Sandoz Development Center
Clinical development

PKPB Modeling for Different Locally-Administered Drug Products

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Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches, online workshop, Sep 30 2021

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Non-oral administration routes

Inhalation

Transdermal

Ocular

Intranasal

Buccal/Sublingual

Intramuscular

Intravenous

Subcutaneous

Intraarticular

Intrathecal

Rectal

Vaginal

Intramuscular injection

Formulation – solution, suspension, LAI (micro/nanoparticles, implants, in situ forming depos, oil-based formulations)

PBPK model

- One compartment with specified drug-dependent and physiological parameters
  - Absorption into the lymph or systemic circulation
  - Drug binding
  - Local clearance
- Dissolution and absorption
- Immune response – inflammation – additional barrier

Intramuscular injection

Case study – oily solution of API

Goal → predict *in vivo* behavior and BE of test formulation and RLD

Collect literature data on API properties, c_p profiles

Develop model in GastroPlus

Which dosage form to select? Solution, suspension, controlled release?

Intramuscular injection

What is affecting *in vivo* behavior of oily solutions?[1]

- API concentration in the oil
- Diffusion layer thickness and diffusion coefficient in the oil and aqueous phase
- Depot surface area (injection volume, absorption and distribution of the oil vehicle, extent of spreading of the depot)
- Partition coefficient between oil and tissue fluid

What can be measured and used as a model input to evaluate the difference between test and RLD?

Intramuscular injection

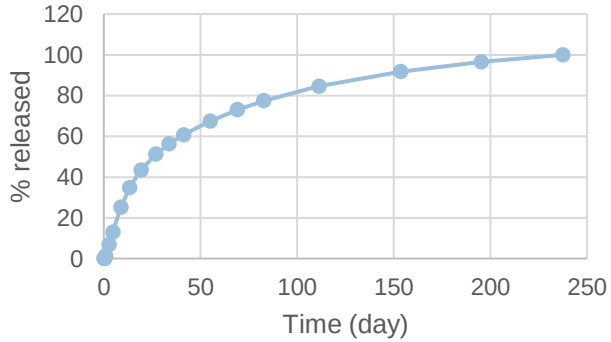
Controlled release formulation

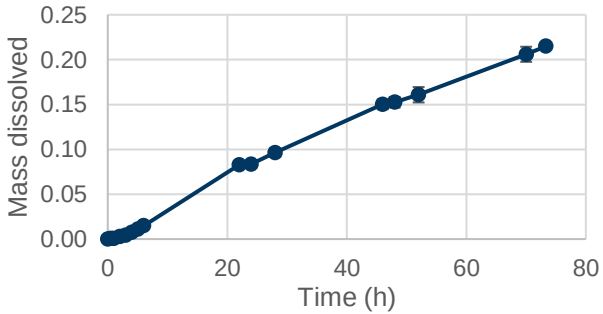
→ *in vitro* release test to include differences between test and RLD

Deconvolution – absorption > 3 months

Challenge – no *in vitro* test long enough

→ time scaling (3 days *in vitro* = 18 days *in vivo*)





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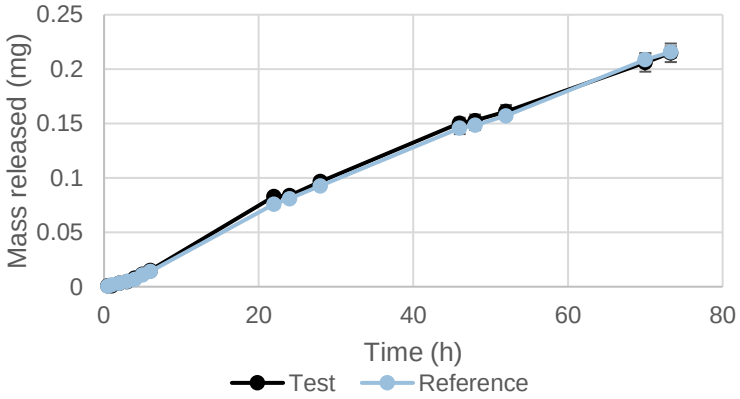
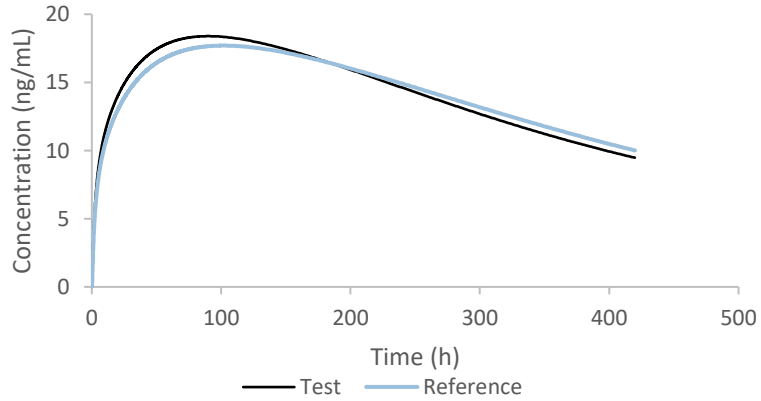
Intramuscular injection

