KNOWLEDGE-BASED PREDICTION OF MULTICOMPONENT FORMS OF NEVIRAPINE

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ABSTRACT

Nevirapine (NVP), an antiretroviral drug used in AIDS/HIV treatment [1], is a class II drug, according to the Biopharmaceutical Classification System (BCS) [2], presenting low solubility and high permeability. The low solubility leads to formulation difficulties and a considerable decrease in the bioavailability. A strategy to improve physicochemical properties, including the solubility, is the preparation of modified crystals of NVP. A crystalline modification frequently used is based on the inclusion of other molecules in the drug crystalline structure, forming multicomponent structures. NVP presents a rigid amide group and it is expected an NVP-co-former interaction in this point [3]. Among the possible multicomponent structures are the cocrystals, salts, solvates and eutectic systems. 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 [4]. So, it is necessary to optimize and to rationalize the co-formers selection using knowledge-based supramolecular chemistry. This work proposes a rational strategy in the design of the crystalline modifications based on the utilization of statistic tools developed by the Cambridge Crystallographic Data Centre (CCDC) [5], in order to predict the molecular complementarity between NVP and other molecular entities [6-8]. The prediction method validation is obtained through the preparation of multicomponent solids (solvates, cocrystals and eutectic systems) using a variety of crystallization techniques. The materials are characterized by X-ray diffraction, thermal analysis, optical microscope, Raman spectroscopy and, solid-state nuclear magnetic resonance spectroscopy.

Keywords: crystalline modification, molecular interaction prediction, nevirapine, CCDC tools

References:

[1] E. De Clercq, Int. J. Antimicrob. Agents, 33(4), 307 (2009)
[2] M. Lindenberg, S. Kopp, J. B. Dressman, Eur. J. Pharm. Biopharm., 58(2), 265 (2004)
[3] M. R. Caira et al., CrystEngComm, 14(7), 2541 (2012).
[4] L. Fábian, Cryst. Growth Des., 9(3), 1436–1443, (2009).
[5] C. R. Groom et al., Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater., 72 (2), 171-179, (2016).
[6] L. Infantes; W. D. S. Motherwell, Z. Krist., 220, 333–339, (2005).
[7] P. T. A. Galek et al., Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater., B70(1), 91–105, (2014).
[8] P. A. Wood et al. Knowledge-based approaches to co-crystal design. CrystEngComm, v. 16, n. 26, p. 5839–5848, 2014.

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