Cocrystals can deliver unique physical properties, but taking full advantage of these improved properties requires a new approach to cocrystal formulation.

Pharmaceutical drug discovery efforts have yielded compounds with higher efficacy, but many of these compounds also have low water solubility, which can significantly hinder the drug product performance. Cocrystals are crystalline forms that can improve the water solubility of a drug compound, but in order to take full advantage of the improved cocrystal properties, a suitable cocrystal formulation is required. The current drug delivery approaches for cocrystals are failing to control the parameters critical to optimizing performance of poorly soluble cocrystallized drugs. Triclinic has been conducting extensive R&D in this critical area of cocrystal formulation and our exclusive experience makes us the preferred partner for your cocrystal project.

Cocrystal technology has significant advantages over competing technologies. The physical properties of cocrystals are superior to the physical forms used in other technologies targeting improved bioavailability, and the intellectual property protection is stronger, which creates an increased commercial incentive for adopting cocrystal technology. Triclinic has the experience and knowledge to make cocrystals of your API into a significant enabling technology that can be used to realize the full therapeutic potential of your API.
What is a cocrystal and why are they useful?

A cocrystal is a crystalline solid that consists of two or more molecular components (Figure 1). The molecular components consist of stoichiometric amounts of the API plus another molecule that does not form a salt, but rather a hydrogen bonded complex. This second molecule, referred to as the “coformer” must be a pharmaceutically acceptable non-toxic molecule in order to be acceptable to the FDA. Previously the choice of crystalline forms for an API that does not form salts was limited to any polymorphs or hydrates that could be identified. With cocrystals as an option, the large number of non-toxic coformers available creates an enormous potential for discovering a new and useful crystalline solid forms of an API.

The discovery and characterization of cocrystals has become a well developed field in the last decade and the potential for these new crystalline forms to improve physical properties of an API has been well documented; however, published approaches to delivering cocrystals in oral formulations highlights a critical gap that remains between the potential benefits that a cocrystal can provide and the knowledge required for the successful application of this technology to the goal of improving the in-vivo performance of poorly soluble drugs. The research efforts at Triclinic are filling this gap by creating a cocrystal drug delivery system that can be applied to the formulation of high solubility cocrystals of poorly soluble drugs.

Bridging the gap between cocrystal pre-formulation efforts and the formulation development group

Cocrystal screening processes are a relatively new addition to the pharmaceutical scientist’s toolbox, but formulation of cocrystals is an even more underexplored field. Triclinic is the only CRO with a dedicated cocrystal team with the proven, published experience required to not only screen, but also accurately characterize cocrystals of your API.

Cocrystals have unique aspects that make them behave quite differently compared to polymorphs and salts, and this make the solid form selection process atypical for cocrystals. We have seen viable cocrystals rejected from the development process because the routine characterization and analysis techniques used for evaluating dissolution rate were incorrectly applied to cocrystal systems. Triclinic has the hands-on experience with a wide variety of real-world cocrystal systems to help you avoid similar pitfalls. We have dedicated scientists that work exclusively on cocrystals, and working with Triclinic will bring this experience and focus to your team and improve the cocrystal development process at your company.
Cocrystals create supersaturating systems

In order to improve the bioavailability of poorly soluble APIs, a variety of different formulation approaches are available. For example, one could choose to use amorphous materials, salts, solid solutions, API dissolved in a liquid carrier, or a lipid base formulation. The majority of these approaches can be classified as supersaturating drug delivery systems. Cocrystals can also create supersaturated solutions, and with proper formulation cocrystals represent an alternative to traditional methods of increasing bioavailability.

A supersaturated system is one in which the concentration of the API in solution is higher than the solubility of the least soluble API crystal form that crystallizes under those conditions. A supersaturated system is not at equilibrium and demonstrating control over the dynamic between kinetic and thermodynamic solubility is essential in order to maximize the potential of a cocrystal tasked with improving the bioavailability of an API.

Transformation in supersaturated systems

The high solubility of many cocrystals containing poorly soluble APIs is what makes cocrystals potentially useful; however, once the cocrystal has dissolved, the supersaturated API can precipitate if the system is not adequately controlled. This rapid and uncontrolled precipitation can lead to incorrect conclusions about cocrystal utility if routine solubility and dissolution techniques are applied without carefully considering the unique aspects of a particular set of API cocrystals.

For example, intuitively a cocrystal with a higher solubility would be preferred, but in fact most often this is not the case. At a certain point the rapid dissolution gives rise to supersaturation levels that generate high nucleation and growth rates of the least soluble API crystal form. A cocrystal with 22X higher solubility will often, in practice, have a lower effective solution concentration over time compared to a cocrystal with 4X higher solubility (Figure 3).

Triclinic has worked with a wide variety of cocrystal systems and we have insight into the effects of dose, solubility, effective supersaturation level, supersaturation in the diffusion layer, particle size, agglomeration, nucleation and growth rate of the API, and how the use of surfactants and additives can alter the dissolution profile. Tell us about your cocrystal system and find out if we can help you improve the performance of your formulation.
Cocrystal formulation process for bioavailability improvement ...

