Science-Based Approach in Product Development and Product Quality

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Eli Lilly

CHICAGOLAND PHARMACEUTICAL DISCUSSION GROUP
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Pharma industry challenges are numerous and are challenging both innovation and productivity.

- Increased R&D costs and reduced productivity.
- Challenging product portfolios and pipelines.
- Inability to recoup R&D costs for innovator products.
- Aggressive generic competition.
- Pricing and marketing pressures form insurance companies.
- Loss of internal skill sets and technical capabilities (with job losses).
- Lowered public reputation and trust.

Jayne Hastead, JDP Pharma Consulting, LLC
Enhancing productivity in pharma: Business models for increased productivity

• Shift from conventional integrated to virtual or distributed product development.
  – Large pharma companies cut back or abandon their own early stage drug development programs, and switch to less costly in-licensing model.
  – Small, more nimble and innovative biotech companies should discover drugs.
  – Partner with academic institutions for discovery.
  – Off shoring research and development to reduce costs.
  – Utilize CRO’s to compensate for limited internal resources and expertise.
Key learning's: The way we do development is changing.

• In-licensing from small biotech and pharma companies allows large pharma to “cherry pick” their molecules.
  – Timing: after POC is established to reduce development risk.

• Reduce CMC effort until after POC is established.
  – “Fast to fail” approaches reduce upfront investments and missed opportunity costs.

• Outsource technical expertise and capabilities
  – Utilize external CRO’s and CDMO’s and distributed development approaches instead of internal resources and integrated development approaches.
  – Successful alliances require elevated levels of program management (collaboration and communication) and an understanding of the external technology.
Why do drugs fail?

• Failures are mainly due to lack of efficacy.
  – Compounds with novel mechanisms and/or difficult clinical end points/biomarkers carry higher risk of failure.

• What about CMC issues:
  – Can lack of efficacy be linked to formulation design and/or product performance? YES.
  – Are there products that have been recalled, never launched, or simply pulled from the market due to technical design issues? YES.
  – Can potential phase III failures be mitigated during POC? YES.
Development strategies, POC, science and the patient.

• Product development strategies to increase productivity only work when the **path is understood and the science is good**.
  – Determine “Fast to fail” versus “fast to market” approach early on.
  – Distributed development or Integrated development?
    • Collaboration and relationship building= **PARTNERING** instead of contract development and manufacturing.
    • Clarity of roles and responsibilities and great project management are essential to the success.

• Well designed POC studies add value to the product throughout the development cycle.
  – Target product profile will evolve with the product development.

• Understanding the technology and science needed to differentiate the product.
  – Applicable to both internal and external development strategies.

• Design products with an understanding of how the patients will interact with them.

JDP Pharma Consulting, LLC
Typical questions asked as molecules move form POC to commercialization

• Successful POC – How soon can we get ready for pivotal phase III?
• What is POC for the molecule: early biomarker study, smaller efficacy trial.
• What does pivotal studies mean to your company (standard vs. adaptive trial design)?
• Which group is responsible for product commercialization (early phase vs. late stage)
Drug Development Paradigm at Lilly: Integrating science-driven development in CMC.

- FHD → Phase II → POC Trials → Phase III

Enabling Clinical Trials/Material Generation Strategy

Appropriate risk assessments/decision trees

Relevant Information

Information Generation/Readiness for Commercialization

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Typical Drug Product Pivotal Phase III Requirements

- Prototype dosage form introduced into the pivotal trials, further refinements in composition/process conducted throughout the pivotal phase study
  - Parenteral vs. oral
  - Bio-linking strategy (Rel. Bioavailability vs. Bioequivalence)

- Dosage form composition is locked, only process optimization is conducted during this phase
  - Bio-linking strategy (Rel. Bioavailability)

- Dosage form composition/process is fixed, scale up and tech transfer has occurred, pivotal material is made at final commercial manufacturing site
Science based Approach: Using QbD in Dosage Form Development.

