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Rapid Preclinical Assessment for Extended Release Drug Delivery Viability

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Jennifer Chu

FreeThink Technologies

Session Description and Objectives

- A case study using an extended release osmotic capsule to evaluate drug absorption throughout the gastrointestinal tract will be presented. Extended release capsules were rapidly developed and dosed into dogs. In vivo dog data from the extended release capsule provided data critical for development of the human clinical dosage form.

- Describe oral extended release dosage form options.
- List the benefits of osmotic oral extended release dosage forms.
- Demonstrate use of osmotic extended release capsule in an *in vivo* animal study.

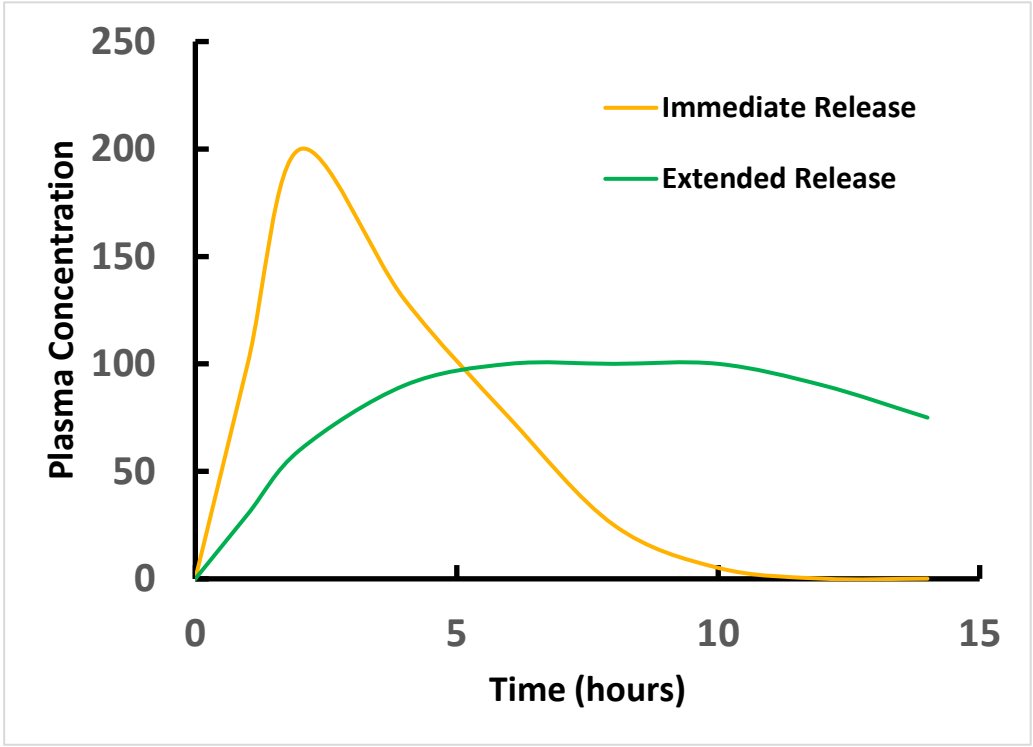
Biography and Contact Information

- Jennifer Chu, Ph.D., is the head of the Engineering and Formulation Sciences group at FreeThink Technologies, Inc.
- She received her B.S.E degree in chemical engineering from Princeton University and her M.S. and Ph.D. in chemical engineering from The University of Texas at Austin. She spent 7 years at Pfizer followed by a series of smaller companies directing pharmaceutical development and processing.
- She has more than 20 years of experience with a variety of dosage forms, including immediate release and modified release tablets, capsules, softgels, oral liquids, and injectables.
- Email: jennifer.chu@freethinktech.com

Why Extended Release

Extended release delivery of drugs provides advantages over immediate release

- Reduced dosing frequency
  - May enable qd (once daily) or bid (twice daily) dosing over tid (three times daily) or qid (four times daily)
- Decreased peak blood levels of drug
  - Reducing high peak blood levels (C_{max}) can decrease side effects and safety issues
- This can significantly improve patient compliance



Challenges with Extended Release

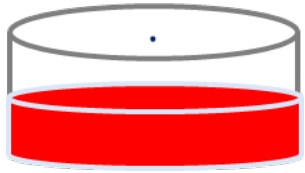
- GI regional absorption
  - Absorption can be limited past the duodenum (first part of small intestine)
- First pass metabolism
  - Extending the drug release may lead to greater first-pass metabolism
- Efflux
  - Drug can be pumped back into the GI track after absorption: greater tendency in lower GI tract
- Dosage form performance *in vivo*
  - pH varies
  - Water content varies
  - Shear forces change

