Do Excipients Matter to Clinical Pharmacology and Therapeutics?

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Importance of Excipients

- FDA approves drug **products**
- Excipients have activity and function and side-effects that affect safety, efficacy and equivalence

Active vs. Inactive Ingredients

- An Active Ingredient (per 21 CFR 210.3(b)(7))
  - Any component of a drug product intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body.

- An Inactive Ingredient (per 21 CFR 210.3(b)(8))
  - Any component of a drug product other than the active ingredient

Three Intersections of Clinical Pharmacology and Excipients

- Excipients effect on oral bioavailability
- Safety of excipients
- Excipients in locally acting products

Generic Drug Program

- Generic drug development is first and foremost product development
- GDUFA (Generic Drug User Fee Amendments) has focused FDA on research and regulatory needs that impact generic drug development
- Clinical Pharmacology impacts decisions about generic drug development and review

Factors Affecting Oral Absorption

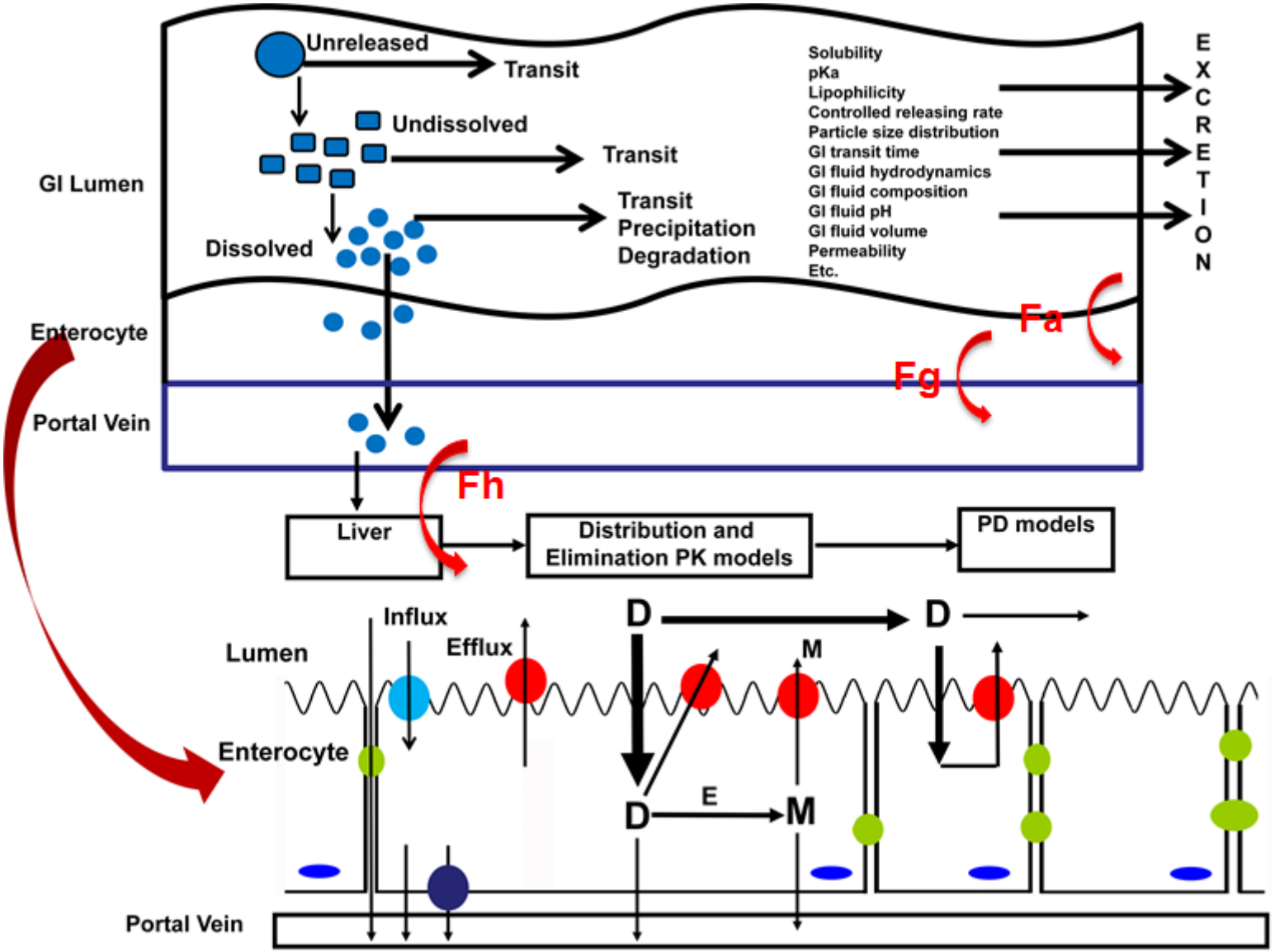


Figure Adapted from Dr. Xinyuan (susie) Zhang

Food Effects and Fed Bioequivalence (BE)

