Co-crystals and their advantages for APIs with challenging properties

KEYWORDS: co-crystal, active pharmaceutical ingredient, solid state property, bioavailability, hygroscopicity.

Abstract

Active pharmaceutical ingredients (APIs) often have disadvantageous solid state properties. These properties depend on the solid state and can be modified by changing the solid form (polymorphs, solvates, hydrates, salts and co-crystals). The co-crystal concept can be applied to the vast majority of solid APIs and allows, in contrast to all other solid-state modifications, to increase in many cases the dissolution-rate even for non-charged APIs without compromising on the thermodynamic stability.

In this paper new co-crystals of APIs with improved properties regarding physical stability and bioavailability are presented. It is discussed that the new solid state properties could lead to a second generation drug product with easier formulation, lower limitations for storage, lower amount of API per drug product with all its improvements regarding safety and costs.

INTRODUCTION

Screening a vast number of chemical compounds is the first part of drug discovery. After an active pharmaceutical ingredient (API) with good biological activity, toxicology profile etc. is found, formulation is the next step to make a drug product. As further optimisation of the compounds concerning their biological performance using in-vitro enzyme activity leads to more and more lipophilic compounds, formulation development often has to deal with low bioavailability. The development of co-crystals can be one possibility to improve bioavailability without altering the API per se. Besides bioavailability, several other properties can also be improved by solid state engineering, e.g. dissolution rate, physical stability, hygroscopicity, chemical stability, purification process-ability and flowability (Table 1).

Table 1. Properties for new generation drugs.

Even after the first successful launch of an API formulation in the market, improved properties can be the basis of a better product with easier formulation and lower production or storage requirements (1). It can be an interesting feature for new drug products without starting to screen for new molecules (2). Therefore, co-crystals are widely discussed as one option when solid state properties need to be modified (3).

A co-crystal consists of at least two components that are solid at room temperature (Figure 1). In contrast to salts, at least one of the components is unionized, so that the co-crystal concept can also be used for APIs that cannot be ionized. Co-crystals are new solid state forms that have new solid state properties. Even solubility related problems of salts can be improved by making a co-crystal (4).
As discussed, improving solubility related properties is often the main topic when developing formulations of APIs. Faster dissolution and higher solubility leading to better bioavailability can also be obtained by changing the solid state form in other ways than using co-crystals, e.g., using metastable polymorphs, salts, amorphous API or solid solutions/dispersions in polymers. In contrast to co-crystals and salts, metastable polymorphs, amorphous API or solid dispersions lack the thermodynamic stability of the solid form of the API in the formulated product. The amorphous form and metastable forms are per definition not the most stable form and can convert to more stable crystalline forms. For solid solutions it is difficult to know, if a thermodynamic stable solution is obtained [5]. Solid solutions may be stable but always need to be controlled whether re-crystallisation occurred. Especially for amorphous API and solid solutions/dispersions the improvement of increased dissolution rate or higher kinetic solubility can quickly vanish after first crystal seeds of the stable crystalline form appear. Such seeds trigger the crystallisation of the API into the stable solid form. Improvement with regards to bioavailability can therefore be limited.

To the best of our knowledge escitalopram oxalate tablets are the only marketed drug product containing a co-crystal. The API received FDA approval in 2002 as escitalopram oxalate. At that time it was not known that in fact it is a co-crystal consisting of escitalopram oxalate and oxalic acid, a co-crystal of a salt [6]. In the meantime FDA and EMA have presented discussion papers on how to classify co-crystals [7, 8] and new co-crystals entered clinical trials [9]. While the published discussion papers serve as interim guidelines only, they nevertheless set a trend: EMA suggests to deal with co-crystals similar to polymorphs and salts and FDA considers co-crystals as drug product intermediates. Agrochemists have shown how new properties of co-crystals can be used in new product formulations and successfully launched in the market: Faban® is a new innovative formulation containing a co-crystal of two fungicides Pyrimethanil and Dithianon [10]. The co-crystal reduces the volatility of Pyrimethanil and results in higher levels of disease control.