Benefits of Osmotic Oral Extended Release

Common oral extended release technologies

matrix tablets

coated beads



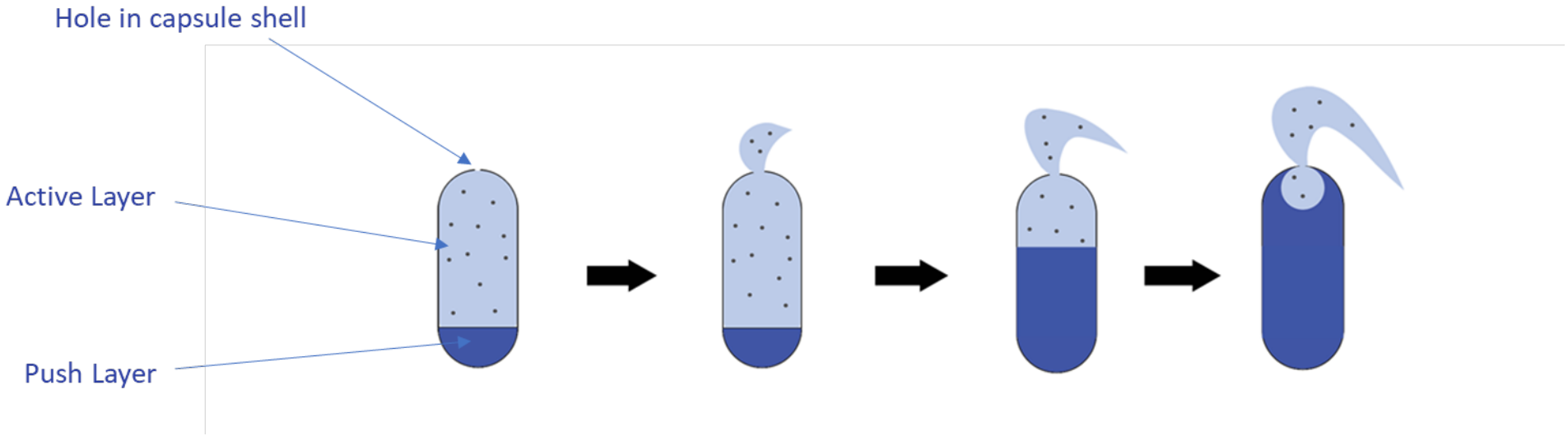
osmotic tablets

- Osmotic tablets
  - Advantages
    - Robust drug delivery independent of drug solubility/pH sensitivity
    - Best in vitro-in vivo correlation
    - Less affected by fed state
  - Disadvantages
    - Require specialized/expensive equipment (e.g. bilayer tablet press, solvent coater, side recognition, laser drill)
    - Longer development time due to complex manufacturing

OzmoCAP® - The Extended Release Capsule

- OzmoCAP® provides benefits of osmotic controlled release tablets without manufacturing/timeline disadvantages
- Because OzmoCAP® is a capsule rather than a coated tablet, the team can quickly develop formulation and suitable analytical methods
- Formulations can be developed with fast (t_{80} ~ 5 hours), medium (t_{80} ~ 10 hours), and slow (t_{80} ~ 15 hours) drug release profiles
- Supplies rapidly produced for feasibility/proof-of concept studies in animals
- The results from the animal studies can be used to assess viability of extended release dosage forms