Model was used for:

- Estimation of time when AUC_t > 80% of AUC_{inf} (last sampling time in the study)
- Making BE predictions based on performed *in vitro* tests





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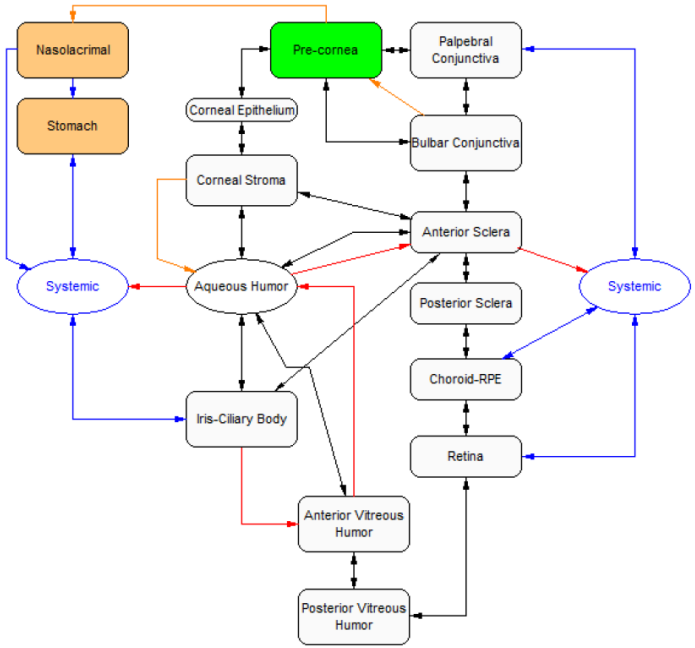
Ocular administration

Formulation – eye drops (solution/suspension), ointment, gel, intravitreal injection, intravitreal/subconjunctival implants

PBPK model (GastroPlus OCAT)[2]

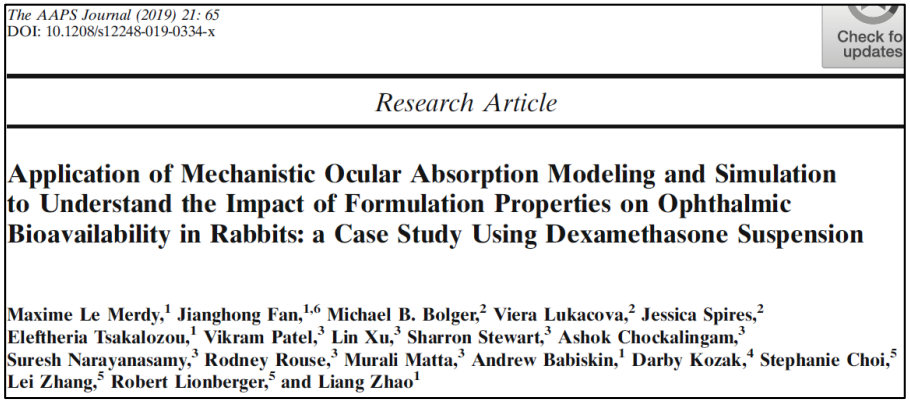
- 13 compartments
- Nasolacrimal drainage
- Clearance – systemic absorption, metabolism
- Distribution – permeability, melanin binding



