A Novel Mechanistic Approach to Predict the Steady State Volume of Distribution (V_{ss}) using the Fick-Nernst-Planck Equation

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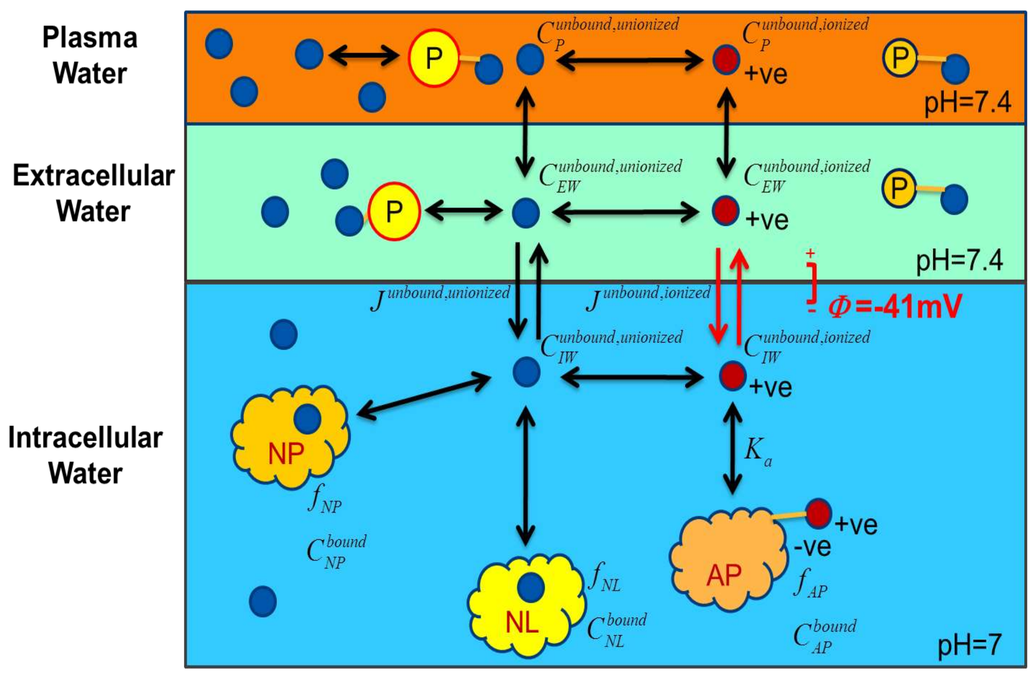
Background

- Rodgers and Rowland method (R&R) for predicting tissue:plasma partition coefficient (Kp) and volume of distribution (V_{ss}) at steady state assumes the unbound unionized drug concentrations are in equilibrium between intracellular and extracellular water, expressed as $Kp_{uu,uu}$=1 [1, 2].
- Ionised compounds can passively diffuse across cell membranes dependent on the degree of ionisation and the potential difference across the membrane that is maintained by the cell, resulting in $Kp_{uu,uu}$≠1 for ionisable drugs.
- The impact of incorporating membrane potential-dependent $Kp_{uu,uu}$ within the R&R method on Kp and V_{ss} prediction is evaluated in a big dataset.

Method

Model structure

The R&R model for prediction of Kp and V_{ss} are expanded to account for the membrane potential and the passive permeation of both neutral molecules (Fick's law) and ionized molecules (Nernst-Planck equation) across the cell membranes [3].



