The penetration mechanism through the stratum corneum depending on the structure of microemulsions

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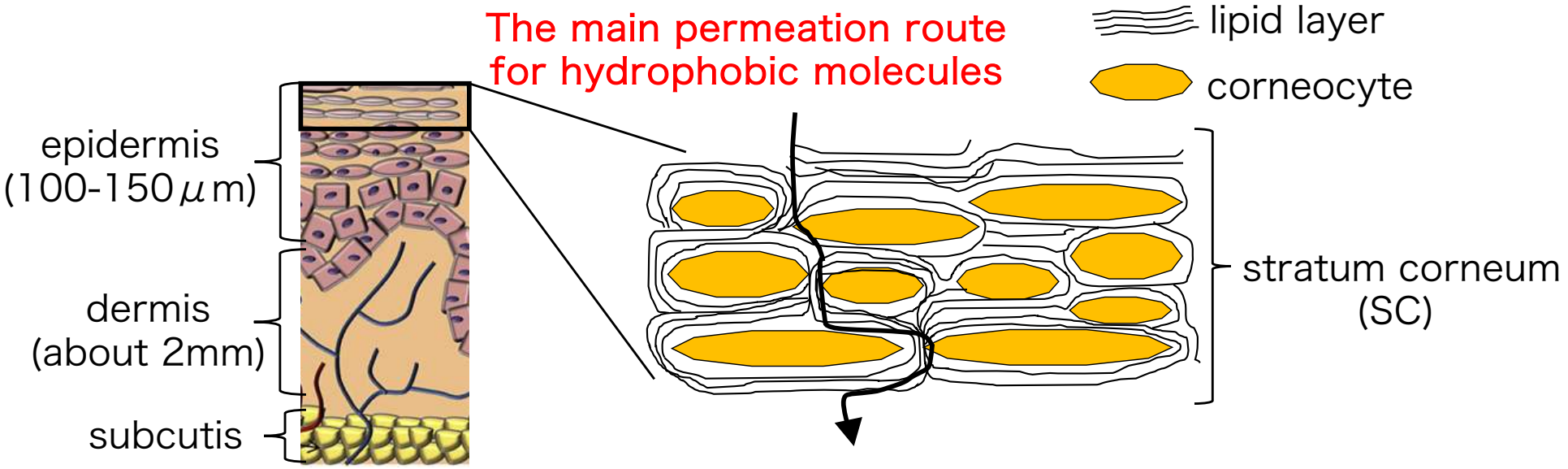
Background

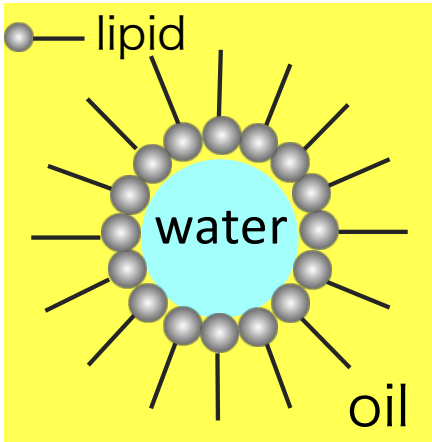
Transdermal drug delivery system (TDDS)

non-invasiveness, sustained release, self-administration,
enhancement of therapeutic efficiency



R. Liuzzi et al. *Colloids and Surfaces B: Biointerfaces* 139 (2016) 294–305

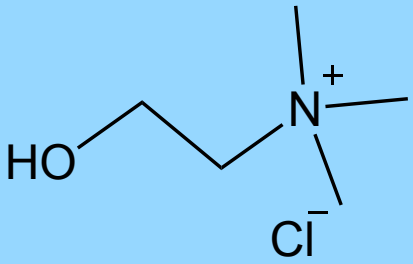
TDDS of poorly soluble drugs in oil can be achieved by using water-in-oil microemulsion (W/O ME)



TDDS of drugs that poorly soluble in both oil and water is still difficult.

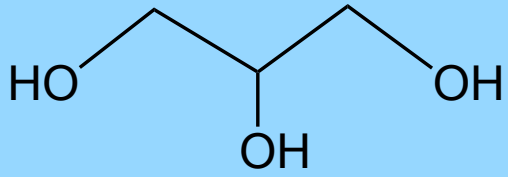
Deep eutectic solvent (DES)

hydrogen bond acceptors (HBA)



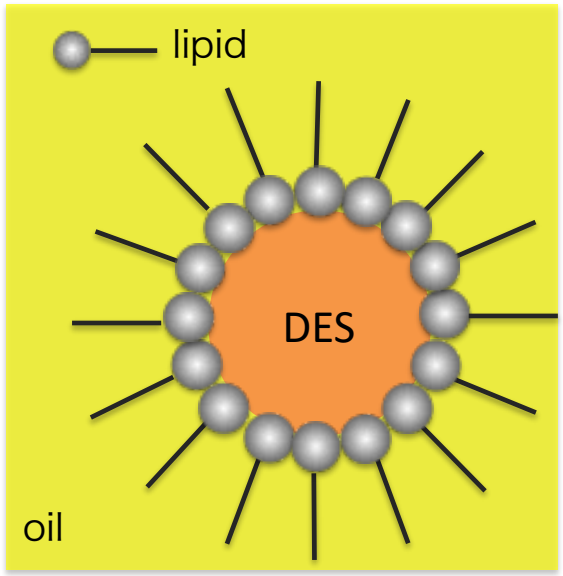
choline chloride

hydrogen bond donors (HBD)



