32nd IFSCC Congress
London 19–22 September 2022
"WHERE BEAUTY, SCIENCE AND INNOVATION MEET"

NIHON KOLMAR CO., LTD.

Poster ID : 230

Stratum corneum symmetry breaking: the polarity for permeability

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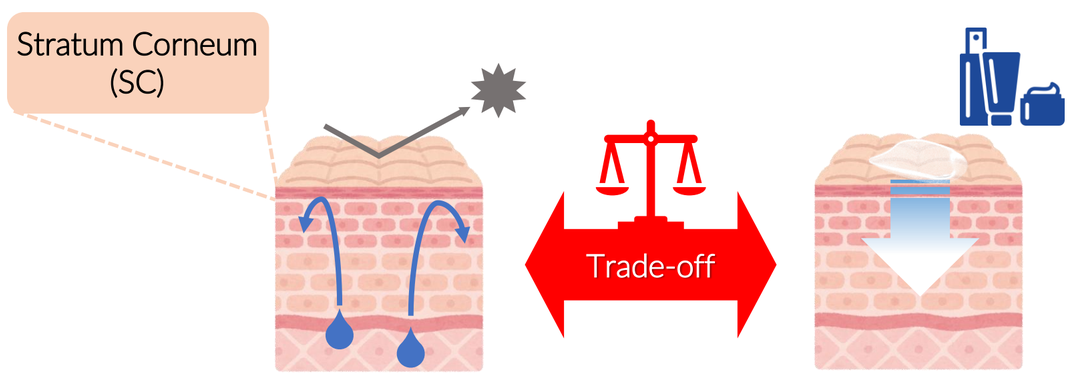
Introduction:

Trade-off relationship between the barrier function and the permeation of the SC



the barrier function

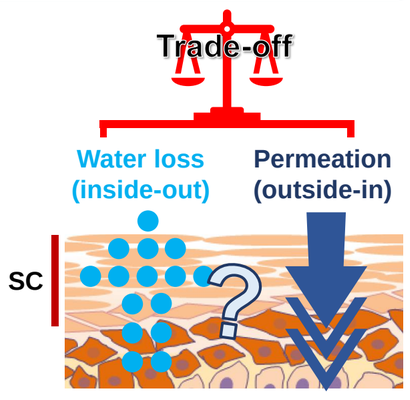
The outermost layer of the skin plays a barrier function to protect the human body from water transpiration and invasion of foreign substances.

the permeation

There are various kinds of active ingredients and base agents contained in cosmetics and topical products. These ingredients need to be delivered efficiently to their respective target sites when applied to the skin.

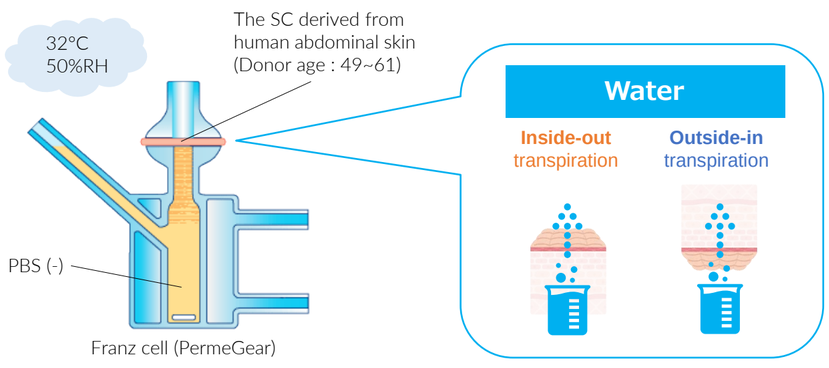
In this study

In order to solve this problem, we hypothesized that the SC does not have a homogeneous barrier function, but rather that there is a polarity, or "symmetry breaking", with respect to inside-out and outside-in permeability. Thus, we attempted to elucidate a novel SC function by focusing on the direction of its permeability.