Fick-Nernst-Planck equation

$$J = J^{unbound,unionized} + J^{unbound,ionized}$$
$$= P^{unbound,unionized} A\left(C_{EW}^{unbound,unionized} - C_{IW}^{unbound,unionized}\right)$$
$$+ \sum_{i=1}^{2}\left(P^{unbound,ionized\_i} A \frac{N_i}{e^{N_i}-1}\left(\begin{matrix} C_{EW}^{unbound,ionized\_i} \\ - C_{IW}^{unbound,ionized\_i} e^{N_i} \end{matrix}\right)\right)$$

V_{ss} prediction

$$V_{ss} = V_p + V_{RBC} \cdot EP + \sum\left(V_{tissue} \cdot Kp_{tissue}\right)$$

Model parameters

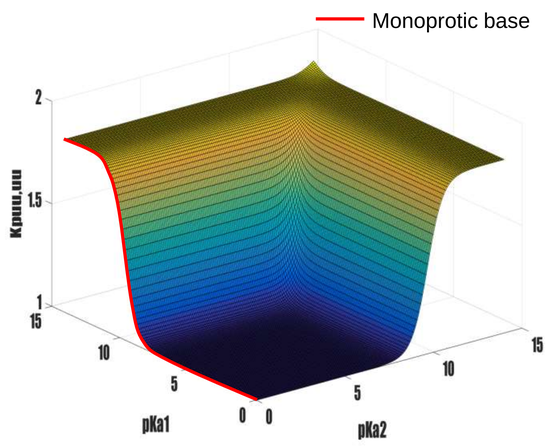
- Physiologically relevant membrane potential (-10 mV for red blood cells and -41 mV for all tissue cells) and passive permeability for electrolytes (2-4 log-unit lower than neutral molecules) were assumed.
- Reference volumes for plasma, red blood cells and various tissues in an adult male (20 years old and 81 kg) in Simcyp Healthy volunteer population with default plasma pH, tissue composition and volume were used.
- A library of compounds (n=72, including 7 neutral compounds, 35 monoprotic bases, 13 monoprotic acids, 6 diprotic bases and 11 ampholytes) were tested.
- The performance of the new method was evaluated by comparing the predicted V_{ss} to those predicted by R&R method and observed.

J: flux; N: Nernst constant. P: passive permeability; A: membrane surface area; ω: ionization parameter; fu: unbound fraction in plasma; f_{EW}: fraction of extracellular water; f_{IW}: fraction of intracellular water; f_{NL}: fraction of neutral lipids: f_{NP}: fraction of neutral phospholipids; [AP^-]: negative charged acid phospholipids; $P_{o:w}$: octanol: water partition coefficient; K_{aPR}: protein binding constant; $[PR]_{tissue}$: binding protein concentration in tissue; K_{aAP}: Acid phospholipid binding constant; V_p: plasma volume; V_{RBC}: red blood cell volume; EP: red blood cell partition coefficient; V_{tissue}: tissue volume.

