Delft Solids Solutions

Tendency of blends for segregation

Methods for measuring the segregation potential

Louk Peffer

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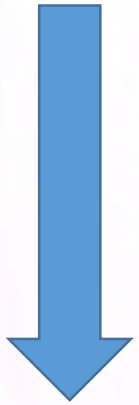
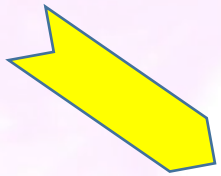
Outline/Themes

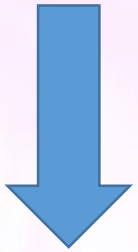
- Blends unmix?
- Validation blend quality
- Sampling equipment
- Representative sampling
- Visual inspection?
- Segregation mechanisms
- Investigation techniques / quantifying segregation
- Reduction of segregation

Mixing

Conveying / transport
Storage (charge / discharge)
Filling / tableting

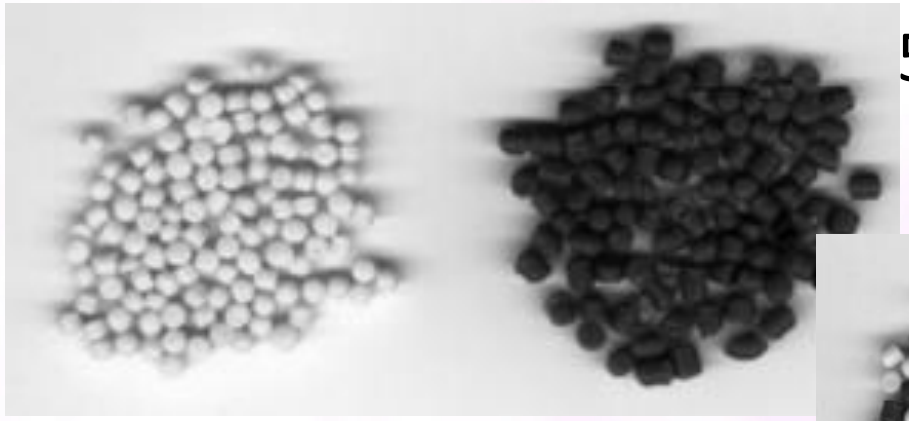




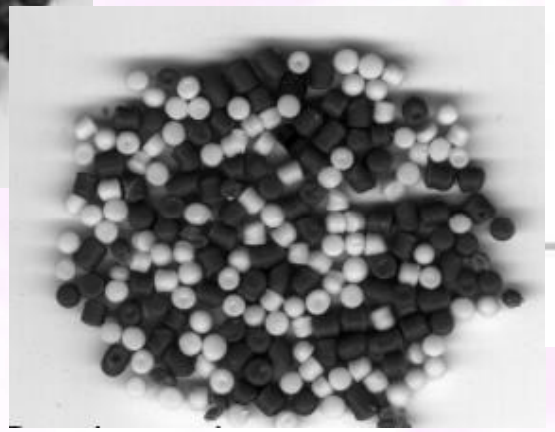


- Blend homogeneity?
- Validity

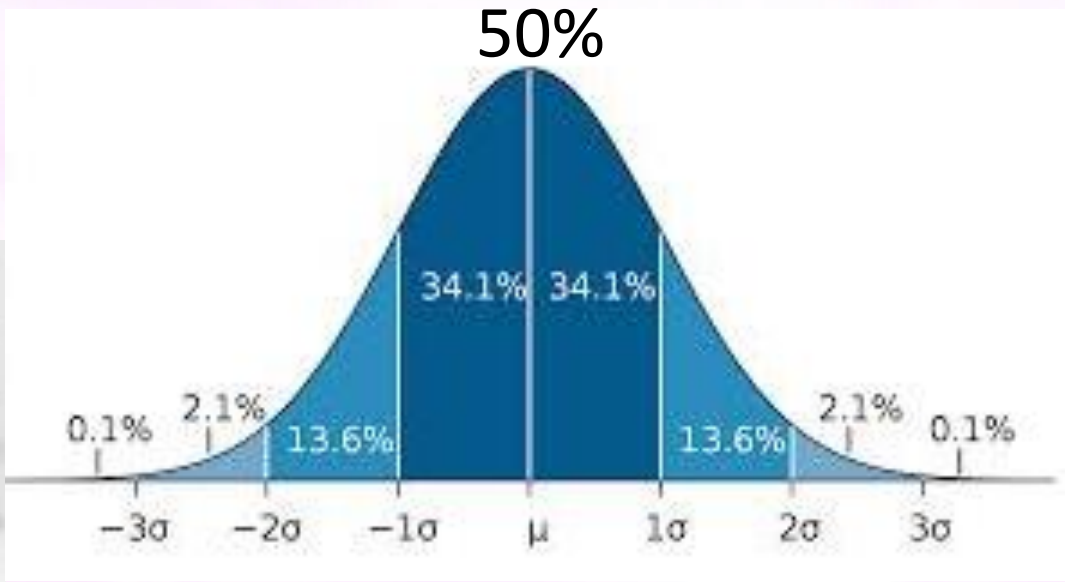
- Segregation tendency?
- Investigation of representative lots



