Dissolution-/Permeation-Analysis of Marketed Fenofibrate Nano- and Microparticle Formulations for Prediction of Oral Bioavailability: A Proof of Concept Study

D. Sironi¹, J. Rosenberg², A. Bauer-Brandl¹, M. Brandl¹
¹University of Southern Denmark, ²AbbVie Deutschland GmbH & Co. KG

Purpose

In vitro dissolution is an essential characteristic in formulation development. Obtaining meaningful in vitro-in vivo correlations (IVIVC) for enabling formulations of poorly soluble drugs, however, is challenging with conventional dissolution testing. We thus propose to combine small-scale dissolution (under non-sink conditions) with an absorptive compartment, separated by a robust, artificial permeation barrier. Aim of the current study was to test two marketed formulations of fenofibrate based on nano-/microparticle technology in such a combined setup in order to check if dissolution-/permeation-analysis allows for a more profound insight into the underlying mechanisms and a better comparability with in vivo behavior than conventional dissolution testing.

Methods

A combined dissolution/permeation setup consisting of a pair of side-by-side diffusion cells (5 ml each) with a cellulose membrane mounted in between was implemented for testing of fenofibrate formulations. Dissolution of fenofibrate powder, Lipidil® 200 mg (microparticles) and LIPIDIL 145 ONE® (nanoparticles) was tested in three different media, i.e. phosphate-buffered saline (PBS), fasted state simulated intestinal fluid (FaSSIF) and fed state simulated intestinal fluid (FeSSIF). In all experiments, the acceptor medium for drug permeation was 0.6 % (w/v) Labrasol® in water. Capsules were opened and tablets ground in order to employ a dose equivalent to 1/50 of the clinical dose. Dissolution of LIPIDIL 145 ONE® in PBS was also tested without a permeation barrier while all other parameters remained unchanged. In all dissolution experiments, donor samples of 1 ml were filtered through 0.1 μm Anotop® syringe filters and replaced with fresh medium. The solubility of the different formulations in different media was determined with the shake-flask method. Permeability studies were also carried out with solutions of Lipidil® 200 mg and LIPIDIL 145 ONE® in FaSSIF. Fenofibrate was quantified via UHPLC/UV and all tests were run over five hours.

Results

Dissolution of ground LIPIDIL 145 ONE® in PBS resulted in true supersaturation over one hour (increase by a factor of 3.5). In presence of a permeation barrier, both a higher initial degree and a longer duration of supersaturation were observed, as compared to the simple dissolution experiment. Under the same conditions, Lipidil® 200 mg yielded concentrations close to the solubility limit within the first sampling interval, and fenofibrate powder led to poorly reproducible dissolution profiles without reaching the solubility limit. Steady state flux values across the permeation barrier determined with the nanoparticle formulation were higher than those determined with the microparticle formulation. In the case of the microparticles, the cumulative amount that had permeated into the acceptor compartment after four hours exceeded the amount dissolved in the donor compartment at that time and later; for the nanoparticles, this point was reached after three hours. With FaSSIF or FeSSIF as donor medium, both micro- and nanoparticles yielded donor concentrations close to the solubility limit within the first sampling interval. No significant difference in flux was found for a given formulation, when using different media: as long as undissolved particles are present, micelle-bound drug molecules do not increase the flux. Only the molecularly dissolved fraction seems to permeate. However, notable drug permeation was observed when employing FaSSIF solutions. After five hours of permeation, the amount in the acceptor compartment was around half of the amount of molecularly dissolved drug present in the donor compartment at the beginning of the experiment. However, the permeation rate was constant. Therefore, molecularly dissolved drug molecules must have been released from the micelles in order to maintain a constant permeation rate.

Conclusion

Through combined dissolution/permeation testing, it could be demonstrated that transient supersaturation (nanoparticles) and rapid dissolution (microparticles) are the underlying mechanism for enhanced permeation across the barrier. The in vitro dissolution/permeation data obtained here correlate reasonably with human duodenal and plasma concentrations reported in literature. The current study demonstrates that combined dissolution/permeation is more predictive for enabling formulations than conventional dissolution testing.