Abstract

Biopharmaceutical characterisation of enabling formulations is challenging. Upon ingestion of an enabling formulation, the drug is often present in various states: solid (i.e. crystalline or amorphous), dissolved (i.e. eventually supersaturated) and associated with solubilizing constituents (e.g. colloidal phases such as micelles). How the different states of drug present in the gastrointestinal tract contribute to overall drug absorption (i.e. oral bioavailability) is often not well understood. It has been demonstrated that the in vivo performance of supersaturating enabling formulations can be predicted more accurately when testing dissolution in an absorptive environment. This experimental design is closer to the in vivo situation where dissolution and permeation happen concurrently. Unfortunately, the throughput of these coupled dissolution/permeation approaches is often low due to e.g. the nature of the permeation barrier and the design of the device.

The aim of this thesis was to explore if coupled dissolution/permeation approaches with higher throughput could be developed. Furthermore, this thesis strived to gain a better understanding of the interplay of dissolution, colloidal phases, and permeation leading to oral absorption. For this purpose, dissolution/permeation approaches were regarded as useful. Together with an industry partner, a 96-well plate with two compartments and comprising the Permeapad® barrier was developed – the starting point to obtain the desired throughput profile. Permeability studies using 14 model compounds followed by comparison to various measures for oral absorption (i.e. F_a and permeability assays) showed the potential of this industrially produced tool. A protocol for dissolution/permeation screening in 96-well format was developed using a tadalafil ASD as example formulation and by evaluating different experimental parameters. As compared to traditional dissolution testing, the novel protocol predicted the formulations' in vivo performance more accurately. To study the interplay of dissolution, colloidal phases and permeation in detail, solid phospholipid dispersions were prepared. Here, (amorphous) celecoxib was embedded in a phospholipid matrix, which upon dispersion formed solubilizing colloids. For the first time, two phospholipids, monoacyl and diacyl phospholipid forming different colloids, were systematically compared in an (apparent) solubility, a dissolution/permeation, and an AF4-MALLS study. Interestingly, monoacyl and diacyl formulations differed in terms of solubility but were equal in terms of dissolution/permeation behaviour. To relate the in vitro findings to the in vivo scenario, celecoxib absorption from monoacyl and diacyl formulations was studied in rats. In conclusion, both the in vitro dissolution/permeation study and the in vivo study showed: Inducing and maintaining supersaturation governs oral absorption whereas the solubilization capacity and the morphology of the colloidal phases seem to be less important.