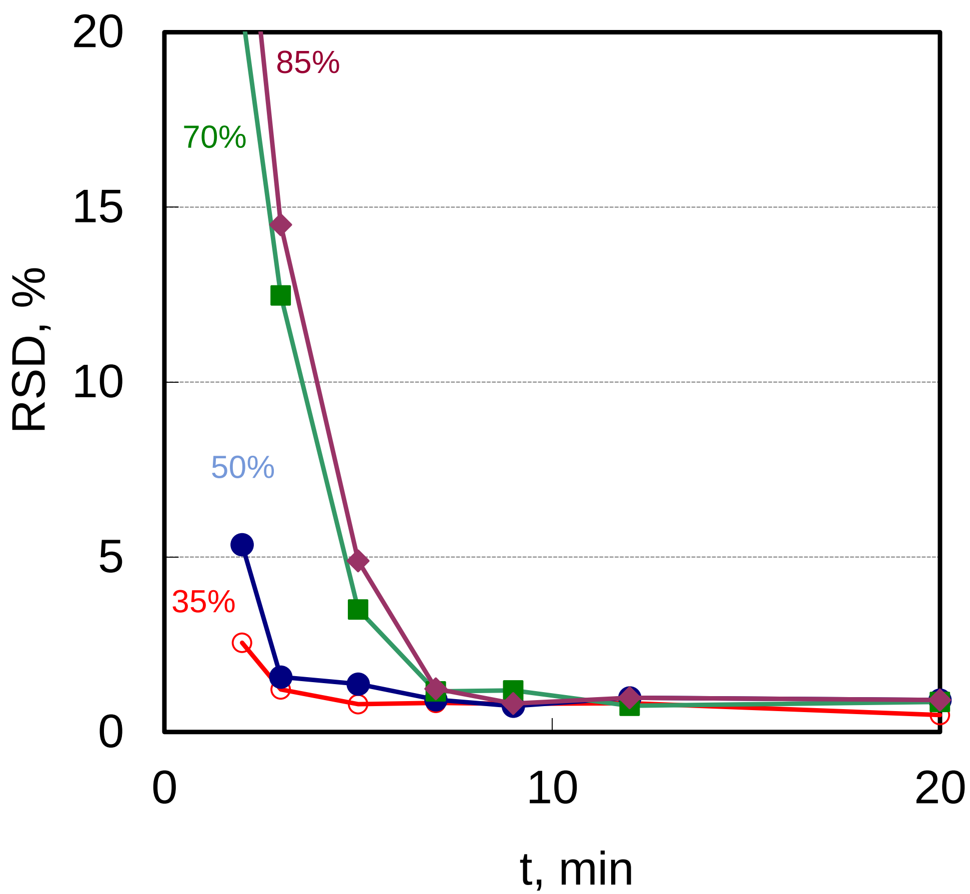
Scale change...

... small processes differ from the great ones



Even the size of the batch can play the role ...

... the effect of filling factor



Similarity theory in fluid dynamics

- For turbulent systems, the solution of the Navier Stokes equations is difficult
- Experimental study of the system is necessary
- Possible transfer of knowledge between similar systems
- Similar systems - the same values of the **similarity criteria**

The most important similarity criteria
(similarity of flow regime)

- Reynolds number

$$\mathrm{Re} = \frac{uL}{\mu} = \frac{\rho uL}{\eta}$$

  - ratio of inertial forces to viscous forces
- Froude number

$$Fr = \frac{gL}{u^2}$$

  - relationship between gravitational and inertial forces

Flow regimes transition

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  - ratio of inertial forces to viscous forces
- Re < 2300 … laminar flow
- Re > 10 000 … turbulent flow

Dissipation of energy in flowing liquid

- Bernoulli's equation

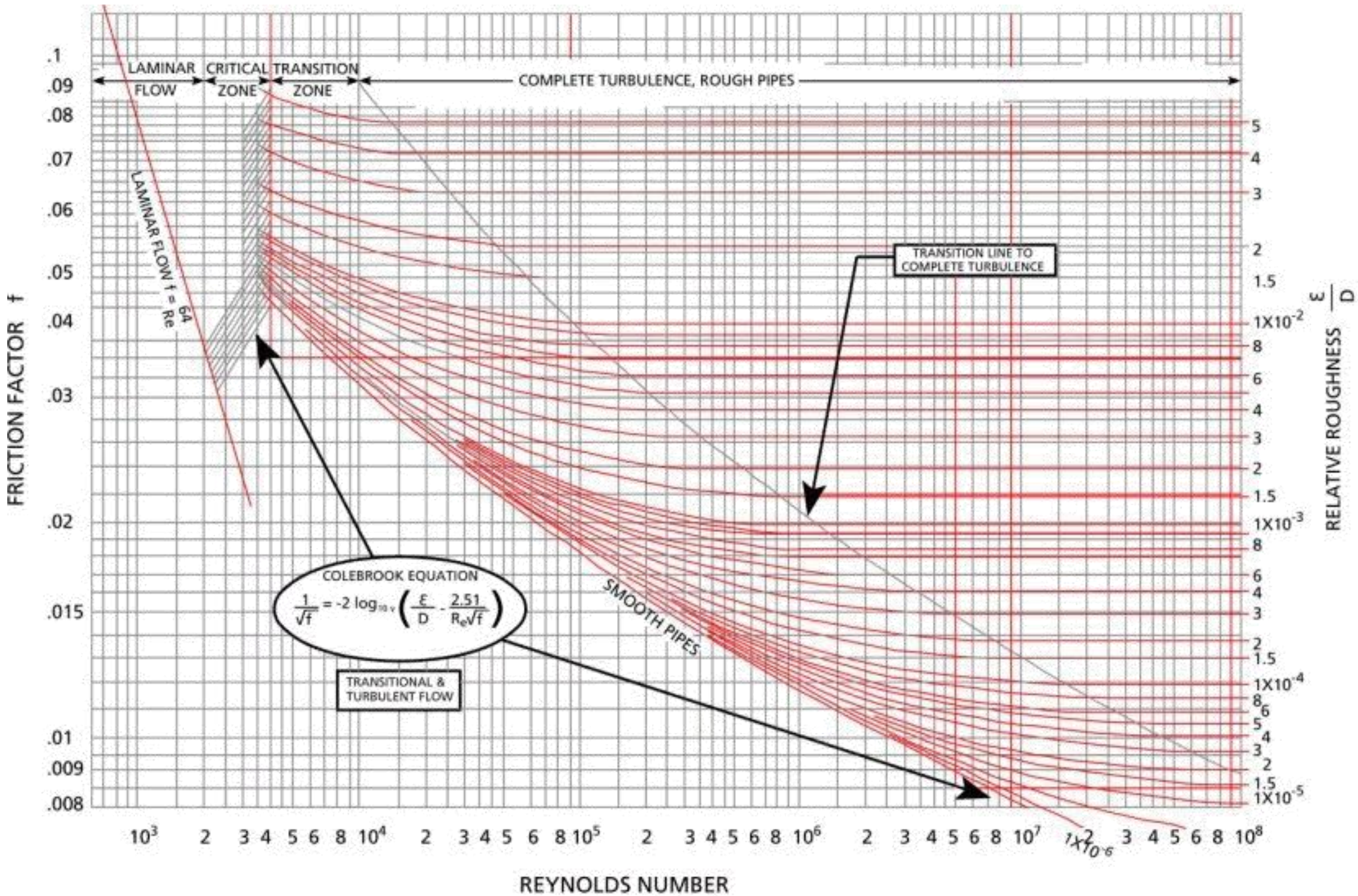
$$\frac{1}{2}u_{A,stř}^2 + \frac{P_A}{\rho} + z_A g = \frac{1}{2}u_{B,stř}^2 + \frac{P_B}{\rho} + z_B g + E_{dis}$$

  - u … velocity
  - z … height
  - P … pressure
  - E_{dis} … specific dissipated energy

$$E_{dis} = f\frac{l}{d}\frac{u^2}{2}$$

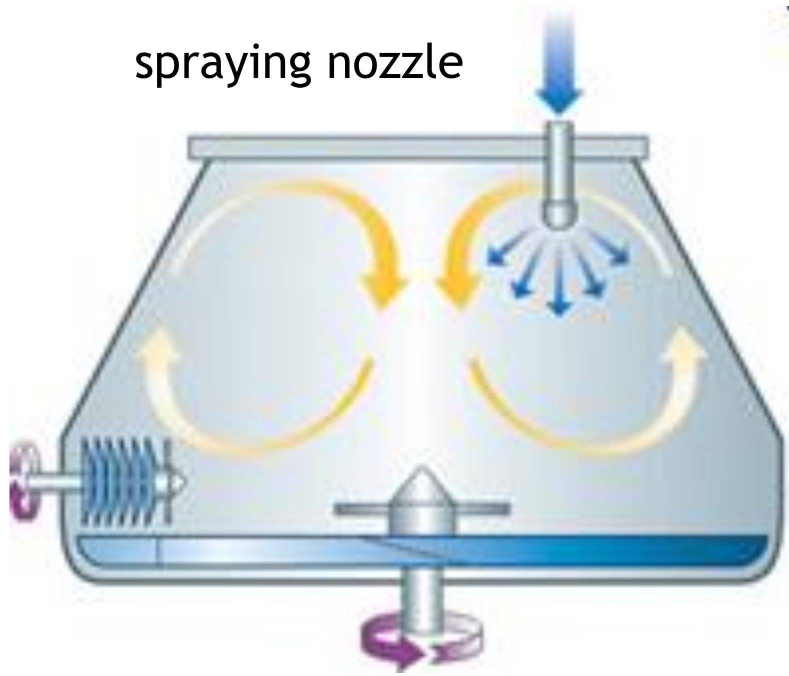
  - f … friction factor

Moody diagram



Scale-up in wet granulation

spraying nozzle



chopper

impeller

Critical process parameters

- Amount of liquid
  - granulation rate, size and properties of granules
  - experimental setup
  - transfer to different material
    - π … 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

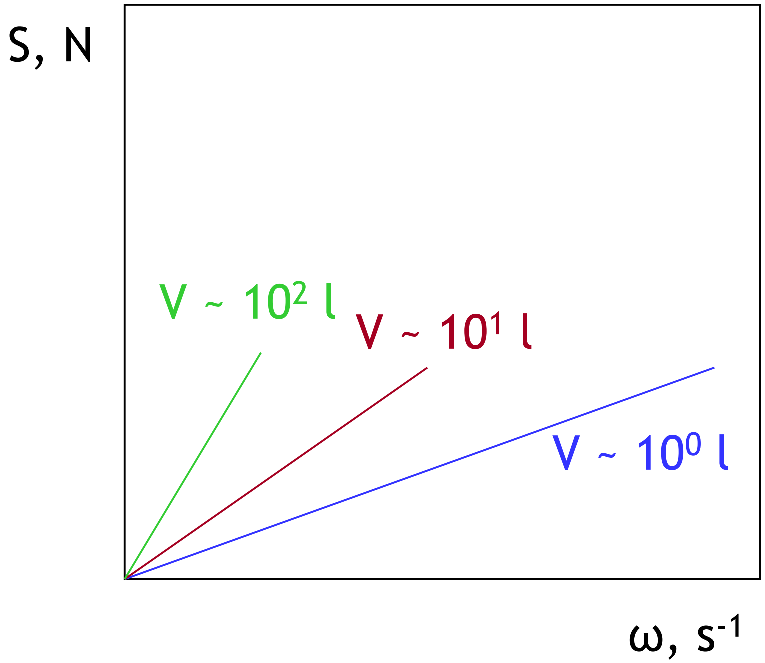
$$\pi = \frac{V - V_M}{V_S - V_M}$$

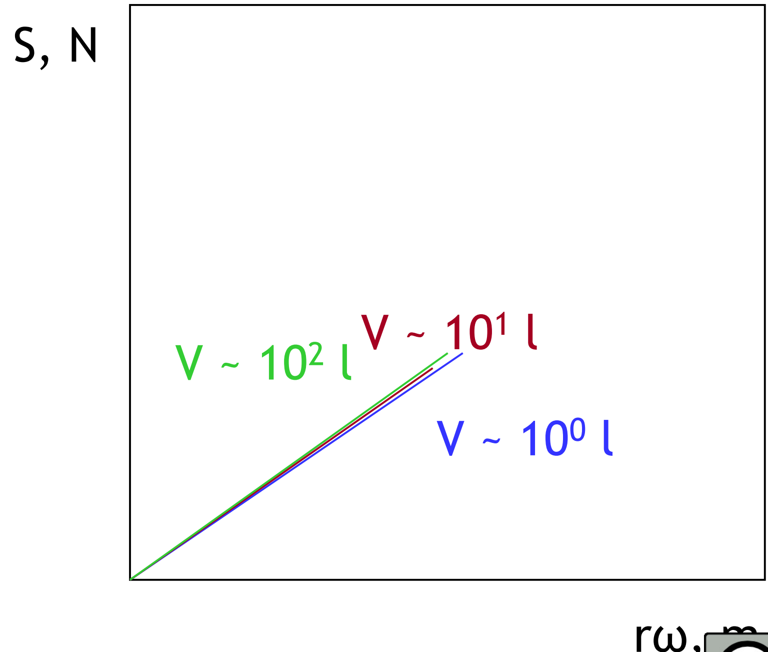
Critical process parameters

- Geometry
- Powder properties
- Liquid amount and spraying quality
- Impeller frequency
  - decrease number of lumps (extremely large granules)
  - increasing mean granule size (with exception of lumps)
  - eliminating fines

Impeller frequency effect

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





Granulating process similarity

- Important variables and constants (7)
  - ΔP … 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, $kg.m^{-3}$
  - η … 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 $\boxed{N_P = \frac{\Delta P}{\rho N^3 D^5}}$
  - Reynolds' number $\boxed{\mathrm{Re} = \frac{\rho N D^2}{\eta}}$
  - Froude number $\boxed{Fr = \frac{D N^2}{g}}$
  - Geometric number $\boxed{\frac{h}{D}}$

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Engineering in Chemical and Pharmaceutical Processes

Fluid flow and transport in pharma applications

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Fluids in pharmaceutical industry

- Liquids
  - solvents
  - liquid API formulations
  - dispersions
- Gases
  - Air-conditioning
  - Drying
  - Fluidized-bed operations

Ideal liquid

- Ideal liquid is incompressible, but does not exhibit any shear stress or strain.

Conservation of mass

Continuity equation

- Volumetric flow Q of a liquid is maintained
- if the incompressible fluid in one point flows through cross-section S_1 and in another point S_2, then:

$$S_1 v_1 = Q_1 = Q_2 = S_2 v_2$$

- For compressible fluids the mass flow is conserved and the following applies: $S_1 v_1 \rho_1 = S_2 v_2 \rho_2$

Conservation of energy

Bernoulli's equation

$$\frac{1}{2}u^2 + \frac{P}{\rho} + z\ g = konst$$

- Dimension [J.m^{-3}]

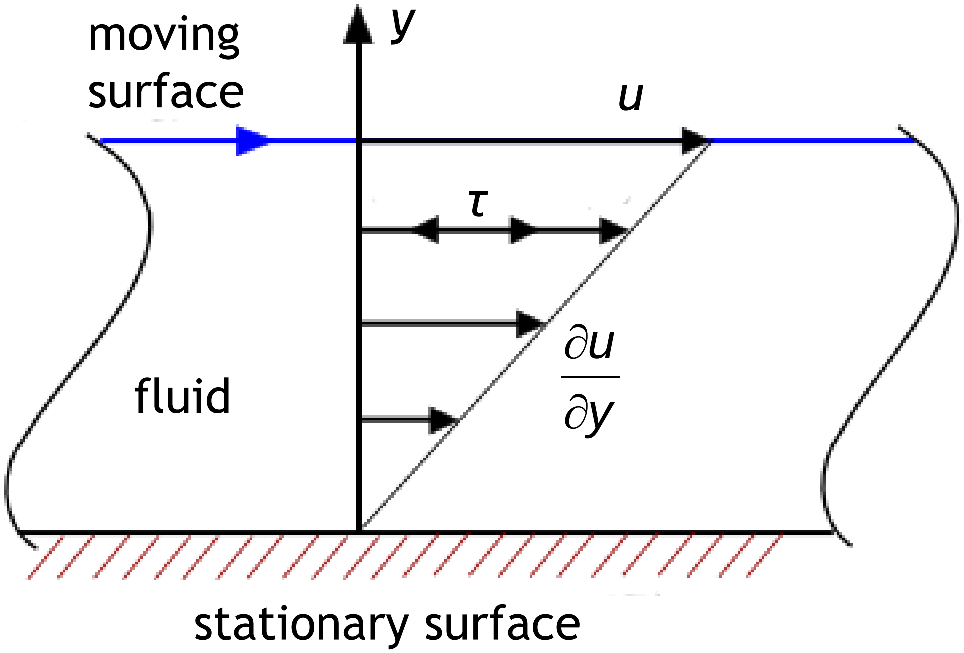
- u … velocity
- z … height
- P … pressure

Real liquid - viscosity

- Dynamic viscosity, η [Pa.s]

$$\tau = \eta \frac{\partial u}{\partial y}$$

  - τ ... shear stress
  - valid for Newtonian fluids



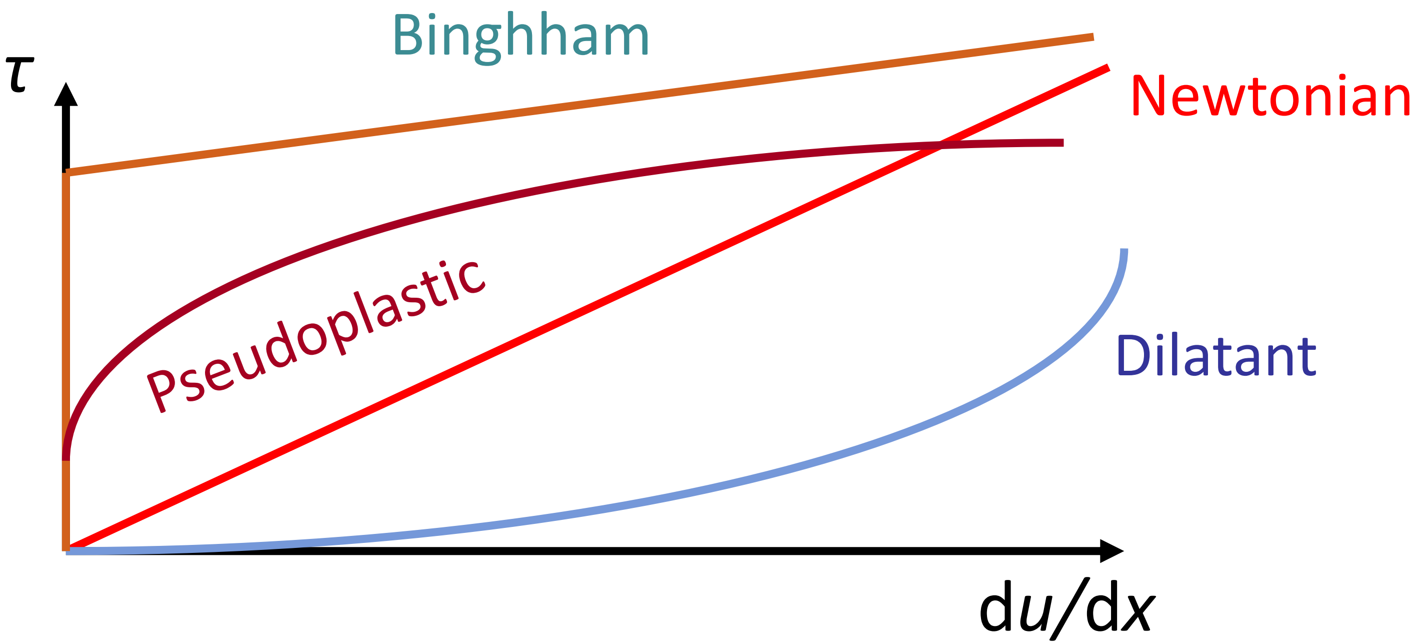
Types of viscosity

- η dynamic viscosity
  - $[\eta] = kg.m^{-1}.s^{-1} = N.m^{-2}.s = Pa.s$
  - Older unit Poise $P=g.cm^{-1}.s^{-1}=0,1\ Pa.s$
- Viscosity related to density, ie. kinematic viscosity
  - $\nu = \eta / \rho$