Cocrystal dissolution experimental considerations

The methods used to characterize the dissolution profile of a polymorph or salt that does not precipitate as a lower solubility crystal form will be very different from the techniques required to accurately evaluate the dissolution profile of a supersaturating cocrystal. For example, the intrinsic dissolution profile under standard conditions will often suggest that the cocrystal of an API has essentially the same dissolution rate as the API, but this is rarely true. It is common for the cocrystal to immediately form a thin layer of precipitated API on the disk surface when exposed to aqueous media (causing the perceived solubility equal to the API), which often goes undetected in post-experiment XRPD or other spectroscopic analysis because the layer is so thin.

A more effective determination of cocrystal utility can be obtained using well designed non-sink powder dissolution experiments. Triclinic has the experience necessary to design, perform, and analyze powder dissolution profiles of your cocrystal in order to determine the real-world potential. This kind of analysis is necessary in order to confidently select the most appropriate cocrystal for further development (which might not be the most soluble cocrystal).

Two phase approach to creating a supersaturating system

The innovative aspect of Triclinic’s approach to cocrystal formulation is the identification and control over the supersaturation levels achieved during cocrystal dissolution. This is achieved by directly manipulating the cocrystal solubility using pharmaceutically acceptable excipients that are incorporated into a supersaturating drug delivery system. By using these excipients to tune a system for optimal performance, the highest practical supersaturated solution concentrations can be achieved while avoiding the precipitation of the API. The two phases of cocrystal formulation development are designed to 1) create and then 2) maintain API supersaturation. These two phases are often referred to in the literature as the “spring” and “parachute”.

1) Optimize the Spring
Study the transformation profile by observing transformation characteristics, performing particle size and agglomeration evaluation, determine the cocrystal dissolution rate/solubility and supersaturation levels tolerated, evaluate nucleation behavior of API, determine API crystal growth rate relative to CC dissolution, and determine the influence of surfactants on the system.

2) Optimize the Parachute
Increasing the solution concentration of a drug above the solubility level for a crystalline form of a drug will result in a driving force that will attempt to relieve that supersaturated state by crystallizing the API. Identifying crystallization inhibitors in screening experiments and incorporate them into the formulation (Figure 4).

Figure 4. Crystallization inhibitors are used to create a formulation that extends the metastable zone width of the supersaturation event. The inhibition of API crystallization in combination with generating the highest effective initial supersaturation levels will result in an extended period of the supersaturated state, which in turn will lead to higher plasma levels.
There is a considerable amount of effort in the pharmaceutical field being directed towards the use of cocrystals as pharmaceutical dosage forms, but without a rational and general approach to the successful formulation and delivery of cocrystals, the potential for taking advantage of the improved cocrystal properties and making meaningful, improved pharmaceutical products may not be realized in many cases.

An effective drug delivery system for cocrystals requires a simultaneous consideration of all variables that can affect the measurable pharmacokinetic (pk) parameters. Triclinic brings a unique insight that will complement the formulation experience in your own labs in order to identify and control these variables and maximize the potential of your cocrystal system.

Set up a meeting to talk with Triclinic about your cocrystal screening, characterization, formulation and intellectual property project.

**Targeting an in-vivo/in-vitro correlation**

The most pressing issue in the effort to validate cocrystals as viable alternative crystalline solid forms is to demonstrate that increased cocrystal solubility can be translated into increased bioavailability in a controlled predictable manner. To date, only a handful of cocrystal bioavailability studies have been published, but none of them illustrate a systematic approach to cocrystal formulation in order to maximize the utility of the cocrystal properties.

Internal R&D efforts at Triclinic have been directed at creating solid oral dosage forms for animal bioavailability studies with properties that maximize the dissolution profile of the cocrystal relative to the alternative solid forms of the API. Our approach typically follows these steps:

1. **Physical characterization of the cocrystal(s)**
2. **Characterization of the cocrystal transformation process**
3. **Demonstrate control over the powder dissolution profile**
4. **Formulation of an appropriate oral dosage form**
5. **Dissolution testing of the oral dosage form to optimize the system**

**Make Triclinic a partner in your cocrystal characterization and formulation projects**

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**Figure 5: A 1 mg sample from 0-30 minutes had an AUC of 0.095 whereas the 2 mg dose had an AUC of only 0.051. The higher dose caused a correspondingly higher degree of supersaturation and this in turn caused a more rapid nucleation and crystal growth rate compared to the lower dose data. This caused a lower exposure for the higher dose. The process of evaluating the dose effect in dissolution experiments is an important aspect of the formulation process.**
Request a No-Obligation Scientific Consultation!

*We are happy to discuss your specific analytical needs and our suggested approach - please contact us.*

**Contact:**

Scott L. Childs, Ph.D.
Triclinic Labs, Inc.
1201 Cumberland Avenue, Suite S
West Lafayette, IN 47906 USA

Phone: +1 404-377-7876
Fax: +1 765-588-6200

schilds@tricliniclabs.com

[www.tricliniclabs.com](http://www.tricliniclabs.com)

Triclinic Labs was founded in 2009 by David E. Bugay, Shawn C. Comella, G. Patrick Stahly and Scott L. Childs. Those individuals were the scientific and marketing drivers behind the growth of SSCI, a solid-state contract laboratory that was an industry leader prior to its recent acquisition. Collectively, the team has over 75 years of contract research experience, conducted more than 400 solid-form screening and selection projects, countless analytical experiments, consulted for 90% of the top 50 global pharmaceutical companies, and provided expert services in more than 100 intellectual property matters worldwide.