pH-SPECIFIC PREDICTION MODELS FOR MEMBRANE PERMEABILITY

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Approved drugs include about 85% of ionisable compounds. Majority of drug-related properties in the early stage of drug research are measured at the neutral pH, while properties of ionisable compounds depend on the pH of the environment. The pH range in gastrointestinal tract varies in the large scale (from pH ~2 to ~9) and therefore influences human intestinal absorption. The robust experimental method to analyse pH influence to human intestinal absorption is the parallel artificial membrane permeability assay (PAMPA). So far pH-profiles of membrane permeability have not been studied in detail. Ignoring analysis of pH-profiles of membrane permeability may lead to false conclusions during discovery of new active compound and cause retraction of potential new drug candidates in the late development phase.

The aim of current research is to consider influence of pH to the membrane permeability and derive QSAR models for wide pH range, i.e. predict pH-profiles of membrane permeability. Membrane permeability values were measured at pH 3, 5, 7.4 and 9 using PAMPA method. The experimental values were analysed and used for *in silico* modelling resulting in QSAR models. In addition to pH-specific models, highest membrane permeability over selected pH-s was modelled. Multi-linear QSAR models were developed using stepwise forward selection of molecular descriptors.

The results show that membrane permeability of chemicals is highly depending on pH and their ionization state. Obtained QSAR models for various pH-s are statistically significant and able to predict membrane permeability at certain pH. Also more precise and universal model was developed using only highest membrane permeability values over selected pH-s. In conclusion, considering different pH-s during the modelling gives valuable information on behaviour of chemicals in the membrane and also make possible to predict more precisely absorption in intestine.

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