Viscosity of liquids

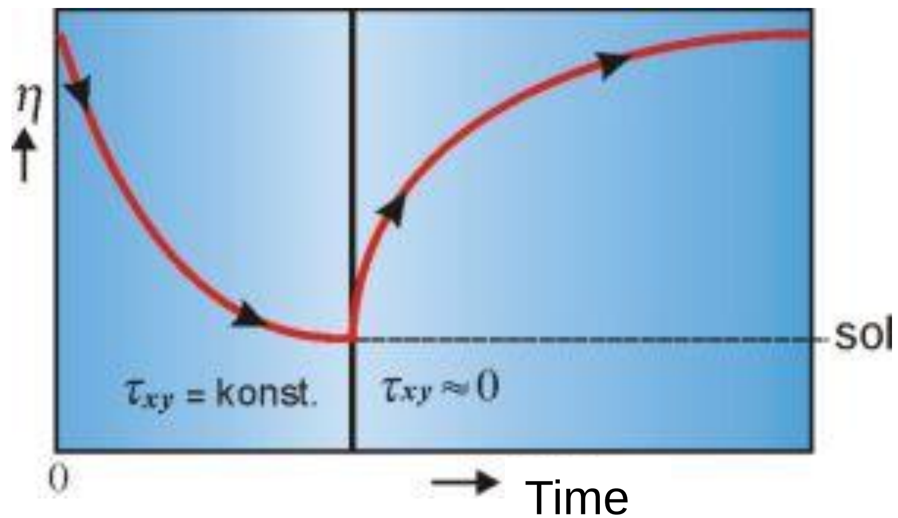
Substance	Dynamic viscosity, [Pa.s]
Air	2×10^{-5}
Liquid N_2	2×10^{-4}
Water	9×10^{-4}
Oil	8×10^{-2}
Glycerol	1×10^{0}
Ointment base	2×10^{5}

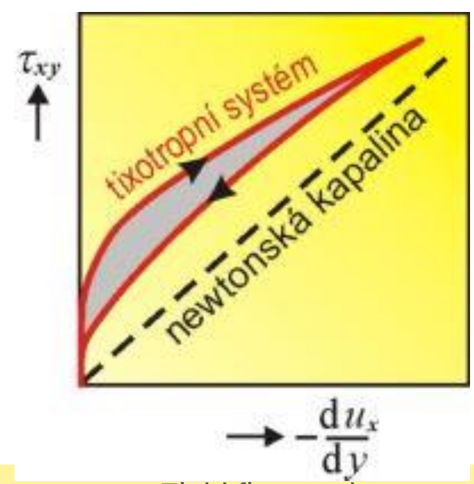
Non-newtonian liquids



Non-newtonian liquids

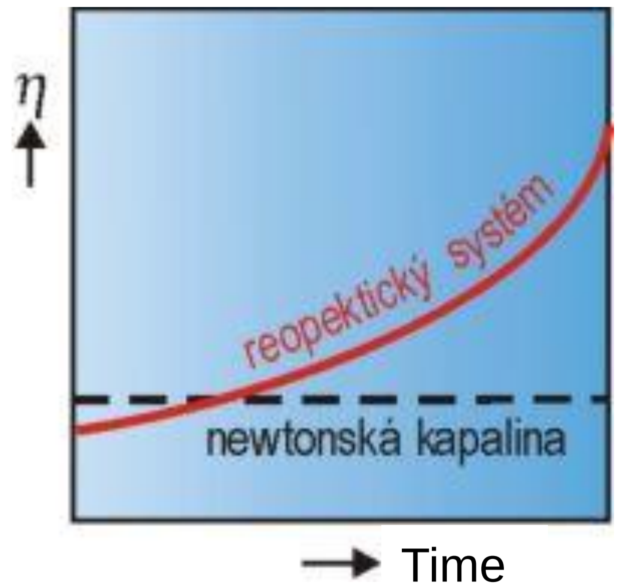
- Apparent viscosity may also depend on the time under stress. Some pseudoplastic and plastic systems exhibit behaviour:
  - Thixotropic - viscosity decreases with time under stress

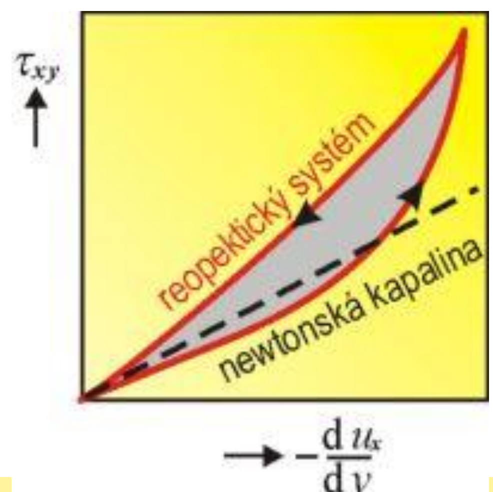




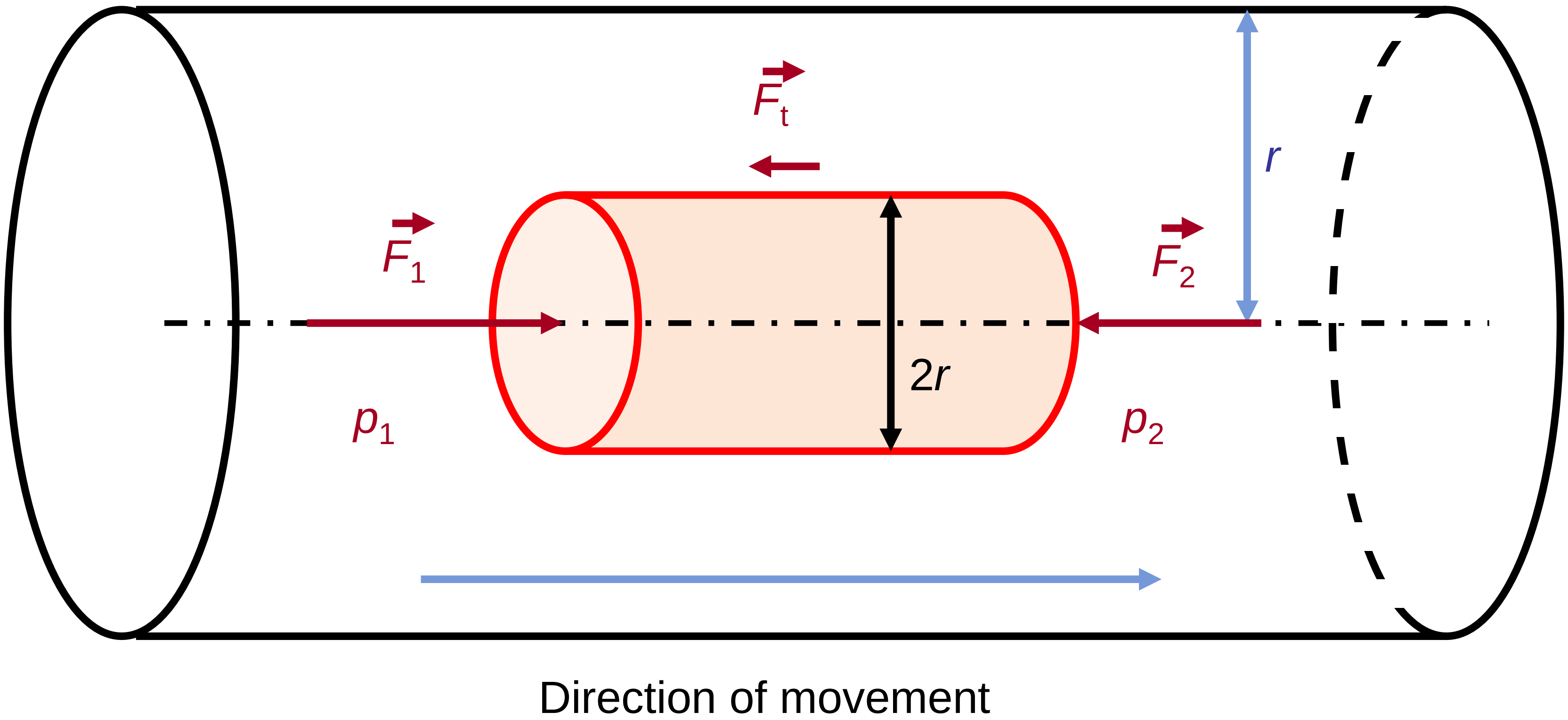
Non-newtonian liquids

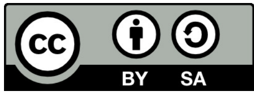
- Apparent viscosity may also depend on the time under stress.
- Some dilatant systems exhibit behaviour:
  - rheopectic - viscosity increases with time under stress





Flow of viscous liquid





Flow of viscous liquid
balance of forces

- Compressive forces
  - acts on the bases
  - cylinder wall - friction force caused by the friction on surrounding layers.
- If the cylindric element moves steadily, all the forces acting on it are in equilibrium:

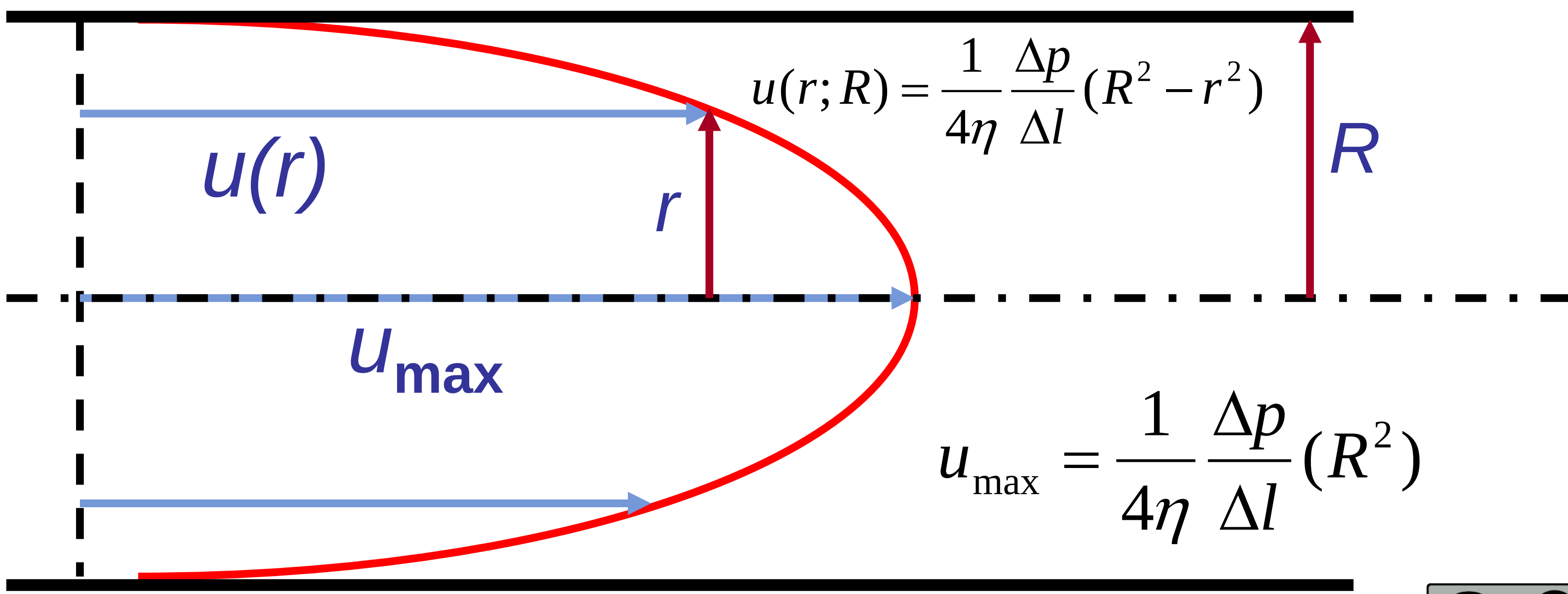
$$\pi r^2 (p_1 - p_2) + 2\pi r \Delta l \eta \frac{du}{dr} = 0$$

$$du = -\frac{1}{2\eta} \frac{\Delta p}{\Delta l} r \, dr$$

Flow of viscous fluids

in a round tube

- boundary condition *u(R) = 0* :
  - zero velocity at the tube wall



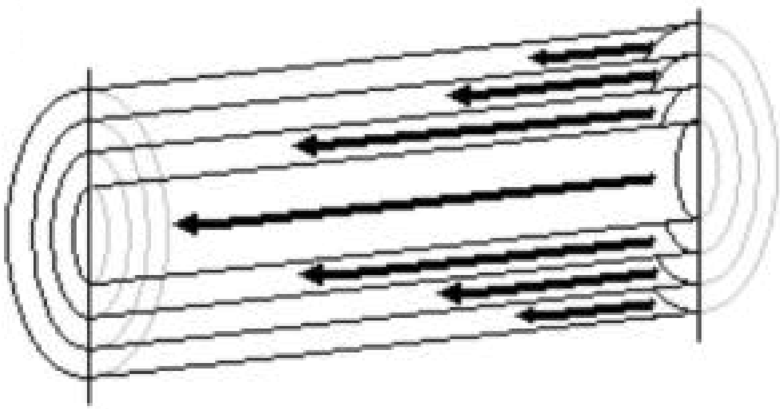
$$u(r;R) = \frac{1}{4\eta}\frac{\Delta p}{\Delta l}(R^2 - r^2)$$

$$u_{\max} = \frac{1}{4\eta}\frac{\Delta p}{\Delta l}(R^2)$$

Poiseuille law

» Laminar flow through pipe

$$u = \frac{1}{4\eta}\frac{\Delta p}{l}\left(R^2 - r^2\right)$$



$$u_{\max} = \frac{1}{4\eta}\frac{\Delta p}{l}R^2$$

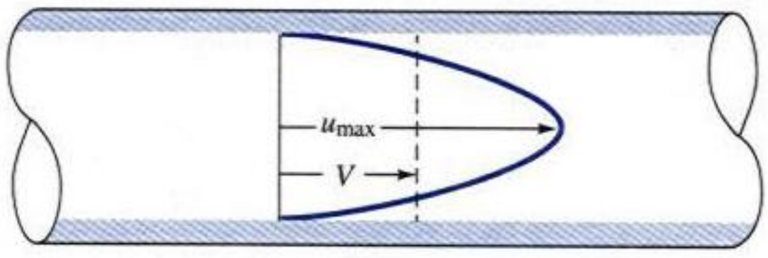
$$Q = \int_A u dA = \int_0^R u 2\pi r dr = \int_0^R \frac{1}{4\eta}\frac{\Delta p}{l}\left(R^2 - r^2\right) 2\pi r dr$$

$$Q = \frac{\pi}{8\eta}\frac{\Delta p}{l}R^4$$

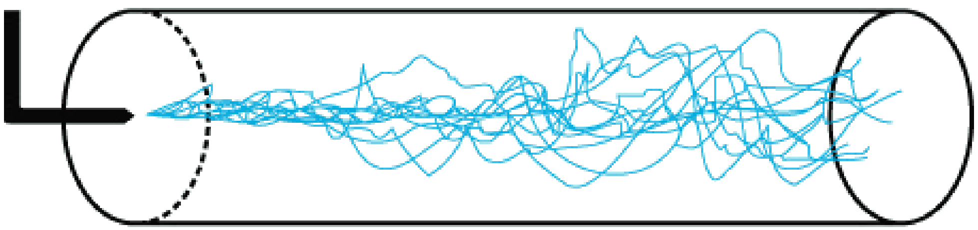
Hagen-Poiseuille equation

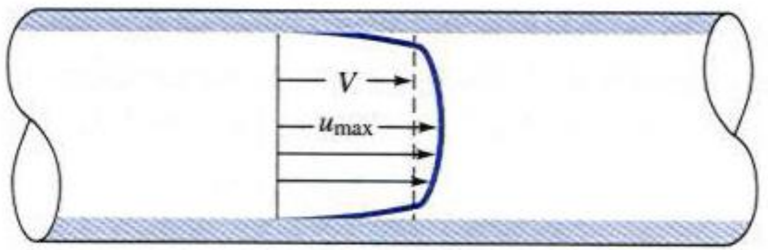
Flow regime

- Laminar



- Turbulent





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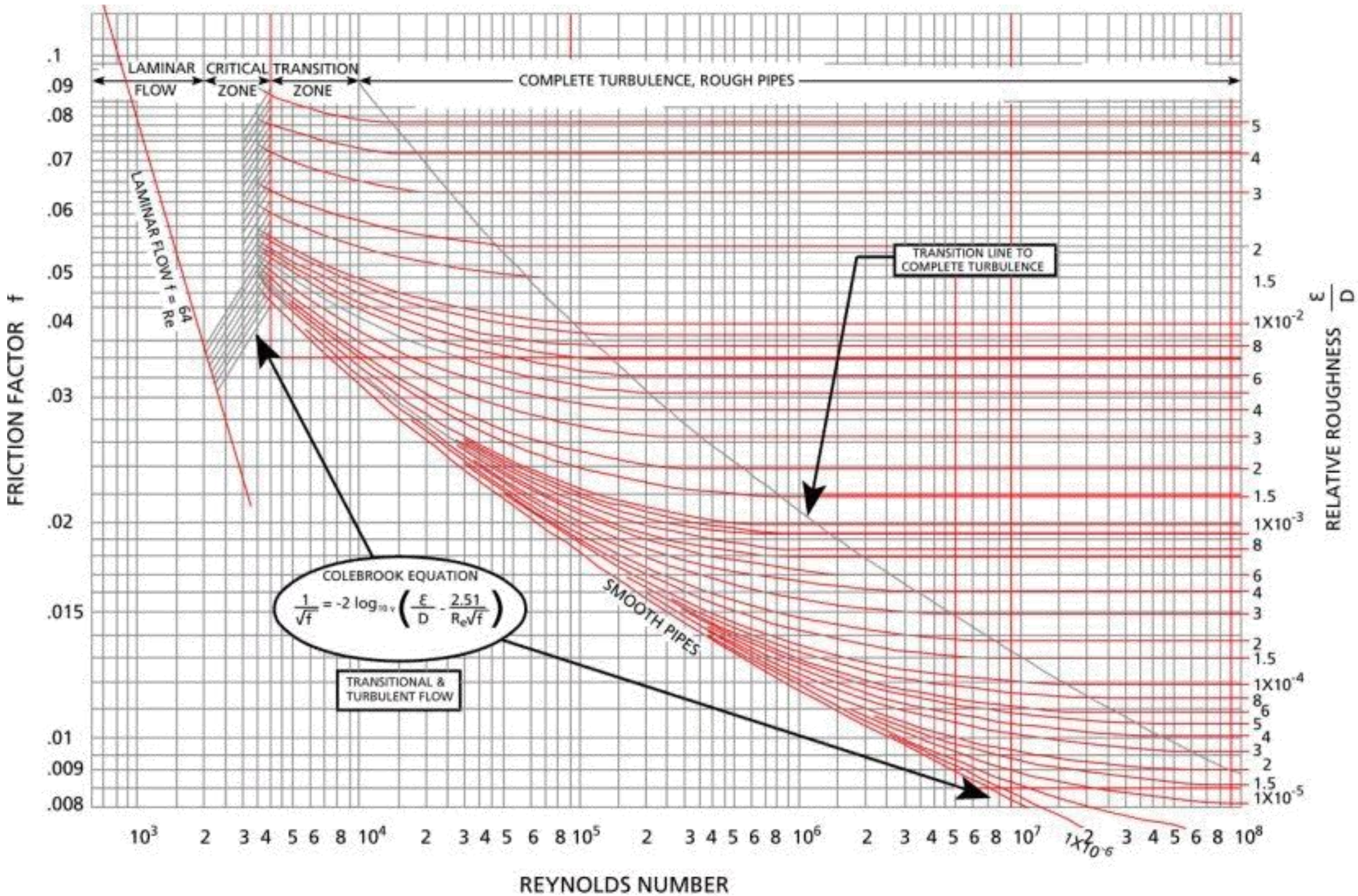
  - E_{dis} ... specific dissipated energy

