Developing spray dried dispersions for early phase clinical trials and beyond

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Presentation outline

- Formulation strategies and the Developability Classification System (DCS)
- Benefits of spray-drying to address poor drug solubility
- Fit-for-purpose systems in early clinical research and effectively transitioning to solid oral dosage forms
- Adaptive clinical manufacturing “tailored” to the clinical study and patient recruitment
Formulation strategies and the Developability Classification System (DCS)
Understanding the drug candidate

- Robustly evaluating the molecule properties is the first key step for today's formulators
  - Chemical and physical stability
  - Desired final product attributes for patient compliance
  - Solubility and permeability limitations

- This knowledge must be gathered efficiently to minimize “time to clinic”
Developability Classification System: the “DCS”
Drives formulation strategy

- **Class I** (Dissolution limited)
- **Class IIa**
- **Class IIb** (Solubility limited)
- **Class III**
- **Class IV**

Human jejunal permeability

Aqueous dose solubility ratio
# Formulation technology selection

<table>
<thead>
<tr>
<th>Formulation technology</th>
<th>DCS class</th>
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<tbody>
<tr>
<td></td>
<td>Class I</td>
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<tr>
<td>API only</td>
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<tr>
<td>Micronization</td>
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<td>Nanomilling</td>
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<td>Dissolution enhancers</td>
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<td>Amorphous dispersions</td>
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<td>Lipidic systems</td>
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<td>Complexation</td>
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<td>Efflux inhibitors</td>
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<td>Permeation enhancers</td>
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## DCS IIb formulation options

<table>
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<tr>
<th>Formulation approach</th>
<th>Advantages</th>
<th>Considerations</th>
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| Amorphous dispersions         | High drug loading possible  
Inclusion of different functional excipients  
Easily scaled  
Flexibility of dose presentation | Need to maintain amorphous state through packaging  
Prediction of long term stability |
| Lipidic systems               | Solubilised dosage form  
Can reduce PgP efflux  
Can help overcome food effect | Drug loading per unit dose may be limited  
Some lipid excipients not well tolerated by pre-clinical species  
Consistency of lipidic excipients |
| Cyclodextrin systems          | High drug loading possible  
High solubility and low viscosity  
Can provide physical stability | Complex can compromise exposure if disassociation not achieved  
Tox profile of some CDs          |
Formulation strategy for DCS class IIb molecules

- **Target Product Profile consideration**

- **Rapid screening of formulation approaches**
  - Use biorelevant media to identify discriminatory dissolution method
    - Dissolution profile
    - Precipitation
    - Stability testing / predictions

- **Selection of lead formulation prototypes**
Developing a spray drying process
Spray drying development for new molecules

- **API characteristics**
  - Product format
  - Unit dose required

- Solubility screen to identify feedstock components (i.e. solvent or mixtures of solvents), maximum feedstock concentrations. Feedstock stability

- Identification of suitable excipients based on drug characteristics (is it required as bulking agent, stabiliser, precipitation inhibitor, solubiliser, flavours etc.)

- Experimental runs looking at critical process parameters such as outlet temperature, solution feed rate and atomisation parameters

- **XRPD**
  - Amorphous nature

- **mDSC**
  - Glass transition

- **DVS**
  - Critical RH

- **Biorelevant dissolution**
  - Precipitation
Transitioning SDD to solid oral drug product

- Production of SDD for delivery as Powder in Bottle suspension is often suitable for initial human trials
  - Wettability can be controlled by selection of vehicle and reconstitution method
  - Bed-side preparation to reduce stability requirements

- The final dosage form preference however is often tablet, this requires a number of considerations
  - Drug loading within the SDD
  - Particle size differences between SDD and blend excipients
  - Wetting properties of the SDD
Designing an SDD tablet product

Drug dose required
Maximum tablet weight
Baseline SDD parameters

Densification method for SDD material

Identification of suitable disintegrant and filler excipients and required levels

Experimental design to identify tablet composition using dissolution profile

Experimental design to identify operating parameters

- XRPD
  - Amorphous nature
- mDSC
  - Glass transition
- Residual solvent
- Biorelevant dissolution
  - Wetting, Disintegration
Case study: Accelerated development of an oral SDD product from FIH to POC
Background and objectives

**Background**
- Poorly soluble NCE
- Spray drying identified as preferred formulation strategy
- Integrated CMC program required to accelerate FIH-POC

**Programme objectives**
- Rapid initiation of first in human development (200g SD batch size)
- Manage transition to solid oral dosage form for patient POC (2,000 unit batch size)
- Scale-up and supply Phase II product (20,000 unit batch size)
- Avoid critical path impact on program
Program design

CMC development
- Real-time GMP manufacture of FIH drug product (PiB)
- Development and clinical validation of IR tablet
- Scale up and manufacture of POC drug product

Clinical development
- SAD/MAD Trial (healthy volunteers)
- Relative BA study (healthy volunteers)
- Phase II patient sites
Powder in bottle for first-in-human (FIH) study

- **SDD process established on ProCepT spray dryer**
  - Process parameter scouting, drug loading confirmation

