Physiologically Based Pharmacokinetic Absorption Modeling to Support BCS-Based Waiver of in vivo Bioequivalence Studies

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Disclaimer

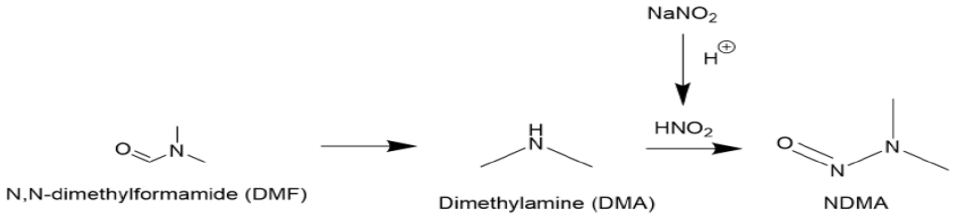
This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Outline

- Background
  - Approaches to control the levels of nitrosamine impurities
  - One of the approaches to support waiver of in vivo relative bioavailability and bioequivalence (BE) studies for reformulated products (Biopharmaceutics Classification System (BCS) based waiver)
- Physiologically based pharmacokinetic (PBPK) absorption modeling to support expanding BCS-Based waiver to non-Q1/Q2 formulations, evaluate the impact of excipients (including antioxidants) on bioequivalence of BCS Class III drug products (Case Example: Acyclovir immediate release tablet)
- PBPK Modeling to support expanding BCS-Based waiver to non-very rapidly dissolving BCS Class III drug products (Case Example: Nadolol oral tablet)
- Next research topics

Background

- Nitrosamine drug substance-related impurities (NDSRIs) generally form in the drug product through nitrosation of APIs (or API fragments) that have secondary or tertiary amines when exposed to nitrosating agents such as residual nitrites in excipients used to formulate the drug product.
- Nitrosamines are formed by interaction between a secondary amine and a nitrosonium ion.



- One approach in controlling the levels of these Nitrosamine impurities is using antioxidants and/or pH modifiers in the formulations (when reformulating products).

Reference: Guidance for Industry: Recommended Acceptable Intake Limits for Nitrosamine Drug Substance Related Impurities (NDSRIs) (August 2023). Link: https://www.fda.gov/media/170794/download

Possible NDSRI mitigation strategies

- Addition of antioxidants, e.g., ascorbic acid (vitamin C) or alpha-tocopherol (vitamin E) to formulations
- Incorporation of pH modifiers, e.g., sodium carbonate, that modify the micro-environment to neutral or basic pH
- Other innovative strategies to reduce the formation of NDSRIs to acceptable levels in drug products

Reference: Updates on possible mitigation strategies to reduce the risk of nitrosamine drug substance-related impurities in drug products. Link: https://www.fda.gov/drugs/drug-safety-and-availability/updates-possible-mitigation-strategies-reduce-risk-nitrosamine-drug-substance-related-impurities

Research Question

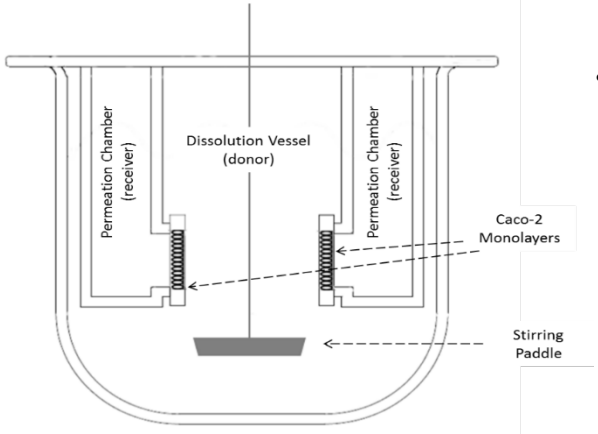
Adding antioxidants can reduce nitrosamine levels

- Do these antioxidants and pH modifiers impact the bioavailability and/or bioequivalence of generic products?
- If an applicant adds antioxidants to formulation to reduce nitrosamine levels, can studies other than in vivo BE studies support these reformulated products?

