“Case Studies on Making Complex Formulations Simple”

Use of extemporaneous preparation to evaluate controlled release drug delivery to meet medical needs

Alfred Berchielli (Pfizer Drug Product Design)

IQ Workshop: Best Practices & Application of GMP’s for Small Molecule Drugs in Early Development
February 5th, 2014 (Washington DC)
Outline

• **Background (EP Tablets / EP CR)**
  – History of EP at Pfizer
  – When/why to compound EP tablets
  – How to compound EP tablets

• **Case Studies (Results from Pfizer Studies)**
  – (1) EP Matrix Tablet (controlled release)
  – (2) EP Osmotic Capsule (controlled release)

• **Summary and References**
Extemporaneous Preparation (EP) History at Pfizer

• Pfizer’s first EP study (~1996)

• Pfizer’s first EP study with a CR tablet dosage form (2006)
  – Platform (controlled release matrix)
  – Goal: evaluate feasibility of QD dosing, test two release rates of simple matrix formulations
    • Premix of microcrystalline cellulose and hypromellose (HPMC) (changed HPMC grade for different release rates, short and long duration)
    • Active ingredient is blended with pre-mix for unit dose and compressed into tablets

• Today
  – Many different formulations/dosage forms have been compounded in the pharmacy at Pfizer
    • Solution, suspension, API powder in capsule, pre-manufactured beads in capsule, IR tablet, CR tablet, & CR osmotic capsule
When & Why to Compound EP Tablets?

• When
  – Early in Development (Pre-POC)
  – Later in Development (Post POC)
  – Product Enhancement (Post Commercial Launch)

• Why
  – Formulation flexibility or Optimization (multiple concepts/formulations/doses)
  – Reduced material waste/cost (API, drug product, no release testing/ no long term stability)
  – Reduced iteration time and speed to clinic (~3 months)
  – When there is low probability of success
  – Demonstration of new product ideas (for buy up)

IQ Workshop, Berchielli, Feb 05, 2014

Project Team:
Can Controlled Release Drug Delivery Help?
- Provide QD dosing
- Achieve Cmin target
- Reduce adverse Events…
### How to Compound Tablets

**• Small Scale Processing Equipment**

- Finding innovative ways to scale a batch down to 1 unit (~1g)

<table>
<thead>
<tr>
<th>Weighing</th>
<th>Blending Containers</th>
<th>Blenders (Excipient Premix + Active Ingredient)</th>
<th>Tablet Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand Weigh</td>
<td>Glass Vials</td>
<td>Turbula T2F (low shear)</td>
<td>Carver C12 Press</td>
</tr>
<tr>
<td><img src="image" alt="Hand Weigh" /></td>
<td><img src="image" alt="Glass Vials" /></td>
<td><img src="image" alt="Turbula T2F" /></td>
<td><img src="image" alt="Carver C12 Press" /></td>
</tr>
<tr>
<td>Xcelodose Weigh</td>
<td>Gelatin Capsules</td>
<td>Silamat S6 (high shear)</td>
<td>Natoli NP-RD10 Press</td>
</tr>
<tr>
<td><img src="image" alt="Xcelodose Weigh" /></td>
<td><img src="image" alt="Gelatin Capsules" /></td>
<td><img src="image" alt="Silamat S6" /></td>
<td><img src="image" alt="Natoli NP-RD10 Press" /></td>
</tr>
</tbody>
</table>

Very uniform blends/tablets
Quality Checks in the Pharmacy

• Component and Tablet weight
  – Within weight range

• Visual Inspection after preparation
  – Confirm tablet is intact and meets appearance standard

• Tablet thickness
  – Within thickness range

• Capsule closure and package
  – Confirm that capsule is locked
  – Place tablet in an HDPE bottle and store at appropriate conditions (not shown)
Regulatory Aspects (A Formulators Perspective)

- File appropriate regulatory documents
  - Example: IND for US study

- Formulation sections:
  - P1 Description & Composition of Drug Product
  - P2 Pharmaceutical Development
  - P3 Manufacture
    - EP is not manufacturing, but some information may be needed for pre-manufactured components
    - Generally include the preparation steps and process flow diagram for EP (very limited information/development for EP)

- EP practices rely on the standards of quality in a clinical pharmacy (governed by local laws, good clinical practices)
  - Formulators need to be ready to answer regulatory queries from FDA or for studies outside the US Pharmacist may handle this (e.g., Singapore).
Case Study # 1 (250 mgA PF-00708093) CR Feasibility (Matrix Tablet)

• Medical Need
  – Candidate for the treatment of serious Gram-positive bacterial infections including those that required long-term therapy (>28 days).