50%/50%

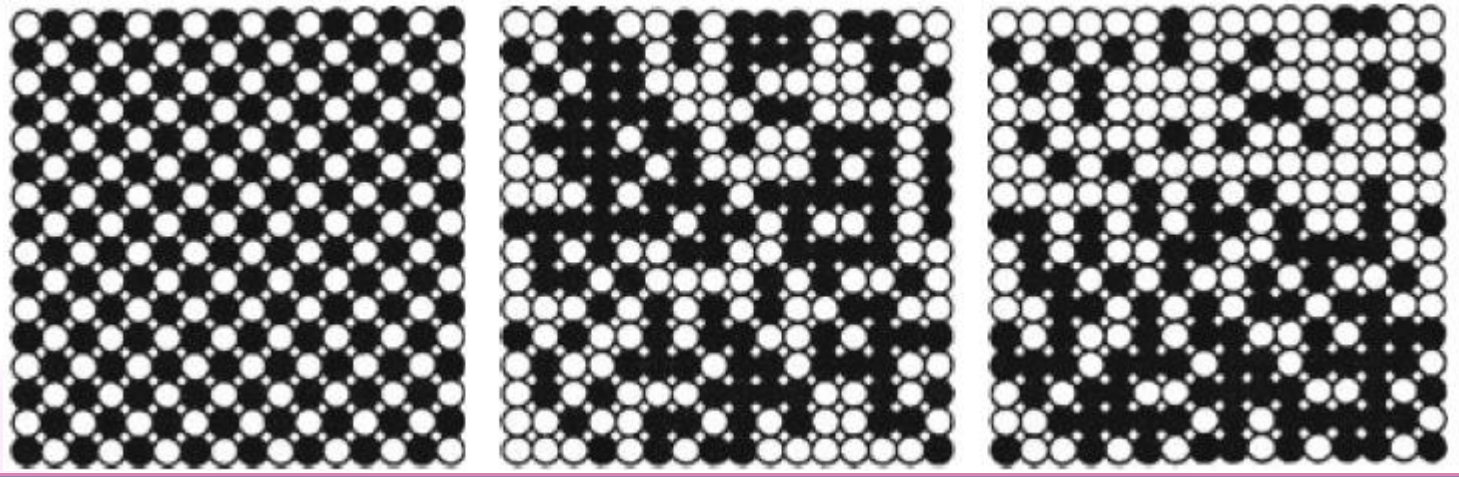


Theoretically



Gaussian distribution

Error still
1 pellet



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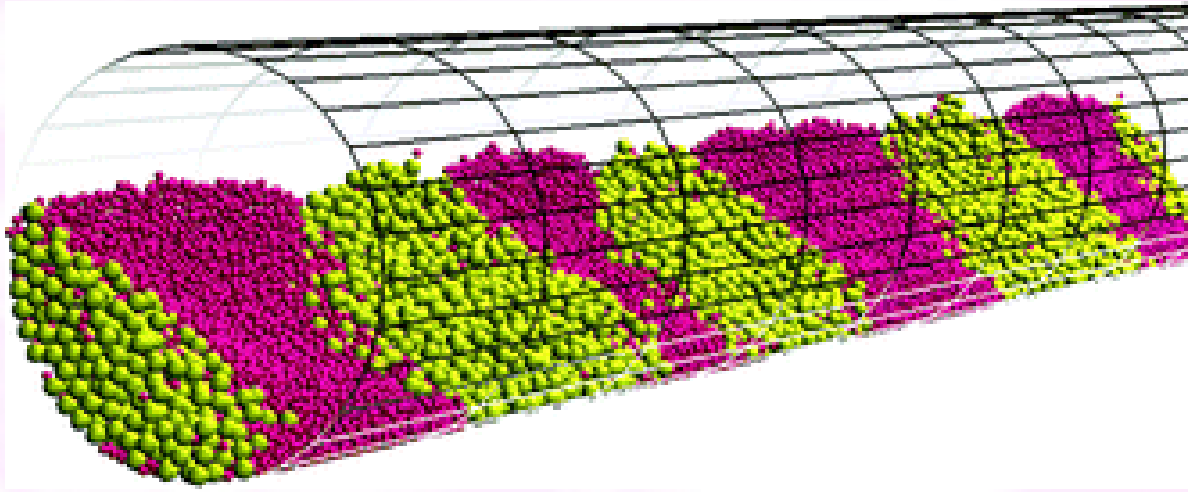
Reality?

3D simulation discrete elements (DEM)
50.000 grains



Even if particles are originally mixed, they will tend to unmix (segregate) on handling e.g. transport, pouring, conveying, processing.

De-mixing or segregation is mainly caused by differences in size and shape of constituent particles but also density.

Particle size and (bio) chemical composition of the product may be off specification e.g. blends of pharmaceuticals, food, feed, chemicals.

Visual Inspection
Segregation visible?

Animal Nutrition

Steak seasoning

Medicine

Washing Powder

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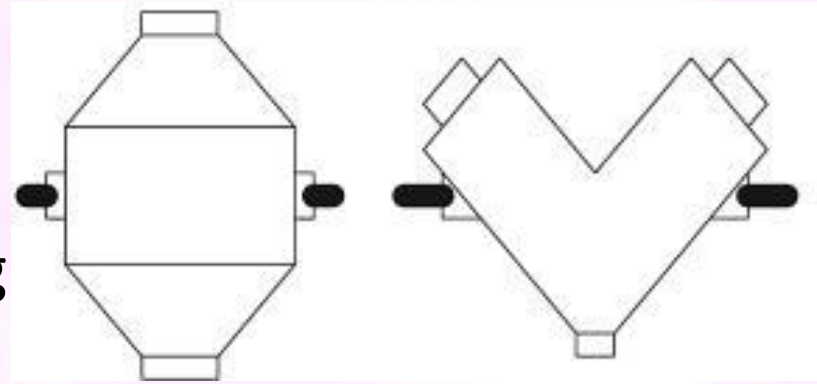
Mechanism of Segregation

