Mechanisms of stratum corneum penetration enhancement by topical microemulsions

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Introduction

Continued optimization of microemulsion formulations is described, and further characterization of the permeation of both the model drug and individual constituents of the vehicle itself is reported. This level of detail is rarely, if ever, obtained when the performance of a topical formulation is assessed.

Techniques such as attenuated total reflection infrared spectroscopy provide unique molecular-level information on the mechanisms by which different penetration enhancers elicit their effects and, hence, the underlying reasons why some formulations work better than others.

Methodology

1-The microemulsions comprised oleic acid as the oil phase, and Tween 20 and Transcutol as surfactant and co-surfactant, respectively, in the (w/w) ratio of 20:40:40.

2-The effects of the microemulsion, and of its individual components, on the conformational order of the intercellular lipids of the SC, and on the hydration level of the barrier, were assessed by attenuated total reflectance-Fourier transform infrared spectroscopy.

3-Measurements were made as a function of depth into the SC by progressively tape-stripping the membrane in the normal way.

4- SC uptake of the microemulsion components was determined via extraction and analysis of the collected tape strips using LC-MS.

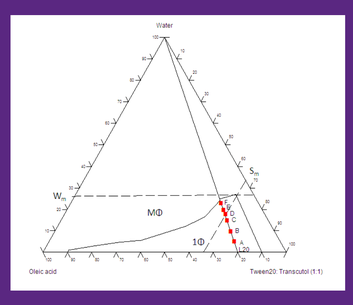
5- LSCM was used to optically section through the skin to produce a z-stack series of images showing the penetration pathway as a function of depth into the SC and upper epidermis.

Results and Discussion

Table1 Selected microemulsion formulations (%w/w)

	A	B	C	D	E	F
Oleic acid	19	18	17	16.2	16	15.4
Tween20	38	36	34	32.9	32	30.8
Transcutol	38	36	34	32.9	32	30.8
Water	5	10	15	18	20	23

Fig.1 Phase diagram



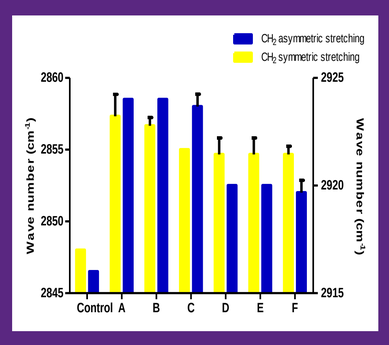


Fig.2 Changes in SC lipid CH_2 symmetric and asymmetric peak positions after application of selected microemulsions.

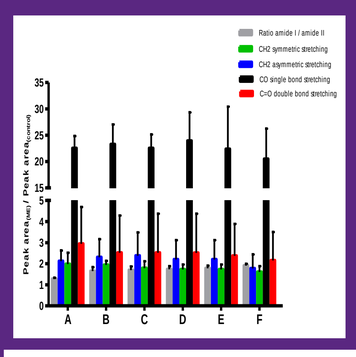


Fig.3 Changes in the SC lipid fundamental peaks areas after application of selected microemulsions.

Oleic acid Effects

Fig.4 Frequency shifts of CH_2 a) asymmetric and b) symmetric stretching

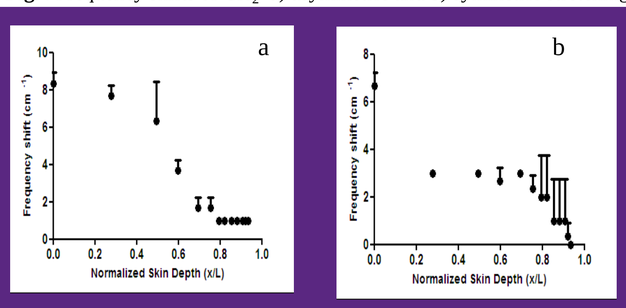
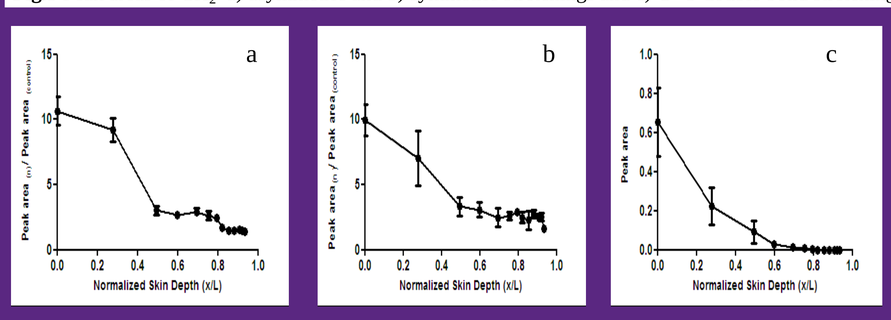


