Mitigating Patient Risks Using Dissolution Testing in Manufacturing Extended Release Products

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Dissolution Testing and Specification for ER Products in Emerging Regulatory Initiatives

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Extended Release Dosage Forms and Drug Release

Understanding Drug Release of ER Products
  • API property, product, process and test method

Ensuring Consistent Drug Release in Commercial Manufacturing

Understanding Drug Release Variability
  • Case Studies

Summary
Extended Release Solid Dosage Forms

• Oral Extended Release (ER) Systems
  – Conventional ER
    ▪ Reservoir
    ▪ Osmotic pump
    ▪ Matrices (hydrophobic, hydrophilic)
  – Complex ER
    ▪ IR+ER
    ▪ DR+ER
    ▪ ...

<table>
<thead>
<tr>
<th>ER System</th>
<th>Tablet Dosage Form Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>Monolithic tablet; Layered tablet; Mini-tablets in capsule; Compression coated tablet</td>
</tr>
<tr>
<td>Reservoir</td>
<td>Coated monolithic tablet; Coated mini-tablets in capsule; Compressed tablet of coated pellets</td>
</tr>
<tr>
<td>Osmotic</td>
<td>Coated monolithic tablet; Coated layered tablet</td>
</tr>
</tbody>
</table>
Drug Release of Extended Release Solid Dosage Forms

- One of the most important CQAs
  - Serve as a critical tool to ensure consistent quality and performance of both development and commercial products
    - Evaluate relative product performance resulting from changes in formulation and/or manufacturing process
  - Prior to regulatory filing
    - Guide formulation and process development, scale-up and optimization
    - Facilitate assessment of CPP, design space, risks, and development of control strategy, etc
  - Post-approval
    - Assure batch-to-batch consistency of product and process performance in commercial manufacturing
      - May be over- or under-discriminating
    - Support certain changes in formulation and manufacturing process
      - Raw materials, formulation, process, scale, equipment, site, test methods and specifications, etc.
Drug Release of Extended Release Solid Dosage Forms

• Opportunity for correlation with in vivo performance (IVIVC)
  – Use *in vitro* test as a surrogate to predict *in vivo* performance
    ▪ Bridge a critical gap between drug release and clinical performance
  – Serve as an important tool for product and process understanding
    ▪ Provide significantly increased assurance for product quality and performance
    ▪ Set meaningful specifications to assure safety/efficacy
  – Justify waiver of *in vivo* BE studies to support product development and post-approval changes
  – Minimize risks to patients by ensuring in vivo performance throughout the life cycle of a product
Understanding Drug Release from ER Dosage Forms
Extended Release: Drug Release Control

• Common ER Systems
  - Reservoir
  - Osmotic pump
  - Matrices
    - Hydrophobic
    - Hydrophilic

• Basic ER mechanisms
  - Diffusion controlled
  - Dissolution/diffusion/swelling controlled
  - Osmotic pressure controlled
  - Other: ion-exchange, slow-dissolving complexes, etc.

• Drug property and technology dependent
  - Mechanism: Solubility, dose (loading) and technology
  - Mechanism: May differ depending on formulation design
Factors Affecting Drug Release Rate and Kinetics

- API, formulation and release control principle
  - API properties (solubility, ionization, solid phase, surface area, wettability)
  - Type, grade and concentration of the rate-controlling polymer
  - Drug loading, dosage form type, size, sensitivity to environmental changes
  - Properties of other excipients

```
Dry tablet
Drug release
Complete release
```

```
Coated Tablet
Osmotic: EOP
Push-Pull
```

```
Hydrophobic matrix
Hydrophilic Matrix
```

- *Performance of the same technology also depends on formulation*
Factors Affecting Drug Release Rate and Kinetics

- Formulation, manufacturing process and type of ER technology
  (I) **Reservoir** - Coating uniformity and consistency
    - Film thickness, permeability, porosity and mechanical strength
      - Plasticizer, pore former, solvent, solid content, coating parameters, curing, scale
    - Film integrity upon compaction
  (II) **Osmotic pump** - Coating uniformity and consistency
    - Film thickness, permeability and mechanical strength
      - Flux enhancer, solvent, curing, polymer variability, coating parameters, scale
    - Core tablet (configuration, osmotic agent and polymer)
    - Orifice
  (III) **Hydrophobic matrices** – Porosity and tortuosity
    - Granulation (e.g., Dry vs. wet vs. melt), compression, solid phase transition
  (IV) **Hydrophilic matrices** – Structure integrity and homogeneity
    - Less sensitive to processing condition
    - Granulation (e.g., DC vs. RC vs. WG)
    - Release mechanism and coating (non-functional)
Factors Affecting Drug Release Rate and Kinetics

- Test method/condition and type of ER technology
  - Apparatus, agitation/shearing, temperature
  - Medium (pH, surfactant, ionic strength, solvent, etc.)

