Deducing high-pressure behavior for chemically fragile systems: the polymorphism of spironolactone

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In the case that different crystalline polymorphs of active pharmaceutical ingredients (API i.e. drug molecules) have been observed, the study of their stability ranking becomes important, because they risk being prone to changes in the formulation and 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 polymorphs are more than 70 degrees apart, which is very rare as can be seen in the graph representing a major part of molecular (pharmaceutical) polymorphs observed in the last 50 years (Figure 1).

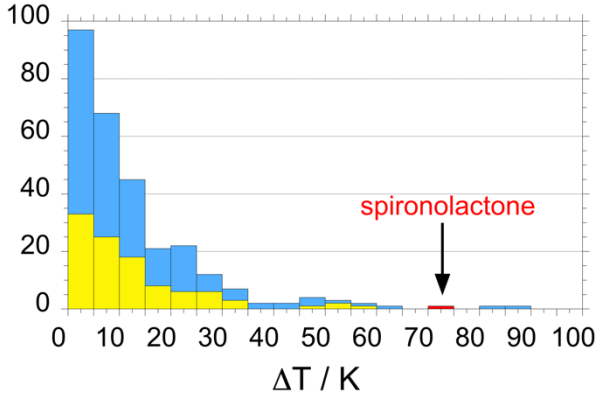

Figure 1. Differences in the melting points between the highest melting polymorph and other observed polymorphs for over 200 pairs

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. It is however still possible to construct a pressure-temperature phase diagram based on data that has been obtained by calorimetry and X-ray diffraction as a function of temperature.

By calorimetry, it has been found that the melting point of form II is 479.6 ±0.6 K with an enthalpy of 54.0 ±1.5 J g^{-1}. The melting point of form I is 408 ±3 K, however, the melting enthalpy for form I is inaccessible, because the melt recrystallises instantly into form II. Some samples of spironolactone convert from form I into form II before melting at a temperature of around 375 K leading to an enthalpy between the two polymorphs of −6.9 ±0.3 J g^{-1} (exothermic). In addition, the specific volume of both polymorphs as a function of the temperature from 100 K up to the melting point have been obtained.

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 because form I is denser it is 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, a relatively reliable 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 (Figure 2). 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 reach of any pharmaceutical process.

To conclude, 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 does in fact 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 that causes the appearance of the metastable form I in the first place [1].

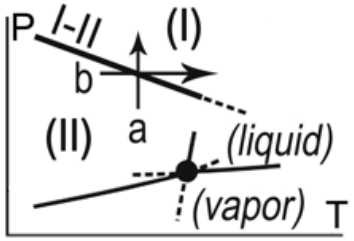

Figure 2. Schematic phase diagram of spironolactone dimorphism based on the Le Chatelier principle

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