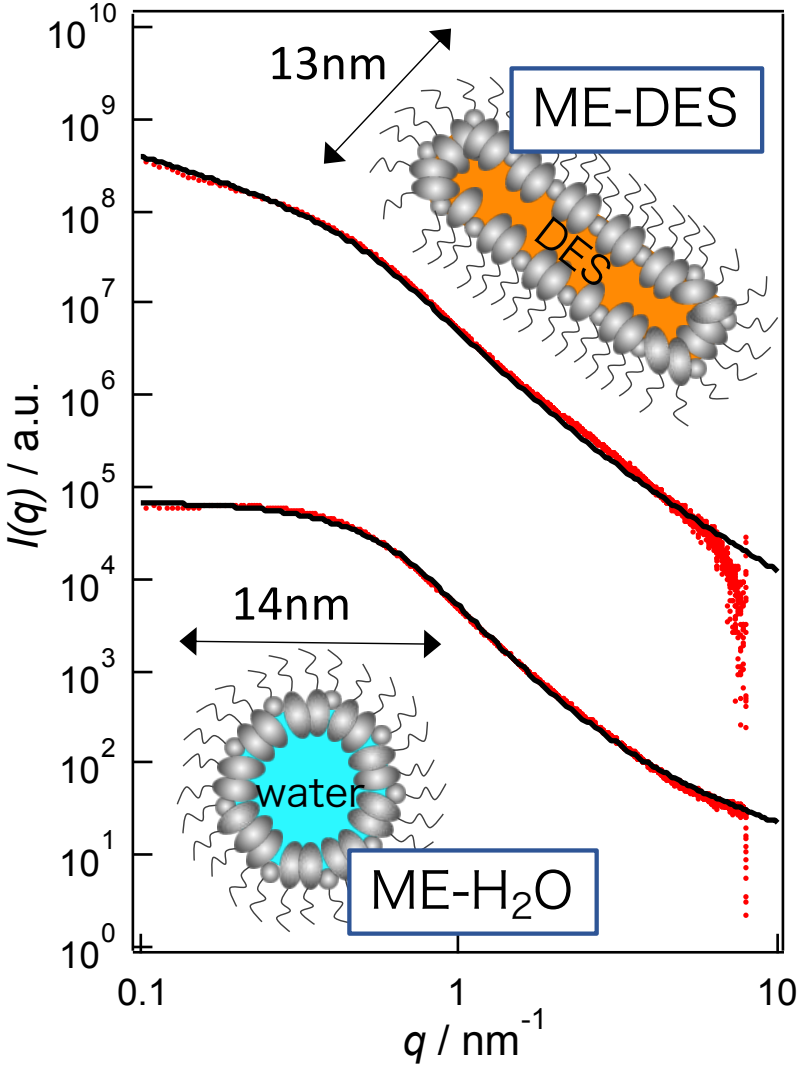
glycerol

1 : 2

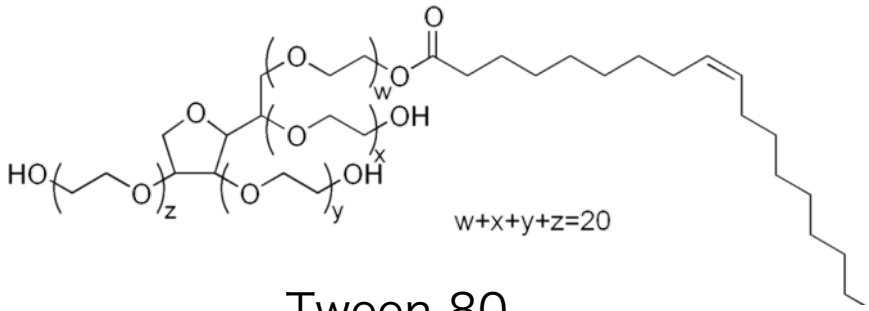


- Self-association through hydrogen bond interactions
- Low cost and biocompatible components
- Similar properties and phase behaviors to ionic liquids
- **DES can dissolve many types of poorly soluble compounds** (polyphenol, danazol, itraconazole, chitin and protein)

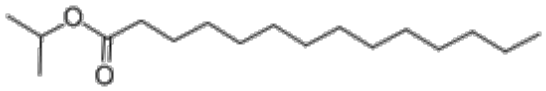
DES-in-oil microemulsions (MEs) could be used for a potential carrier of various type of drugs.



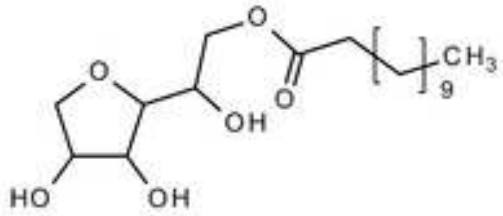
M. Sakuragi et al. *Langmuir* 2018,



Tween 80



Isopropyl myristate (IPM)
suitable oil for
pharmaceutical use



Span 20

Tween-80/Span-20 = 3 / 1 (wt/wt)
Surfactant / IPM (solvent) / H_2O or DES
= 20 / 76 / 4

DES leads to the structural transition from a sphere to a cylinder occurred

We investigated the relationship between the structure of ME and the penetration mechanism of the SC

