Screening and Development of Spray Dried Amorphous Solid Dispersions

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Agenda

Development of ASD
- Excipients selection
- Physical stability considerations
- Performance assessment

From the lab to market - overview of ASD technologies
- Spray drying
- Co-precipitation
Introduction
Development of a new ASD

- Increase solubility;
- Maintain supersaturation;
- Extend drug exposure;
- Enhance bioavailability.

- Amorphous stability;
- Avoid recrystallization;
- Drug-polymer miscibility;
- Long-term storage.

- Assay and impurity profile;
- Drug-polymer chemical compatibility;
- Toxicological effects.

- Process selection;
- Process optimization;
- Scale-up considerations;
- Downstream processing.
Predicting Physical Stability
Evaluating drug-polymer miscibility/phase behavior

Late 90’s
- Empirical
  - Low throughput methods
  - DSC – 1x T_g vs 2x T_g s
  - XRPD – amorphous halo
  - Fox and Gordon-Taylor equations

From 2000 onwards…
- Miniaturization
  - Amorphous films
  - Solvent casting
  - Spin-coating
  - Typical characterization
  - Broader design space

…2010
- Computational
  - Empirical / mechanistic models
  - Solubility parameters
  - Flory-Huggins Theory
  - Temperature-composition phase diagrams
Predicting Physical Stability
Evaluating drug-polymer miscibility/phase behavior

**INPUTS**
1) Thermodynamics: Flory-Huggins Theory
2) Kinetics: Components Diffusion
3) Process: Evaporation Rate

**OUTPUTS**

*in silico* drug-polymer miscibility estimates
(TKE model)*

* I Duarte *et al*, Pharm Res, Jan 2015, 32(1), 222-37
Predicting Performance
Evaluating supersaturation/precipitation inhibition

Late 90’s
Empirical

- Low throughput methods
- Powder dissolution
- USP dissolution testing
- Compendial media
- Poor IVIVC

2007-2011
Miniaturization

- 96-well microplate format
- Casted film dissolution
- Solvent- /pH-shift methods
- Biorelevant dissolution
- Membrane methods

...2010
Computational

- Mechanistic modeling
- Statistical (i.e. PCA, PLS)
- Physiological-based models
- Molecular descriptor-based models
Predicting Performance
Multivariate analysis

- After outlier’s identification 23 observations;
- Log \( \frac{AUC_{\text{in vivo, ASD}}}{AUC_{\text{in vivo, REF}}} \);
- \( R^2 = 0.499 \) and \( Q^2 = 0.344 \);
- Interpretation purposes ☑️

![Diagram with variables and observations](image-url)
Hovione screening methodology

Validation of the screening program

Selection of polymeric carriers

Performance

Prototypes production

Prototypes analytical characterization

Physical stability

INPUTS:
- Target drug product profile;
- Drug’s physicochemical properties (e.g. S, Log P, stability, T_M, T_g, # H-bonds);
- Polymer’s physicochemical properties (e.g. S, HLB, T_g, # H-bonds);
- Manufacturability issues.

DELIVERABLES:
- Small group of potential polymeric excipients.

DELIVERABLES:
Performance:
- Polymer ranking based on precipitation inhibition effect;
- Preliminary assessment of supersaturation potential.

Physical stability:
- Drug-polymer miscibility estimates;
- Preliminary assessment of optimal drug load range;
- Solvent casting.

DELIVERABLES:
Prototype production:
- Lab-scale spray-drying;
- Definition/optimization of drying process conditions;
- Fine-tuning of formulation variables.

Analytical Characterization:
- Physical stability (fresh product and long-term storage):
  - mDSC, XRPD;
- Performance (in vitro):
  - Powder dissolution;
  - Non-sink conditions, biorelevant medium.

6-7 SYSTEMS

4-5 SYSTEMS

2-3 SYSTEMS
Drug A is poorly water soluble, Tm/Tg ~1.28, cLogP ~4.8

- Correlation between experimental and screening data;
- False-negatives can be observed;
- Importance of small-scale “bench” screening to re-evaluate unexpected results.

**Physical Stability**
(computational analysis and solvent casting)

- Model: Solvent Casting
- Solvent: ITZ
- Drug Load (% w/w): 15, 35
- Formulations: HPMC, HPMCAS, PVPVA 64, Eudragit® L100

**Performance**
(supersaturation – solvent-shift method)

- AUC<sub>0-240</sub> [mg·h/L]: 5, 10, 15, 20, 25, 30, 35

- Supersaturation (solvent-shift)
- Powder Dissolution

- Correlation between the powder dissolution and the supersaturation screening results;
- Ability to maintain the performance ranking initially defined.
Agenda

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From the lab to market - overview of ASD technologies

- Spray drying
- Co-precipitation
## Overview of ASD technologies

<table>
<thead>
<tr>
<th>Spray Drying</th>
<th>Hot Melt Extrusion</th>
<th>Other (e.g. Coprecipitation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="INTELENCE" /></td>
<td><img src="image2" alt="New Fenoglide 120mg" /></td>
<td><img src="image3" alt="Zelboraf" /></td>
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<tr>
<td><img src="image4" alt="Cesamet" /></td>
<td><img src="image5" alt="KALETRA" /></td>
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<td><img src="image6" alt="INCIVEK" /></td>
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<td><img src="image8" alt="kalydeco" /></td>
<td><img src="image9" alt="Fenoglide 120mg" /></td>
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<td><img src="image10" alt="Zelboraf" /></td>
<td><img src="image11" alt="Fenoglide 40mg" /></td>
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</tbody>
</table>
Spray Drying Principles

