Computer-Aided Construction and Investigation of a Thermodynamically Stable Mouth-Dissolving Film Containing Isoniazid

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Purpose

To design and characterize a thermodynamically stable mouth-dissolving film containing isoniazid employing *in silico* and *in vitro* techniques. Isoniazid (solubility = 140 mg/mL and log P = -0.64 at 25°C) is a first-line antibiotic indicated for the prevention (as a single entity) and treatment (in combination with other medicines) of active tuberculosis infection.

Methods

Molecular simulations and calculations were conducted employing the Accelrys Materials Studio, version 7.0 software. The study explored 4 different isoniazid-loaded film formulations symbolized by F_1, F_2, F_3 and F_4. The selection of formulation components was based on a one-factor-at-a-time approach employing different ratio combinations of vinylpyrrolidone-vinyl acetate and macrogol-poly (vinyl alcohol) copolymers, polyethylene glycol, other biocompatible inorganic and organic excipients as well as isoniazid. Each film matrix was constructed *in silico* as a single framed entity based upon an atom-to-atom fusion utilizing the COMPASSII forcefield of the Amorphous Cell Component of the Materials Studio software. This led to the *in silico* construction of film architectures with varying thermodynamic stability potentials at the point of geometric convergence. The total internal energy indicative of the system's stability potential was then computed using the Forcite Module. Computer-aided calculations were validated by manufacturing films with formulations F_1 - F_4 via solvent casting at standard temperature/pressure conditions. The surface structure of each film formulation was examined using light microscopy. F_2 (the most thermodynamically stable based on *in silico* model) was subjected to further testing which included thickness and weight, mechanical properties (Young's modulus, break stress and break strain), drug content, film disintegration and dissolution in simulated saliva under biorelevant conditions. All tests were carried out in triplicate.

Results

Computed total energy values were F_1 = 14,852.41 kcal mol^{-1}, F_2 = 2,279.62 kcal mol^{-1}, F_3 = 21,123.07 kcal mol^{-1} and F_4 = 2,729.80 kcal mol^{-1}. Based on the *in silico* calculations, F_2 was the most thermodynamically stable film as it had the lowest total energy value. Generally, the surface topographies F_1, F_3 and F_4 revealed varying degrees of segregation of component compounds while F_2 had a surface characterized by a continuous structure with no visible component phase separation. These results confirmed the outcome of the computer-aided calculations. F_2 weighed 487.30 ± 1.55 mg, contained 94.67 ± 1.86% isoniazid, was 161.67 ± 14.19 µm thick and disentangled quite rapidly in simulated saliva (disintegration time = 24.05 ± 2.28 seconds , dissolution time = 296.00 ± 18.68 seconds). The mechanical stability of F_2 was displayed with Young's Modulus = 75.44 ± 14.01 MPa, break stress = 2.89 ± 0.36 MPa and break strain = 33.13 ± 6.02%.

Conclusion

Systematic molecular-based dynamic modeling enables *a priori* estimation of the thermodynamic stability and thus formulation optimization of isoniazid-loaded mouth-dissolving films. Computational modeling can serve as a useful tool for guiding excipient selection and processing conditions leading to the design of high quality drug products. A thermodynamically stable mouth-dissolving film loaded with isoniazid was successfully developed and characterized.