Cocrystals in the pharmaceutical and fine chemicals industry: from an option to an opportunity

Introduction

In the drug discovery and development arena it is well known that the choice of the right solid form can have a dramatic influence on the successful development of an active pharmaceutical ingredient (API). Solid forms can shape the pharmacokinetic and formulation properties of a drug candidate to such an extent that the right solid form can be key to the success of the project. A suboptimal one can even compromise the whole project. Therefore, to avoid unpleasant surprises during the development phases of a product, it is strongly recommended to address solid form studies in the early phases, even when a molecule is still in the discovery stage.

In fine chemicals manufacturing, solid forms also play an important role, mainly related to purifications, chiral resolutions and the stability both of the final products and intermediates. Undoubtedly, crystallization is a preferred method to purify products and resolve racemic mixtures in the fine chemicals industry. The outcome of a crystallization step or the stability of a product depends on several parameters, a crucial one being the choice of the appropriate solid form to crystallize. The selection of the right solid form can facilitate the fine tuning of a crystallization process to provide a stable product which is easy to filter and with the desired purity.

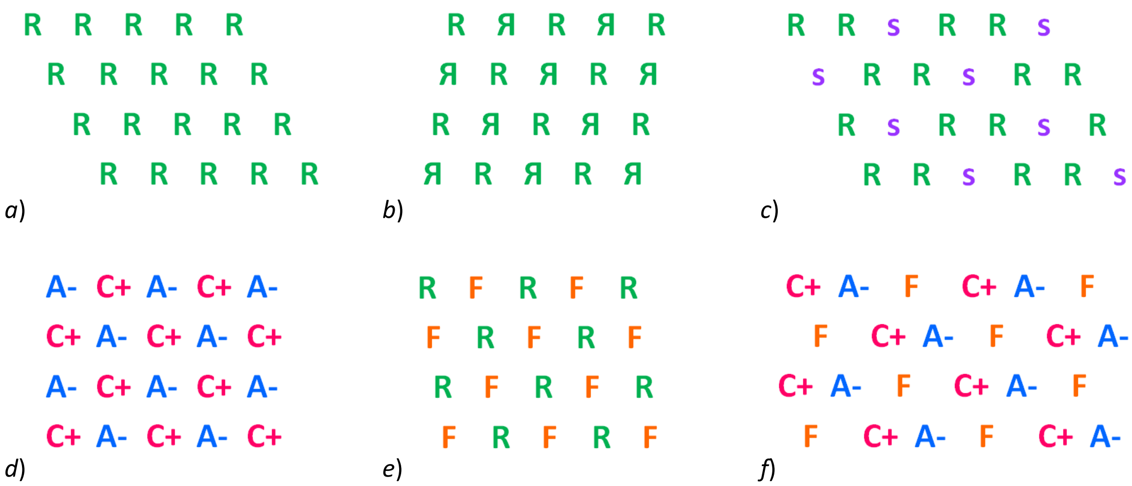
In the pharmaceutical and fine chemicals industries, salts and single component solids have been the classical targets to tackle the different topics mentioned above. Recently, however, cocrystals have emerged as a new alternative that has stirred the interest of both sectors since cocrystals show unique applications and interesting advantages when compared to other solid forms.

Types of solid forms

Depending on the composition of their solid form, many organic compounds can be classified according to the following categories:

- Mono-component: just one compound forms the solid material.
- Multi-component: the solid comprises more than one compound. The component of interest (be it an API or an intermediate) can be found together with one or more additional components, according to the nature of which we can find:
    - Solvates or hydrates. In the solid form, the API (let's assume the component of interest is an API) is bound to one or more molecules of solvent. When the solvent is water then we refer to hydrates.
    - Salts. The solid form is composed of an ionized API and its counter-ion. The vast majority of APIs in the market are salt solids.
    - Cocrystals. The API crystallises with one or more neutral components. The interactions between the counterparts are weak intermolecular forces like hydrogen bonds, van der Waals interactions and π-π stacking.

This is a very simple classification and the reality can be much more complex, *e.g.*, a salt can be solvated or a salt can also cocrystallize with an additional neutral guest. In the latter case, we talk of a cocrystal of a salt.



Schematic bidimensional representation of the structure of: (a) and (b) two polymorphs of a mono-component crystal; (c) a solvate; (d) a salt; (e) a cocrystal; and (f) a cocrystal of salt. (**R**: drug molecule, **s**: solvent molecule, **A-**: anionic moiety, **C+**: cationic moiety, **F**: neutral coformer molecule)

According to the internal molecular arrangement of the components, solid forms can be also classified in two different groups:

- Amorphous materials when, in the internal structure of the solid form, the orientation and the position of the components do not follow any particular pattern so there is no internal organized structure and molecules are attached one to another more or less in a random fashion; or
- Crystalline materials, the opposite situation, in which all the constituents have a specific position in space following an orderly repeating pattern.

A common phenomenon found in solid APIs is polymorphism. This is observed when, for the same chemical composition (the same components), a solid can exhibit different crystalline arrangements. As an example of polymorphism, paracetamol it is known to exist in three different crystalline structures [a], and we say it has three polymorphs.

In drug development, crystalline salts and crystalline mono-component systems have been the most popular types of solid forms due to ease of obtention, higher stability, and more suitable pharmacokinetic and pharmaceutical properties compared to amorphous forms.

