MS28 Navigating crystal forms in molecular and pharmaceutical materials

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The pressure-temperature phase diagram of tetramorphic pyrazinamide by vapour pressure and synchrotron X-ray diffraction under pressure

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Abstract

The phase behaviour of drug molecules is important to control the desired polymorph in drug formulations, whether it is to ensure better stability of the formulation or better solubility (solubilization) of the drug. In the case of pyrazinamide, a drug against tuberculosis, four polymorphs are known to exist labelledα,β,γ, andδ [1,2]. Stability studies of this active pharmaceutical ingredient have been complicated due to the very slow transition kinetics observed in DSC measurements [1,2]. Using vapour pressure measurements, in which the reluctance of phase transformation is in fact an advantage, all solid-solid phase transformation temperatures have been determined. This method has been key to map the phase behaviour of pyrazinamide.

The use of high-pressure measurements with synchrotron X-ray diffraction at several temperatures from room temperature up to 120 °C has allowed to construct the pressure-temperature phase diagram of the four solid phases of pyrazinamide and the liquid phase (Figure 1). The equations of state of the four polymorphs have been determined at various temperatures in addition to the thermal expansion.

Theαform was found to be the stable form at room temperature. One striking feature of pyrazinamide is that one polymorph, theδform, has a very large thermal expansion and strong compressibility, which was not found in the other three forms. This gives rise to curved solid-solid transition equilibria in the pressure-temperature phase diagram, which is not commonly observed in the pressure range of 0 to 1 GPa for transitions between polymorphs.

References

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