Combining modified CCDC tools to predict multicomponent formation: co-crystals of nevirapine and benzoic derivatives

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In the pharmaceutical area, the screening of multicomponent forms of a drug is a well-known strategy to assess new crystalline forms with improved physicochemical properties, such as solubility, dissolution, absorption, and others [1-3]. Among the possible multicomponent forms, co-crystals, salts, and solvates, are obtained from the inclusion of other suitable molecules (co-formers) within the target molecule's crystalline structure. The process to obtain multicomponent crystalline forms of a drug could be an expensive and long-term process, since there is an infinity of possible co-former molecules, in addition to the large number of crystallization techniques that can be used [4]. Thus, it is necessary a strategy to help in the screening of new multicomponent forms of a target molecule through the rationalization of co-former selection, associated with lower consumption of materials and other costs, such as the final disposal of toxic waste. Aiming this, it is proposed a new methodology to optimize and to rationalize the co-former selection using knowledge-based supramolecular chemistry [5]. This new methodology aims to predict the formation of a multicomponent form through the evaluation of the molecular complementarity and the possible intermolecular interactions between the target molecule and the co-former through the use of three statistical tools developed by the Cambridge Crystallographic Data Centre (CCDC) [6]. The SFIMP (Statistical Analysis of Frequency of Interaction for Multicomponent Prediction) method [7] was developed based on the optimization of three CCDC tools – Molecular Complementarity (MC), Coordination Value likelihood calculation (CV), and H-Bond Propensity (HBP) [4, 8-10] – to perform a multicomponent analysis and to allow the combination of their results to obtain a single multicomponent score. Nevirapine (NVP), an antiretroviral drug that exhibits low-aqueous solubility, was used as the target molecule in this study. A bunch of 470 possible co-former molecules was evaluated and the multicomponent score obtained for each one was used to rank these molecules according to the possibility of forming a NVP multicomponent. The SFIMP method was validated through an experimental screening of new multicomponent forms of NVP. The results obtained from the prediction were used in the experimental screening and it enabled the obtention of four new co-crystals of NVP with benzoic acid, 3-hydroxybenzoic acid, 4-hydroxybenzoic acid, and 2,5-dihydroxybenzoic acid [5, 11]. The crystalline structures of these new co-crystals were characterized through single-crystal and powder X-ray diffraction, and differential scanning calorimetry. The SFIMP method shows improvements compared to what is currently available in the CSD system for the analysis and prediction of multicomponent forms. Besides, the results show this methodology as a promising strategy to evaluate the possibility of multicomponent formation in new systems.

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