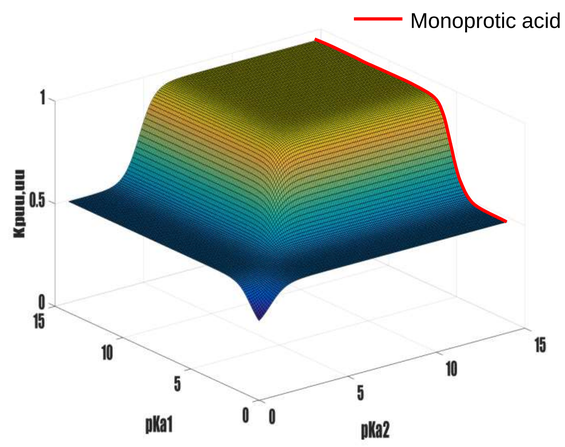
Results

$Kp_{uu,uu}$ prediction

- Basic compounds



- Acidic compounds

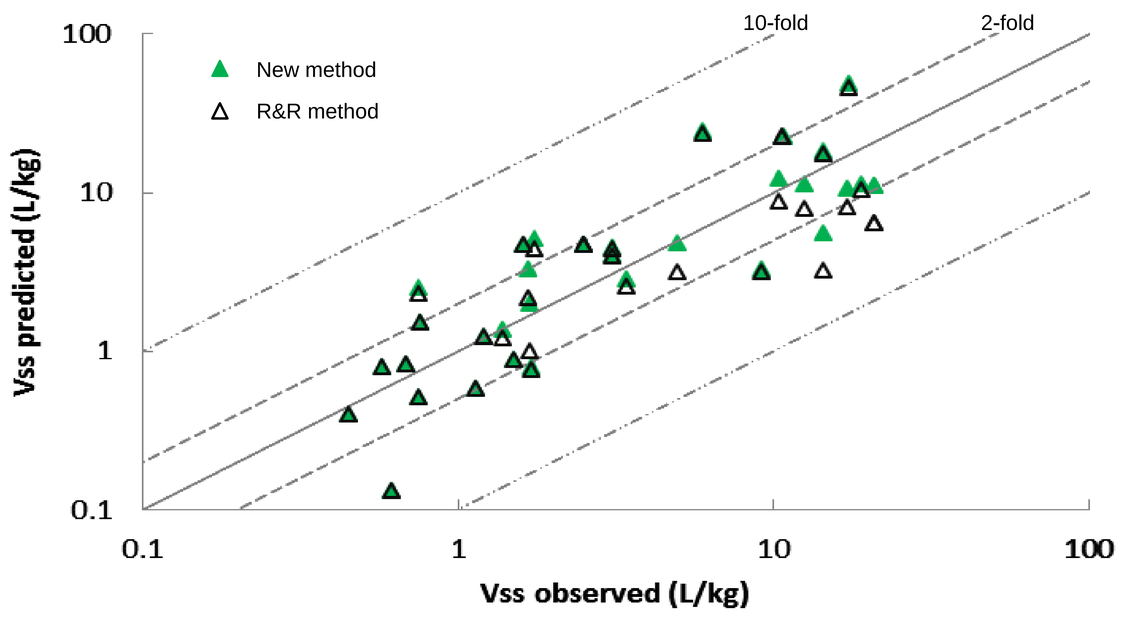


V_{ss} prediction

Compared to the R&R method, the new method predicted higher V_{ss} for basic compounds, but lower V_{ss} for acidic compounds.

The new method improved V_{ss} prediction for strong bases (pKa ≥ 7; n = 22). V_{ss} was predicted within 2 or 3 -fold of observed values for 15 and 20 compounds, respectively.

The original R&R method predicted V_{ss} within 2 or 3 -fold of observed values for 13 and 18 compounds, respectively.



Discussions

- For neutral compounds where all molecules are unionized and $Kp_{uu,uu}$=1 the new method performance is the same as the R&R model.
- If the cell membrane potential is zero, the new method results in $Kp_{uu,uu}$=1.
- For weak basic or weak acidic compounds, membrane potential has less impacts on $Kp_{uu,uu}$.
- Membrane potential values are essential system parameters that affect the model performance. However, tissue-specific membrane potential is lacking in the literature.
- Permeability parameters generated from *in vitro* systems generally represents a total effect of passive penetration of neutral and ionized drugs across the membrane.
- Modelling such the *in vitro* systems using the FNP equation allows defining the permeability ratio of ionized molecules *vs*. neutral molecules.
- Impact of membrane potential-dependent $Kp_{uu,uu}$ on drug distribution (V_{ss}) has been evaluated in a dataset of compounds. Its impacts on metabolism, drug-drug interaction and the drug efficacy and toxicity can be further explored if the tissue models are modified accordingly within the dynamic PBPK models.

Conclusion

- A novel semi-mechanistic approach to predict the Kp and V_{ss} using the Fick-Nernst-Planck equation is developed.
- The results show accounting for electrolyte passive permeation has an impact on the prediction of V_{ss}.
- The V_{ss} predictions for the strongly basic compounds (pKa ≥ 7) investigated were improved, compared to R&R method.
- Model performance depends on tissue-specific membrane potential and the ratio of passive permeability of ions *vs.* neutral molecules.

References

[1] Rodgers T, et al., J Pharm Sci, 2005, 94:1259-1276.
[2] Rodgers T & Rowland M, J Pharm Sci , 2006, 95:1238-1257.
[3] Trapp S, et al., European Biophysics Journal, 2008. 37:1317-1328.

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