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Review Article on Analytical and Characterization Techniques in High Throughput Crystallization

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ABSTRACT

In High Throughput crystallization process, when crystallization has occurred, the HT crystallization plates are passed for the analysis for identification of the produced solid forms under each set of test conditions. Multiple approaches for physical form discovery must be used so as to maximize the number of forms encountered during the search. Once all solid-state forms produced in the screen are identified, each form is fully characterized through determination of crystal structure and establishing thermodynamic relationships between forms and relative thermodynamic stabilities.

Keywords : HT Crystallization Plates, Crystallization Process, Polymorphs, Pseudopolymorphs, Cocrystals, Salts, Amorphous

I. INTRODUCTION

For investigation of polymorphs, pseudopolymorphs, cocrystals, salts, amorphous and other crystalline solid forms of active pharmaceutical ingredients screening is a common practice for already existing, new chemical entities and marketed products too. Scientific point of view as well as regulatory it becomes essential to identify and characterize the solid-state forms by suitable analytical methods/techniques in early stages of development of solid dosage forms [(1)]. Different solid forms exhibit differences in various properties such as- solubility, bioavailability, stability and crystallinity etc. which in turn can affect performance of the formulations containing these different solid forms during formulations and later stages such as transportation and storage of drug products. [(2)] Traditional screening techniques such as solvent evaporation, anti-solvent addition, change in cooling rate, temperature and pH, crystallization from liquid melts, sublimation, heat induced transformation, desolvation of solvates, salting out etc. have sufficient reviews. [(3-7)] Automation in these methods saves time as well as material per experiment when dealing with a large number of samples, still crystallization conditions become limited. [(8)] High-throughput screening has become nowadays a technology in demand for estimating potential polymorphic forms by avoiding as much as possible surprises during advance phases of development. However, high throughput technology is being used by few big pharmaceutical companies where it has contributed a lot in gaining better knowledge about the various properties of probable solid forms of any drug. This technology, though not sufficient alone in selecting solid form for development, has proven to be a good platform in evaluating the potential candidate forms in the process of crystallization of newer solid forms of a drug. [(9)] A wide range of analytical methods/techniques are available for effective identification and characterization of polymorphic,

pseudopolymorphic and other soild/crystalline forms of chemicals including APIs. Important and most frequently used methods/ techniques [10] for this purpose are as follows:

- X-Ray Powder Diffraction analysis (XRPD)
- Single Crystal X-Ray Differaction (SCRD)
- Scanning Electron Microscopy (SEM)
- Polarizing Microscopy
- Hot Stage Microscopy (HSM))
- Particle Size Distribution
- Thermal analysis
- Differential Scanning Calorimetry (DSC)
- Thermo Gravimetric Analysis (TGA)
- Solid State FTIR spectroscopy
- Sorption Isotherm Analysis
- Karl-Fischer (KF) Analysis
- Vapor Pressure Analysis
- Dynamic Vapor Sorption
- Heat Capacity Measurements
- Solubility Relationships
- Dissolution Rate Studies
- Slurry Conversion Studies
- Bioavailability / Pharmacokinetics studies
- CCD-Raman spectroscopy
- 13C–1H CP-MASNMR

