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Review Article on High Throughput Screening

A Demanding Technique in Polymorph Selection

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ABSTRACT

Polymorph screening is an effort in the direction of finding out whether a given compound exists in polymorphic forms or not, if yes then how many polymorphic forms of the given compounds exist? In simple words, Polymorph screening is the process of identification and characterization of nearly all possible but relevant polymorphs of any compound. [(1)] The practice of screening is different from that of polymorph or crystal selection. In the screening polymorphic forms and their identities are found out, whereas in the polymorph selection, the properties of various forms found in the screening are investigated to determine which one has the best properties for a particular use. It is polymorph selection that is being practiced in industry rather than simple screening since polymorph screening of some APIs, having complexity in polymorph profile, is somewhat difficult and challenging. [(2)] Polymorph screening helps in the selection of the solid form to be prepared for any active pharmaceutical ingredient (API). During polymorph screening several solid forms of the drug candidate are generated and analyzed at small level of preparation and then characterized by commonly available techniques, for example, solvent evaporation crystallization, antisolvent addition, cooling of saturated solutions of API at different rates, making slurries for extended periods. [(2)] It is self understood that other solid forms should not be neglected as they too may possess properties which make them suitable for further development.

Keywords : Polymorph, Active Pharmaceutical Ingredient

Various important reasons [(3)] for performing a polymorphic screening of an API are as follows-

- Polymorphs generally have differences in their physicochemical properties, such as - melting points, solubilities and dissolution rates and which may also lead to differences in their stability, biological activity and even pharmacodynamic performance. This is why polymorphic forms of an API are considered as different entities by drug authorities worldwide.
- Rejection of the API due to transformation of existing thermodynamically unstable polymorphic form in the formulation to another stable form during storage or other similar issues.
- So that the desired forms, which are being used, can be manufactured consistently.
- So that the effect of storage conditions on the dosage form can be evaluated and predicted.

Polymorphic screening consists of two steps: Preparation of polymorphs and Characterization of polymorphs. Second step further involves- Physical characterization and Chemical characterization. [(4)]

From the point of view of polymorphic study, physical characterization is far important than chemical characterization since they represent the different physical solid states of the same chemical compound.