• Define quality target product profile
• Design and develop product and manufacturing processes
• Identify critical quality attributes, process parameters, and sources of variability
• Use of appropriate risk assessment tools
• Control manufacturing processes to produce consistent quality over time
Quality Target Product Profile

*Beginning with the end in mind*

- **Quality Target Product Profile**
  - Quality characteristics (attributes) that the drug product should possess in order to reproducibly deliver the therapeutic benefit promised in the label

- **Dynamic** as it will change as knowledge of the product increases

- **Quality Target Product Profile** (e.g., For a tablet)
  - Dosage Form
  - Appearance
    - Shape, size etc.
  - Identity
  - Strength
  - Assay
  - Uniformity
  - Purity/Impurity
  - Stability, and
  - Release rate
    - Pharmacokinetics and bioequivalence

- **Others**

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Lawrence Yu-PDA presentation
Key Information Needed At Start Of The Commercial Platform And Process Selection

• **BCS classification**
  – pH-solubility at 37 °C using stability indication method
  – Absorption/permeability studies

• **Final polymorph selection**

• **Solid state studies**
  – Intrinsic dissolution
  – Particle size distribution
  – Crystallinity
  – Solid state stability
  – Moisture sorption

• **Physico-mechanical studies**
  – Bulk density
  – Flow properties
  – Compactability
  – Compressibility

• **Solution state studies**
  – pKa, log P, log D Vs pH (electrolytes)
  – log P (non-electrolytes)
  – pH-solubility
  – Solubility in simulated biological fluids (SGF and SIF)
  – Solubility in pharmaceutically relevant systems
  – pH solution stability
  – Mechanism of degradation
  – Rate studies
  – Stabilization/stabilizer

• **Drug excipient compatibility**

• **Process Induced Phase Transformation Studies (PIPT)**
Do you accept API properties and select appropriate DP manufacturing platform OR engineer API to enable preferred DP mfg platform?

Engineering API properties is preferred if *in-vivo* performance is not an issue for the compound. DP control strategy is simplified. If *in-vivo* performance is an issue then select an optimum DP formulation/process platform – *in-vivo* performance defines the strategy.
**Potential Impact of API Attributes On Drug Product Attributes**

<table>
<thead>
<tr>
<th>DP CQAs</th>
<th>Particle Size</th>
<th>Salt form</th>
<th>Moisture</th>
<th>Crystallinity</th>
<th>Morphology</th>
<th>Stability</th>
<th>Solvent content</th>
<th>Purity</th>
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**Potential Impact of Excipients On Drug Product CQAs**

<table>
<thead>
<tr>
<th>DP CQAs</th>
<th>Microcrystalline Cellulose</th>
<th>Lactose Monohydrate</th>
<th>Croscarmellose Sodium</th>
<th>Magnesium Stearate</th>
<th>Talc</th>
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Pharmaceutical development case study: Ace Tablets, Conformia CMC-IM, 2008
• Process design/screening

• Process development
  – Manufacturing sequence or steps, unit operations
  – Equipment settings (such as speed and feed rate)

• Process optimization
  – Understanding relationship between CQA’s and CPP’s and material attributes
  – Determines a design space

• Process scale up/tech transfer

• Process Robustness
  – Mostly conducted after product is transitioned to manufacturing
Process Design

- Process design is the initial stage of process development where an outline of the commercial manufacturing processes is identified.

  - A clear understanding of predefined product quality objectives/attributes

  - Properties of the materials (API and raw materials)
  - Preferred manufacturing platforms by the company
  - Facility,
    - Equipment, environmental controls
    - Containment capability, engineering controls, material transfer
    - Manufacturing variables
Science Should Always Drive the Selection Of a Particular Manufacturing Process

- Solubility
  - Low Typically <0.1µg/mL
  - Other non preferred formulation approaches

- Aqueous stability
  - Poor
  - • Roller compaction
  - • Direct compression
  - • Fluid bed granulation
  - • Solvent granulation
  - Adequate
  - • High shear

- Dose
  - Acceptable
  - Low <0.5% w/w
  - Wet granulation tablets
    - • High shear
    - • Fluid bed (concentrated granules)
  - High >60% w/w
  - • High shear

- Tablets
  - Wet granulation
  - Direct compression

- Capsules
  - • High shear
  - • High shear

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Risk Matrix Tool: Risk Assessment to Identify Variables Potentially Impacting Product Quality

<table>
<thead>
<tr>
<th>DP CQAs</th>
<th>Formulation Composition</th>
<th>Blending I</th>
<th>Roller Compaction</th>
<th>Milling</th>
<th>Lubrication</th>
<th>Compression</th>
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Pharmaceutical development case study: Ace Tablets, Conformia CMC-IM, 2008
Bio-Linking Strategy of POC Formulation To Pivotal Formulation

• No explicit guidance by the regulatory agency on the requirements prior to start of the pivotal trials
• Generally is a risk based approach, based on the BCS classification of the molecule and the number of changes being incorporated between the two formulations.
  – Strength, platform, excipients, polymorph, salt form etc.
  – Manufacturing site/process changes for API/DP (biologics)
• Risk Tolerance by the company
  – Conducting a relative bioavailability study versus a fully powered bioequivalence study.
  – In rare cases, BCS Class 1, justification can be made based on in-vitro data.
  – Collect PK/PD data whenever possible.

