Understanding development and scale up challenges to commercialization of complex oral solid dosage forms

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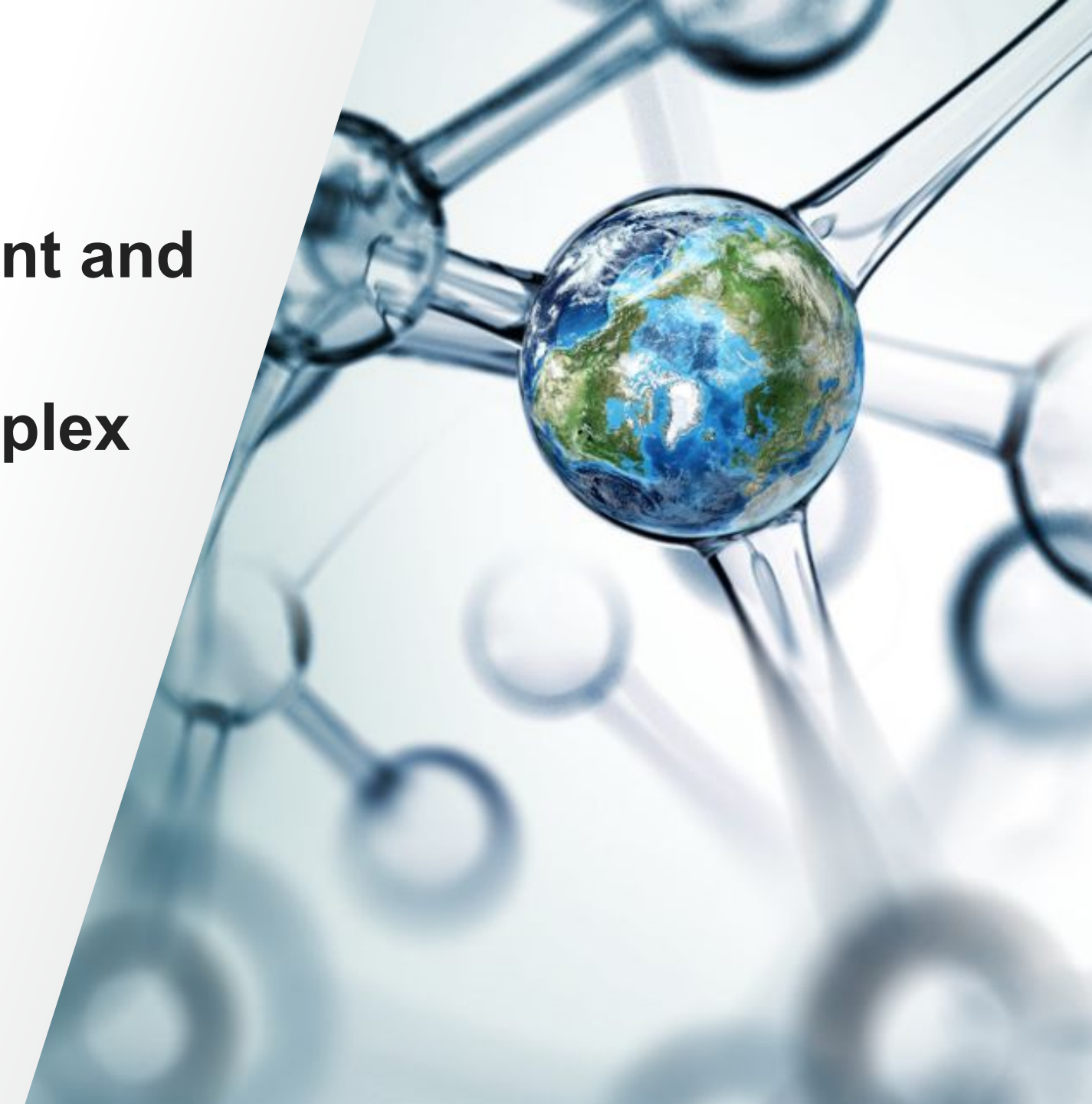

