Pharmaceutical Formulation

Schrödinger's Materials Science Suite offers a group of physics-based modeling and simulation toolsets and automated workflow solutions to facilitate the fast and efficient development of new drug formulations.

Keywords: formulation, solubility parameters, glass transition, stability, drug excipients, molecular dynamics, quantum chemistry

BACKGROUND

With the accelerating pace of drug discovery in the 21st century, fast and efficient ways to both preformulate and formulate new drugs are critical elements of the pharmaceutical development. The latest advancements in atomistic-scale modeling and simulation technology have enabled *in silico* screening capability through a large number of candidate materials and formulations, based on fully physics-based models.

APPLICATION: DRUG STABILITY TOWARDS CHEMICAL DEGRADATION

Chemical stabilities of active pharmaceutical ingredients (API) and drug excipients are crucial variables in determining optimal formulation. Schrödinger's Materials Science Suite provides an automated simulation workflow for quantum chemical analysis over the stability of drug compounds towards various degradation mechanisms such as oxidation, hydrolysis, and photo-degradation (Figure 1). Such chemical stability can often be well described by bond dissociation energies of the weakest link in compounds[1]. Table 1 lists a set of predicted 1st and 2nd hydrogen abstraction energy of several drug compounds, obtained from the automated simulation workflow. The following example illustrates how the degradation analyses over multiple chemical moieties in high-throughput fashion could provide useful criteria for rapid screening of formulation scenarios.

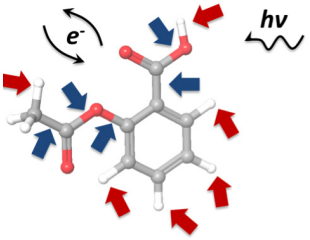

Figure 1. Bond dissociation scenarios for aspirin indicated by the acyclic single bonds (red: H-involved, blue: all else) and the energy source (electrons (*e*-) for oxidative reaction and lights (*hv*) for photo-degradation).

Table 1. Hydrogen abstraction energies for the weakest-bound (H1) and the 2nd-weakest-bound (H2) hydrogen atoms of well-known drug compounds. All values were obtained via automated quantum chemical calculations powered by Bond and Ligand Dissociation module from Schrödinger Materials Science Suite.

Drugs	ΔE_{H1}, kcal/mol	ΔE_{H2}, kcal/mol
Morphine	84.7	86.1
Codeine	75.9	83.0
Caffeine	99.0	100.1
Tetrazepam	82.3	84.4
Diazepam	84.6	99.1
Ibuprofen	86.0	91.6
Aspirin	101.8	108.1
Flupirtine	84.3	86.6
Escitalopram	85.5	94.9

APPLICATION: MISCIBILITY OF PHARMACEUTICAL INGREDIENTS

Miscibility among compounds is often acknowledged as one of the key prerequisites for formulation with thermodynamic stability. The solubility parameter has been a useful classifier for miscibility to screen large sets of compounds with. However, prediction of solubility parameters from a full-physics-based model has been limited for most pharmaceutical ingredients to date, owing to the difficulty in obtaining a representative equilibrium model for compounds in amorphous phase.

Schrödinger's latest GPU-accelerated molecular dynamics (MD) technology helps overcome prior limitations by providing easy access to reliable predictions of solubility parameters for a wide variety of chemistry. Table 2 showcases an example of quick miscibility screening for Ibuprofen. Using a single general-purpose GPU (GPGPU) card, solubility parameters for all drug carriers towards Ibuprofen can be computed in only a few hours, providing accurate miscibility indices without perfoming any parameterization or data fitting.

Table 2. Solubility parameter differences between Ibuprofen and five known drug carriers. Solubility parameter predictions were computed using GPU-accelerated MD simulations powered by the molecular dynamics engine of Schrödinger Materials Science Suite, Desmond.