$$E_{dis} = f\,\frac{l}{d}\,\frac{u^2}{2}$$

  - f ... friction factor

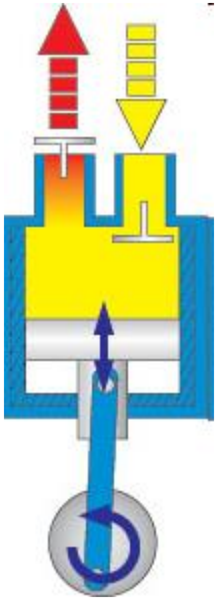
Moody diagram

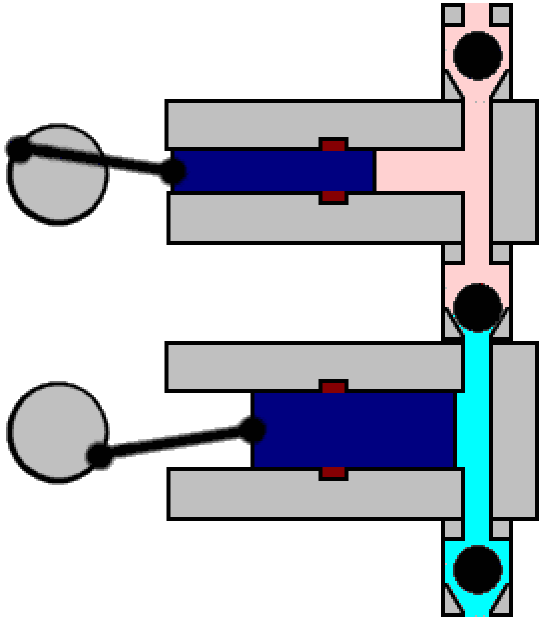


Transport of liquids - pumps

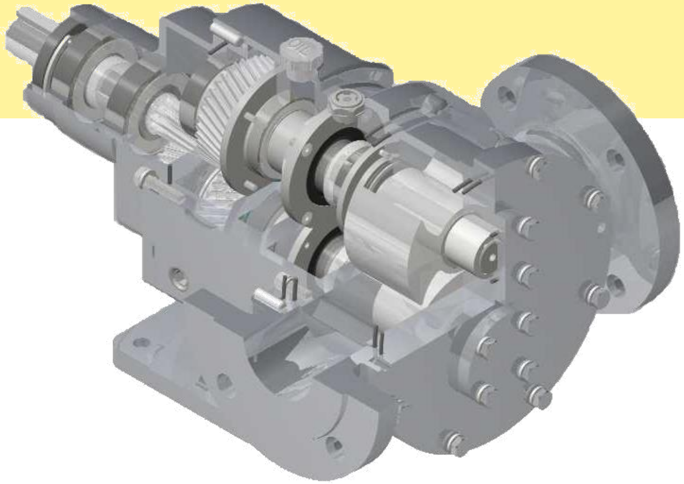
- Hydrostatic (positive displacement)
  - direct transforming work to pressure in the pump body
  - plug, vane, gear, membrane, etc.
  - main drawbacks is pulsing flow and/or cost
- Hydrodynamic
  - transforming work into kinetic energy, then into the pressure
  - axial, radial (centrifugal)
  - main drawback is the cavitation

Reciprocating plug pumps

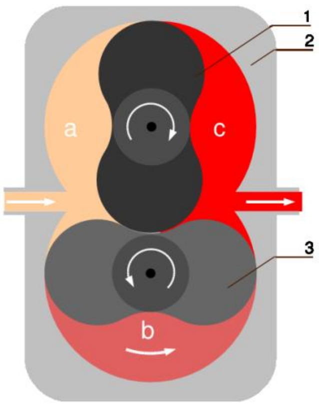


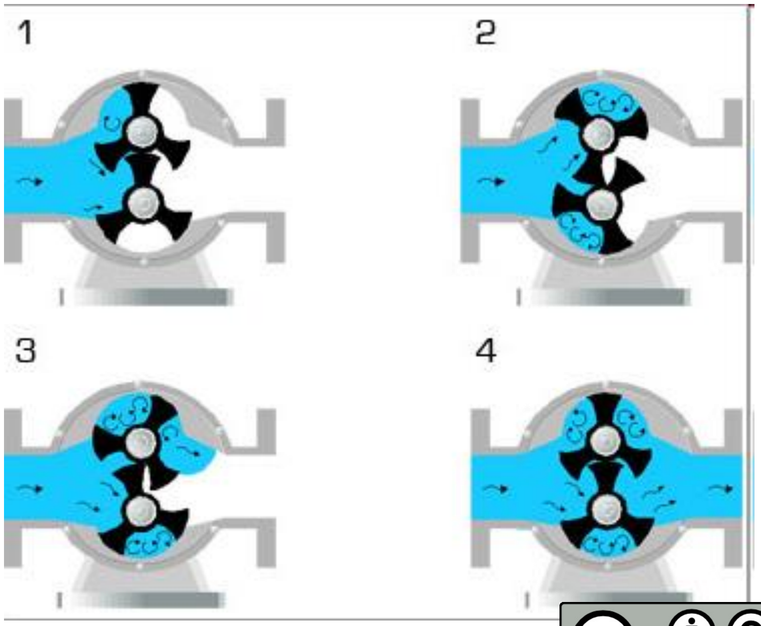


Gear pumps

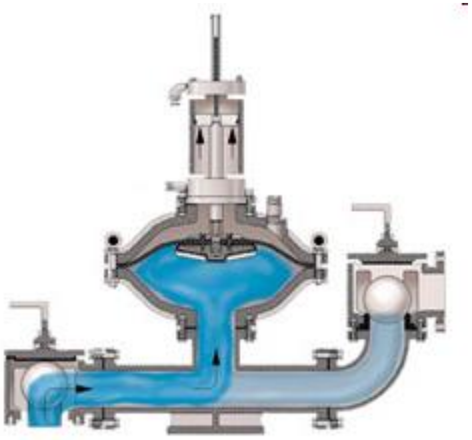


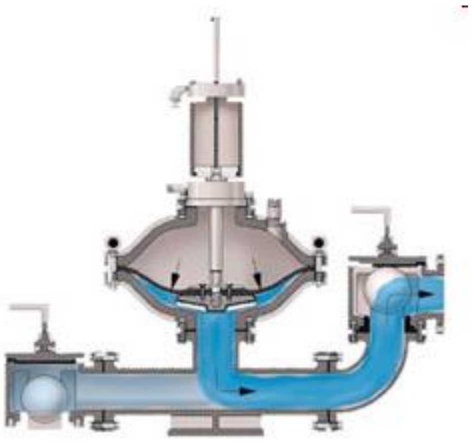
- Pumping special fluids
  - viscous
  - abrasive
  - with solids



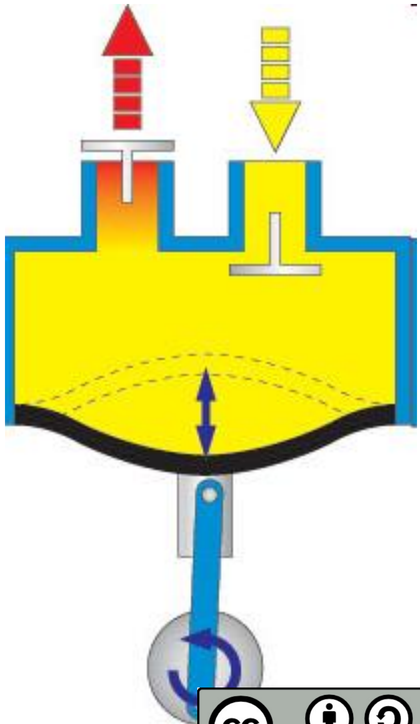


Membrane pumps

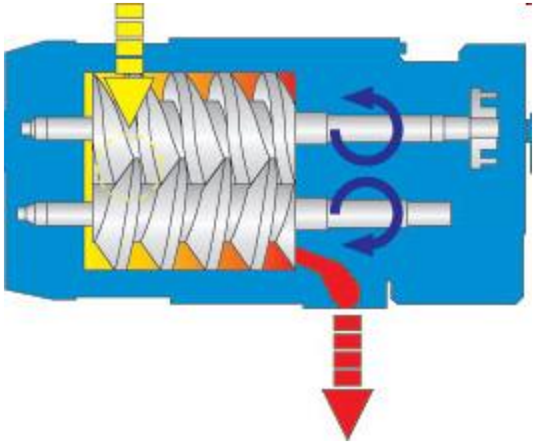


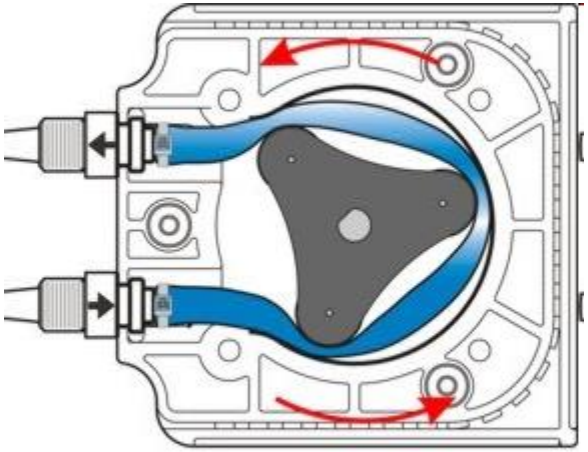


- Membrane operated by
  - plug
  - compressed gas
- Pump mechanism separated from the pumped liquid
- Resistance to a aggressive media



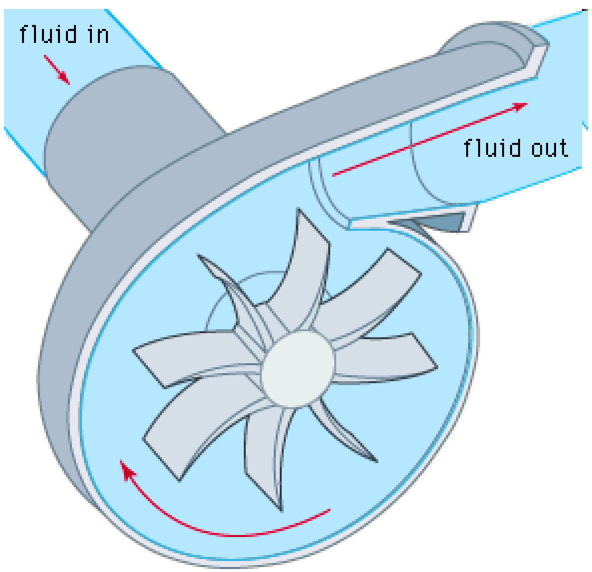
Screw and peristaltic pumps





Hydrodynamic pumps

Centrifugal



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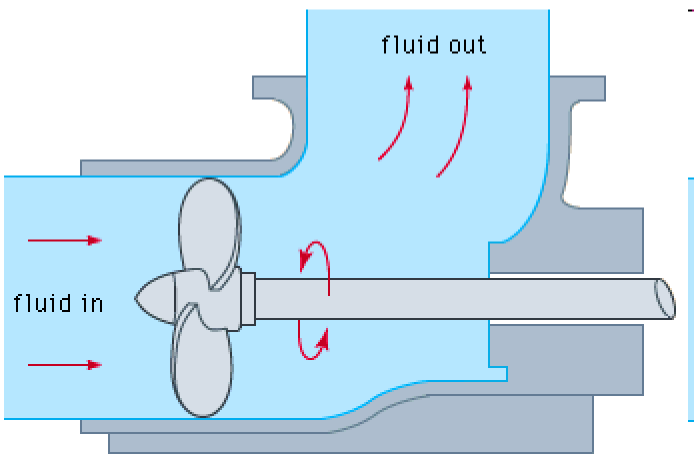
Axial



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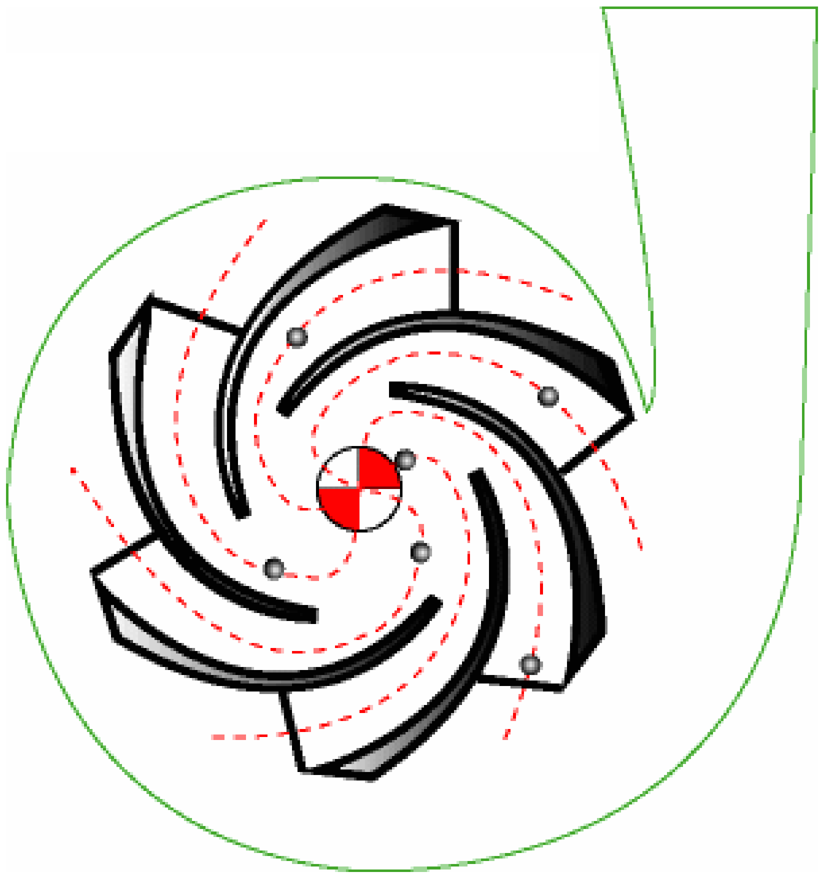
Operation of the centrifugal pump



Transport of gases

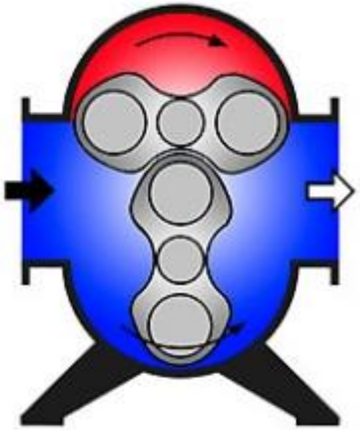
- Pressure
  - fans
  - blowers
  - compressors
- Vacuum
  - vacuum pump
  - ejector

Fans

- Characteristics
  - Transport of large quantities of gases at low pressure (0.1 to 0.11 MPa)
- **radial (beam) fan**
- **axial fan**

Blowers

- **Characteristics**
  - transport of gases at medium pressure (from 0.11 to 0.3 MPa).
- **Roots blower**
- **Sliding vane blower**



Compressors

- Characteristics
  - machines to transport and compress gases that develop pressure 0.3 - 100 MPa.
  - Compression is accompanied by significant temperature increase, therefore compressors must be cooled
- **Reciprocating Compressors**
- **Rotary vane turbo compressors**

