

Introduction

The model drug CIS-1114 is a very lipophilic drug that shows anti-inflammatory, antipruritic and antibacterial effects. Therefore, it could be used for the treatment of skin conditions such as acne, rosacea and pruritus. The aim of this study was to find a formulation that is suitable for the delivery of CIS-1114 into the stratum corneum. Due to their positive effect on skin penetration in a first step a microemulsion, an ethanolic solution and liposomes were considered as possible formulations for CIS-1114. Skin penetration of CIS-1114 from these formulations was also compared to the penetration from a suspension of CIS-1114 in the amphiphilic industrial ointment basis Ultraphil[®].

Subsequently, microemulsions were of interest. An advantage of microemulsions is their stability, but on the other hand the potential of skin irritation is high due to their high content of surfactant and co-solvent. The irritating potential of the utilized microemulsion has already been shown in previous studies [1]. This is a considerable disadvantage, especially since the formulations should be applied on skin that is already damaged.

Thus, the next step was to find a microemulsion with a similar composition but a lower content of surfactant and co-solvent in order to improve skin-friendliness. Therefore, a pseudo-ternary phase diagram was assessed (figure 2).

Experimental Methods

Formulations

Liposomes were prepared using the film method with a dipalmitoyl phosphatidyl choline content of seven point five percent; the microemulsion that was tested first, hereafter referred as microemulsion 1, was composed of twenty percent water, twenty percent isopropyl myristate as oily component, thirty percent Lipoid S75 as surfactant and thirty percent isopropanol as co-solvent. Three percent CIS-1114 were incorporated in all formulations.

In vitro skin penetration

Skin penetration was determined by tape stripping. Therefore, porcine ears were purchased from a local butcher and stored at minus twenty degrees Celsius. To prepare them for the experiments, they were thawed and hair on the dorsal skin was carefully removed using scissors. Two milligram of formulation per square centimeter were applied, rubbed in for a minute and after an exposure time of one hour the upper layers of the stratum corneum were subsequently removed with tape strips. Corneocytes and CIS-1114 were determined by NIR and HPLC, respectively.

