SEQENS 'Lab

Polymorph Screening Services

Different crystalline solid forms (polymorphs, salts, cocrystals) of an active pharmaceutical ingredient (API) can have very different physico-chemical properties. Those differences can impact bioavailability, solubility, dissolution rate, first pass metabolism, side effect incidence, stability and manufacturability. Most of APIs can exist in multiple solid forms, including polymorphs, hydrates, solvates, salts, cocrystals and non-crystalline forms. The objective in screening is to produce an optimal solid form based on parameters such as crystallinity, stability, solubility, hygroscopicity and ease to production. Understanding the crystallization process is essential for reproducibility during drug development and manufacturing.

WHY CHOOSE SEQENS' LAB

- **We have a long-term expertise to support custom and proprietary drug substance development.**
- **We provide a comprehensive solution to support solid state characterization to enhance bioavailability.**
- **We provide state of the art equipment's with high throughput capacity and analytical expertise allowing high capacity and fast turn-around.**
- **We supply you with consistent data in line with a regulatory frame, with a experienced team always available to answer any questions and coordinate the project.**

As the Center of Innovation and Research of the Seqens group, the Seqens'Lab provides polymorph screening services. The objectives of the polymorph screen study are:

Identify the most stable form

To confirm the most appropriate crystalline form to develop

Investigate the tendency to produce polymorphs including solvates/hydrates especially in process solvents and under typical process/formulation conditions

Gather some data for an IP perspective

Material characterization

The material is initially characterized using the following analytical techniques to act as a reference for solids produced as part of this study:

Nuclear magnetic resonance (proton NMR)

Thermal analysis (DSC and TGA)

X-Ray powder diffraction (XRPD)

Polarised light microscopy (PLM) and/or Scanning electron microscopy (SEM)

DVS analysis

Screening experiments

The solubility of the compound is estimated in several solvent systems by aliquot addition and/or temperature cycling to aid in the planning of the polymorph screen. The best solvents will be selected based on the following parameters:

Known or determined solubility of drug substance

Solvents to be used in the manufacturing process (N-1 included)

Solvents exhibiting a wide range of polarities and structural functionalities

Water and/or water mixtures (for hydrates)

Crystallisation experiments are carried out under a wide and diverse range of nucleation conditions, designed to mimic the process conditions used during development and formulation. Accessing such diversity is not possible when only employing solvent based experiments or a high throughput screening approach. Another key objective is to obtain amorphous material for screening, as such solids have no 'memory' and subsequent stressing maximizes the chances of discovering novel crystal forms. In cases where amorphous material is very unstable at ambient temperature, disordered (poor crystallinity) material may be used instead. Hydrate formation will typically be explored by use of a range of water activities in conjunction with different techniques.

Crystallisation experiments are carried out using various techniques, based on the information gathered as described above.

Solution experiments

- Cooling
- Evaporation
- Slurry at high and low temperature
- Anti-solvent
- Kinetic ripening
- Nucleation by sonication

Solid-state experiments

- Desolvation of hydrates & solvates
- Grinding/milling (wet and dry)
- Melt quench
- Thermal, vapour stress
- Humidity stress
- Spray drying and/or freeze drying where applicable

All solids from the crystallization experiments are analyzed at least by XRPD and the resulting patterns compared to the as-received material. Where sufficient material is available, further analysis (e.g. NMR or TGA/DTA) will be conducted on solids with novel XRPD patterns to tentatively assign its nature (polymorph, solvate, impurity). Physical stability of suspected hydrates or solvates may be assessed using XRPD under different storage conditions e.g. ambient storage or 40°C/75% RH and/or CHC chamber.

Determination of the thermodynamically most stable form and inter-relationships between polymorphs

In most cases, the thermodynamically most stable polymorph under ambient conditions is the one selected for API development thus, it is primordial to define it as early as possible to develop a crystallisation process accordingly. However, it is also very important to understand the inter-relationships at different temperature and relative humidity (eg. for hydrates).

Inter-conversion slurry experiments of suspensions seeded with all relevant forms will be performed to determine the thermodynamic most stable anhydrate at 2-3 temperatures. With the presence of hydrated forms, water activity experiments will be conducted to determine the region of stability for hydrates and anhydrates at a specific temperature (typically ambient temperature).

Intellectual Property generation

When there is a requirement for supporting submission documents and/or generate intellectual property (IP), the selected form is produced for further characterization, typically using the following techniques:

- Chemical purity and stoichiometry (e.g. 1H NMR, chromatography)
- Identification (FT-IR and/or Raman)
- Crystallinity and powder flow (XRPD, appearance, polarised light microscopy, bulk/ tapped density)
- Thermal properties (TGA/DTA, DSC, and/or hot stage microscopy)
- Hygroscopicity (DVS) with post DVS XRPD
- Water content (for hydrates)
- Physical and chemical stability for 1 week at 40°C/75%RH (XRPD and 1H NMR

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