Transport liquids by pumps

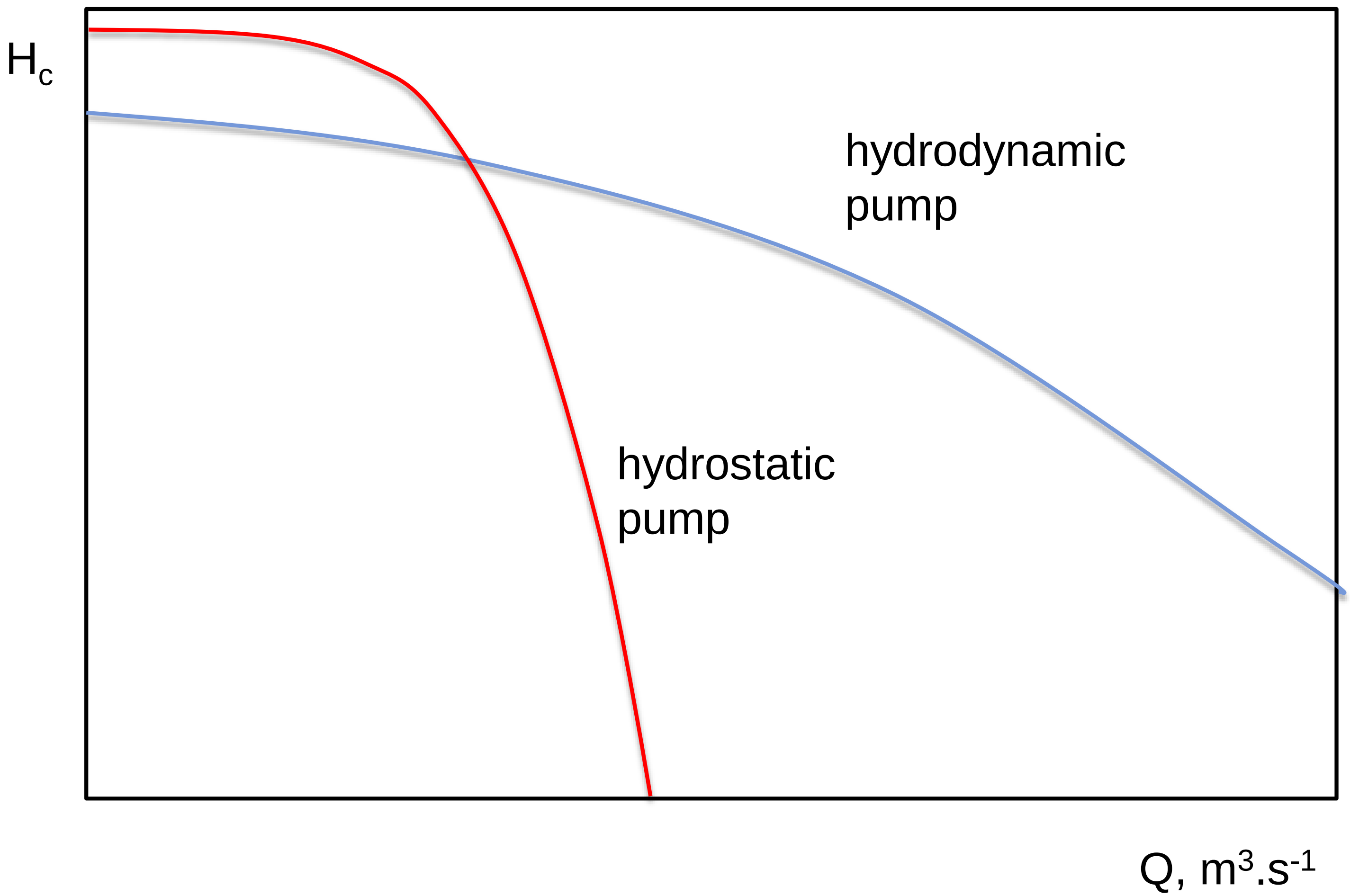
» Bernoulli's equation

$$W_A + \frac{1}{2}u_{A,stř}^2 + \frac{P_A}{\rho} + z_A g = \frac{1}{2}u_{B,stř}^2 + \frac{P_B}{\rho} + z_B g + E_{dis}$$

$$H_C = \frac{W_A}{g} = \frac{u_B^2 - u_A^2}{2g} + \frac{P_B - P_A}{\rho g} + z_B - z_A + \frac{E_{dis}}{g}$$

- » H_C … piping characteristics
  - » Required pump height

Pump characteristics



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Engineering in Chemical and Pharmaceutical Processes

Particulate solid - fluid interaction

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Flow in porous media

- Porous Media
  - porous solids
  - membranes
  - layers of particulate solids
- Important to describe
  - filtration processes
  - fluidized-bed processes
  - operations on dispersions

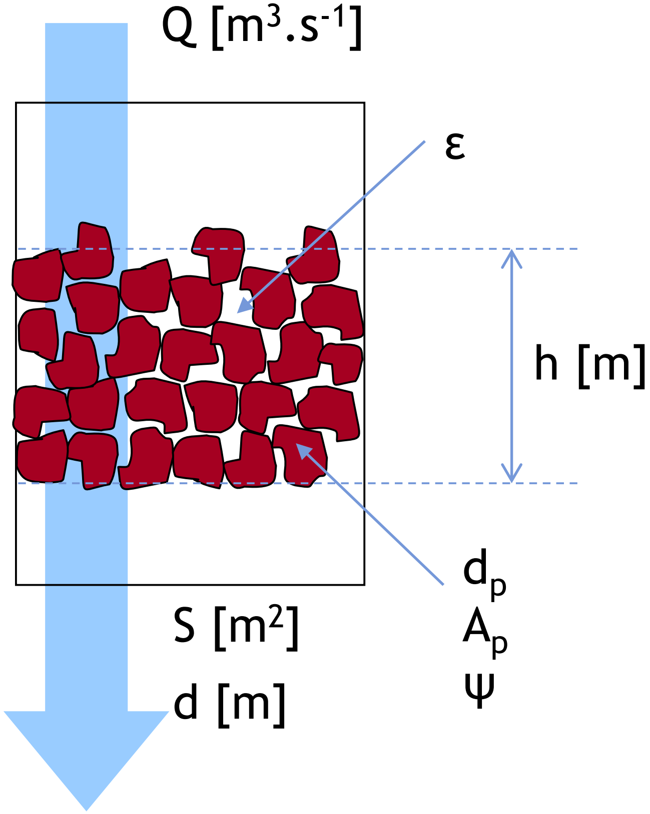
Flow through non-circular cross-section

- Equivalent hydraulic diameter

$$d_{ekv} = \frac{4S}{O}$$

  - S ... cross section of flow channel
  - O ... internal wetted perimeter of the cross-section
- Usage
  - non-circular pipes
  - flow through porous media

Variables to describe the flow in the layer



- ## Flow velocity
  - superficial, u [m.s^{-1}]

$$u = \frac{Q}{S}$$

  - mean in pores, u_f [m.s^{-1}]

$$u_f = \frac{Q}{S\varepsilon} = \frac{u}{\varepsilon}$$

- ## Density of surface *a*

$$a = \frac{A}{V}$$

Density of surface

- Layer of spherical particles

$$a = \frac{A}{V} = \frac{A(1-\varepsilon)}{V_s} = \frac{nA_p(1-\varepsilon)}{nV_p} = \frac{6(1-\varepsilon)}{d_p}$$

- Layer of generic particles

$$a = \frac{A_p(1-\varepsilon)}{V_p} = \frac{A_{k,ekv}(1-\varepsilon)}{\psi V_{k,ekv}} = \frac{6(1-\varepsilon)}{\psi d_{k,ekv}}$$

Model of flow in porous media

- Approximating the medium by uniform parallel channels of
  - identical porosity
  - identical density of surface

$$a = \frac{A}{V} = \frac{A\varepsilon}{V_k} = \frac{nO_k h\varepsilon}{nS_k h} = \frac{4\varepsilon}{d_{ekv}}$$

- Dissipated energy and Re

$$E_{dis} = f\frac{l}{d_{ekv}}\frac{u_f^2}{2} = f\frac{al}{4\varepsilon}\frac{u_f^2}{2}$$

$$\mathrm{Re} = \frac{\rho u_f d_{ekv}}{\eta} = \frac{\rho u_f 4\varepsilon}{\eta a}$$

Calculation of the friction coefficient

- **Ergun equation**, empirical coefficients

$$f = \frac{K}{\mathrm{Re}} + B \qquad f = \frac{133}{\mathrm{Re}} + 1{,}75$$

- Laminar region, spherical particles

$$f = \frac{K}{\mathrm{Re}}$$

$$\frac{9K}{8} \approx 150$$

  - basis for describing the filtration

$$E_{dis} = \frac{3}{4}\frac{K}{\mathrm{Re}}\frac{h}{d_p}\frac{1-\varepsilon}{\varepsilon^3}u^2 = \boxed{\frac{9K}{8}\frac{\eta}{\rho}\frac{h}{d_p^2}\frac{(1-\varepsilon)^2}{\varepsilon^3}u}$$

Application of porous media flow

- Flux through a layer of spheres + Ergun equation

$$E_{dis} = 150 \frac{\eta}{\rho} \frac{h}{d_p^2} \frac{(1-\varepsilon)^2}{\varepsilon^3} u$$

- Bernouli equation
  - Δh ~ 0; Δu ~ 0

- Result: Blake-Kozeny equation

$$\rho E_{dis} = \Delta p$$

$$\Delta p = 150 \eta \frac{h}{d_p^2} \frac{(1-\varepsilon)^2}{\varepsilon^3} u$$

Application of porous media flow

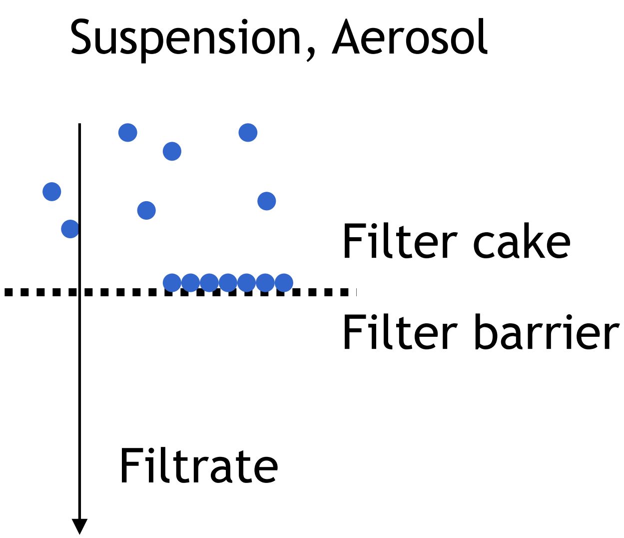
» Flow through porous layer is affected by

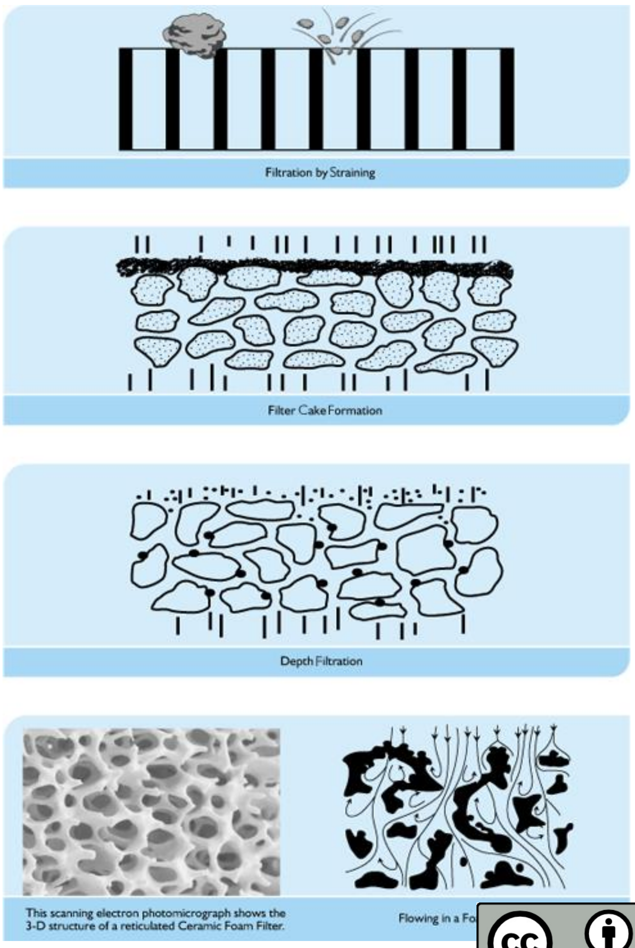
  » pressure
  » viscosity
  » filter surface
  » thickness of the filter
  » The permeability coefficient ... K

$$Q = uA = \frac{\Delta p A}{\eta h} \frac{d_p^2 \varepsilon^3}{150(1-\varepsilon)^2} = \frac{\Delta p A}{\eta h} K$$

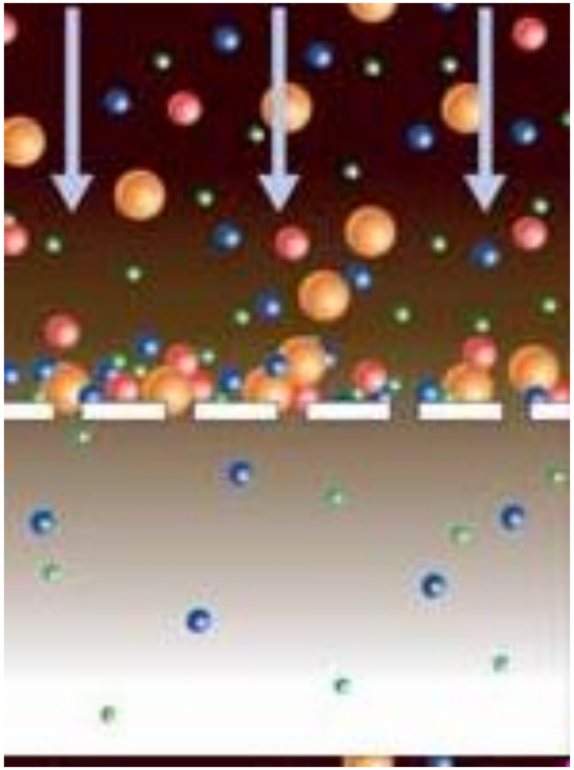
The principle of filtration

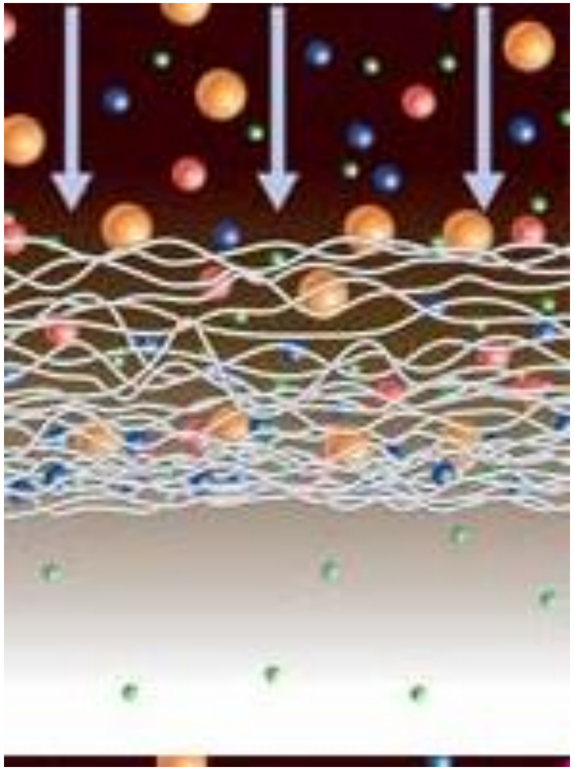
- Separating solids from the liquid on the porous filter barrier





Surface vs. depth filtration



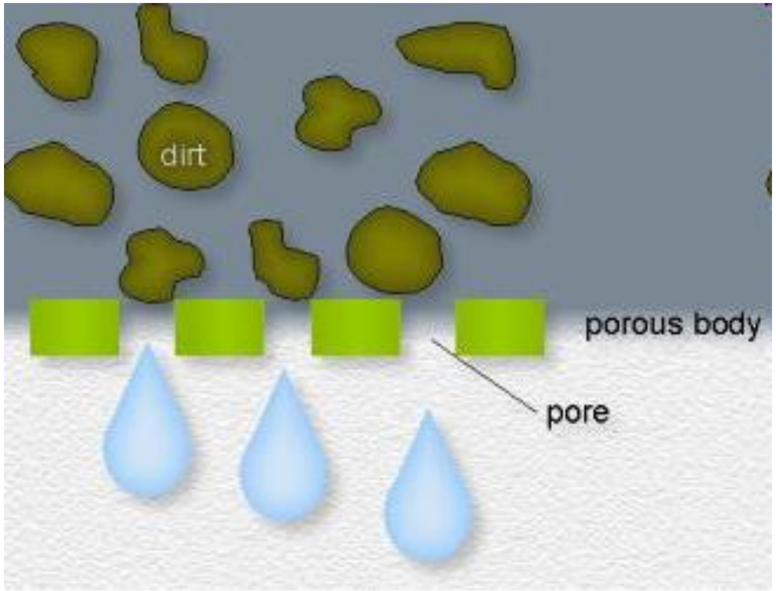


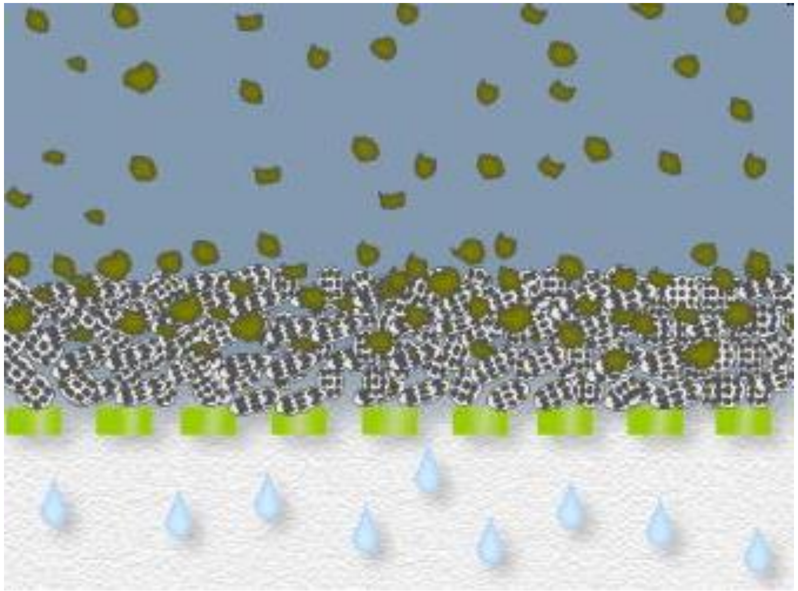
Types of filters

- Absolute
  - Thin filter barrier with a pore size smaller than the particle to be captured
  - - cake is formed during the filtration
- Relative (depth)
  - captured particles may be much smaller than the pore size
  - capture efficiency depends on the thickness of the filter layer
  - capture takes place by action of surface roughness, surface-particle forces, electrostatic forces

Surface (cake) filtration

» The filter cake may substitute the filtration barrier





Filter barrier

- Layers of granular materials
- Layers of fibrous material
- Paper Materials
- Compact porous materials
- Fabrics
- Perforated plate, sieve
- Macroporous membranes

