

Deducing stability behaviour for chemically fragile systems: the polymorphism of spironolactone

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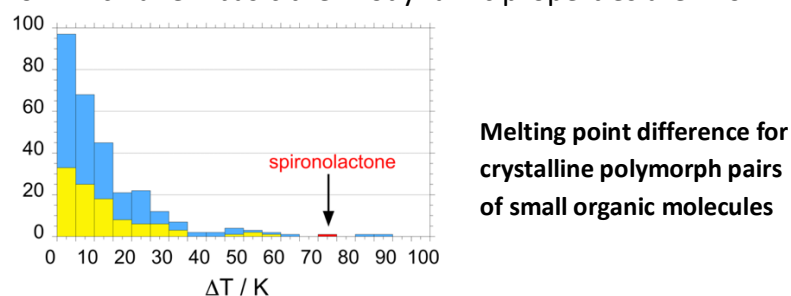
Stability ranking of different crystalline polymorphs of pharmaceuticals is important, because they may be prone to change in a formulation resulting in a decrease of bioavailability due to a sudden polymorph transformation. In the case of spironolactone, an aldosterone agonist used as a diuretic, the melting points of the two known crystalline polymorphs are more than 70 degrees apart, which is very rare as can be seen in the graph representing melting point differences between a major part of molecular polymorph pairs observed in the last 50 years. Form I, which has a melting point of 408 K compared to the melting point of form II of 480 K, possesses the highest density making it likely the more stable form under pressure. However, spironolactone is chemically not very stable under pressure and it is therefore difficult to obtain reliable pressure data on the phase behaviour.

The fact that form II melts at a higher temperature and the observation that form I turns into form II with an exothermic transition clearly indicates, through the Le Chatelier principle, that form I does not possess a stable temperature domain under atmospheric pressure, however, pharmaceutical processing may include pressure changes and it is therefore important to have a clear estimate of the position of the possible II-I equilibrium under pressure.

Using the Clapeyron equation, the Le Chatelier principle and the fact that state functions do not depend on the path taken, i.e. the topological method, an estimate of the position of the I-II equilibrium can be obtained. It can be shown that at least in terms of phase behaviour a stable I-II equilibrium exists, which has a negative slope, indicating that form I tends to get more stable with increasing temperature. Nevertheless, it can also be shown that the triple point, where both solids melt at the same temperature and pressure conditions can be found at 760 MPa, which is far beyond the conditions that any pharmaceutical process will bring the molecule.

It is interesting to see that a crystalline polymorph, which has a melting point that is 70 degrees lower than that of the stable polymorph in fact does possess a stable pressure-temperature domain that in terms of physical pressure conditions is very low (< 1 GPa) and it is most likely the relatively close proximity of this stable domain in a thermodynamic sense (Gibbs energy) that causes the appearance of the metastable form I [1].

This topological method to determine the stability hierarchy between crystalline polymorphs can be applied to any system for which a few basic thermodynamic properties are known.



- [1] I.B. Rietveld, M. Barrio, P. Lloveras, R. Céolin and J.-Ll. Tamarit, *Int. J. Pharm. Sci.* **2018**, 552, 193-205.