(I) Osmotic pump
- In vitro release generally insensitive to test conditions
- Lack of flexibility to adjust test condition to match in vivo performance

(II) Reservoir and hydrophobic matrices
- In vitro release typically sensitive to test conditions (hydrodynamics, API-medium and/or polymer-medium interactions)
- Possible to adjust test condition to match in vivo performance

(III) Hydrophilic matrices
- In vitro release sensitive to test conditions (hydrodynamics, shearing, API-medium and/or polymer-medium interactions)
- Gel strength and matrix integrity changing during the test, may affect rate and mechanism of drug release depending on formulation design
- Possible to adjust test condition to match in vivo performance
Ensuring Consistent Drug Release in Commercial Manufacturing
Understanding Variability of Drug Release

• For a given formulation and process, release rate usually varies
  o Between batches and upon storage
  o Due to variation of manufacturing process and raw materials

• Extent of drug release variation depends on
  (A) Formulation design
    – ER technology, composition, API and polymer properties
  (B) Release mechanism
    – Diffusion, erosion, osmotic pressure
  (C) Dissolution test
    – Test apparatus
    – API-medium interaction (e.g., pH, surfactant, EtOH)
    – API-polymer interaction (e.g., ionic, hydrophobic)
    – Polymer-medium interaction (e.g., pH, surfactant, ionic strength, EtOH)
      ▪ Can alter magnitude/extent of polymer “natural” variation
Understanding Variability of Drug Release

• High variability in drug release can result in
  ❖ L2, L3 Stage testing, OOS and investigations
  ❖ Lot failures, product recalls or shortage
  ❖ Low degree of assurance of product quality and manufacturing control
    ➢ Impact on patients

• Challenges to achieve consistent drug release
  ❖ Ability to understand and control key polymer property and/or process parameters
    (I) Reservoir
      – Influence of composition, process, curing, scale and compaction
    (II) Osmotic pump
      – Influence of polymer properties (use test), curing and scale
    (III) Hydrophobic matrices
      – Influence of property of polymeric and non-polymeric rate-controlling materials, process and its impact on materials
    (IV) Hydrophilic matrices
      – Influence of rate-controlling polymer properties; Blending of polymers
Understanding Drug Release Variability: 

*ER Hydrophic Matrices*
Extended Release Hydrophilic Matrices

• Most common type of ER dosage forms
  o > 75% marketed ER products*

• Polymers: Water soluble and/or swellable, gel-forming
  o Natural
    – Natural gums of polysaccharides (Alginate, xanthan gum, locus bean gum)
  o Semisynthetic
    – Cellulose esters and ethers (HPMC, HPC, HEC); cross-linked high amylose starch (Contramid)
  o Synthetic
    – Homopolymer of ethylene oxide, Cross-linked homopolymers and copolymers of acrylic acid (Polyox, Cabopol)

• Basic release control mechanisms
  o Diffusion, polymer swelling, dissolution/erosion

* Colorcon
Variation of Rate-Controlling Polymer: 
Hydroxypropyl Methylcellulose (HPMC)

• HPMC: Widely used
  o Performance
    – Effective release control and pH-independency
    – Versatility (availability of multiple grades, API solubility, drug loading, multi-layer system, tailored drug release...)
  o Manufacturing
    – Amenable to conventional process trains, equipment/facility
    – Reliable and reproducible process, cost effective, environmental friendly (vs. reservoir and osmotic systems)
HPMC Grades

- Compendial types defined by substitution
  - MeO
  - HPO
- Each type has a substitution range
- Sub-graded by viscosity
- K grade designed for use in ER

<table>
<thead>
<tr>
<th>Substitution Type</th>
<th>MeO (%)</th>
<th>HPO (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2910 (E)</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>2906 (F)</td>
<td>27</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>7.5</td>
</tr>
<tr>
<td>2208 (K)</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

\[ R = H, \text{CH}_3, \text{CH}_2\text{CH(OH)CH}_3 \]
HPMC Products and Specifications

• Brands
  – Methocel, Premium CR (Colorcon/Dow)
    – K100 LV, K4M, K15M, K100M
  – Benecel (ASI)
    – K100LV, K250, K750, K1500, K4M, K15M, K35M, K100M, K200M
  – Metolose (Shin-Etsu)
    – 90SH100SR, 4000SR, 15000SR, 100000SR

