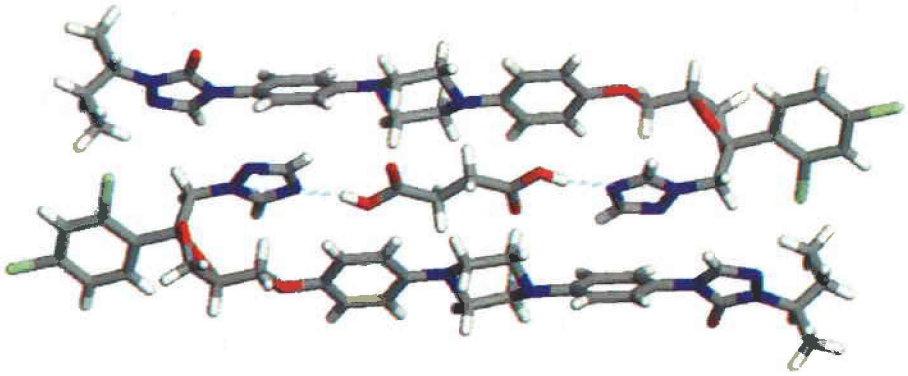

Fig. 8. Trimer unit of the itraconazole succinic acid co-crystal from single crystal X-ray structure (from [44], with permission).

aqueous medium was studied to assess their potential impact on bioavailability of the drug from a solid dosage form. Fig. 9 compares the dissolution profiles of the co-crystals into 0.1 N HCl to those of crystalline itraconazole-free base (95 % of all crystalline particles <10 μm) and commercial Sporanox® beads (amorphous itraconazole). The malic acid co-crystal rivals the dissolution of the commercial product. In general, the co-crystals behave more similarly to Sporanox® than the crystalline-free base. The co-crystal forms achieve and sustain 4- to 20-fold higher concentrations than that achieved from the crystalline-free base. The practical implication is significant, since the ability to form a supersaturated solution, even transiently, can have dramatic impact on absorption and bioavailability.

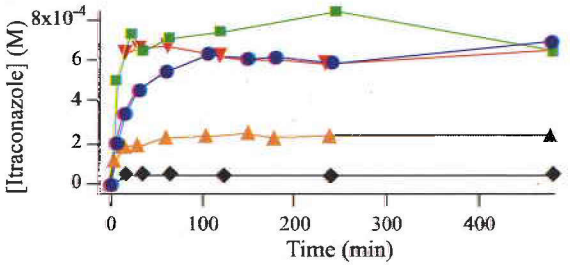

Fig. 9. Dissolution profiles into 0.1 N HCl at 25 °C plotted as itraconazole concentration ([itraconazole]) as a function of time for Sporanox® beads (■), crystalline itraconazole-free base (♦) and co-crystals of itraconazole with L-malic acid (▼), L-tartaric acid (●) and succinic acid (▲) (from [44], with permission).

Co-crystals represent a class of pharmaceutical materials of interest, both in terms of projected diversity and applicability. The study of co-crystals, along with polymorphs, solvates, salts and hydrates, is perfectly suited to HT crystallization experimentation and should be considered part of the form selection processes.

4. Post-screening analyses and form selection

Several functional characteristics must be considered in the selection of a suitable crystal form for a pharmaceutical dosage form. HT crystallization has the potential to create a larger pool of crystal forms for which functional parameters, such as dissolution rate, chemical stability, flow and compressibility, must be determined and compared. Strategies to accomplish ranking of the numerous forms must be devised. An example is the adaptation of HT for solubility measurement. The plot in Fig. 9 illustrates results of a plate-based kinetic dissolution assay in which various forms of a compound were placed in simulated gastric fluid and monitored for dissolution as a function of time. The schematic in Fig. 10 shows how such an analysis can be accomplished in a 96-well filter plate. The concentration at a given time point is determined after filtration of the suspension by quantification using either UV or HPLC with UV detection.

