Designing a New Multi-Component API Form Based on a Known Structure

Aim

This use case addresses the topic of how to design new multi-component, crystalline forms of an API purely based on the knowledge of one or more existing forms. The production of new multi-component forms will allow the physico-chemical properties of the solid to be modified (e.g. solubility, crystal habit and stability) without changing the biological efficacy of the API compound. If an isostructural series of API forms can be generated in this way, then tuning of physical properties may even be feasible.

Introduction

Pharmaceutical co-crystal design has commonly been based on using well known hydrogen-bonding synthons[1] like the carboxamide $R_2^2(8)$ dimer[2] or the strong carboxylic acid to pyridine interaction.[3] Even the strongest synthons do not form 100% of the time though,[4] and it is also possible that the API that is being worked upon does not contain a functional group for which an obvious strong synthon can be selected.[5] In the design of a new solid form it is therefore sensible to utilise whatever structural information is available pertaining to the API of interest.

For a given API it is often the case that there is some structural information about solid forms, whether it is a known polymorph, a salt structure, a co-crystal or even a solvate. These known structures can potentially be used as seeds of knowledge to determine further, structurally-related, solid forms.

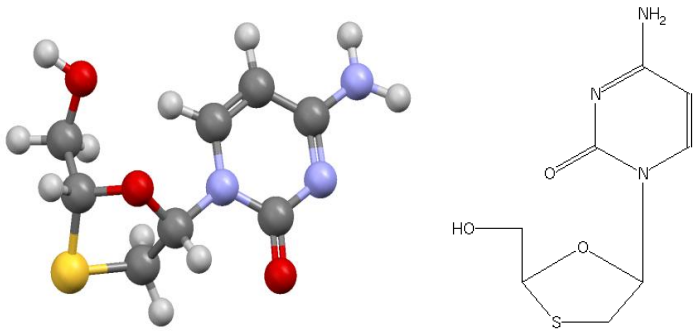

Figure 1 - Lamivudine chemical structure

The API lamivudine (Figure 1), marketed as EPIVIR, is one of the most commonly used nucleoside reverse transcriptase inhibitors (NRTIs) for anti-HIV drug therapy. There are currently 8 known solid forms of lamivudine including one pure form, two hydrates, two co-crystals and three salt structures

- each of these structures contains useful data about the intermolecular packing of the API. Martins and co-workers[6] observed that the known lamivudine saccharinate salt structure[7] could potentially be modified to replace the saccharinate guest with an alternative counterion whilst keeping the host (API) framework intact. This use case is based primarily on their work and is focussed on a salt structure, but the principles and methods shown are equally applicable to co-crystals and solvates.

Method

The first step in utilising the known structure for design is to visually inspect the packing pattern of the crystal structure around the guest molecule to be replaced - this can be achieved quickly and effectively using Mercury.8 Figure 2 shows an image of the crystal structure, viewed in Mercury, showing the hydrogen-bonds formed between the guest molecule (the saccharinate counterion) and the lamivudine host framework. The saccharinate counterion accepts three hydrogen bonds from the API framework - the three hydrogen-bonding acceptor atoms are highlighted with yellow mesh in Figure 2.

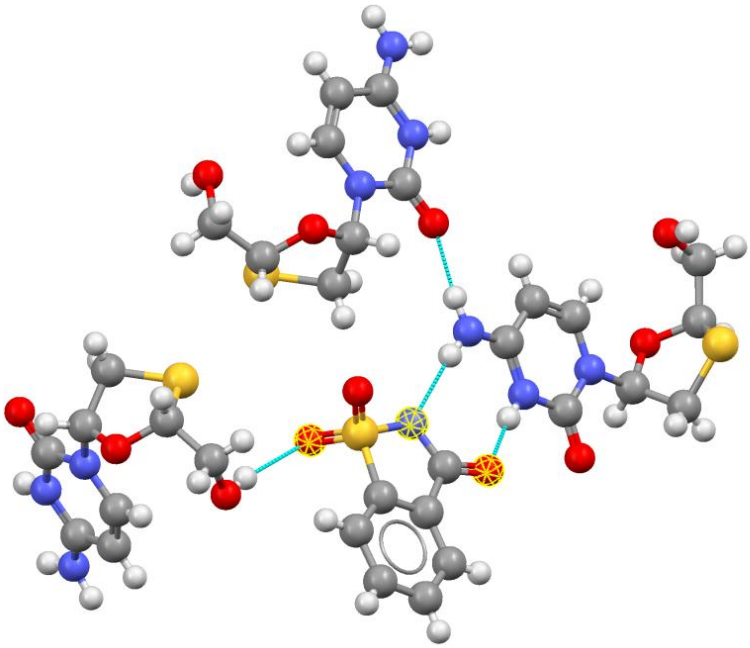

Figure 2 - Lamivudine saccharinate packing pattern

In order to identify a replacement counterion for the API host framework we need to find anions with the same spatial distribution of hydrogen-bonding acceptor atoms. Before performing this type of search, however, it is useful to identify a dataset of feasible compounds for which we have 3D structural information. We can use the program ConQuest[9] to search the Cambridge Structural Database (CSD)[10] quickly for structures of feasible replacement counterions. A search was therefore performed in ConQuest to identify structures with at least one negatively charged atom, at least two chemical residues (*i.e.* not zwitterionic), no elements heavier than sulfur, less than 50 atoms in total and not polymeric. This provided a dataset of roughly 4,500 small, organic, anionic compounds with 3D structural data for each.