Past FDA Research

- Assuming that an antioxidant does not impact dissolution or solubility (easy to measure!), then the BE risk is the impact of an addition of an antioxidant on drug permeability/absorption
- BCS Class I and Class II---High permeability drugs
  - Low risk, so not included in FDA research
- BCS Class III drugs---Low permeability drugs
  - FDA conducted and supported studies on a set of BCS III drugs and antioxidants:
    - Use of a Novel Technology, the In Vitro Dissolution Absorption System, to Investigate the Effects of Antioxidants on the Intestinal Permeation of BCS Class III Drugs (by Pharmaron (Exton) Lab Services LLC);
    - Effects of Antioxidants in Drugs Products on Intestinal Drug Transporters (by University of California, San Francisco);
    - Physiologically Based Pharmacokinetic Absorption Modeling to Evaluate the Impact of Excipients on Bioequivalence of BCS Class III drug products (by FDA, OGD/ORS).

In Vitro Permeability Testing by IDAS System

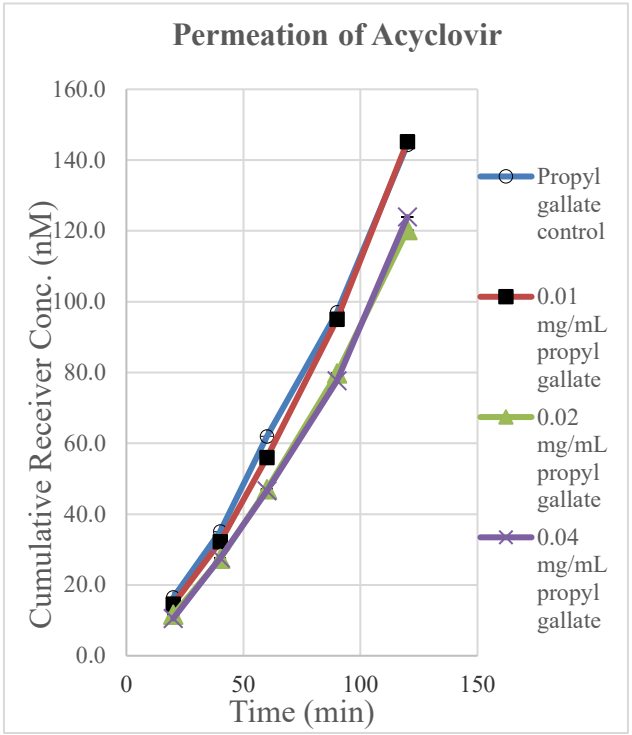


in-vitro Dissolution Absorption System (IDAS)

- Validated an LC-MS/MS analytical method for the quantification of four BCS Class III model drugs:
  - Acyclovir
  - Atenolol
  - Cimetidine
  - Ranitidine
- Used IDAS to measure the rate of permeation of the model drugs (pre-dissolved and dosed individually*) in the absence and presence of 4 antioxidants (one at a time), each at three concentrations and with a parallel control (no antioxidant)

***Reference**: Chris Bode, Presentation in 2023 June CRCG Nitrosamine workshop "Use of a Novel Technology, the In Vitro Dissolution Absorption System, to Investigate the Effects of Antioxidants on the Intestinal Permeation of BCS Class III Drugs".*

Effect of Propyl Gallate on Permeation of Acyclovir



Treatment	Analyte	P_{app} (10^{-6} cm/s)	
		Mean	SD
Control	Acyclovir	**0.425**	0.058
0.01 mg/mL		**0.435**	0.031
0.02 mg/mL		**0.362**	0.042
0.04 mg/mL		**0.372**	0.054

***Reference**: Chris Bode, Presentation in 2023 June CRCG Nitrosamine workshop*

Results with Antioxidants and BCS Class III Model Drugs

- Based on an FDA contract project with PHARMARON

Effects	Antioxidant	Model Drugs
No effect on permeation	Alpha-tocopherol	Acyclovir, atenolol, cimetidine, ranitidine
	Ascorbic acid	Acyclovir, atenolol, cimetidine, ranitidine
	Cysteine	Acyclovir, atenolol, cimetidine, ranitidine
	Propyl gallate	**Acyclovir**, atenolol, cimetidine, ranitidine

