Reducing development cost of pharmaceutical drugs through risk evaluation on particle and crystalline properties

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Crystalline properties of pharmaceutical drugs: Costs can be reduced during development through risk evaluation on particle properties.

Development of pharmaceuticals is always a very costly affair, but in order not to waste time and money, it is important to know the difference between “need-to-have” and “nice-to-have”.

This also goes for *polymorph (crystal) screenings*: You can easily spend a million dollars on experiments to test “all” possible scenarios. However, you can also choose to perform a slim screening where most common scenarios are tested - and in many cases, *enough* information is obtained from this approach.

At Particle Analytical we have specialised in a scientifically well-founded, but a very slim, test set-up for screenings- and we are therefore able to perform polymorph screenings is two weeks.

This set-up is sufficient for minimizing the risk that transformations of the drug will occur during development - which would otherwise be very critical and costly!

Background

Most pharmacists have heard the frightening story about Ritonavir: a drug against HIV that suddenly changed crystal structure, leading to a drastic reduction in bioavailability with severe consequences for the patients. The company (Abbott Laboratories) lost an estimated $250 million in sales as well as hundreds of millions of dollars to recover the original polymorph/crystal form. This case made everybody aware of the existence of polymorphs and the danger of not having the crystal form under control.

Still, most solid pharmaceuticals are dosed as crystals.

Almost all pharmaceuticals can arrange in different crystal lattices/polymorphs giving rise to different properties of the drug. As these polymorphs are not equally stable, a potential risk of a spontaneous transformation from a less stable to a more stable crystal form always exists.

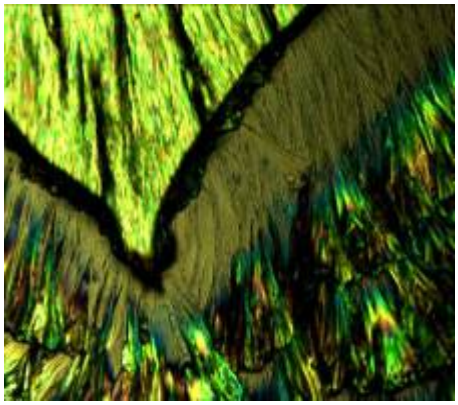

Figure 1: A real-life example of formation of different crystals during a heating experiment, as observed in a polarized light microscope.

The ICH guidelines state that a "polymorph screening," i.e., a search for other crystal forms, should always be performed to ensure control of the crystal form in development and thereby control of bioavailability and stability. However, nothing is stated about the *extent* of the screening.

Only imagination sets the limits for possible experimental procedures! The nature of crystallization is fascinating, but unfortunately it is also quite unpredictable: You never know how many forms you will find, and you can *never* be sure that you have actually found the *most* stable form.

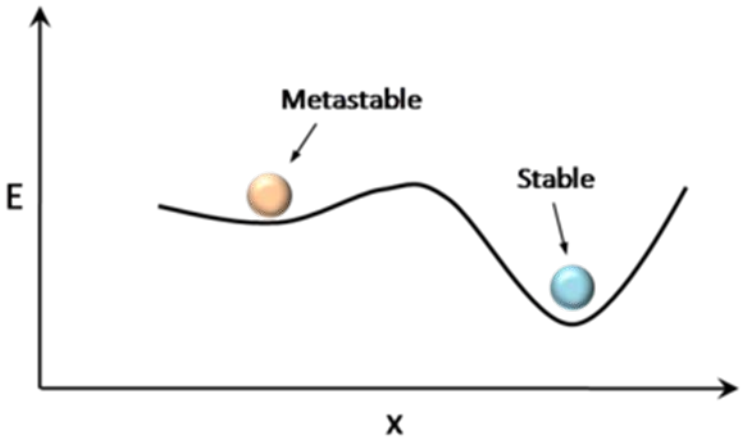

Figure 2: For almost all drugs, several polymorphic forms exist. At a given temperature, one of these forms will always be "more stable". However, additional metastable forms might exist, and these forms might not transform into the stable form easily. Thus, in many cases a metastable form is used in the drug product.

Some wise person once said that if you find only *one* polymorphic form, you did not search well enough. There are always different possibilities of ways for the molecules to attach; who knows if a new form will crystallize from a mixture of acetone and hexane at 43 degrees when adding water gently under stirring? Or maybe a form will crystallize when freezing a supersaturated water/ethanol solution fast in liquid nitrogen! It is not hard to picture that this screening can be quite time consuming and expensive. Herein lays a major challenge: understanding the difference between nice-to-have and need-to-have in order to properly balance the level of information needed and the development costs.

The experimental work put into a screening should be based on a risk assessment. What is the risk that other polymorphs exist (probably high)? What is the risk that they will have fundamentally different properties (depends on the molecule in question)? What impact will it have on bioavailability (depends on solubility and therapeutic window)? The more critical a transformation is, the more experimental work should be put into it. To create as many crystal forms as possible, you must create as many different environments as possible.

For instance, you will increase the possibility of a completely different conformation if you change the solvent properties maximally (e.g., water versus hexane). Further, creating a wide range of concentration might induce new ways of arranging. Overall, the experimental work does not have to be that extensive—as long as the experimental parameters are based on a scientifically well founded approach. The earlier you perform the screening the better, as this will de-risk your development program and potentially save you unpleasant and expensive surprises later on (like the Ritonavir case).

At Particle Analytical we used a well-known API to test our simple polymorph screening set-up. From the literature, this drug was known to have 6 different polymorphic forms. What we did during the screening, was to expose the drug to 3 solvents with very different properties with regard to physical properties. The drug in solution was further exposed to different temperatures during crystallizations (hot/cold/intermediate). Furthermore, the drug as powder was exposed to various temperatures, humidifies and pressures. The outcome of these experiments was that 5 of the identified 6 forms were formed (the last form was known to be very unstable). Thus, using a very basic set-up almost all forms were reproduced! If ”the right” conditions are selected, the extent of the screening can be reduced. Please contact us at info@particle.dk if you want to know more about the possibilities – or ask for a quote.

Youtube video of crystal melting and recrystallising:

https://www.youtube.com/watch?v=t0kRNcokR4U