In silico modelling of permeation enhancement potency in Caco-2 monolayers based on molecular descriptors and random forest

Structural traits of permeation enhancers are important determinants of their capacity to promote enhanced drug absorption. Therefore, in order to obtain a better understanding of structure–activity relationships for permeation enhancers, a Quantitative Structural Activity Relationship (QSAR) model has been developed. The random forest-QSAR model was based upon Caco-2 data for 41 surfactant-like permeation enhancers from Whitehead et al. (2008) and molecular descriptors calculated from their structure. The QSAR model was validated by two test-sets: (i) an eleven compound experimental set with Caco-2 data and (ii) nine compounds with Caco-2 data from literature. Feature contributions, a recent developed diagnostic tool, was applied to elucidate the contribution of individual molecular descriptors to the predicted potency. Feature contributions provided easy interpretable suggestions of important structural properties for potent permeation enhancers such as segregation of hydrophilic and lipophilic domains. Focusing on surfactant-like properties, it is possible to model the potency of the complex pharmaceutical excipients, permeation enhancers. For the first time, a QSAR model has been developed for permeation enhancement. The model is a valuable in silico approach for both screening of new permeation enhancers and physicochemical optimisation of surfactant enhancer systems.