

## **Polymeric micelle nanocarriers for the cutaneous delivery of tacrolimus: a targeted approach for the treatment of psoriasis.**

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### **Abstract**

Tacrolimus (TAC) suffers from poor cutaneous bioavailability when administered topically using conventional vehicles with the consequence that although it is indicated for the treatment of atopic dermatitis, it has poor efficacy against psoriasis. The aim of this work was to formulate TAC loaded polymeric micelles using the biodegradable and biocompatible methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer and to investigate their potential for targeted delivery of TAC into the epidermis and upper dermis. Micelle formulations were characterized with respect to drug content, stability, and size. An optimal 0.1% micelle formulation was developed and shown to be stable over a period of 7 months at 4 °C; micelle diameters ranged from 10 to 50 nm. Delivery experiments using human skin and involving quantification by UHPLC-MS/MS demonstrated that this formulation resulted in significantly greater TAC deposition in skin than that with Protopic (0.1% w/w; TAC ointment), ( $1.50 \pm 0.59$  and  $0.47 \pm 0.20$   $\mu\text{g}/\text{cm}^2$ ), respectively). The cutaneous biodistribution profile of TAC in the upper 400  $\mu\text{m}$  of tissue (at a resolution of 20  $\mu\text{m}$ ) demonstrated that the increase in cutaneous drug levels was due to improved TAC deposition in the stratum corneum, viable epidermis, and upper dermis. Given that there was no increase in the amount of TAC in deeper skin layers or any transdermal permeation, the results suggested that it would be possible to increase TAC levels selectively in the target tissue without increasing systemic absorption and the risk of side effects in vivo. Micelle distribution and molecular penetration pathways were subsequently visualized with confocal laser scanning microscopy (CLSM) using a fluorescently labeled copolymer and fluorescent dyes. The CLSM study indicated that the copolymer was unable to cross the stratum corneum and that release of the micelle "payload" was dependent on the molecular properties of the "cargo" as evidenced by the different behaviors of DiO and fluorescein. A preferential deposition of micelles into the hair follicle was also confirmed by CLSM. Overall, the results indicate that MPEG-dihexPLA micelles are highly efficient nanocarriers for the selective cutaneous delivery of tacrolimus, superior to the marketed formulation (Protopic). Furthermore, they may also have significant potential for targeted delivery to the hair follicle.