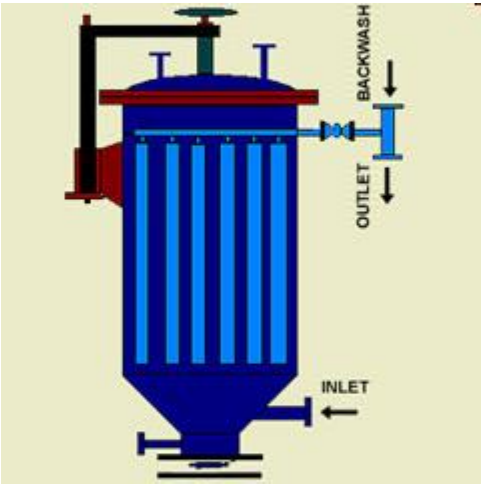
Eligibility criteria for filters

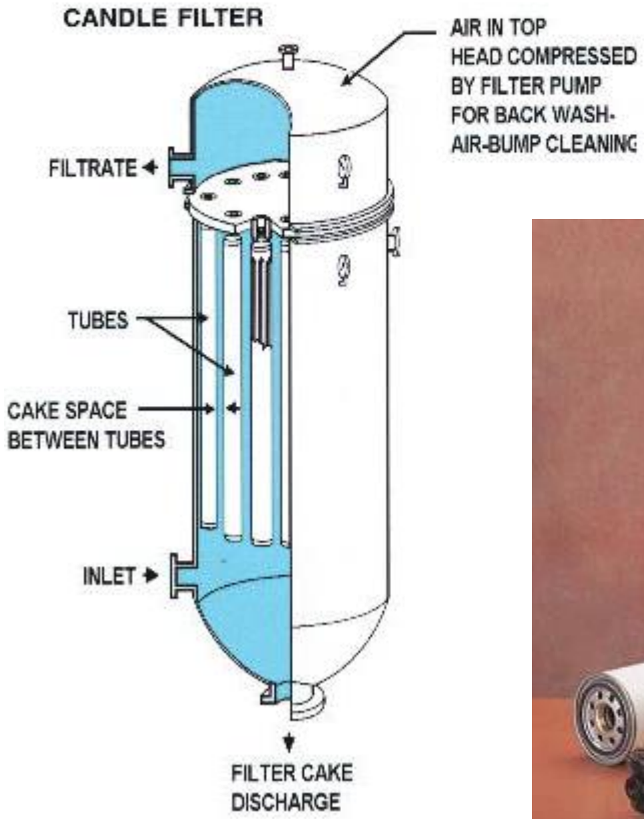
» Filtration speed
» Filtration efficiency
» Chemical stability of the filter
» The affinity to the filtered liquid
» Adsorption of filtered components on the filter surface

Nutsche filter

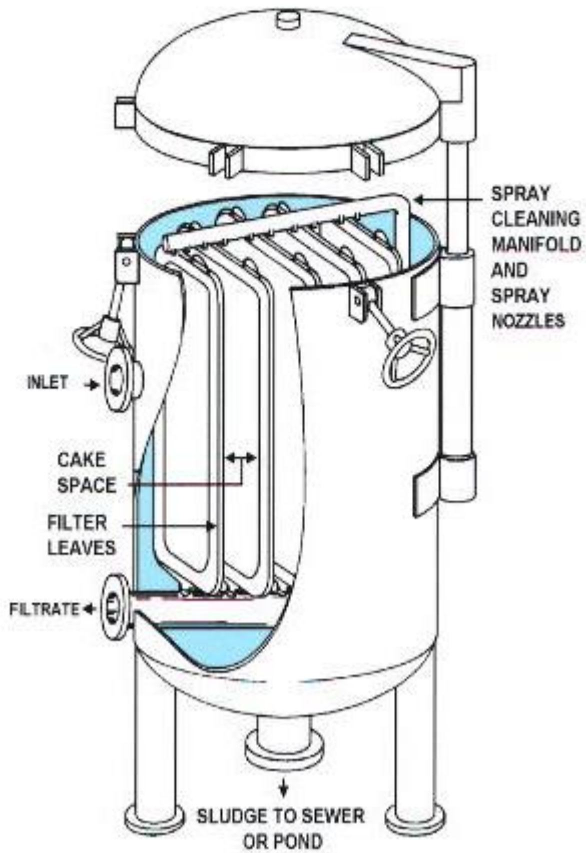
- Simple pressure or vacuum filters
  - e.g. for the separation of crystals from mother liquor

Candle filters

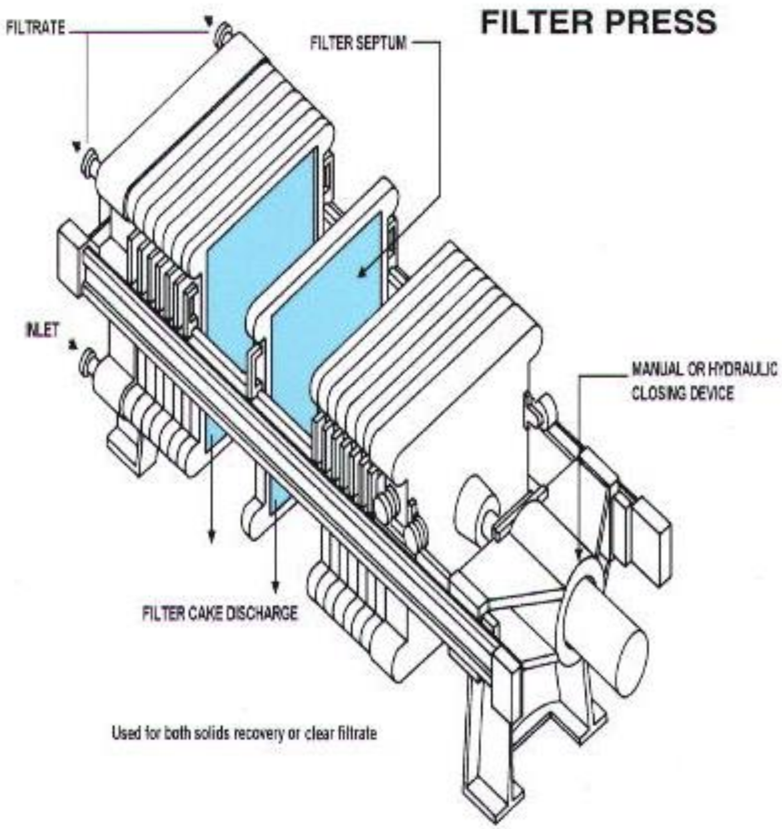




Leaf filters



Filter press



Filtration in pharmaceutics

- Clarification (clearing filtration)
  - the desired product is the filtrate
  - solids are very few, small
  - special case = sterile filtration
    - must capture all microorganisms
    - 0.2 – 0.45 μm
- Cake filtration
  - filter cake is the desired product
  - solid particles up to 20 %
  - 100% efficiency not necessary

Factors affecting the filtration rate

- Pressure
  - higher pressure difference (pressure / vacuum) accelerates filtration
  - there is a limit given by the strength of the filtration barrier
- Viscosity
  - higher viscosity of liquid slows down the filtration
  - can be influenced by temperature,
- Filter surface area
  - higher surface speeds up the filtration
  - slows down the increase of the filter cake thickness

Factors affecting the filtration rate

- The thickness of the filter / cake
  - slows down the filtration
- The coefficient of permeability
  - function of particle size (pore) and porosity
  - porosity is greatly reduced for particulate solids of wide PSD
  - additives for higher cake porosity
    - flocculation

Retention of particles at depth filtration

- The particles are retained on the pore walls of the filter material
- Contact with the wall is provided by
  - inertia
  - Brownian motion
  - gravity
- Efficiency increases with
  - turbulence
  - decreasing flow

Parameters of the depth filter

- Thickness

$$\frac{dc}{dx} = -Kc$$

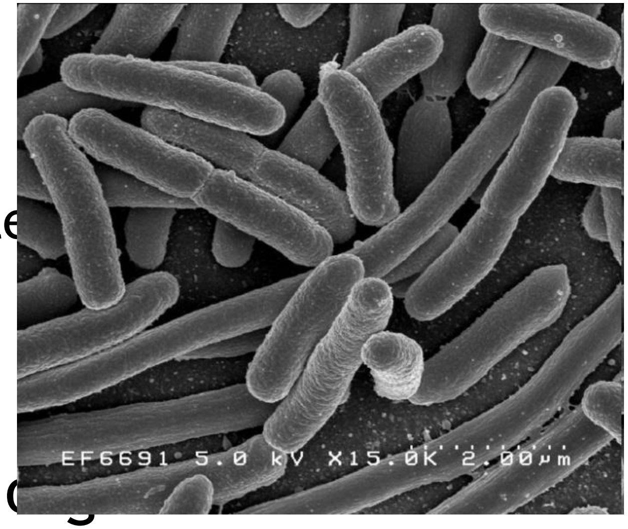
  - c ... solid content
  - x ... thickness of the filter
  - K ... the capture coefficient
- Service life
  - effectiveness of the filter decreases during use, because it reduces the cross-section of the pores and thus increasing the flow velocity

Sterile filtration

- 1960
  - < 0.45 µm regarded as sterile
- 1967 – 1987
  - *Brevundimonas (Pseudomonas) diminuta*
  - organism penetrates 0.45 µm filters
  - 1987: FDA standard 0.2 / 0.22 µm
- Present
  - 0.1 µm - voluntary initiatives by leading manufacturers
  - mycoplasma organisms *(Acholeplasma laidlawii)*

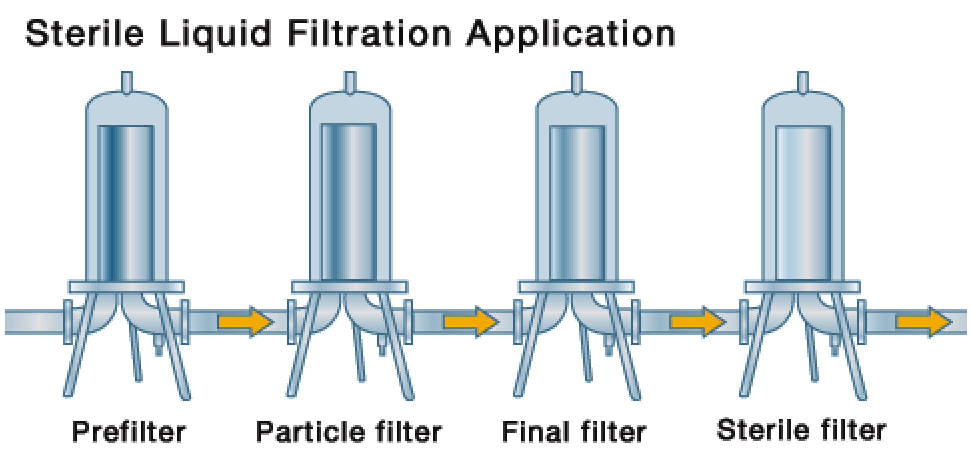
Validation of sterile filtration

- Sterile filter should be validated (porosity of <0.2 μ m is not sufficient for validation)
  - test organism *Brevundimonas diminuta*
    - verify passage through 0.4 μm filte
  - filter loading > 10^{7} cfu.cm^{-2}
  - prove the filtrate sterility
  - optional extra tests with other o

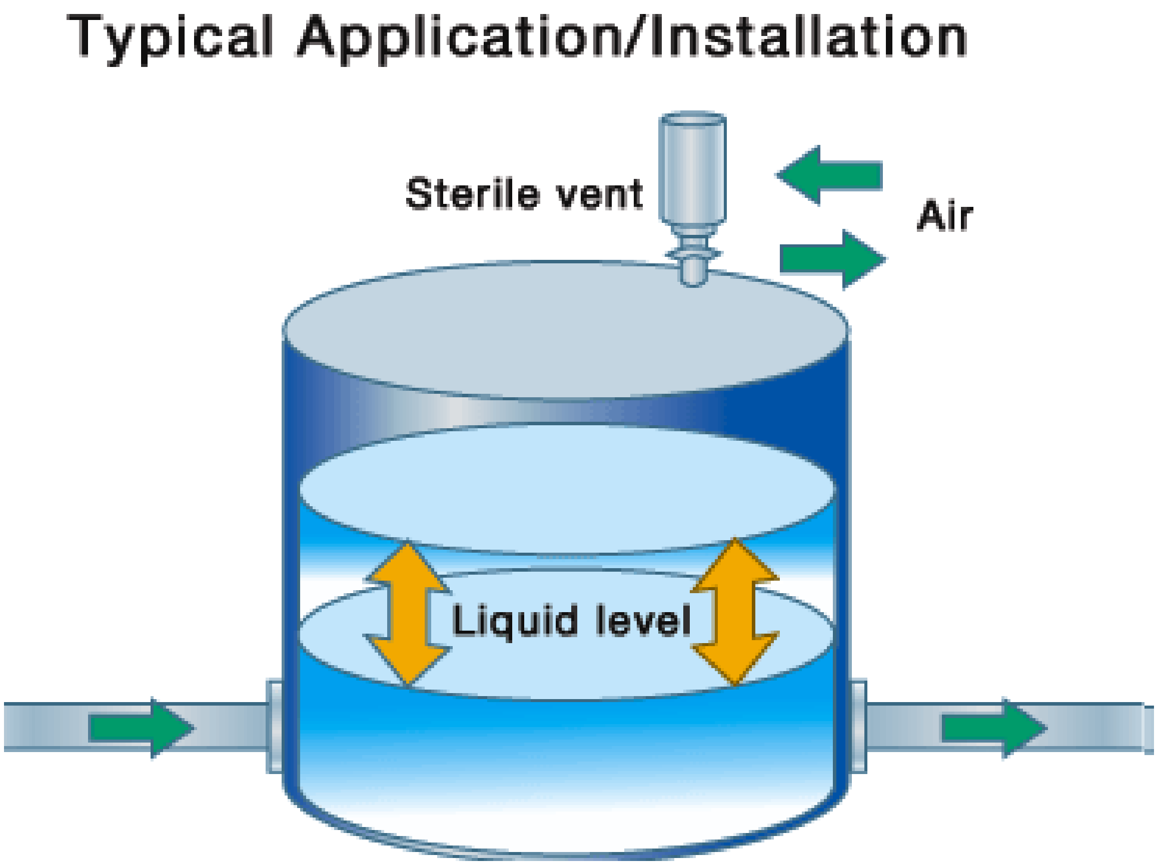


Process order for sterile filtration

- Sterile filter is prone to clogging by large number of particles
- Filtration is carried out in stages



Sterile storage of liquids



HEPA filters

- High Efficiency Particulate Air filter
  - capture dust particles and microorganisms
  - very clean rooms, fermenters
  - Efficiency:
    - > 99.97% particle size of 0.3 μm
    - larger or smaller particles are captured more easily
  - collection efficiency decreases in wetted filter (dew point warning)
    - intensity diffuse movement in liquids is much lower than in gases

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Engineering in Chemical and Pharmaceutical Processes

Applied reaction kinetics

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- The lecture series is based on recommended books, from which some of the materials are reproduced

  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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Chemical reactions and reactors

- Number of phases
  - homogeneous
  - heterogeneous (multiphase)
- Chemical reaction
  - non-catalytic
  - catalytic
  - bioreactors (fermenters)
- Character of the flow
  - ideally mixed
  - plug flow
  - imperfect mixing

Chemical reactions and reactors

- Heat Exchange
  - without exchange of heat (adiabatic)
  - with heating
  - with cooling
  - isothermal (a special case of a reactor with heating or cooling)

Micro-kinetics and makrokinetics

- Micro-kinetic features
  - the same for all devices
  - related to the behaviour of small particles - molecules
  - studied by physical chemistry
  - such as diffusion coefficient, rate constant
- Macro-kinetic features
  - dependent on the specific equipment
  - related to the system as a whole (reactor size)
  - studied by chemical engineering
  - for example, the volume of the reactor, the heat transfer coefficient

Rate of formation of reaction components

- The number of moles of component per unit volume formed per unit time

$$r_A \left[mol_A m^{-3} s^{-1}\right]$$

- Directly measurable variable
- + component amount increasing
- - component amount decreasing

The reaction rate

- Definition stoichiometric equation

$$\Delta H_r + \nu_A A + \nu_B B \longrightarrow \nu_C C + \nu_D D$$

  - stoichiometric equation can be any multiple of the numbers in reaction scheme

- The reaction rate

$$r = \frac{r_A}{-\nu_A} = \frac{r_B}{-\nu_B} = \frac{r_C}{\nu_C} = \frac{r_D}{\nu_D}$$

  - value of the reaction rate depends on the stoichiometric equation

Rate equation

- A simple irreversible reaction

$$r = f_T(T) f_c(c_i, c_{kat}, \ldots)$$

- Ideal behaviour

$$r = k \prod_{reactants} c_i^{molecularity}$$

$$A \longrightarrow B \qquad r = kc_A$$

$$2A \longrightarrow B \qquad r = kc_A^2$$

$$A + C \longrightarrow B \qquad r = kc_A c_C$$

Empirical rate equation

» Real system

$$A \longrightarrow B \qquad r = k c_A^a$$

$$A + C \longrightarrow B \qquad r = k c_A^a c_C^c$$

- reaction order
  - expresses non-ideality of reaction rate sensitivity to concentration
  - in ideal behaviour r.o. is identical with the molecularity
  - may be fractional
  - must be determined experimentally
- it is also possible to use other functions than the power law
  - use in specialized areas

The dependence of the rate constant on temperature

» Arrhenius equation

$$k = k_0 \exp \frac{E(T - T_0)}{RTT_0}$$

$$k = k_\infty \exp \frac{-E}{RT} = A \exp \frac{-E}{RT}$$

Extent of reaction

» the number [moles] of reaction turnovers

$$\xi = \frac{n_i - n_{i0}}{\nu_i}$$

» Component i - any of the reactants

Conversion

- The proportion of reacted starting material

$$X = \frac{n_{A0} - n_A}{n_{A0}} = -\frac{\nu_A}{n_{A0}}\xi$$

- Key component A
  - substance present in the smallest stoichiometric amount

Conversion in system of more reactions

- A key component is the starting material from which all products originate
- The total conversion of the substance indicates the conversion to all products
- Partial conversion indicate the proportion of substance converted into individual products

Selectivity and yield

- The main product × by-products
- Yield = x_i / x
  - proportion of transformed key components, which transformed into the product i
  - integral value
- Selectivity = r_H / r_V
  - instantaneous rate ratio of the rate of the main reaction to side reactions

Reversible reaction

- The reaction that takes place in both directions simultaneously
- forward and reverse reaction rates change during the reaction progress
- Leads to equilibrium

$$A \underset{\overleftarrow{r}}{\overset{\overrightarrow{r}}{\rightleftarrows}} B$$

$$\overrightarrow{r} = \overrightarrow{k} \prod_{edukty} c_i^{\,n_i}$$

$$r = \overrightarrow{r} - \overleftarrow{r}$$

$$\overleftarrow{r} = \overleftarrow{k} \prod_{produkty} c_i^{\,n_i} = \frac{\overrightarrow{k}}{K} \prod_{produkty} c_i^{\,n_i}$$

