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PREDICTING DRUG DEGRADATION USING BIOVIA MATERIALS STUDIO AND BIOVIA PIPELINE PILOT

APPLICATION BRIEF

Chemical degradation and stability in formulation is a recurrent issue in pharmaceutical development of drugs. The pharmaceutical properties of drug candidates are routinely characterised during their development and manufacturability assessment. The objective of the present study was to develop an in silico risk assessment of active pharmaceutical ingredients' stability with respect to autoxidation (i.e., hydrogen abstraction).

INTRODUCTION

New chemical entities coming out of the discovery process are submitted to a batch of tests to assess their physical, chemical and biological properties. Stability and solubility are the two most important issues at this stage. During formulation, it is not uncommon for Active Pharmaceutical Ingredients (APIs) to undergo some form of chemical degradation leading to an increased level of genotoxic impurities, reduced bioavailability and drug potency. There are two main modes of chemical degradation of APIs commonly reported in the literature: hydrolysis and oxidation by molecular oxygen (a.k.a. Autoxidation). Molecular modelling tools are routinely used at the preformulation stage to compute key properties of the APIs. In particular, quantum mechanical tools based on the Density Functional Theory (DFT) are amongst the most widespread due to their high accuracy for a relatively low computational cost. A previous study on drug substances stability using molecular modelling techniques suggested that the DFT could be reliably used to predict the most stable hydrogen-abstracted radicals[1].

Peroxides are commonly present as trace impurities in drug formulation and can act as initiators of the radical oxidation mechanism. The chemical reactions to study here are:

$$RH \rightarrow R^{\cdot} + H^{\cdot}$$

$$ROO^{\cdot} + H^{\cdot} \rightarrow ROOH$$

$$RH + ROO^{\cdot} \rightarrow ROOH + R^{\cdot}$$

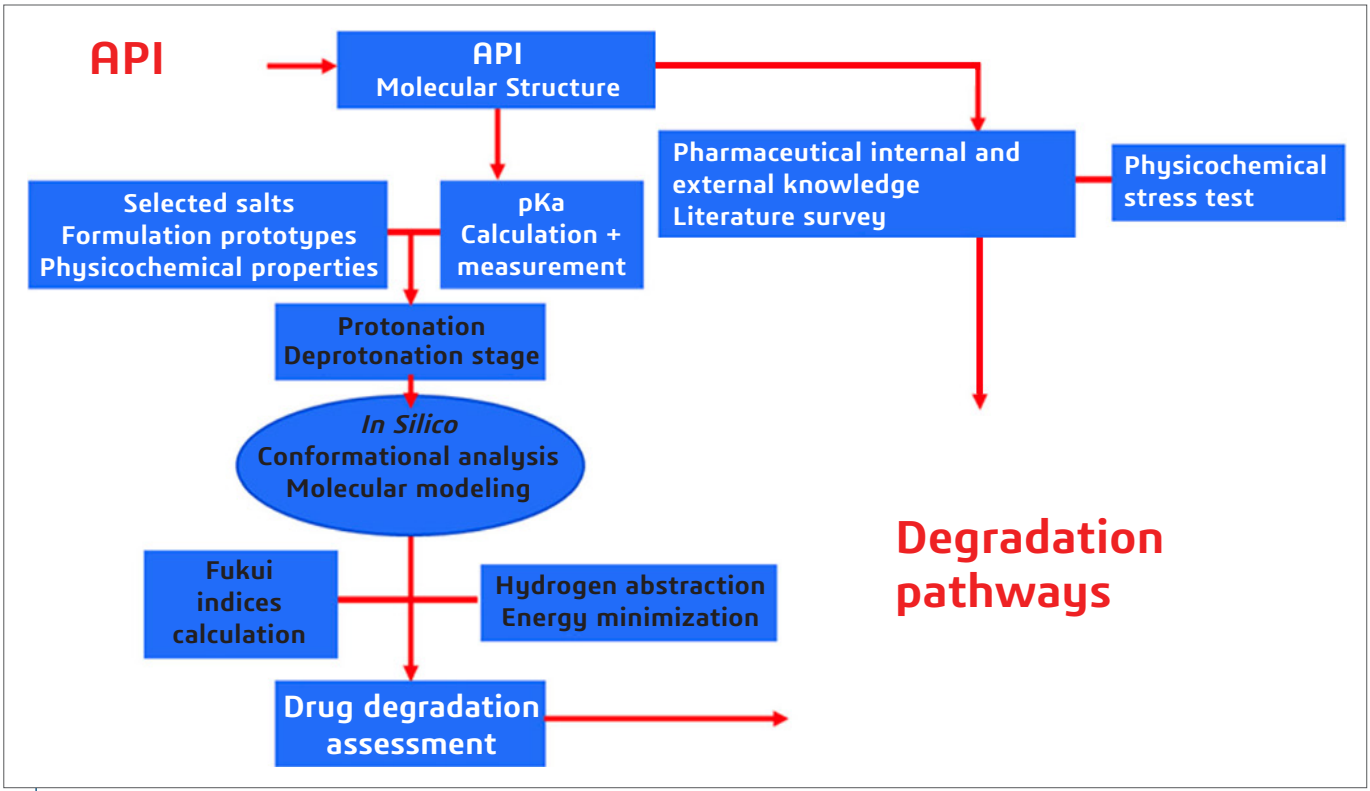

Figure 1: Schematic overall logic flow of drug degradation anticipation

By estimating the Bond Dissociation Energy (BDE) leading to the formation of the radical(s), the energetic balance can be obtained. Such BDEs can be measured experimentally and have also been the subject of recent computational studies[2]. It is assumed that the propensity toward autoxidation is characterized by the bonding strength of the weakest hydrogen.