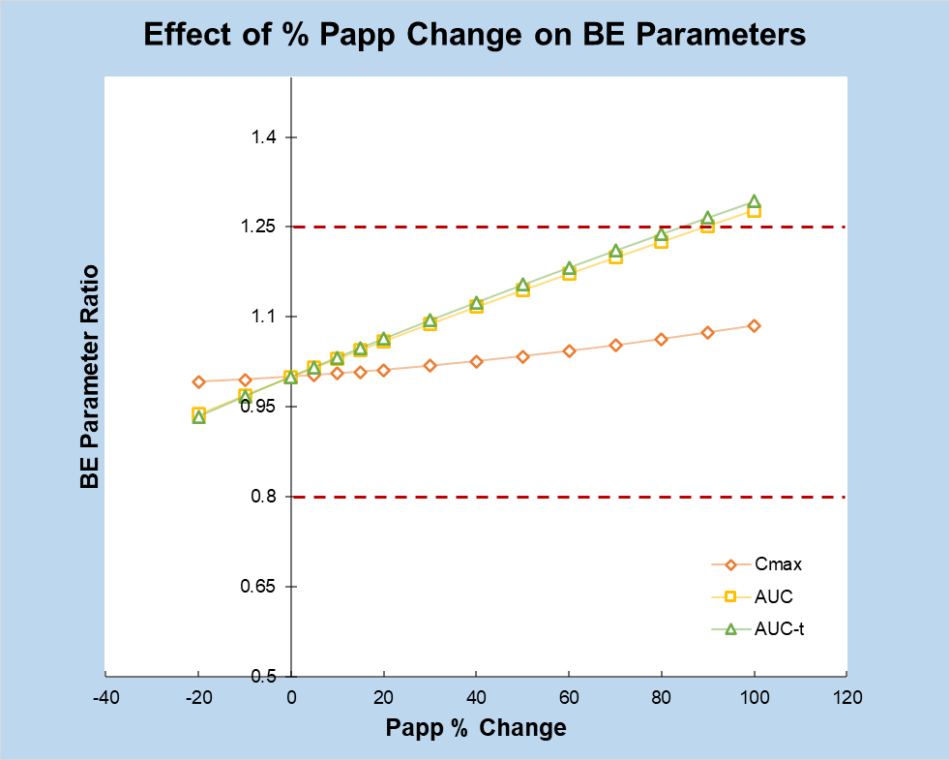
- **Notes**: The antioxidants tested, at the concentrations tested, had little or no effect on the permeation of the four Class III model drugs, (in combination with PBPK), which could suggest that reformulating drug products to include an antioxidant may be a feasible approach for reducing the formation of NDSRIs.

***Reference**: Chris Bode, Presentation in 2023 June CRCG Nitrosamine workshop*

Research Question

- Can we use PBPK model to predict the impact of antioxidant on BE, by incorporating the permeability change data from the in vitro study?

Effect of Excipients on Virtual Bioequivalence (VBE) of Acyclovir IR Tablet-800 mg



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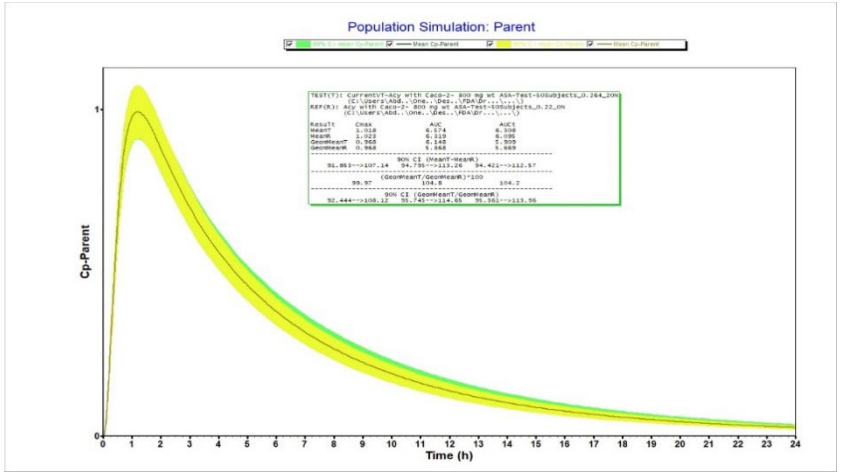
Effect of Excipient on VBE of Acyclovir IR Tablet-800 mg

