# STRUCTURAL CHARACTERIZATION OF A SOLID DISPERSION OF CLARITHROMYCIN WITH MEFENAMIC ACID COFORMER VIA DFT STUDY

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The antibiotic clarithromycin (CLA) is incorporated into the polychemotherapy treatment of leprosy, being crucial to fight this disease[1]. Additionally, mefenamic acid (MEF) is classified as a nonsteroidal anti-inflammatory drug (NSAID)[2,3]. CLA and MEF belong to Class II of the Biopharmaceutical Classification System (BCS), characterized by reduced aqueous solubility and high membrane permeability[1]. The preparation of drug solid dispersions (DSDs) is an interesting alternative to obtain new pharmaceutical formulations with desirable physicochemical characteristics, contributing to improved water solubility as well as to an increased dissolution rate[4,5]. This work focused on the structural characterization of the DSD of CLA-MEF through a DFT study, including the investigation of intermolecular interactions between CLA and MEF in the CLA-MEF heterodimer, aiming to better understand the formation of the solid dispersion. For this purpose, computational calculations based on density functional theory (DFT) were performed with Gaussian 16 using the $\omega$B97X-D functional in association with the basis set 6-31G(d), including solvation effect simulations with the integral equation formalism of the polarizable continuum model (IEFPCM), considering methanol as the solvent. Basis set superposition error (BSSE) was considered for improved accuracy in the calculation of thermodynamic parameters of the interactions in the heterodimer. The DSD of CLA-MEF was obtained by our group through the slow solvent evaporation method, and characterized using X-ray diffraction (XRD) and differential scanning calorimetry (DSC). The DFT calculations provided the optimized geometries of the starting compounds CLA and MEF, and of the CLA-MEF heterodimer, from which structural, electronic, and thermodynamic properties were obtained. The calculated HOMO-LUMO gap (HLG) in vacuum for CLA and MEF are 10.17 eV and 7.89 eV, respectively. Additionally, the interaction in the CLA-MEF heterodimer resulted in $\Delta H$ = -25.66 kcal/mol, $\Delta G^{298}$ = -9.93 kcal/mol, and $\Delta E_{ZPVE}$ = -25.68 kcal/mol, indicating that the interaction through hydrogen bonding is favorable and endothermic. It explains the formation of the DSD as observed from XRD experiments. The DSC results showed that only the stoichiometric ratio of CLA-MEF (1:2) exhibited a single melting event at approximately 175 °C. Experimental FT-IR results and simulated spectroscopic data suported the interactions studied. In this way, the DFT study reported herein allowed a deeper understanding of the formation of the DSD of CLA-MEF, contributing to a detailed characterization of this material, which is relevant for pharmacological applications.

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