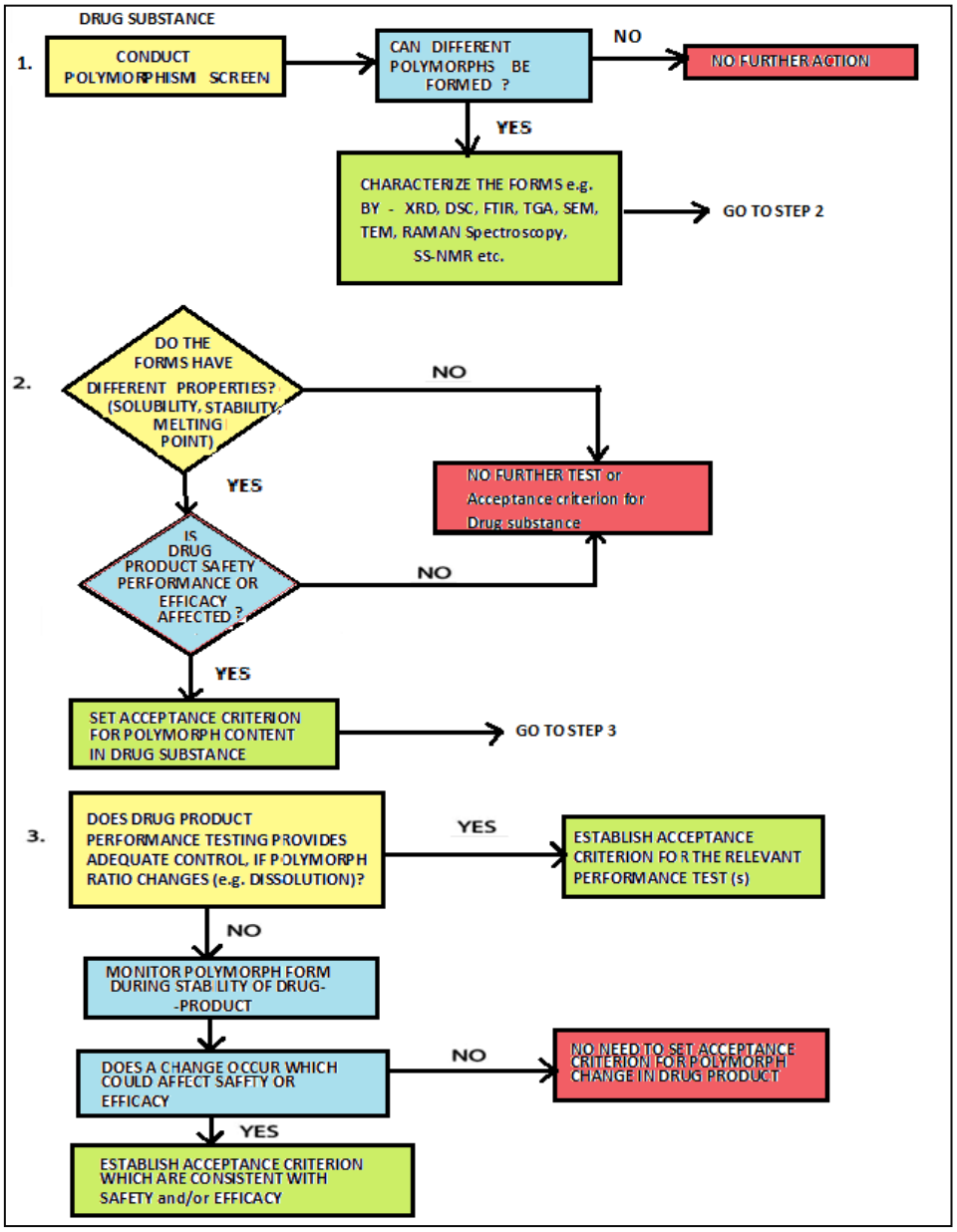

Figure 1: Strategic plan or ICH decision tree for polymorph screening [5]

Preparation of polymorphs and other solid state forms of a substance of pharmaceutical interest (APIs and excipients) and their solid-state characterization by traditional method has always been time taking and labor demanding. Hence, the conventional methods of polymorph screening are being replaced with new technology based methods for accelerating the process of polymorph exploration as per the need of the time. High throughput screening [4] method of polymorph screening is also such type of advanced integrated approach for preparation, characterization and analysis of related data.

HIGH THROUGHPUT (HT) POLYMORPH SCREENING [6,7, 8, 9]

Emerging strategies and technologies are pacing pharmaceutical development to recognize solid form diversity in pharmaceutical substances and this has also resulted in the emergence of HT crystallization technologies. Though the primary diversity often relates to polymorphic forms of pharmaceutical compounds, however, different salt forms, hydrates and solvates, co-crystals are also a subject of study under HT crystallization screening systems. It has made it possible to screen a larger number of samples for polymorph screening

simultaneously. These advanced systems utilize automation and robotics for finding out the best possible screening methods for generating polymorphs under a variety of conditions and also their characterization by new and advanced techniques. This screening utilizes the various databases and software for analysis of collected data regarding polymorph generation and characterization. HT crystallization systems have been developed with the aim of rapid and comprehensive exploration of the multi-parameter conditions and possibilities which contribute to the diversity of solid forms of a drug or compound. Under this methodology a combinatorial approach is used for generation of different solid forms of a compound where large number of possible conditions and compositions are processed in parallel. Experiments are performed on small scale so that the material demand remains at minimum and the largest number of possible conditions may be employed. In these experiments a large number of crystallization trials are done under differential experimental conditions, and thus probability of occurrence of a particular form is increased by a HT approach resulting in highly non-linear time dependence of crystallization. Additionally, in the combinatorial approach using of many solvent mixtures also allows experimentalist to know what underlying physical or chemical processes are required to produce a particular solid form of compound. When all the conditions that can be used to prepare a specific crystal form on the micro-scale are recognized in the HT screening, scale-up studies are conducted for optimization of the process for laboratory scale production. HT screening for crystallization can subdivided into 3 experimental steps-

i. Design of experiment (DoE),
ii. Execution of experimental protocols and
iii. Analysis of data.