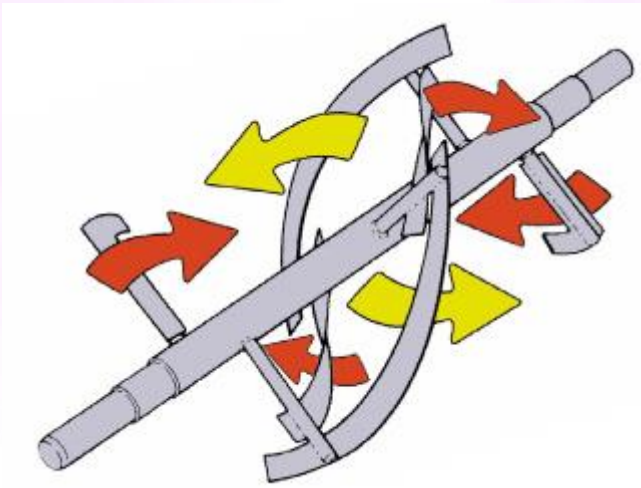
Rhodes, Johanson, Schulze

- **Sifting** → Fine particles sift down through a matrix or grid of coarse particles
- **Angle of Repose** → Piles formed during charge or discharge concentrate large particles at the slope of the pile
- **Air Entrainment** → Entrained air with a falling stream of particles dislodges fine particles
- **Impact Fluidization** → A (semi)-fluidized state coarse and heavy particles penetrate in fluffy powder
- **Brazil nut effect** → Very large particles rise by shocks

Justification of Blend Sample Sizes and Acceptance Criteria



- Number of Sampling Locations
  - At least 10 locations should be used for tumbling mixers to adequately map blender
  - At least 20 locations should be used for convection mixers, which are more likely to have dead spots
- Replicates Per Location
  - At least 3 samples/location required to perform component variance analysis to detect the presence of sampling error



Blend Validation

Blend: 10 locations 3 samples per location
Assay 1 sample per location

↓

Acceptance Criteria:
RSD ≤ 5.0%
All individuals within +/- 10% of mean

Fail ↙

Assay 2nd and 3rd blend samples from each location

↓

Mixing problem identified

Yes ↙

Blend is not uniform. Go back to development

No ↘

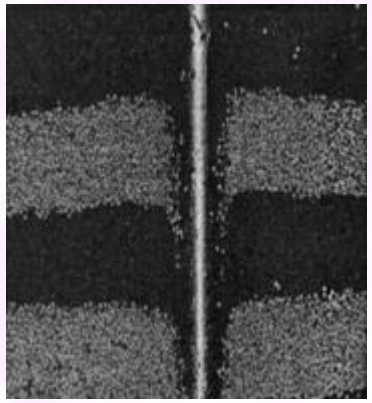
Investigation points to sampling bias or some other attributable cause →

Proceed to Stage 2 Dosage Unit Testing

Pass ↘

Proceed to Stage 1 Dosage Unit Testing

Sampling probes “sample thiefs” bulk interior

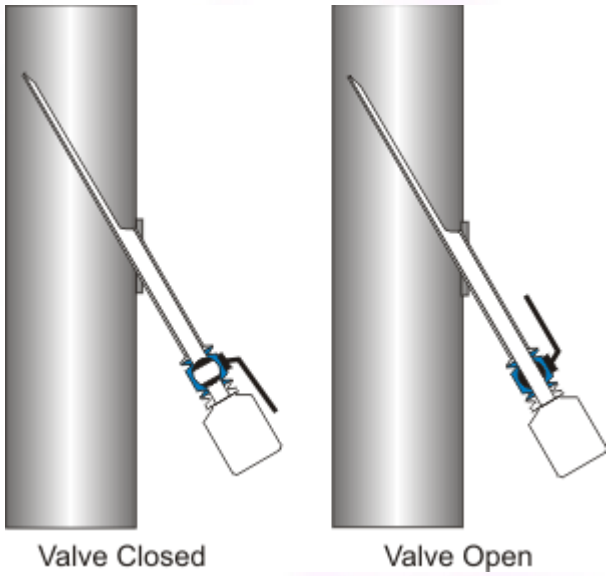


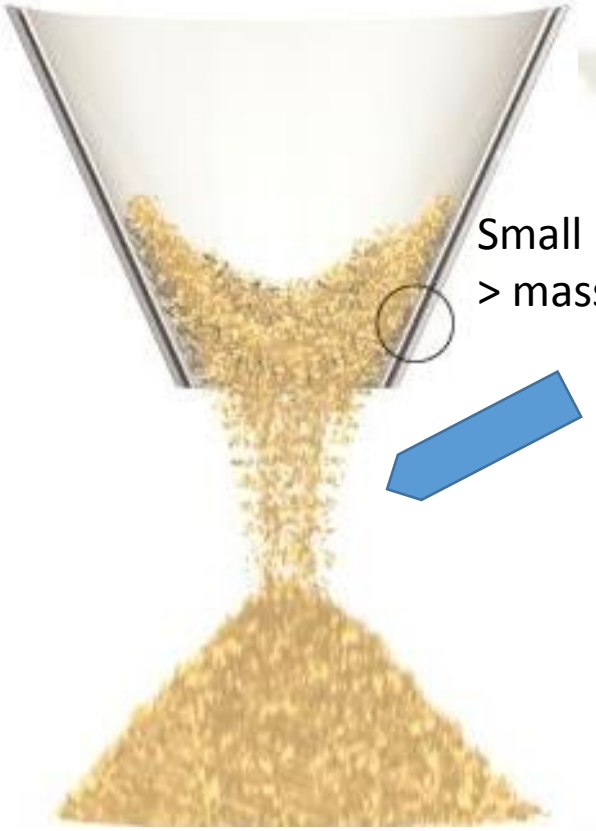
- Pos: easy
- Neg: operator bias
  perturbs bulk

