O 15

Amorphous solid dispersions: True supersaturation measured in a time-resolved manner by microdialysis

Annette Bauer Brandl

University of Southern Denmark, Denmark

To enable oral bioavailability of poorly soluble drugs, formulations that enhance dissolution and create supersaturation (*e.g.* ASDs) are widely used.
In recent years, we have understood that the dissolution process of ASDs - apart from truely dissolved drug molecules - gives rise to the formation of various drug association states. Binding of drug molecules to micelles leads to enhanced apparent solubility (*i.e.* apparent supersaturation), may they originate from ASD excipients, biomimetic media, or in intestinal lumen where a variety of colloids of bile salts and (phospho-) lipids) are present. Furthermore, formation of yet another apparently dissolved species, namely phase separation into amorphous sub-micron drug-rich particles, contributes to apparent supersaturation. However, such apparently dissolved species are less prone to overcome biological barriers as compared to the molecularly dissolved drug.
Thus, for rational ASD development and the prediction of their performance, differentiating between molecularly dissolved and the apparently dissolved (colloid-associated) states of the drug are needed.
Equilibrium measurement of apparent solubility is the classical experiment. Kinetic studies combining dissolution and permeation through biomimetic barriers may serve as a powerful surrogate of bioavialability and for performance-ranking of the formulations. A recent approach describes simultaneous time-resolved measurements of molecularly dissolved drug concentrations by microdialysis, micelle-associated drug concentrations by nanofiltration, and drug concentration in the form of drug-rich submicron particles (1,2). These analytical tools give unprecedented mechanistic insights into enabling formulations. Case studies have demonstrated that submicron particle formation from ASDs may be the root-cause for molecular supersaturation, enhanced permeation, and better bioavailability (3,4). Implementation in kinetic dissolution/permeation experiments is discussed.

References:

(1) Holzem FL et al., Microdialysis and nanofiltration allow to distinguish molecularly dissolved from colloid-associated drug concentrations during biomimetic dissolution testing of supersaturating formulations. (2022). *Eur. J. Ph. Sci.,* 174, art. no. 106166.
(2) Nunes PD et al., In vitro dissolution/permeation tools for amorphous solid dispersions bioavailability forecasting I: Experimental design for PermeaLoop™, (2023) *Eur. J. Pharm. Sci.* 188, art. no. 106512.
(3) Holzem FL et al., Combining in vitro dissolution/permeation with microdialysis sampling: Capabilities and limitations for biopharmaceutical assessments of supersaturating drug formulations (2023). *Eur J Pharm Sci* 188, art. no. 106533.
(4) Nunes PD et al., In vitro dissolution/permeation tools for amorphous solid dispersions bioavailability forecasting II: Comparison and mechanistic insights (2023) *Eur. J. Pharm. Sci*., 188, art. no. 106513.