Generally, systems which carry out these experiments consist of both the hardware and the software components which drive and track the experimentation and permit the data storage, retrieval of data and its analysis. These HT screening systems are designed to be flexible and scalable so that a variety of experimental procedures can be carried out in serial or concurrent manner, thereby making the system worth employable at different stages of drug development. These systems find their basis in the concept of first performing experiments under a variety of conditions to generate data and then its mining to set functional model and then using these knowledge based models to provide guidance for further experiments.

The technologies consistently developed in last two decades have enabled experts of the field to perform automated high throughput polymorph screening onto even very small quantities of drugs. Ever increasing convergence of automation, experimental design, sensitive and rapid analytical techniques with sophisticated data analysis tools is paving the way to enhance the speed of research in the areas of finding out maximum possible polymorphic forms to be generated, screened, quantified and assessed for newer APIs. In addition, these automated processes provides unambiguous fingerprint and structural data on polymorphic forms, exercise better control over solid form as the product advances through formulation, stability, scale-up and manufacturing stages of product development and launch. Cost effectiveness is an additional feature of high throughput screening along with time efficacy. [8]

The goal of HT screening is to reach to a small number of successful outcomes which can be passed to the next stage of development. In HT screening little efforts are made to learn on “why certain outcomes were positive? and why others were negative?”. Whereas, in case of HT experimentation the objective is to go through each

and every point of experiment which can produce multiple types of data which can be interpreted and used to set the guidelines about the experimental process for a successful outcome. [9]

High Throughput crystallization

HT crystallization experiments focus on comprehensive coverage of all the processes and all the assumptive variable experimental conditions, such as temperature variation as a function of time, and other parameters to be performed and assessed for solid form discovery. These additional process variables cover near to maximum diversity in the experimental space and thereby increasing the likelihood of achieving comprehensive coverage. Another difference between HT screening and HT crystallization/experimentation is the "chance of success" or the relative "hit rates". In both cases a "hit" is taken as a set of conditions that results into a desired or successful outcome. For HT screening the desired result/hit is typically an activity or potency which exceeds a predefined threshold. For HT crystallization, a hit is known as an incidence of formation of a solid form. The hit rate is typically as low as 0.1% of the total number of sample analyzed in case of HT screening, whereas, HT crystallization experiments can yield a hit-rate ranging from tens to nearly 100% depending on the type of experiment and the process/mode(s) used. For example only a limited number of compounds from a pool of thousands may succeed to show the required potency through HT screening, on the other hand 10–50% of crystallization trials may yield solid forms. [10]

A fully integrated HT crystallization system [11] is made up of a variety of components which includes experimental design, execution software, robotic dispensing & handling hardware, automated high-speed analytical tools, end-to-end sample tracking, and integrated chemo-informatics analysis software for visualization of data, modeling and mining of model. A Chemspeed technology [12] is one such company catering the related research services. A schematic pattern of the workflow of a fully HT crystallization system has been shown in fig. 2.

These features are expected to be supported by a comprehensive informatics database which is used to process the large amount of generated data. Special informatics tools are used for designing statistically relevant and diverse experiments; automation in hardware for performing the specific operations, and equipped with an analytical function for analysis, comparison and sorting of the experimental results. Most important feature of these systems is their ability to mine and modeling of experimental data for using the generated knowledge towards further guidance on experiments. A relational database is required to support these functions for providing a communication mechanism between components of the system.

