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

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

Real mixture

- **Random**
  - well flowing particulate solid

- **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**

- Random variable
  - variable, the value of which is given by the result of random event
    - throwing dice result
    - API content in sample of random mixture
- mean value of a random variable
  - sum of all possible results of random event multiplied by their probability
    - mean value of dice throw result
      \[ E(X) = 1 \cdot \frac{1}{6} + 2 \cdot \frac{1}{6} + 3 \cdot \frac{1}{6} + 4 \cdot \frac{1}{6} + 5 \cdot \frac{1}{6} + 6 \cdot \frac{1}{6} = 3.5 \]

**Mean value of a random variable**

- mean value of API content in sample taken from a bulk mixture
  \[ E(X) = \lim_{N \to \infty} \frac{1}{N} \sum_{i=1}^{N} x_i \]
  - number of random sampling results is almost infinite
- Selective mean value - arithmetic average
  - mean value of API content in taken sample, calculated from selection of finite number of carried out experiments
  \[ \bar{X} = \frac{1}{N} \sum_{i=1}^{N} x_i \]

**Standard error of a random variable**

- measure of variability of random variable
  - random variable result will be within \( \pm \) standard deviation from average with approximately 2/3 probability
  - random variable result will be within \( \pm 2 \times \) standard deviation from average with very high probability
  \[ s = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{X})^2} \]

**Selective standard error**

- measure of random events variability
  - API content variability in taken samples
  \[ s = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{X})^2} \]

**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)
  \[ RSD = \frac{s}{\bar{X}} \times 100 \% = \frac{1}{\bar{X}} \times \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (x_i - \bar{X})^2} \times 100 \% \]
**Evaluating homogeneity**

- **Relative selective standard error of taken samples**
  - simple
  - frequently used
  - not in 0 - 100 % range

- **Mixing index**
  - multiple definitions
  - 0 - 100 % range
  - $\sigma_{\text{MAX}}$ ... completely segregated state
  - $\sigma_{\text{MIN}}$ ... minimum achievable non-homogeneity

(analytical error)

**Random mixture properties**

- **Variability of taken samples**
  - Assumption of (pseudo) binary mixture of similar components
  - $w = \frac{1}{n}$

  - $W_{\text{MAX}}$ ... single component content 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

**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

**Convective and dispersion mixing**
Mixing particulate solids

- Tumbling blenders
  - rotating vessels with elements
  - convection and diffusion
  - rotating frequency $5 \text{ – } 30 \text{ s}^{-1}$

- Convective blenders
  - static vessel equipped by convey
  - convection, shear
  - good for agglomerating mixtures
  - difficult cleaning

Mixing particulate solids

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

Blender selection

- Idealized blender
  - 3D movement of particles (not agglomerates)
  - eliminating dead zones

- Real blender
  - trade-off between mixing quality and process compatibility

- Blender selection
  - eliminate inadequate types
  - select optimal blender by mixing efficiency, throughput, price

Selected factors influencing the blender choice

- Process requirements
  - Particle comminution during blending
  - Cleaning
  - Continuous / Batch
- Mixing / Segregation relationship
  - Better for convection, worse for dispersion
- Effect of particulate solid flowability

Process parameters of tumbling blenders

- Key parameters
  - rotating frequency $\ldots f [\text{s}^{-1}]$
  - filling ratio $\ldots \phi$ [%]
  - equipment size
- Critical rotating speed
  - causes centrifugal movement of particles $= \text{no mixing}$
  
$$f_c \approx \frac{1}{2\pi} \frac{g}{R}$$
**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

- **Rolling and cascading motion**
  - Depends on the filling ratio
  - Mixing proceeds only in the active zone

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**Filling ratio**

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

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**Processes taking place in powder homogenization**

- Mixing is reversible process

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**Mixing kinetics**

\[
RSD = a + b e^{-\frac{t}{\tau}} + c
\]

\[
\frac{dRSD}{dt} = -k_1 RSD + k_2 (RSD_0 - RSD)
\]
## 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

## Wall segregation

- Flow of particulate solid near wall
- Adhesive discrimination between particles
- Some particles possess higher affinity to equipment wall

## Segregation examples

- Segregation in different blenders
- 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