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Agenda

1. Scale up challenges in IR capsules and tabl
2. Scale up challenges in liquid filled capsules / softgels
3. Challenges in spray drying + tableting scale u
4. Scale up challenges in extrusion / spheronization, drug layering as IR / MR
5. Scale up challenges in matrix, OROS MR ta
6. Regulatory considerations for commercialization
7. Conclusions

Scale up challenges – IR capsule

- Capsules developed for Phase I
  - **Neat API in capsule**
  - Small scale
  - Manual filling or using Xcelodose
  - Poor powder flow properties
    - Static
    - Flow issues
    - Low density
    - Poor compactability
    - Hygroscopicity (?)
    - Low dose

  - Change of API source or route of synthesis or solvents of recrystallization

Scale up challenges – IR capsule

- Capsules developed for Phase I
  - **Formulated API + excipient blend in capsule**
  - Small scale
  - Manual filling or using Xcelodose
  - Poor powder flow properties
    - Static
    - Flow issues
    - Low density
    - Poor compactability
    - Hygroscopicity (?)
    - Low dose
  - Change of API source or route of synthesis or solvents of recrystallization

Scale up challenges – IR capsule

- Capsules developed for Phase I need to be scaled up to automated encapsulators

- Choice of encapsulators

  - Dosators
  - Dosing disks

  - MG2
  - Zanasi
  - Bosch
  - IMA
  - Harro Hoffliger
  - Others

Scale up challenges – IR tablet

- Tablets developed for Phase I
  - **Formulated as API + direct blending of excipient compressed in a tablet**
  - Blending and compression of small-scale batches
  - **On scale up, parameters to watch out for**
    - Poor powder flow properties
    - Flow issues
    - Low density
    - Poor compactability
    - Hygroscopicity (?)
    - Low dose drugs – content uniformity
    - High drug loading - compactability

  - Change of API source or route of synthesis or solvents of recrystallization

Scale up challenges – IR tablet

- Tablets developed for Phase I
  - **Formulated as API + blending of excipient > roller compacted and compressed in a tablet**
  - blending and compression of small-scale batches
  - **On scale up, parameters to watch out for**
    - Compressibility on a rotary press
    - Impact of speed on hardness, friability, disintegration and dissolution
    - Tooling design, choice of cams is critical
    - Tablet lamination, sticking, picking, surface properties
    - Low drug load – content uniformity challenges
    - High drug load – compressibility challenges

  - Change of API source or route of synthesis or solvents of recrystallization

Scale up Challenges – Liquid Filled hard capsules / softgels

- **On scale up, parameters to watch out for**
  - Critical Quality attributes during processing –
- Impact of type of capsule shell (gelatin / HPMC), the size of the capsule shell, fill formulation, amount of hydrophilic components in the fill, moisture ingress on
  - Physical integrity of capsules
  - Potential for leakage
  - The need for banding
  - Drug release from the capsule
  - Stability

- If a band is applied
  - Impact of banding solution composition, type / quantity of the polymer, quantity, solvent type / quantity and in some cases curing of coatings on…….
  - Release rates, variability on stability

SOFTGELS

HARD SHELL CAPS

Scale up Challenges – mini tablets filled into capsules

- **On scale up, parameters to watch out for**
  - Critical Quality attributes during processing –
- Impact of mini tablet formulation, granulation type, the robustness of granules, particle size of the drug, drug loading, size of the capsule shell, drug loading, size and dimensions of the mini tablet on
  - Physical integrity of mini tablet
  - Drug uniformity in the mini tablet
  - Drug release from the mini tablet
  - Stability

- If multi-tip tooling is required for an improved output / efficiency
  - Impact of composition, compression forces, weight variation on friability, dose uniformity, release rates, variability on stability
- Multiple mini tablet filling by count in capsules

