pharmaceutics

# Supplementary Materials: Multivariate Analytical Approaches to Identify Key Molecular Properties of Vehicles, Permeants and Membranes That Affect Permeation through Membranes

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### Appendix I: Definitions of molecular descriptors used in PCA analysis

The molecular descriptors used in PCA analysis were determined using Molecular Operating Environment 2012, produced by Chemical Computing Group Inc., Montreal, Canada. and by HSPiP software version 4.0.04

| Code | Description |
|---|---|
| Solvent uptake | Amount of oil sorbed by membrane |
| solubility | Solubility of the permeants in the oil |
| density | Molecular mass density: Weight divided by vdw_vol (amu/Å$^3$) |
| Weight | Molecular weight (including implicit hydrogens) in atomic mass units with atomic weights taken from [1] |
| Mpoint | Melting point |
| $\delta_D$ | The dispersive component of HSP |
| $\delta_P$ | The polar component of HSP |
| $\delta_H$ | The hydrogen bond component of HSP |
| $\delta_T$ | Hildebrand solubility parameter |
| LogP (o/w) | Log of the octanol/water partition coefficient (including implicit hydrogens). This property is calculated from a linear atom type model with $r^2 = 0.931$, RMSE=0.393 on 1,827 molecules |
| Log $K_{o/w}$ | Log of the octanol/water partition coefficient (including implicit hydrogens). This property is an atomic contribution model that calculates LogP from the given structure; i.e., the correct protonation state (washed structures). Results may vary from the LogP(o/w) descriptor. The training set for SlogP was ~7000 structures |
| ovality | A measure of how the shape of a molecule approaches an oval shape |
| Mwt | Molecular weight |
| Mvol | Molecular volume |
| TPSA | Polar surface area (Å2) calculated using group contributions to approximate the polar surface area from connection table |

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| | information only. The parameterization is that of Ertl et al. [2] |
| vdw_vol | van der Waals volume (Å3) calculated using a connection table approximation |
| vdw_area | Area of van der Waals surface (Å2) calculated using a connection table approximation |
| a_nH | Number of hydrogen atoms (including implicit hydrogens). This is calculated as the sum of hi over all non-trivial atoms i plus the number of non-trivial hydrogen atoms |
| a_nC | Number of carbon atoms: #{Zi \| Zi = 6} |
| a_nO | Number of oxygen atoms: #{Zi \| Zi = 8} |
| b_1rotN | Number of rotatable single bonds. Conjugated single bonds are not included (e.g., ester and peptide bonds). |
| b_1rotR | Fraction of rotatable single bonds: b_1rotN divided by b_heavy |
| b_ar | Number of aromatic bonds. |
| b_count | Number of bonds (including implicit hydrogens). This is calculates the sum of (di/2 + hi) over all non-trivial atoms i |
| b_double | Number of double bonds. Aromatic bonds are not considered to be double bonds |
| b_rotN | Number of rotatable bonds. A bond is rotatable if it has order 1, is not in a ring, and has at least two heavy neighbors |
| b_rotR | Fraction of rotatable bonds: b_rotN divided by b_heavy |
| b_single | Number of single bonds (including implicit hydrogens). Aromatic bonds are not considered to be single bonds |
| lip_acc | The number of O and N atoms |
| lip_don | The number of OH and NH atoms |
| opr_brigid | The number of rigid bonds [3] |
| opr_nring | The number of ring bonds [3] |
| opr_nrot | The number of rotatable bonds from [3] |
| chi0 | Atomic connectivity index (order 0) [4,5]. This is calculated as the sum of 1/sqrt(di) over all heavy atoms i with di > 0 |
| chi0_C | Carbon connectivity index (order 0). This is calculated as the sum of 1/sqrt(di) over all carbon atoms i with di > 0 |
| chi1 | Atomic connectivity index (order 1) [4,5]. This is calculated as the sum of 1/sqrt(didj) over all bonds between heavy atoms i and j where i < j |
| chi1_C | Carbon connectivity index (order 1). This is calculated as the sum |

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|---|---|
| | of 1/sqrt(didj) over all bonds between carbon atoms i and j where i < j |
| chi0v | Atomic valence connectivity index (order 0) [4,5]. This is calculated as the sum of 1/sqrt(vi) over all heavy atoms i with vi > 0 |
| chi0v_C | Carbon valence connectivity index (order 0). This is calculated as the sum of 1/sqrt(vi) over all carbon atoms i with vi > 0 |
| Kier1 | First kappa shape index: (n-1)2 / $m^2$ [5] |
| Kier2 | Second kappa shape index: (n-1)2 / $m^2$ [5] |
| Kier3 | Third kappa shape index: (n-1) (n-3)2 / p32 for odd n, and (n-3) (n-2)2 / p32 for even n (Hall, 1991) |
| KierFlex | Kier molecular flexibility index: (KierA1) (KierA2) / n [5] |
| balabanJ | Balaban's connectivity topological index [6] |
| Q_VSA_HYD<br>PEOE_VSA_HYD | Total hydrophobic van der Waals surface area. This is the sum of the vi such that \|qi\| is less than or equal to 0.2. The vi are calculated using a connection table approximation. |
| Q_VSA_FPOL<br>PEOE_VSA_FPOL | Fractional polar van der Waals surface area. This is the sum of the vi such that \|qi\| is greater than 0.2 divided by the total surface area. The vi are calculated using a connection table approximation |
| Q_VSA_FHYD<br>PEOE_VSA_FHYD | Fractional hydrophobic van der Waals surface area. This is the sum of the vi such that \|qi\| is less than or equal to 0.2 divided by the total surface area. The vi are calculated using a connection table approximation |
| Q_VSA_POL<br>PEOE_VSA_POL | Total polar van der Waals surface area. This is the sum of the vi such that \|qi\| is greater than 0.2. The vi are calculated using a connection table approximation |

**References**


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