Transdermal experiments

Penetration of hydrated SC

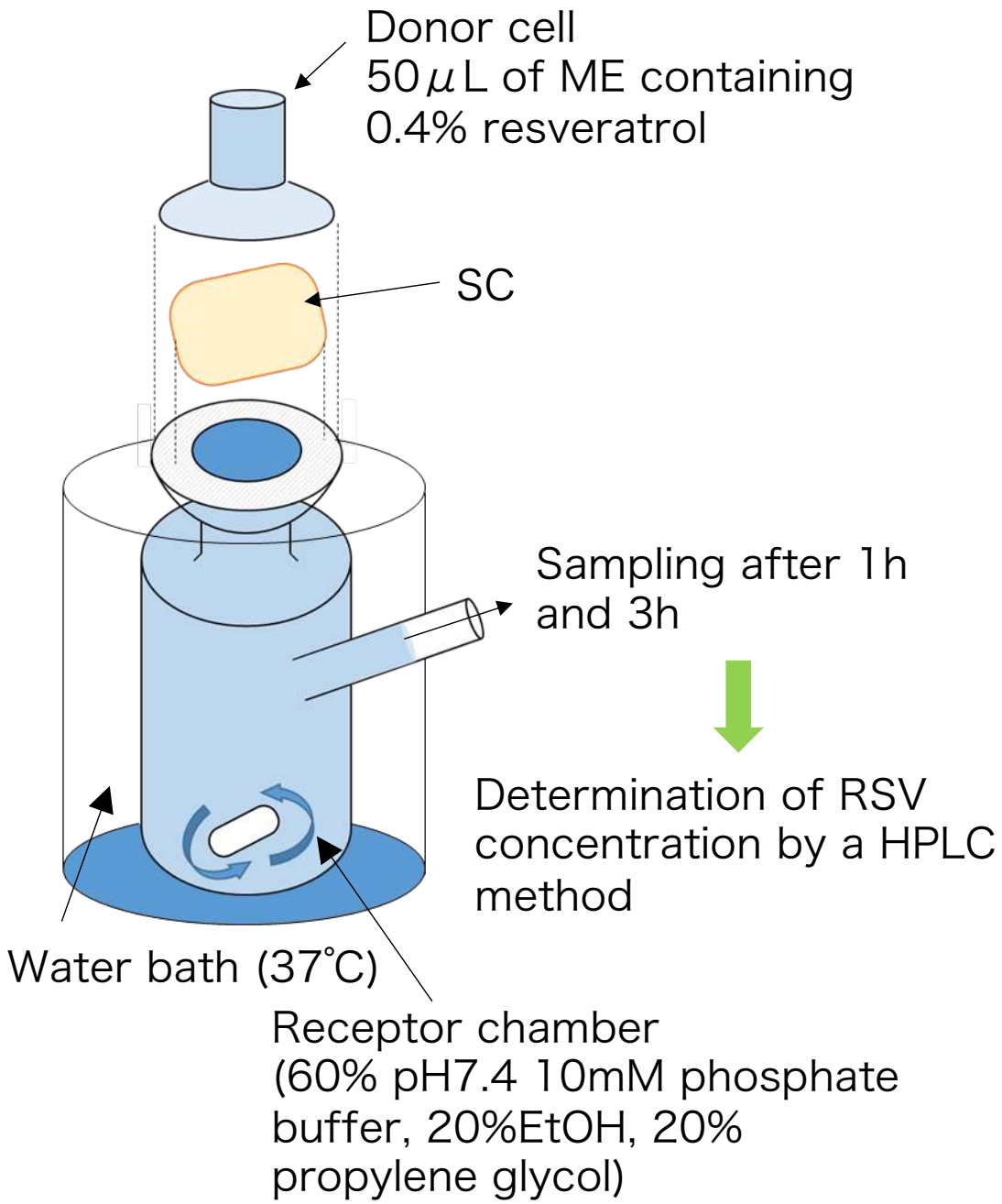
The SC was separated from the hairless mouse skin by enzyme treatment with trypsin.

