Microfluidic Blood-Milk Barrier and Physiologically Based Pharmacokinetic Model to Predict Lofexidine Secretion into Breast Milk

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Background and Significance

- ❑Lofexidine (LUCEMYRA®): The only FDA-approved, non-opioid, non-addictive α2-adrenergic receptor agonist for treating opioid withdrawal symptoms.
- ❑ Postpartum and pregnant women affected by the opioid crisis require safe treatment options that do not compromise infant health.
- ❑ Challenge: Limited data on Lofexidine secretion into breast milk, creating uncertainty in prescribing it to lactating mothers.

Objectives

1. Develop a microfluidic blood-milk barrier model to mimic in in-vivo conditions of drug transfer in lactating women.
2. Utilize a physiologically based. pharmacokinetic (PBPK) model to simulate Lofexidine's transfer into breast milk
3. Estimate and validate Milk-to-Plasma (M/P) ratios of Lofexidine using multiple approaches.

Methods Overview: Multi-Model Approach to Predict Drug Transfer

1. Microfluidic Device Design: Mimics the mammary epithelium environment, integrating fluid shear stress to simulate blood and milk flow.
2. Static Transwell Model: Uses normal human mammary epithelial cells (MCF10A-TJ) forming tight junctions and assess drug permeability.
3. Physiologically Based Pharmacokinetic (PBPK) Model: Simulates Lofexidine's pharmacokinetics in plasma and breast milk, predicting concentration-time profiles.

Simulation Designs:

- **Design A:** Single oral dose (1.2 or 2 mg) in healthy lactating women over 35 hours.
- **Design B:** Multiple doses (0.4 mg BID on day 9, 0.8 mg BID on day 10) in healthy lactating women.
- **Design C:** Multiple doses (1.2 mg BID or 0.8 mg TID) over 7 days in opiate-dependent patients.

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Simcyp Population-based Simulator, Certara

Results

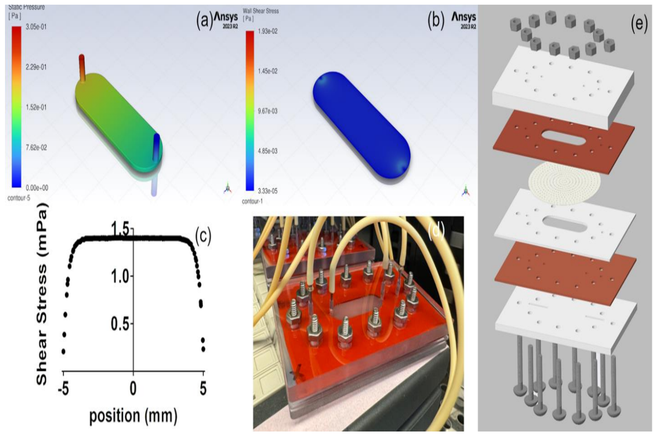

Figure 1: Computational simulation of the device (a) Static pressure contour throughout the apical chamber of the device (b) shear stress contour on the bottom plane of apical chamber (c) Shear stress distribution on a transverse line in the bottom plane of apical chamber (d) Final assembled device with tubing (e) Exploded view of all the parts in the device.

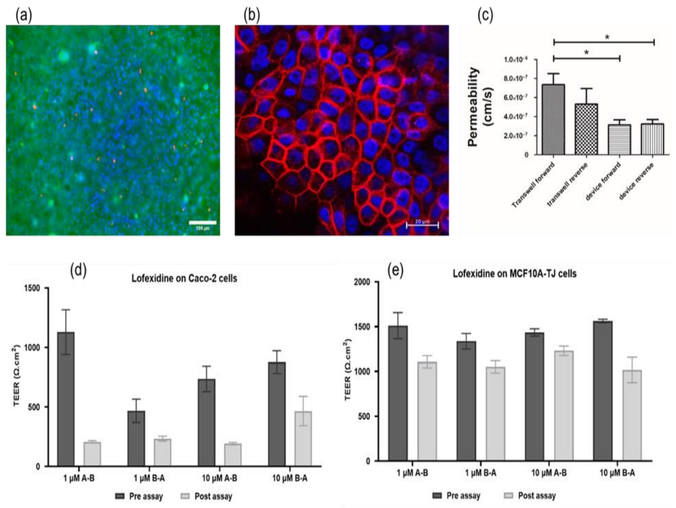

Figure 2: In vitro mammary epithelial barrier formation in microfluidic device, TEER of microfluidic device and transwell system (a) live/dead assay showing higher percentage of live cells (green: calcein AM, red: Propidium Iodide, blue: Hoechst) (b) tight junction formation in static culture (red: anti-occludin, blue: Hoechst) (c) Lucifer yellow permeability comparison in static and dynamic condition. TEER values pre and post assay for lofexidine on (d) Caco2 cells in microfluidic device and (e) MCF10A-TJ cells in transwell system.