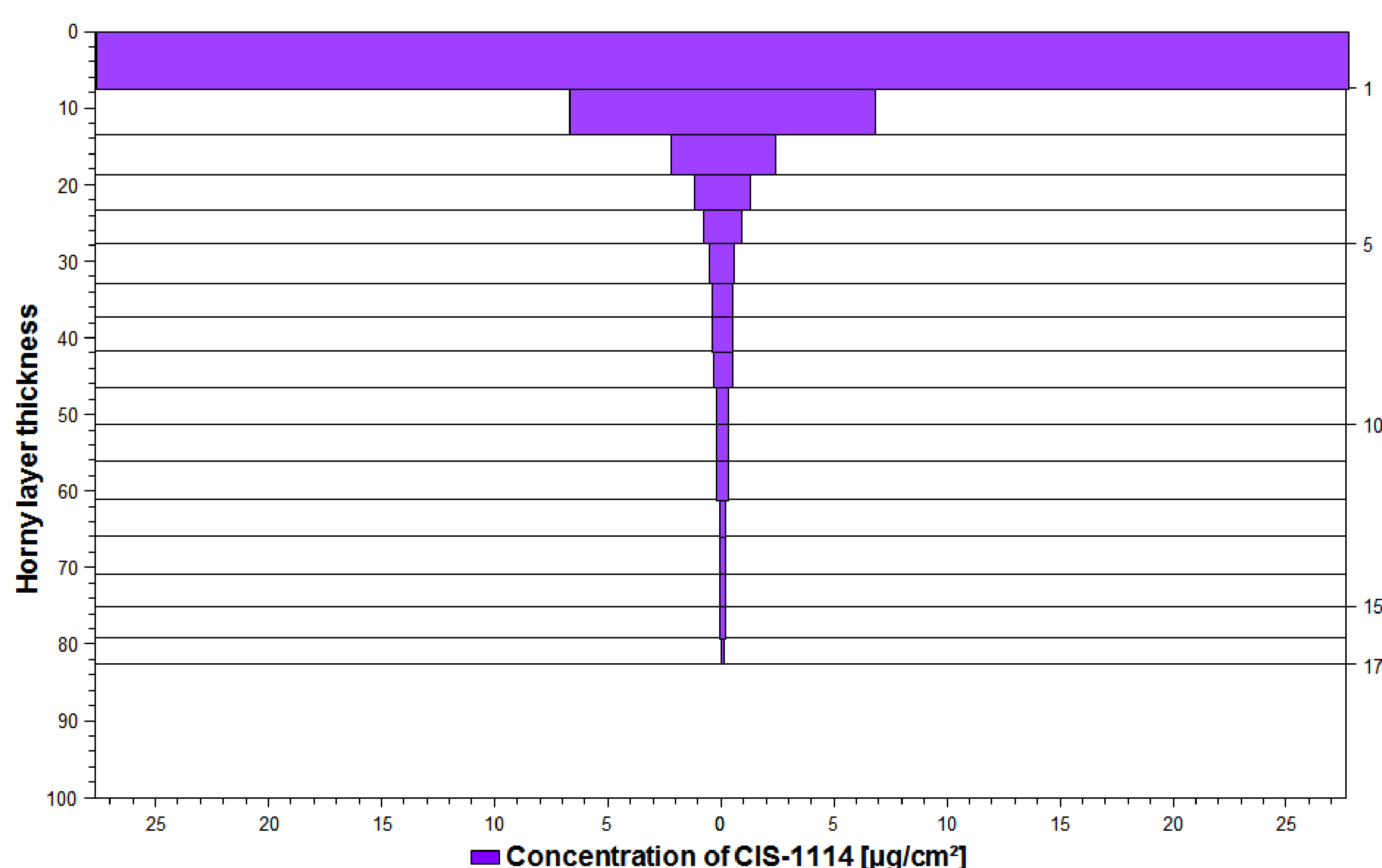


Figure 1: Representative skin penetration profile of CIS-1114 from microemulsion 1.

