PHARMACEUTICAL COCRYSTALS AND THEIR APPLICATION

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Introduction

When speaking of multicomponent solid forms of organic molecules, terms such as solvates, hydrates, salts and cocrystals are often used. From these forms, the cocrystals have recently gained much attention. By the term cocrystal, a stoichiometric multicomponent solid with host and guest molecules arranged in a common crystal lattice, is meant. In the case of pharmaceutical cocrystal, one of the components is an active pharmaceutical ingredient (API); the other is a pharmaceutically acceptable coformer [1]. In the generic pharmaceutical industry, cocrystals are used to widen the portfolio of solid forms of APIs, from which the form with the optimal physico-chemical properties is chosen for the drug product formulation.

To obtain as many solid forms of API as possible, a systematic screening is undertaken during the early development stages of the compound. Thus, polymorphs and solvates are obtained from various solvent-based techniques. When combining API to counter ions or coformers (in many cases the counter ions and coformers are the same compounds), a salt or a cocrystal can be prepared. Such forms can be further screened for polymorphs and solvates/hydrates.

The uniqueness of the novel crystalline form is usually confirmed by X-ray crystallography. In the past, the powder X-ray diffraction (PXRD) patterns were used to differentiate between the forms of pharmaceutical substances (especially in patent literature); more recently, single crystal X-ray diffraction is the most common technique for structure determination.

In the presented case studies, two cocrystals of pharmaceutical substances are introduced and their application in the industry is discussed.

Methods

Single crystal X-ray diffraction (SXRD) was used for structure determination. Data were collected using an Xcalibur PX^{TM} four-circle diffractometer with OnyxCCD area detector and graphite monochromated CuK radiation.

Powder X-ray diffraction (PXRD) was used for identification of the phases. Data were collected at room temperature with laboratory X´PERT PRO MPD PANalytical diffractometer with parafocusing Bragg-Brentano geometry, using CuK radiation (= 1.54184 Å), measurement range 2- 40° 2 , a step size of 0.01° 2 and a counting time of 0.5 s/step. Samples were ground in an agate mortar and stacked on a Si holder (zero background).

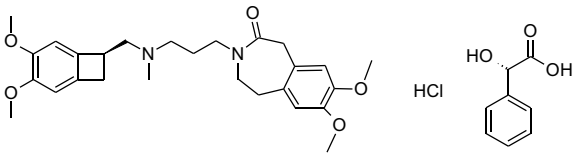

Figure 1. Molecular formula of the cocrystal of ivabradine hydrochloride.

Results and discussion

Case study 1

A pharmaceutical hydrochloride salt used for the treatment of angina pectoris (Figure 1) forms various polymorphs and it could be prone to form cocrystals.

Therefore, the cocrystal screening was performed, using 25 coformers. Slow crystallization from ethanol was chosen as a screening method. A hit with (*S*)-mandelic acid was identified. Upon structure determination from SXRD

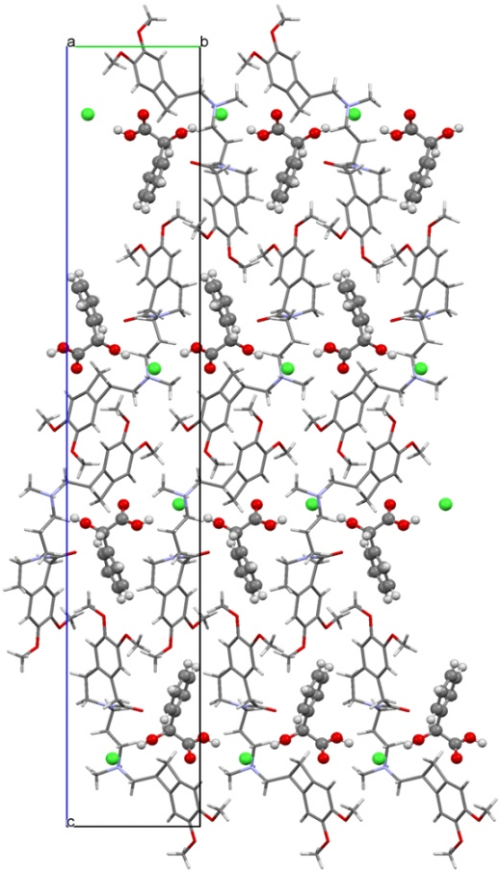

Figure 1. The packing of cocrystal ivabradine hydrochloride (*S*)-mandelic acid (1:1). H-bonds are formed between hydroxy group of (*S*)-mandelic acid, chloride anion and carboxyl group of the next (*S*)-mandelic acid molecule.

