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Drug permeability: commonly misinterpreted bioavailability governing factor

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Permeability is a crucial molecular property in drug discovery that influences pharmacokinetics when drugs cross phospholipid bilayers, such as cell membranes, the gastrointestinal tract, or the blood-brain barrier. Numerous methods exist for determining permeability, including cell line assays (CACO-2, MDCK), cell-free systems like parallel artificial membrane permeability assay (PAMPA), black lipid membrane (BLM), or liposome-based assays. Various *in silico* approaches have also been developed.

We have analyzed already published permeability data (MolMeDB and ChEMBL databases) evaluated four experimental and two computational methods. Results showed poor repeatability even within the same method. For PAMPA, intrinsic and apparent permeabilities can differ by orders of magnitude, suggesting caution when using literature data.

The unstirred water layer permeability (permeability of drug through stationary water layer on the surface of the membrane) causes discrepancies between methods and is often cause of misinterpretation.

Furthermore, we have identified the limitations of studied methods and transferred the hardly imaginable permeability values into real life drug permeation examples which can serve community in order to better interpret both own and literature data. In conclusion, caution is recommended when interpreting or combining permeability data.