Crystallization of molecular glass: from amorphous state to new polymorphic forms in the API sodium naproxen

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The solid form of an active pharmaceutical ingredient (API) is usually governing its material properties such as solubility or tableting characteristics. Several strategies have been put into place to improve solubility as this is often a major issue. Naproxen is a poorly soluble API, but its solubility can be improved by synthetizing corresponding sodium salt. Another alternative to improve solubility is to stabilize an amorphous state [1], however it has been shown that naproxen is a typical non glass former [2].
For ceramic materials, it has been demonstrated that crystallization from glass can be a successful approach [3] to stabilize new polymorphic forms of technological relevance. In this contribution, we have been applying a similar approach investigating sodium naproxen as an example. When heating up sodium naproxen above its melting point, various phases can be stabilized at room temperature depending on the heat treatment: new polymorphs or glass phases. This is in significant contrast to pure naproxen which was identified as non-glass former. We show in Fig. 1 the temperature dependence of the initially formed glass phase as function of temperature. Upon heating, the initial amorphous state (1) evolves towards a second amorphous state (2) before recrystallizing into previously unreported polymorphic forms of sodium naproxen (regions (3) and (4)). For instance, the crystal structure present in the region (4) can be stabilized at room temperature and varies from the initially reported crystal structure of sodium naproxen [4] only by the orientation of the methoxy group (Fig. 1 b).

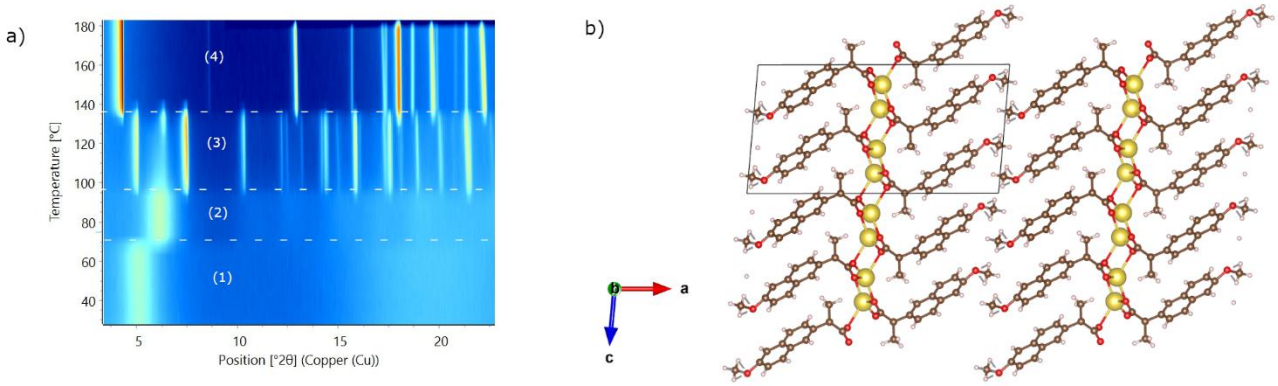


Figure 1. *a) Isoline plot of the recrystallization of amorphous sodium naproxen as function of temperature and b) crystal structure of the new polymorph of sodium naproxen appearing at high temperature (section 4).*

In addition, we report in this contribution the Pair Distribution Function measurements of the 2 glass phases and compared it to the known polymorphs. Those results are provided valuable information about the nature of the glass phases and how the local order is changing between the crystalline states and the amorphous phases. While molecular glasses are investigated to attempt stabilizing amorphous phases of APIs in the pharmaceutical industry, this work demonstrates that their crystallization can be also an alternative route for the stabilization of new polymorphic forms of API.

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