– appropriate for granular, dry, flowable solids

End & side samplers

Sampling probes during discharge





Small hopper angles
> mass flow

sampling

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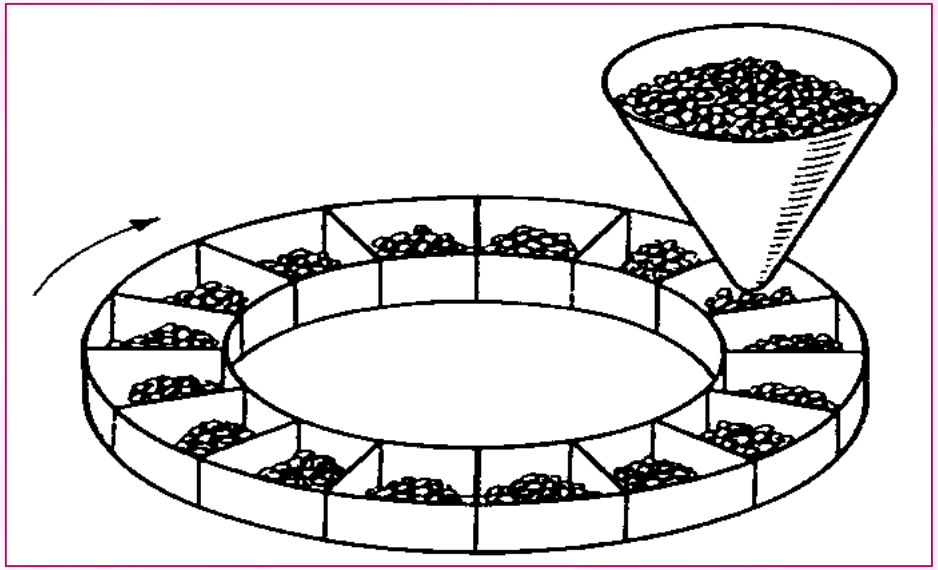
Off-line sample preparation

Cube Mixer

- Mixing constituents
- Representative sampling

Rotary riffling



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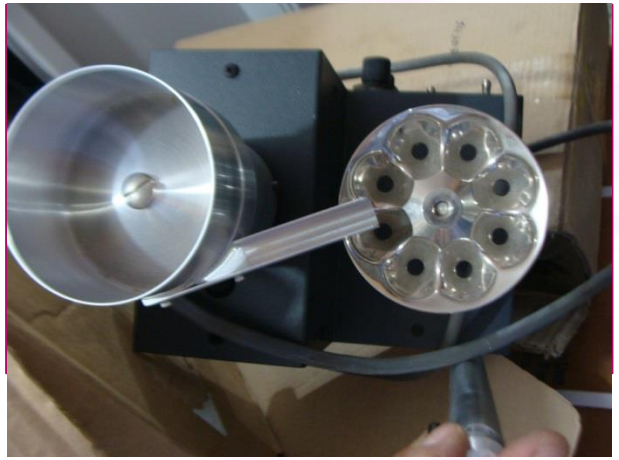
Representative lots



Rotary Riffler

2-1600 L

Max. 2-5 L

Micro

Representativeness sampling methods

RELATIVE RELIABILITY OF SAMPLING DEVICES

Method	Relative Standard Deviation (%)
Cone & Quartering	6.81
Scoop Sampling	5.14
Table Sampling	2.09
Chute Splitting	1.01
Spin Riffling	0.125