RESULTS AND DISCUSSION

Example 1: Light stability

Light stability is an issue for the drug substance as well as for the drug product as light needs to be controlled or excluded during drug substance synthesis, storage and drug product formulation and storage. Higher light stability could lead to easier formulation and packaging while keeping or improving shelf life time of the product. Rosuvastatin is a lipid lowering drug substance. It inhibits the HMG-CoA reductase and is formulated as amorphous hemicalcium salt. The amorphous salt is light sensitive. Several crystalline forms of Rosuvastatin hemicalcium are reported [11]. The vanillin co-crystal of Rosuvastatin hemicalcium overcomes the light sensitivity [12]. A remarkable improvement regarding degradation can be detected by HPLC (Table 2) and by eye (Figure 2). The new solid state form also shows a good thermal stability and is easy to prepare. Further tests regarding formulation showed that it is directly compressible and an uncoated tablet from a standard dry formulation can be developed.

<table>
<thead>
<tr>
<th>solid form of Rosuvastatin hemicalcium salt</th>
<th>HPLC purity 0 d (area%)</th>
<th>HPLC purity 15 d (area%)</th>
<th>Δarea% 15 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>amorphous (sample 1)</td>
<td>98.43</td>
<td>89.88</td>
<td>-8.55</td>
</tr>
<tr>
<td>amorphous (sample 2)</td>
<td>99.05</td>
<td>88.50</td>
<td>-13.15</td>
</tr>
<tr>
<td>crystalline, form A</td>
<td>99.94</td>
<td>94.15</td>
<td>-5.49</td>
</tr>
<tr>
<td>co-crystal with vanillin 1.05</td>
<td>96.60*</td>
<td>97.33*</td>
<td>-1.67*</td>
</tr>
</tbody>
</table>

Table 2. Light stability results of Rosuvastatin solid state forms.

Example 2: Hygroscopicity

Hygroscopicity describes the water uptake when applying different relative humidity. The more hygroscopic the compound the higher the difference in the water content at different relative humidity. APIs that change water content during formulation processes and in the final formulation need to be handled with more care with regard to climate control during production and packaging. Nilotinib is a tyrosine kinase inhibitor. It is used in the treatment of chronic myelogenous leukemia. The drug product is a formulation of the Nilotinib hydrochloride monohydrate. Nilotinib hydrochloride exists in several different solid forms [13]. The selected monohydrate of the API salt is slightly hygroscopic. Hygroscopicity can be reduced by producing a co-crystal with fumaric acid. The crystal structure proves that in the 1:1 co-crystal of Nilotinib hydrochloride and fumaric acid, Nilotinib is protonated and fumaric acid is neutral. The hygroscopicity of Nilotinib hydrochloride monohydrate and the co-crystal of the mentioned salt [14] is shown in Figure 3. On the basis of hygroscopicity classification of pharmacopoeia [15], the hydrochloride salt is slightly hygroscopic whereas the co-crystal of the salt is not hygroscopic. Reduced hygroscopicity simplifies drug substance handling during manufacturing and storage of the drug product; shelf life time may be increased and packaging costs reduced.

Figure 2. Amorphous Rosuvastatin hemicalcium salt (left) and Rosuvastatin hemicalcium salt vanillin co-crystal (right) after 15 d exposure to sun light.

Figure 3. Hygroscopicity of Nilotinib hydrochloride monohydrate vs. Nilotinib hydrochloride fumaric acid co-crystal.
Example 3: Various polymorphic forms
If different solid forms of the API exist, the producer has to make sure to always obtain and retain the desired form. During formulation and storage the solid form should not change. A special control of the solid form has to confirm the registered form throughout the whole process.

Nilotinib hydrochloride exists in several crystalline forms: dihydrate, monohydrates, anhydrates and solvates (14). A new solid form that does not show polymorphism would be a great advantage. The fumaric acid co-crystal of Nilotinib hydrochloride in all experiments only resulted in one crystalline form. This form is therefore much more stable under various conditions regarding the crystalline form compared to the selected hydrochloride salt.

Example 4: Solubility related properties: kinetic solubility, dissolution rate, bioavailability
As mentioned above, low solubility leads to low dissolution rates and bioavailability. APIs with low solubility are bundled in biopharmaceutics classification system (BCS) classes II and IV. Many projects of formulation scientists deal with increasing solubility of these APIs. Besides its hygroscopic behaviour, the marketed solid form of Nilotinib also shows disadvantageous solubility. Although the Nilotinib hydrochloride salt was selected as API form for the drug product, it has a very low bioavailability.

