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Prediction of ADMET properties of Ligands



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Prediction of ADMET properties:-

A- Absorption

D- Distribution

M- Metabolism

E- Excretion

T- Toxicity

Absorption

- For a compound to reach a tissue, it usually must be taken into the bloodstream - often via mucous surfaces like the digestive tract (intestinal absorption) - before being taken up by the target cells. Factors such as poor compound solubility, gastric emptying time, intestinal transit time, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a drug is absorbed after oral administration.



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- Drugs that absorb poorly when taken orally must be administered in some less desirable way, like intravenously or by inhalation (e.g. zanamivir). Routes of administration are an important consideration.
- In chemistry, **absorption** is a physical or chemical phenomenon or a process in which atoms, molecules or ions enter some bulk phase – liquid or solid material. This is a different process from adsorption, since molecules undergoing absorption are taken up by the volume, not by the surface (as in the case for adsorption). A more general term is *sorption*, which covers absorption, adsorption, and ion exchange. Absorption is a condition in which something takes in another substance.



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- In many processes important in technology, the chemical absorption is used in place of the physical process, e.g., absorption of carbon dioxide by sodium hydroxide – such acid-base processes do not follow the Nernst partition law.
- For some examples of this effect, see liquid-liquid extraction. It is possible to extract a solute from one liquid phase to another without a chemical reaction. Examples of such solutes are noble gases and osmium tetroxide.
- The process of absorption means that a substance captures and transforms energy. The absorbent distributes the material it captures throughout whole and adsorbent only distributes it through the surface.
- The process of gas or liquid which penetrate into the body of adsorbent is commonly known as absorption.



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- Absorption in drug PK refers to the process of how drugs go through the organs of the body to reach the systemic circulation. Drugs have various routes of administration – oral, intravenous, intramuscular, intraperitoneal, ocular, nasal, rectal, intratracheal, and subcutaneous.
- The most popular in vitro absorption assays are the parallel artificial membrane permeability assay (PAMPA), the cell-based assay, and the human intestinal absorption (HIA) assay.
- Several QSAR models have been developed using experimental data from in vitro methods. Since PAMPA uses artificial lipid membranes, it is convenient and offers good reproducibility; therefore, it is broadly used for absorption tests.
- However, the membrane does not have transporters or drug metabolizing enzymes (DMEs). Thus, it is an adequate assay method for testing passive transport but it cannot be used for the prediction of active transport. Since transporters and DMEs are expressed on the cell membrane, cell-based assays, to some extent, reflect active transport as well as passive transport.



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- Caco-2 cells derived from human colon adenocarcinomas are broadly used for drug absorption assays. Caco-2 cells exhibit transporters like OCT, OAT, and PEPT1 and CYP3A enzymes. Another popular cell-based assay is the Madin-Darby canine kidney (MDCK) cell assay. Absorption (or permeation) is represented by the permeability coefficient (P_{eff}) defined as,

$$P_{eff} = C_t / (A \cdot C_i \cdot t)$$

- P_{eff} is obtained by dividing the amount of drug transported through the membrane (C_t) by the product of the surface area (A) of the membrane monolayer, the time (t) taken until the system reaches steady state, and the initial concentration of the drug (C_i). HIA is measured by dividing the absorbed drug by the drug dose. In vitro cell assays, such as those in caco-2 cells, show good correlation with human absorption. In vivo animal studies are also used to predict HIA.

$$\text{HIA (\%FA)} = \text{total mass absorbed/dose}$$

- Bioavailability (BA) is the fraction of drug absorbed into the systemic circulation. BA is calculated based on the blood concentration profile obtained through in vivo testing.



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$$BA (\%F) = [AUC_{\text{oral}} \times \text{dose}_{\text{IV}} / AUC_{\text{IV}} \times \text{dose}_{\text{oral}}] \times 100$$

- AUC is the area under the curve of the blood concentration profile in oral administration (AUC_{oral}) and in intravenous (IV) administration (AUC_{IV}), respectively, and dose_{IV} and dose_{oral} represent the dose with IV and oral administration, respectively.

- The major method used for the prediction of absorption is QSAR. Various regression QSAR models have been developed to predict the PAMPA assay (Akamatsu et al. 2009), cell-based assay (Hou et al. 2006), and BA (Hou et al. 2009). Since the absorption of cell-based assay results vary depending on how the cells are cultured, these results are not suitable for quantitative model construction; therefore, the assay results are converted to qualitative data with certain criteria in order to combine data from several laboratories (Pham The et al. 2011).

- The interaction of drugs with the membrane is studied and applied in the MDCK permeation prediction model (Chen et al. 2005).



