PARACELLULAR AND FOLLICULAR PATHWAYS IN TRANSDERMAL DRUG DELIVERY – IMPLICATIONS OF PHYSICAL DIMENSIONS

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SHOULD COSMETIC INGREDIENTS CROSS THE SC?

Cosmetics – enhances beauty, superficial

Drugs – prevent, diagnose or treat disease or modify any structure or function of the body

Cosmeceuticals -- ???
RJ Schueplein & IH Blank
PERMEABILITY OF THE SKIN
Physiological Reviews 51:702-747, 1971

PATHWAYS ACROSS BARRIER

- Hair follicles
- Sweat ducts
- Intercellular (SC)
- Transcellular (SC)
CONTENT AND COMPOSITION OF PIG EPIDERMAL CELLS

GM GRAY & H YARDLEY
Ceramide Nomenclature

Fatty acid

Cholesterol

N  non-OH FA
A  alpha-OH FA
O  omega-OH FA

EOS

NS

P  phytosphingosine

H  6-OH-sphingosine

E  ester-linked FA

Motta S et al. Ceramide composition of the psoriatic scale BBA 1993
Covalently Bound Lipids
TRILAMELLAR LIPID STRUCTURES: Broad-Narrow-Broad Lucent Bands

Transmission electron micrographs displaying three, six, or nine lamellae within the intercellular space of stratum corneum. Bar = 25 nm. Swartzendruber et al. 1989
Molecular models of the intercellular lipid lamellae from epidermal stratum corneum

*Biochimica et Biophysica Acta (BBA) Biomembranes* Volume 1616, Issue 2, 13 October 2003, Pages 121-126

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Densitometer Tracing of the Six-Band Pattern of Lamellae from the Intercellular Space of Stratum Corneum

Shaded boxes represent the pattern of reduced ruthenium on the micrograph. The first set of tick marks beneath the boxes indicate the centers of the electron dense bands, while the lower set of tick marks indicate the centers of the lucent bands. (Hill & Wertz BBA 2003)
Molecular Model for the Three-Band Pattern Between the Edges of Adjacent Corneocytes

The shaded boxes represent the pattern of reduced ruthenium on a corresponding portion of a transmission electron micrograph. (Hill & Wertz BBA 2003)
Molecular Model of the Central Three Bands of the Nine-Band Pattern

Note the linoleate tails of acylceramide molecules in the central lamella. Shaded boxes represent the pattern of reduced ruthenium on a corresponding portion of a transmission electron micrograph. (Hill & Wertz BBA 2003)
Cryo-EM of Vitreous Section of Human Skin

with permission from Lars Norlen
INTERCELLULAR PATHWAY THROUGH STRATUM CORNEUM

MK Nemanic & PM Elias  In Situ Precipitation: A Novel Technique for Visualization of Permeability Pathways in Mammalian Stratum Corneum
J Histochem Cytochem 28:573-579, 1980

CA Squier & CA Lesh  Penetration pathways of different compounds through epidermis and oral epithelium. J Oral Path 17:512-516, 1988
SC -- EXPECTATIONS

• Small molecules could diffuse through the intercellular space
• Vesicles and most particles (>13 nm) should not penetrate the SC
• The smallest particles may penetrate into the intercellular spaces of the stratum corneum
Characteristics Favorable for Diffusion of Molecules Across the SC

- MW $\leq 400$
- $P_{o/w} \sim 1$

R.H. Guy, J Hadraft Selection of Drug Candidates for Transdermal Drug Delivery Drugs and the Pharmaceutical Sciences 35:59-81, 1989
NANOPARTICLES

< 100 nm diameter

Liposomes
Quantum Dots
Nanoparticles (polymeric)
Nanoemulsions
TiO$_2$
LIPOSOMES

AD Bangham, MM Standish, JC Watkins
Diffusion of univalent ions across the lamellae of swollen phospholipids.

Cambridge
Bob Horne – EM
Gerald Weissmann -- lysosomes
LIPOSOMAL DIAMETERS

• SUV – 25 – 50 nm
• LUV – 50-500 nm
• MLV – 500-10,000 nm
• MVV – 350-500 nm
CONVENTIONAL LIPOSOMES DO NOT PENETRATE SC


FLEXIBLE VESICLES

- Transfersomes
- Niosomes
- Ethosomes
FLEXIBLE VESICLES

- Transfersomes
- Niosomes
- Ethosomes
FLEXIBLE VESICLES PENETRATE THROUGH THE INTERCELLULAR SPACES OF THE SC

• A Schatzlein, G Cevc  In: G Cevc, F Paltauf (Eds.) Phospholipids – characterization, metabolism and novel applications, AOCS Press, Champaigne IL, 1993, pp 189-207


JA Bouwstra, PL Honeywell-Gnuyen Advan Drug Delivery Rev 54S:S41-S55, 2002
NANOPARTICLE INTERACTIONS WITH THE STRATUM CORNEUM


X Wu, GJ Price, RH Guy  Molec Pharmaceutics 6:1441-1448, 2009
X Wu, GJ Price, RH Guy  Molec Pharmaceutics 6:1441-1448, 2009
DIAMETER OF HAIR FOLLICLE OPENINGS AT THE SKIN SURFACE

Terminal Hair Follicles – 172 +/- 70 μm

Sebaceous Follicles – 86 +/- 37 μm

FOLLICLES -- EXPECTATIONS

- Molecules could diffuse into hair follicles
- Particles or vesicles up to 50 µm could penetrate
FOLLICULAR TRANSPORT ROUTE – RESEARCH PROGRESS AND FUTURE PERSPECTIVES

F. Knorr, J Lademann, A Patzelt, W Sterry, U Blume-Peytavi, A Vogt

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