Complex Oral Dosage forms – Immediate release

- Spray Dried intermediate – compressed into tablet
- Holt melt extrudate, milled and compressed into a tablet
- Oral disintegrating tablet
- Oral dispersible tablet
- Others

Scale up challenges - Spray dried intermediate – compressed into an IR tablet

- **Spray drying - on scale up, parameters to watch out for**
  - Critical Quality attributes during processing – thermodynamics & drying kinetics
- Impact of Solution Feed Rate, Drying Gas Flow Rate, Inlet Temperature, Condenser Temperature, Nozzle Type, Outlet temperature, Dew Point, Droplet size on
  - Stability of Drug, Amorphous Character, Particle Size, Compressibility, Dissolution Performance, Residual Solvent

- **Drug product manufacture**
  - Roller Compaction – critical quality attributes
  - Impact of roll gap, roll speed, roll force on compressibility, hardness vs dissolution
  - Confirming amorphous API stability

Scale up Challenges – HME intermediate – compressed into an IR tablet

- **HME - On scale up, parameters to watch out for**
  - Critical Quality attributes during processing –
- Impact of Polymer concentration, screw configuration, feed rate, cooling rate, rod cutting and pellet size on
  - Stability of Drug, Amorphous Character, Particle Size, Compressibility, Dissolution Performance,

- **Drug product manufacture**
  - Critical quality attributes
  - Impact of intermediate granule properties on compressibility, hardness vs dissolution
  - Finished drug product specifications
  - Confirming amorphous API stability

Scale up challenges – oral disintegrating / dispersible tablets

- **On scale up, parameters to watch out for**
  - Critical Quality attributes during processing –
- Impact of drug loading, granulation type, particle size distribution on
  - Compressibility, Friability, Moisture pick up (?), Dissolution Performance, stability

- High Speed tablet press may have an impact on
  - Compressibility and tablet properties…….

Complex oral dosage forms – modified release

- Extrusion Spheronization – filled into capsules
- Drug layered pellets filled into capsules
- Matrix tablet formulation
- Osmotic Release tablet
- Combination of IR / MR release in beads/pellets/tablets
  - IR layer + MR layer bi / trilayer tablets
  - Tablet-in-tablet

Scale up challenges – extrusion spheronization and polymer coating – filled into capsules

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of drug loading, granulation type, wet massing, spherule size on
  - Friability of the pellets, dissolution performance, stability, residual solvents (if solvent is used)

- Polymer coating parameters
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of pellets on…….
  - Release rates, variability on stability

Scale up challenges – drug layered pellets filled into capsules

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of drug quantity to be layered / coated, particle size of the drug to be layered, solvent type / quantity on
  - Drug uniformity on the layered pellets, dissolution performance, stability, residual solvents (if solvent is used)

- Polymer coating parameters
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of pellets on…….
  - Release rates, variability on stability

  - Damage of layered pellets / polymer coating during encapsulation

Scale up challenges – matrix-controlled release tablets

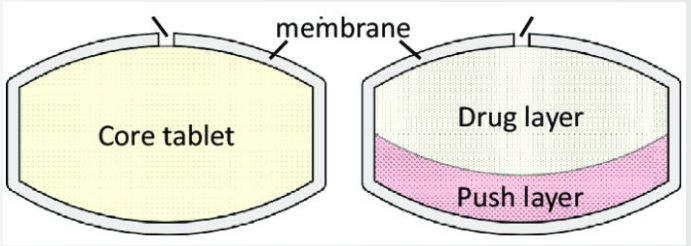
- Polymer matrix, wax matrix, combination of matrix + coating

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of polymer type / quantity on
  - Erosion, diffusion, release of the drug from the core tablet
  - Release rate on stability

