CLASSIFICATION MODELS FOR MEMBRANE PERMEABILITY AND THEIR APPLICATION FOR THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM

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Absorption in the gastrointestinal tract (GIT) is an important characteristic for orally administrated drug substances. GIT consists of various regions with different properties, which have important role in absorption process. One of these properties is pH, which varies from acidic (pH~3) to basic (pH~9) and influences absorption of ionizing compounds. Absorption is determined by the solubility and permeability of the compound. Both these properties form the base for the biopharmaceutical classification system (BCS) that is used by the United States Food and Drug Administration (FDA) for selecting suitable biowaivers. FDA requires that solubility is measured for wide pH range, but it is not required for permeability measurements. The omission of pH during the permeability evaluation leads to false conclusions during the selection of biowaivers.

The purpose of the current study is to develop classification models for membrane permeability for full pH range in the GIT. Membrane permeability values for 238 drug substances were measured by the parallel artificial membrane permeability assay (PAMPA) at pH 3, 5, 7.4 and 9. The cut-off value of high and low permeable classes was determined using known human intestinal absorption data as a reference. Classification models using logistic regression are developed for four pH-s to describe full pH-range in the GIT, for the highest membrane permeability over four pH-s that describes maximum absorption in the GIT and for the intrinsic membrane permeability to describe the absorption of uncharged drug substances. Derived classification models are statistically significant and include mechanistically relevant descriptors. All models are triple-validated with validation set, external validation set and FDA reference drugs for permeability classes in BCS. The identification of BCS permeability classes was further improved with decision tree that consolidated predictions from classification models.

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