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Novel micelle formulations to increase cutaneous bioavailability of azole antifungals.

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Abstract

Efficient topical drug administration for the treatment of superficial fungal infections would deliver the therapeutic agent to the target compartment and reduce the risk of systemic side effects. However, the physicochemical properties of the commonly used azole antifungals make their formulation a considerable challenge. The objective of the present investigation was to develop aqueous micelle solutions of clotrimazole (CLZ), econazole nitrate (ECZ) and fluconazole (FLZ) using novel amphiphilic methoxy-poly(ethylene glycol)-hexyl substituted polylactide (MPEG-hexPLA) block copolymers. The CLZ, ECZ and FLZ formulations were characterized with respect to drug loading and micelle size. The optimal drug formulation was selected for skin transport studies that were performed using full thickness porcine and human skin. Penetration pathways and micellar distribution in the skin were visualized using fluorescein loaded micelles and confocal laser scanning microscopy. The hydrodynamic diameters of the azole loaded micelles were between 70 and 165nm and the corresponding number weighted diameters (d(n)) were 30 to 40nm. Somewhat surprisingly, the lowest loading efficiency (<20%) was observed for CLZ (the most hydrophobic of the three azoles tested); in contrast, under the same conditions, ECZ was incorporated with an efficiency of 98.3% in MPEG-dihexPLA micelles. Based on the characterization data and preliminary transport experiments, ECZ loaded MPEG-dihexPLA micelles (concentration 1.3mg/mL; d(n)<40nm) were selected for further study. ECZ delivery was compared to that from Pevaryl® cream (1% w/w ECZ), a marketed liposomal formulation for topical application. ECZ deposition in porcine skin following 6h application using the MPEG-dihexPLA micelles was >13-fold higher than that from Pevaryl® cream (22.8±3.8 and 1.7±0.6μg/cm(2), respectively). A significant enhancement was also observed with human skin; the amounts of ECZ deposited were 11.3±1.6 and 1.5±0.4μg/cm(2), respectively (i.e., a 7.5-fold improvement in delivery). Confocal laser scanning microscopy images supported the hypothesis that the higher delivery observed in porcine skin was due to a larger contribution of the follicular penetration pathway. In conclusion, the significant increase in ECZ skin deposition achieved using the MPEG-dihexPLA micelles demonstrates their ability to improve cutaneous drug bioavailability; this may translate into improved clinical efficacy in vivo. Moreover, these micelle systems may also enable targeting of the hair follicle and this will be investigated in future studies.