• Project Challenges
  – Very limited API supply, not enough for manufacturing, but plenty for an EP study (API reload was not endorsed),
  – Can develop the formulation with as little as 5 or 10g of API
  – PF-00708093 is an efflux substrate which could result in poor colonic absorption

• Recommendation
  – Assess colonic absorption using EP-Controlled Release matrix tablet to confirm simulations of CR dosing (dose 2 x 250mgA tablets with two durations (~5 and ~7 hr for 80% released)
Case Study # 1 (what we learned)

- Assessment of colonic absorption
  - Colonic absorption was moderate to high

- PK Results and Study Goal
  - Both formulations (A and B) met the acceptance criteria
    - $C_{\text{min}} > \text{MIC}$ with dose <1g

- EP provided a way to test a concept with available resources

Simulation of multidose steady PK state profile from single dose EP study
Case Study # 2 (5mgA PF-04620110)  
CR Feasibility (Osmotic Capsule)

• Medical Need
  – Provides a new option for diabetes mellitus type 2 treatment
  – DGAT-1 inhibition to be tested for lowered glucose (blood sugar) and weight loss due to inhibiting triglyceride synthesis in liver, adipose, and intestinal cells

• Project Challenges
  – Current clinical studies with PF-04620110 have shown adverse events (e.g., diarrhea)
  – The team is interested to test if CR (delivering the drug lower in the GI) can help to reduce AEs while achieving efficacy (i.e., test for systemic vs. local effects)

• Recommendation
  – Assess food effects and colonic absorption using EP-osmotic capsule to confirm simulations of CR dosing
Osmotic Capsules for EP Controlled Release
Developed by Pfizer in collaboration with Bend Research

• Benefit: Osmotic drug delivery provides highly reliable IVIVC
  – Similar PK performance for compounded and manufactured dosage forms

• Pre-manufactured components (2 durations off the shelf)
  – Capsule Body/Cap, Push/Sweller tablet released by Pfizer QA (GMP)
  – Available in Pfizer Inventory Management for supply to PCRU on demand

• EP components
  – Drug layer (i.e., the active tablet) is compounded in the Pfizer Pharmacy by established EP compounding practices
  – Capsule is assembled by Pharmacist
Case Study # 2 (what we learned)

- Osmotic capsule (CR delivery) provided very good PK results
  - Tested short duration (~7 hr) & Long Duration (~14 hr)

- EP-osmotic capsules gave two distinct controlled-release PK profiles (textbook CR profile for long duration), colonic absorption (good!)
  - Food effect (Cmax and AUC48 higher in fed state than fasted state for both durations)

- Recovery of EP-Capsules from subjects indicates that ≥95% of the drug was released in-vivo for expected transit times
Summary

• 16 EP tablet, controlled release tablet or capsule studies have been completed by Pfizer in the last 8 years
  – 9 with tablets and 7 with osmotic capsules
  – The EP formulation is selected based on drug delivery target (Pfizer formulation assessment/feasibility/selection process)

• We are currently scaling up a CR project in production where the first CR dosage was administered from an osmotic capsule

• Extemporaneous preparation is an important tool in the research and development toolbox
Acknowledgements

• Pfizer Drug Product Design
  – Amy Antipas, Catherine Ambler, Cindy Oksanen, Scott Herbig, Eric Eisenhart*, Avi Thombre, Sheri Shamblin, Ken Waterman*, Scott Goeken, Bruce MacDonald, and Vidya Swaminathan*

• Pfizer Analytical
  – Tim Graul, Jim Morgado, Paul Gerst, and Michael Likar

• Pfizer Clinical Research Units
  – Janyce Rogers and Ann Lee*

• Meeting Organizers
  – William Marinaro and John Skoug

*Not currently working at Pfizer
Thanks for listening and I hope you enjoyed the talk / case studies

For Reference

- Accepted for publication in Drug Discovery Today (for publication some time in 2014)

“EXTEMPORANEOUSLY PREPARED CONTROLLED RELEASE FORMULATIONS FOR ACCELERATING THE EARLY PHASE DEVELOPMENT OF DRUG CANDIDATES”, A. Thombre, A. Berchielli, and J. Rogers

- Published


Assessment of the feasibility of oral controlled release in an exploratory development setting.

Thombre AG.
Extra Slides (template)

• Abc
  – Abc
  –

• Abc
  – Abc
  –

• Abc
Considerations

• Practical limitations to the size and duration of a clinical trial supported by EP
  – Typical number of tablets prepared ranges from ~20 to 100 or more for a single study (tablets may be prepared on multiple days with multiple formulation types)

• Shifted resources – shorter timelines up front can increase development time later in a compound’s progression
  – Project timelines can require going from 20 tablets EP to 20,000 manufactured tablets
  – Time is still needed to develop the manufacturing process, test longer term stability…

• Local regulations may limit use of EP in addition to availability of clinical site with EP capability.

• Not every compound is suitable for EP
  – Examples (Highly potent compounds, penicillin…)
Controls to Ensure Subject Safety

• Extemporaneous Dispensing Record (EDR) verified analytically

• Practice run conducted at CRU prior to preparation of subject doses

• Double signatures during execution of compounding steps

• Pfizer Advisory Board
  – Multidisciplinary group to guide and decide upon proposals for non-standard Pfizer EP requests