Scale up challenges – osmotic release MR tablet

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of the polymer, combination of polymers used, whether the tablet is formulated as a single layer or bilayer tablet, push / pull strategy – osmogens used, semipermeable membrane coating thickness, size / dimensions / number of laser drilled orifice on
  - Drug release rates, variability of release on stability, residual solvents (if solvent is used)

- Polymer coating parameters
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of tablets on…….
  - Release rates, variability on stability

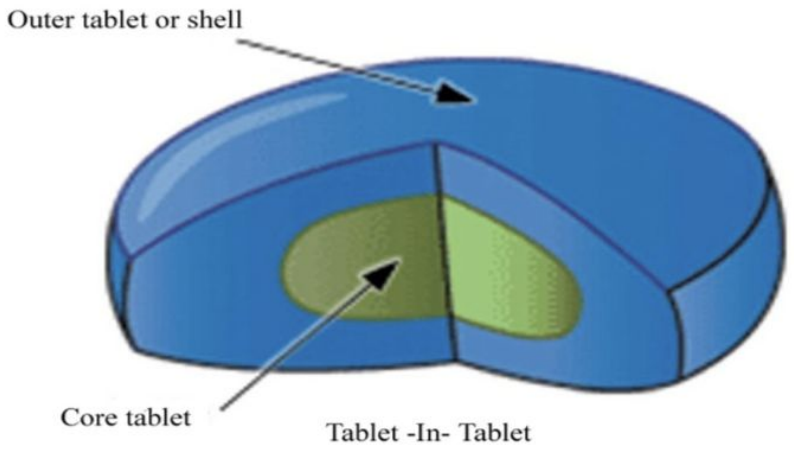


Scale up challenges – IR layer + MR layer bi / tri-layer tablets

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of IR layer composition, MR layer composition – polymer type/quantity on swelling, erosion on
  - Adhesion of the bilayer / trilayer tablet
  - Drug release from the IR layer
  - Drug Release from the MR layer
  - Drug uniformity in both the layers
  - Stability

- If an additional polymer coating is applied
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of coatings on…….
  - Release rates, variability on stability

Scale up challenges – tablet-in-tablet (IR core / MR coat)



- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of IR layer composition, MR layer composition – polymer type/quantity on swelling, erosion on
  - Centering of the inner core tablet into the outer matrix granules
  - Adhesion of the layers / tablet
  - Drug release from the IR layer
  - Drug Release from the MR layer
  - Drug uniformity in both the layers
  - Stability

- If an additional polymer coating is applied
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of coatings on…….
  - Release rates, variability on stability

Scale up challenges – fixed dose combinations (multi-layer tablets)

- **On scale up, parameters to watch out for**
  - Critical quality attributes during processing –
- Impact of individual layer composition, IR/ MR layer composition – polymer type/quantity on swelling, erosion on
  - Adhesion of the layers
  - Drug uniformity in both the layers
  - Drug release from the IR layer
  - Drug Release from the MR layer
  - Stability of each API in each layer

- If an additional polymer coating is applied
  - Impact of polymer type, quantity, solvent type / quantity and in some cases curing of coatings on…….
  - Release rates, variability on stability

Regulatory considerations for commercialization

- Meeting all compliance requirements of starting materials, drug substance, intermediates, drug product, packaging materials to meet specific regulatory agency or global requirements

- Meeting all requirements and data / justification to confirm robustness of drug substance, intermediates, drug product manufacturing by adopting QbD studies, validation studies to confirm manufacturability, scalability, safety and efficacy of the drug product.

Conclusions

- Problems / situations start in development

- Having a thorough understanding of the potential challenges on scale up and generating sufficient pre-formulation data / information ahead of scale up phase is the key.

- Adoption of a systematic scale up predictions, risk assessment, failure mode effect analysis (FMEA) will help plan and address impact of critical processing parameters (CPP's) on critical quality attributes (CQA's) early.

- Bringing in the right expertise / resources in-house and from a CDMO helps resolve challenges

Thank you

Please feel free to reach out if you have any questions or would like more information.