Impact of Solid-state in Early Development

API phase and formulation should be able to reach desired exposures and have adequate chemical and physical stability for GLP toxicology and first in human (FIH) studies. Any changes to form or formulation will incur significant time and resource penalties.

You've determined the best candidate based on activity, potency, and metabolism that meets the target profile for the disease, now what? Hopefully you know what solid form and particle size was used in your PK studies (both as pure API and immediately before dosing). If not, send us a few mg of the batches and using our FAST analysis, we can get that baseline information.

Now your focus shifts to enabling multiple day oral dosing studies and dose range-finding studies to support preclinical toxicology and dose-limiting toxicity (DLT) studies. High dose PK in at least one species and at least one dose in a non-rodent species should be carried out to ensure that the phase and formulation are suitable for the DLT and dose-ranging studies. Your solid form now needs the following attributes:

- Sufficiently chemically and physically stable in SGF, FaSSIF and in selected formulations
- Sufficient solubility in SGF, FaSSIF (or equivalent pH solubility)
- Solubility in formulations and on dispersing in biorelevant media or a formulation that provides desired exposure multiples of at least 10x
- Chemical and physical stability in dosing formulation, preferably for 24h

At this stage, it makes sense to determine the optimal API form for clinical development. Once human trials start, switching API form may involve expensive bridging studies and, at the very least, a bio-waiver, all costing significant time and money. If it is determined the free form of your compound is acceptable from both a processing and bio-performance perspective, you should now perform a polymorph screening on this compound to determine:

- The most stable anhydrous form at normal processing conditions
- Any solvates that exist that could impact API isolation
- Any hydrates that exist

At minimum, the API phase must be characterized, for example using polarizing microscopy or X-ray powder diffraction to determine crystallinity of the drug compound. The physical form (polymorphic form or amorphous) can significantly affect the solubility and bioavailability characteristics of the drug molecule. It is also important to define whether it is a solvate, hydrate and to determine whether it would be preferable to identify other suitable phases, for examples, salts that could provide improved physicochemical properties and be more developable. The minimal requirements for the API phase at this stage should include:

- Purity of the compound is preferred to be >97.0% with no single impurity greater than 1.0%, (>95% in certain cases).
- The phase is preferably chemically stable and crystalline
- The phase is preferably non-hygroscopic.

Once you have decided what crystal form you would like to develop, you now need a process to make that form. This is where engineering meets materials and analytical science. With the proper baseline information including form stability, solubility, and metastable zone width (MSZW), we can use our crystallization development strategy to design a robust isolation process to isolate the right form with the best yield, purity profile and productivity.

Let's assume your free form won't cut it for one of many reasons. Depending on the pKa and/or hydrogen bonding

motif's in your molecule, you may want to investigate salts or co-crystals. The salt selection process can be modified to meet your specific program needs. This includes screening for all and every type of situation, whether your compound is very difficult to crystallize or even if you cannot isolate the free form. Every selection, however, will involve manual screening for hits, scale-up and confirmation of salt formation, in addition to property analysis to determine which of the isolated salts best fits your program.

If you think co-crystal screening is the same as salt screening, think again! This is why we have worked with our prestigious SAB board to come up with what we feel is the optimal strategy for finding co-crystals. We've worked on some fairly odd co-crystals in live development programs, so we feel quite comfortable in characterizing and developing co-crystals.

Formulating the API for multi-dose tox and FIH studies must go hand-in-hand with the form selection process. The best solid form has to fulfill requirements from both the formulation and API processing perspective. This again is why we developed our SMART program for the most efficient development.

Let us assume your compound is BCS II/IV (aka brick dust) and no crystal form we've isolated will be acceptable from a bio-performance perspective. Now is the time to look into non-conventional formulations. Every formulation shop will attempt to sell you their "quick fix" to your problem. We've got no "skin in the game", we just want the fastest, most optimal development phase and formulation for your program. Our approach is a fundamental understanding of your API and properties that will drive the best non-conventional approach to take, if it is necessary at all. The worst feeling in the world must be wasting money on a non-conventional formulation when your beautiful, crystalline free base would have worked just fine. We can guide you as to when you need to go down that road or not.

Summary

- Identification of stable phase and formulation suitable for GLP safety toxicology and FIH studies.
- Know when salts/co-crystals/amorphous forms are necessary.
- Understand relevant crystal forms in your system.
- Have a reproducible process to isolate your desired API form.

References

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