Chemické inženýrství A/B

Granulace

Granulation

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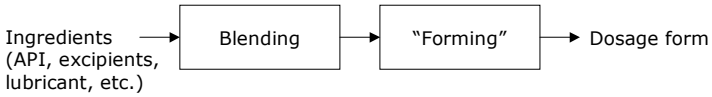
Evropský sociální fond
Praha & EU: Investujeme do vaší budoucnosti

Pharmaceutical Process Development

1) API manufacturing - "primary" processing
   - Reaction route selection
   - Solids isolation (crystallisation, filtration, drying)
2) Dosage form manufacturing - "secondary" processing
   - Types of dosage forms
   - Processing routes

Primary:

Secondary:



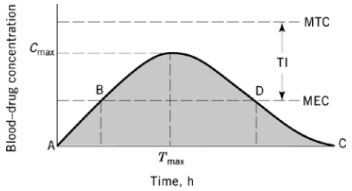
Dosage form design

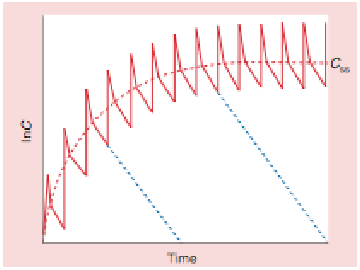
Administration routes:

- **oral** (tablets, capsules, liquids)
- **pulmonary** (aerosols, inhalation powders)
- **transdermal** (creams, controlled-release adhesive patches)
- **intra-venous** (e.g. vaccines, insulin, antibiotics)
- **"direct application"** (e.g. eye drops, skin cream)
- **implantable controlled-release devices**

Pharmacokinetic considerations:

- Bioavailability
- Required dose (drug "potency")
- Instant release vs. delayed/controlled release
- One off vs. chronic administration



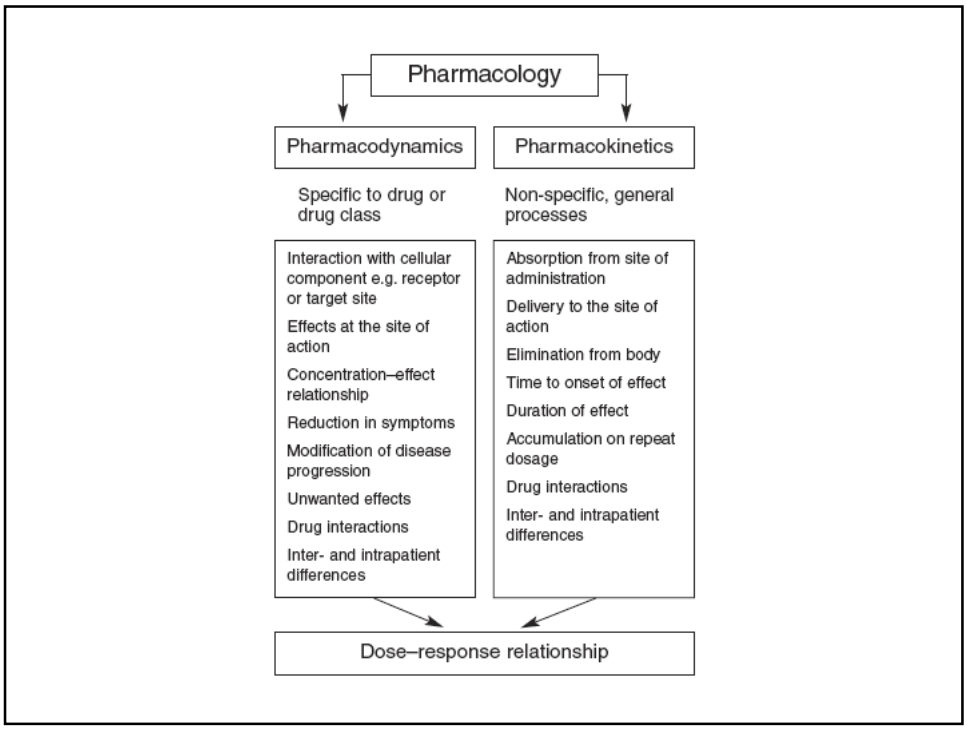


1. Absorption
2. Distribution
3. Elimination
    - 3.a Metabolism
    - 3.b Excretion

Bioavailability F = the fraction of the administered dose that reaches the systemic circulation as the parent drug (not as metabolites)

