Common Manufacturing Process Deficiencies for Complex Dosage Forms (TDS, MDI, DPI)

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Overview

- Transdermal Systems
  - Manufacturing unit operations
  - Manufacturing control strategy
  - Common process related deficiencies & considerations
- Dry Powder Inhalers (DPI) and Metered Dose Inhalers (MDI)
  - Manufacturing unit operations and process risks
  - Common process related deficiencies & considerations
- Conclusions

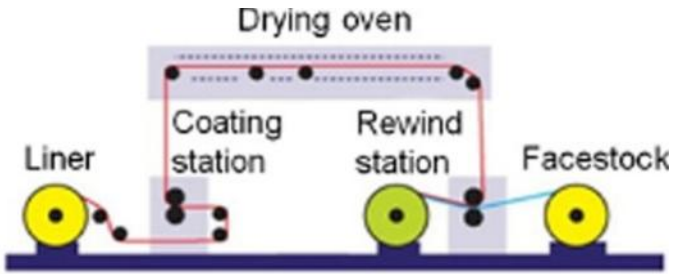
Transdermal Systems – Typical Unit Operations

Mixing

- Blend API & excipients (e.g., adhesives, permeation enhancers)

Coating/Drying/Laminating (CDL)

- Mixture applied on a substrate (e.g., release liner)
- Solvent removal (oven)
- Combine multiple layers into a single laminate
- Editing (removal of flagged defective portions)



Converting

- Slitting – cut to appropriate width
- Die-cutting to individual patches
- Pouching (heat sealing)

Image credit: British J Pharmacology, Volume: 172, Issue: 9, Pages: 2179-2209, First published: 05 January 2015, DOI: (10.1111/bph.13059)

Transdermal Systems – Typical Process Parameters

Mixing
Mixing speed
Mixing time
Temperature
Deaeration, oxygen/light controls

CDL
Die gap
Line speed
Air flow rate
Zone temperature, humidity
Lamination pressure

Converting
Cutting speed
Die pressure
Dwell time
Sealing conditions (temperature, pressure, time)

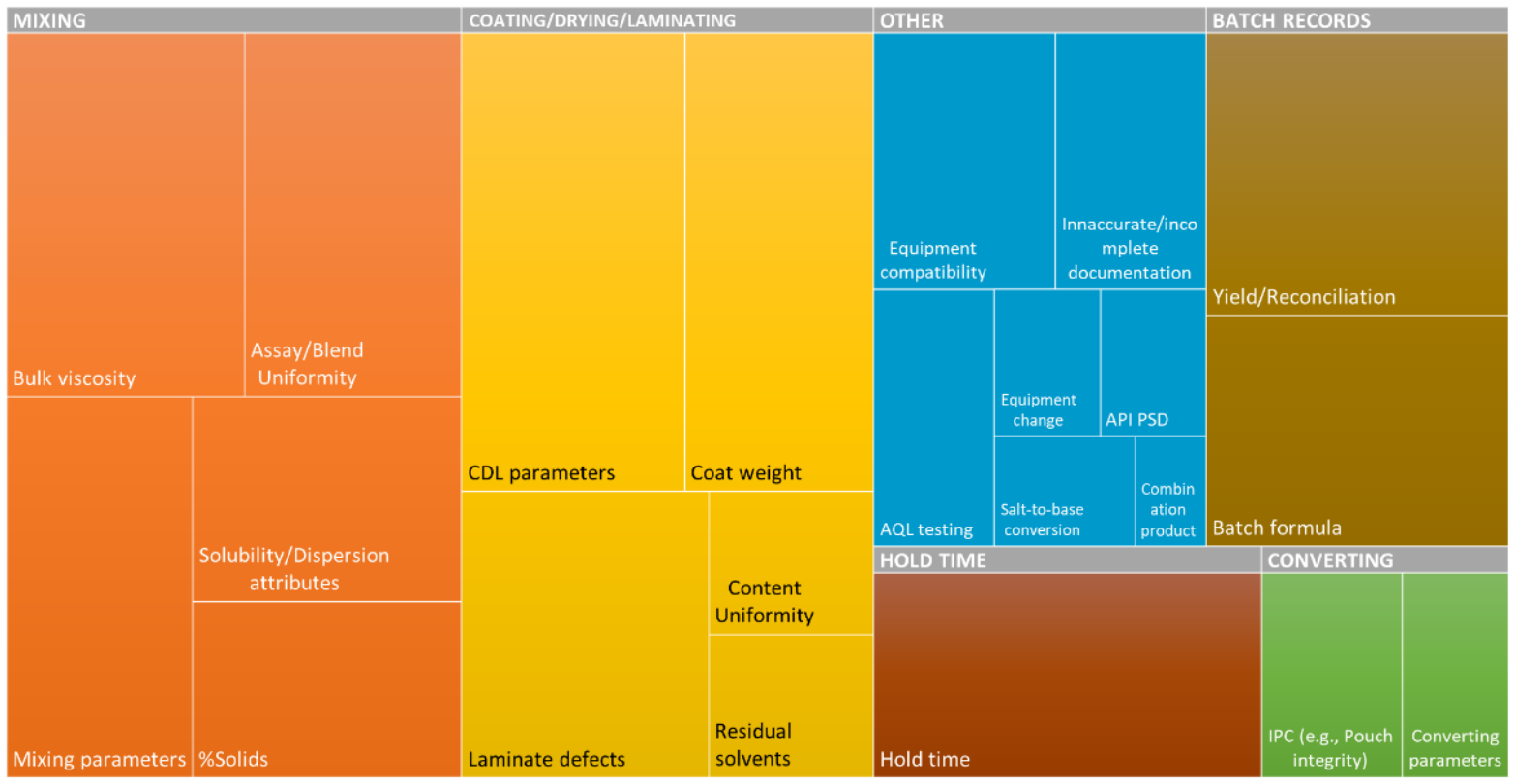
Transdermal Systems – Typical In-process Tests