Results of dissolution experiments of Nilotinib hydrochloride and its co-crystal at pH 1.2 are shown in Figure 4. The co-crystal has a much higher dissolution than the hydrochloride salt. The co-crystal also reaches a much higher kinetic solubility which is stable for 2 h, the time of the experiment. This higher solubility is a kinetic effect as the solubility of the pure Nilotinib hydrochloride is lower and crystal seeds of the hydrochloride would lead to crystallisation of this crystalline form. However, retaining a metastable solubility for 2 h is sufficient to enhance the absorption of the API due to higher concentration gradient.

To make use of solubility related properties, in vitro experiments like increased dissolution rate and higher kinetic solubility need to be confirmed by tests of the bioavailability. Studies with several APIs showed that the higher dissolution rate and higher kinetic solubility in buffer media can increase bioavailability by 70% without further formulation development (2, 16). The same can be shown for Nilotinib hydrochloride. The bioavailability of different solid state forms of Nilotinib was tested. Without formulation optimisation the fumaric acid co-crystal showed doubled bioavailability compared to the hydrochloride salt, just by simply using the co-crystal of the API.
EXPERIMENTAL SECTION

Rosuvastatin vanillin co-crystal
Rosuvastatin was dissolved in acetonitrile and diluted in water (1:1). HPLC was performed on an Agilent 1100 Series using a Waters Acquity UPLC using a Waters Acquity BEH shieldC18 1.7μm 2.1 x 50mm column at 25°C. 10μL sample solution were injected. Eluent A (water + 0.005 M ammonium formate pH 4.0) and eluent B (acetonitrile) were set as following: 0.0 min: 90% B, 3 min: 5% B, 4 min: 90% B; 1.0mL/min. Concentration was detected at 245±4nm. Nilotinib: Samples were obtained in aqueous buffer pH 1.2 and diluted in water (1:10 to 1:20). HPLC was performed on an Agilent 1100 Series using a Waters Xterra RP18 250x4.6mm column at 25°C. 10μL sample solution were injected. Eluent A (water + 0.1% H3PO4, 85%) and eluent B (0.1% H3PO4) were set as following: 0.0 min: 60% B, 28.5 min: 64% B, 43.0 min: 64% B, 43.1 min: 60% B, 50.0 min: 60% B; 1.0mL/min. Concentration was detected at 245±4nm. Nilotinib hydrochloride fumaric acid co-crystal was prepared according to WO2014/060449 by re-crystallisation of nilotinib free base, fumaric acid and hydrochloric acid in methanol (14).

Light stability
20 mg to 70 mg of the samples were placed in closed Supelco glass vials (white glass, air atmosphere) and exposed to sunlight for 15 days.

HPLC
Rosuvastatin: Samples were dissolved in acetonitrile and diluted in water (1:1). HPLC was performed on an Agilent 1100 Series using a Waters Acquity UPLC using a Waters Acquity UPLC BEH shieldC18 1.7μm 2.1 x 50mm column at 40°C. 1μL sample solution were injected. Eluent A (acetonitrile / water 9/1 + 0.1% H3PO4, 85%) and eluent B (acetonitrile) were set as following: 0.0 min: 90% B, 3 min: 5% B, 4 min: 90% B; 1.0mL/min. Concentration was detected at 245±4nm.

Dissolution experiment
Drug substance was suspended in aqueous hydrochloride pH 1.2 and stirred for 120 min. Every 10 min a sample is collected, filtered using a 0.2 μm filter and the concentration is determined using HPLC. After 120 min the solid material was collected and analysed using PXRD.

CONCLUSION

Solid state properties differ depending on the crystalline form. By changing the solid state form of the API, properties like solubility, bioavailability, chemical or physical stability can be improved. Solid state forms can be polymorphs, solvates, hydrates, salts, co-crystals or amorphous forms. The special advantage of co-crystals is that the co-crystal concept can be applied to the majority of APIs and that important physical parameters can be improved including dissolution rates and bioavailability without compromising on the thermodynamic stability. These few examples of co-crystals of existing APIs leading to new solid state properties show that co-crystals are highly attractive not only for new APIs but also for registered APIs, where improvements of API properties open possibilities for a second generation drug product. A new, better drug product can be thought without starting a screening for a new drug.

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REFERENCES

15. European Pharmacopoeia B.D. chapter 5.11.