BLENDING, COMPRESSION, AND COATING SCALE-UP

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Blending Scale-Up

- Blending is a critical operation that determines how well the product is to perform in the next phases.
- Achieving and maintaining homogenous mixing of powders is critical, especially in formulations involving small amounts of high-potency components.
- ***Lack of blend uniformity at the blending stage may result in lack of CU in the finished product dosage forms.***
- **Tumbling blenders** are typically used. The most common types of blenders are **In-Bin** and **V-shell** blenders.
  - **In-Bin blenders** are typically used for high drug-load blends and are good for storage of said blend.
  - **V-shell blenders** are used in intermediate drug-load blends.
- The main difference in these blenders is the geometry

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Blending Scale-Up

In-Bin blender

V-shell blender

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Blending Mechanisms

Topic 2 - Design of Solid Dosage Formulations

Convection

- causes large groups of particles to move in the direction of flow (orthogonal to the axis of rotation), the result of vessel rotation.

Dispersion

- is the random motion of particles as a result of collisions or inter-particle motion, usually orthogonal to the direction of flow (parallel to the axis of rotation).

Shearing

- separates particles that have joined due to agglomeration or cohesion and requires high forces.

https://youtu.be/VS1fLNOLfyM?t=16

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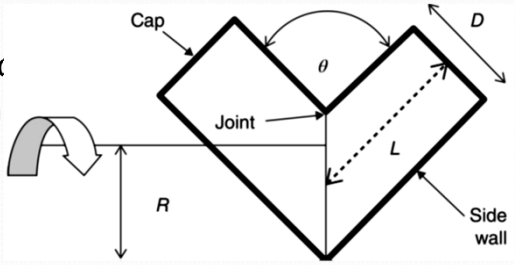
Blending Scale-Up

- There are three mechanisms of particle mixing: **convection**, **dispersion**, and **shearing**.
- In tumbling blenders (e.g. V-shell), convective and dispersive mixing are dominant, unless intensifier bars or chopper blades are added to cause shear mixing.
  - For example, within a V-shell blend **convective** blending occurs within each shell side during tumbling, and **dispersive** mixing happens between shells.



- Blending in a DC case consists of a pre-lubricant and a post-lubricant blend ahead of compression. Lubricants such as Sodium Starch Fumarate (SSF) and Magnesium Stearate (MgSt) are normally used.

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Blending Process

- Mixing in Tumbling Blenders
  - Loading of multiple ingredients will have a dramatic effect on mixing rate if dispersion is the critical blending mechanism.
  - Care must be taken when loading a minor (~1%) component into the blender
  - The order of constituent addition can also have significant effects on the degree of final homogeneity, especially if ordered mixing (bonding of one component to another) can occur within the blend
- Intershell flow is the slowest step in a V-blender, because it is dispersive in nature, while intrashell flow is convective.
  - Both processes can be described by similar mathematics, typically using an equation such as: • Where σ2 is mixture variance, N is the number of revolutions, A is an unspecified constant, and k is the rate constant.
  - The rate constants for convective mixing are orders of magnitude greater than for dispersive mixing.

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Process Parameters

- One parameter consideration that arises is whether rotation rate should change with variations in size. • When far from the critical speed of the blender, the rotation rate does not have strong effects on the mixing rate • The number of revolutions was the most important parameter governing the mixing rate.
- Given a geometrically similar blender and the same mixture composition, the fill level should also be kept constant with changes in scale. • However, an increase in vessel size at the same fill level may correspond to a significant decrease in the relative volume of particles in the cascading layer compared to the bulk. • □A large decrease in mixing rate.

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Blending Scale-Up

Important Parameters

CMA/CPP	CPP/CQA/CBA It Can Affect
Particle shape and size	Blend uniformity, content uniformity, compressibility
Powder density	Blend uniformity, content uniformity, compressibility
Fill level	Blend uniformity, content uniformity
Loading procedure	Blend uniformity, content uniformity
Number of rotations (pre- and post-lube addition)	Blend uniformity, content uniformity
Rotation speed	Blend uniformity, content uniformity
Blender size	Throughput
Room humidity	Degradants, compressibility