Carrier	$\Delta\delta_{Ibuprofen}$, $(MPa)^{1/2}$		Miscible?
	Predicted	Experiment[2]	
PVP	2.8	1.6	✓ Yes
LutrolF68	3.6	1.9	✓ Yes
Maltose	9.3	18.0	✗ No
Sorbitol	10.1	17.3	✗ No
Xylitol	11.0	16.2	✗ No

APPLICATION: THERMOPHYSICAL STABILITY WITH GLASS TRANSITION POINT

Another key benefit of GPU-accelerated MD technology in formulation science is the ability to generate accurate predictions of glass transition points (T_g) of amorphous solids. T_g is an important indicator not only to indicate thermodynamic stability of compounds in solid state, but also to work as an important materials classifier for manufacturing processes. Schrödinger Materials Science Suite provides simple automated workflow panels for generating the density-temperature curves and finding the best fit for them automatically. Figure 2 shows an example of automated *in silico* T_g analysis for Glafenine, whose glass transition point is measured to be 336 K from DSC data[3].

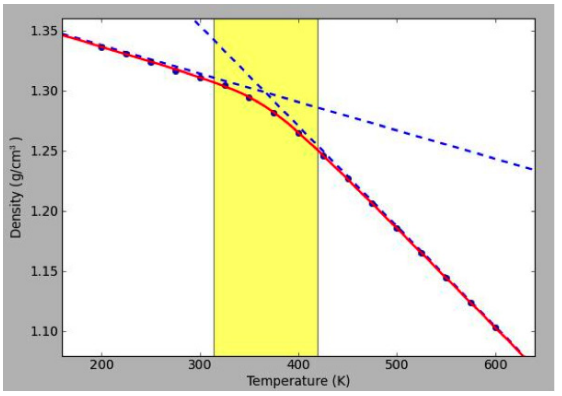

Figure 2. Density-temperature curve automatically generated for Glafenine. The simulated glass transition point locates at 366 K which is within 30 K of the measured T_g.

APPLICATION: CONTROLLED RELEASE: SUPRA MOLECULAR STRUCTURES IN FORMULATION

Many controlled release formulations utilize the ability of lipid or polymer based aggregates in solution to sequester, solubilize and deliver drugs in a controlled and tunable manner. Modern GPU-based simulation of drug/excipient solutions model the formation and structure of such aggregates as well as predict the positioning of the active molecules within them. Such structural information is difficult to obtain from experiment yet is an important component of rational, structure-driven formulation.

Simulated using Schrödinger Materials Science Suite Coarse-Grained Modeling Tool based upon the work of Guo et al [4]. Water molecules are excluded from images for clarity.

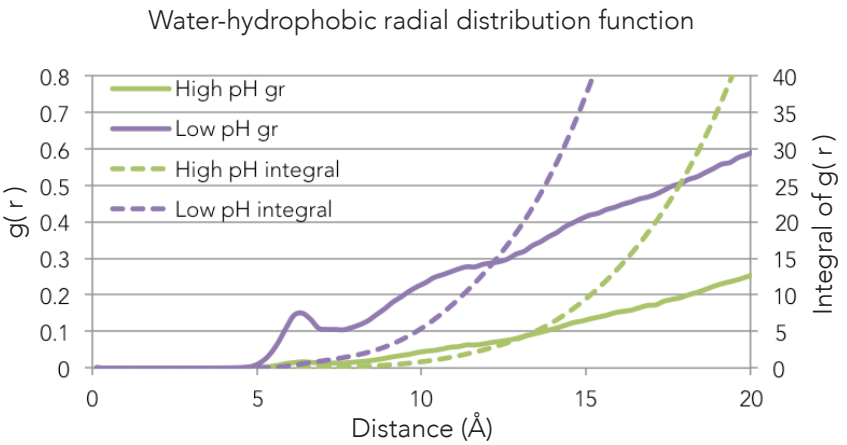

Figure 3. An example of simulations of a pH-sensitive formulation.

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