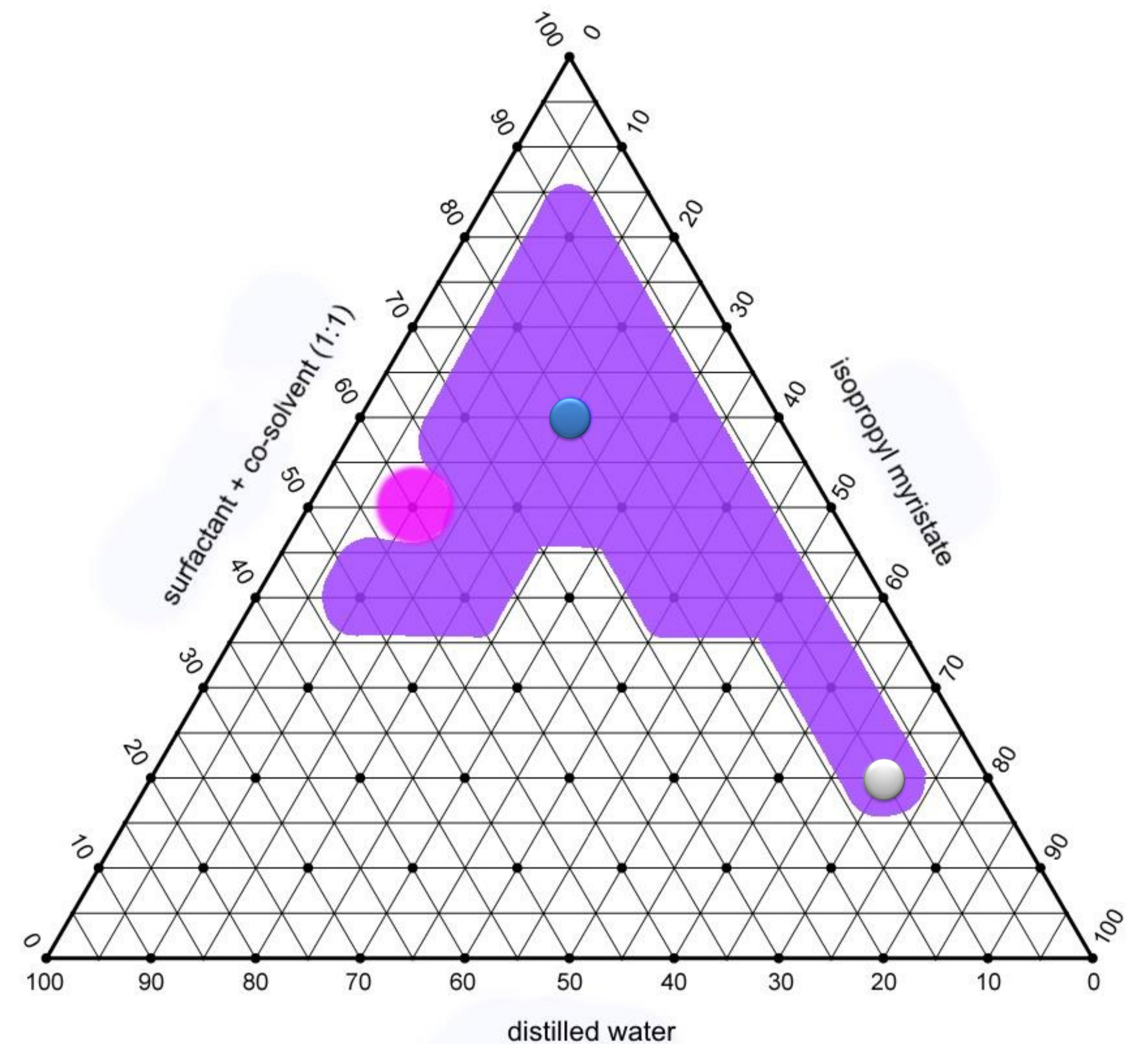


Figure 2: Pseudo-ternary phase diagram; the purple coloured area represents the formation of isotropic microemulsions, the pink area indicates liquid crystals.

Blue spot: microemulsion 1 (30 % isopropanol, 30 % Lipoid S75, 20 % isopropyl myristate, 20 % distilled water)

White spot: microemulsion 2 (10 % isopropanol, 10 % Lipoid S75, 70 % isopropyl myristate, 10 % distilled water)

Results and Discussion

CIS-1114 penetrated into the stratum corneum from all formulations, whereas the deepest skin penetration could be observed from the ethanolic solution. The microemulsion and the liposomes delivered comparable results, but the liposomes were unstable and already showed macroscopically visible coalescence after three weeks. Skin penetration from Ultraphil[®] was higher than from the microemulsion. After the preliminary trials, especially microemulsions were of interest; figure 1 shows a representative skin penetration profile of CIS-1114 from microemulsion 1.

By analyzing a pseudo-ternary phase diagram (figure 2), a formula for a microemulsion with a lower content of surfactant and co-solvent, referred as microemulsion 2 (figure 2, white spot), could be found. In future studies, skin penetration from the two microemulsions will be compared and the influence of microemulsion 2 on skin hydration, sebum content, pH and TEWL shall be determined. Also semisolid formulations with emollient properties will be in the focus of further studies.

Acknowledgements

This work was financed by CIS GmbH and the research platform "Characterisation of Drug Delivery Systems on Skin and Investigation of Involved Mechanisms", University of Vienna.

References

[1] Mahrhauser, D., et al, 2015. "Influence of a Multiple Emulsion, Liposomes and a Microemulsion Gel on Sebum, Skin Hydration and TEWL," International Journal of Cosmetic Science, 181–86.