Similarly, in process development, the most preferred solid forms are crystalline salts due to their simple obtention, improved filtration, higher purity and overall ease of handling.

However, in some occasions, these preferred solid forms cannot be obtained or do not provide the desired properties. It is in these situations when cocrystals can be the way to go.

Cocrystals

The use of cocrystals in the pharmaceutical sector (generic and innovator) is growing steadily. The draft guidance *Regulatory Classification of Pharmaceutical Co-Crystals* issued quite recently by the FDA [b], will certainly generate even further interest in these industries for this promising solid form technology. This draft provides basis for the regulation of pharmaceutical cocrystals for NDA or ANDA submissions and paves the way for cocrystals in future pharmaceutical products.

The physicochemical properties of a solid form have a major influence on the biopharmaceutical properties of an API and on the performance of many chemical manufacturing processes. Since different solid forms can exhibit different physicochemical profiles, the use of cocrystals gives scientists a new tool to overcome those problems associated with suboptimal properties of a solid form.

One of the major advantages of cocrystals is that they can be formed with non-ionizable molecules where salt formation is not possible. Therefore, for those molecules that have no acidic or basic moiety, forming cocrystals gives a straightforward access to different solid forms. However, it is important to bear in mind that it is also possible to form cocrystals of ionizable products or their salts.

Cocrystals have found an array of different applications:

- For pharmaceuticals (innovators and generics).
    - Improvement of pharmacokinetic properties. One of the main issues associated with products in research and development pipelines is the obtention of a suitable pharmacokinetic profile (bioavailability, half-life, Cmax, AUC). Many candidates coming from drug discovery programs are abandoned because of their unsuitable pharmacokinetic profile, where in most cases a low dissolution rate is responsible for an inefficient absorption of the API. There are already numerous examples in the literature reporting cocrystals of class II and IV APIs (biopharmaceutical classification) intended to increase their dissolution rate and consequently their absorption rate [c].
    - Improvement of pharmaceutical properties. Cocrystals can also be used to improve pharmaceutical properties of APIs (among others stability, hygroscopicity, flowability and compressibility) [d, e].
    - Intellectual property. Pharmaceutical cocrystals can be patented as a product, a key consideration for companies aiming to broaden the patent scope of their products, and can be used for lifecycle strategies management or to circumvent solid form patents of a given product.
- For fine chemicals manufacturing companies.
    - Purification. Cocrystals have been demonstrated to be complementary or, at least, equal to salts for purification purposes, so products can be isolated using

cocrystallization processes in order to obtain the desired specifications [f]. In certain situations, cocrystals can be the preferred purification method, *e.g.*, an oily product that cannot form salts can, as a cocrystal, be converted into a solid material which, in turn, can be easily crystallized.

- Resolution of racemic mixtures. Cocrystals have also found applications in the chiral resolution of products. Again, this approach is very attractive for compounds that cannot form salts, or where classical resolution by diastereomeric salt formation fails and industrial chiral chromatography is a costly alternative. Diastereomeric cocrystallization can also be applied where IP restrictions preclude salt crystallization. An example that illustrates this approach is the resolution of omeprazole to obtain esomeprazole using a process developed at Enantia [g]. Also in relation to chiral molecules, cocrystals have been said to be better than salts for absolute stereochemistry determination [h].

- Stabilization of products. For products that are not stable as the parent compound or salt derivatives, cocrystals can also be considered a way to improve such stability.

When compared to other solid forms, cocrystals also show some advantages:

- Industrialization. Finding cocrystals for a particular product is not so obvious a task as salt screening can be. This can be attractive for many companies since the approach can confer a certain technological barrier to competitors. Once the right coformer has been found, industrializing a cocrystallization process is not necessarily more complex than for a salt and no special equipment is needed.

- Long list of coformers. There is a larger number of acceptable cocrystal formers (coformers) than acids or bases for pharmaceutically acceptable salts.

- Stability. When compared to certain solid forms, amorphous materials for example, cocrystals tend to be more stable. Additionally, cocrystals are less prone to show polymorphism than other solid forms due to their higher structural complexity.

Conclusions

From a technical perspective, it is clear that cocrystal technology is able to solve problems that are difficult to tackle using more classical techniques. On occasion, they can provide a more straightforward solution, or simply the only solution, to a variety of problems. Furthermore, cocrystals are not just a laboratory curiosity but a real applicable technology with processes already running at industrial scale.

Cocrystals have stirred significant interest not only for their applications but also for being a remarkable business opportunity. For instance, for biopharmaceutical companies, cocrystals can contribute to R&D output since products rejected from pipelines due to poor pharmacokinetic properties can now be revisited in their cocrystal forms. Cocrystals should also be taken into account when designing lifecycle management strategies for products in the development stage. In the case of fine chemicals companies, the introduction of cocrystal technologies into a process can provide a competitive advantage when facing, for instance, a process that is patent protected. In the face of a protected resolution or purification process using standard crystallization steps, a cocrystallization approach can offer an exclusive opportunity to tackle that project.

Enantia has a track record in applying cocrystals to biopharmaceutical and fine chemicals projects [i]. Although a significant number of compounds are prone to form cocrystals, the conditions to obtain the first samples of such cocrystals tend to be tricky and non-obvious. Enantia's team has its own particular approach to cocrystal screening and cocrystal scale-up, offering a combination of rational design and a powerful set of synthetic and analytical techniques.

References

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