Table 1. Crystallograhic data of the cocrystal.

System	Orthorhombic
Space group	P $2_12_12_1$
a (Å)	7.4447(4)
b (Å)	8.5027(4)
c (Å)	52.159(2)
(°)	90
(°)	90
(°)	90
Volume (Å^3)	3301.67

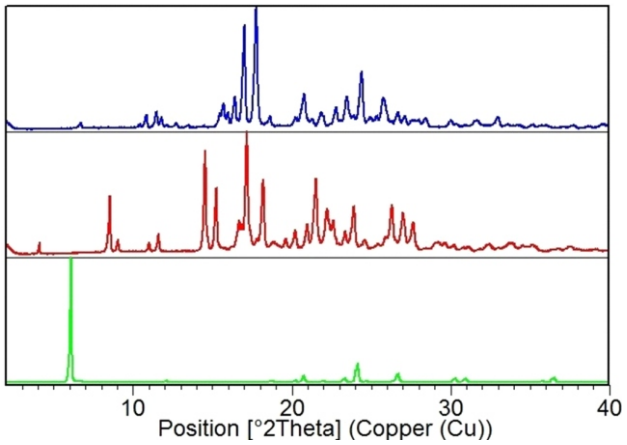

Figure 3. Powder patterns of a hit (top), API in the screened form (middle) and a coformer (bottom). The pattern of hit does not correspond with any previously described forms of the API.

(Table 1) and characterization by X-ray diffraction (Figures 2-4), the formation of cocrystal was confirmed [2].

The properties of the cocrystal were then studied, as it follows: from dynamic vapor sorption curves it was concluded that the cocrystal was not hygroscopic; the melting point of 160 °C was determined by differential scanning calorimetry. The Raman and infrared spectra confirmed the interactions of (*S*)-mandelic acid functional groups within chloride anion of ivabradine salt as were observed from SXRD determined structure. Moreover, the stability of the cocrystal was compared with two other solid forms of the

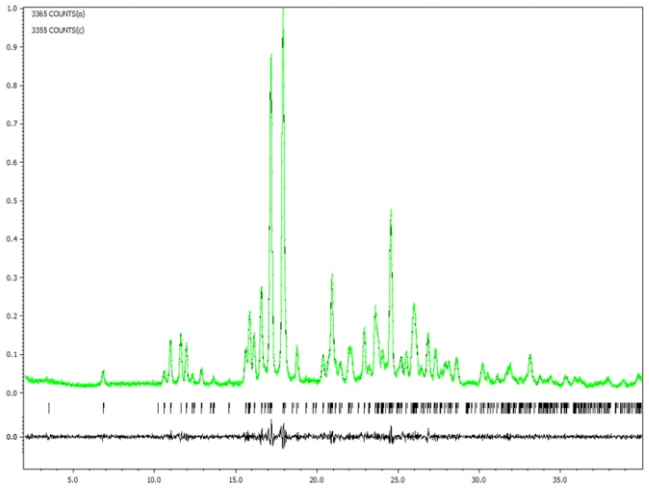

Figure 4. Final Rietveld plot of the cocrystal showing the measured and calculated data. Calculated Bragg positions are shown by vertical bars.

API: Form , which is present in the original drug product, and Form II. The samples were treated for 3 and 10 days at 0 and 75% RH. The physical and chemical stability were tested by PXRD and UPLC, respectively (Table 2).

Both physical and chemical stabilities were satisfactory, selecting the cocrystal as a drug form comparable with Form , which is used in the original drug product. After the optimization of formulation process, the generic drug product with the cocrystal can be used for early market entry (basic patent expiry).

Case study 2

In this study, the cocrystal of the API with fumaric acid (2:1) was an undesired stable form, appearing as impurity in the developed drug product of a prodrug (Figure 5).

Relationship between the desired pharmaceutical salt (fumarate, 1:1) and the cocrystal (2:1) was investigated to avoid conversion to the cocrystal during the formulation process. Both the excipients (their pH) and formulation process (wet granulation) could contribute to the conversion, causing physical impurities in the bulk [3]. Firstly, pH dependent conversion of pure API was studied. It was found that increased pH accelerated the conversion of API to the cocrystal. The most basic excipient in the formulation was identified: Croscarmellose sodium (Cros.Na), which played the role of the disintegrant in the tablet and could be responsible for the conversion. Therefore, the pla-

Table 2. Comparison of physical and chemical stability of solid forms of ivabradine hydrochloride: polymorphs II and and the cocrystal with (*S*)-mandelic acid.