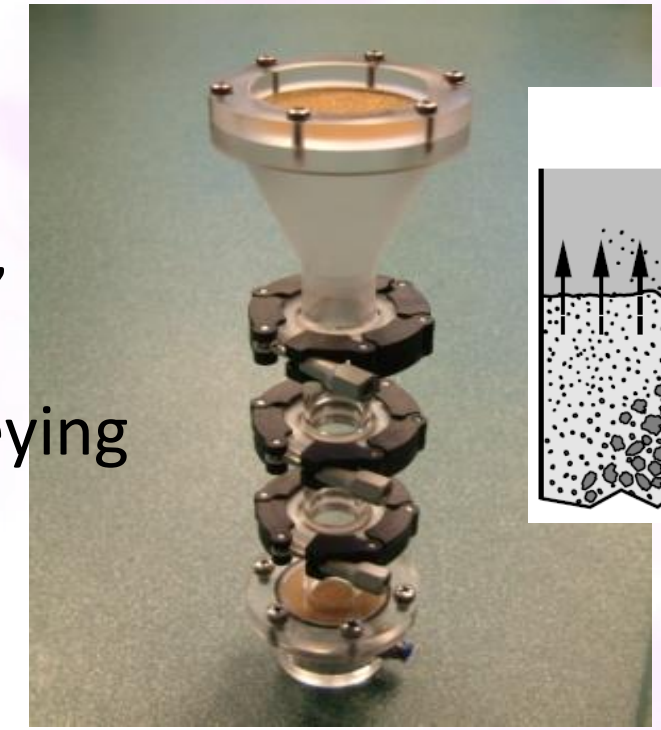
Allen 1981

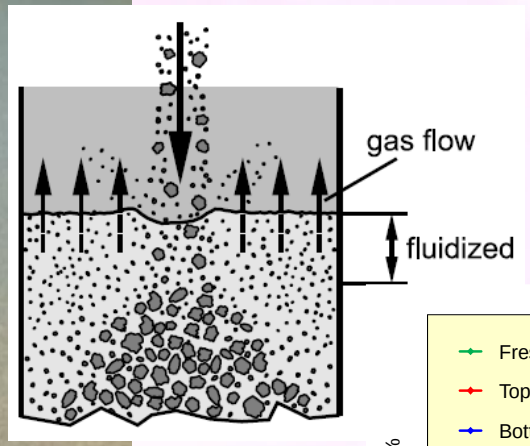
Fluidization Segregation

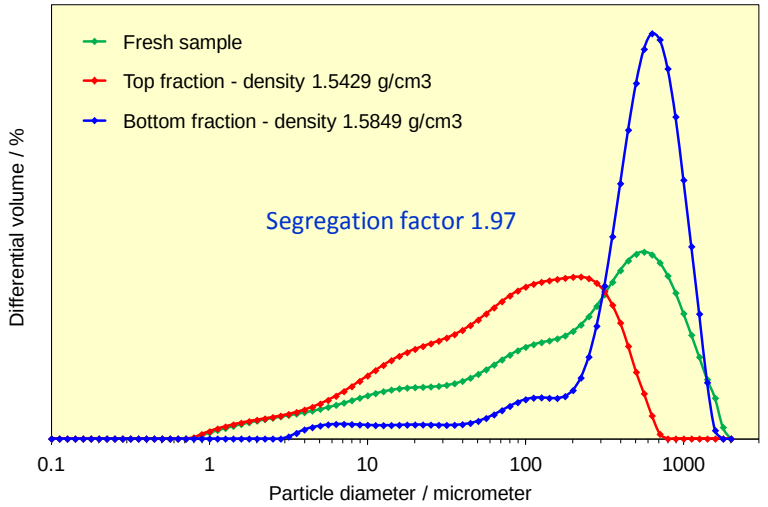
Simulates the top-to-bottom segregation effects of gas flow through a bulk material

Mechanism

- upon filling a bin,
- rapid blending,
- pneumatic conveying







Allows comparison of one material to another

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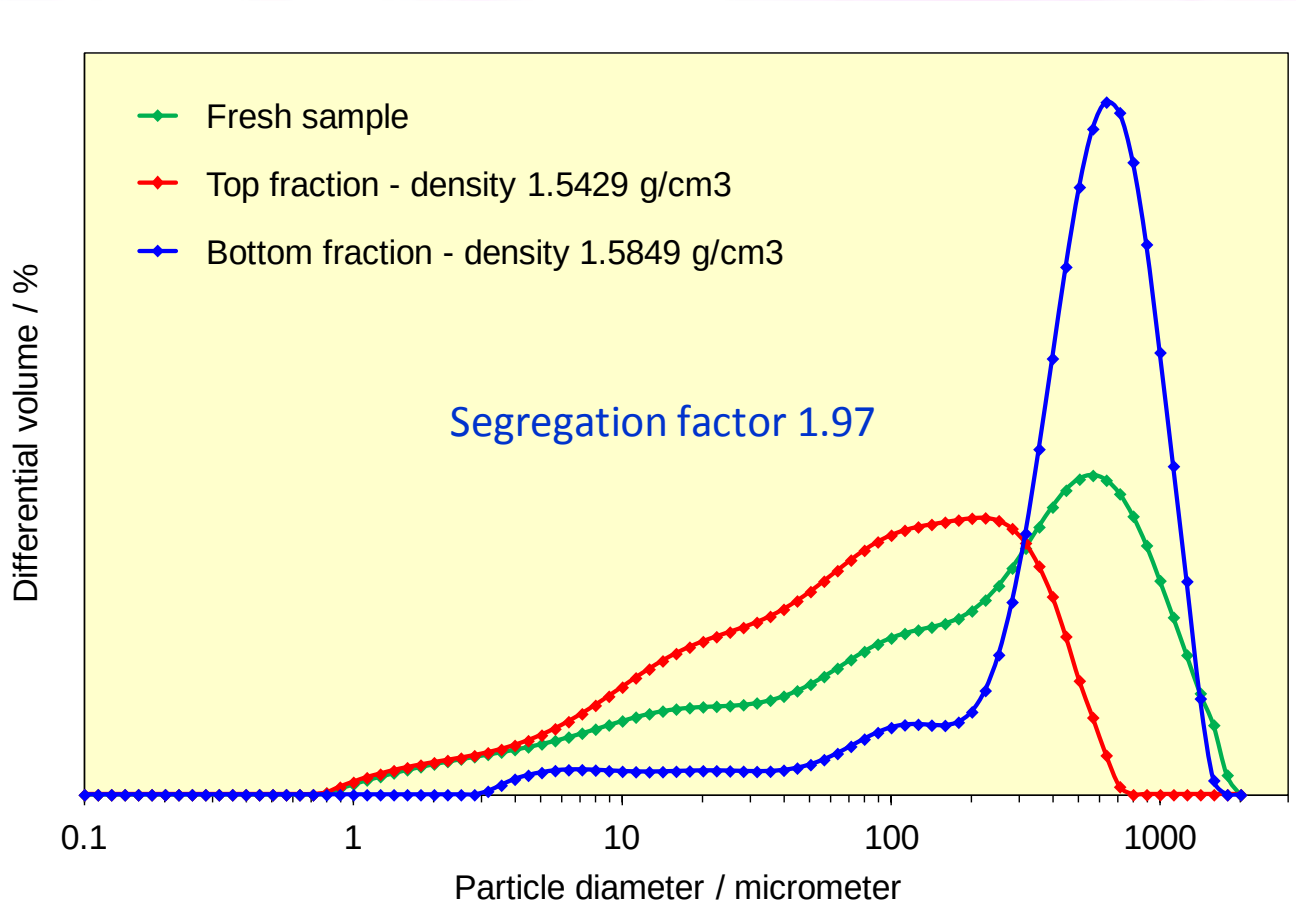
Fluidization Segregation