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Blending Scale-Up

- There are many ways to determine if a blend is well mixed.
- Three simple ways are to
  1. Use online Process Analytical Technology (PAT) such of as Near Infrared (NIR) technology
  2. Sample blend using a thief over time and testing potency
  3. Simply compress the blend material and assess compressibility and CU

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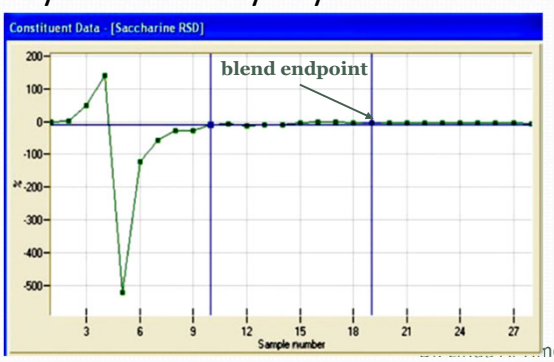
Blending Scale-Up

- The **NIR region** spans the wavelength range 780–2526 nm, in which absorption bands correspond mainly to overtones and combinations of fundamental vibrations.
- NIR spectroscopy is a fast and nondestructive technique that provides multi-constituent analysis of virtually any matrix.



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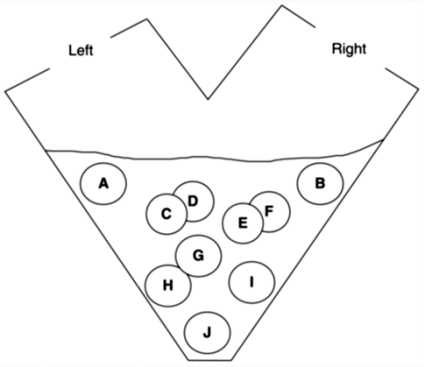
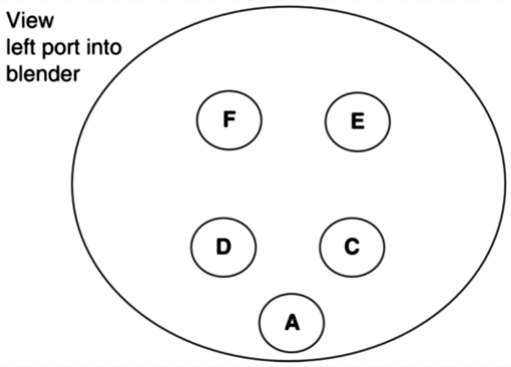
Blending Scale-Up

- If PAT tools cannot be used, a more traditional sample method is used.
- Samples are commonly pulled from many locations within the V-shell blender in order to understand if there is any location bias versus blend uniformity.





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Blending Scale-Up

- Usually blenders are scaled from V-shell (laboratory, pilot scale, and commercial scales).
- However, depending on the product and manufacturing needs the blending operation may be transferred to an In-Bin Blender (pilot, commercial scales).
- Change in geometric characteristics of tumbling blenders may lead to different mixing behaviors; therefore, a straightforward transition cannot be accomplished unless engineering principles are used.
- Some scale-up approaches are matching **Froude (Fr) number**, matching **tangential/wall speed**, or scaling **particle surface velocities**.

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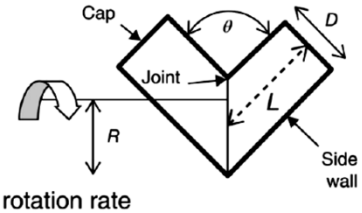
Blending Process

Common Scale-up Techniques

1. Matching of froude number (Fr), $Fr = [\Omega^2 R]/g$
2. Matching of tangential speed (wall speed) of blender, $2\pi\Omega R$
3. Scaling of particle surface velocities,

$$V = kR\,\Omega^{2/3}\left(\frac{g}{d}\right)^{1/6} \quad \text{for } \Omega \leq 30 \text{ rpm}$$

$$V = kR\,\Omega^{1/2}\left(\frac{g}{d}\right)^{1/4} \quad \text{for } \Omega > 30 \text{ rpm}$$



Ω - rotation rate
d - vessel diameter
k, K - dimensionless constants
V - particle velocity
d - particle diameter