Apparent volume of distribution

V = Total amount of drug in the body / Plasma concentration



Solid oral dosage forms (tablets & capsules)

Source: Zhang et al., Adv. Drug Del. Rev. 56 (2004) 371-390

Powder Blending

Measure of mixedness - variance of composition

$\sigma^2 = \Sigma(w_i - w_{avg})^2 / n$ (n…number of samples, w_i…mass fraction)

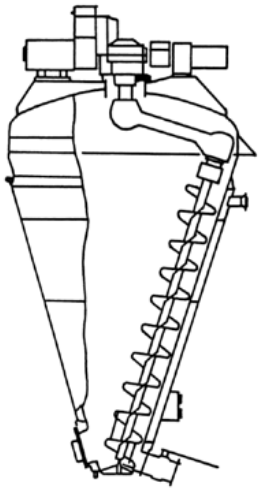
Mixing number N_{mix} - number of unit mixing operations required for the system to reach a given state of mixedness

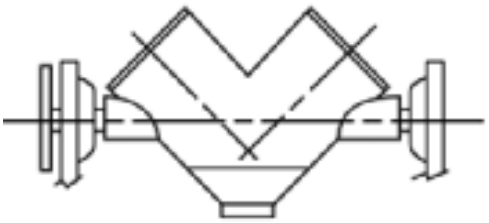
Segregation - natural tendency of powders to de-mix due to difference in particle size, shape, density or surface properties (friction, cohesion)

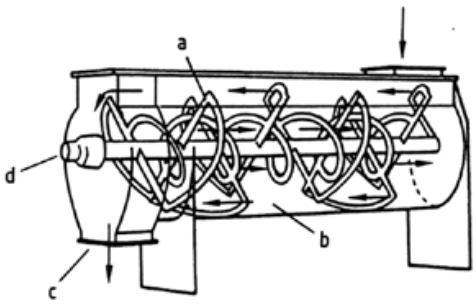
- occurs during transport (conveying) or storage (IBCs) of powders
- need to "freeze" a well-mixed state immediately after blending

Mixing equipment
- both batch and continuous
- mechanical agitation
- commonly used: V-blender

Powder blending equipment







Wet Granulation

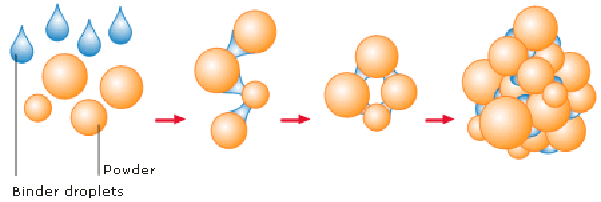
Principle: contact powder with a liquid binder, wet powder particles become cohesive, agglomeration occurs during particle collisions, binder sets to form mechanically stable granules.

Binder types:
- melt binders ~ melts, solidify upon cooling (e.g. PEG)
- aqueous binders ~ solutions, solidify upon drying (e.g. HPC, PVP)
- water ~ partial dissolution and recrystallisation of ingredient(s)

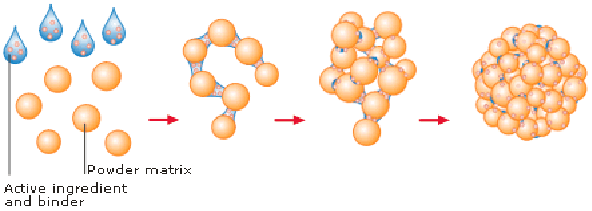
Binder application:
- spray (liquid atomisation) for low-shear processes
- mechanical dispersion in high-shear processes

Granulation processes:
- fluid bed granulation
- high-shear mixer granulation

Wet granulation



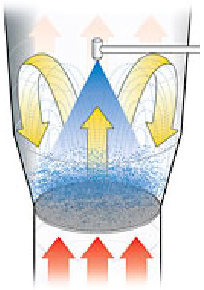
API is part of primary particle blend



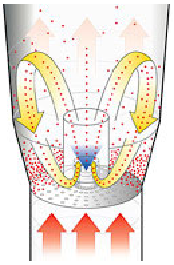
API is suspended in binder

Fluid bed granulation

Top spray



Bottom spray
(Wurster coater)