Materials & Methods:

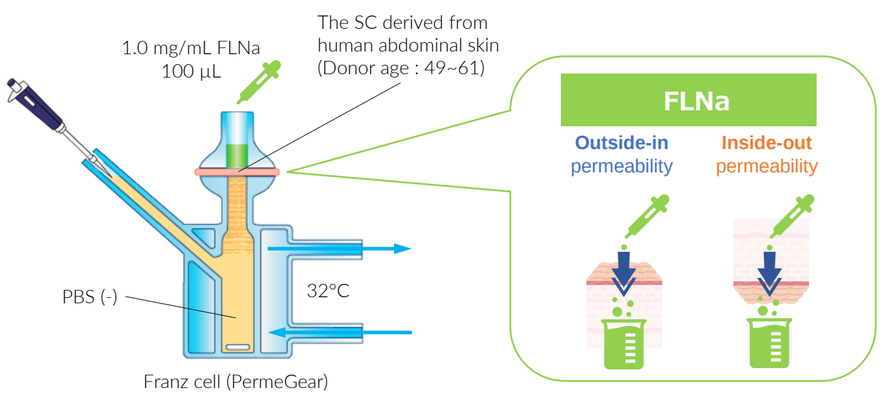
1. Measurement of water transpiration through the SC



The inside-out transpiration was evaluated making the surface side of the SC faces upward, and the outside-in transpiration was evaluated by making the back of the SC face upward.

After acclimation, the weight containing Franz cells was measured up to 24 hours.

2. Evaluation of Sodium Fluorescein (FLNa) permeability through the SC



The outside-in permeability was evaluated making the surface side of the SC faces upward when set in the Franz cell, and the inside-out permeability was evaluated by making the back of the SC face upward.

A volume of 150 µL of receptor fluid was collected up to 24 h, and an equal volume of PBS(-) solution was added to the receptor compartment. Fluorescence intensity was measured at 495 nm excitation/ 550 nm measurement wavelength.

The apparent permeation parameter of FLNa was calculated from the following equation derived from the diffusion model.

$$Q = \frac{KCvD}{L}t - \frac{KCvL}{6}$$

Q : the cumulative permeated amount
L : the thickness of the SC
Cv : the drug concentration in the donor phase
t : time
K : the apparent partition coefficient
D : the apparent diffusion coefficient

3. Molecular localization analysis of SC by TOF-SIMS

Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS) analysis of vertical cross sections was performed in SC.

Results & Discussion 1:

1. Measurement of water transpiration through the SC

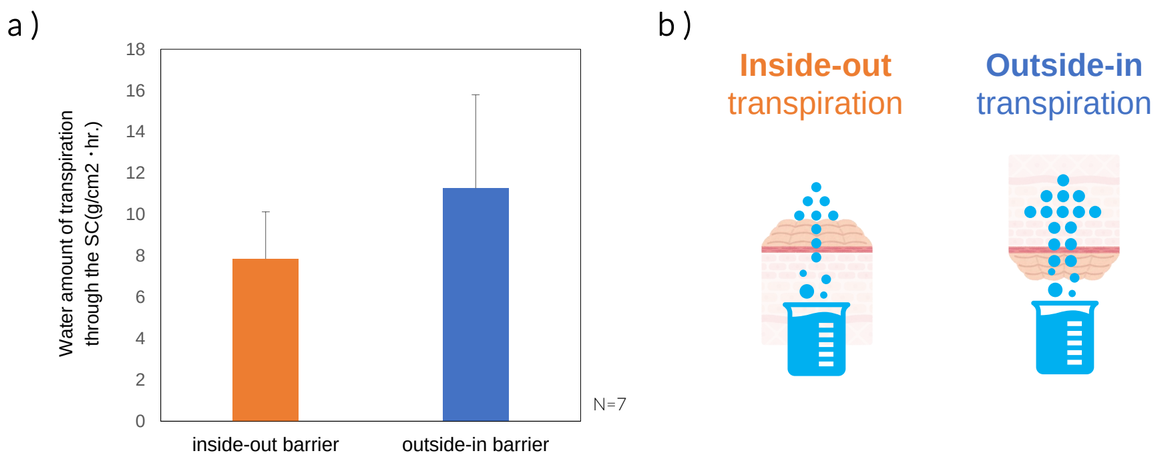


Figure 1. a) Water loss of transpiration through the SC per unit area and unit time. The experiment is performed under 32°C and 50%RH. The value is mean ± SD.
b) Experimental conditions for each legend. The inside-out transpiration was evaluated making the surface side of the SC faces upward, and the outside-in transpiration was evaluated by making the back of the SC face upward.

In the evaluation of the inside-out and outside-in permeability of water transpiration, differences were observed in the two models.
It is suggested the existence of polarity within the SC.