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- Information from drug interactions with transporters (Kim et al. 2014a) and DMEs (Xu et al. 2012) modifies the results of BA prediction. For BA prediction, Zhu (Zhu et al. 2011) reviewed the relationship between physical properties and oral BA.
- Not only physicochemical and structural properties but also in vitro data (in vitro permeability, intrinsic clearance, and animal data) and in silico prediction results (permeability and intrinsic clearance) were used to build the model (Wang and Hou 2015).

Distribution

- Distribution in PK is defined as the transportation of drugs from one tissue/organ to another tissue/organ. Among all tissues, blood delivers drugs mainly into other tissues in affinity-dependent manner.
- Generally, drugs interact with proteins in the blood and membranes of the tissues. These interactions are crucial for determining the amount of drug delivered to the site of action; therefore, assay systems are designed to measure free drug in the blood and in the volume of tissue, where drugs can be transferred. These two measurements are the parameters that predict drug distribution.



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- The blood brain barrier (BBB) is the set of endothelial cells that protect the brain by allowing the absorption of only those chemicals that are necessary for brain metabolism. The BBB fills cell margins with tight junctions; therefore, it blocks penetration of hydrophilic or charged compounds.
- Distribution of drugs into the brain is an important focus in the discovery of drugs that target the central nervous system (CNS). QSAR and molecular modeling have been applied to predict BBB penetration.

Metabolism

- Metabolism is the biotransformation or chemical modification of exogenous compounds to increase their hydrophilicity and water solubility to facilitate their excretion.
- A compound that increases in hydrophilicity is removed from the circulatory system through the kidney. Metabolism can be classified into two main phases, phase I and phase II. Phase I metabolism is governed mainly by cytochrome P450 enzymes (CYP) and includes oxidation, reduction, and hydrolysis reactions. The CYP enzymes involved in phase I drug metabolism.



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- Phase II metabolism consists mainly of conjugation reactions. Moieties increasing hydrophilicity are added to exogenous compounds or its metabolites. Metabolites obtained as a result of phase-I and/or phase-II reactions in the liver may go through further biotransformation reactions by interacting with other enzymes.
- The phase I reaction usually generates the conjugation reaction sites for phase II; however, phase I does not necessarily precede phase II. Drugs and their metabolites from phase I and/or phase II metabolism interact with transporters and/or nuclear receptors.
- Transporters are expressed in various organs and pump compounds into or out of the cell across the cell membrane, a process also called active transport.
- In the liver, transporters pump drugs into hepatocytes and pump out drugs and metabolites into the systemic circulation or bile duct.
- Drugs and metabolites are pumped out through transporters into the systemic circulation, and then circulate through blood vessels, are distributed among organs, and are finally excreted through the kidney.



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- Drugs and metabolites transferred to the bile duct are excreted through the gastrointestinal (GI) tract. Nuclear receptors in the liver are activated by the binding of drugs or metabolites and then transferred into the nucleus where they increase gene expression of phase I and phase II enzymes and transporters.
- This pathway leads to the increase of the metabolic reaction rate due to the increase of the concentration of enzymes. In vitro methods of drug metabolism are performed mainly with hepatic microsomes that contain hepatic CYP enzymes in order to test the metabolic stability of a drug to the CYP enzymes.
- Liquid chromatography/mass spectrometry (LC/MS) or liquid chromatography/tandem mass spectrometry (LC/MS/MS) allows identification of the site of metabolism (SoM). NMR is used to elucidate the structure of metabolites. However, these techniques cannot be performed in high-throughput screening (HTS); therefore, it is necessary to develop in silico methods for rapid screening of compounds with moderate metabolic stability.



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Excretion

- Excretion is the removal of chemicals from the body, and clearance (Cl) is a parameter to measure the elimination of drug. QSAR models have been developed for clearance prediction.
- Compounds and their metabolites need to be removed from the body via excretion, usually through the kidneys (urine) or in the feces. Unless excretion is complete, accumulation of foreign substances can adversely affect normal metabolism.
- There are three main sites where drug excretion occurs. The kidney is the most important site and it is where products are excreted through urine. Biliary excretion or fecal excretion is the process that initiates in the liver and passes through to the gut until the products are finally excreted along with waste products or feces. The last main method of excretion is through the lungs (e.g. anesthetic gases).
- Excretion of drugs by the kidney involves 3 main mechanisms:
- Glomerular filtration of unbound drug.



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- Active secretion of (free & protein-bound) drug by transporters (e.g. anions such as urate, penicillin, glucuronide, sulfate conjugates) or cations such as choline, histamine.
- Filtrate 100-fold concentrated in tubules for a favorable concentration gradient so that it may be secreted by passive diffusion and passed out through the urine.

Toxicity

- Sometimes, the potential or real toxicity of the compound is taken into account (**ADME-Tox** or **ADMET**). Parameters used to characterize toxicity include the median lethal dose (LD_{50}) and therapeutic index.
- Computational chemists try to predict the ADME-Tox qualities of compounds through methods like QSPR or QSAR.
- The route of administration critically influences ADME.