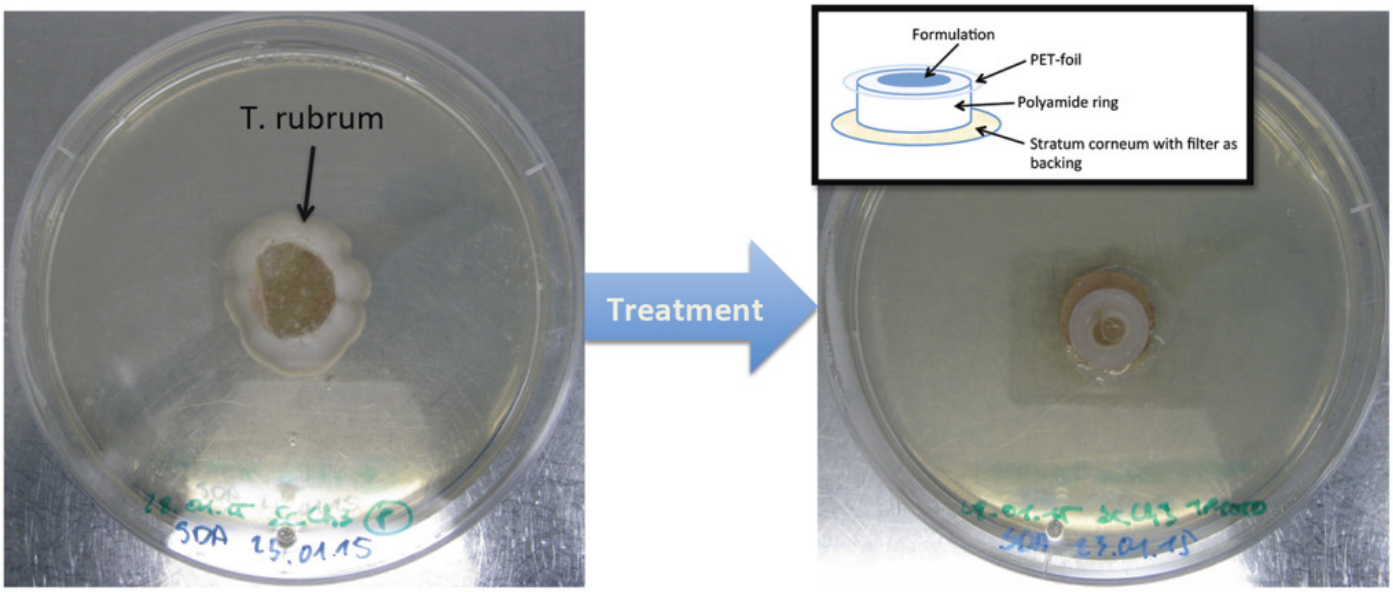
One for two – one medicine against two diseases

Superficial fungal skin infections belong to the most common infections worldwide. They affect more than 20 – 25 % of the world's population with an increasing trend due to an increasing life expectancy and decreasing immunity of the elderly. Further risk factors are occlusive footwear causing a warm and humid climate, communal bathing facilities as well as diseases such as diabetes. The most prevalent trigger is the dermatophyte fungus *Trichophyton rubrum*. Due to the fungus' ability to feed on keratin of the nail and the skin, it is mostly located in the human nail plate and the horny layer of the skin, i.e., the stratum corneum (SC). If the toe web is infected, the disease is called athlete's foot. It is characterised by peeling and maceration of the skin, itching and foul odour. The treatment is usually done with topical formulations containing active antifungal ingredients such as ciclopirox olamine (CPX) and takes up to 4 weeks. Since the fungi may enter the nail plate via fissures and gaps, athlete's foot often goes along with fungal nail infections being considerably more difficult to treat. A convenient approach supporting the patient's compliance would be a single formulation treating both diseases simultaneously. Hitherto, no such formulation is marketed due to the distinct barrier properties of nail and skin. The nail is considered as a hydrophilic gel membrane with an additional lipophilic pathway, whereas the skin represents a lipophilic partition membrane.



Infected stratum corneum model

Successfully treated stratum corneum model

We developed such a simultaneous formulation from hydrophilic and lipophilic compounds and incorporated antifungal CPX. Variations in composition of the ingredients led to different consistencies (liquid to semi-solid). The antifungal efficacy of the formulations was tested in a novel *in vitro* model, in which human SC was infected with *T. rubrum*. After 6 days of incubation, a variety of our liquid formulations indicated complete fungal growth inhibition, whereas a marketed

antifungal cream for the treatment of athlete's foot, which was included as a reference, did not inhibit fungal growth.

Moreover, our formulations with high incorporated CPX contents caused a loosening of the tight microstructure of the SC. This loosening aided drug penetration resulting in a better fungal growth inhibition.

Additionally, we performed one-year stability studies at 30 °C and investigated the CPX content as well as the macroscopic appearance during storage. After 12 months, all the formulations exhibited CPX contents > 95 % (with one exception). The semi-solid formulations did not show any phase separation phenomena, while some of the liquid formulations indicated reversible creaming.

Combining these data with previously published results, *in vitro* antifungal efficacy against *T. rubrum* on infected SC as well as on artificial nail models was proven. *In vitro* permeation studies across SC and nail models indicated promising permeation behaviour for a variety of our formulations. Therefore, we suggest a simultaneous antifungal therapy as a future therapy approach.

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Publication

In vitro model of infected stratum corneum for the efficacy evaluation of poloxamer 407-based formulations of ciclopirox olamine against Trichophyton rubrum as well as differential scanning calorimetry and stability studies.
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