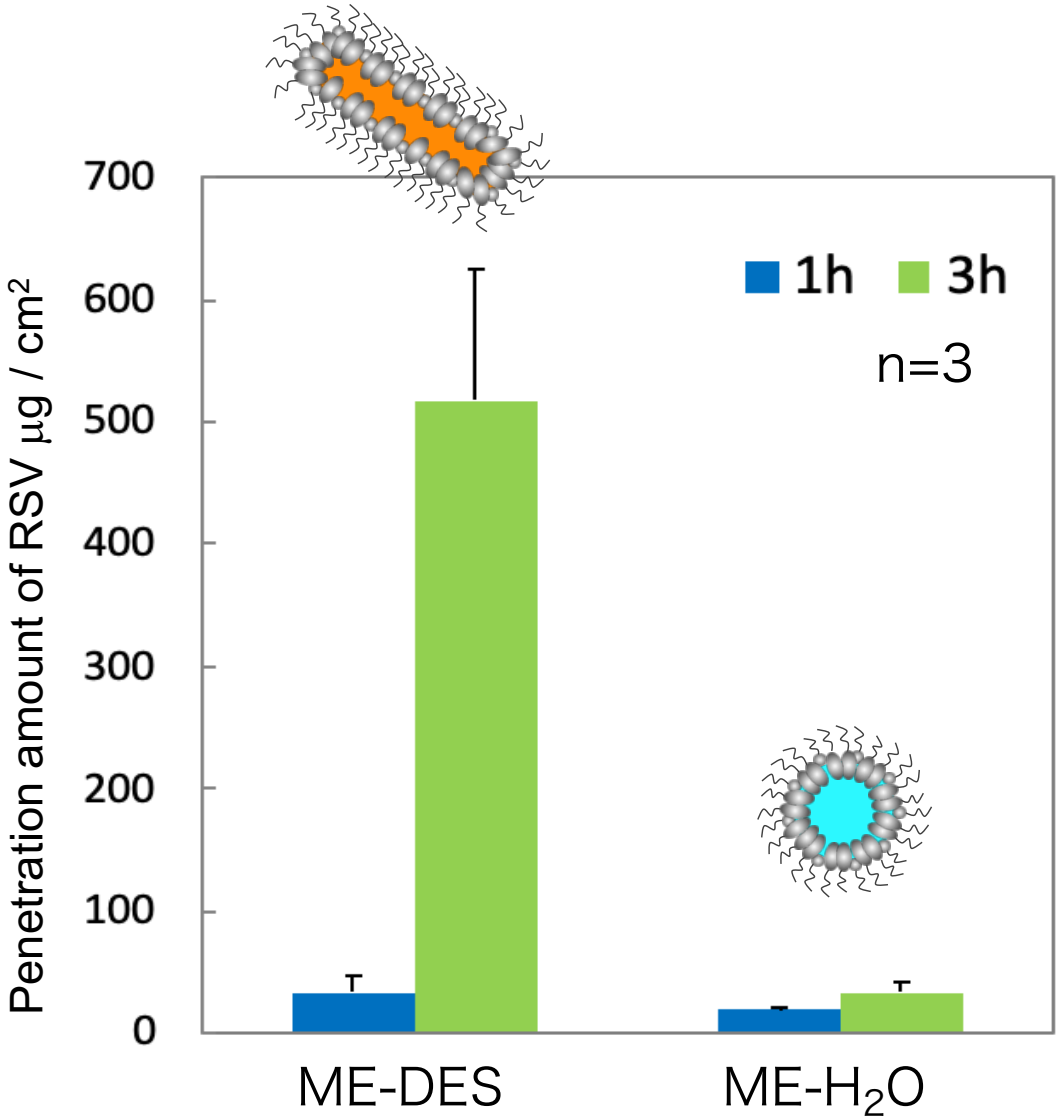
↓

The SC was dried in vacuum, and then the SC was immersed in water.

↓

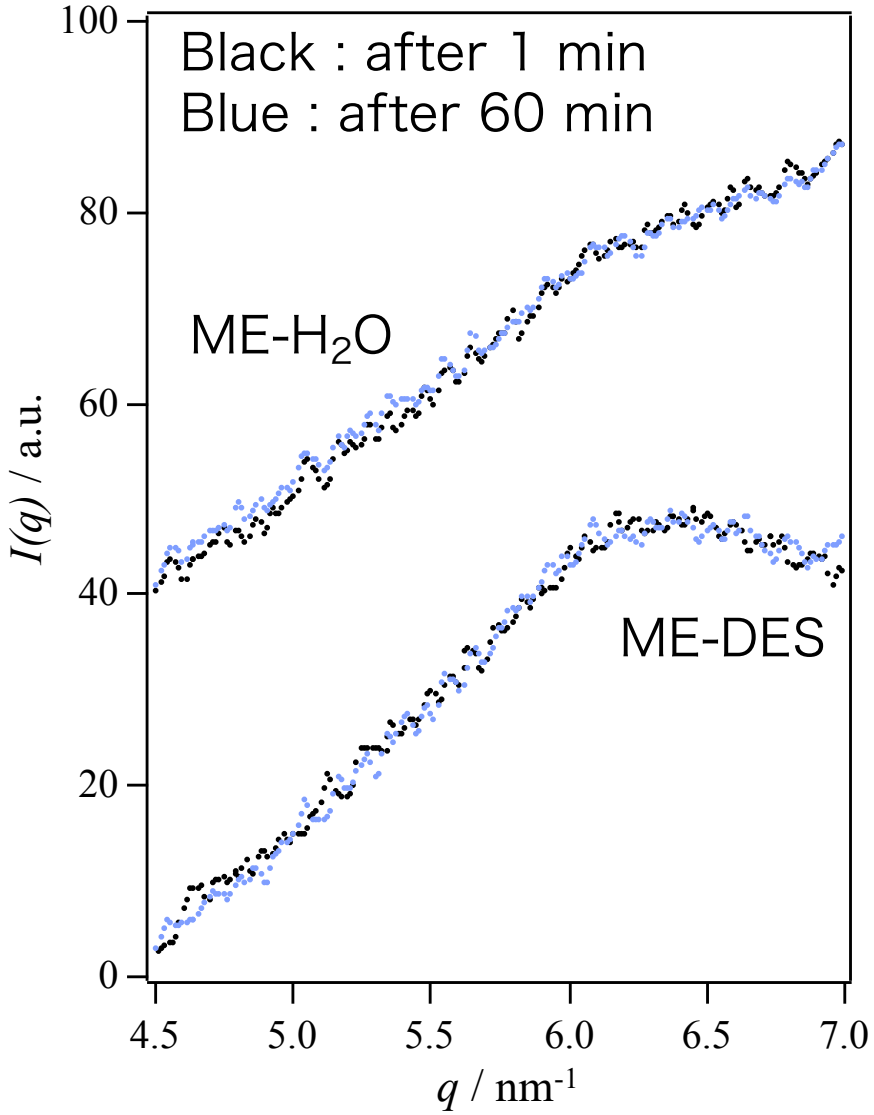
The SC was dehydrated under an air flow until it reached 30wt% water contents.

