Long-Term Amorphous Drug Stability Predictions Using Easily Calculated, Predicted and Measured Parameters
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Purpose
Driven by the low intrinsic aqueous solubility of many new candidate drugs, formulations comprising drug in an amorphous state are growing in importance. For such formulations, knowledge of the physical stability of pure amorphous drug is highly desirable in order to guide the formulation strategy. In this study models are proposed to predict the amorphous stability of poorly soluble drugs.

Methods
A set of 25 compounds were selected that were representative of the diverse chemistry and physicochemical properties of marketed poorly soluble drugs. The sample set was chosen using clustering and principal component analysis (PCA; Image 1). An amorphous form of every drug was prepared by melt/quench cooling and their stability, under controlled-conditions, was assessed using polarised light microscopy over a 6-month period (Image 2). The data were used as a response variable in a statistical model, in which the explanatory variables: molecular, thermodynamic and kinetic parameters were calculated, predicted or measured using differential scanning calorimetry.

Results
Several multiple linear regression models were derived as a basis with which to predict amorphous stability. Inclusion of measured parameters was found to significantly improve the models’ predictive-ability. The model incorporating only two variables with the most extreme correlations with amorphous stability (molecular weight, Mw, and enthalpy of melting, Hf) resulted in a prediction accuracy of 59%. It was possible to increase this to 82% using Equation 1, which incorporates melting and glass transition temperatures (Tm and Tg), Hf, configurational free energy (Gc), relaxation time (τ), number of hydrogen bond donors (HBD), lipophilicity (clogP) and the ratio of carbon to hetero-atoms (CHA).

\[
\log \text{Stability} = -0.02T_m -0.05H_f +0.03T_g +0.28G_c -0.01\tau +0.23\text{HBD} -0.28\text{clogP} +0.17\text{CHA} + 6.42
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Conclusion
The proposed statistical models are the first of their kind to predict long-term amorphous drug stability. The models include readily-accessible parameters that will support faster decision-making, especially in an early drug development setting.