Penetration Enhancer Effect of Sucrose Esters

Boglarka Balazs¹, Gabor Vízseralek², Konstantin Tsinman³, Maria Budai-Szucs¹, Szilvia Berko¹, Krisztina Takacs-Novak², ³, Balint Sinko¹, ², Erzsébet Csányi¹

¹Department of Pharmaceutical Technology, University of Szeged, Szeged, Hungary ²Department of Pharmaceutical Chemistry, Semmelweis University, Budapest, Hungary ³Pion Inc., Billerica, MA, USA

PURPOSE

The aim of this study was to investigate the behavior of promising penetration enhancers through two different skin test systems. Hydrogel based transdermal formulations were developed and were compared to ibuprofen (IBU) as a nonsteroidal anti-inflammatory drug (NSAID). Transcutol (TR) and sucrose esters (SEs) were used as bioadhesive penetration enhancer excipients.

The permeability measurements were performed by ex vivo Franz diffusion cell method[1] and a newly developed Skin-PAMPA model[2,3]. Franz diffusion cell measurement is a commonly used research tool for studying diffusion through in vitro synthetic membranes or penetration through ex vivo human skin, while Skin-PAMPA is a recently published technology for the fast prediction of skin penetration. Transdermal preparations were investigated containing 2.64% concentrations of different SEs and/or TR, while the IBU concentration (5%) has been kept constant to be able to see the effect of penetration enhancers.

RESULTS

Table 1. presents the penetration parameters of IBU through excised human epidermis and Skin PAMPA. The SEs increased the IBU penetration through skin appreciably compared to the enhancer free Control gel, but the TR gel did not enhance the IBU permeation. Ex vivo fluxes indicate that sucrose laurate induce faster IBU release than sucrose myristate, however the amount of penetrated IBU after 16 h was higher in case of Sucrose myristate gels, therefore sucrose laurate was not better penetration enhancer for IBU than sucrose myristate in our experiments. In contrast with TR alone application, sucrose myristate-TR gels showed the best penetration parameters and profile for IBU in human skin experiments (Figure 1). Sucrose laurate-TR gel resulted lower penetration than Sucrose laurate gel, but results were not statistically significant. The possible reason of this phenomenon could be that the TR depot effect predominated in case of SL-TR gel, because sucrose laurate could not be able to cause as big lipid disruption. Looking at the skin PAMPA data, lower standard deviation and higher penetration can be observed, however the penetration profiles obtained by Skin-PAMPA and ex vivo Franz cell methods were in good agreement in most cases. PAMPA results clearly indicate the TR depot phenomena, that was proved by the decreased permeated amount of IBU from TR gel against to the Control gel, which was statistically significant after 3 hours (p < 0.001∗∗∗). Penetration enhancer effect of SEs can be seen obviously. While even Sucrose laurate increases the penetration of IBU efficiently, Sucrose myristate gel provided significantly higher penetration profile compared to the Control gel and compared to the Sucrose laurate gel. Combination of sucrose laurate and TR also showed lower penetration profile as it can be seen in case of ex vivo result. The penetration profile of IBU from the Sucrose myristate-TR gel showed the earliest significantly increased IBU amount compared to the Control gel and to the Sucrose laurate gel. The highest average penetration profile of IBU was resulted by this gel.

The determination coefficients (R²) of linear regression of correlation between penetrated amount of IBU through human skin and penetrated amount of IBU through Skin-PAMPA indicated good correlation. The determination coefficients between the in vitro PAMPA measurements and the ex vivo Franz cell methods were found in the range of 0.88-0.99. According to our results, the ex vivo and the in vitro Skin-PAMPA data are in same order of magnitude in all five cases.

CONCLUSIONS

In summary, the results demonstrated that ex vivo or in vitro measurements need to investigate the enhancers’ properties to select the best for in vivo study because of the differences between these data and synthetic membrane values. The new PAMPA membrane was resulted acceptable correlation with Franz cell method. It seems to be effective prediction model of acting mechanism of penetration enhancements as well as drug permeation to the skin. Furthermore our results indicate that TR as cosolvent with sucrose myristate improve significantly the surfactant penetration to the skin and promote to reach the maximum penetration effect. Sucrose myristate and TR could be a potential nontoxic biocompatible penetration enhancer combination for IBU in the transdermal delivery systems.

REFERENCES