Joint meeting

VII Latin American Crystallographic Association

and

XXVII Brazilian Crystallographic Association

BOOK OF ABSTRACTS

October 14 to 17, 2025

Fortaleza, Brazil

New Hydrochlorothiazide cocrystals with improved permeability

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Hydrochlorothiazide (HTZ), is an antihypertensive drug assigned to class IV in the Biopharmaceutics Classification System (BCS) [1]. Despite being extremely used since its approval by the Food and Drug Administration in 1959, several attempts have been made as to modulate its solubility and/or permeability profiles. Although some successful trials have been reported, manufacturability/stability issues hindered the new compounds to evolve to new final products containing HTZ [2]. By considering the importance of pharmaceutical cocrystals, in this work we report two new cocrystals containing HTZ, with improved solubility and permeability when compared to the parent drug presenting at the same time acceptable manufacturability and stability characters. These properties make them potential candidates for pharmaceutical formulations. The new cocrystals were obtained with the zwitterionic aminoacid L-proline (HTZLP) and the prodrug 5-Fluorocitosine (HTZ-5FC). Both coformers where chosen particularly by possibility of forming NH···O and NH···N supramolecular interactions with HTZ, being crystal engineering based on the occurrence of the synthons [3]. Both cocrystals were satisfactorily synthesized via mechanochemistry, allowing to analyze them by single crystal and powder X-ray diffraction, thermal analysis, permeability, stability, and relative aqueous solubility. Both cocrystals crystallized in the monoclinic crystal system, at space group $P2_1$ for HTZLP, and $P2_1/n$ for HTZ-5FC. The structures are mainly stabilized by the expected synthons involving the NH···O and NH···N hydrogen bonds. HTZLP melts at 191,0 °C and HTZ-5FC melts at 238.0 °C, i.e., below the raw HTZ (267 °C). The relative solubility tests at room temperature showed that HTZ-5FC exhibits improved HTZ solubility when compared to the raw and the HTZLP cocrystal ones. Concerning permeability studies, although both cocrystals have exhibited improved profiles when compared to raw HTZ, the HTZ-5FC cocrystal reached levels consistent with high-permeability compounds, revealing to be a good candidate for pharmaceutical application.

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Keywords: Pharmaceutical Cocrystal; Hydrochlorothiazide; Permeability;

Acknowledgements: The authors are grateful to the Brazilian funding agencies FAPESP(2024/18554-7) (CCPS), (2017/15850-0), CNPQ (312505/2021-3) (JE) and 160856/2021-3 (P.P.F) and CAPES (88887.641946/2021-00 (P.P.F). This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. The University of Bologna is acknowledged (F.G., P.P.F.).).