PROCESS OPERATIONS AND SCALABILITY OF DOSAGE FORM

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

Process Operations and Scalability of Dosage Form

- There are many considerations in scaling-up unit operations that manufacture solid dosage forms.
- Scaling-up through **Preclinical** ➔ **Early Clinical (Phase I and Phase II)** ➔ **Late Clinical (Phase IIb and Phase III)** ➔ **Registration** ➔ **Engineering/Validation** batches has many challenges.
- Scale-up usually takes the course of laboratory experiments, pilot-scale tests, and then commercial-scale operation and continuous improvement.

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

Typical Scale-Up

Stage	Typical Material Required	REASON
Preclinical	0.05–1 kg	Early toxicology testing
Phase I and II	0.2–50 kg	Healthy volunteers and early proof of concept
Phase IIb and III	10–1000 kg	Proof of concept and verification trials
Registration	>100 kg and >100 000 unit dosages and minimum 1/10th commercial batch size	From FDA guidance
Engineering/ validation	Based on registration and expected product demand	Final process testing and process confirmation runs

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

Process Operations and Scalability of Dosage Form

- Beyond development, scale-up or scale-down also occurs **after approval**, in which changes are governed by Post-Approval Changes guidelines.
- Also, **Tech Transfer (TT)** is needed if multiple plants or CMOs (Contract Manufacturing Organizations) are required.
- Pharmaceutical process scale-up shall consider **formulation, process development, and marketing needs**.
- **Risk-based approach** is used to examine how the TPP of the drug is affected by CQAs of the final dosage form and the DS of the process.
- **Quality by Design (QbD) principles** are used to ensure a safe and efficacious product. DS, controls, and specifications are continuously improved through continuous learning.
- Another useful tool during scale-up is **process Failure Modes Effects Analysis (pFMEA)**, which is used to understand the failure modes of the CQAs to help mitigate risks in unit operations.

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

process Failure Modes Effects Analysis (pFMEA)

- pFMEA is done by understanding the **severity**, **occurrence**, and **detection** of any or all potential failure modes.
- pFMEA is different from Root Cause Analysis (RCA) as a RCA is performed after deviations have already occurred.
- **Risk Prioritization Numbers (RPNs**; scores from 1 to 1000) are calculated using pFMEA

  RPN = severity [1–10] × occurrence [1–10] × detection [1–10]
- RPNs point the engineer toward corrections that are implemented to **reduce risk** to the drug product.
  - Usually, an engineer starts to look to ameliorate problems with high RPN numbers.

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

Process Operations and Scalability of Dosage Form

- In addition to CQAs, **Critical Business Attributes (CBAs)** are also considered.
  - Business decisions that involve scale-up can relate to choice of CMO, batch size, operators needed, equipment purchases, use of PAT (process analytical technology) tools, etc.
- It is imperative to learn the **CPPs (Critical Process Parameters)** of the unit operation at hand.
  - This is done through an evolution of understanding the engineering principals and the processing knobs at the engineer's disposal.
  - These CPPs affect any or all of the CQAs of the DP

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

Topic 2 - Design of Solid Dosage Formulations

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Roller Compaction	Ribbon density Degradants Downstream dissolution	Roll speed Feed screw speeds Roll force/pressure Roll separation/gap Room temperature/humidity	Ribbon density variation High degradation
Slugging	Hardness Dissolution	Slugging force	Too little or too much
Wet granulation	Particle size Powder density Degradants Downstream dissolution	*Granulation fluid mixing time, mixing speed, amount, addition rate, and temperature* Spray nozzle air volume Dry mixing time, Wet mixing time Impeller speed, Chopper speed Power consumption	Too little or too much

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Fluid bed granulation	Particle size Powder density Powder wetness Degradants Downstream dissolution	*Granulation fluid mixing time, mixing speed, amount, addition rate, and temperature* Spray nozzle air volume Bed mixing time Supply air flow rate, temperature, dew point Product bed temperature Exhaust air temperature, dew point Filter shaking intervals	Loss of yield, Powder degradation
Milling	Particle size Degradants	Impeller speed, Feed rate Room temperature, Humidity	Undesired particle size, Degradation
Lyophilization	Degradants Physical form Product wetness	Pretreatment, freezing, drying temperature, Cycle times, Chamber pressure	Degradation, Loss of stability, Yield loss

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

Topic 2 - Design of Solid Dosage Formulations

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Blending	Blend uniformity Content uniformity	Blend time (pre- and post-lube) Rotation rate Agitator speed Room temperature, humidity	Under-blending may lead to bad CU. Over-blending may lead to poor compressibility
Encapsulation	Powder density Downstream dissolution Weight	Speed, dosing	Improper weight, broken capsules, too dense powder in capsule
Tableting	Hardness Thickness Weight Dissolution Degradants Content uniformity	Tablet weight Press (turret) speed Main compression force Pre-compression force Feeder speed Upper punch entry Room temperature, humidity	Capping if dwell time is too low Low weights or high weight variability if powder flow is bad

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

CQAs and CPPs for Some Unit Operations

Unit Operation	CQAs	CPPs	Potential Failure Mode
Tablet coating	Appearance Dissolution	*Coating suspension mixing time, mixing speed, solids' load* Atomization pressure Preheat time Jog time #, number of guns, type of guns Gun to bed distance	Twinning if tablet shape is not round Spray drying of coating suspension if temperature is too high Nonuniform coating if pan speed is too slow Tablet defects if pan speed is too fast
Tablet printing	Appearance Degradants	Ink dosage amount, force, location	Ink degrades product

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

Topic 2 - Design of Solid Dosage Formulations