Results & Discussion 2:

2. Evaluation of FLNa permeability through the SC

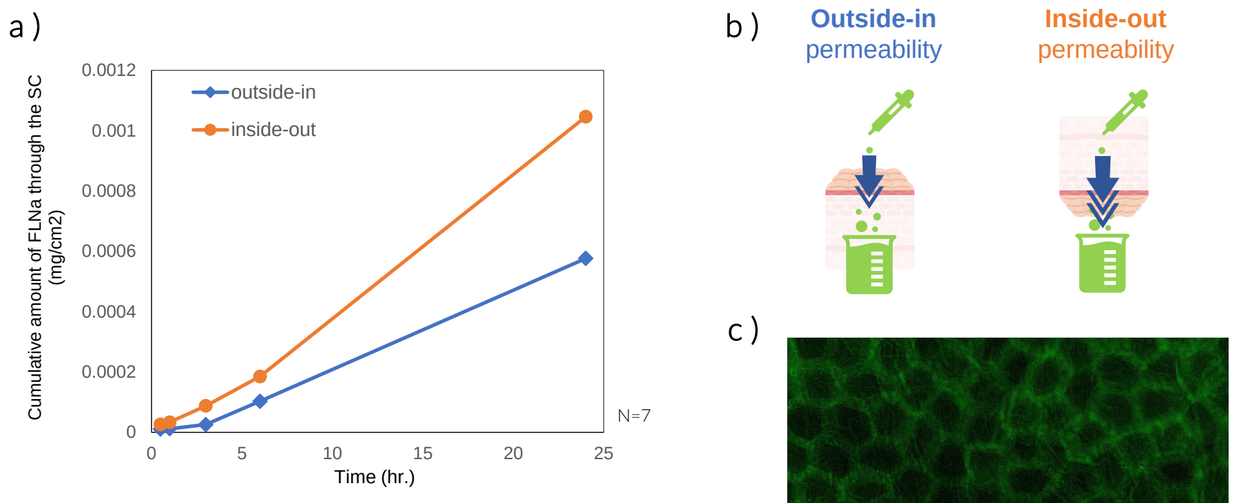


Figure 2. a) Cumulative amount of FLNa through the SC per unit area.
b) Experimental condition of each legend. The outside-in transpiration was evaluated making the surface side of the SC faces upward, and the inside-out transpiration was evaluated by making the back of the SC face upward.
c) Fluorescence microscopic image of the SC after evaluation of FLNa permeability.

The amount of permeated FLNa and permeation parameter differed between the two models. Therefore, the SC seems to have the polarity in term of the permeability.

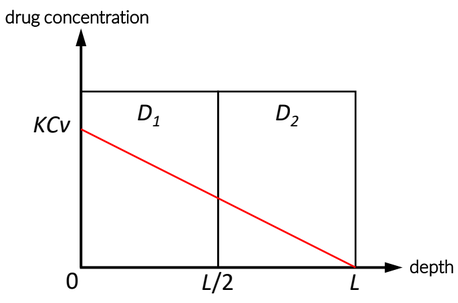
Table 1. Calculated permeation parameter. Where K is apparent partition coefficient and D is apparent diffusion coefficient in each model.

	Outside-in	Inside-out
K (-)	0.160	0.211
D (cm²/hr.)	3.28×10^{-7}	4.39×10^{-7}

In terms of the permeation pathway, it is considered that intercellular lipids are involved in the FLNa permeation pathway.

SC equal division model

We hypothesized a equal division model in which the SC is divided into two in the depth; upper SC and lower SC. The relationship of parameters is expressed following equation.



$$P = \frac{KD}{L}$$

$$\frac{1}{P} = \frac{1}{P_1} + \frac{1}{P_2}$$

$$D_{\text{outside-in}} = \frac{2}{\frac{1}{D_{\text{upper}}} + \frac{K_{\text{upper}}}{D_{\text{lower}}}}$$

$$D_{\text{inside-out}} = \frac{2}{\frac{1}{D_{\text{lower}}} + \frac{K_{\text{lower}}}{D_{\text{upper}}}}$$

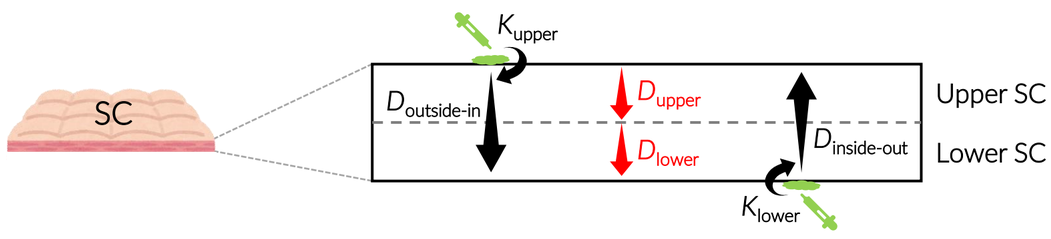
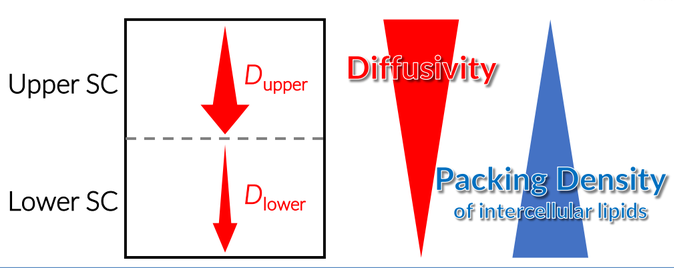


Table 2. Calculated apparent diffusion coefficient in each division.