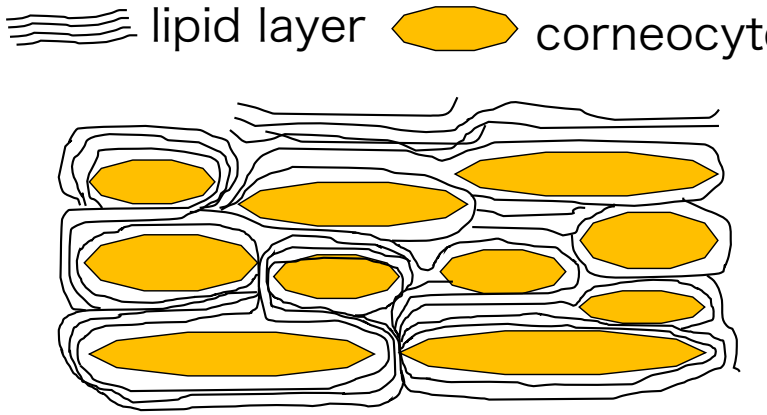




ME-DES penetrates the SC much more than ME-H_2O although the size of ME-H_2O is smaller than ME-DES.

Structural transition of soft keratin in corneocyte

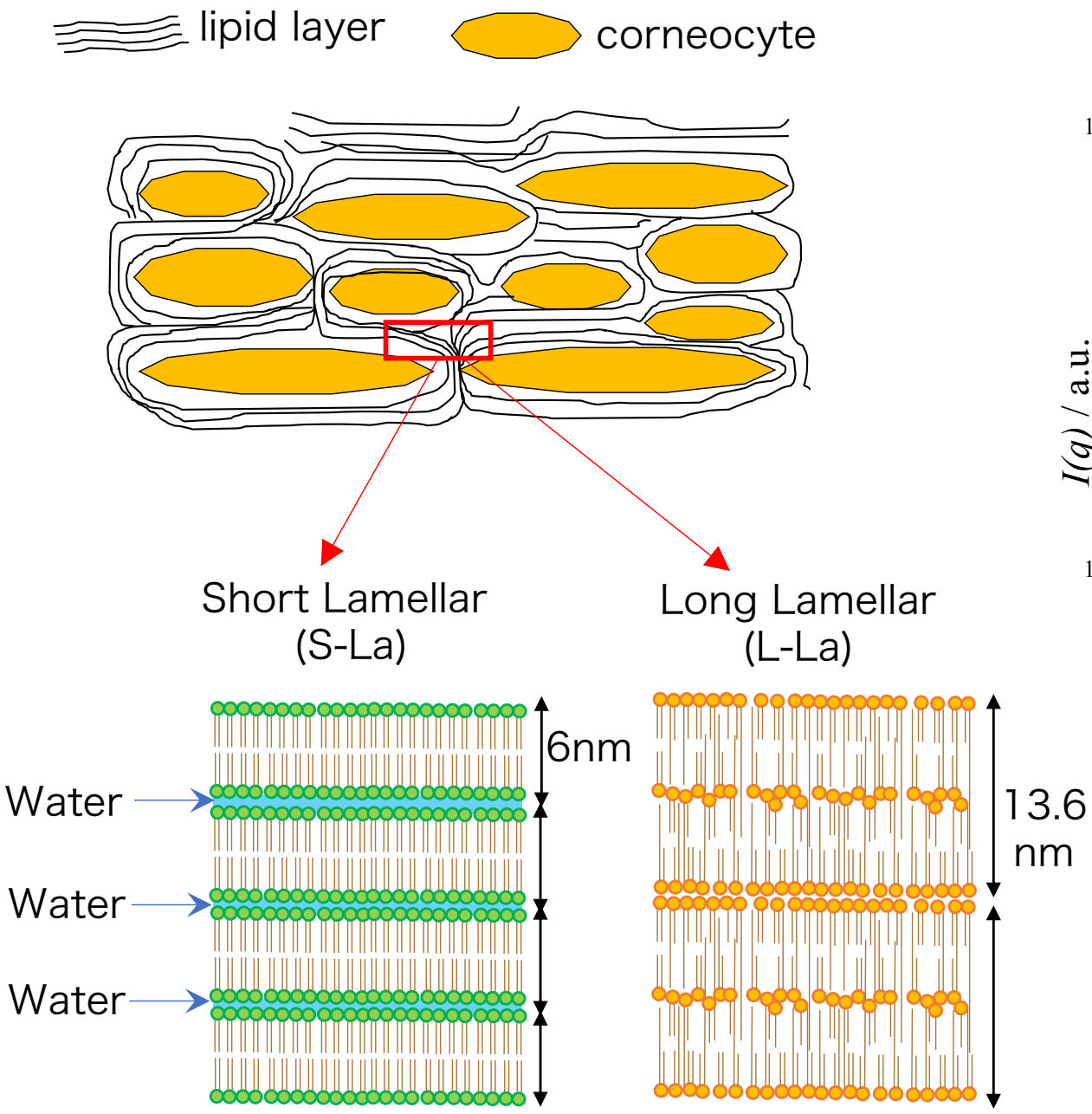


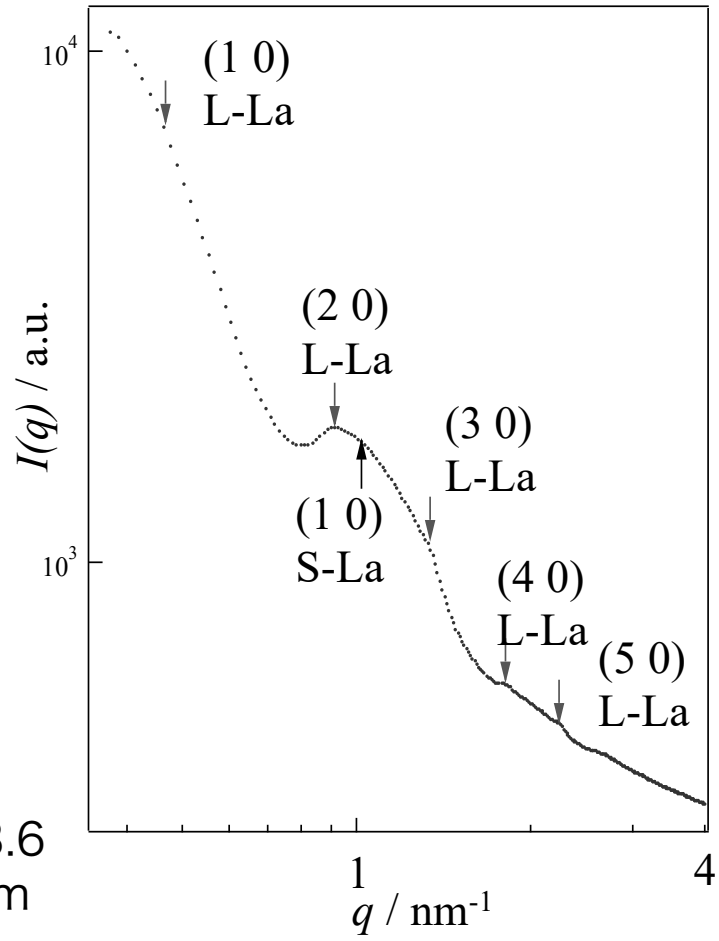


The shape and size of the broad peak with lattice spacing of 1 nm derived from the packing of soft keratin did not change with time after application of both MEs.

Both MEs did not penetrate the corneocyte.

