Abstract

Poor solubility in aqueous media is the main reason for the low bioavailability of many new chemical entities. Hence, the use of enabling formulations that enhance the solubility of the drug molecule is increasingly common. Yet, the evaluation of supersaturation and solubilization with *in vitro* dissolution testing can be challenging and misleading. A better prediction may be obtained by incorporating an absorptive compartment, because *in vivo* dissolution and permeation are expected to occur simultaneously.

As starting point, combined dissolution/permeation studies of formulations with micro- or nanoparticles of fenofibrate were performed in a side-by-side diffusion cell separated by an artificial membrane. Studies in buffer and simulated intestinal fluids revealed the important role of undissolved particles and micelle-bound drug molecules for the overall amount that can be absorbed. Subsequent studies with slowly releasing tablets and with solutions of hydrocortisone elucidated the relevance of the ratio between permeation area and dissolution volume for the mass transfer from the donor into the acceptor compartment.

With this knowledge, an experimental setup with a novel geometry was developed for small-scale dissolution/permeation studies (PermeaLoop®). The area-to-volume ratio of PermeaLoop® amounts to 60 – 70 % of the ratio assumed to be found *in vivo*; this is significantly higher than the ratio of side-by-side diffusion cells, which have so far been the prevailing experimental setup for combined dissolution/permeation testing. The high permeation rate achieved with PermeaLoop® allowed the transfer of substantial amounts of the poorly soluble compound ABT-869 into the acceptor compartment, thus significantly altering the dissolution profile. At elevated temperature, dissolution became rate-limiting instead of permeation. The surprisingly low dissolution rate at 35 °C could be attributed to reduced solubilization through the excipients; this resulted in immediate precipitation of drug molecules on the surface of the amorphous solid dispersion. All in all, PermeaLoop® appears to be a valuable tool for the assessment of enabling formulations of poorly soluble drugs.