Temperature and reaction rate

$$\overrightarrow{k} = \overrightarrow{k}_0 \exp\left(\frac{\overrightarrow{E}(T-T_0)}{RTT_0}\right) \qquad \overleftarrow{k} = \overleftarrow{k}_0 \exp\left(\frac{\overleftarrow{E}(T-T_0)}{RTT_0}\right)$$

$$\frac{\overrightarrow{k}}{\overleftarrow{k}} = \frac{\overrightarrow{k}_0}{\overleftarrow{k}_0}\exp\left(\frac{(\overrightarrow{E}-\overleftarrow{E})(T-T_0)}{RTT_0}\right) = \frac{\overrightarrow{k}_0}{\overleftarrow{k}_0}\exp\left(\frac{\Delta H_r (T-T_0)}{RTT_0}\right)$$

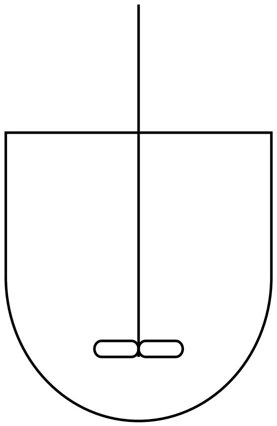
- Exothermic reaction
  - Increasing temperature favours the backward reaction
- Endothermic reaction
  - Increasing temperature favours the forward reaction

State of the highest reaction rate

$$r = kc_A^0\left[(1-x) - \frac{x}{K}\right] = k_0 c_A^0 \exp\left(\frac{E(T-T_0)}{RTT_0}\right)\left[(1-x) - \frac{x}{K_0}\exp\left(\frac{-\Delta H_r(T-T_0)}{RTT_0}\right)\right]$$

- Maximum rate $\left(\frac{\partial r}{\partial T}\right)_x = 0$
- For reversible exothermic reaction, there is such a temperature at which the overall reaction rate is highest. The value changes with conversion
  - Trajectory of maximum reaction rate

Batch reactor



- The batch is homogeneous
- The composition depends on the time
  - dynamic system
  - balance in the form of differential equations
- Basic breakdown by mode of heat transfer
  - including heat exchange
    - special case (isothermal)
  - adiabatic

Mass balance of *i*-component

- Balance volume: entire reactor
- Balancing time: dt

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
+ 0	+ $\nu_i r V dt$	- 0	- dn_i	= 0

- In the reaction system, of *j* reactions

$$\frac{dn_i}{dt} = V \sum_j \nu_{ij} r_j$$

$$\frac{dc_i}{dt} = \sum_j \nu_{ij} r_j$$

$$-c_A^0 \frac{dx_i}{dt} = \sum_j \nu_{ij} r_j$$

... Conversion of *key* component A

Energy balance of the reactor

- Balance volume: entire reactor
- Balancing time: dt

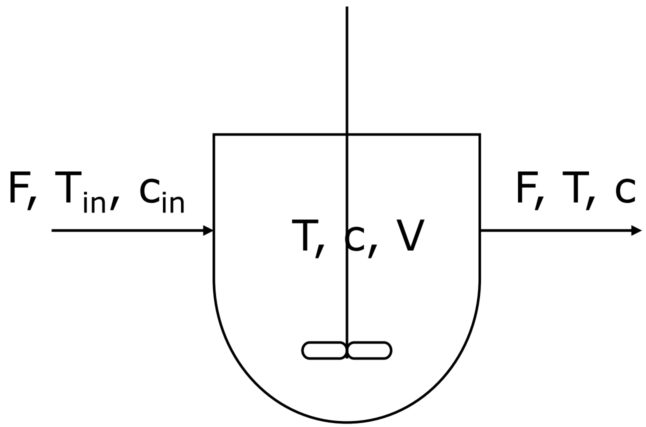
+ INPUT	**+ FORMATION**	**- OUTPUT**	**- ACCUMULATION**	**= 0**
+ $q_o A\mathrm{d}t$	**+ $(-\Delta H_r) r V \mathrm{d}t$**	**- $q_c A\mathrm{d}t$**	**- $c_p \rho V \mathrm{d}T$**	**= 0**

$$V\rho c_\mathrm{p}\frac{\mathrm{d}T}{\mathrm{d}t} = V(-\Delta H_\mathrm{r})r + (q_\mathrm{o} - q_\mathrm{c})A$$

$$qA = \dot{Q} = KA(T - T_c)$$

$$V\rho c_\mathrm{p}\frac{\mathrm{d}T}{\mathrm{d}t} = V\sum_j (-\Delta H_{\mathrm{r},j})r_j + (q_\mathrm{o} - q_\mathrm{c})A$$

Continuous stirred tank reactor (CSTR)



- no differences in the composition or temperature
- Steady state may be achieved
- A steep change in concentration at the feed inlet

Mass balance of *i*-component

- Balance volume: entire reactor
- Balancing time: dt

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
$+ \dot{n}_{in,i}dt$	$+ \nu_i r V dt$	$- \dot{n}_i dt$	$- dn_i$	= 0

$$\frac{dn_i}{dt} = \nu_i r V + \left(\dot{n}_{\text{in},i} - \dot{n}_i\right)$$

$$\frac{dc_i}{dt} = \nu_i r + \frac{F}{V}\left(c_{\text{in},i} - c_i\right) = \nu_i r + \frac{c_{\text{in},i} - c_i}{\bar{\tau}}$$

mean residence time

Mass balance at steady state

- Balance volume: entire reactor
- Balancing time: steady state (balance of flows)

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
$+\ \dot{n}_{\mathrm{in},i}$	$+\ \nu_i r V$	$-\ \dot{n}_i$	$\cancel{-\ dn_i}$	= 0

$$\frac{dc_i}{dt} = 0 = \nu_i r + \frac{c_{\mathrm{in},i} - c_i}{\bar{\tau}}$$

$$\frac{c_i - c_{\mathrm{in},i}}{\bar{\tau}} = \nu_i r(c_i)$$

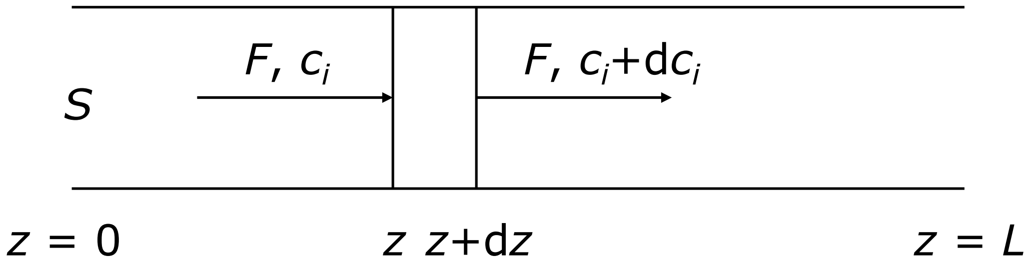
Energy balance of the reactor

- Balance volume: entire reactor
- Balancing time: dt

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
$+ q_o A\mathrm{d}t$ $+ \Sigma(h_{\mathrm{in},i} n_{\mathrm{in},i})$	$+ (-\Delta H_r) r V \mathrm{d}t$	$- q_c A\mathrm{d}t$ $- \Sigma(h_i n_i)$	$- c_p \rho V \mathrm{d}T$	= 0

$$V\rho c_p \frac{\mathrm{d}T}{\mathrm{d}t} = V(-\Delta H_r)r + (q_o - q_c)A + \sum_i h_{\mathrm{in},i} n_{\mathrm{in},i} - \sum_i h_i n_i$$

Plug flow tube reactor (PFTR)



- The composition depends on the longitudinal coordinate of the reactor
- Composition at a given location is often dependent on the time
  - steady state in time
  - balance in the form of differential equations
- Frequently used with intensive heat exchange

Mass balance of *i*-component

- Balance volume: $\mathrm{d}V = S\mathrm{d}z$
- Balancing time: $\mathrm{d}t$

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
$+\ \dot{n}_i(z)\mathrm{d}t$	$+\ \nu_i r \mathrm{d}V \mathrm{d}t$	$-\ \dot{n}_i(z+\mathrm{d}z)\mathrm{d}t$	$-\ (\ n_i(t+\mathrm{d}t) - n_i(t)\ )$	= 0

$$\frac{c_i(t+\mathrm{d}t)-c_i(t)}{\mathrm{d}t} = -\frac{F}{S}\frac{c_i(z+\mathrm{d}z)-c_i(z)}{\mathrm{d}z} + \nu_i r$$

$$\frac{\partial c_i}{\partial t} = -\frac{F}{S}\frac{\partial c_i}{\partial z} + \nu_i r$$

Mass balance at steady state

- Balance volume: dV = Sdz
- Balancing time: steady state (balance of flows)

+ INPUT	**+ FORMATION**	**- OUTPUT**	**- ACCUMULATION**	**= 0**
$+\ \dot{n}_i(z)$	$+\ \nu_i r dV$	$-\ \dot{n}_i(z+dz)$	$\cancel{-\ (n_i(t+dt) - n_i(t))}$	**= 0**

$$0 = \frac{\partial c_i}{\partial t} = -\frac{F}{S}\frac{\partial c_i}{\partial z} + \nu_i r$$

$$\frac{dc_i}{dz} = \frac{S}{F}\nu_i r$$

Energy balance of the reactor

- Balance volume: dV = Sdz
- Balancing time: steady state (balance of flows)

+ INPUT	+ FORMATION	- OUTPUT	- ACCUMULATION	= 0
$+ q_o dA$ $+ \Sigma(\ h_i(z)n_i(z)\ )$	$+ (-\Delta H_r) r S dz$	$- q_c dA$ $-\Sigma(h_i(z+dz)$ $n_i(z+dz))$	- 0	= 0

Comparison of basic reactors

- The time needed to reach a specific conversion in different reactors
  (for positive order reaction)
  - time required in a batch reactor and plug flow reactor are equal
  - time required in a CSTR is longer
  - the batch reactor requires operating time (the exchange of batch)

Comparison of basic reactors

for the first-order reaction

- ## Batch reactor

$$\frac{dc_A}{dt} = -kc_A \qquad c_A = c_{A0}e^{-kt}$$

$$c_{A1} = c_{A0}e^{-kt_{vsádky}} \qquad t_{vsádky} = \frac{1}{k}\ln\frac{c_{A0}}{c_{A1}}$$

- ## CSTR
  - steady state

$$kc_{A1} = \frac{c_{A0} - c_{A1}}{\bar{\tau}} \qquad \bar{\tau}_{CSTR} = \frac{c_{A0} - c_{A1}}{kc_{A1}}$$

Comparison of basic reactors

for the first-order reaction

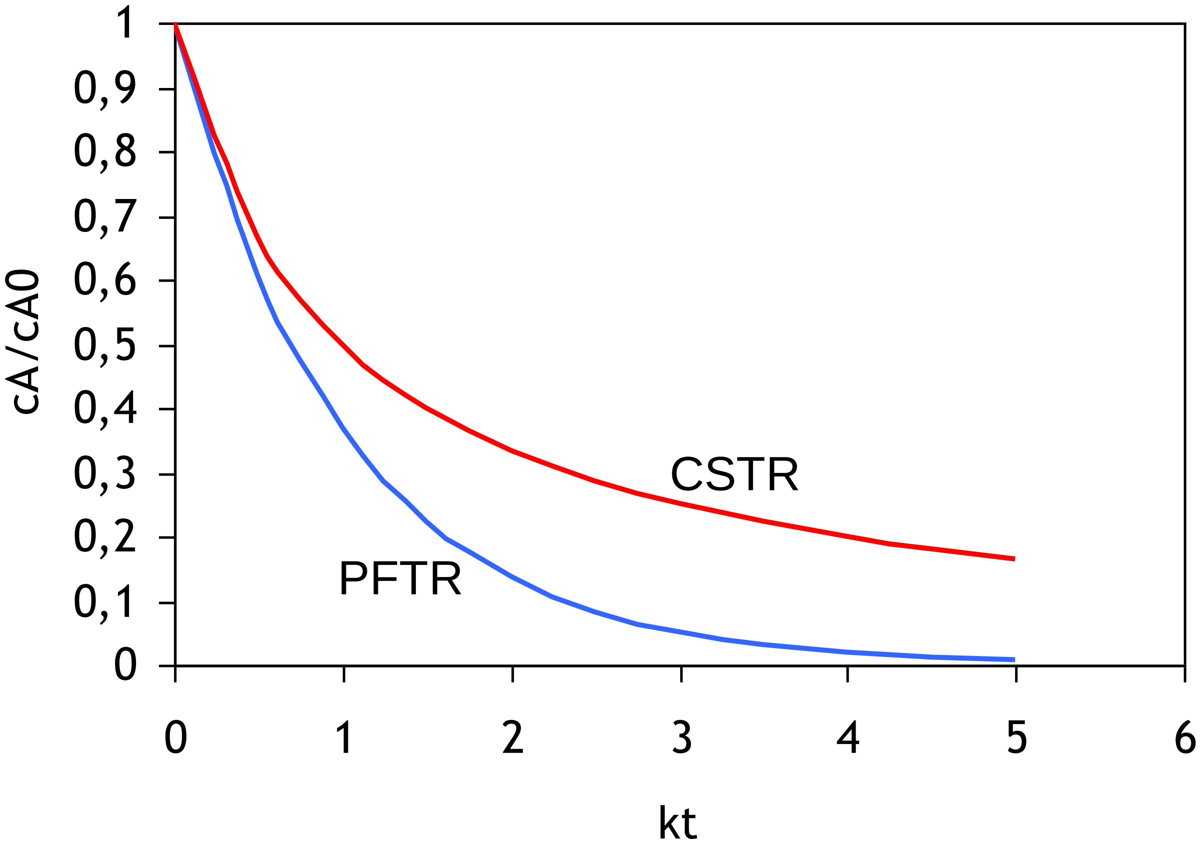
- Tubular reactor with plug flow (PFTR)
  - steady state

$$\frac{\mathrm{d}c_A}{\mathrm{d}z} = -\frac{S}{F}kc_A$$

$$-\int_{c_{A0}}^{c_{A1}} \frac{\mathrm{d}c_A}{kc_A} = \int_0^L \frac{S}{F}\mathrm{d}z \qquad \frac{1}{k}\ln\frac{c_{A0}}{c_{A1}} = \frac{V}{F} = \tau_{PFTR}$$

Conversion in different reactors

at the same residence time, the first-order reaction



Conversion in different reactors

time required, the first-order reaction

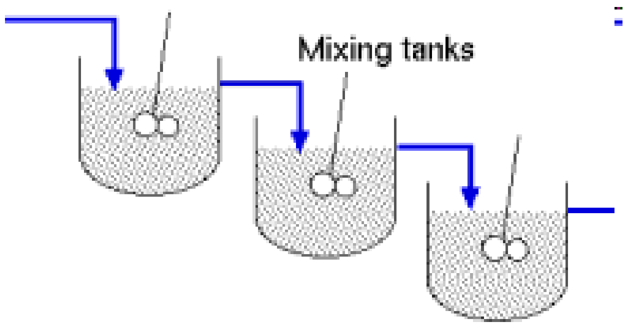
Conversion,%	τ_{CSTR}/ τ_{PFTR}
0	1.0
0.5	1.44
0.9	3.91
0.95	6.34
0.99	21.5
0.999	145

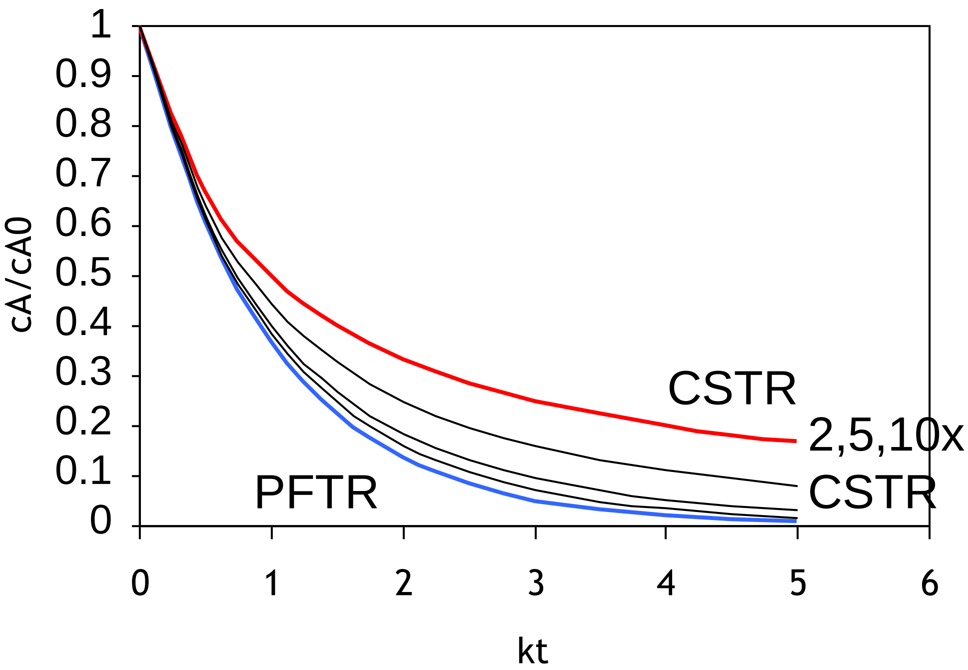
Semibatch reactor

- Usage
  - ideally mixed batch reactor from/to which there are
    - continuously drawn some products
    - continuously fed some starting material
  - small-scale production (lab. autoclaves)
  - fermentors
- Modelling
  - in essence, a CSTR at unsteady state

Cascade of ideal mixers

» The distributing the ideal mixer volume among a "cascade" of smaller mixers increase their efficiency





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Reaction kinetics in biotech systems