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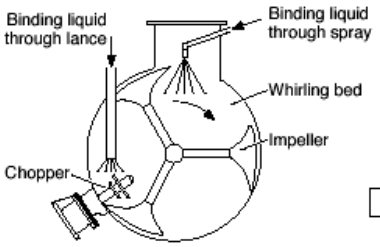
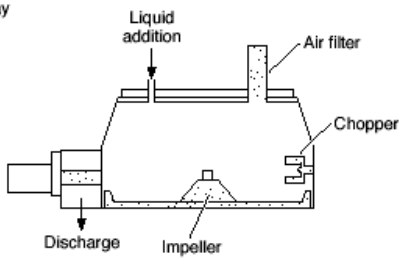
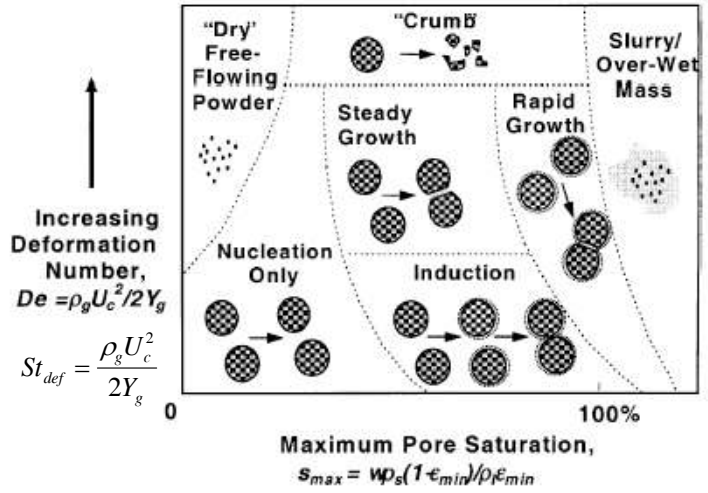
Batch high-shear mixer-granulator





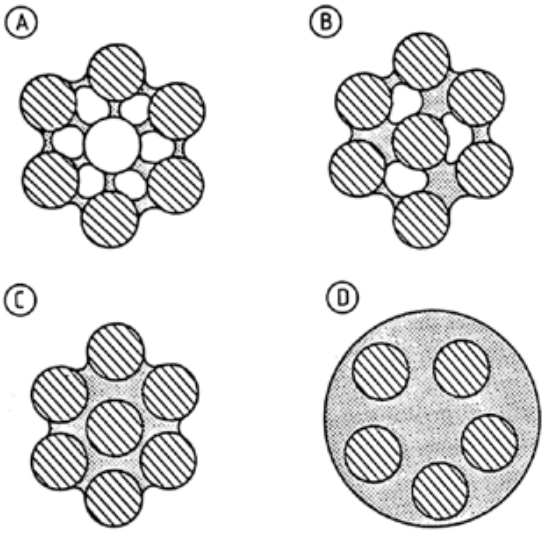
Growth regime map (Iveson & Litster, *AIChE J* **44**, 1510, 1998)



$$St_{def} = \frac{\rho_g U_c^2}{2Y_g}$$

$$s_{\max} = \frac{w\rho_s(1-\varepsilon_{\min})}{\rho_l \varepsilon_{\min}}$$

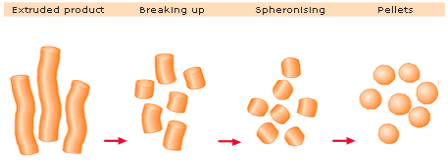
Liquid distribution in a wet granule:



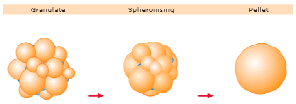
A) pendular
B) funicular
C) capillary
D) droplet

Extrusion-spheronisation

Principle of operation:
-Prepare a paste from API, excipients, binder, water
-Extrude paste through screen to form "noodles"
-Contact extrudates with a high-speed rotating disk
-Dry resulting spherical pellets