Mixing
Appearance
Assay / Blend uniformity
Viscosity
% Solids
pH
Degradation products

Converting
Appearance
Slit width
Dimensions
Release liner slit functionality, Dimple verification
Pouch integrity (e.g., Leak test)

CDL
Film appearance (continuous monitoring for defects)
Microscopic appearance
Coat weight
Content uniformity
Critical excipient content
Residual solvents, Residual adhesive impurities
Adhesive properties

Transdermal Systems - Most frequently identified process deficiency topics (2021-2025)



Deficiency topic frequency is proportional to the size of the corresponding rectangle

Transdermal Systems – Deficiencies & Considerations (Mixing Unit Operation)

Topic	Common deficiency	Considerations
Mixing parameters	Increase in temperature during mixing	Implement temperature control and/or upper limits for mixing parameters
	Missing development data for re-dispersion after holding	Perform development studies. Implement mixing controls.
Bulk viscosity	Bulk viscosity test is not proposed. Proposed limits are not adequately justified.	Implement bulk viscosity test with meaningful limits.

Transdermal Systems – Deficiencies & Considerations (Mixing Unit Operation)

Topic	Common deficiency	Considerations
% Solids	% Solids/solvent content in adhesive not adjusted (or) wide range proposed	Potential variability in the composition. Wide ranges may impact API solubility, CDL process, etc.
Dispersion attributes	Risk of aggregation of the dispersed phase	Evaluate risk during development. Establish process controls and hold times.

Transdermal Systems – Deficiencies & Considerations (CDL Unit Operation)

Topic	Common deficiency	Considerations
CDL parameters	CPPs (e.g., line speed, zone temperature, air flow rate) are not defined. Range listed as 'TBD'	Evaluate these CPPs (e.g., development study data). Propose ranges accordingly.
	Process parameters were established with an earlier formulation	Process performance (e.g., drying efficiency) may be impacted.
Coat weight	Sampling strategy & specifications	Application specific. Test frequency/locations should cover the entire CDL process.

Transdermal Systems – Deficiencies & Considerations (CDL Unit Operation)

Topic	Common deficiency	Considerations
Laminate defects	Defect assessment of rate-controlling membranes is missing	Establish controls (e.g., visual inspection) for this critical component; defects may impact drug delivery.
	Significant defects (e.g., streaks) observed in the laminate	Identify & address root cause in the mixing or coating equipment

Transdermal Systems – Example consideration

CDL – Volatile components

Challenge: Evaporation during drying (e.g., volatile permeation enhancers)
Risks: CQA variability: Assay, drug release

Common development strategy:

- Evaluate risk of evaporation
- DOE studies - assess CDL process parameters & establish control ranges (e.g., line speed, dryer temperature, air flow)

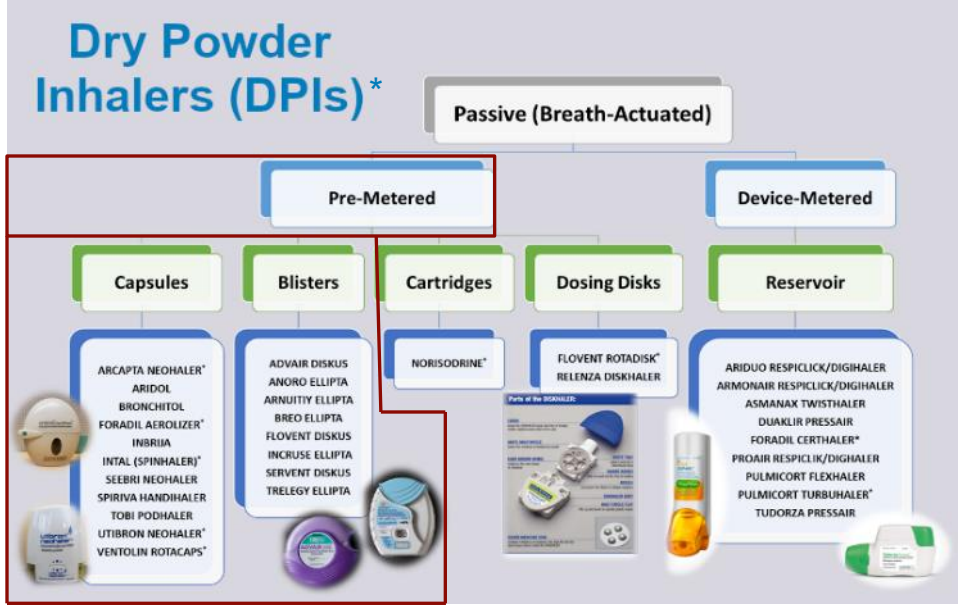
Additional considerations:

- Justify excipient excesses
- CPP ranges based on the proposed formulation & batch size
- Humidity of the drying air – potential source of variability

Transdermal Systems – Additional Deficiencies & Considerations

Topic	Common deficiency	Considerations
Converting	Missing IPCs (e.g., Release liner functionality, pouch integrity)	Release liner functionality – to verify cut through the release liner (without cutting the other layers). Pouch integrity – Required to assure product stability
Equipment change (Scale-up)	Variation in equipment capacity utilization between exhibit and commercial scale	Evaluate risk. Implement in-process controls to mitigate risk.
In-process tests	Incomplete solvent removal – may result in poor/variable adhesion	Revise residual solvent limits based on formulation and process capability.
Yield & Reconciliation	Low and/or variable yields are not discussed	Not specific to TDS. Provide justification & mitigation strategy.

Dry Powder Inhalers (DPI) and Metered Dose Inhalers (MDI)



- Pre-metered DPI examples : capsule, blister, disc

- Blister and capsule DPIs have been the main generic DPIs submitted to the FDA since 2015; this section focuses on these DPIs.

*N.ElGendy, et.al, Advanced Drug Delivery Reviews, 2022, volume 189, p114519

Capsule & Blister DPIs

- Key Manufacturing Unit Operations
  - Powder blending
  - Filling
  - Blister strip/device assembly (blister DPI only)
- Examples of Process Risks on Drug Product Critical Quality Attribute (DPCQA)
  - High product content uniformity (CU) risk due to low drug loading, potential blend segregation.
  - Blister strip physical damage, misaligned components (e.g., device subassembly, blister strip in device) can impact DP CQAs.

Capsule & Blister DPIs – Common Deficiencies & Considerations

Unit Operations	Common Deficiencies	Considerations
Blending	Missing justification for blend uniformity (BU) sampling size	Provide details on BU test sampling location, size, and acceptance criteria. A scientific justification should be provided for any sample size exceeding the typical 1x–3x unit dose weight
Filling	Insufficient individual net fill weight control information	Provide details on individual net fill weight test method, frequency and acceptance criteria. Acceptance criteria should be supported by development/exhibit batch data.
	Insufficient in-process stratified CU test information	Provide in-process stratified CU test data with statistical sampling plan and acceptance criteria (e.g., ASTM E2709/E2810) to demonstrate product uniformity throughout the filling run.

Metered Dose Inhalers (MDIs)

- Key Manufacturing Process Steps
  - Liquid compounding
  - Crimping & filling
  - Water bath stress testing, layover, functional testing
  - Filled canister and inhaler assembly

https://en.wikipedia.org/wiki/Metered-dose_inhaler

- Examples of Process Risks on DP CQAs
  - Propellant evaporation to the pressurized manufacturing tank head space can affect DP CQAs, such as assay, delivered dose uniformity (DDU), aerodynamic particle size distribution (APSD)
  - Improper valve crimping can result in valve damage, propellant leakage
  - Poor mixing and sedimentation can lead to high product CU risk in low drug loading suspension systems

MDIs – Common Deficiencies & Considerations

Process Steps	Common Deficiencies	Considerations
Compounding & Filling	Inadequate justification for propellant compensation	The proposed propellant compensation during compounding and filling should be supported by theoretical calculation and verified by in-process test data (e.g., assay, DDU, APSD before and after each propellant compensation point).
Compounding & Filling	Incomplete CPP information	CPP information (e.g., mixing/homogenization/ recirculation time & speed, crimping & filling pressures, speed, etc.) should be provided with supporting data.

MDIs – Common Deficiencies & Considerations

Process Steps	Common Deficiencies	Considerations
Filling	Insufficient fill weight control information	Provide details on individual net fill weight test frequency and acceptance criteria with justification. The 100% in-line gross weight check limit should also be justified.
Filling	Insufficient product uniformity data	Provide test data (e.g., assay, water content, alcohol content, APSD, DDU, as applicable), ensuring representative sampling throughout the filling/package run.
Functional Testing	Insufficient spray function test information	Provide details on the 100% spray function test. Weight check limits should be clearly indicated and justified to ensure final product weight control/verification.

Conclusions

- Goal is implementation of a control strategy that:
  - Assures consistent manufacture of product with desired quality
  - Mitigates manufacturing and scale-up risks
- Transdermal Systems
  - Most common process related deficiency topics: Mixing, CDL, in-process tests, yield & reconciliation and hold time
- MDI and DPI
  - Most common process related deficiency topics: Mixing, Filling, Functional Testing
- Considerations:
  - Data to support proposed process parameter ranges
  - Appropriate in-process controls to enhance detectability and mitigate risks
  - Providing necessary process related information in the submission – Minimizes Information Request/review cycles

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