- Generally accepted that co-administration with food can change bioavailability
  - Routinely evaluated in new drug development and used to inform product label
  - Food effects can arise from both the active ingredient and the formulation
  - Routinely evaluated in generic drug development as part of evaluation of bioequivalence (fed BE study)
    - Some difference between EMA and FDA on when fed BE is needed

Biopharmaceutics Classification System (BCS) based Biowaivers

- BCS class I (high solubility , high permeability)
  - Waivers when the drug product (test and reference) is rapidly dissolving
- BCS class III (high solubility , low permeability)
  - Waivers when the drug product (test and reference) is **very** rapidly dissolving
  - **the product formulations are qualitatively the same and quantitatively very similar**
    - Based on a concern that excipient might affect bioequivalence

Biopharmaceutics Classification System 2015 Draft Guidance
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf

Excipients and Drug-Drug Interactions (DDIs)

- DDIs are generally expected to be the same for brand and generic products
- If DDIs occur in the GI tract, then differences in excipients could change the DDIs
  - Uptake and efflux transporters
  - Gut wall metabolism
  - Interactions with proton pump inhibitors (PPI)

Future Directions

- PBPK models of absorption should be able to predict all of these effects on a mechanistic basis
- Clinical and Quantitative Pharmacology input into size of acceptable differences
  - What size food effect or DDI effect impacts labeling or BE?
- GDUFA research support because of the impact on key generic drug regulatory decisions

Excipient Safety Assessments

- For new drug products, clinical studies are conducted using the drug product (including its excipients)
  - Novel excipients submit pre-clinical data
- For generic drug products, safety evaluation of excipients is generally based on prior knowledge (no new pre-clinical or clinical safety studies)
  - FDA's prior knowledge on excipients (Inactive Ingredient Database) is organized based on route of administration
  - The review is focused on safety of the proposed excipient for the patient population
    - Route, dose, duration of use, existing safety info
    - Patient population: drug toxicity, disease

FDA Guidance for Industry: **Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients**
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

Bridging Excipient Safety Data: Polymeric Excipients

- Endorsed by FDA guidance
  - "Large polymers that differ from previously characterized excipients only in molecular weight (chain length) can be adequately characterized in an abbreviated manner using less safety data, provided that the new excipient and the previously studied excipient are sufficiently similar with regard to physical state, pharmacokinetics, and levels of unreacted monomers and other impurities."
- How to implement in generic drug review

FDA Guidance for Industry: **Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients**
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf

Example: Grade and Patient Population

- Oral suspension for chronic use
  - Patients age 2 to adult will take this on an intermittent, chronic basis
  - proposed maximum daily intake of 900 mg excipient
- Approved levels – 53 mg excipient approved in another oral drug
  - Chronic use, indicated in adults
- Nonclinical tox summary consisted of data from various excipients in class ranging in molecular weight
- Molecular weight of the excipient grade is markedly lower than grades which are evaluated in available published information
  - Absorption of this lower MW grade is not characterized
- Proposed level is 18-fold higher than approved levels for this route
- Safety in pediatrics is not addressed
- Conclusion: Clinical and P/T information on long-term safe use of this excipient grade needed

Example: Higher Amount of Polymer

- A CNS stimulant: chronic oral product for children to adults
- Proposed 80 mg/day of grade X
- 37.5 mg of grade X is approved for chronic oral use
- Grade Y is approved at higher levels

- Pharm/Tox data
  - Grade X is poorly absorbed and well-tolerated in general tox studies (up to 6 months in rodent alone)
  - Negative across several genetic toxicology studies
  - No safety signal in developmental and reproductive tox data
- Conclusion: The proposed amount was acceptable based on totality of information: Pharm/Tox info, prior use, similarity with other grades at higher levels

Future Direction

- A better understanding of the pharmacological activity of excipients will support better decisions on safety evaluations that involve exposure of a particular patient population to an excipient in a generic drug application
- Evaluation of grades of polymeric excipients needs to consider sensitivity of activity and exposure to molecular weight

Clinical Pharmacology for Locally Acting Drug Products

- Products directly deliver drug and excipients to the site of action
- Systemic drug exposure (PK) is often a side effect and may not be measurable
- Clinical pharmacology and bioequivalence assesments are harder

