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Predicting and Obtaining New Solvates of Curcumin, Demethoxycurcumin and Bisdemethoxycurcumin Based on the Ccdc Statistical Tools and Hansen Solubility Parameters

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Abstract : The solubility of active pharmaceutical ingredients (APIs) is challenging for the pharmaceutical industry. The new multicomponent crystalline forms as cocrystal and solvates present an opportunity to improve the solubility of APIs. Commonly, the procedure to obtain multicomponent crystalline forms of a drug starts by screening the drug molecule with the different coformers/solvents. However, it is necessary to develop methods to obtain multicomponent forms in an efficient way and with the least possible environmental impact. The Hansen Solubility Parameters (HSPs) is considered a tool to obtain theoretical knowledge of the solubility of the target compound in the chosen solvent. H-Bond Propensity (HBP), Molecular Complementarity (MC), Coordination Values (CV) are tools used for statistical prediction of cocrystals developed by the Cambridge Crystallographic Data Center (CCDC). The HSPs and the CCDC tools are based on inter- and intra-molecular interactions. The curcumin (Cur), target molecule, is commonly used as an anti-inflammatory. The demethoxycurcumin (Demcur) and bisdemethoxycurcumin (Bisdcur) are natural analogues of Cur from turmeric. Those target molecules have differences in their solubilities. In this way, the work aimed to analyze and compare different tools for multicomponent forms prediction (solvates) of Cur, Demcur and Biscur. The HSP values were calculated for Cur, Demcur, and Biscur using the chemical group contribution methods and the statistical optimization from experimental data. The HSPmol software was used. From the HSPs of the target molecules and fifty solvents (listed in the HSP books), the relative energy difference (RED) was determined. The probability of the target molecules would be interacting with the solvent molecule was determined using the CCDC tools. A dataset of fifty molecules of different organic solvents was ranked for each prediction method and by a consensus ranking of different combinations: HSP, CV, HBP and MC values. Based on the prediction, 15 solvents were selected as Dimethyl Sulfoxide (DMSO), Tetrahydrofuran (THF), Acetonitrile (ACN), 1,4-Dioxane (DOX) and others. In a starting analysis, the slow evaporation technique from 50°C at room temperature and 4°C was used to obtain solvates. The single crystals were collected by using a Bruker D8 Venture diffractometer, detector Photon100. The data processing and crystal structure determination were performed using APEX3 and Olex2-1.5 software. According to the results, the HSPs (theoretical and optimized) and the Hansen solubility sphere for Cur, Demcur and Biscur were obtained. With respect to prediction analyses, a way to evaluate the predicting method was through the ranking and the consensus ranking position of solvates already reported in the literature. It was observed that the combination of HSP-CV obtained the best results when compared to the other methods. Furthermore, as a result of solvent selected, six new solvates, Cur-DOX, Cur-DMSO, Bicur-DOX, Bircur-THF, Demcur-DOX, Demcur-ACN and a new Biscur hydrate, were obtained. Crystal structures were determined for Cur-DOX, Biscur-DOX, Demcur-DOX and Bicur-Water. Moreover, the unit-cell parameter information for Cur-DMSO, Biscur-THF and Demcur-ACN were obtained. The preliminary results showed that the prediction method is showing a promising strategy to evaluate the possibility of forming multicomponent. It is currently working on obtaining multicomponent single crystals.

Keywords : curcumin, HSPs, prediction, solvates, solubility
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