

Abstract

Pharmaceutical excipients such as nonionic surfactants which are used to prepare different drug formulations and considered inert substances can alter the function of membrane transport proteins. These proteins are solute carriers (SLC, referred to as carriers) and ATP-binding cassette (ABC) efflux transporters (referred to as transporters). Previous research has suggested that many surfactants can inhibit P-glycoprotein (P-gp) *in vitro*, however, little research has been performed to investigate surfactant-mediated P-gp inhibition *in vivo*. The aim of the Ph.D. project was to investigate the inhibitory effects of nonionic surfactants on P-gp *in vitro* and select potential surfactants to inhibit intestinal P-gp, thereby improving the oral bioavailability of P-gp substrates *in vivo*.

Studies in cell cultures using Caco-2 and MDCKII MDR1 cells showed that nonionic surfactants inhibited P-gp mediated efflux of digoxin, etoposide, and calcein-AM. Some surfactants may also possess transcellular and/or paracellular permeation enhancing effects on the cell monolayers, as well as toxic effects at high concentrations. Among the investigated surfactants, polysorbate 20 (PS20) had the most potent P-gp inhibitory properties *in vitro*; thus PS20 was further investigated *in vivo*.

In wild-type (WT) rats, PS20 at 5% and 10-25% enhanced the oral bioavailability of etoposide and digoxin, respectively. Investigations in *mdr1a* deficient (KO) rats showed that PS20 specifically inhibited intestinal P-gp at these concentrations in WT rats. However, high concentration (25%) of PS20 decreased the oral absorption of etoposide in KO rats likely due to incorporation of etoposide in PS20 micelles. In addition, oral formulations that contained high concentrations of etoposide were successfully prepared aiming to saturate intestinal P-gp and enhance the oral absorption. Using these formulations, high doses of etoposide were administered orally to WT rats and the systemic exposure of etoposide enhanced dose-proportionally. However, this enhancement could not unequivocally be attributed to P-gp saturation.

Collectively, pharmaceutical excipients may affect the function of transporters/carriers and the transcellular and/or paracellular permeability of drug substances across the intestinal membrane, as well as the thermodynamic activity of the substances in the formulation and in the intestine after oral administration. Knowing and understanding such effects may assist pharmaceutical industry to make enlightened choices on the excipient(s) for formulating P-gp substrates to improve the intestinal permeation, thus increase the bioavailability.