…but it is also possible to carry out spheronisation after wet granulation

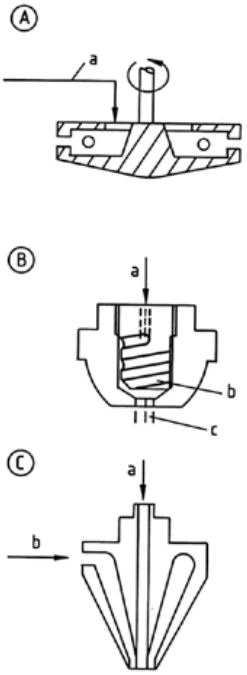


Spray drying

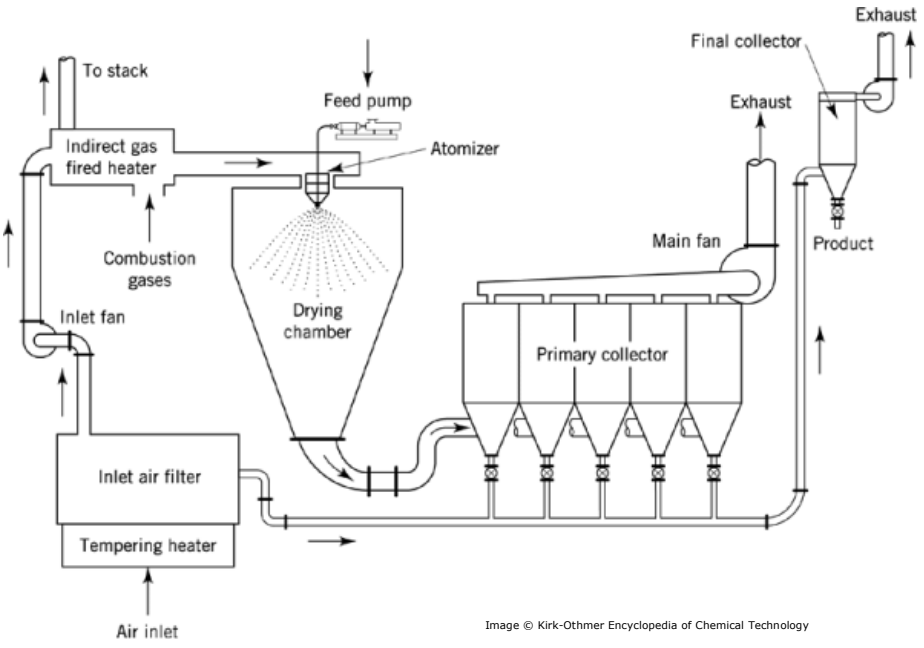
Step 1: solution or slurry preparation = dissolution/suspension of primary solid particles in a liquid

Step 2: liquid atomisation = formation of droplets of the slurry
nozzle types:
- rotary nozzle
- single phase pressure nozzle
- two phase nozzle

Step 3: particle formation = evaporation of liquid from the droplets leaves behind a (porous) solid structure



Spray drying - process set-up



Spray drying - process equipment

Pilot plant scale

Calculation of drying time

Evaporation rate: $m' = Q / \Delta h_v$

Heat-transfer rate: $Q = h_q A \Delta T$

Heat-transfer coefficient from gas to a single droplet:

$Nu = 2.0 + 0.60\ Re_p^{1/2}\ Pr^{1/3}$

($Nu = h_q d/\lambda$ $Re = ud\rho_g/\mu$ $Pr = c_{pg}\mu/\lambda$)

