Modeling the Impact of Amorphous Drug-Polymer Colloids on the Absorption of Poorly Soluble Drugs

Aaron M. Stewart, Michael E. Grass, David T. Vodak

Lonza Pharma and Biotech—Small Molecule R&D, Bend, OR, USA

PURPOSE

The intent of this work is to calculate a nano-modified effective permeability ($P_{eff,nano}$) with a simple calculation to account for amorphous drug colloids. This approach applies to modeling efforts to describe absorption from poorly soluble drugs that produce nano sized colloids upon dissolution (typically from amorphous solid dispersions), where diffusion across the unstirred water layer is the largest barrier to absorption.

OBJECTIVE(S)

Evaluate a method for modifying the effective permeability in an absorption model to account for amorphous drug colloids that may contribute to absorption for poorly soluble drugs. Evaluate the method for three different drugs that have shown an absorption benefit from the presence of amorphous drug colloids: itraconazole[1], anacetrapib[2] and enzalutamide[3].

METHOD(S)

Required In Vitro Data

In Vitro Data	Impacts?	Analytical
Concentration of drug colloids	c_{nano}	Centrifuge + HPLC
Concentration of bile-bound drug	c_{SIF}	Ultracentrifuge + HPLC
Free drug	c_u	Ultracentrifuge + HPLC
Size of nanospecies/colloids	d_{nano}	Dynamic Light Scattering
Size of bile salt micelles	d_{SIF}	Dynamic Light Scattering

Calculation

This calculation utilizes only the standard effective permeability, P_{eff}, and the following measurements: (1) c_u, the amorphous solubility of the API in blank intestinal buffer (e.g. PBS at pH 6.5); (2) c_{SIF}, the amorphous solubility of API in simulated intestinal fluid (e.g "SIF"), (3) c_{nano}, the estimated concentration of drug-containing nanoparticles in the intestine upon administration, and (4) d_{nano}, the average diameter of nanoparticles formed (diffusivity, D, is then calculated from size, d). Equation 1 is the general form of the nano modified permeability equation that captures the impact of added drug shuttles (micelles and/or colloids) in the effective permeability term. Equation 2 is a combined final form after simplification of equation 1.

Key assumption: the rate limiting step to absorption for the drug of interest is diffusion across the unstirred water layer, a common attribute of BCS Class II drugs.

eq 1 $$P_{eff,nano} = P_{eff}\left(1 + \frac{D_{nano}}{D_{SIF}} \cdot \frac{c_{nano}}{c_{SIF}}\right)$$

eq 2 $$P_{eff,nano} = P_{eff}\left(1 + \frac{7 \cdot c_{nano}}{d_{nano} \cdot (0.95 \times 10^{-6} \cdot D_u \cdot c_u + c_{SIF} - c_u)}\right)$$

RESULT(S)

Modeling predictions using GastroPlus v9.7 and a calculated/reported baseline P_{eff} resulted in significant underpredictions of the observed data sets. By accounting for the size and abundance of amorphous drug colloids reported from each of these studies, the nano-modified permeability method resulted in much better prediction accuracy.

CONCLUSION(S)

For some poorly soluble drugs, absorption can be improved via shuttles across the UWL in the form of amorphous drug colloids. Capturing this phenomenon *in silico* can be useful for aiding key formulation decisions or for *in vivo* data understanding.

REFERENCES

Full open access publication is available at:

1. Stewart, A. M., & Grass, M. E. (2019). *Molecular Pharmaceutics,* 17, 1, 180–189.
2. Kesisoglou, F., Wang, M., Galipeau, K. et al. (2019). *Journal of Pharmaceutical Sciences*, 1–9.
3. Wilson, V., Lou, X., Osterling, D. J. et al (2018). *Journal of Controlled Release*, *292*, 172–182.

aaps PharmSci 360

ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

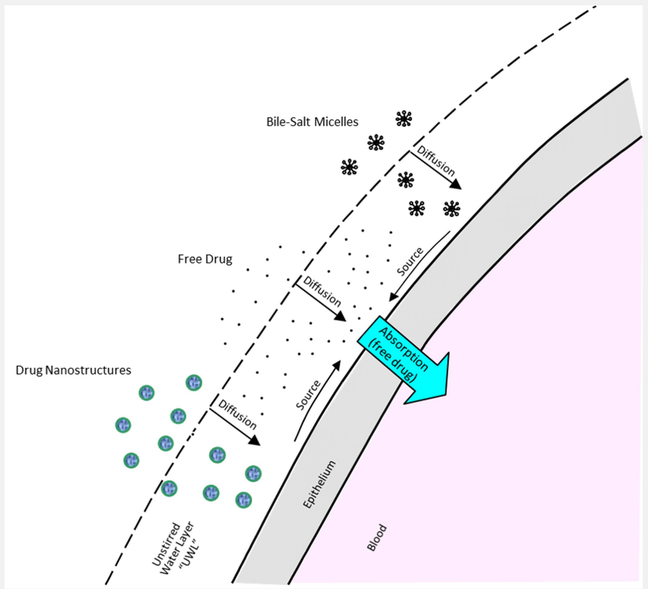
Nano-sized amorphous drug colloids may improve absorption of some poorly soluble drugs by acting as a “shuttle” across the unstirred water layer

IMPORTANCE

For UWL-limited drugs, absorption can be improved via shuttles across the UWL

- Drug in bile salt micelles (physiological)
- Drug in nano-sized colloids (formulation driven)

Capturing impact in silico can be useful for key formulation decisions or in vivo data understanding

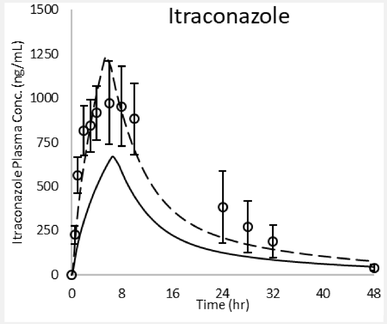


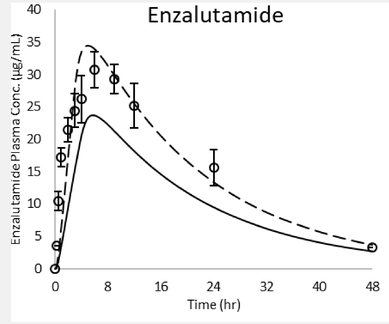
HOW?

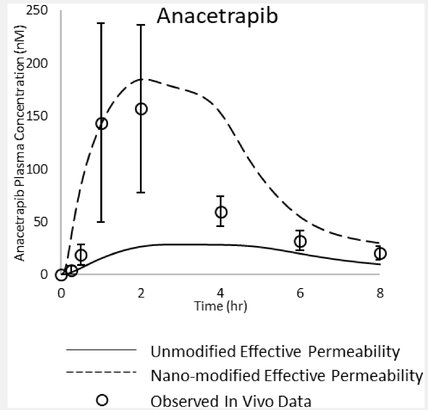
Nano-modified Permeability

Modify the measured or calculated effective permeability to account for amorphous drug colloids as a “shuttle” by taking into account their size and concentration relative to other drug species (unbound, micelle-bound) using routine analytical methods.

$$P_{eff,nano} = P_{eff}\left(1 + \frac{7 \cdot c_{nano}}{d_{nano} \cdot (0.95 \times 10^{-6} \cdot D_u \cdot c_u + c_{SIF} - c_u)}\right)$$







CONTACT INFORMATION: aaron.stewart@Lonza.com