- **Drug product process development**
  - SDD in bottle format
  - Reconstitution process confirmation with in-use stability

- **SDD regulatory batch**
  - Provision of batch analysis data
  - Stability data to support 7 day shelf life

- **Flexible GMP manufacturing for SAD/MAD**
  - Balance of API stock levels and shelf life of drug product
IR tablet development

- **SDD**
  - Dry granulation
  - Develop & qualify QC methods

- **Formulation & analytical development**
  - Biorelevant dissolution
  - Formulation selection

- **In vitro characterization**
  - Batch release data
  - 1 week stability data
  - 1 month extension plan

- **CMC batches for regulatory filings**

- **Integrated CTM & clinical dosing**

![Graph showing drug release over time](image)
Clinical validation of the IR tablet

Interim decisions

- Reference (SDD in buffer)
- Lead tablet system (X mg)
- Lead tablet system (Y mg)
- Lead tablet system (Y mg fed)

Interim decisions

- Multiple dosing cohort

- 4 period crossover
- 12 healthy volunteers to achieve data sets in 8
- Subjects on-site from evening before until 48 hours after dosing

- 10 days BID dosing with selected formulation
- N=10 healthy volunteers (8 active: 2 placebo)
Program outcome

- Desired exposure achieved with SDD formulations
- Integrated program delivered
  - SDD PiB supply for SAD/MAD
  - IR tablet developed and validated
  - Frel 100% vs suspension
  - Acceptable performance with food
  - IR tablet scaled up and delivered for patient POC
  - No impact on critical path to POC
  - IR tablet activities in parallel to SAD/MAD
Adaptive clinical manufacturing “tailored” to the clinical study and patient recruitment
Drug product supply

- **Today’s challenges to conventional clinical supply paradigms**
  - Increasing research focus in oncology, orphan and pediatric disease
  - Challenging and sporadic patient recruitment
  - Multiple sites and countries
  - Tuned formulations required based on patient attributes (e.g. body weight, phenotype)

- **Implications for CMC supply chains**
  - Getting the right product to the right patient at the right time
  - Flexibility in dose required for clinical success
  - Smaller more flexible batch size requirements
Flexible & adaptive manufacturing for Phase I

The challenges: Small batch sizes, API quantity limitations, dose flexibility, project timelines

- Quick read on molecule whilst knowing final TPP is achievable
  - Project investment prior to first clinical signal

- Matching batch size to clinical trial design
  - Small quantities of drug product required, working with limited quantities of API
  - Avoid waste of clinical drug supply
  - Creative approached to minimise generation of large stability package

- Ensuring adequate drug supply is available
  - Manufacture flexible doses (when dose is linked to weight or surface area) or bulk product to support clinical design
  - Avoid expiry of clinical drug supply
Flexible & adaptive manufacturing for Phase II

- **Matching batch size to clinical trial design**
  - Move to drug product presentation required for patient trials
  - Rapidly scale process trains to meet needs of clinical study – typically <3,000 units required for Phase IIa but ~20,000 units required for Phase IIb
  - Parallel tracking of stability studies to ensure shelf life requirements are met

- **Ensuring adequate drug supply is available**
  - Growth in orphan, rare diseases, paediatric trials can put strain on drug product requirements
  - Seed clinics at start of study or work with sites to provide drug product on demand
  - Manage global clinical drug supply to meet clinical demands

*The challenges: Manufacturing scale to meet demands of patient trials, patient recruitment rate, balance of drug product across sites*
Case study: flexible & adaptive manufacturing

Proof-of-concept in Alagille Syndrome (ALGS) and Progressive Familial Intrahepatic Cholestasis (PFIC)

Program requirements/challenges:

- Pediatric patient population
- Solution formulation, limited stability
- Patient packs required for home dosing
- Recruitment sporadic and unpredictable (n=1)
- Patients dosed based upon body weight
- Dose varies during treatment (fixed volume)
- Dose adjustment in response to emerging data

Program design:

- Randomized and blinded design
- On demand, personalized drug product supply
- GMP manufacturing, labelling and packaging
- QP released and shipping
- Supplied up to 124 weeks for daily dosing
- Resupplied every 1-3 months
- >180 patients, >1000 shipments
- >25 sites across 8 countries

Product available for dosing globally within 1-3 weeks of confirmed subject eligibility
Summary

- **Poorly soluble compounds are prevalent in pipelines today**
  - Options open to formulators depend on the molecule classification
  - Rapid in-vitro screening is required to identify lead candidates for clinical evaluation

- **Spray drying is widely used in drug product development to overcome solubility and stability challenges**
  - Ability to incorporate excipients into the formulation
  - Flexibility to further process into solid oral dosage forms for longer term product presentation
  - Processes are scalable supporting late stage development
  - Established technology already used in commercial products providing regulatory familiarity

- **Drug product supply can require creative solutions in early stage clinical studies**
  - Adaptive manufacturing strategies can balance the needs of the clinical trial design, API availability and patient recruitment
Assess. Adapt. Accelerate.