Ocular administration

- Literature case studies[3,4,5]

  OCAT model



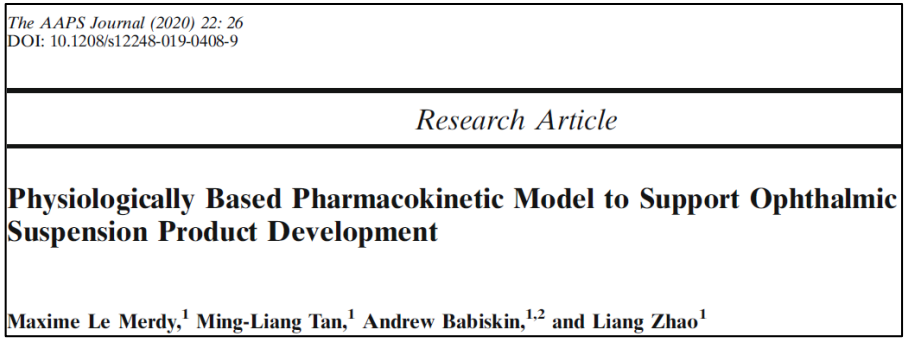
The AAPS Journal (2019) 21: 65
DOI: 10.1208/s12248-019-0334-x

Check for updates

Research Article

Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: a Case Study Using Dexamethasone Suspension

Maxime Le Merdy,[1] Jianghong Fan,[1,6] Michael B. Bolger,[2] Viera Lukacova,[2] Jessica Spires,[2] Eleftheria Tsakalozou,[1] Vikram Patel,[3] Lin Xu,[3] Sharron Stewart,[3] Ashok Chockalingam,[3] Suresh Narayanasamy,[3] Rodney Rouse,[3] Murali Matta,[3] Andrew Babiskin,[1] Darby Kozak,[4] Stephanie Choi,[5] Lei Zhang,[5] Robert Lionberger,[5] and Liang Zhao[1]



The AAPS Journal (2020) 22: 26
DOI: 10.1208/s12248-019-0408-9

Research Article

Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development

Maxime Le Merdy,[1] Ming-Liang Tan,[1] Andrew Babiskin,[1,2] and Liang Zhao[1]

Pharm Res (2020) 37: 245
https://doi.org/10.1007/s11095-020-02965-y

Check for updates

RESEARCH PAPER

Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations

Maxime Le Merdy[1] • Jessica Spires[1] • Viera Lukacova[1] • Ming-Liang Tan[2] • Andrew Babiskin[2] • Xiaoming Xu[3] • Liang Zhao[2] • Michael B. Bolger[1]

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Ocular administration

Case study – eye ointment

Goal → evaluate the impact of API particle size on drug *in vivo* behavior and predict BE of test formulation and RLD

Collect literature data on API properties, concentration profiles

- Scarce data in humans, more data for rabbits
- Data for different compartments (AH, conjunctiva, ICB, tear)
- Inconsistent data from different studies

Develop model in GastroPlus

- Which dosage form to select - solution, suspension, ointment?

Ocular administration

Suspension

- To evaluate the effect of API particle size
- Lower nasolacrimal drainage rate to account for gel (higher viscosity)

