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DESIGN, SYNTHESIS, AND PROPERTIES OF BINARY SYSTEMS COMPRISING LINEZOLID

By

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The research presented in this thesis focuses on exploring cocrystals involving the antibiotic linezolid (LIN) with the ultimate aim of improving its suitability for drug delivery systems, particularly through using mesoporous silica nanoparticles (MSNs). The study begins with experimental mechanochemical screening, which led to the discovery of nine new crystal phases, including four neat cocrystals: linezolid-2,3-dihydroxybenzoic acid (LIN-2,3DHBA), linezolid-3,5-dihydroxybenzoic acid (LIN-3,5DHBA), linezolid-2,4-dihydroxybenzoic acid (LIN-2,4DHBA), linezolid-2,6-dihydroxybenzoic acid (LIN-2,6DHBA), and five cocrystal hydrates: linezolid-gallic acid hydrate (LIN-GA-H_2O), linezolid-2,4-dihydroxybenzoic acid hydrate (LIN-2,4DHBA-H_2O), linezolid-3,4-dihydroxybenzoic acid hydrate (LIN-3,4DHBA-H_2O), linezolid-2,5-dihydroxybenzoic acid hydrate (LIN-2,5DHBA-H_2O), and linezolid-p-aminobenzoic acid hydrate (LIN-PABA-H_2O). In addition, two cocrystals reported previously but without structural details, *i.e.* linezolid-benzoic acid (LIN-BA) and linezolid-p-hydroxybenzoic acid hydrate (LIN-PHBA-H_2O), were obtained. A comprehensive investigation into the factors influencing the formation of these phases was conducted, encompassing diverse experimental conditions, such as polymorphic forms of LIN and the presence of various solvents to create liquid-assisted grinding conditions. These experimental results were compared with predictions from the established virtual cocrystal screening tools, including molecular complementarity, hydrogen bond propensity, and molecular electrostatic potential maps. It was observed that these predictive methods offer valuable

insights into a molecule tendencies to form cocrystals with specific coformers, highlighting the role of molecular conformation.

To structurally characterize the obtained crystalline phases, the conducted research successfully produced five single crystals from cocrystals of this antibiotic. This enabled their characterization using single-crystal X-ray diffraction, further supplemented by solid-state NMR spectroscopy, powder X-ray diffraction, and differential scanning calorimetry. Each cocrystal exhibited distinct structural features, variations in water content, and different heterosynthons, revealing multiple intermolecular interactions preferred by the LIN molecule. Furthermore, based on the frequency of the observed supramolecular synthons, an intriguing hierarchy of hydrogen-bond acceptor sites for linezolid was established, along with a recognition of the significant role of aromatic-aromatic interactions in structure stabilization. Notably, some of these cocrystals displayed modified thermal properties, making them suitable candidates for drug delivery systems.

Addressing challenges related to solid microcrystalline powders, which hinder the usage of single-crystal X-ray diffraction for crystal structure determination, further research introduced an innovative approach to crystal structure determination by combining knowledge-based approach to narrow down the vast conformational space of LIN and some of the coformers with quantum chemical calculations, followed by high-resolution solid-state NMR experiments and crystal structure prediction (CSP) calculations. As a result, it was possible to overcome obstacles posed by molecules with substantial conformational flexibility. This combined protocol successfully elucidated the crystal structure of a LIN cocrystal with 2,3-dihydroxybenzoic acid and identified the most probable conformations of LIN within the LIN cocrystal with 2,4-dihydroxybenzoic acid, despite LIN cocrystals presenting complex conformational landscapes.

Investigating the factors and techniques that impact the incorporation of binary components into mesoporous materials, together with unveiling any unforeseen interactions, have a capacity to guide the identification of the optimal strategy for loading LIN cocrystals into MSNs. To do that, the loading process into MSNs of model binary systems comprising benzoic acid and fluorobenzoic acid was studied and followed by preliminary studies of loading LIN and its selected binary system into MSNs. By conducting these latter studies, employing both established and refined methodologies, the aim was to forge novel pathways towards augmenting drug delivery systems *via* the judicious modification of APIs through cocrystallization.

The broader context of this research arises from the critical need for innovative drug delivery systems. Traditional administration of drugs faces limitations related to solubility, permeability, and targeting. Consequently, the utilization of MSNs as drug delivery systems has garnered significant

attention due to their exceptional properties, including high loading capacity, biocompatibility, and ease of functionalization. This thesis contributes valuable insights into the development of LIN cocrystals with enhanced properties, holding promise for the future of drug delivery system.