Avenues for cocrystallisation of pharmaceuticals using solid state methods.

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Keywords: Cocrystallisation, Liquid assisted grinding, Pharmaceutical cocrystals, Powder diffraction

Crystal engineering principles may be applied to a variety of materials with the goal of optimising their physical properties without chemical alterations. This is especially useful when considering active pharmaceutical ingredients (API). Cocrystallisation of APIs is carried out using coformers which are found on the generally regarded as safe (GRAS) list. The large variety of materials that are found on this list gives a lot of potential for cocrystal synthesis, however coformer selection is not a trivial process and simple trial and error can result in a large volume of physical experimentation. Computational methods may be used to tackle this issue and narrow down a list of coformers which are suitable for cocrystal formation with different API molecules.

This study employs different methods of coformer selection to synthesize binary and even ternary cocrystals of an API which for this work is ganciclovir (GCV). GCV is an antiviral drug which is used for treatment of cytomegaloviruses, its chemical structure is seen in figure 1. [1]

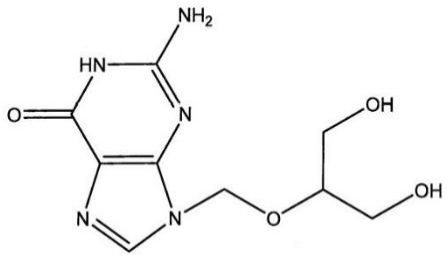

Figure 1: Structure of GCV. [1]

Liquid assisted grinding (LAG) is a solid-state method which has proved to be more successful in cocrystal formation when compared to more conventional solution methods, moreover the solubility limitations present when using these methods make solid state methods such as LAG more viable and versatile. Apart from this, LAG also has the additional advantages of being simple to carry out, cheap and environmentally friendly.

The methods for coformer selection used are the following:

[1] Screening by molecular complementarity (Fabian's method) which considers a list of steric and geometric factors of functional groups from a supramolecular perspective. [2]

[2] Screening by hydrogen bond (HB) lengths and angles between the functional groups of GCV and the individual coformers.

[3] Using acids on the GRAS list of different strengths (based on their pKa values) for interaction at different sites on GCV for the synthesis of ternary cocrystals (based on Etters HB rules). [3],[4]

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