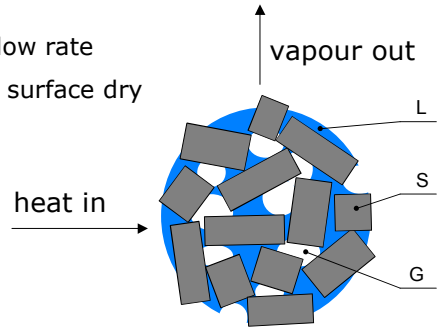
u … relative air velocity

Fast initial rate of drying => Skin formation

Energy balance: Gas temperature and flow rate

Residence time need to be sufficient for surface dry particles to be formed

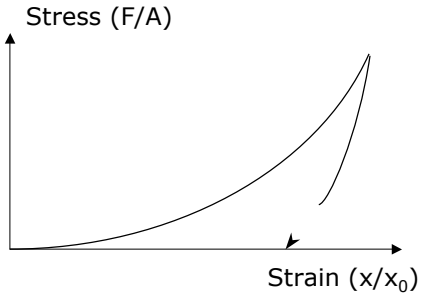
Often followed by fluid bed drying

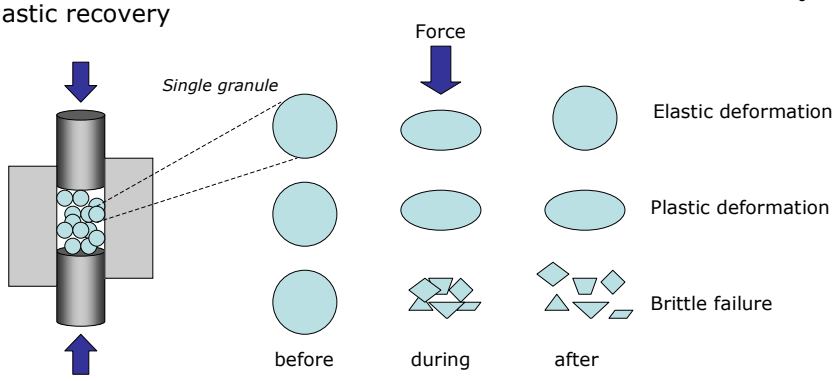


Tabletting

<u>Powder compressibility</u>

Phenomena:
- Rearrangement
- Elastic deformation
- Plastic deformation
and/or viscous flow
- Brittle failure
- Elastic recovery





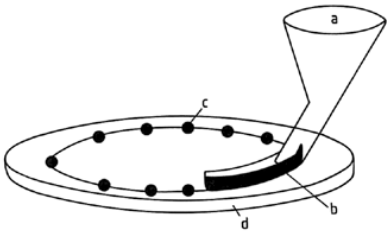
Tablet compaction

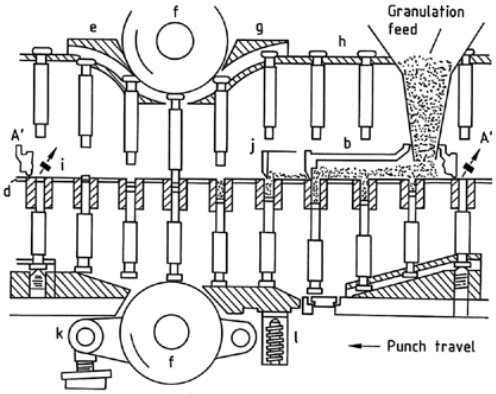
Cyclic operation:

- Feed
- Pre-compact
- De-aerate
- Final compaction
- Eject

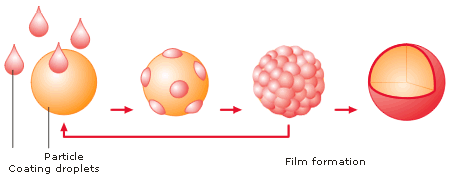
Need to use lubricants (e.g. magnesium stearate) to avoid sticking to punch or die walls and reduce wear.

Problems:
capping, de-lamination





Coating



Aims of coating:
-Taste masking
-Visual appeal (coloured tablets)
-Protective layer (abrasion)
-Delayed release effect (gastric fluid resistance)
-Functional coating of carrier particles - API

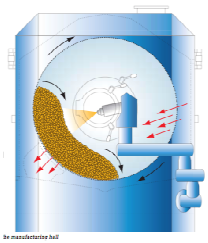
Typical film thickness 5-50 μm

Coating rate determined by:
-Bed turnover rate
-Drying rate

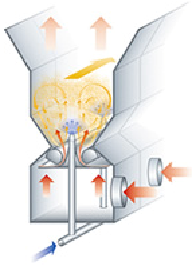
Criteria for coating vs. agglomeration:

$$St_v = \frac{8\tilde{m}u_0}{3\pi\mu\tilde{D}^2} \leq St_v^* = 2\ln\left(\frac{\lambda}{h_a}\right)$$

St_v : viscous Stokes number
$\tilde{m}$: reduced particle mass
$\tilde{D}$: reduced particle diameter
u_0 : velocity of collision
μ : binder viscosity
λ : thickness of binder layer
h_a : particle surface roughness



1. Drum coater



2. Spouted bed

3. Wurster coater (see earlier)

Plant layout

Vertical flow principle:

- processing stations on different levels
- gravity flow

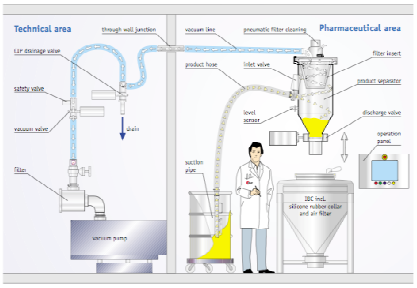
Horizontal flow principle:

- processing stations on the same floor
- transport by IBC's or pneumatic conveying system

Solids handling

IBC = Intermediate Bulk Container

Pneumatic conveying



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