Fig.5 Peak areas of CH_2 a) asymmetric and b) symmetric stretchings and c) C=O double bond stretching



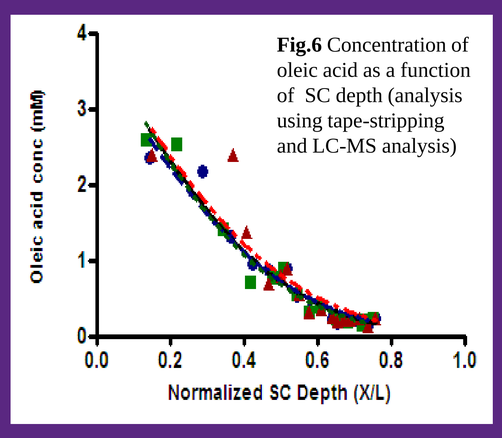
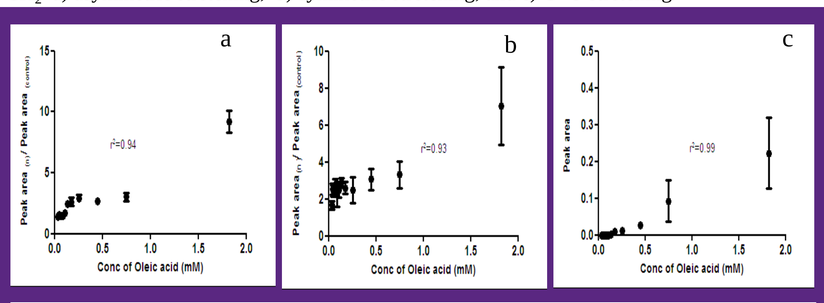


Fig.6 Concentration of oleic acid as a function of SC depth (analysis using tape-stripping and LC-MS analysis)

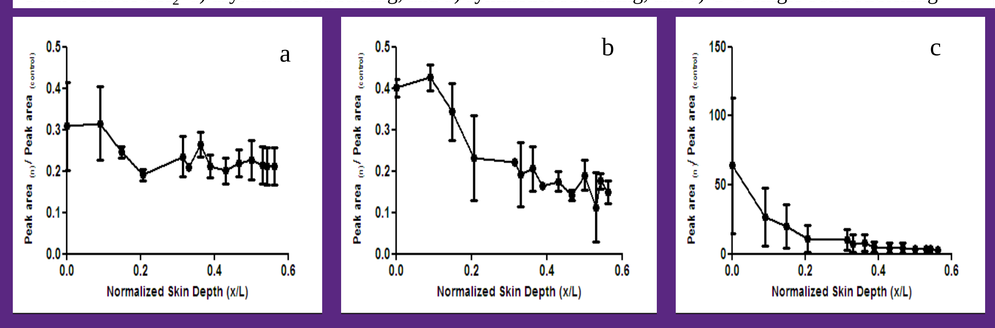
Fig.7 Correlations between oleic acid concentrations as a function of SC depth and peak areas of CH_2 a) asymmetric stretching, b) symmetric stretching, and c) C=O stretching



The results show the penetration of oleic acid through the SC barrier, with lipid disordering and phase separation.

Tween20 effects

Peak areas of CH_2 a) asymmetric stretching, and b) symmetric stretching, and c) C-O single bond stretching.



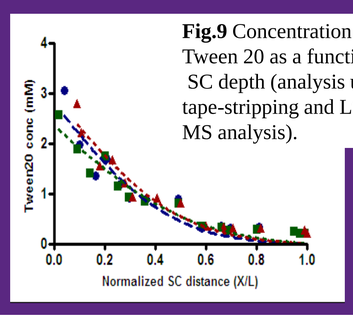


Fig.9 Concentration of Tween 20 as a function of SC depth (analysis using tape-stripping and LC-MS analysis).

