IN VITRO PERMEATION AND PENETRATION OF CICLOPIROX OLAMINE FROM POLOXAMER 407-BASED FORMULATIONS - COMPARISON OF ISOLATED HUMAN STRATUM CORNEUM, BOVINE HOOF PLATES AND KERATIN FILMS

Anja Täuber, Christel C. Müller-Goymann

Institut für Pharmazeutische Technologie
Technische Universität Braunschweig
Mendelssohnstraße 1
38106 Braunschweig

INTRODUCTION: Topical antifungal therapy of skin and/or nails is preferable in comparison to systemic therapy. However, it is accompanied by major challenges due to the low permeability of these tissues. Since fungal skin and/or nail infections (tinea pedis and onychomycosis, respectively) are common diseases, the objective of the present study was the development of dermal formulations targeting both. Therefore, the antifungal agent ciclopirox olamine (CPX) was incorporated into a variety of poloxamer 407-based formulations and analysed regarding its in vitro permeation and penetration performance across keratin films (KF) and bovine hoof plates as artificial nail models as well as across human stratum corneum (SC). The novel compositions consisted of poloxamer 407 (P407), double distilled water, propylene glycol (PG), isopropyl alcohol (IPA) and medium chain triglycerides (MCT) in given ratios.

EXPERIMENTAL METHODS: The P407-based formulations were weighed in an Unguator® jar and automatically stirred at 1440 rpm for 1.5 min with an Unguator® e/s (GAKO Konietzko GmbH, Bamberg, Germany). Subsequent storage was done for 24 h at 20 ± 1 °C to ensure sufficient equilibration. All the formulations were given codes reflecting their quantitative composition, e.g. 1P1050 represented a formulation loaded with 1 % CPX, while the vehicle itself contained 10 % P407/MCT (4:1), 50 % IPA/PG (1:1) and 40 % double distilled water (all w/w). Rheological measurements were performed with a HAAKE RheoStress 6000 rheometer (Thermo Fisher Scientific, Karlsruhe, Germany).

In vitro permeation studies (infinite dose technique) were carried out with modified Franz diffusion cells at 32 °C for 32 h. The receiver solution consisted of phosphate buffered saline (PBS) of pH 7.4. The quantification of the permeated and penetrated CPX amount was done
with high performance liquid chromatography (HPLC) (Waters, Eschborn, Germany). Moreover, infected nail plate studies were performed according to Lusiana et al.[1]

RESULTS: All analysed P407-based formulations exhibited semi-solid to liquid consistencies and were isotropic under a polarising microscope Leica DM LM (Leica Microsystems GmbH, Wetzlar, Germany). Upon CPX incorporation, the formulations became softer and the yield stresses decreased. Permeation coefficients from P407-based formulations across KF and bovine hoof plates and normalised retained CPX amounts in KF and bovine hoof plates were higher in comparison to a marketed nail lacquer as a reference. Data of KF and bovine hoof plates were comparable. With regard to SC permeation, the permeation coefficients were in the same range or higher compared to a semi-solid skin formulation, while the normalised retained CPX amounts in SC were higher in comparison with the reference. Infected nail plate studies with the dermatophyte fungus Trichophyton rubrum indicated complete growth inhibition on KF and bovine hoof plates for several P407-based formulations. On SC, 1P1050 completely inhibited fungal growth (score: 0), whereas the marketed semi-solid formulation did not show any inhibition after 6 days of incubation (score: 10).

CONCLUSION: P407-based formulations with a broad range of macroscopical appearances have successfully been developed being applicable to both skin and nail. In vitro permeation studies showed superior permeation for the P407-based formulations across the artificial nail models and equal to superior permeation across SC. Moreover, microbiological studies indicated complete fungal growth inhibition for several P407-based formulations. Data of KF and bovine hoof plates were comparable, so that KF are supposed to serve as an artificial nail model for in vitro permeation and infected nail plate studies besides the well-accepted model of bovine hoof plates.