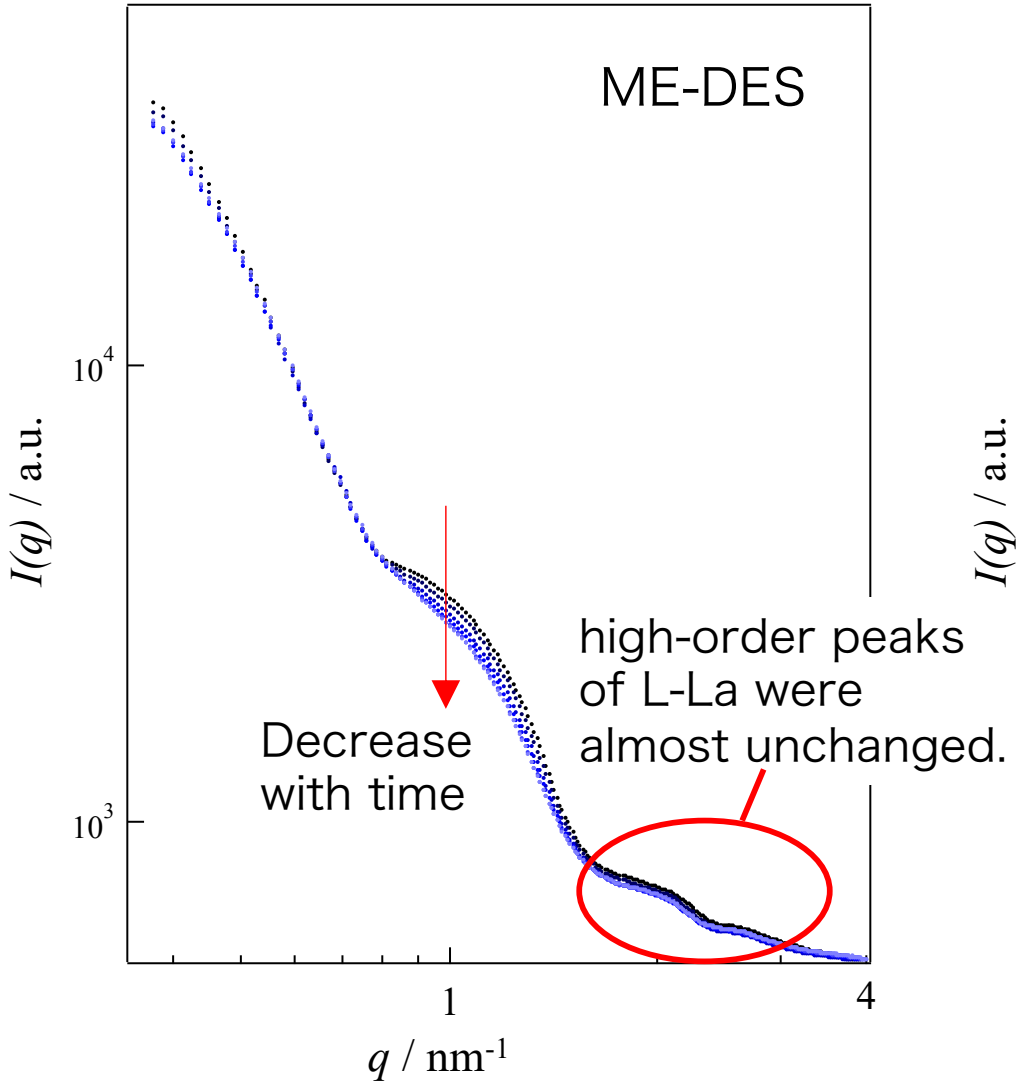
Lamellar structures of lipids in SC



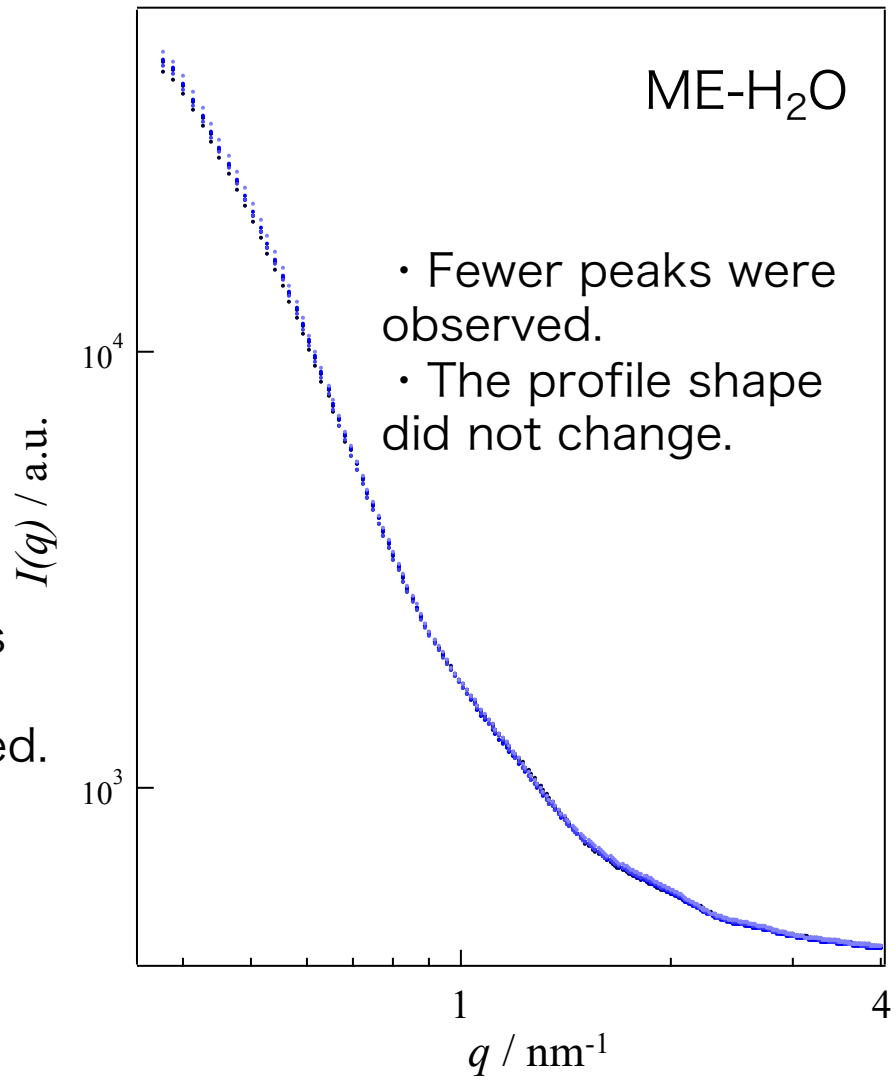


N Ohta et. al., *Chem phys lipids* 2003, 123 (1), 1-8.

Structural transition of lipid lamellar structures from 1 to 60 min after applying MEs