- True density
  - Top 1.5429 g/cm^3
  - Bottom 1.5849 g/cm^3
- Segregation factor 1.97

$$S_{PSD} = \frac{8 \mid (\text{Mode}^{\text{Top}} - \text{Mode}^{\text{Bottom}}) \mid}{\left(D_{90}^{\text{Top}} - D_{10}^{\text{Top}}\right) + \left(D_{90}^{\text{Bottom}} - D_{10}^{\text{Bottom}}\right)}$$

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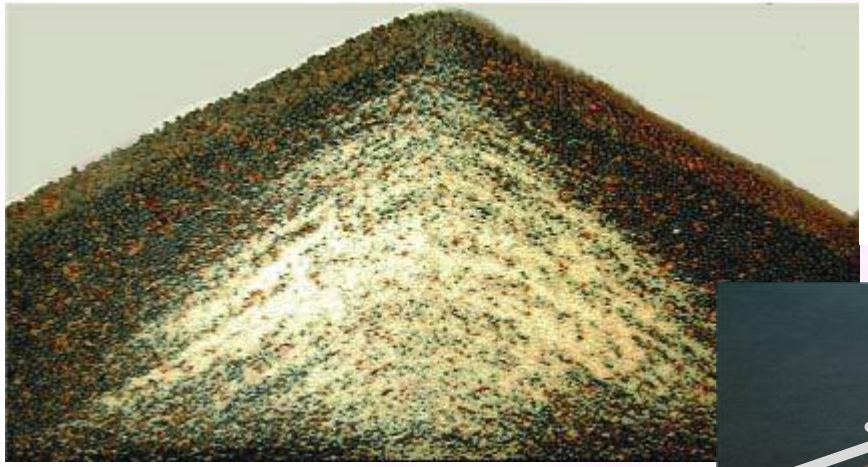
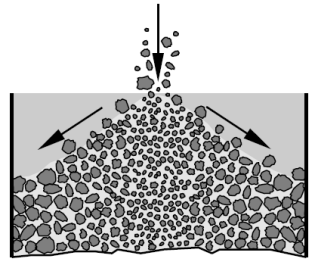
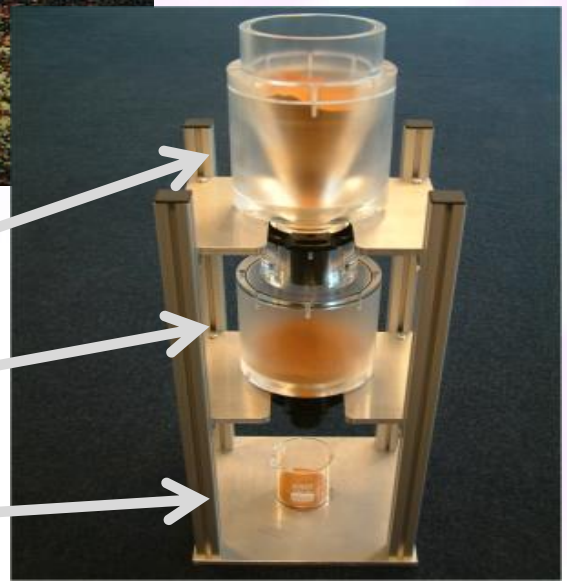
Sifting Segregation

