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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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1. Introduction

In the recent drug discovery and development process, in silico prediction of absorption, metabolism, distribution, and excretion (ADME) is recognized as a key technique (van de Waterbeemd and Gifford, 2003). Among ADME properties, oral absorption has been most intensively investigated for in silico prediction. As an oral absorption parameter, the fraction of a dose absorbed in humans (Fa%), the effective intestinal membrane permeability in humans (P_{eff}), Caco-2 permeability, etc., have been studied as targets for in silico prediction (Wessel et al., 1998; Winiwarter et al., 1998; Zhao et al., 2001; Yamashita et al., 2002). Oral absorption from a solid dosage is determined by the dissolution rate, the solubility, and the intestinal membrane permeability (Yu and Amidon, 1999). Intestinal membrane permeation consists of transcellular, paracellular, and unstirred water layer (UWL) permeation. Most of the previous in silico prediction studies scrambled these absorption processes, and the contribution of each process cannot be predicted. In addition, the previous in silico methods often used descriptors that are not easy to translate into better drug design.

Previously, the theoretical passive absorption model (TPAM) had been proposed for describing passive intestinal membrane permeation (Camenisch et al., 1996, 1998). The TPAM consists of three partial models, i.e., the transcellular, paracellular and UWL permeation models. The TPAM is beneficial for qualitatively comprehending the membrane permeation from the viewpoint of both the physiology of the intestine and the chemical structure of drugs. However, the predictability of the TPAM for the oral absorption in humans has not been examined. The purpose of the present study was to quantitatively examine the oral drug absorption predictability of the TPAM.

2. Calculation

2.1. Transcellular permeation model

Passive transcellular permeation is diffusion across a lipid bilayer. Therefore, the permeability depends on the lipophilicity of the permeant. In the previous TPAM, the passive transcellular permeability (P_{trans}) was expressed by the 1-octanol/buffer distribution coefficient (D_{ow}), with the help of so-called Collander equations (Collander, 1950, 1951; Camenisch et al., 1998).

$$P_{trans} = a \cdot D_{ow}^{\alpha} \quad (1)$$

To reflect the pH at the intestinal epithelial membrane surface, the D_{ow} at pH 6.0 was employed (Maxwell et al., 1968). The pragmatic reason for using the 1-octanol/buffer system is its high publicity in the drug discovery process (Kerns and Di, 2003). Furthermore, various computational prediction systems have been developed for 1-octanol/buffer system (van de Waterbeemd and Gifford, 2003). Because the intrinsic octanol/water partition coefficient of ionized species is negligibly small, Eq. (1) represents the permeation of non-ionized species (pH-partition hypothesis) (Hogben et al., 1959). However, recently, the permeability of basic compounds was found to be larger than expected from the D_{ow} (Sugano et al., 2001). It was suggested that cationic species of basic compounds can permeate the negatively charged membrane with the aid of anionic lipids in the membrane, depending on the lipophilicity of the cationic species (Neubert et al., 1988; Ozaki et al., 2000; Sugano et al., 2001, 2004). The intestinal epithelial membrane contains anionic lipids (Proulx, 1991; Lipka et al., 1991). Therefore, Eq. (1) was extended for the permeability of mono-cationic species of basic compounds. The lipophilicity of the cationic species may be scaled by the octanol–water partition coefficient (P_{ow}) of neutral species, with the help of Collander equations (Collander, 1950, 1951). Eq. (1) was extended to:

$$P_{trans} = a \cdot D_{ow}^{\alpha} + b \cdot f_{+1} \cdot P_{ow}^{\beta} \quad (2)$$

where f_{+1} is the fraction of mono-cationic species. The f_{+1} was calculated from the pK_a. Coefficients a, b, α, and β are fitting parameters to be optimized in the present study.

2.2. Paracellular permeation model

Paracellular permeation is diffusion through the negatively charged tight junction between the intestinal epithelial cells, and was modeled by a size-restricted diffusion within a negative electrostatic field-of-force (Adson et al., 1994, 1995; Sugano et al., 2002, 2003). Small and cationic species can easily permeate the paracellular pathway, whereas large and anionic