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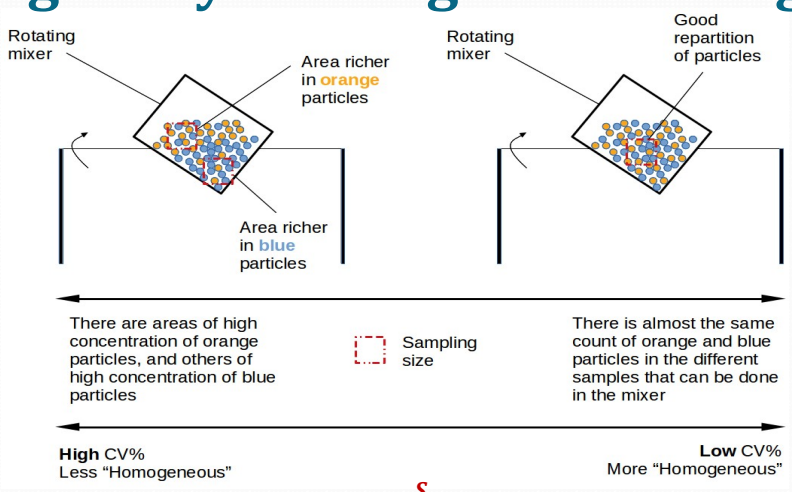
Blending Process

Homogeneity and Degree of Mixing



CV% = Coefficient of Variation of the mixture = $\frac{S}{\mu} \times 100\%$

where S = samples standard deviation, μ = arithemic average of the samples concentration

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Compression Scale-Up

- Compression is important to make robust tablets.
  - Tablets that are too soft cannot withstand the downstream coating or packaging processes without chipping or breaking and losing tablet weight/active component.
  - Tablets that are too hard cannot dissolve effectively and therefore also cannot be efficacious when considering the TPP.
- Compression is typically used to make solid oral dosage forms of core tablets. Many types of equipment are manufactured; some include single station, rotary presses.
  - Typical manufacturers are Korsch, Elizabeth Hata, SMI, GEA Courtoy, and Manesty.

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Compression Scale-Up
Parameters Critical in Tablet Production

CPP	CQA It Affects
Incoming blend	Tablet weight (flowability), compressibility in general
Feeder speed	Tablet weight
Fill depth	Tablet weight
Press speed (Dwell time)	Appearance (defects via capping or lamination)
Pre-compression	Tablet hardness
Main compression	Tablet hardness
Upper punch entry	Tablet hardness
Room humidity	Compressibility in general, degradants, tablet water content
Press temperature over time	Tablet hardness, degradants, possible change in physical form

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Compression Scale-Up

- Tablet dies and tooling may be the same from laboratory to pilot to commercial scale; the change is in tooling dwell time.

$$\text{Dwell time} = \frac{60\,000 \times \text{punch head flat diameter}}{\pi \times \text{pitch circle diameter} \times \text{press speed}}$$

- Different dwell times can cause problems such as tablet capping or lamination.

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Coating Scale-Up

- Tablet coating is the unit operation consisting of spray coating functional or nonfunctional/aesthetic coating onto the surface of the already compressed tablets.
- There are various sizes of tablet coaters, ranging up to 60" + coating pans.
- Coating pans are either perforated or nonperforated.
- PAT tools may be implemented, for example, NIR for water content.

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Coating Scale-Up
Important Parameters

CPP	CQA It Affects	Potential Problems
Pan load	Appearance, tablet water content	Improper pan loading for the scale being used
Spray gun to bed distance	Appearance	Improper spray to tablet bed
Number of spray guns	Appearance	
Exhaust temperature	Degradants, tablet water content	Spray drying of coating suspension
Atomization air flow rate	Appearance, tablet water content	Improper spray
Pattern air flow rate	Appearance, tablet water content	Improper spray
Spray rate	Appearance, tablet water content	Improper spray

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Coating Scale-Up
Important Parameters

CPP	CQA It Affects	Potential Problems
Spray formulation	Appearance, dissolution	May impede tablet dissolution
Weight gain	Appearance, dissolution	Too high may impede tablet dissolution, too low may not cover tablets/appearance
Pan speed	Appearance	Too high of pan speed
Jogging	Appearance	Too much or too little jogging of the tablet bed
Incoming tablets	Appearance, dissolution	Too soft tablets Too much disintegrant, especially on the surface of the tablets

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