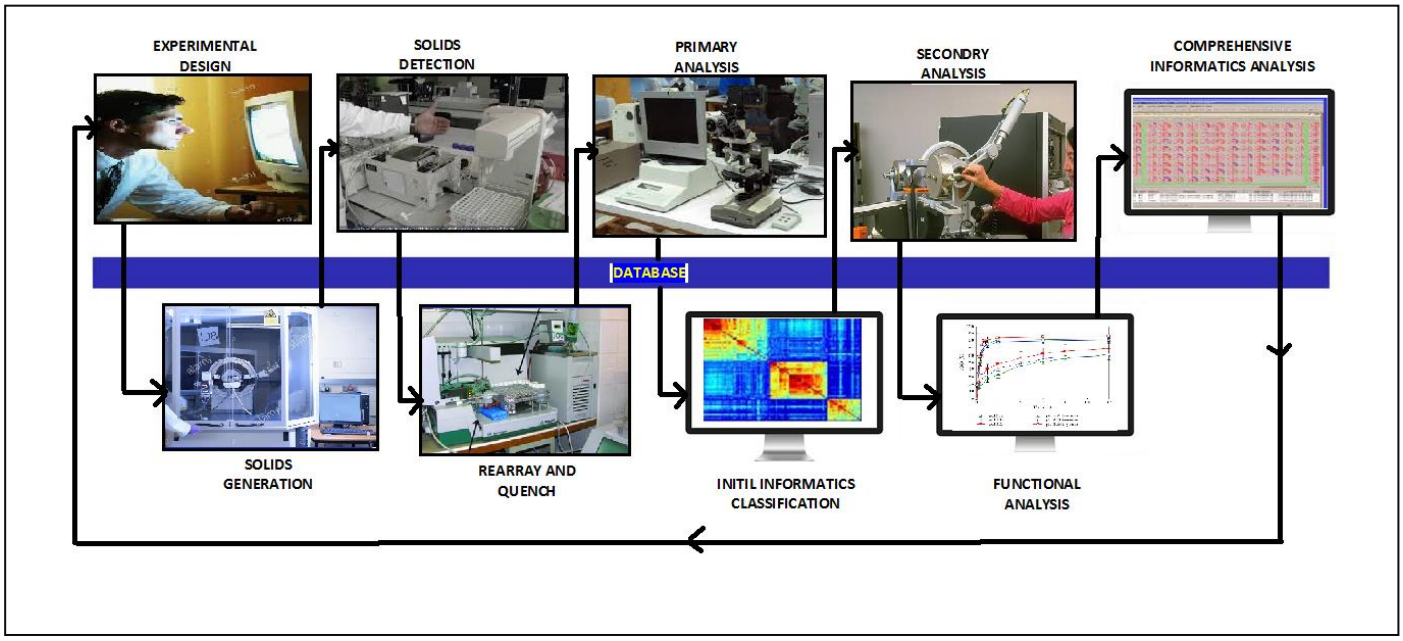

Figure 2: A schematic illustration of workflow for a fully integrated HT crystallization system

For solid form screening in the early stages of drug development, only a small amount of compound is generally available, and therefore, on small scale, high-throughput approaches using multi-well plates can prove to be very useful. Example of a high-throughput crystallization system, using 96 wells plate for polymorph crystallization, is HT crystallization for an Angiotensin II antagonist MK996 [13], which unfolded evidence for 18 crystalline forms, which are twice to those possible through traditional manual crystallization screening approach.

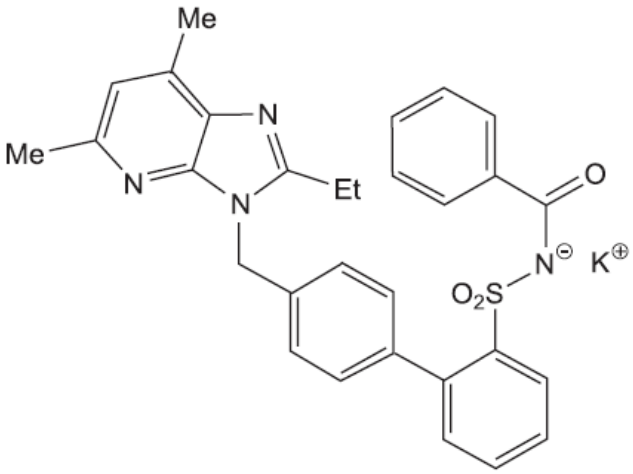

Figure 3 : Angiotensin II antagonist MK996

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