Mucus-Penetrating Antibiotic Prodrug Nanosuspension for Treatment of Infections at the Mucosal Surface

Y. Cu, P. Novak, W. Ong, J. Bourassa, A. Popov, H. Chen
Kala Pharmaceuticals, Inc.

Purpose

Antibiotic treatments topically delivered to infected mucosal tissues, including those of the eye, lung, gastrointestinal, and reproductive tract, may be preferred over systemic administration as they supply drugs directly to the site of infection while minimizing systemic exposure and toxicity. Substantial efforts have been made to improve topical delivery to mucosal surfaces by formulating drugs into micro and nanoparticles. However, conventional particles (i.e., formulated from polymers or lipids) carry practical limitations, including inherently limited drug loadings and manufacturing complexities. Furthermore, the efficiency of topical administration with these particles is greatly hindered by the mucus lining that entraps most foreign particles, including therapeutic carriers, and expels them by natural mucus turnover. To address these challenges, we have formulated mucus-penetrating particles (MPPs) containing an enzymatically hydrolyzable prodrug of meropenem, a broad spectrum antibiotic. Unlike traditional nanoparticles, the MPPs were comprised entirely of the drug core with only a thin, non-covalent coating of an MPP-enabling surfactant. The particle size and surface chemistry of MPPs are specifically tailored to enable rapid penetration of the mucus barrier, to improve drug particle distribution and retention at the mucosal surface.

Methods

MPPs were prepared by a one-pot process which involved nanomilling of the prodrug in the presence of an MPP-enabling surfactant. MPPs formulated as a ready-to-use aqueous suspension and lyophilized powder for reconstitution were evaluated for their ability to penetrate human mucus in ex vivo assay, and chemical and physical stability (particle size and morphology) for up to 30 days at 4°C or room temperature.

Results

MPP nanosuspensions were stable with particle diameter ~270 nm (PDI<0.2) and were able to rapidly penetrate mucus, exhibiting an ensemble average velocity of 6.2 μm/s (vs. 0.6 μm/s for a mucoadhesive control). The aqueous suspension and lyophilized powder were chemically stable, retaining 100% and 95%, respectively, of their content after 30 days under all storage conditions tested. Furthermore, the MPPs preserved the ability to penetrate mucus and exhibited no change in particle morphology.

Conclusion

These data demonstrate proof-of-concept for an antibiotic nanoparticle formulation with enhanced mucus transport properties for treatment of bacterial infections at the mucosal surface.