- Flash drying
- Mild process
- Control of SDD attributes (particle engineering)
- Scalable
- Commercially demonstrated
- Solvent based process
Spray Drying Principles

1. Thermodynamics
   - Spray Drying conditions determined through heat and mass balance.
   - Detect abnormal conditions of operation

2. Atomization
   - Droplet size estimation as a tool for scale-up
   - Achieve target particle size distribution

3. Drying Kinetics
   - Effect on powder properties: e.g. morphology and BD.

4. Computational Fluid Dynamics
   - Optimize powder performance
   - Identify pitfalls
Case Study
Spray drying

- High RS_out (high solvent content in the powder)
- High F_feed (equipment limitations)
- Low RS_out (low solvent content in the powder)
- Low F_feed (process is inefficient)
- High T_in (equipment limitations)
- High T_out (impact on powder properties)

Outlet temperature
Inlet temperature
Feed flow rate
Spray Drying Principles
Atomization modelling

- Droplet size is the main factor affecting particle size
  - Droplet size = $f$ (nozzle configuration, feed pressure / rate, solution properties)
  - Droplet size can be maintained constant for attaining a similar particle size across scales
- Droplet size correlations were developed by Hovione for different spray nozzles
  - Pressure nozzles, Two fluid nozzles

- Pressure nozzle
  - Narrow PSD
  - Particle size manipulation depends directly on the feed rate / feed pressure
  - Not suitable for very high viscous feeds

- Two fluid nozzle
  - Wider PSD
  - Droplet size easily manipulated
  - Lower sensitivity to feed viscosity
Spray Drying Principles  
Drying Kinetics

- Droplet and particle size are intrinsically connected, however particles can follow different formation pathways depending on drying kinetics and product properties.
- Drying kinetics can be controlled by outlet temperature and relative saturation.

<table>
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<tr>
<th>Fast Drying</th>
<th>Properties</th>
<th>Slow Drying</th>
</tr>
</thead>
<tbody>
<tr>
<td>High $T_{\text{out}}$ / Low $RS_{\text{out}}$ / High HMT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflated Particles</td>
<td>Spherical, Shriveled, Decrease</td>
<td>Low Bulk Density, High</td>
</tr>
<tr>
<td></td>
<td>Low Residual Solvent, High</td>
<td>Low Bulk Density, High</td>
</tr>
<tr>
<td></td>
<td>Inflated (breakage may occur)</td>
<td>Particle size, Decrease</td>
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<td></td>
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</tr>
<tr>
<td>Slow Drying</td>
<td></td>
<td>Inflated, High</td>
</tr>
</tbody>
</table>

Shrunken Particles

Fast Drying Properties
- Spherical Morphology
- Low Bulk Density
- Low Residual Solvent
- Inflated (breakage may occur)
Development by Design

Traditional

1. Tech Transfer
2. Scale-Up Dev.
3. Clinical Supplies
4. Scale-Up Dev.
5. Registration
6. Clinical Supplies
7. Validation

DbD

1. Tech Transfer
2. Clinical Supplies
3. Registration
4. Clinical Supplies
5. Process Intensification
6. Design Space definition
7. Validation
Spray Drying Scale up – Development by Design

Example

Powder properties vs scale independent parameters

- Straight to GMP manufacturing: process (direct) scale-up based on scale-independent correlations (Hovione thermodynamic and atomization models).
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  - Co-precipitation
Other platforms - Amorphous Nanoparticles by co-precipitation

- Solvent(s)
- Anti-solvent
- Solvent – Anti-solvent ratio
- Solids concentration

- Working pressure

- Mixing conditions

- Cooling Phase

- Isolation step
Part I – Study the effect of critical formulations variables on typical CQAs of ASDs

The precipitation path is key for:
- precipitation rate,
- Composition – “Polymer rich phase” / “Polymer poor phase”
Part I – Study the effect of critical formulations variables
Thermodynamics of mixing
Amorphous Solid dispersions: co-precipitation vs SD
Carbamazepine – BCS class 2a example

20 wt.% CBZ:Eudragit®L100 8 wt.% C_feed, by SCP

20 wt.% CBZ:Eudragit®L100 8 wt.% C_feed, by SD

60 wt.% CBZ:Eudragit®L100 8 wt.% C_feed, by SCP

Surface Area
81.7 m²/g
Surface Area
9.1 m²/g
Surface Area
19.7 m²/g

NanoAmorphous
MicroAmorphous
NanoCrystalline

Nano vs Micro
Amorphous vs Crystalline
Amorphous Solid dispersions: co-precipitation vs SD
Carbamazepine – BCS class 2a example

- Both the nano-amorphous and the nano-crystalline formulations, produced by co-precipitations, exhibited faster in vivo dissolution rates, when compared with the micro-amorphous produced by Spray Drying or pure crystalline samples.
Key messages

- ASD is nowadays a proven platform with several APIs in the market;

- Computational tools can be used in screening programs to support understanding, predictability, while saving time and resources;

- Polymer properties are key both to performance and physical stability of ASD

- Manufacturing technology is product/formulation dependent

- Strong science & process understanding (thermodynamics, atomization, particle formation) make scale up a straightforward and predictable task
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Thank you for your attention.

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