Simulates the core flow hopper effect during discharge



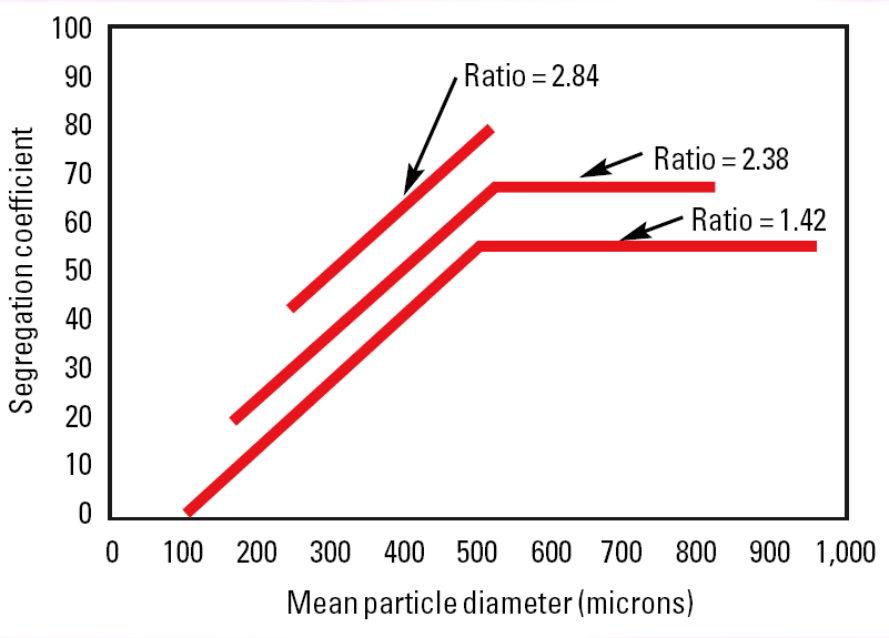




Mass flow hopper

Core flow hopper

20 Fractions



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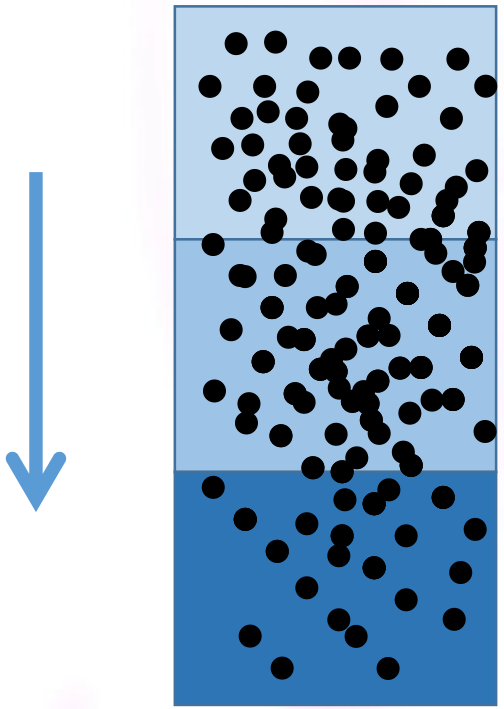
Segregation coefficient (k_0)

Active ingredient(s), ratio between fractions



$$k_0 = \frac{C_{f1-n}}{C_0}$$

C_0 = target concentration

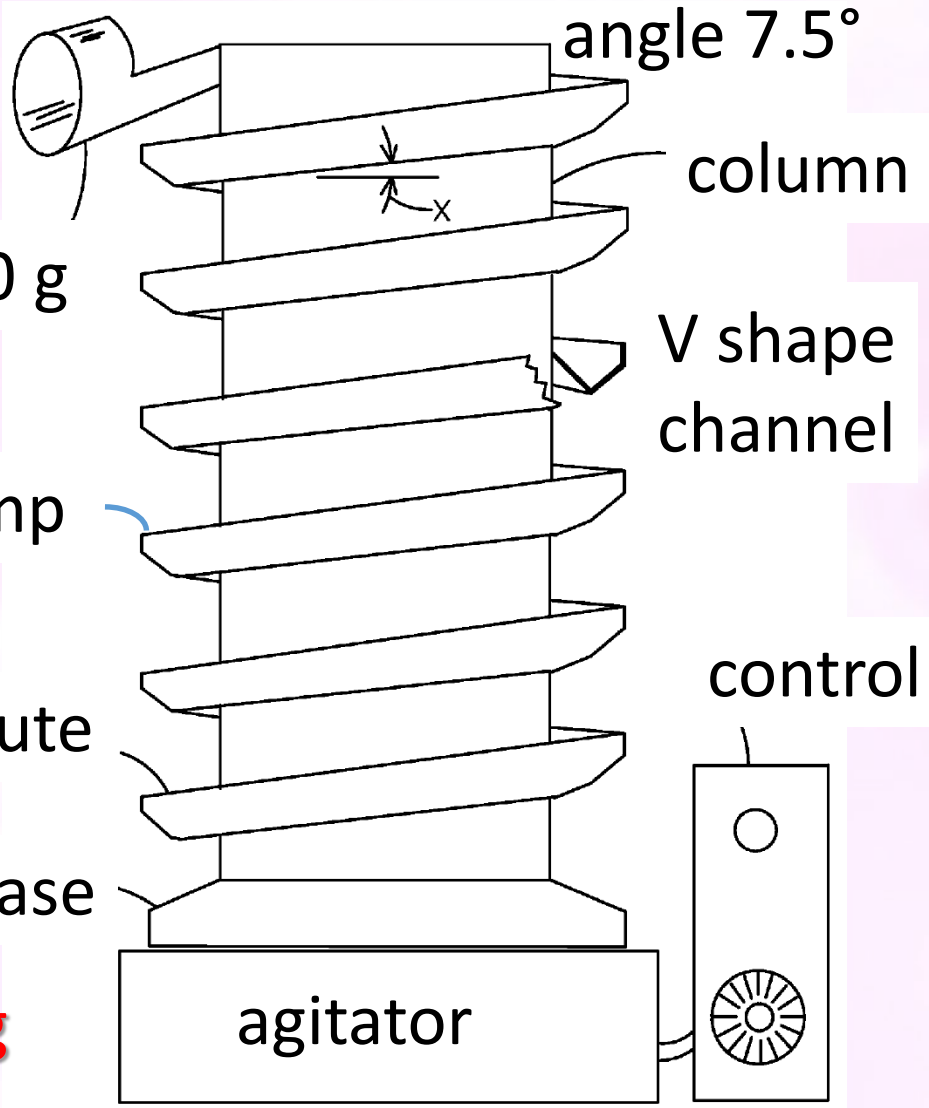
C_f = concentration fractions

USA Patent Application 2015

Accelerated testing of powder blends for component segregation.

Suitable:

- Pharmaceuticals,
- Food,
- Cosmetics,
- Chemical formulations.



e.g. 10 units 1 g

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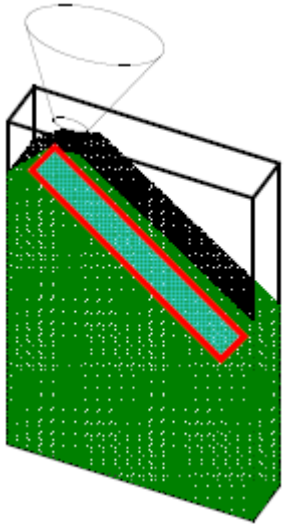
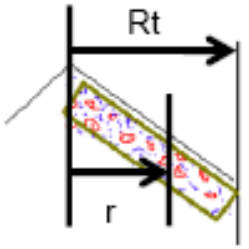
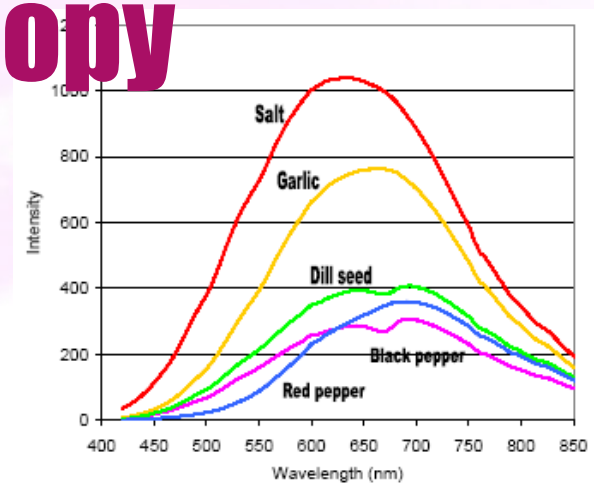
Determination of degree of segregation
Collected unit doses