Though, one or more of these analytical techniques can be used very effectively used to distinguish different crystalline or amorphous forms of an API, crystallization using high-throughput methods generally results into very small amounts of recrystallized material in the form of non-uniformly deposited matter around the base or walls of the vessel. Analysis of such samples further produces challenges in locating the position of solid within each well. This challenge can be faced by analysis of multiple points across the well and/or using optical systems for location of material. In High Throughput screening, mostly, solid is dispensed into individual wells of the plate in the form of a concentrate solution and the solvent is evaporated so as to leave the solid API for recrystallization. [10] Individual solvents or solvent mixtures can be used according to predefined protocols from a HT library which in turn is selected to cover a diverse range of physicochemical properties. Chemoinformatics and drawings based on a range of multivariate statistical methods can be used to quantify the diversity within the screening library and then to cluster solvents according to the degree of similarity and dissimilarity, and thus HT screening enables the rational selection of solvents. When solvent is dispensed, plates are warmed and agitated to facilitate dissolution prior to being subjected to a controlled cooling or evaporation cycle to achieve supersaturation which promotes crystallization. It is better to optically inspect the samples between steps for identifying the wells without dissolution occurred prior to the crystallization step. When crystallization has occurred, these HT crystallization plates are passed for the analysis for identification of the produced solid forms under each set of test conditions. A detailed inspection of results can also be used to assess the completeness of the experimental screen and for identification of experimental factors controlling polymorphic outcomes from solution crystallization. Multiple approaches to physical form discovery should be used, whenever possible, in order to maximize the number of forms encountered during the search. Alternatives and variations to solution crystallization which may be included as part of the comprehensive screening approach, may include -contact line crystallization, crystallization in constrained environments such as nanometer-scale pores in glass beads, on self-assembled monolayers and in glass capillaries, mechanically induced changes, slurries, heteroseeding and templating, growth from the vapor phase via reverse sublimation, polymer heteronuclei and microarrays, crystallization under

high pressure, in situ thermal transformations, and recrystallization from amorphous solids. Once all solid-state forms produced in the screen are identified, each form is characterized fully via determination of crystal structure and establishing thermodynamic relationships between forms and relative thermodynamic stabilities. Primary analysis technique(s) used for performing analysis under HT screening should ideally identify each crystal sample clearly for- whether it is composed of known or novel polymorphs; whether it is a pure phase or a mixture of solid forms. The speed of analysis in HT screening is of utmost importance when metastable polymorph or solvate forms have formed since they may transform relatively quickly to other forms produced in the search. The most popular techniques for identification and characterization of crystalline salts generated on crystallization platform include melting point estimation, Raman spectroscopy, aahigh pressure liquid chromatography (HPLC) and X-ray Powder diffraction (XRPD). [11]

Single-crystal diffraction is matchless in the structural analysis of organic molecular crystals which provides details on all of the atomic positions within the material including unit cell, space group, molecular conformation and intermolecular packing. These data provide a detailed description of each crystalline form. Single-crystal samples of at least 100μ are generally required for structure determination using modern laboratory instruments. However, much smaller as well as weakly scattering crystals may also yield sufficiently good data to allow structure determination when data is collected using synchrotron sources. If suitable single crystal samples (or microcrystals) are not available for a specific solid form of API, Structure Determination from Powder Data (SDPD) is a powerful alternative approach, requiring only a few milligrams of polycrystalline sample. It can provide good quality data (readily accessible using well calibrated laboratory instruments) and knowledge of the chemical composition of the sample. XRPD is widely applied in the identification of polycrystalline powders produced during experimental crystallization screening and in addition to potential application to SDPD studies. XRPD can also provide information on whether the sample is crystalline or amorphous; whether it contains a single or mixture of crystalline phases; whether any known single-crystal structures are representative of the bulk material. In combination with sample temperature control, it can allow direct study of structural transformations [12]. Since different solid forms of a compound produce an unique characteristic XRPD pattern, it is used as a fingerprint for particular solid form of a compound. In High throughput salt screening, XRPD also indicates the crystallinity and polymorphic stability of the salt form. Salt form definitely has a different XRPD pattern to that of the drug candidate and its counterion. The similarity in the XRPD patterns of the sample and drug candidate or counter-ion implies that solid form in the sample is not the salt form. However, XRPD method has limitations for non-solid nature of counterions and in case of multiple polymorphisms in drug candidate. In such cases acquisition and interpretation of XPRD patterns become complicated [12].

The application of synchrotron powder diffraction data to the structural characterization of “amorphous to X-ray” samples using pair distribution function (PDF) analysis also exhibits considerable potential in further extending the role of powder diffraction in the development of pharmaceuticals compounds. Cowans refers XRPD as quintessential tool for making distinguishment between various crystalline forms of any compound [9]. New generation instruments excellently provide sharp and high quality diffractograms, required for better identification. When combined with indexing

software, screening efficiencies of XRPD is enhanced and makes it able in providing critical information.

