BDDCS Class Prediction for New Molecular Entities - DTU Orbit (15/12/2018)

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The Biopharmaceutics Drug Disposition Classification System (BDDCS) was successfully employed for predicting drug–drug interactions (DDIs) with respect to drug metabolizing enzymes (DMEs), drug transporters and their interplay. The major assumption of BDDCS is that the extent of metabolism (EoM) predicts high versus low intestinal permeability rate, and vice versa, at least when uptake transporters or paracellular transport is not involved. We recently published a collection of over 900 marketed drugs classified for BDDCS. We suggest that a reliable model for predicting BDDCS class, integrated with in vitro assays, could anticipate disposition and potential DDIs of new molecular entities (NMEs). Here we describe a computational procedure for predicting BDDCS class from molecular structures. The model was trained on a set of 300 oral drugs, and validated on an external set of 379 oral drugs, using 17 descriptors calculated or derived from the VolSurf+ software. For each molecule, a probability of BDDCS class membership was given, based on predicted EoM, FDA solubility (FDAS) and their confidence scores. The accuracy in predicting FDAS was 78% in training and 77% in validation, while for EoM prediction the accuracy was 82% in training and 79% in external validation. The actual BDDCS class corresponded to the highest ranked calculated class for 55% of the validation molecules, and it was within the top two ranked more than 92% of the time. The unbalanced stratification of the data set did not affect the prediction, which showed highest accuracy in predicting classes 2 and 3 with respect to the most populated class 1. For class 4 drugs a general lack of predictability was observed. A linear discriminant analysis (LDA) confirming the degree of accuracy for the prediction of the different BDDCS classes is tied to the structure of the data set. This model could routinely be used in early drug discovery to prioritize in vitro tests for NMEs (e.g., affinity to transporters, intestinal metabolism, intestinal absorption and plasma protein binding). We further applied the BDDCS prediction model on a large set of medicinal chemistry compounds (over 30,000 chemicals). Based on this application, we suggest that solubility, and not permeability, is the major difference between NMEs and drugs. We anticipate that the forecast of BDDCS categories in early drug discovery may lead to a significant R&D cost reduction.
Keywords: BDDCS, ADMET, GRID, MIF, drug disposition, drug−drug interactions, VolSurf+, FDA solubility, machine learning

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