- Particle size distribution
- (Bio)Chemical assay
  - Pharmaceuticals e.g. API (*standard requirement <6%*)
  - Food e.g. composition
  - Feed e.g. minerals, vitamins, nutrients
- True density
- Visual inspection e.g. color
- Taste e.g. powder drink mixes

Sifting segregation, Angle of Repose, Reflectance spectroscopy







Visible
NIR

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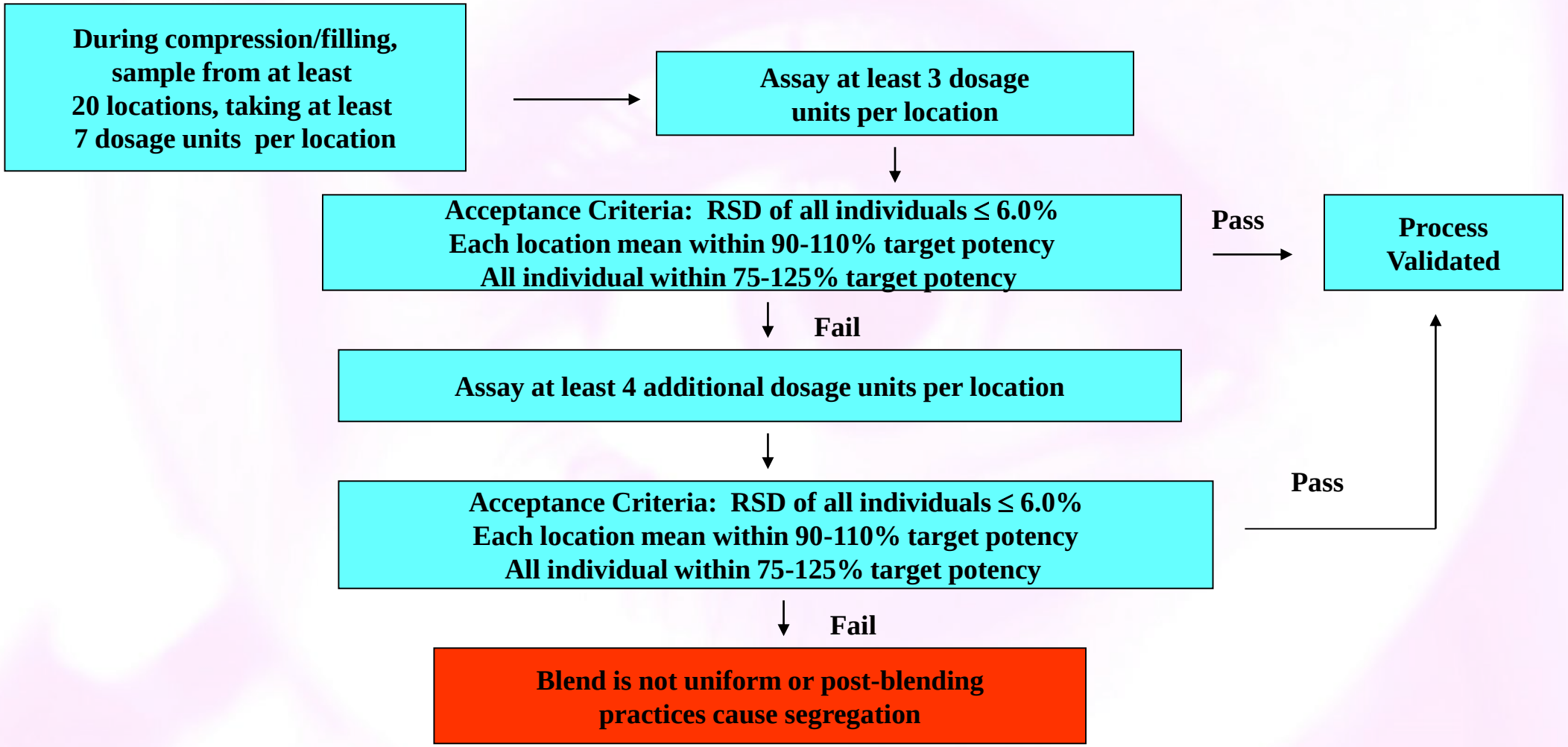
Process Validation



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Investigation Segregation

Off-line study

- Minimum amount of blend
  10 g, 80 ml, 1L
- Formulation
- Quality control

Homogeneous Blend!

In-line study

- Run the complete process
- Loss of product
- Assay of the final product
- Sampling at different unit operations
- Formulation

Reduction of Segregation

- As similar as possible the size distribution of constituents
- Reducing the span (broadness) of the particle size distribution
- Reduction of particle size to < 30 µm (interparticle forces)
  Van der Waals, electrostatic, humidity
- Addition of small quantities of liquid binder (reduced mobility)
  - Maltodextrine in water
  - Vegetable oil

Measures may lead to flow problems

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Thank you for your attention!