D_{upper} (cm²/hr.)	2.96×10^{-7}
D_{lower} (cm²/hr.)	1.80×10^{-7}

Diffusion coefficients are different between the upper and lower SC. This results suggest that the formulation of polarity in term of permeability within the SC is dependent on heterogeneity in diffusivity.



Some reports have revealed that the lower part of the SC has more tightly packing of intercellular lipids.
This may be related to diffusivity.

Results & Discussion 3:

3. Molecular localization analysis of SC by TOF-SIMS

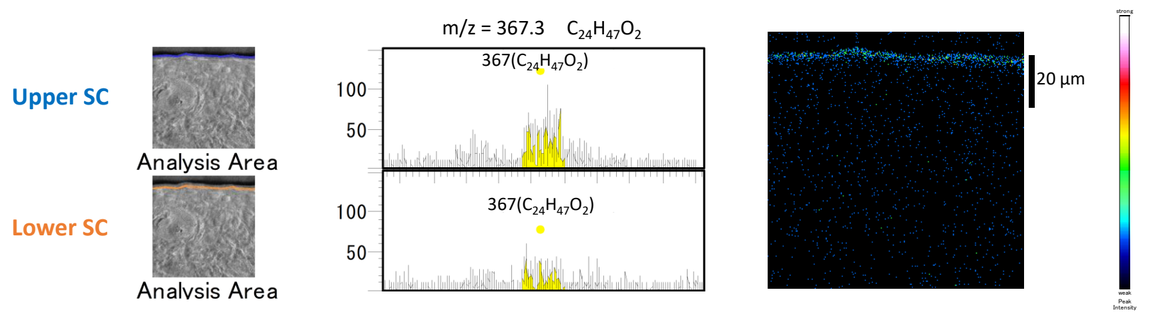


Figure 3. The localization of fatty acids analyzed by TOF-SIMS.

The localization of fatty acids was observed on the surface side of the SC. The localization of fatty acids observed on the surface side of the SC may represent the degradation products of ceramides during turnover.

Conclusions:

Our research has revealed that there are differences in the outside-in and inside-out permeability of the SC, even for the same substance . It is suggested that the SC forms quantitative, qualitative, and structural changes due to turnover and that it may strategically establish spatial barrier. We believe that this elucidation about function of the SC is a breakthrough for both strengthening barrier function and improving transdermal permeation.

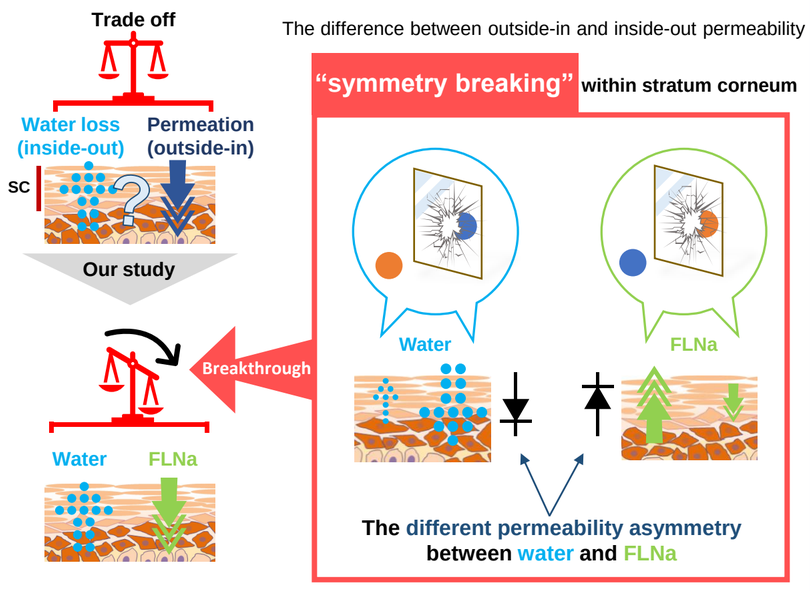


Figure 4. Our study schematic diagram