• A well designed clinical study requires close interaction between CMC, Clin. Pharm, Medical and regulatory.
  – Understanding the patient population (co-medications, co-morbidity) is essential in designing the appropriate study.
Why science driven development is (still) important

- **Case Study 1.**
  - Considerations for change of dosage form and manufacturing platform (externally) from early phase to a commercial product.

- **Case Study 2.**
  - Understanding of the physicochemical property of the molecule in helping set manufacturing control strategy to ensure product quality.

- **Case Study 3.**
  - Understanding of the role and mechanism of excipient in enhancing bioavailability of a poorly soluble drug.

- **Case Study 4.**
  - Understanding of the behavior of the enteric polymeric systems to explain selection of optimum coating parameters in a multiparticulate dosage form.
Case Study 1. (Compound Y)

- Initial dosage form and clinical studies for Compound Y was developed externally
- A HSWG capsule dosage form was used for the clinical studies
  - HSWG composition was a part of their standard platforms, and included surfactant, glidant, and non-standard lubricant
- A more stable form of Compound Y was also discovered during phase II studies
- What is the dosage form design as we take this molecule (Compound Y) forward to Phase III?
# Compound Y Capsule Formulation

<table>
<thead>
<tr>
<th>Function</th>
<th>Intra-Granular</th>
<th>Extra-Granular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ingredients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
<td>Compound Y</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Diluent/Filler</strong></td>
<td>Pregelatinized Starch</td>
<td>43</td>
</tr>
<tr>
<td><strong>Diluent/Filler</strong></td>
<td>Microcrystalline Cellulose (PH101)</td>
<td>43</td>
</tr>
<tr>
<td><strong>Binder</strong></td>
<td>Hydroxypropyl Methylcellulose (E5P)</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Disintegrant</strong></td>
<td>Sodium Carboxymethylcellulose</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>Glidant</strong></td>
<td>Colloidal Silicon Dioxide</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Surfactant</strong></td>
<td>Polysorbate 80</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Glidant</strong></td>
<td>Colloidal Silicon Dioxide</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Lubricant</strong></td>
<td>Glyceryl Behenate</td>
<td>2.0</td>
</tr>
<tr>
<td><strong>Vehicle</strong></td>
<td>Gelatin Capsules Size &quot;0&quot;, opaque blue</td>
<td>300 mg/capsule</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Capsule Strength</th>
<th>2.5 mg</th>
<th>15 mg</th>
<th>100 mg</th>
</tr>
</thead>
</table>

*Too many excipients*
Relevant physico-chemical properties for dosage form design

• Solid state and Stability
  -Crystalline free acid
  -Stable, non-hygroscopic,

• Needle morphology
  Two polymorphic forms I & II
  -Enantiotropically related – Form II is stable at room temperature
  -transition temperature approximately 70ºC
## Comparison Between Form I and Form II

<table>
<thead>
<tr>
<th>API</th>
<th>Form I</th>
<th>Form II</th>
</tr>
</thead>
</table>
| **Thermal Properties** | Endotherm onset = 148.98°C  
Heat of fusion = 65.98 J/g  
peak = 151°C  
ΔH= 64.5 J/g | Endotherm onset = 138.95°C  
Heat of fusion = 66.98 J/g  
peak = 139°C  
ΔH= 60.9 J/g |
| **Solubility** | <1 µg/mL (pH 2 and 4);  
2 µg/mL (pH 6);  
0.017 mg/mL (pH 8)  
SGF$^4$ 0.071 mg/mL  
Fasted SIF 0.509 mg/mL  
Fed SIF 0.271 mg/mL | <1 µg/mL (pH 2 and 4);  
5 µg/mL (pH 6);  
0.9 mg/mL (pH 8)  
SGF$^5$ 0.008 mg/mL  
Fasted SIF 0.578 mg/mL  
Fed SIF 0.501 mg/mL |
Wettability / IDR

- Wettability ranking of Compound Y (Form II) in four 0.01N HCl solutions:
  
  0.05% Pluronic F68 > 0.05% SLS >
  0.00015% Tween 80 ≈ no wetting agent.

