

Preparation, Characterization and *Ex Vivo* Evaluation of an Orally Disintegrating Film Formulation Containing Pyrazinamide

O. A. Adeleke¹, P-C. Tsai², B. B. Michniak-Kohn²

¹ Council for Scientific and Industrial Research, ² Rutgers - The State University of New Jersey

Purpose

To prepare, characterize as well as assess the *ex vivo* buccal drug delivery and cytotoxicity of an orally disintegrating film (ODF) loaded with pyrazinamide. Pyrazinamide (solubility = 15 mg/mL at 25°C; log P = -1.884) is an antimicrobial agent indicated for the treatment of tuberculosis (TB) especially in HIV-infected persons with TB co-infection as well as for multi-drug and extensively drug resistant TB.

Methods

The ODF was prepared using a combination of biocompatible polymeric and non-polymeric additives coupled with pyrazinamide as the model drug. The ODF was produced employing the solvent casting method under room conditions (temperature: $23 \pm 3^\circ\text{C}$; humidity: $70 \pm 5\%$). ODF mass and thickness were measured employing a laboratory weighing balance and screw gauge respectively. Drug content was calculated (actual drug content / total drug content $\times 100$) while *in vitro* drug release analysis was performed in a closed system containing 5 mL simulated saliva (pH = 6.75) in a shaking water bath ($37 \pm 0.1^\circ\text{C}$; 10 rpm) over 30 minutes. Drug release kinetics was mathematically fitted using the KinetDS, version 3.0 open source software. ODF fragmentation and dissolution times in simulated saliva were measured at $37 \pm 0.1^\circ\text{C}$ in a water bath (10 rpm). Subsequently, the pH (pH_{diss}) of the resulting physically clear solution was determined with a pH meter. The surface structure of the ODF was viewed utilizing light and scanning electron microscopy. An initial check was done to evaluate the stability of the ODF under room storage conditions over 2 weeks. The *ex vivo* permeation of pyrazinamide molecules across the porcine buccal mucosal tissue was assessed utilizing a magnetically stirred Franz diffusion cell ($37 \pm 0.1^\circ\text{C}$) with simulated saliva and plasma contained in the donor and receiver compartments respectively. A cytotoxicity assay was performed on human dermal fibroblasts (HDF) using the AlamarBlue[®] assay over 48 hours. Three replicate samples were tested for every experiment.

Results

The ODF formulation (diameter = 1.59 cm) weighed 39.33 ± 2.75 mg, was 0.17 ± 0.01 mm in thickness and contained $97.37 \pm 2.91\%$ of pyrazinamide. The ODF disintegrated within 56.49 ± 3.49 seconds of inserting it in simulated saliva and was completely dissolved (physical viewing) within 9.96 ± 0.80 minutes producing a solution with a pH_{diss} of 6.66 ± 0.01 which is comparable to the pH of normal saliva. Measured drug release rate was 3.49% per minute and model fitting showed that the ODF exhibited a zero order release kinetics ($R = 0.97$). The ODF's microscopically viewed surface geometry showed an even, bilayered distribution of the ODF component molecules. The films were stable under room conditions over 2 weeks. The ODF enabled and sustained the permeation of pyrazinamide ($78.32 \pm 2.78\%$ in 2 hours) across the porcine buccal mucosa. Moreover, the ODF displayed no potential cytotoxicity with the HDF cell culture over the 48 hour exposure period.

Conclusion

A potentially stable and non-toxic orally disintegrating film formulation was successfully fabricated and evaluated for the rate-modulated delivery of pyrazinamide. The developed formulation appears to be a promising alternative for the effective management of tuberculosis.