Interpreting the Physicochemical Meaning of a Molecular Descriptor Predictive of Dispersion Formation in PVPva Co-Polymer

M. Bookwala; K. DeBoyace; A. Gumireddy; I.S. Buckner; P.L.D. Wildfong
Duquesne University, School of Pharmacy, Division of Pharmaceutical Sciences

Purpose

Poorly water-soluble drugs can potentially be formulated as amorphous solid dispersions (ASDs), allowing improvement in API apparent aqueous solubility. Oftentimes, this approach requires trial-and-error experiments to determine the viability of the strategy. The atomic mass weighted 3rd order autocorrelation index molecular descriptor (R3m) has an overall 86% accuracy predicting ASD formation in the co-polymer polyvinylpyrrolidone-vinyl acetate (PVPva) for a library of 15 API, at two drug-loadings (15% and 75% w/w), using three preparation methods (melt-quenching and solvent removal by rotary evaporation or spray drying). Since R3m is a complex molecular descriptor, direct physical interpretation was not obvious, although its meaning is more evident after systematic analysis. The goal of this work is to demonstrate how the molecular attributes of an API combine to R3m values above/below the critical value predictive of dispersion formation in PVPva (R3m>0.632).

Methods

API values for R3m and the proportional contributions of individual intramolecular atoms were calculated using a MATLAB (2018b) code written in-house. First, the canonical SMILES format of the molecule was converted to 3D using Open Babel, which was then used to calculate R3m. Briefly, calculation begins by populating a molecular matrix (**M**), which contains 3 columns (the 3D XYZ coordinates of the atoms) and A rows (where A is the number of atoms in the molecule). **M** is then used to calculate the molecular influence matrix (**H**), where the diagonal of **H** reflects the leverage values of each intramolecular atom, with higher leverage values attributed to atoms further from the geometric center of the molecule. Another matrix called the geometric matrix (**G**) calculates the Euclidean distance between two atoms, i and j, allowing calculation of the influence/distance matrix ($\mathbf{R_{ij}}$), which takes the quotient of the square root of the product of the leverage of two atoms (i and j) and their Euclidean distance. Finally, $\mathbf{R_{ij}}$ is multiplied by the atomic mass for atoms (i and j) at topological connections where the distance, k=3. The summation of R3m values for each atom (with respect to the number of connections it makes at a distance of 3) represents the atomic breakdown; whereas, summation of values of all atoms represents the molecular R3m value.

Results

The topological complexity of an indomethacin molecule is captured by its R3m=0. 691, as illustrated in Figure 1a. The N10 atom makes 11 connections with other atoms at a topological distance (k) of 3; overall, the molecule has 86 such connections. Additionally, the branching and cyclic motifs of indomethacin increase its overall intramolecular interatomic connectivity, resulting in a topologically complex molecule with a relatively high R3m value. Beyond topology, other components used to calculate R3m dictate its magnitude. For example, Figure 1b shows the distance of each atom in indomethacin from its geometric center in a red (closest), white, and blue (farthest) scheme. Figure 1c shows the leverage value of each atom, illustrating that distance from the geometric center of the indomethacin molecule gives greater leverage to an intramolecular atom. Notably, higher atomic mass elements located further from the

geometric center of molecules have been shown to increase the value of R3m. Table 1 shows the atomic breakdown for the 6/41 atoms in indomethacin heavier than carbon, which sum to 54% (0.378) of the total R3m=0.691. Importantly, the influence of a lone peripheral Cl atom represents 23.68% of the total R3m=0.691, indicating its importance in establishing a value greater than the threshold predictive of ASD formation in PVPva. In comparison, cloperastine (R3m=0.514; predicted/confirmed not to disperse in PVPva) has 120 topological connections where k=3. In the atomic breakdown of cloperastine (Table 2), however, only 3/47 atoms are heavier than carbon, which sum to 0.198 (38.5% of the total R3m), almost all of which (31%) is attributable to the peripherally oriented Cl.