- API (Form II) was compressed to pellets for IDR testing in the same four 0.01N HCl solutions

  Dissolution rates were lower than detection limit to distinguish the dissolution rates
Particle Size and Micrograph of Milled Form II

d(0.1): 1.322 µm

d(0.5): 4.617 µm

d(0.9): 12.171 µm
Compressibility

- Compound Y (Form II) is a cohesive and adhesive powder
- It is moderately brittle and formed strong compacts under typical pressures
- No evidence of PIPT
Process Induced Phase Transformation (PIPT) Studies

- API (Form II) was compressed under a pressure of 2000 pounds for 1 min
- API (Form II) was milled by mortar and pestle with (1) water, (2) 1% SLS solution, (3) 1% Tween 80 solution, and (4) 1% Lutrol F68 solution
- API (Form II) was equilibrated in (1) water, (2) pH 2 phosphate buffer, (3) pH 4.1 acetate buffer, and (4) pH8 phosphate buffer (little residue collected) at room temperature for overnight

No form change was observed.
Compound Y Form I & II Monkey Bridging Study

![Graph showing concentration vs time for LY2409021 Form I (15 mg/kg/day) and Form II (15 mg/kg/day).]

LY2409021 Form I (15 mg/kg/day)
LY2409021 Form II (15 mg/kg/day)
Formulation Design Strategy for Compound Y (Phase III Studies)

• Solid oral tablet using standard platforms
  – Adequate exposure with conventional formulation
  – API is not moisture/temperature sensitive
  – Determined that surfactant was not needed for bioavailability reasons

• Roller Compaction Option
  – Potentially high drug load
  – Adhesive/cohesive API
  – Platform change from early clinical formulation

• Wet Granulation Option
  – Leverage current formulation platform
  – Greatest potential for minimizing size
  – Ease of functional excipient addition for processability (e.g. surfactant)
API Modification To Enable Platform Selection And Robust Control Strategy

Roller Compaction platform

• Preferred Lilly platform
• Considerable sticking observed on the tablet die and punches
• Would lead to a more complex control strategy

Direct Compression platform

• API particle engineering was conducted to improve habit - Flow and sticking
• Successful API modification allowed change in platform selection
• A simpler platform was enabled based on all the science based information
Bio-linking Strategy

• Continue with Form I for Clinical Capsule Supply through Phase 2 (avoids risk of no bridge)

• Conduct formulation dosage form design using Form II

• Bridge Form I Capsules to Form II Tablet before Phase 3 clinical trials
Case Study 2 (Compound Z)

• The hydrochloride form of the salt was selected at candidate selection.
• Studied in the clinic as a solid oral tablet.
• Salt is unstable in presence of moisture, thus a dry manufacturing process was selected.
• A salt to base conversion (acid-base reaction) of the API occurs in the tablet in the presence of a Na salt of the disintegrant.
Fundamental Studies to Understand Salt-to-Base Conversion

• Two kinetic studies utilizing multi-variate design of experiments were conducted to elucidate the rate of conversion in powder blends and tablets and to study impact of:

  – Relative Humidity
  – Temperature
  – Disintegrant level
  – API Specific Surface Area
  – Time
Understanding Conversion – Water Activity is the Main Driver

- Tablets were stored at various relative humidities and different temperatures
- XRPD measurements were carried out at different time points
- Relative humidity / water activity is the main driver for conversion
- Below a relative humidity / water activity of 0.2 the rate of conversion is considerably slower
Key Information Regarding Salt-to-Base Conversion Control

♦ Kinetic studies established that initial conversion in tablets is first order

♦ Relative Humidity (or Aw) is a key variable in rate of conversion:
  • Lower % RH will decrease rate and amount
  • Higher %RH will increase rate and amount

♦ Conversion is not reversible

♦ Key lever in our current manufacturing process control strategy
Case Study 3: Agenerase™
(Amprenavir (APV))

- An HIV protease inhibitor, used in AIDS therapy.

- APV has a low solubility in water and is poorly wetted.

- Conventional oral formulations (capsules and tablets) had no detectable drug in the blood after administration.

- High daily dose (1200 mg/b.i.d).
Drug Absorption – Issues in the case studies

Stability

Permeability

Solubility

Efflux

Metabolism

Manufacturability

Tox.