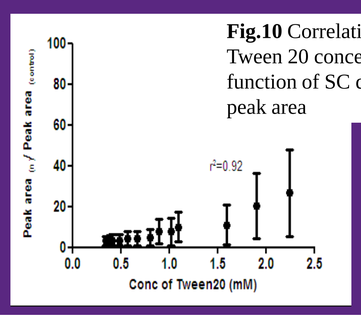


Fig.10 Correlation between Tween 20 concentration as a function of SC depth and C-O peak area

The results show the penetration of Tween 20 and evidence of lipid extraction

Transcutol effects

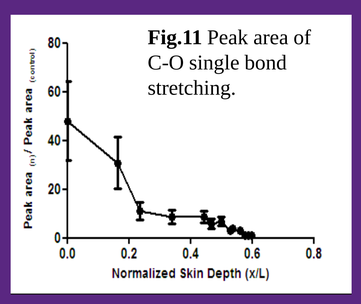


Fig.11 Peak area of C-O single bond stretching.

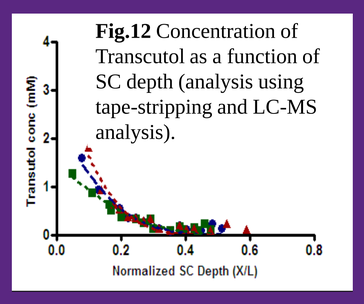


Fig.12 Concentration of Transcutol as a function of SC depth (analysis using tape-stripping and LC-MS analysis).

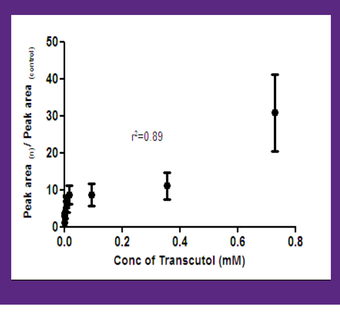


Fig.13 Correlation between Transcutol concentration as a function of SC depth and C-O peak area

Results show the penetration of Transcutol and evidence of H-bonding

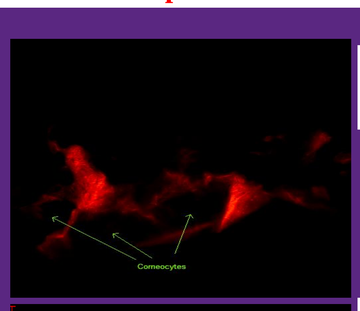
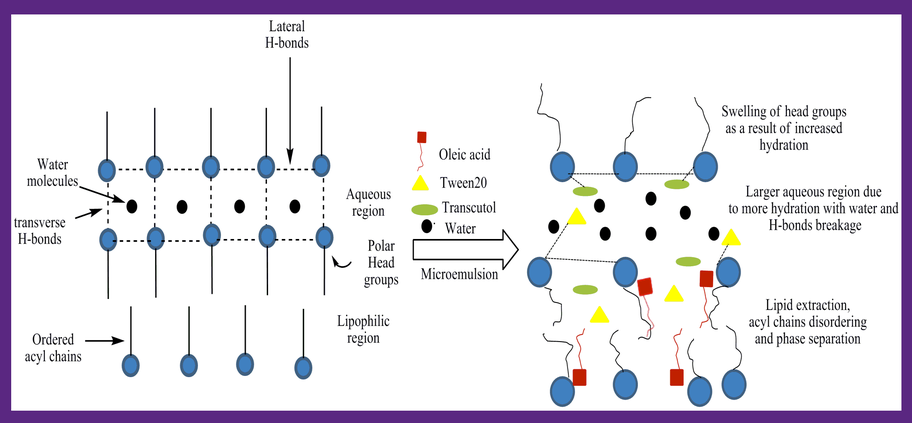


Fig.14 Recostructed Z-stack LSCM image of skin treated with microemulsion A containing Nile red as the fluorophore.

Penetration Pathway is mainly through the intercellular lipids.

Fig.15 xz-plane LSCM image after sectioning through a xy-plane using one projection at 0º angle.

Summary



Conclusion

The SC structure was perturbed by all components of the microemulsion system studied and the degree of the effects detected was proportional to the level of the respective component present in the skin.

Reference

[1] Alberti I, Kalia YN, Naik A, Bonny JD, Guy RH. 2001. In vivo assessment of enhanced topical delivery of terbinafine to human stratum corneum. Journal of Controlled Release 71:319-327.