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Combined Atomistic Molecular Calculations and Experimental Investigations for the Architecture, Screening, Optimization, and Characterization of Pyrazinamide Containing Oral Film Formulations for Tuberculosis Management

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Abstract

To date, effective treatment, prophylaxis, and control of tuberculosis (TB) infection is mainly dependent on the use of drugs. However, patient noncompliance with prescribed anti-TB treatment schemes remains a major problem confronting successful pharmacotherapeutic outcomes. Thus, the development of alternative delivery systems that can improve adherence for the existing anti-TB bioactives has been intensified in recent times. The aim of this investigation was to engineer an optimal, thermodynamically stable oral film (OF) formulation containing a key anti-TB agent, pyrazinamide (PYZ), employing molecular modeling and experimental tools. Four PYZ-loaded film variants (OF 1, OF 2, OF 3, OF 4) were constructed in silico and then prepared in vitro using the Accelrys Materials Studio software and solvent casting method, respectively. Screening and selection of the optimal OF was based on the computation of the total interaction energy (ET), kinetic energy (EK), solubility parameter (S), and cohesive energy density (CED) as well as determining mass, thickness, dissolution and disintegration times, dissolution pH, drug loading capacity, and surface morphology in vitro. OF 2 was selected as the optimal formulation as it displayed the lowest ET (−8006.28 kcal/mol), dissolution time (9.96 min), disintegration time (56.49 s), and weight (39.33 mg); moderate EK (1052.98 kcal/mol); highest S (44.55 (J/cm3)0.5) and CED (1.99 × 109 J/m3), slim dimension (166 μm), good and unvarying drug loading capacity (98.04%), acceptable dissolution pH (6.70), and well-layered surface topography. The drug release behavior of the optimal OF 2 was best elucidated with the zero order (R2 = 0.97) and Korsmeyer–Peppas (R2 = 0.99) models. X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC) analyses showed that OF 2 was made of physically mixed multiple component polymeric and nonpolymeric compounds. OF 2 was semicrystalline in nature and displayed a dual

phased ex vivo mucosal permeation pattern. In silico and in vitro physicomechanical quantities revealed OF 2's flexibility, robustness, and compressibility. OF 2 was most stable under controlled environmental humidity, pressure, and temperature conditions in silico and in vitro. OF 2 was potentially non-cytotoxic and biocompatible. Succinctly, this work demonstrated the applicability of a combination of atomistic molecular mechanics and dynamics calculations as well as experimental analyses to the fabrication, screening, optimization, and characterization of drug formulations. Lastly, the fabricated OF 2 formulation can function as a potential alternative for the effective loading and delivery of PYZ.