Dr Ian Wilding
Pharmaceutical Profiles

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(A) Structure and (B) pH-solubility profile of amprenavir free base. The compound has a pKa of 1.97.
Formulation development of amprenavir

- Initial clinical studies utilizing amprenavir dissolved in TPGS in hard gelatin capsules had good bioavailability. Optimization of the formulation/manufacturing platform for commercial manufacture was then undertaken.

- A soft gelatin formulation using a self-emulsifying delivery system was used to increase the bioavailability of APV.

- This formulation includes a self-emulsifier/solubilizer, tocopheryl polyethylene glycol 1000 succinate (TPGS), PEG 400 and propylene glycol.

- The role of TPGS in enhancing the bioavailability of amprenavir was also studied.
Role of TPGS in improving bioavailability of amprenavir

• The solubility ($S$) of amprenavir was improved in the presence of TPGS through micellar solubilization.

• TPGS also enhances the permeability ($P_{\text{eff}}$) of amprenavir.

• Overall, TPGS enhanced the absorption flux ($J = P_{\text{eff}} \times S$) of amprenavir by increasing its solubility and permeability.

• The total drug absorbed is the integral of absorption flux over intestinal surface area and absorption time.

Solubility results

pH 7 phosphate buffer, I = 0.15 M, 37°C

CMC = 0.2 mg/mL
Permeability studies

- Caco-2 cell monolayers
- AP > BL; BL > AP
- Vitamin E-TPGS on AP side
- Apparent Permeability

\[ P_{app} = \frac{1}{AC_0} \frac{dQ}{dt} \]
Permeability results

![Graph showing permeability results for Vitamin E-TPGS concentration ranging from 0 to 2 mg/mL. The x-axis represents Vitamin E-TPGS concentration in mg/mL, and the y-axis represents apparent permeability in units of cm/s × 10^6. The graph compares permeability between AP and BL, with data points indicating a trend where permeability increases with increasing concentration.]

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Permeability: Efflux system

\[
\frac{P_{BL \to AP}}{P_{AP \to BL}} = 1
\]

\[
\frac{P_{BL \to AP}}{P_{AP \to BL}} > 1
\]
Permeability results

![Bar chart showing apparent permeability for Amprenavir, Amprenavir+GF120918, and Amprenavir+Verapamil. The x-axis represents the treatments, and the y-axis shows apparent permeability in cm/sec. The chart indicates that Amprenavir+GF120918 has the highest permeability, followed by Amprenavir and Amprenavir+Verapamil. There is a legend indicating AP > BL and BL > AP.]
Absorption flux for Amprenavir

![Graph showing the absorption flux for Amprenavir as a function of Vitamin E-TPGS concentration (mg/mL).]
Use of multivariate experiments and models to predict solubility.

A more rigorous experimental design was then used to determine the solubility of amprenavir in the matrix components:

Design factors:

- Temperature (25-55°C)
- TPGS Concentration (20-40 % w/w)
- Water concentration (0-10 % w/w)
- Propylene glycol concentration was held relatively constant at 5% w/w
- PEG 400 served as the filler for the remainder of the vehicle

The van’t Hoff relationship was used to extrapolate solubilities outside of the design space to sub ambient temperatures.
Solubility data of amprenavir to aid in manufacturing process development and storage conditions

**Contour of Solubility**

$T = 25.0$

$T = 55.0$

Solubility contour plots for APV form B (mg/g solution) in formulation vehicle mixtures (% w/w) (left isotherm: 25 °C; right isotherm: 55 °C).
Conclusions for Case Study 3.

• Low solubility and poor wetting make amprenavir dissolution rate limited, therefore, a rational approach to increasing bioavailability is by dissolving amprenavir in a liquid matrix.

• TPGS is a self emulsifying delivery system. It is believed that increased bioavailability of amprenavir, is due to the micellar solubilization and change in apparent permeability with TPGS.

• An optimum amount of TPGS is needed for adequate bioavailability. Increased TPGS increases bioavailability at the expense of decreased amprenavir solubility (or decreased drug load).

• Important factors to consider in soft gelatin capsule development include: drug solubility dependence on temperature and the changing water levels of the fill solution.

• Experimentally designed solubility mapping proved useful in the development of this liquid fill formulation.
Case Study 4:

Identification Of Critical Process Variables For The Application & Drying Of The Enteric Layer In A Multiparticulate System

Arup Roy, Ph.D.
Objective

• To identify the critical process variables for the enteric-layer application and drying process for Hydroxypropyl Methylcellulose Acetate Succinate.