Now that a dataset of viable counterions is available, we can try to identify compounds for which there is a matching set of acceptor groups to the lamivudine saccharinate system. The packing feature search tool within the *Materials* module of Mercury allows a search query to be performed directly from a 3D distribution of atoms selected within the visualiser. Using the lamivudine saccharinate structure we can simply select the three acceptor atoms involved in hydrogen-bonding as well as a couple of carbon atoms simply to ensure that some space is filled by the hydrophobic end of the molecule (Figure 3). The only constraints applied to this query, aside from the geometric relationship between the atoms, were that the nitrogen atom was singly negatively charged and that each of the acceptor atoms is either a nitrogen or an oxygen atom.

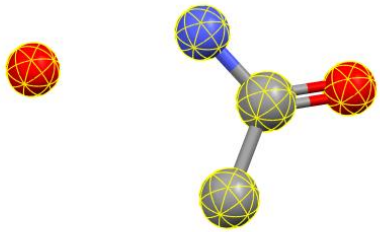

Figure 3 - Atoms selected for 3D search query

Results

Of the 4,500 structures in the dataset used, 111 structures contained a matching substructure to the defined search query. Some of these matches were other structures containing the saccharinate counterion, but there were also a substantial number of chemically distinct anions that may be good candidates for replacement counterions. Figure 4 shows some of the matching substructures that would appear to be good options to test as salt partners (though they are not necessarily considered acceptable by the FDA).

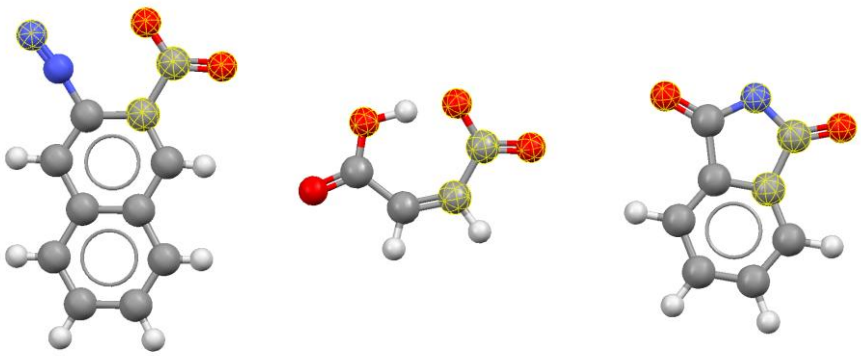

Figure 4 - Matching substructures in the dataset

A number of the matching substructures corresponded to the maleate anion (Figure 4, centre) - this anion was also chosen by Martins and co-workers[6] to test in their lamivudine crystallisation experiments. Martins *et al.* dissolved pure lamivudine in isopropanol, added solid maleic acid to the solution and then used slow evaporation over 5 days to produce single crystals for structure determination. This process resulted in a new solid form of the API, a lamivudine maleate salt, which contains the same hydrogen-bonding network as the known saccharinate structure. In fact, a packing similarity analysis of the lamivudine maleate and saccharinate salts forms in the *Materials* module of Mercury finds that an overlay of 9-molecule clusters (based only on the API molecules) from the two salt structures has a root mean square deviation of just 0.7 Å (Figure 5). This level of similarity highlights the close relationship between the salt structures and underlines the fact that the maleate structure is in fact designed using the saccharinate structure as a template.

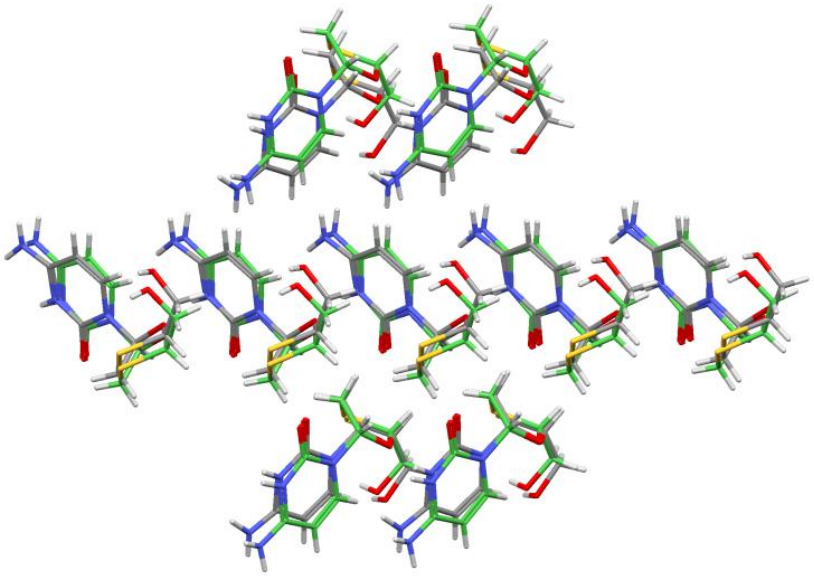

Figure 5 - Overlay of the API frameworks in the maleate and saccharinate structures

Analysis of the water solubility of the saccharinate and maleate salt forms of lamivudine by Martins *et al.* determined that the maleate salt is significantly more soluble than the saccharinate (45 mg/mL compared to 11 mg/mL). This shows that the physical properties of the solid form can be tuned without modifying the API itself or even the intermolecular framework of the API.

Conclusions

A method shown to be successful in designing new multi-component crystalline forms of API compounds based on a known crystal structure has been described. The example presented for the API lamivudine has illustrated the fact that the physical properties of a multi-component API form can be modified by replacement of the guest component. The method described herein is applicable to salts, solvates and co-crystals, so there is a significant potential for use with a range of other API systems.

References

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Products

CSD – the world's only comprehensive, fully curated database of crystal structures, containing over 500,000 entries

Conquest – a flexible CSD search engine

Materials module of Mercury – a powerful visualisation tool for solid state structures