• Key CoA spec
  – PSD
  – Viscosity
  – MeO and HPO substitutions

<table>
<thead>
<tr>
<th>Specification</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyl, %</td>
<td>USP</td>
</tr>
<tr>
<td>Hydroxypropoxyl, %</td>
<td>USP</td>
</tr>
<tr>
<td>USP substitution type</td>
<td>USP/EP</td>
</tr>
<tr>
<td>Chlorides, max., %</td>
<td>EP</td>
</tr>
<tr>
<td>Apparent viscosity, 2% in water at 20°C, cP</td>
<td>USP</td>
</tr>
<tr>
<td>Apparent viscosity, 2% in water at 20°C, mPa·s</td>
<td>EP</td>
</tr>
<tr>
<td>ID Test A, B, C</td>
<td>USP</td>
</tr>
<tr>
<td>ID Test A, B, C, D, E, F</td>
<td>EP</td>
</tr>
<tr>
<td>Opalescence of solution</td>
<td>EP</td>
</tr>
<tr>
<td>Solution color, yellowness, 1% in water</td>
<td>EP</td>
</tr>
<tr>
<td>pH, 1% in water</td>
<td>EP</td>
</tr>
<tr>
<td>Loss on drying, max., %</td>
<td>USP/EP</td>
</tr>
<tr>
<td>Organic impurities, volatile</td>
<td>USP</td>
</tr>
<tr>
<td>Residue in ignition, max., %</td>
<td>USP</td>
</tr>
<tr>
<td>Ash, sulfated, max., %</td>
<td>EP</td>
</tr>
<tr>
<td>Heavy metals, as Pb, max., ppm</td>
<td>USP/EP</td>
</tr>
</tbody>
</table>
### HPMC Products and Specifications

- **Key spec limits**

<table>
<thead>
<tr>
<th>Vendor</th>
<th>MeO (%)</th>
<th>HPO (%)</th>
<th>PSD</th>
<th>Viscosity (cP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>19-24 (USP)</td>
<td>4-12 (USP)</td>
<td>100</td>
<td>400 4K 15K 100K</td>
</tr>
<tr>
<td>Dow</td>
<td>19-24</td>
<td>7-12</td>
<td>99% &lt; 40 mesh 90% &lt; 100 mesh QbD: 60% &lt; 230 mesh</td>
<td>80-120 - 3-5.6K 11.3-21K 80-120K</td>
</tr>
<tr>
<td>ASI</td>
<td>20-24</td>
<td>7-12</td>
<td>99% &lt; 40 mesh 90% &lt; 100 mesh</td>
<td>80-120 300-560 2.7-5K 13.5-25.2K 75-140K</td>
</tr>
<tr>
<td>Shin-Etsu</td>
<td>22-24</td>
<td>8-12</td>
<td>95% , 100 mesh</td>
<td>80-120 300-560 3-5.6K 11.3-21K 75-140K</td>
</tr>
</tbody>
</table>

- “Natural” variability of HPMC due to raw materials and mfg process
  - Property variation **within its spec limits**
  - Variation of properties **not on the spec**
Polymer Variability and *In Vitro* Drug Release

- Natural variability of HPMC
  - Property variation within its spec limits
    - Viscosity
    - Substitution
    - PSD
  - Variation of properties not on the spec
    - Between and within lots (*raw material, batch or continuous process, blending, sampling*)
      - Molecular weight and polydispersity
      - Substitution pattern/heterogeneity

- Impact on drug release of a given formulation/process depends on
  A. Release mechanism
  B. Test method
    - Interplays among API/polymer properties, test condition and release mechanism
    - Shearing impact
Polymer Variability and *In Vitro* Drug Release

A. Impact on *in vitro* drug release depends on release mechanism
   - Diffusion-controlled
     - Less sensitive to property variation within its spec limits
   - Erosion-controlled
     - More sensitive to variation in polydispersity and chemical heterogeneity
     - Can affect hydration, gel strength, polymer disentanglement, polymer-API or polymer-medium interaction (e.g., salt-out, salt-in)
     - Often only partly or not reflected by viscosity of 2% solution or average substitutions within spec limits

B. Release mechanism and interactions can also vary with test condition
   - API-medium and polymer-medium (pH, surfactant, ionic strength, agitation)

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Case Study I: Product A

- **API**
  - pKa = 4.75 (Acid), 2.20 (Base), solubility =~ 18 mg/ml (water)

- **HPMC matrix**
  - High viscosity grade
  - Very high drug loading ~ 80%

- **Dissolution**
  - USP I, 100 rpm, water
  - No API-medium or polymer-medium interaction

- **Release mechanism**
  - Predominantly erosion-controlled (high load/solubility)
Case Study I: Product A

- Dissolution at 20-hr drifted lower intermittently
  - Failed batches
  - OOS lots not explained by the variations within CoA specs
- HPMC
  - Complex structural diversity
    - Within-substitution (HP1/HP2)
    - Monomer
    - Polymer chain
    - Potentially tertiary structure
  - Chemical heterogeneity identified as the root-cause for variability
    - Tools: 1H NMR, 2D NMR and gHMQC (Heteronuclear Single Quantum Coherence)
  - Confirmed by functional test: polymer erosion
  - New test implemented ⇒ Resolution of the problem