• Provide understanding of the design space of the enteric coating application process to help in

1. scale up.
2. further optimization of the cycle time.
Pellet coating success is dependent upon a thermodynamic and hydrodynamic “balancing act”:

- Low inlet air flow and temperature, high spray rate, and low atomization air pressure can lead to better film formation but can also cause pellet agglomeration.

- High inlet air flow and temperature, low spray rate, and high atomization air pressure can lead to attrition and spray drying and failure in dissolution (enteric property).
Understanding design space in a small scale model.
Polymer Application: Introduction

• Many parameters will affect film formation, and are highly dependent on the characteristics of a given polymer.

• An experimental design was used to evaluate critical process variables associated with the application and drying of an applied enteric layer to nonpareil beads.

• Goal: maximize gastric protection provided by enteric layer.
  – minimize dissolution after 2 hours in 0.1N hydrochloric acid media.
Literature Evidence

• Influence of processing and curing condition on beads coated with an aqueous dispersion of Cellulose Acetate Phthalate (CAP)

  – Higher coating efficiencies and better coalescence of films were obtained at a lower coating temperature. The release rate was significantly lower at 36°C vs. those coated at 48°C.

  – A ‘wet’ environment (low temp. and air velocities, high spray rate) and an overall slower drying rate led to a better film formation.

  – ‘Curing’ was dependent on coating temperature. Heat was not the only factor required for the coalescence of CAP films, and curing was not able to proceed without sufficient moisture.

  – Curing at 50°C in an atmosphere containing 75% RH, irreversibly converted poor film formation into better coalescence and increased the mechanical toughness of films.
Enteric Polymer Used

- The enteric layer composed of hydroxypropyl methylcellulose acetate succinate (HPMCAS), triethyl citrate, and talc.

- HPMCAS is a cellulose in which some of the hydroxyl groups are replace with methoxyl, acetyl, succinoyl, and hydroxypropyl groups.

- The succinoyl:acetyl ratio is adjusted to create grades of HPMCAS that dissolve at various pH values.

- The minimum Film Forming temp (MFFT) for HPMC-AS is <23°C.\(^a\)

- The cellulosic derivative enteric polymers are more permeable than acrylic polymers due to their hydrophilicity and less dense molecular arrangement.

\(^a\) Plasticized (TEC = 28%)

Results: SEM

Low dew point
High inlet temperature
High product temperature
Low air flow conditions

High dew point
Low inlet temperature
Low product temperature
High air flow conditions
Results: Dissolution

Dew Point = 0°C

Dew Point = 12°C

Upper Number: Dissolution after 2-hr gastric challenge.
Lower Number: Dissolution after 60-min in pH 6.8 buffer.
Conclusions From The Enteric Coating DOE

- All trials produced acceptable results for coating time, spray efficiency, moisture level, and dissolution after 60-min in pH 6.8 phosphate buffer.

- A higher dew point and high product temperature level allowed the best manufacturing condition for optimal process performance and gastric resistance/dissolution.
Results: Effect of Drying Time on Dissolution in 0.1N HCl

- Higher humidity conditions required a longer drying times for better gastric resistance
- Both long drying times and low humidity conditions would favor the removal of water from the coated beads.
Conclusions for case study 4.

• A desirable effect of lowering the dissolution after 2-hours in 0.1N hydrochloric acid media was achieved by removal of water from the coated beads. This was accomplished by either:
  – An increase in drying time or
  – A decrease in inlet air dew point.

• Unlike latex systems, dispersed polymers coalesce by forming a gel during the drying phase. The removal of all the water is necessary to complete the coalescence process.

• Higher dew points during the application of the enteric polymer coating allows a better film formation process.

• The mechanism for improved gastric resistance during the curing/drying process is coalescence of the dispersed HPMCAS due to water removal rather than a curing or annealing process that occurs with latex polymer suspensions.
Science based approach to product development: Still the best approach

• A thorough understanding of the physical chemical and mechanical properties of the API is the basic information required for drug product design

• Understanding of the bio-pharmaceutics of the molecule, and clinical data (to POC) is critical to achieving the desired drug product performance

• A QTPP should be established for every product that is entering pivotal studies

• Risk assessment tools during the FHD to POC stage can help in systematically identifying the key areas of risk for dosage form design
  – Risk mitigation strategies need to be in place.

• A bio-linking strategy and well designed PK study is essential to link early phase formulation to pivotal formulations
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