Stress conditions	**Form II**		**Form**		**cocrystal**	
	Phys.	Chem.	Phys.	Chem.	Phys.	Chem.
3 days 80 °C	Form II +	0.15 OK	Form	0.05 OK	cocrystal	0.05
3 days 80°C/75% RH	Form	2.12 x	Form	0.05 OK	cocrystal	0.05
10 days 0% RH	Form II	0.15 OK	Form	OK	cocrystal	0.05
10 days 100% RH	Form	0.14 OK	Form	0.05 OK	cocrystal	0.05

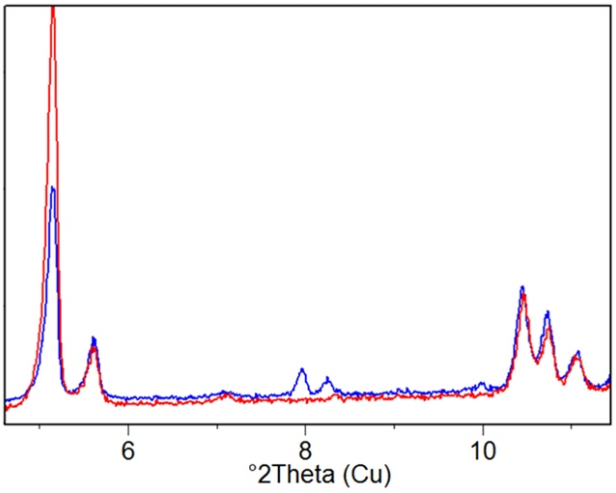

Figure 5. Detail of powder pattern of the desired salt fumarate (red pattern) and the bulk containing cocrystal admixture (blue pattern).

Table 3. Placebo mixtures pH measurement. The measurement divided the disintegrants to those with pH above and below the pK_a of the desired salt.

Mixture without API and with disintegrant	Measured pH when 5 ml of water was added
No disintegrant	4.7
Croscarmellose Na	6.0
Croscarmellose Ca	5.2
Carboxylmethylstarch	6.4
Maise starch	5.0
Hydropropylcellulose Type LH21	4.9
Crospovidone	4.4

cebo mixtures of excipients with various disintegrants were prepared, differing in pH (Table 3). When API was added to the mixtures and the mixtures were granulated with water, it was found that three disintegrants (Cros.Na, croscarmellose calcium - Cros.Ca and carboxymethylstarch - CMS), whose pH was above 5.2 (pK_a of the pharmaceutical salt = 5.2), supported the conversion to the cocrystal. The powder patterns of the mixtures with other tested disintegrants (with pH lower than 5.2) corresponded to the desired phase (Figure 6).

The stabilization of the pharmaceutical salt in the generic drug product was thus achieved by pH adjustment of suitable disintegrants [4].

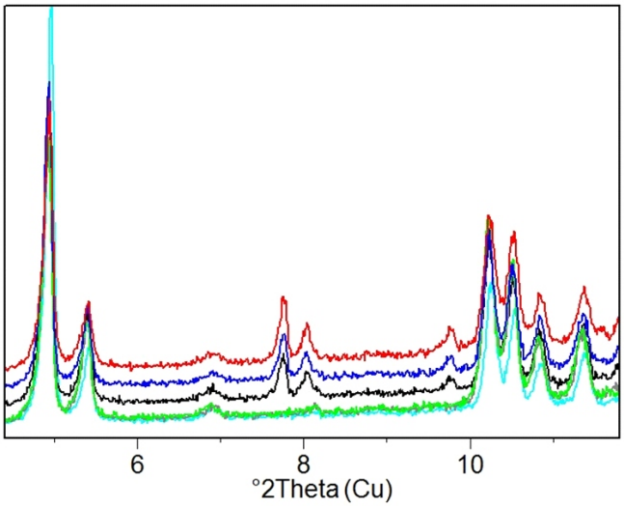

Figure 6. Powder patterns of mixtures of API, excipients and different disintegrants: Red (Cros. Na), blue (Cros.Ca) and black (CMS) patterns contain admixture of the cocrystal.

Conclusion

The cocrystal with (*S*)-mandelic acid was chosen as the form with optimal properties for formulation and appears to be an exemplary pharmaceutical cocrystal. In the other case study we have introduced a cocrystal with fumaric acid which is an undesired phase in the developed drug product. Even though the drug products formulated within cocrystals of APIs are not yet common, the pharmaceutical industry has already adapted to the large scale cocrystal production and formulation.

Acknowledgment

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