The aim of the present study was therefore (i) to estimate, using DFT-based calculations, the BDEs of X-H bonds (X = C, N, O, S) and, for a reference subset of 45 compounds, to validate the computational settings against known published data and (ii) to validate against a known subset of APIs. Following this validation process, the methodology can be used for early compound stability profiling.

METHOD

The DMol^3 program[3] of BIOVIA Materials Studio® modelling and simulation software was used to test various Density Functionals and computational settings such as the grid mesh or the basis set against accuracy and speed. Due to the numerous calculations to be performed, the BIOVIA Pipeline Pilot® workflow automation tool was employed to generate all required structures, systematically perform all calculations and generate a result report.

The following steps were performed on each compound:

1. The geometry of the initial molecule is optimized and its ground state energy, E(RH), calculated
2. The initial structure of every single possible radical is generated one at a time by systematic removal of one hydrogen atom from the initial molecule
3. All structures of radicals are optimized and their ground state energies, E(R), are computed
4. The energy of the isolated H atom E(H) is also computed
5. The hydrogen BDE is calculated for each radical as BDE (R) = E(R) + E(H) – E(RH)
6. Hydrogen BDEs are ranked for analysis and risk assessment

Local density approximation (LDA), generalized gradient approximation (GGA) and Hybrid (B3LYP) functionals were all employed and compared to perform the geometry optimizations of neutral compounds and of radicals using spin-unrestricted DFT.

After the validation study on the 45 test molecules, APIs with known history of degradation were also subjected to our computational methodology.

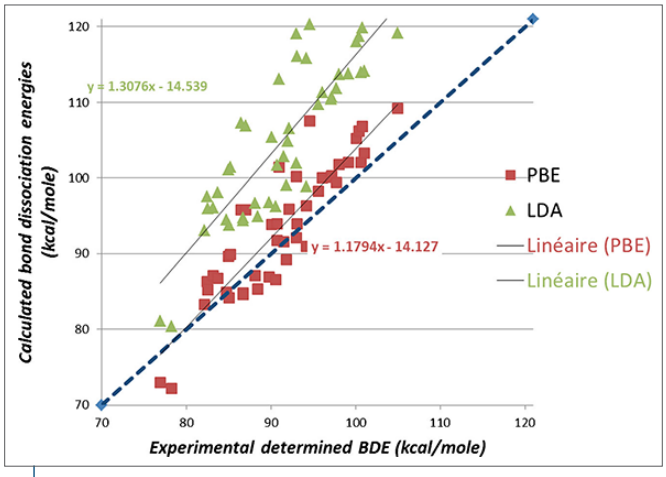

Figure 2: Correlation between calculated and experimental BDEs on the test set (kcal.mol^{-1}).

RESULTS

Our validation work showed first that DFT tools can reliably be employed to estimate bond dissociation energies accurately. As expected, computed Perdew-Burke-Ernzerhof (PBE) results were closer to experimental than those of LDAs, though at a higher computational cost. B3LYP gave the most reliable results but the computational cost was rather high.

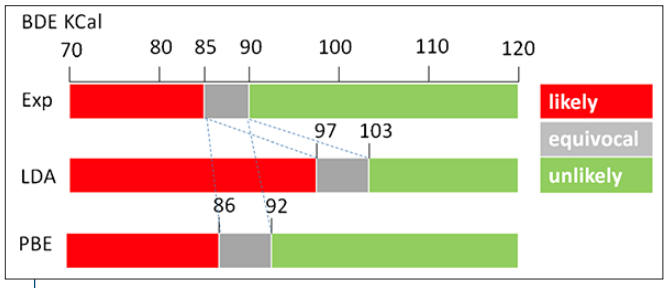

Figure 3: Risk Scale correlation.

It is reported in the literature[4] that thermodynamic C-H bond dissociation is strongly favored for ΔE < 85 kcal.mol-1, unlikely for ΔE > 90 kcal.mol-1 and uncertain for 85 > ΔE > 90 (Figure 3).

APIs with known autoxidation properties (first group with reported autoxidation propensity: Imipramine, methoxamine, Sertraline, Nifedipine and Paracetamol and a second group with no reported autoxidation: Aspirin, Diazepam, Dextromethorphan, SAR501788 and Amibegron) were tested against BDEs calculations. All results were consistent with known experimental data and followed the risk scale as shown in Figure 3.

CONCLUSIONS

A computational method was developed to estimate active pharmaceutical ingredients' propensity for autoxidation. The method, based on DFT using the BIOVIA Materials Studio DMol^3 and BIOVIA Pipeline Pilot packages, was first validated against a test set of small organic molecules to demonstrate its reliability in estimating bond dissociation energies and secondly tested against pharmaceutical ingredients with known degradation history. The study showed that the Perdew-Burke-Ernzerhof (PBE) /Double Numerical Polarized (DNP)/Medium settings gave accurate results at a reasonable computational cost. A risk scale could be built and consequently, preformulation compounds can now be routinely tested complementing experimental stress testing for early compound stability profiling. It is noticeable that there is no need to be a highly skilled computational expert to routinely use our BIOVIA Pipeline Pilot protocols to estimate drug substances autoxidation.

Access the paper here: "Predicting Drug Substances Autoxidation"

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