Raman spectroscopy is capable of probing the crystal lattice vibrations associated with any molecule and provides information about vibrational spectrum with more sensitivity in comparison to Infra-Red spectroscopy [13]. This technique helps in faster selection of polymorphs and salts by providing physical as well chemical information about the solid-state form. Raman spectroscopy and powder X-ray diffraction (PXRD) in combination with General Area Detector Diffraction System (GADDS) are used frequently so that the chances of missing or mistakes in identifying the hits may be minimized. The advantages of both the techniques are that: (1) both don't require the preparation of sample (2) both techniques are able to collect data even from very small individual crystallite material and (3) they together enable individual data sets to be collected very quickly within minutes. The full proof identification of all new forms produced from the individual collected data sets, requires the multivariate tools of data analysis when large number of samples result are found in the screening process. Other instrumental techniques or combinations may be useful in getting even more excellent results, if larger amounts of samples, equal to milligrams, are available for analysis. [15]

In melting point determination technique, recrystallized material is put in a thermal chamber having a device for image scanning, the crystals are then heated at a predetermined rate. An optical signal is produced by image scanner for the sample which is monitored for associated morphological change. Change in birefringence pattern at the melting point can be assessed for determination of melting points of different polymorph, salt crystals of a compound [14]. In HT crystallization birefringence images of each well of substrates from slurry/ cooling/ evaporation or precipitation experiments are taken by suitable microscope such as Zeiss AxioVert 200M microscope. All wells should be captured for the full diameter of each well. Absence of crystalline form is represented by dark images of the wells which are not analyzed whereas wells with crystalline forms are analyzed further with suitable techniques. [16]

Initial information about solubility can easily be obtained through HPLC analysis of supernatant left in crystallization mixture.

High-Throughput Differential Scanning Calorimetry (HT-DSC) offers a considerable advantage over commonly used spectroscopic methods used for the same purpose. Heat changes during binding reactions can be monitored directly without need for receptor modification or labeling. Heat as a "universal signal" is not only be used to detect binding reactions qualitatively but quantification of binding reactions can also be done by providing detailed thermodynamic information [17].

Solid State Nuclear Magnetic Resonance (SSNMR) spectroscopy is better and has several advantages over other techniques used in identification and characterization of solid state in High throughput crystallization. It is neither destructive nor invasive. Even minute quantities of samples can be analyzed and the sample can be utilized for further testing after taking the SSNMR spectra. This technique requires little to no sample preparation. As most of the pharmaceutical excipients occur in a narrow range of the NMR spectrum, it is easy to distinguish the excipient from the NMR resonances of active pharmaceutical ingredient (API). SSNMR spectroscopy also provides quantitative information when performed properly. This technique can quantify mixtures of polymorphic crystalline forms, or of crystalline and amorphous materials [18].

SSNMR spectroscopy is also used to gain know about the structure of the materials along with its associated dynamics. Number of crystallographically

inequivalent sites in the unit cell of a crystalline materials can also be determined through SSNMR. More advance two-dimensional techniques such as rotational echo double resonance can also measure the distances between lattice [19]. SSNMR spectroscopy can also be used to examine the degree of disorder effectively in amorphous materials.

Mobility or stability of different polymorphic forms can also be compared through determination of the spin-lattice relaxation times (T_1 and $T_{1\rho}$). Degree of crystallinity as well as the presence of defect sites or less-crystalline domains in the sample can be easily observed by SSNMR which is otherwise difficult through X-ray powder diffraction. A sample with lower degree of crystallinity exhibits a faster spin-lattice relaxation time (T_1) which has a very minor difference ranging in seconds.

Though SSNMR spectroscopy has numerous advantages over other commonly used High throughput screening techniques, it is no exception to certain disadvantages. Firstly, it requires a deep expertise to run the technique and instrument properly. Secondly, the equipment is expensive. Also automation is quite difficult and requires human efforts as the sample fails to spin often when run by automatic program.

Another issue is analysis times for SSNMR experiments which can range from minutes to few hours and even to couple of days or more depending on the nature of the sample being analyzed and type of NMR experiment in use. Peak assignment in the SSNMR spectrum may be challenging because a single nuclear site or overlapping peaks can present multiple peaks. [20]

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