OzmoCAP® Mechanism

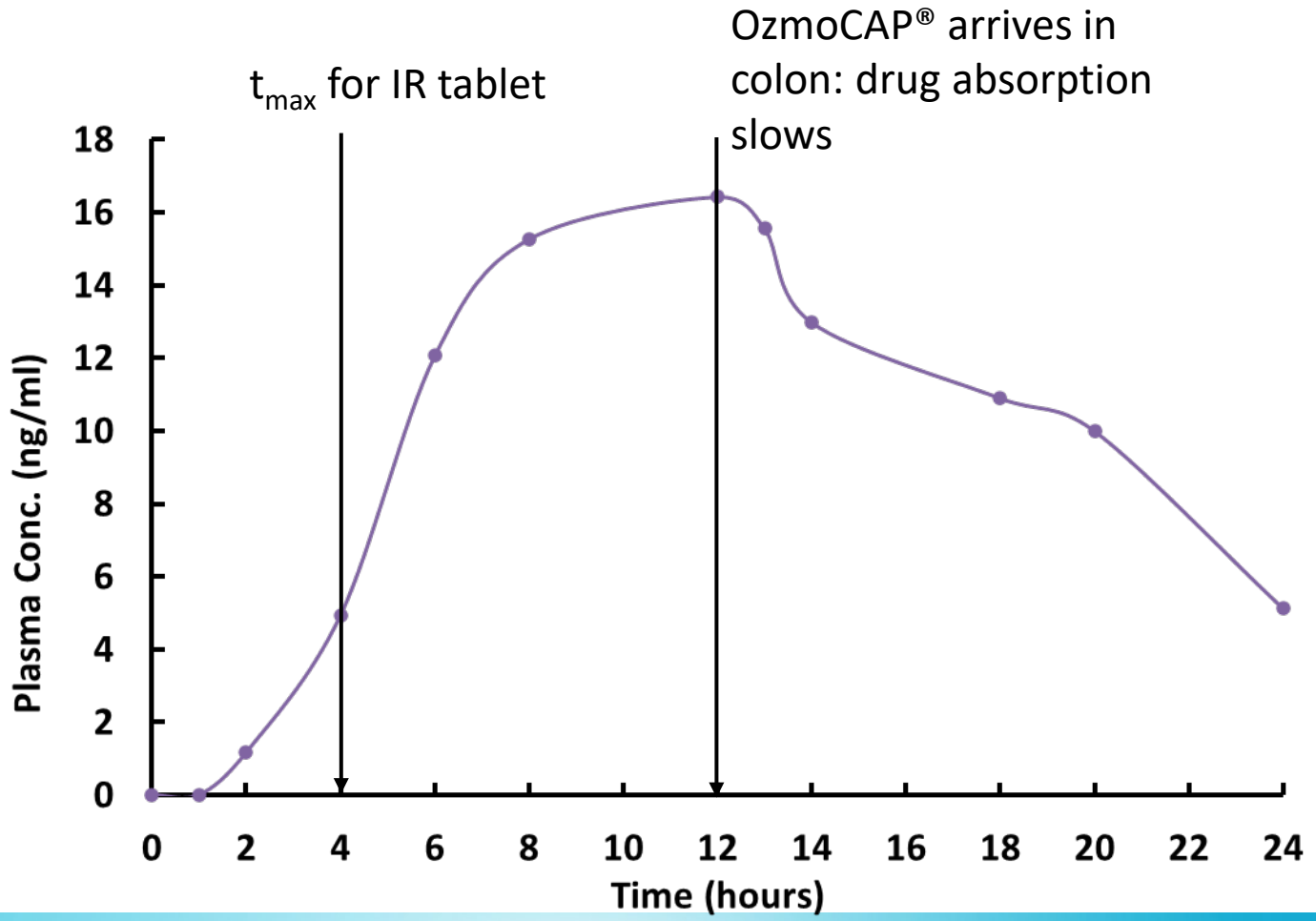


- Osmotic capsule mechanism is similar to osmotic tablet
- Each capsule shell is filled with an active layer containing the drug and a push layer
- When an OzmoCAP® enters the gastrointestinal tract, water is osmotically drawn in at a rate determined by the capsule shell permeability
- Combination of pressure build-up inside the capsule and expansion of the push layer deliver drug as viscous solution/suspension out of hole

OzmoCAP® Case Study – Compound X

- Compound X already an immediate release (IR) oral dosage form for twice daily (bid) dosing
- Once daily (qd) oral product desired
  - Reduced dosing frequency for patient compliance
  - Blunting C_{max} to decrease side effects
- Important to understand drug absorption throughout the gastrointestinal tract
- OzmoCAP® dosage form was developed and dosed into dogs to evaluate extended release drug absorption *in vivo*

Compound X OzmoCAP® Dog Data



- IR tablet peak plasma concentration at ~4 hours in dogs (data not shown)
- 6-hour (t_{80}) OzmoCAP® dosed to dogs in fed state extended absorption and corresponding blood levels
- Absorption drops abruptly when OzmoCAP® reaches colon, consistent with slower release OzmoCAP® formulation dosing (data not shown)
- Based upon these data, further development of an extended release dosage form of Compound X was progressed

Summary

- Extended release dosage forms can be beneficial for improving patient compliance
- Osmotic tablets provide reliable extended release drug delivery but can be time consuming and expensive to develop
- OzmoCAP® enables rapid development and dosing into animals for rapid assessment of extended release drug delivery viability
- Animal data can facilitate an extended release drug development strategy

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Questions

For more information, visit **ozmocap.com** or contact david.lucey@freethinktech.com or jennifer.chu@freethinktech.com