Orally Inhaled Drug Products

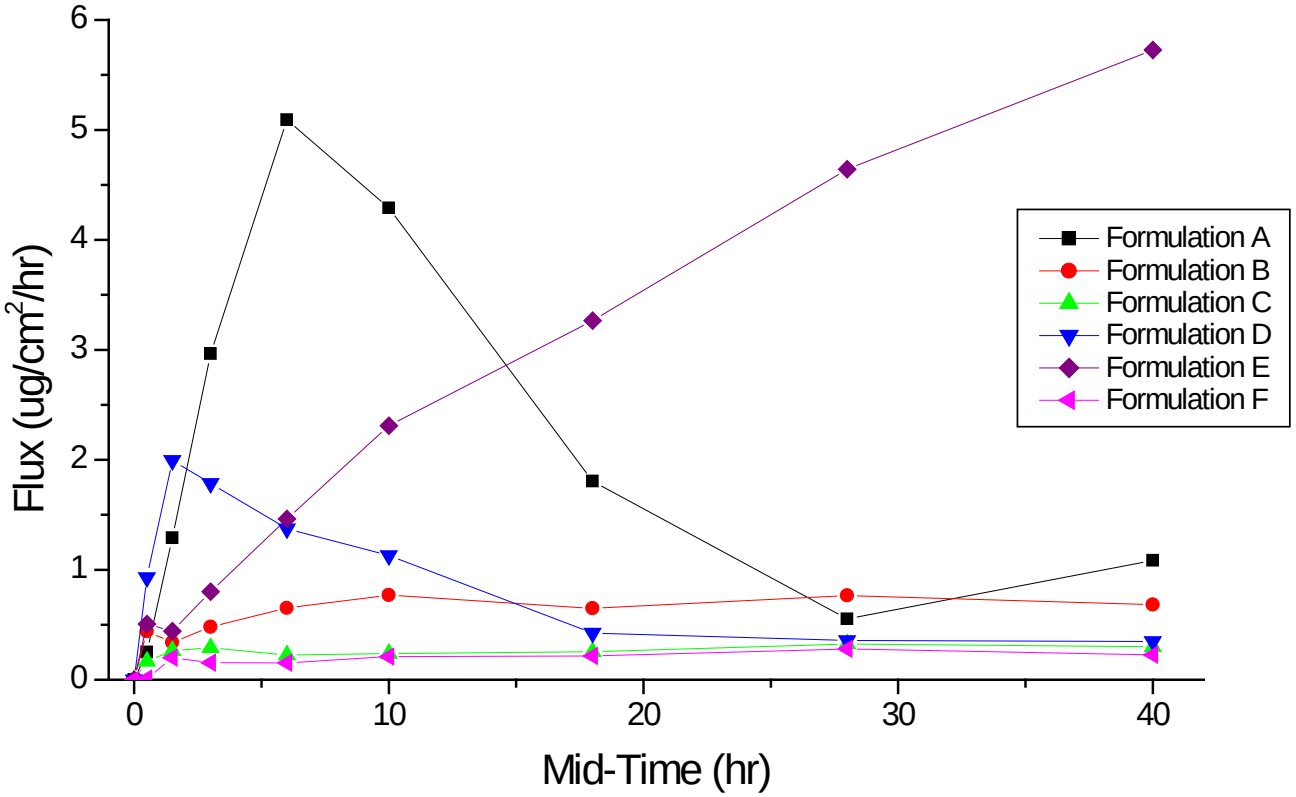
- Factors influencing patient-product interactions and drug bioavailability include:
  - dose percent deposited in the lungs vs. dose percent swallowed and absorbed from the GI tract
  - local solubility/permeability
  - receptor affinity
  - deposition in central vs. peripheral parts of the pulmonary tree
  - pulmonary residence time
  - local clearance (mucociliary transport and reticuloendothelial system uptake)
  - device design
  - effects of formulation differences on product performance

Topical Dermatological Drug Products

- Do topical excipients act on the disease state?
  - Inactive ingredients in a placebo vehicle may account for 40% of the therapeutic effect; the active ingredient may only account for an additional 20% of therapeutic effect.
  - Inactive ingredients may modulate the delivery/bioavailability of the active ingredient, which then acts on the disease state. This is the most widely characterized.
  - Do changes in the quality of topical excipients impact therapeutic effect, either way?

Effects of Excipient Composition

- In vitro permeation (human skin) with different excipients (inactive ingredients)



Data provided courtesy of Paul A. Lehman and Dr. Thomas J. Franz

Excipients Matter to Clinical Pharmacology

- Impact drug exposure and change how patients can use drug products
- Impact drug product safety and a change in drug product source can lead to exposure to different excipients
- Clinical pharmacology for locally acting drugs must include the role of excipients

Clinical Pharmacology can

- Advance the science of excipient selection and regulatory evaluation
  - Regulatory science is decision science
  - Make better and faster decision about excipients
- Encourage innovation in product development
  - Value of excipient function to drug product performance and equivalence
  - Expand access to complex generics

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