INDUSTRIAL PILOT PROJECT

Revealing the nanostructure of pharmaceutical formulations with advanced x-ray technique

THE INDUSTRIAL CHALLENGE

The tailoring of pharmaceutical formulations requires a detailed understanding of what controls the stability of the drug. A crucial parameter is the link between the nanostructure of formulation and release properties. In order to aid rational design of new drug formulations new tools to visualize the structure over multiple length scales (from nm to mm) are desired.

WHY USING A LARGE SCALE FACILITY

New x-ray scattering and imaging techniques can add crucial information on the nanostructure of formulations. The high brilliance of new synchrotron x-ray sources has allowed the development of advanced x-ray imaging methods where one can map the local structure of a material on nm-level over an extended volume. Complementary to imaging are scanning scattering techniques, where for instance a full-size tablet can be mapped with high spatial resolution and high intensity using synchrotron x-ray instruments. This enables fast measurements for systematic studies.

HOW THE WORK WAS DONE

To investigate the nanostructure of model amorphous formulations we performed two experiments at the Swiss Light Source (SLS) at the Paul Scherrer Institute, Switzerland (Fig 1.). The cSAXS beamline at SLS offers unique opportunities, by allowing both ptychographic nano-tomography, to image an extended volume with a sub 100 nm resolution and scanning SAXS to visualize distribution of drug domains varies over a macroscopic sample. A particular feature of the cSAXS beamline is the additional support for sample preparation and analysis by the beamline scientists and we particularly acknowledge Dr. Ana Diaz and Dr. Mirco Holler. The beam time (6 days) was obtained by PSI though the normal proposal rounds.

A joint AstraZeneca and Chalmers team was set up bringing in necessary competence. Solid dispersions of model pharmaceutical drugs and polymers with different drug contents and with two different processing methods, extrusion and solvent casting, were prepared and evaluated.

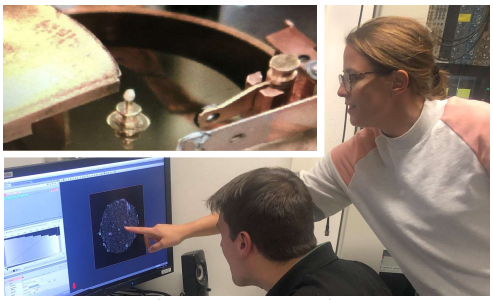

Figure 1. Top. Sample in place for ptychographic tomography. Bottom: On-line reconstruction of the data.

THE RESULTS AND EXPECTED IMPACT

For the first time we have been able to directly image the nanostructure of amorphous pharmaceutical solid dispersion. With the nano-tomography we could resolve the 3D-morphology of the dispersions with a resolution of 100 nm. This enabled us to pinpoint that the morphology is controlled by a phase separation mechanism directly dependent on the processing method.

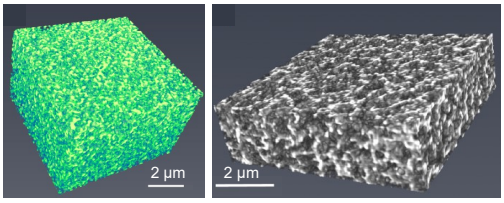

Figure 2.Extrusion (left) and solvent casted (right) solid dirspersions of drug and polymeric carrier.

Extrusion resulted in smaller interconnected domains, whereas from solvent casting a coarser structure was found where a larger tendency for crystallization was observed in the boundary between the domains (Fig 2.). This displays the importance of making advanced tools, such as x-ray imaging and scattering, available during pharmaceutical development.

"This project enabled a new generation of scientists in academia & industry to deepen their knowledge and establish connections valuable for their future career."
/Alexander Liljeblad (MSc), AstraZeneca Gothenburg

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