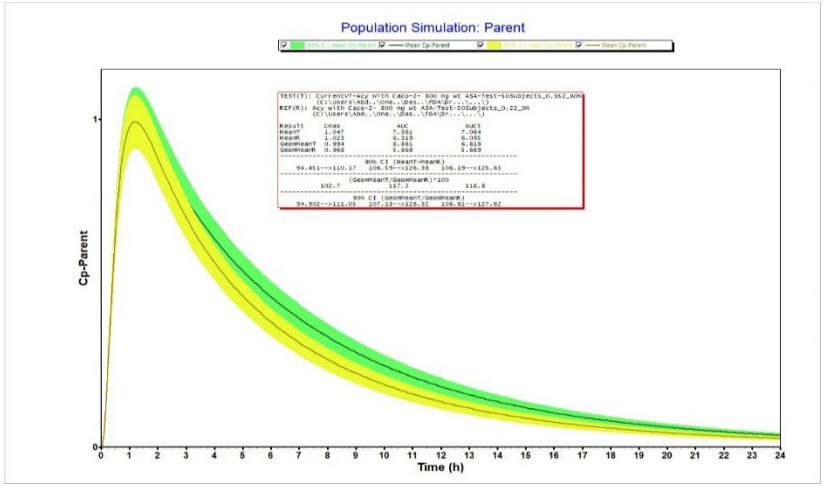
Reference VS Test (10% Increased P_{app})



PK Parameter	Geometric Mean T/R (90% CI)
Cmax	99.97 (92.44-108.12)
AUC0-inf	104.8 (95.74-114.65)
AUC0-t	104.2 (95.36-113.96)

BE Scenario

Reference VS Test (60% Increased P_{app})



PK Parameter	Geometric Mean T/R (90% CI)
Cmax	102.7 (92.99-111.05)
AUC0-inf	117.2 (107.13-128.32)
AUC0-t	116.8 (106.81-127.62)

Non-BE Scenario

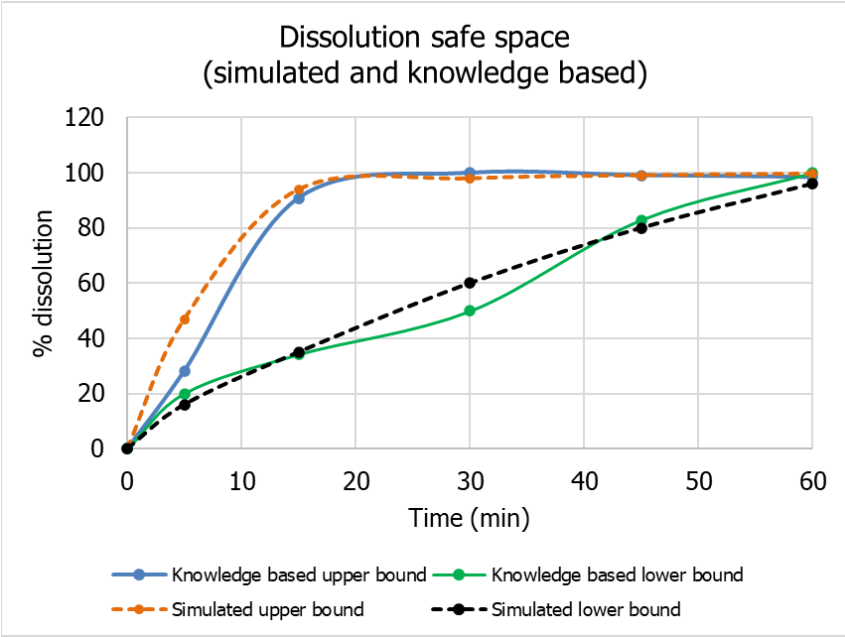
Fasted-Condition

Summary

- In vitro testing systems provided relevant information, e.g., in vivo permeability change by excipients.
- Acyclovir PBPK modeling and VBE trials were used to assess the potential impact of excipient-mediated permeability changes on acyclovir BE.
- The VBE results suggested that more than 60% change of Papp value for test product due to presence of certain excipient may result in failed BE of acyclovir 800 mg IR tablet under fasted conditions (need to double permeability to cause BE failure for acyclovir IR tablet).
- Case by case evaluation

One BCS-Based Waiver Requirement by ICH M9 Guidance: Rapid Dissolution

- For BCS Class III drugs dissolution, >85% dissolution within 15 minutes is recommended in the ICH M9 guidance
- **Case**: For Nadolol oral tablets, the RLD does NOT display very rapid in vitro dissolution
- Research result by applying PBPK modeling: >85% dissolution within 60 minute is consistent with BE



What are Next Research Topics?

- What type of formulation changes to reduce nitrosamines are in the pipeline?

- What scientific data are most useful to support alternatives to in vivo BE studies for nitrosamine-reducing reformulations?

Acknowledgement

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