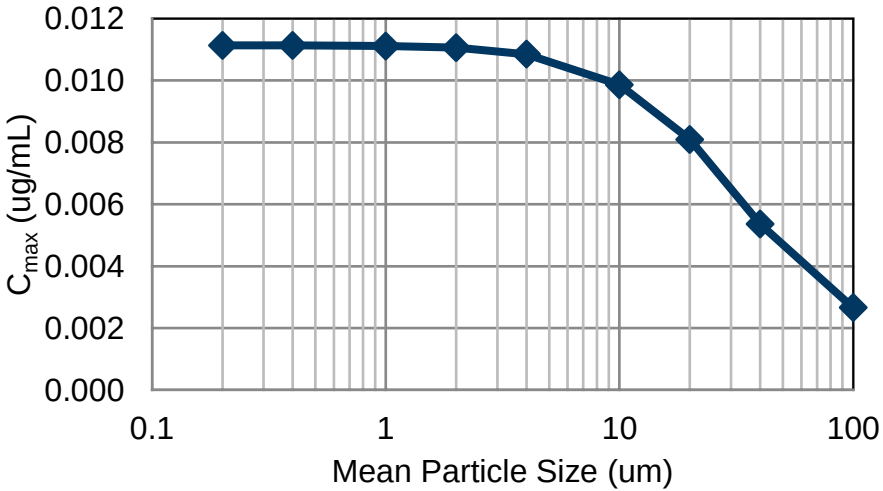
Challenges

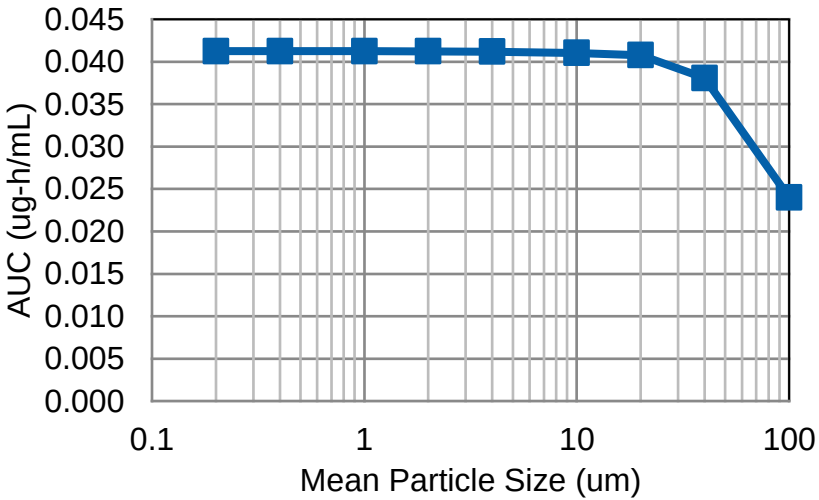
- Many unknown parameters fitted/optimized (permeability, SAR, CL)
- Translation from rabbit to human
- Which literature data to use
- Poor validation due to scarce human data (only AH data)

Ocular administration

Results:

- PSA for C_{max} and AUC in AH





Regulatory utility of PBPK models for other locally-acting drug products

PBPK models for non-oral routes are available and can be used for making decisions **during drug development**.

For the models to be used **for regulatory purposes** (e.g., to support alternative BE approaches), generic industry has to be pay attention to:

- Selection of model parameters (many unknown and difficult to determine)
- Proper model development and validation (scarce and inconsistent literature)

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- Clinical Development
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References

1. Kalicharan RW, Schot P, Vromans H. Fundamental understanding of drug absorption from a parenteral oil depot. Eur J Pharm Sci. 2016 Feb 15;83:19-27. doi: 10.1016/j.ejps.2015.12.011. Epub 2015 Dec 9. PMID: 26690043.
2. Simulations Plus. Inc. GastroPlusTM manual, version 9.6. California. 2018.
3. Le Merdy M, Fan J, Bolger MB, Lukacova V, Spires J, Tsakalozou E, Patel V, Xu L, Stewart S, Chockalingam A, Narayanasamy S, Rouse R, Matta M, Babiskin A, Kozak D, Choi S, Zhang L, Lionberger R, Zhao L. Application of Mechanistic Ocular Absorption Modeling and Simulation to Understand the Impact of Formulation Properties on Ophthalmic Bioavailability in Rabbits: a Case Study Using Dexamethasone Suspension. AAPS J. 2019 May 20;21(4):65. doi: 10.1208/s12248-019-0334-x. PMID: 31111305.
4. Le Merdy M, Spires J, Lukacova V, Tan ML, Babiskin A, Xu X, Zhao L, Bolger MB. Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations. Pharm Res. 2020 Nov 19;37(12):245. doi: 10.1007/s11095-020-02965-y. PMID: 33215336; PMCID: PMC7677276.
5. Le Merdy M, Tan ML, Babiskin A, Zhao L. Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development. AAPS J. 2020 Jan 6;22(2):26. doi: 10.1208/s12248-019-0408-9. PMID: 31907674.

Thank you

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