Conclusions

Examining the constituent pieces of the R3m calculation (topology, atomic mass weighting, geometric distance, and leverage) individually helps clarify its complex meaning, and why higher values predict API predisposed to forming ASDs in PVPva. Molecules having fewer electronegative atoms and/or those atoms located closer to the geometric center, are less likely to form stabilizing, non-covalent interactions with PVPva. In the case of indomethacin, most of the electronegative atoms potentially capable of interacting with the co-polymer are peripherally located, making it better able to interact with PVPva. Cloperastine, in contrast, has fewer of these atoms, which are more centrally located in the molecule. Although both API have highly leveraged peripheral atoms that respectively provide the greatest contribution to the calculation of R3m, the additional exterior N and O atoms on indomethacin are what causes R3m to exceed the critical boundary predictive of ASD formation in PVPva, and what makes drug-polymer interactions more probable.

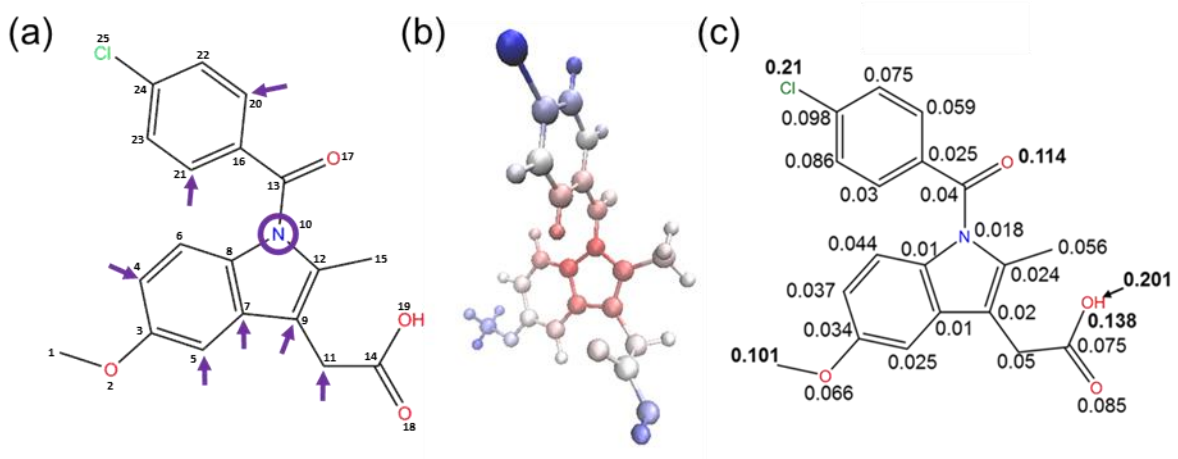
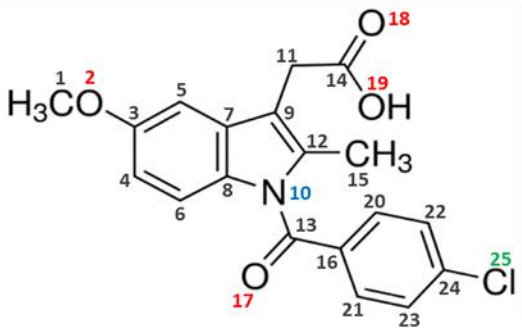
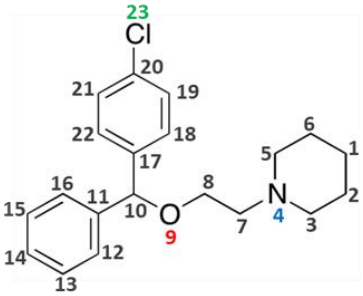


Figure 1: Illustrations of the impact of constituent parts relevant to the calculation of R3m. Indomethacin is used here as an example. (a) A topological distance of K=3 is illustrated with the N6 nitrogen in indomethacin. (b) The distance from the geometric center of the molecule is indicated with a red-white-blue color scheme. (c) The leverage values for each of the atoms in indomethacin are given.



Atoms	% Contribution to R3m
O2	4.44
O17	10.38
O18	5.38
O19	4.98
N10	5.82
Cl25	23.68

Table 1: % contribution to the total R3m value by atoms heavier than carbon is shown for indomethacin.



Atoms	% Contribution to R3m
O9	3.89
N4	3.66
Cl23	31.00

Table 2: % contribution to the total R3m value by atoms heavier than carbon is shown for cloperastine.