Case Study II: Product B

- **API**
  - $pK_a = 4.8$; solubility = 1.3 mg/ml (pH 1.2) and 165 mg/ml (pH 6.8)

- **HPMC matrix**
  - High viscosity grade
  - High drug loading ~ 54%

- **Dissolution**
  1. **Conventional**: USP II, 100 rpm, pH 6.8 phosphate buffer
     - No API-medium or polymer-medium interaction
     - Release mechanism: **Diffusion-controlled**
  2. **IVIVC**: USP II, 100 rpm, pH 1.2 for 0.75 hr + pH 5.5 phosphate buffer/75 mM SDS
     - polymer-medium interaction
     - Release mechanism: **Erosion-controlled**
Product B: Dissolution Failures

- Accelerated dissolution observed following manufacturing of > 100 successful commercial batches
  - Dissolution shifting and lot failures despite very wide spec limits
    - 9 hr: 35 - 70%
    - 12 hr: 44 - 92%

![](chart.png)
Product B: Dissolution Investigation

• Communication with the supplier
  o Manufacturing changes?

• Comparing “good” vs. “bad” lots of HPMC and tablets
  o Key specs on the CoA
    — Could not be directly attributed to variations of viscosity and substitutions
  o Phase behavior
    — Different cloud point (CP) and incipient precipitation temperature (IPT)
  o Stress test of tablets
    — Different gel strengths

![Graph showing transmittance over temperature]

- IPT: T @ 97.5% Transmittance (Dow)
- T90%: T @ 90% Transmittance (Abbott)
- CP (T50%): T @ 50% Transmittance (Dow and Abbott)
Product B: Resolution

- Chemical heterogeneity identified via indirect tests
  - CP/IPT
  - Gel strength of matrix

- Additional tests for key HPMC properties implemented
  - CP, CP-IPT and PS

- Continuous monitoring and improvement
  - Scale-up and process control

- Dissolution changes were not detected by the conventional test
  - Diffusion-controlled

![Graph showing comparison between IVIVC and conventional methods](image)
Summary

Ensuring consistent drug release and assuring supply of ER products

- Understand API, product, process, release mechanism and test method
- Understand the impact of material properties, formulation/process and their interplays with drug release test
- Link *in vitro* quality attribute with *in vivo* performance whenever possible
  - Aid product and process understanding
  - Facilitate setting meaningful spec, assessing and managing risks
  - Support biowaivers
  - Provide a higher degree of assurance for consistent product quality and performance within the life cycle of a product
  - *Reduce/minimize risks to patients*
Acknowledgement

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Kevin Engh
Lynn Faitsch
Devalina Law
Back-ups
Extended Release Solid Dosage Forms

- **Manufacturing process options**
  - **Tablet**
    - Direct compression
    - Wet granulation (e.g., high shear, FBD, extrusion)
    - Dry granulation (e.g., roller compaction)
    - Melt granulation or thermoplastic pelletizing (e.g., high shear, melt-extrusion, spray-congealing)
  - **Round solid beads or pellets**
    - Drug layering of non-pareil seeds, extrusion-spheronization, spray-granulation/spray-drying, and spray-congealing
  - **Coating of tablets or beads for compression**
    - Pan coater, Air suspension (FBD, Wurster), Compression coating
  - **Manufacturing processes and equipment**
    - Conventional process highly preferred
    - Processes with increased complexity may be required for certain types of tablets
      - e.g., multi-layer, compression coating, mixed beads, mini-tablets
Structural Diversity: Spatial (Distribution) Heterogeneity

Levels of Substituent Heterogeneity

- **Heterogeneity at the monomer level**
  - C2, C3, C6 hydroxyls differ in reactivity (C3 least reactive)
  - Substitution of C2 OH enhances reactivity of neighboring C3 OH

  ![Chemical structure](image)

- **Heterogeneity on the distribution along the polymer chain**
  - Crystalline regions are less reactive
  - Substitution causes increased probability around in vicinity
  - Significant non-random substitution along the polymer chain
  - May be characterized by selective enzymatic breakdown

Sara Richardson, Lo Gorton, Analytica Chimica Acta 497, 27-65, 2003
Chemical Heterogeneity and Drug Release

- Heterogeneously substituted HPMC
  - Characterization
    - MW and polydispersity: Size-exclusion chromatography with multi-angle light scattering and refractive index detection
    - Average substituents: NMR
    - Distribution of the substituents along the cellulose chain after acid and selective enzymatic hydrolysis: High-performance anion-exchange chromatography with pulsed amperometric detection

- Finding
  - A correlation was found between polymer release and substituent pattern in addition to polymer chains entanglements
  - Samples with slow release also were more heterogeneously substituted along the polymer