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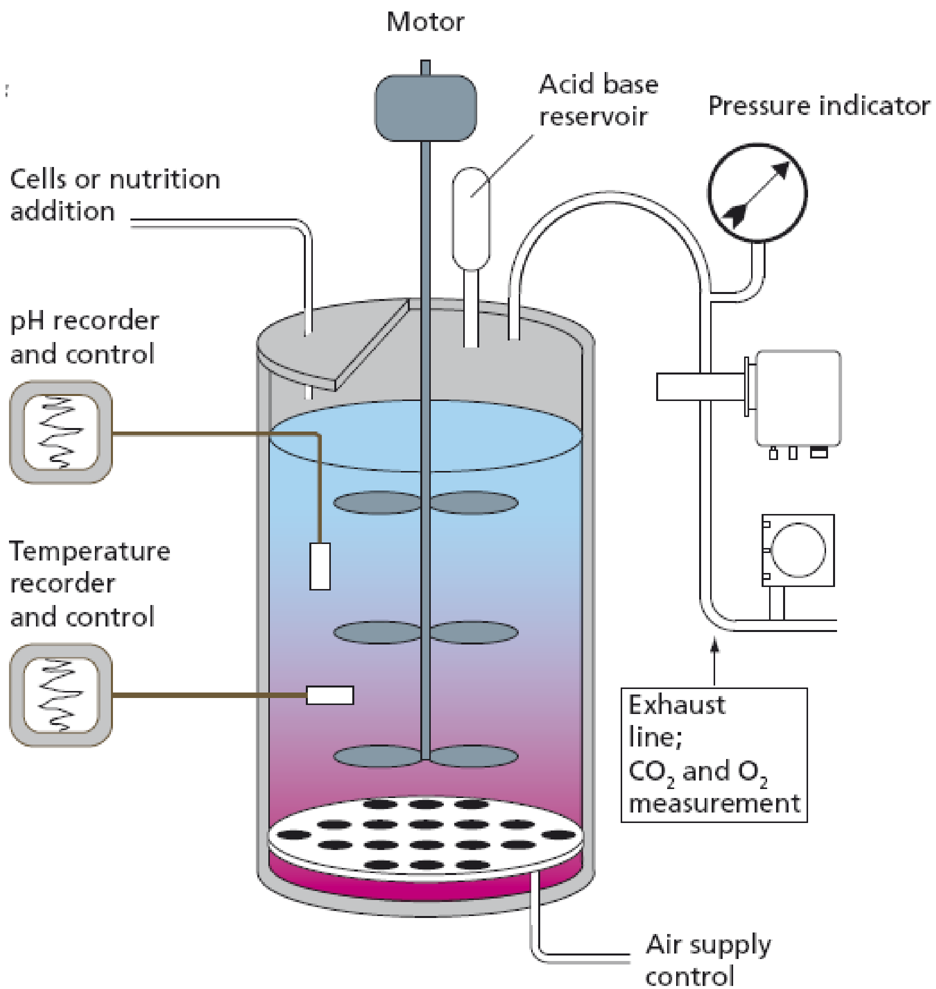
Bioreactors

- Used to transform the chemicals by action of living micro-organisms
- Examples
  - Chemical Industry
    - lactic acid, acetic acid, ethanol,
  - Food industry
    - dairy products
  - Pharmaceutical Industry
    - antibiotics (tetracycline, erythromycin, streptomycin)
    - vaccines
    - insulin

Bioreactor example

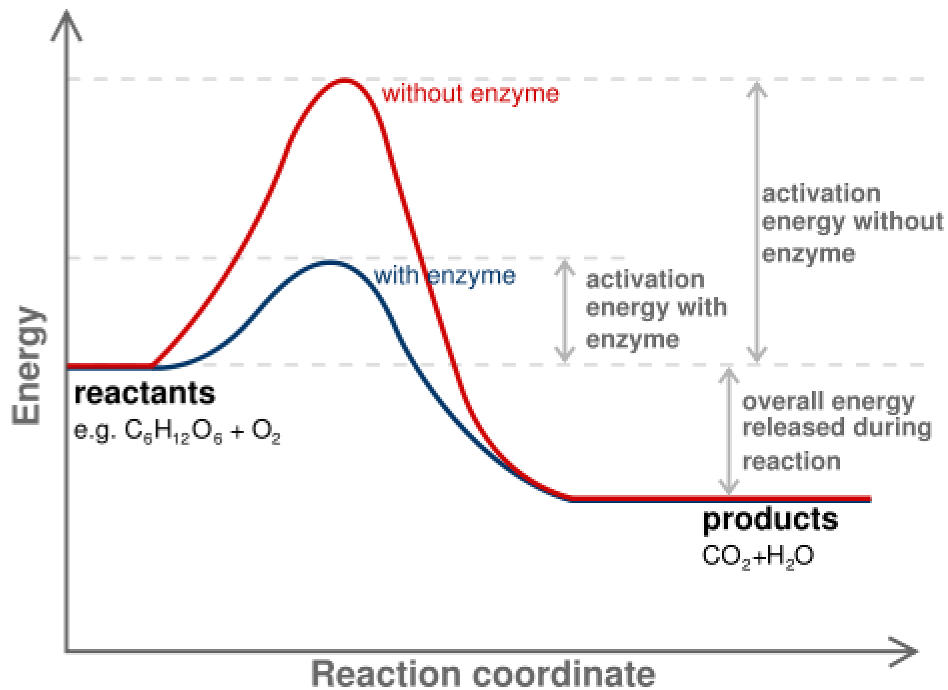


Bio-reaction products

- Their formation is determined by the existence of genetic information in the micro-organism
- Product formation is determined
  - metabolically
  - genetically
- Types of products
  - metabolic
    - produced by living cell to sustain life
  - non-metabolic
    - cell may generate metabolic products instead (growth)

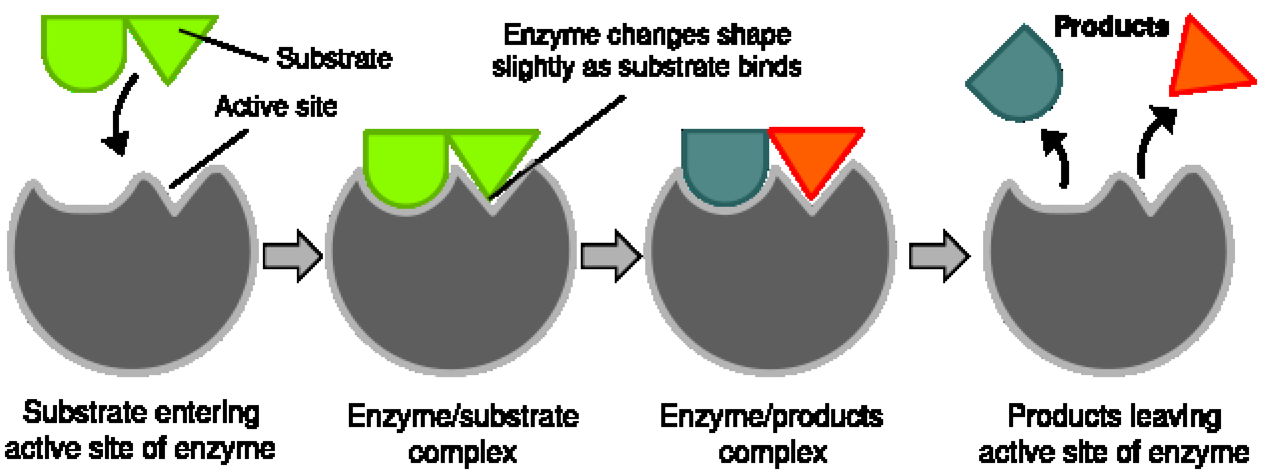
Enzymes

» Most bio-reactions are **catalyzed by** enzymes



The specificity of enzymatic reactions

- Enzymatic reactions are very selective
  - one response, one substrate, one isomer
- The principle of "lock and key"



Kinetics of enzymatic reactions

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \xrightarrow{k_2} E + P$$

- Balance equation:

$$\frac{\mathrm{d}c_\mathrm{P}}{\mathrm{d}t} = k_2 c_\mathrm{ES}$$

$$\frac{\mathrm{d}c_\mathrm{ES}}{\mathrm{d}t} = k_1 c_\mathrm{E} c_\mathrm{S} - k_{-1} c_\mathrm{ES} - k_2 c_\mathrm{ES}$$

$$c_\mathrm{E} = c_\mathrm{E}^0 - c_\mathrm{ES}$$

Kinetics of enzymatic reactions

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

- **Pseudo-stationary state assumption**
  - enzyme-substrate complex is in equilibrium

$$0 = \frac{dc_{ES}}{dt} = k_1 c_E c_S - k_{-1} c_{ES} - k_2 c_{ES}$$

$$c_{ES} = \frac{k_1 c_E c_S}{k_{-1} + k_2}$$

$$c_E = c_E^0 - c_{ES}$$

$$c_{ES} = \frac{k_1 \left(c_E^0 - c_{ES}\right) c_S}{k_{-1} + k_2}$$

$$c_{ES} = \frac{c_E^0 c_S}{\frac{k_{-1} + k_2}{k_1} + c_S}$$

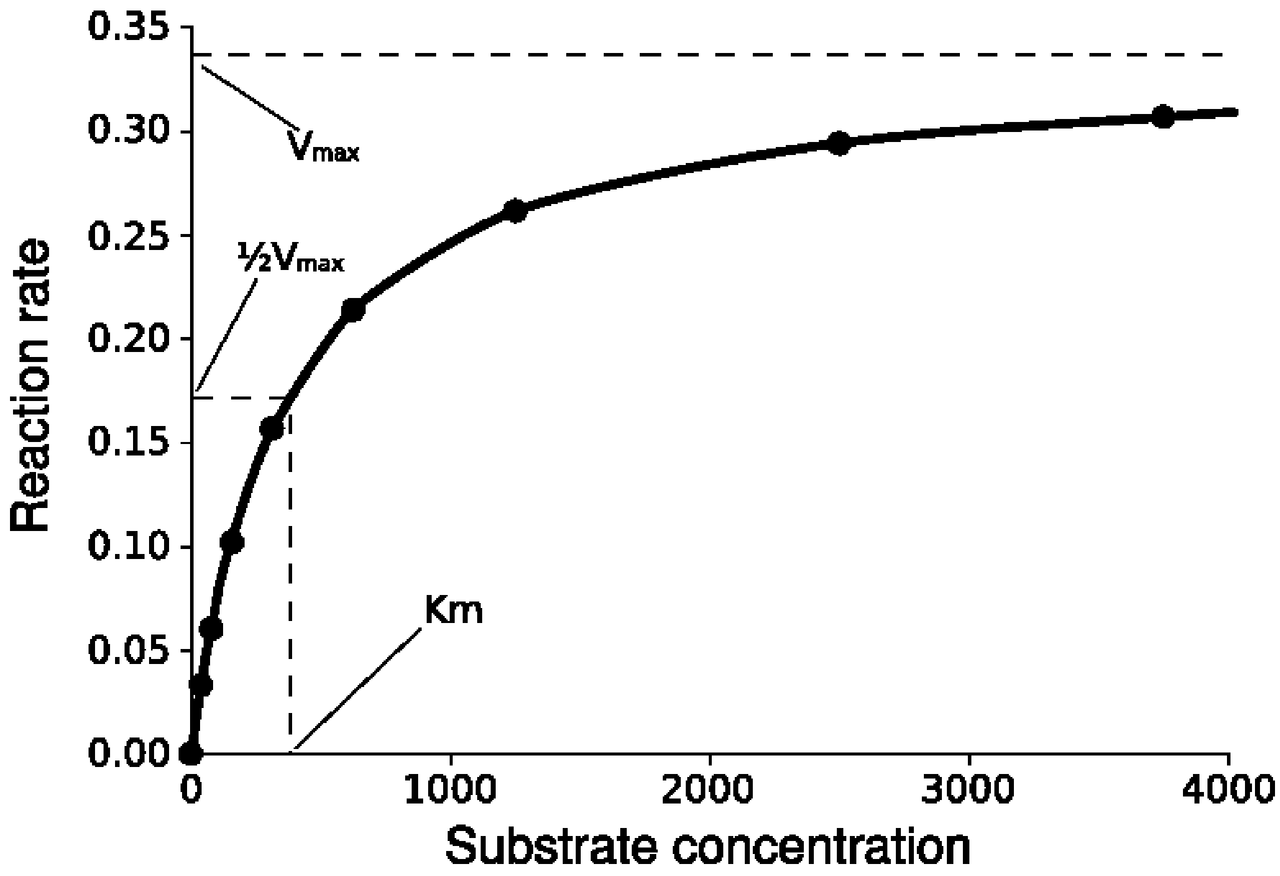
$$\frac{dc_P}{dt} = \frac{k_2 c_E c_S}{\frac{k_{-1} + k_2}{k_1} + c_S}$$

Kinetics of enzymatic reactions

$$\frac{\mathrm{d}c_\mathrm{P}}{\mathrm{d}t} = \frac{k_2 c_\mathrm{E} c_\mathrm{S}}{\frac{k_{-1}+k_2}{k_1}+c_\mathrm{S}} \longrightarrow \frac{\mathrm{d}c_\mathrm{P}}{\mathrm{d}t} = \frac{V_{\max} c_\mathrm{S}}{K_M + c_\mathrm{S}}$$

- Michaelis-Menten equation
  - V_{max} ... maximum reaction rate (for an unlimited amount of substrate)
  - K_M ... the Michaelis constant

Rate of enzymatic reaction

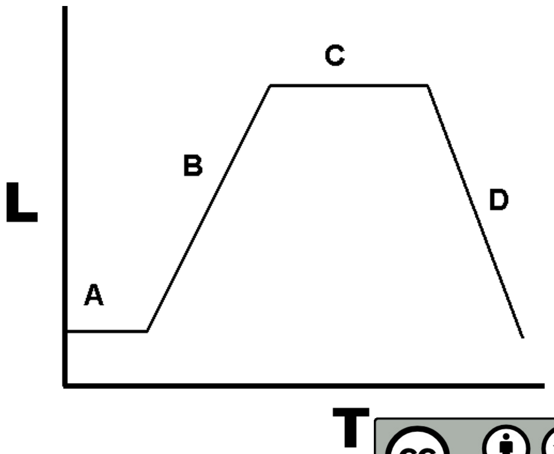


Kinetics of microbial growth

- "Auto-catalytic" reaction
  - Substrates + cells = Products + more cells
  - growth rate is proportional to the number of cells
  - net rate of increase

$$\mu = \frac{1}{c_B}\frac{dc_B}{dt} \qquad \mu = \mu_{hr} - k_d$$

- Growth curve in a batch system
  - A ... lag-phase
  - B ... phase of exp. growth
  - C ... stationary phase
  - D ... phase of extinction



Models of microbial growth

- Exponential models $$\frac{dc_B}{dt} = f(c_B)$$
  - Malthus $$\frac{dc_B}{dt} = \mu c_B$$
  - Ricati $$\frac{dc_B}{dt} = \mu c_B(1-\beta c_B)$$ $$\frac{dc_B}{d\tau} = \mu c_B(1-\beta c_B) + k_{time}\int_0^{\tau} c_B(\tau)d\tau$$
- Models taking into account the availability of substrate
  - Monod

$$\mu = \frac{\mu_{\max} c_s}{K_s + c_s}$$

Evaluation of the bioprocess effectiveness

- Yield coefficients

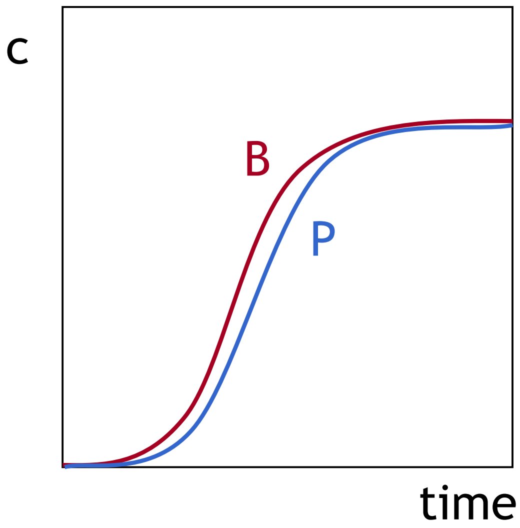
$$Y_{B/S} = -\frac{\Delta c_B}{\Delta c_S} \qquad Y_{B/O_2} = -\frac{\Delta c_B}{\Delta c_{O_2}} \qquad Y_{P/S} = -\frac{\Delta c_P}{\Delta c_S}$$

- Rate of product formation q_p
  - for products associated with growth

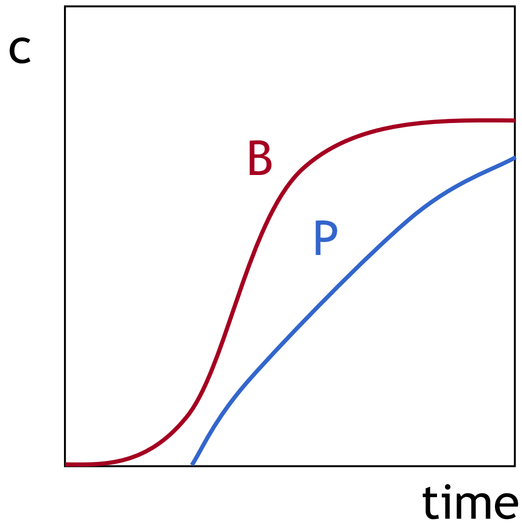
$$q_p = \frac{1}{c_B}\frac{\mathrm{d}c_P}{\mathrm{d}t} = Y_{P/S}\,\mu_{hr.}$$

    - μ_{gr} … gross growth rate
  - for products unrelated to the growth (secondary metabolites) q_p is constant

