

Targeted cutaneous delivery of ciclosporin A using micellar nanocarriers and the possible role of inter-cluster regions as molecular transport pathways.

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Abstract

Oral administration of ciclosporin A (CsA) is indicated in the treatment of severe recalcitrant plaque psoriasis. However, CsA is both nephro- and hepatotoxic and its systemic administration also exposes the patient to other severe side effects. Although topical delivery of CsA, targeted directly to psoriatic skin, would offer significant advantages, there are no topical formulations approved for dermatological use. The aim of this work was to formulate CsA loaded polymeric micelles using the biodegradable and biocompatible MPEG-dihexPLA diblock copolymer and to evaluate their potential for delivering the drug selectively into the skin without concomitant transdermal permeation. Micelle formulations were characterised with respect to drug content, size and morphology. Micelle and drug penetration pathways were subsequently visualised with confocal laser scanning microscopy (CLSM) using fluorescein labelled CsA (Fluo-CsA) and Nile-Red (NR) labelled copolymer. Visualisation studies typically use fluorescent dyes as "model drugs"; however, these may have different physicochemical properties to the drug molecule under investigation. Therefore, in this study it was decided to chemically modify CsA and to use this structurally similar fluorescent analogue to visualise molecular distribution and transport pathways. Molecular modelling techniques and experimental determination of log D served as molecular scale and macroscopic methods to compare the lipophilicity of CsA and Fluo-CsA. The spherical, homogeneous and nanometre-scale micelles (with Z_{av} from 25 to 52 nm) increased the aqueous solubility of CsA by 518-fold. Supra-therapeutic amounts of CsA were delivered to human skin ($1.4 \pm 0.6 \mu\text{g}/\text{cm}^2$, cf. a statistically equivalent $1.1 \pm 0.5 \mu\text{g}/\text{cm}^2$ for porcine skin) after application of the formulation with the lowest CsA and copolymer content ($1.67 \pm 0.03 \text{ mg}/\text{ml}$ of CsA and $5 \text{ mg}/\text{ml}$ of copolymer) for only 1h without concomitant transdermal permeation. Fluo-CsA was successfully synthesised, characterised and incorporated into fluorescent NR-MPEG-dihexPLA micelles; its conformation was not modified by the addition of fluorescein and its log D, measured from pH4 to 8, was equivalent to that of CsA. Fluo-CsA and NR-MPEG-dihexPLA copolymer were subsequently visualised in skin by CLSM. The images indicated that micelles were preferentially deposited between corneocytes and in the inter-cluster regions (i.e. between the clusters of corneocytes). Fluo-CsA skin penetration was deeper in these structures, suggesting that inter-cluster penetration is probably the preferred transport pathway responsible for the increased cutaneous delivery of CsA.