Prediction of oral drug absorption in humans by theoretical passive absorption model
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...Yalkowsky and Valvani, 1980 Avdeef, 2003). Quaternary ammonium compounds and polymers were also excluded because Pallas 3.1 (**CompuDrug**, Hungary) could not calculate logPowadequately. Typical Fa%obsvalues and physicochemical parameters are shown inTable 1.

Prediction of oral drug absorption in humans by theoretical passive absorption model☆

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Abstract

The purpose of the present study was to examine the oral drug absorption predictability of the theoretical passive absorption model (TPAM). As chemical descriptors of drugs, the octanol/buffer distribution coefficient at pH 6.0 (D_{ow}), intrinsic octanol–water partition coefficient (P_{ow}), pK_a, and molecular weight (MW) were calculated from the chemical structure. Total passive intestinal membrane permeation consists of transcellular, paracellular and unstirred water layer (UWL) permeation. Transcellular permeation was modeled based on the pH-partition hypothesis with correction for cationic species permeation, and the independent variables were D_{ow}, P_{ow}, and pK_a. Paracellular permeation was modeled as a size-restricted diffusion within a negative electrostatic field-of-force, and the independent variables were MW and pK_a. UWL permeation was modeled as diffusion across a water layer, and the independent variable was MW. Cationic species permeation in the transcellular permeation model and the effect of a negative electric field-of-force in the paracellular permeation model were the extensions to the previous TPAM. The coefficients of the paracellular and UWL permeation models were taken from the literature. A data set of 258 compounds with observed values of Fa% (the fraction of a dose absorbed in humans) taken from the literature was employed to optimize four fitting coefficients in the transcellular permeation model. The TPAM predicted Fa%, with root mean square errors of 15–21% and a correlation coefficient (CC) of 0.78–0.88. In addition, the TPAM predicted the effective human intestinal membrane permeability with a CC of 0.67–0.77, as well as the

contribution of paracellular permeation. The TPAM was found to predict oral absorption from the chemical structure of drugs with adequate predictability for usage in drug discovery.

Keywords: Oral absorption; Lipophilicity; pK_a; Octanol; In silico; Permeability

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Part of this study was presented at LogP2004 Symposium, Zurich (Sugano, K., Obata, K., Saitoh, R., Higashida, A., Hamada, H., 2004. Processing of biopharmaceutical profiling data in drug discovery).
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N-Oxide analogs of WAY-100635: new high affinity 5-HT_{1A} receptor antagonists
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WAY-100635 [N-(2-(1-(4-(2-methoxyphenyl)piperazinyl)ethyl))-N-(2-pyridinyl)cyclohexanec arboxamide] 1 and its O-desmethyl derivative DWAY 2 are well-known high affinity 5-HT"1"A receptor antagonists, which when labeled with carbon-11...