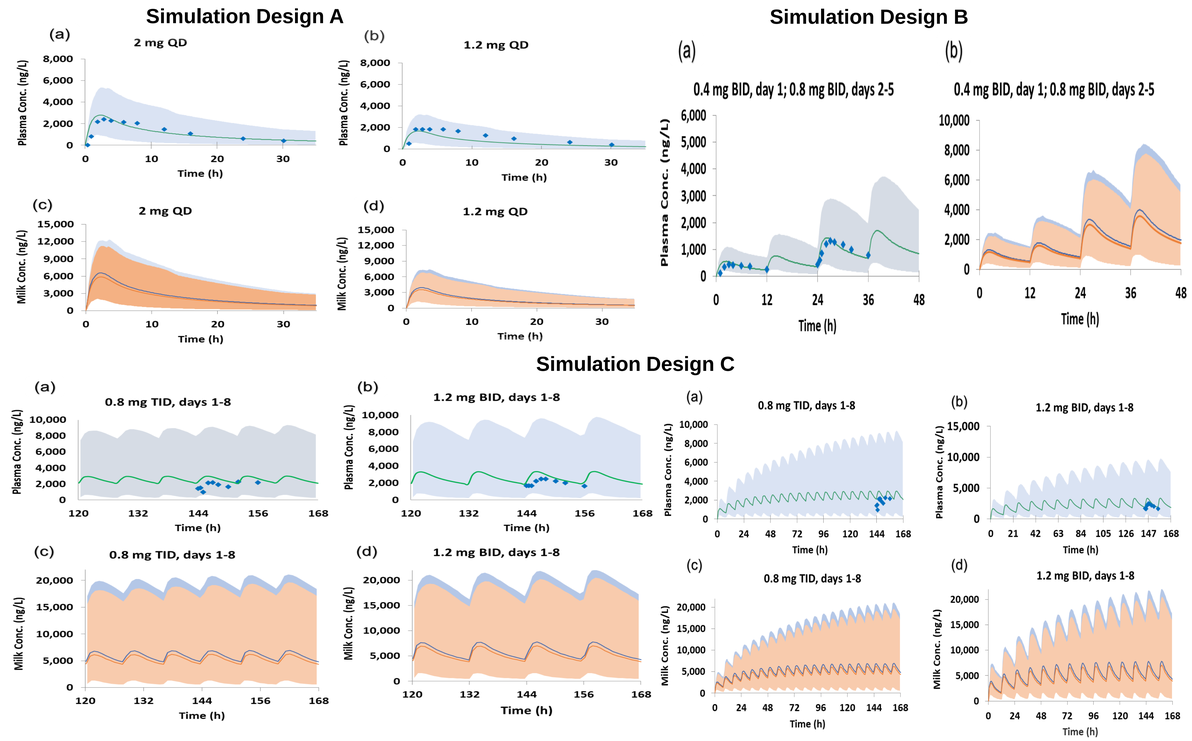

Figure 3: Concentration time profiles of lofexidine in plasma (a), (b) and milk (c), (d) [Simulation design A & C], plasma (a) and milk (b) [Simulation design B] for different dosing in healthy lactating female volunteers. The blue diamonds represent the experimental data, blue line represents simulation done with $\log Pmk_{o:w} = \log Pk_{o:w}$, whereas orange line represents $\log Pmk_{o:w}$ computed from $\log Pk_{o:w}$. No differences in plasma PK was observed in these two simulation settings. The shaded region represents the range between the 5th and 95th percentiles. Data were digitized using GetData Graph Digitizer.

Table 1: Milk to Plasma Ratio of lofexidine Predicted using different approaches

Computation method	Values (using Exp. f_{up}, f_{um})	Values (using Ref. f_{up} and Calculated f_{um}
pH partition (unbound)	3.95	-
Membrane diffusion	0.5	-
Phase distribution	3.13	2.46
Log phase distribution	15.88	14.05
Koshimichi	0.45	0.36
IVIVE MCF10A (Microfluidic Device-HBSS Buffer)	0.75	0.55
IVIVE MCF10A (Static Transwell)	1.35	1
IVIVE MCF10A (Microfluidic Device Milk to Plasma)	5.48	-
IVIVE Caco2 (Static Transwell)	0.4	0.3
Simcyp diffusion model ($log\ Pmk_{o:w} = log\ Pk_{o:w}$)	2.35	-
Simcyp diffusion model ($log\ Pmk_{o:w}$)	2.1	-

Conclusions

- ❑ The first use of a microfluidic device to model the transfer of Lofexidine into breast milk.
- ❑ An in-vitro drug transfer assay was successfully established using human MCF10A-TJ cells.
- ❑ Multiple predictive models, including PBPK and IVIVE, were applied to estimate drug transfer, with further clinical validation necessary to confirm safety for lactating mothers and infants.

References

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