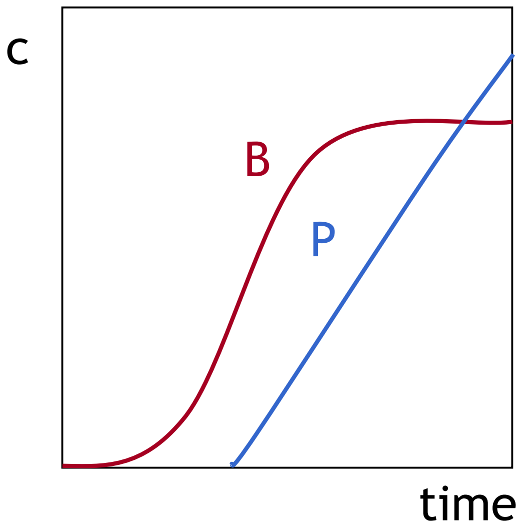
Growth and production profiles



products related to growth

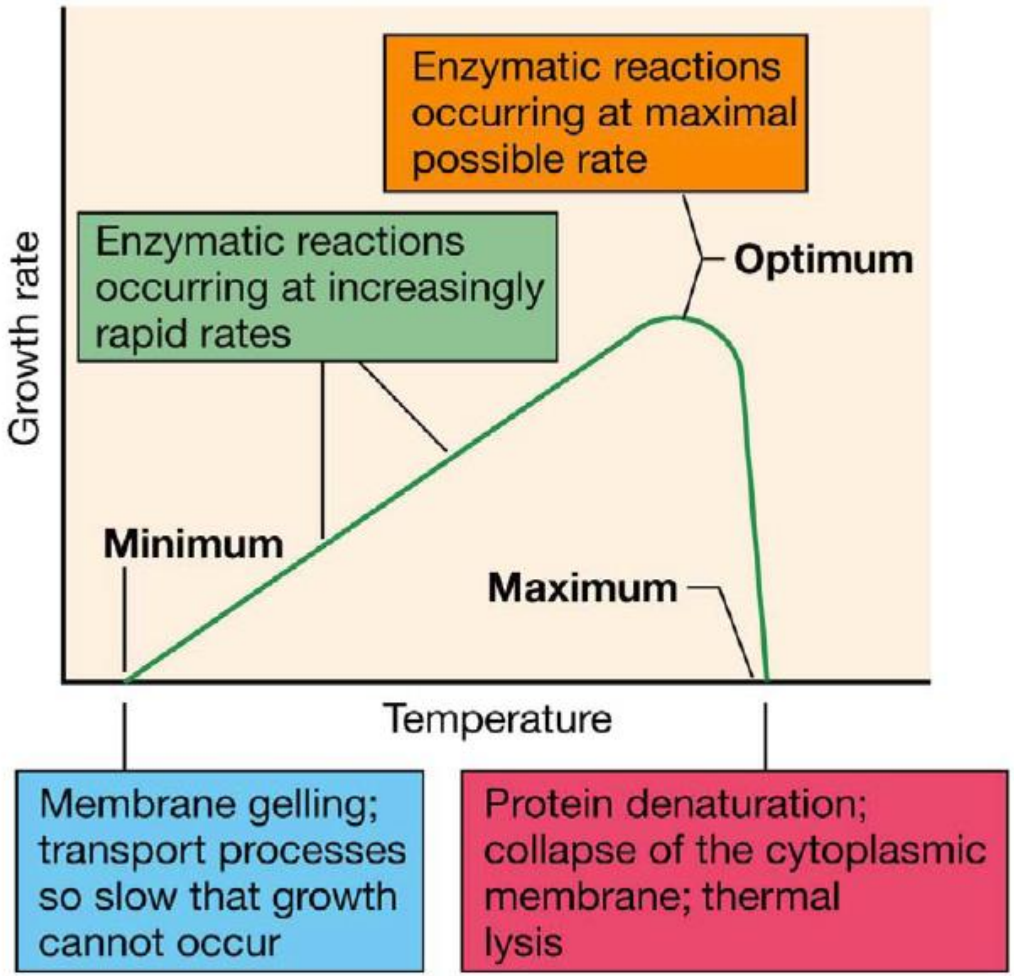


products with combined formation



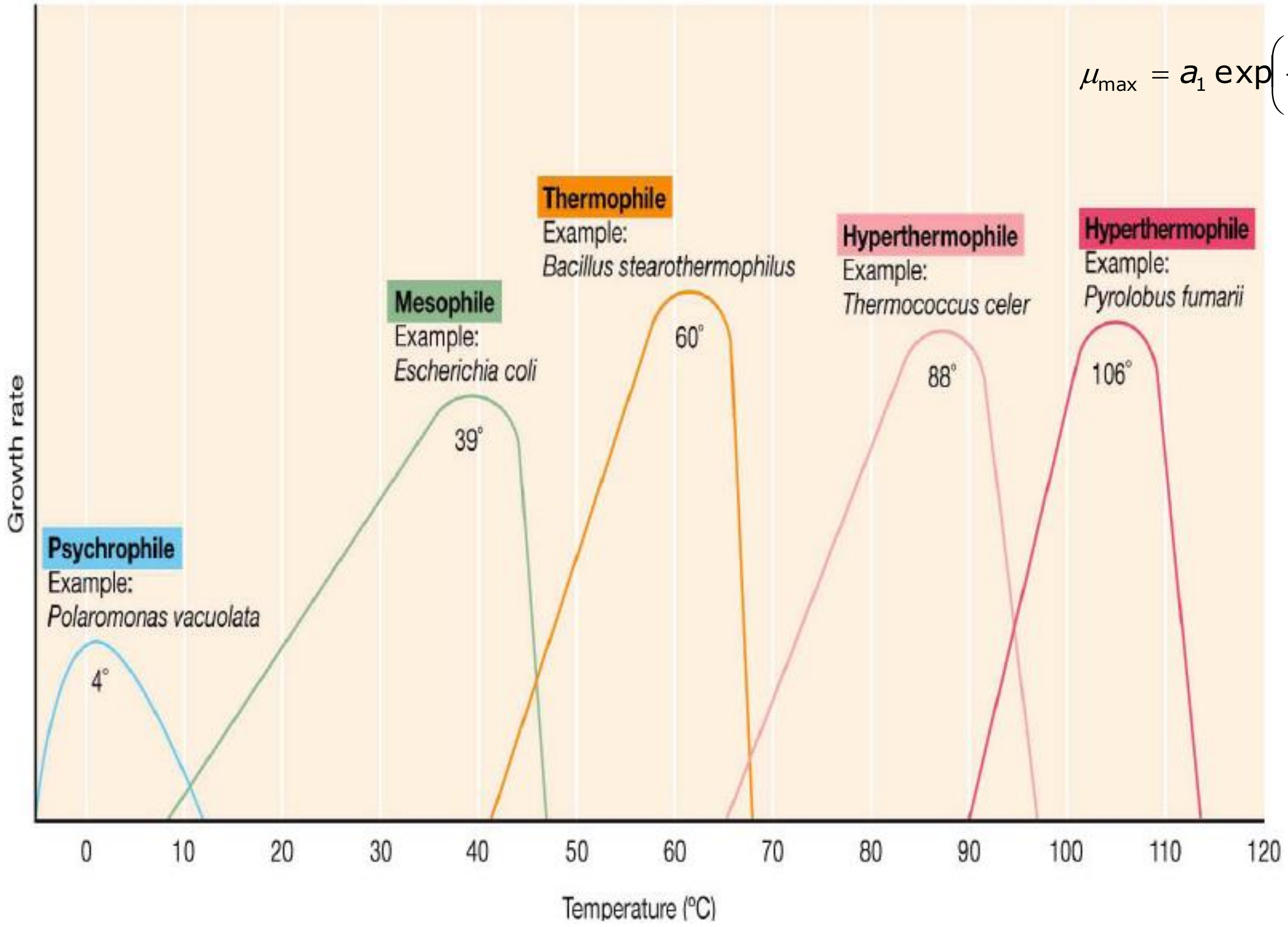
products unrelated to growth

Effect of temperature on the growth of microorganisms



Effect of temperature on the growth of microorganisms

$$\mu_{max} = a_1 \exp\left(-\frac{E_a}{RT}\right) \cdot \frac{1}{1 + K_o \exp\left(-\frac{E_d}{RT}\right)}$$



Effect of temperature

on the growth of microorganisms

- Micro-organisms classification according to the optimum temperature of growth
  - Psychrophiles (T_{opt} < 20 °C)
  - Mesophiles (20 °C < T_{opt} < 50 °C)
  - Thermophiles (T_{opt} > 50 °C)
- Growth rate increases with temperature up to T_{opt} by the Arrhenius equation

Other conditions affecting growth

- pH
  - affects the enzyme activity, including growth
  - optimum pH for growth may be different from the optimal pH for the production of the metabolite
- The concentration of dissolved oxygen
  - critical concentration
    - below this level, the oxygen supply is rate-controlling
    - above the level growth rate is no longer dependent on the rate of oxygen intake

Concentration of dissolved oxygen

- ## Saturation
  - 7 ppm at 100 kPa and 25 °C
  - depends on the pressure
  - decreases with temperature
  - depends on the dissolved substances
- ## Oxygen intake

$$N_{O_2} = k_L a \left(c^*_{O_2} - c_{O_2} \right)$$

  - k_L ... coefficient of mass transfer
  - a ... specific interfacial area ($m^2.m^{-3}$)
  - N_{O2} ... oxygen transfer rate ($g.m^{-3}.s^{-1}$)

Concentration of dissolved oxygen

- Oxygen consumption

$$N_{O_2} = \frac{\mu_{hr}.c_B}{Y_{B/O_2}}$$

- Effect of oxygen on growth

$$r_B = \mu_{\max} \frac{c_S}{K_S + c_S} \cdot \frac{c_{O2}}{K_{O2} + c_{O2}} c_B$$

Other conditions affecting growth

- ## Heat Transfer
  - metabolic processes are generally exothermic
  - heat transfer through wall is generally sufficient except for very large systems
- ## Agitation
  - + Improves mass transfer
  - - Shear stress has a negative effect on the growth of microorganisms

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MINISTRY OF EDUCATION, YOUTH AND SPORTS

Engineering in Chemical and Pharmaceutical Processes

Introduction to process measurement and control

References and study material

- The lecture series is based on recommended books, from which some of the materials are reproduced
  - Rhodes M., Introduction to Particle Technology, Wiley 2008, 0471984833.
  - Fogler H. S.: Elements of Reaction Engineering, Prentice Hall, New Jersey 2000.
  - Levin M.: Pharmaceutical process scale up, Decker, New York 2002.
  - Schultze D.: Powders and Bulk Solids, Springer 2007.

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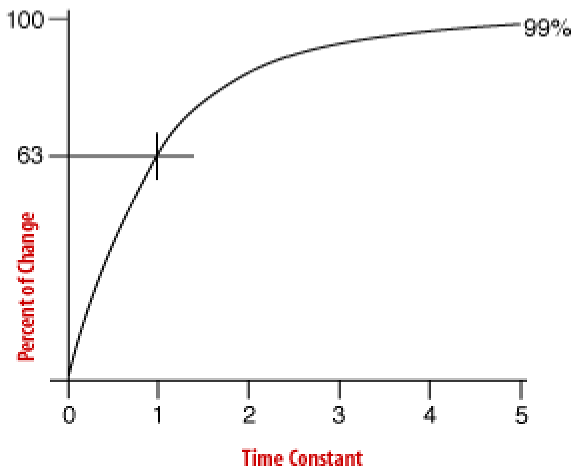
Automated measuring systems

- Sensors
  - thermocouples, pressure indicators, automated balances, conductometers
  - they possess dynamic characteristics
- Analyzers
  - periodical sampling and analysis
  - delay

Dynamic sensor characteristic

$$\frac{dT_s}{dt} = \frac{1}{\tau_{Ts}}\left[T - T_s\right]$$

- time constant
- T … real temperature
- T_s … indicated temperature

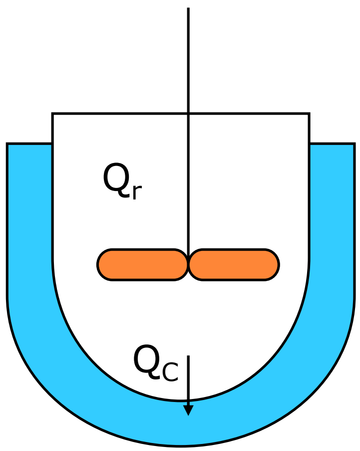


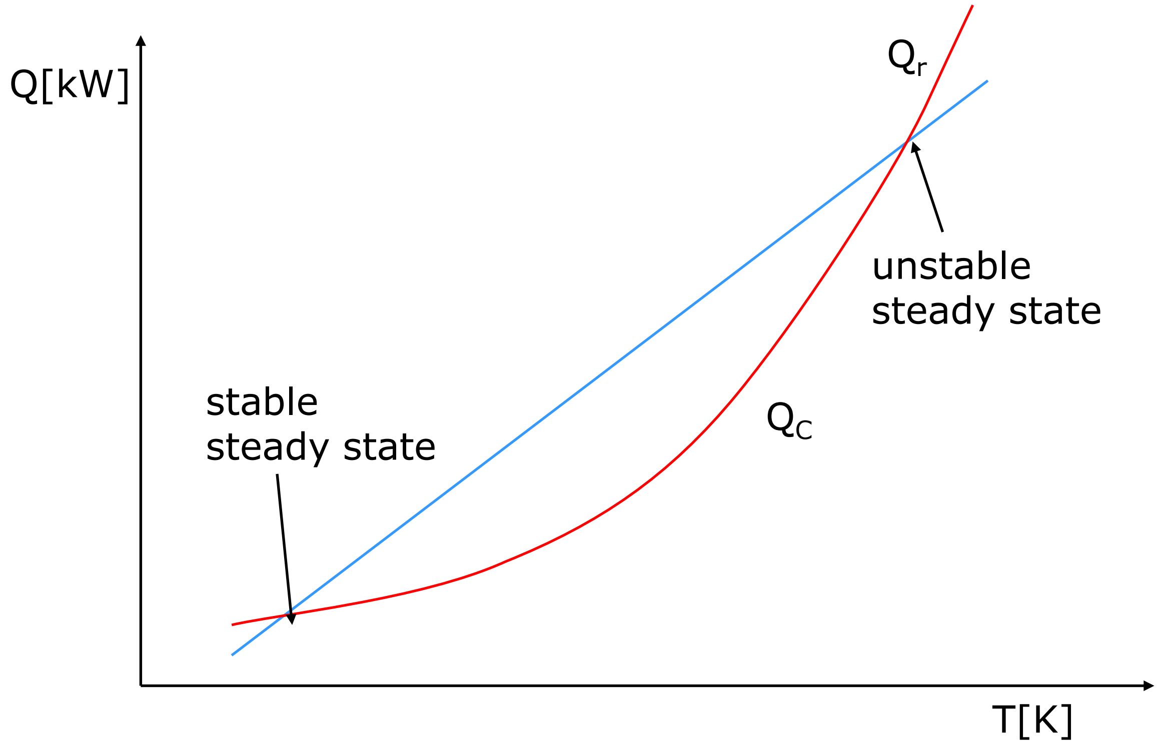
Process control

Example: Exothermic reaction in a reactor

- Dynamic system
  - composition and temperature change in time
- Natural behaviour
  - a. reactor reaches steady state
  - b. reactor increase its temperature to runaway
- ”Force” the reactor to different behaviour
  - PROCESS CONTROL

Exothermal reactor





$$\dot{Q}_C = KA(T - T_0)$$

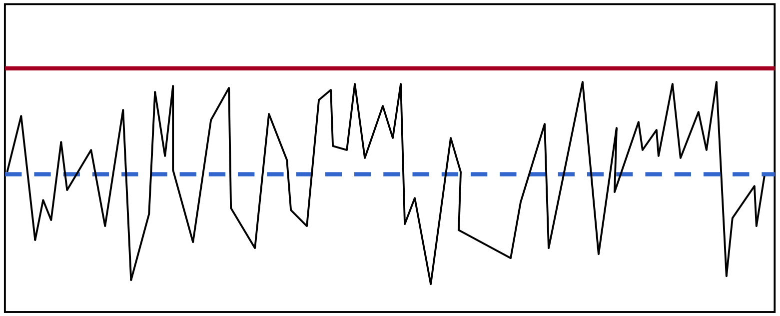
$$\dot{Q}_r = r(T)(-\Delta H_r)V_r = r_0 \exp\left[\frac{E(T - T_0)}{RTT_0}\right](-\Delta H_r)V$$

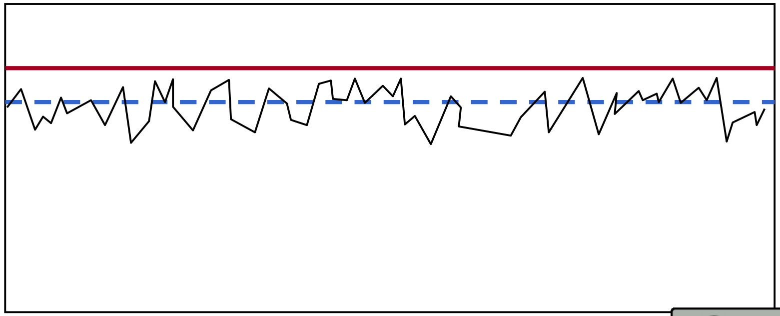
Why proces control?

- E.g. exothermic reaction
  - higher temperature = faster reaction
  - stable steady state cannot be reached at high temperature
- Operation in unstable steady state with process control
  - process control eliminates deviations from steady state

Control quality vs. efficiency

- Some limits cannot be exceeded
- The closer to the limit the process can be operated, the higher efficiency
  - e.g. reaction rate increases with temperature, but side products appear from certain temperature





Terminology

- Setpoint – what is the goal of process control
- Controlled variable – should be close to setpoint
- Controlling variable – can be directly adjusted and controls the value of controlled variable
- Actuator – adjusts the controlling variable
- Sensor – measures the value of a variable
- Controller – controls the actuator
- Disturbance – deviation from normal, causes deviation of controlled variable

Example: car driving

- Setpoint: car on the road ...
- Controlled variable: car position
- Controlling variable: wheel angle
- Actuator: hands of the driver
- Sensor: driver’s eyes
- Controller: driver’s brain
- Disturbance: road bend

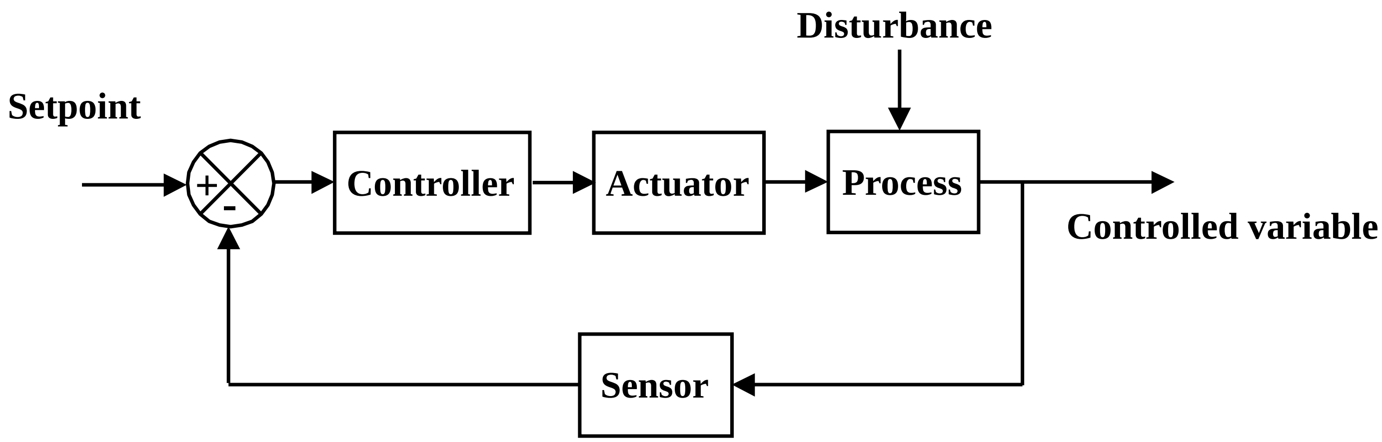
Example: heat exchanger

- Setpoint: Certain temperature of outlet stream
- Controlled variable: Temperature of outlet stream
- Controlling variable: Coolant flow rate
- Actuator: Valve
- Sensor: thermocouple
- Controller: computer
- Disturbance: change of input temperature

Simplest process control

- Fixed inputs
- Limited usability
  - limited settings
  - sensitivity to disturbances

Feedback control



Feed forward control

- Measurement of inputs
- Analysis of disturbances
  - model
  - database
  - experience
- Disturbances are compensated BEFORE they affects the controlled variable

Feedback control

- Current value of controlled variable is measured
- Current and setpoint are compared
- The difference determine the action

Feedback controls

- On-Off, e.g. oven
- Manual control
- PID controllers
  - – proportional, derivative, integral
- Model-based controllers

PID Controllers

- Since 40th of past century
  - simple
  - robust
  - validated
- 80 % installed controllers today

PID equation

$$e(t) = y(t) - y_{set}$$

y … controlled variable
e … error

$$\Delta c(t) = K_c \left[e(t) + \frac{1}{\tau_I} \int_0^t e(t)dt + \tau_D \frac{d\,e(t)}{dt} \right]$$

c … controlling variable
K_c … proportional component
τ_I … integration time
τ_D … derivation time