INDUSTRIAL DEVLOPMENT PROJECTS

Analysis of a metal carrier complex for efficient nutrient supplement treatment with synchrotron X-ray diffraction

THE INDUSTRIAL CHALLENGE

Renapharma is a pharmaceutical company offering nutrient supplements. A new carrier molecule for metal ion supplementation has been developed with a very promising outlook. In early development stages of a pharmaceutical grade drug it is advantageous to determine its atomic 3D-structure, in this case the carrier molecule in complex with relevant metal ions.

WHY USING A LARGE SCALE FACILITY

To determine a molecule's 3D-structure at atomic resolution the most common method of choice is single crystal X-ray diffraction (XRD). It is indeed possible to do this experiment with a lab based XRD. However, lab based XRD is limited when requiring atomic resolution data due to the demands put on the size and quality of the crystal. A synchrotron XRD beamline, with both greater intensity and smaller sized X-ray beam compared to a lab XRD, greatly reduces the requirements on crystal quality. Despite this, there is still a limit to how small a crystal can be, both to handle and to collect single crystal XRD data, also at a synchrotron beamline. The crystals previously grown from this metal carrier complex had turned out to be too small, and we must first grow crystals of appropriate size for synchrotron XRD data collection, usually >0.1 mm.

HOW THE WORK WAS DONE

Since compound purity is known to affect crystallization, this needed to be optimized to improve the size of the crystals. After sample purity was addressed, we proceeded to find correct crystallization conditions. As can be seen in the figure we managed to produce crystals of adequate size for synchrotron XRD (~0.1 mm). Even if crystals are grown, however, it is advantageous to confirm their content before proceeding with XRD data collection. We needed to ensure that the crystals contained both the carrier and the correct amount of metal ions. Indeed, other molecules within the solution did turn out to produce crystals (false positives). Lab based LC-MS, DSC, XRPD and elemental analysis, which could not be used for structure elucidation, confirmed the content of the crystals produced and can be used in later stages once a 3D-structure is experimentally acquired.

Selected crystals were glued on sample holders and data were collected with synchrotron XRD at the ID23 beamline of the European Synchrotron Radiation Facility (ESRF) in France.

THE RESULTS AND EXPECTED IMPACT

We managed to grow large enough crystals to perform X-ray diffraction measurements at a synchrotron beamline, but still not large enough for laboratory XRD.

The initial analysis of the data showed that the crystals were twinned. This means that, although under a microscope it looks like a single crystal, it is in fact two or more crystals growing together in different orientations, while still sharing some of the crystal lattice points.



Figure. One of the larger crystals glued in a crystal loop.

It can be possible to solve structures from data collected from twinned crystals, but that is far from always the case. Our crystals were overall not diffracting very well, possibly due to the twinning. Despite several attempts we were unable to successfully integrate the data and solve the structure of the molecule.

We now need to further refine crystallization conditions to hopefully receive single non- twinned crystals with which to collect X-ray diffraction data sufficient for structure determination.

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