While the entire plate is filtered at one time, different time points can be achieved by timing the addition of dissolution medium such that the aliquot

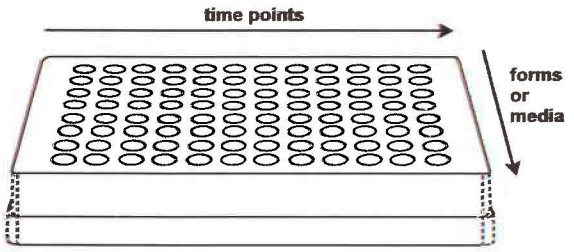

Fig. 10. Schematic of a 96-well dissolution filter plate.

for the longest time point desired is dispensed first and the shortest one comes last. Instead of varying the form along one axis of the plate, one can choose to study the dissolution of a single form into several different media (see Fig. 10). Equilibrium solubility can be determined in a variety of solvents and at different temperatures using a similar principle to the dissolution plate. A demonstration has been provided using automated React-IR analysis [109]. Other functional parameters, such as solid-state stability and thermal properties, can be adapted to HT. Such systems for ranking the stability of forms generated from HT crystallization await publication and review at a future date.

5. Summary and outlook

HT crystallization methodologies are capable of screening hundreds or thousands of crystallization conditions in parallel using small amounts of compound for the identification and characterization of diverse forms of active pharmaceutical ingredients. As demonstrated by numerous case studies from several stages of pharmaceutical development, such technologies have begun to show promise in enabling more comprehensive exploration of solid form diversity. The technologies are likely to provide a landscape of potential operating conditions from which scientists and engineers can design robust and scalable processes for transfer to manufacturing.

The ability to conduct extensive crystallizations with small amounts of material using a variety of solvents, additives and conditions necessarily generates large sets of data. However, the information by itself is of limited value, unless it can be properly analyzed. In order to extract maximum knowledge from the studies, it is essential to have the ability to design experiments, track samples in the process, collect the data in a relational database, and mine the information using statistical techniques and models in property space that assist the scientist to maximize the value of the data. Such models attempt to fit an output variable to physical properties or descriptors using techniques similar to those used in traditional quantitative structure activity relationships (QSAR). These models can be *carefully* extended to mixtures containing compounds that were not included in the original experiments if validation suggests that the models are sufficiently stable. Significant models that are found in the analysis of the data can be stored in the database for later retrieval and use to direct iterative experiments. The power of this approach becomes increasingly more visible when several properties are being co-optimized, as can be very important in the pharmaceutical development process where such properties as oral bioavailability, stability and processability need to be reconciled. The availability of a map of conditions that lead to the formation of different forms (salts, hydrates, solvates, polymorphs, co-crystals) of the drug can be valuable to the process chemists or engineers as they develop scalable processes to produce materials suitable for development and registration.

For many years, the value of composition of matter (CoM) patents on new chemical entities, including where appropriate, pharmaceutically acceptable salts, has been well appreciated. However, it is only within the last decade or so that the application of CoM patents has been significantly extended to cover all forms of the compound, including hydrates, solvates, co-crystals and polymorphs. Unlike salts, which for the most part can be prophetically claimed based on an understanding of the chemical structure of the compound and its ionization constants, the existence and identity of hydrates, solvates, co-crystals and polymorphs have defied prediction. Therefore, in order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them and evaluate their properties as valuable new pharmaceutical materials.

In general, discrete crystal forms are considered non-obvious and patentable. Given the diversity and greater complexity of chemical structures of today's

drug candidates [110], coupled with the advanced technology to identify novel forms, it is common to find multiple forms of drugs **[61]**, some similar, some dramatically different in terms of their in vivo performance. These forms are all candidates for separate intellectual property protection. Therefore, it is incumbent on the innovator of a new drug candidate to identify and patent these forms in order to optimally protect their investment in the compound. Recent case studies suggest that identifying and patenting all forms of new chemical entities should be a primary strategy of all innovators of novel drugs. In this regard, the use of HT crystallization technologies for rapid, comprehensive discovery and characterization of solids form diversity offers significant advantages for the development of a strong intellectual property position.

With the advent of HT crystallization methods, appreciation for the landscape of physical form for drug development has begun to change. Use of these systems has the potential to facilitate drug development by saving valuable time in selecting the optimal physical or chemical form of a given compound. HT systems that generate rich datasets offer the ability to develop a more fundamental understanding of the crystallization process, based on knowledge generated from large numbers of experiments on diverse compounds. Having such information at an early stage minimizes the risk of process modifications resulting in form changes and provides the opportunity to gain more comprehensive intellectual property coverage. In addition, comprehensive form data help address important regulatory questions related to the number of solid forms of an API and the relationships between them.

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