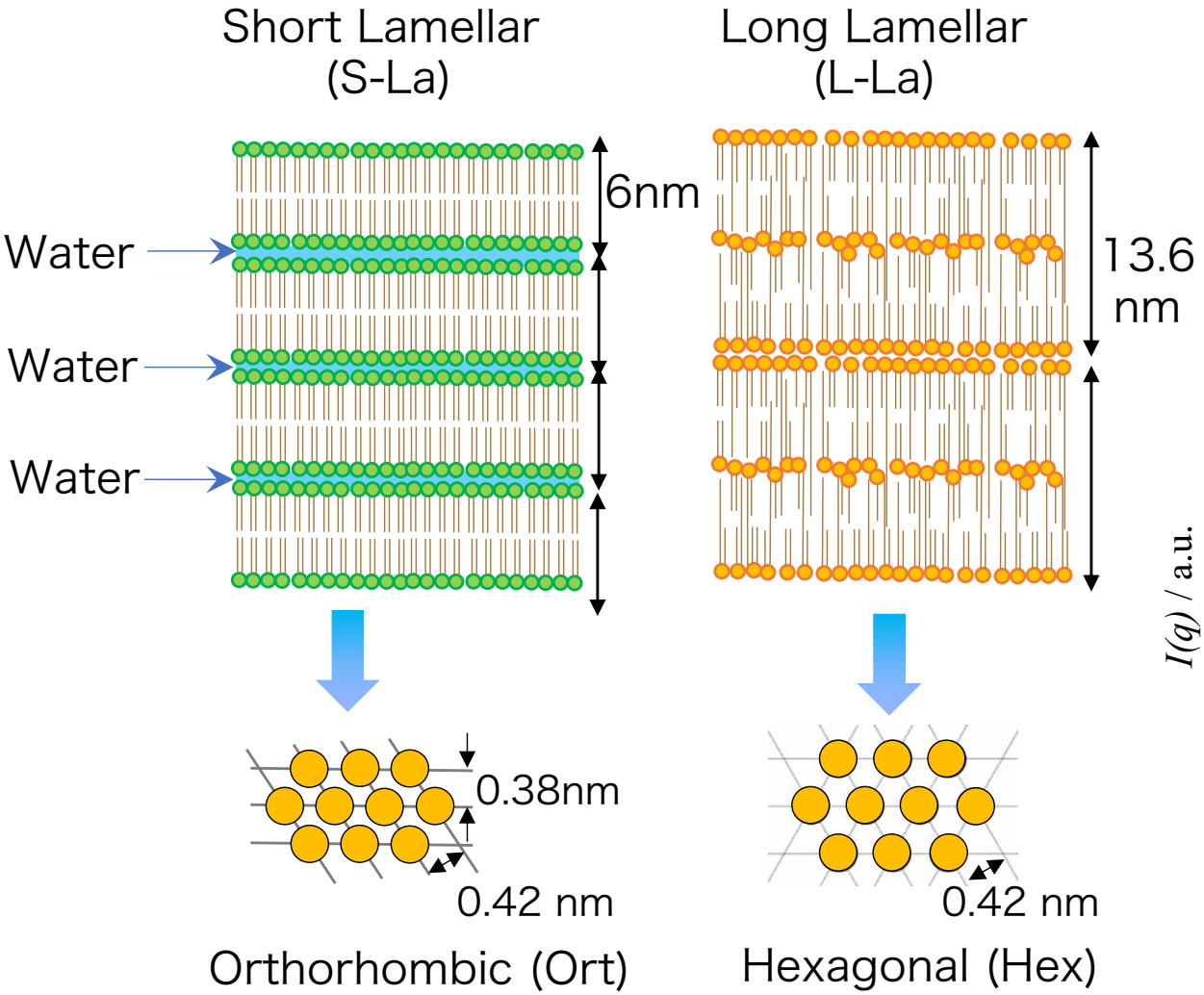


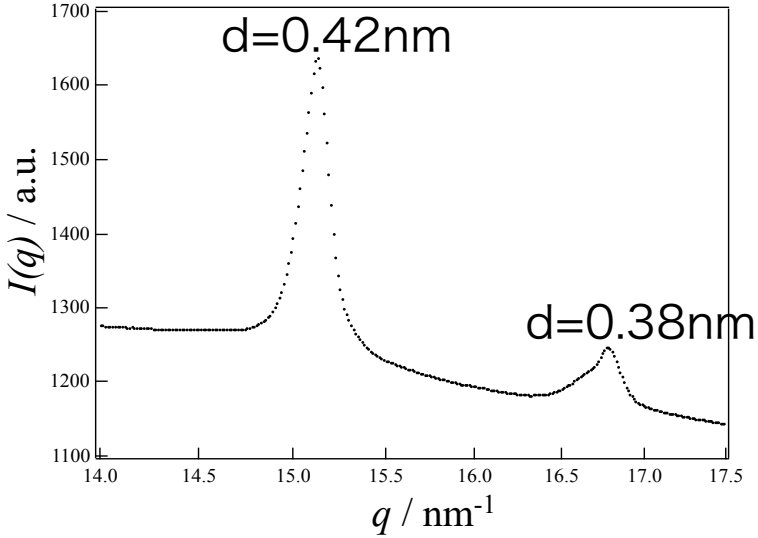
ME-DES mainly disrupt S-La.
→ME-DES might penetrate S-La



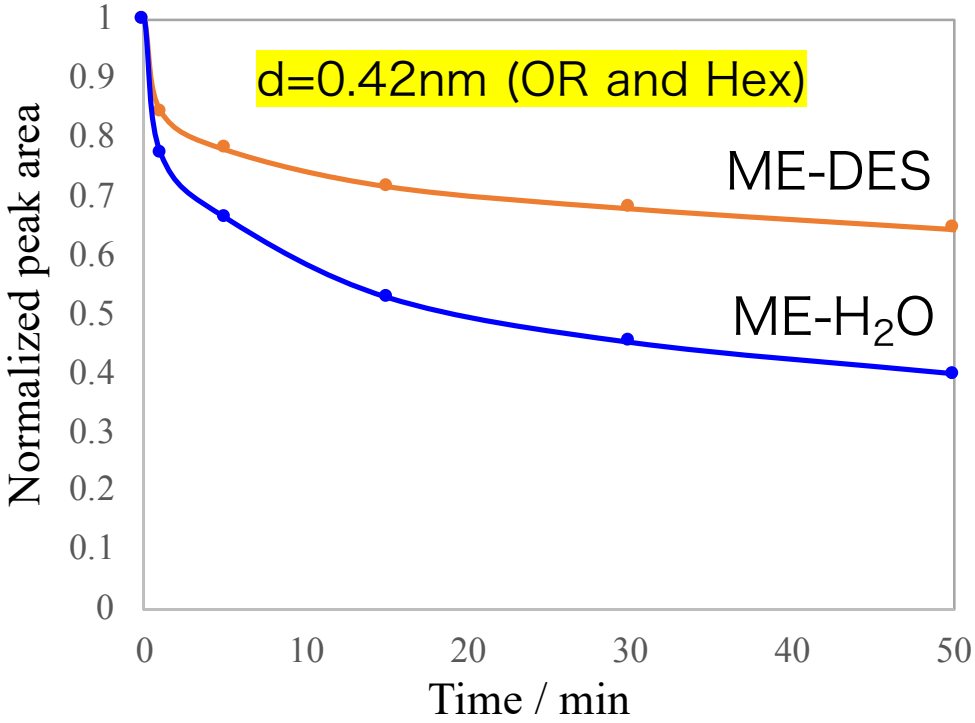
ME-H_2O may strongly interact with both lamellar immediately after application of ME. After that, ME-H_2O did not disrupt the lamellar structures.

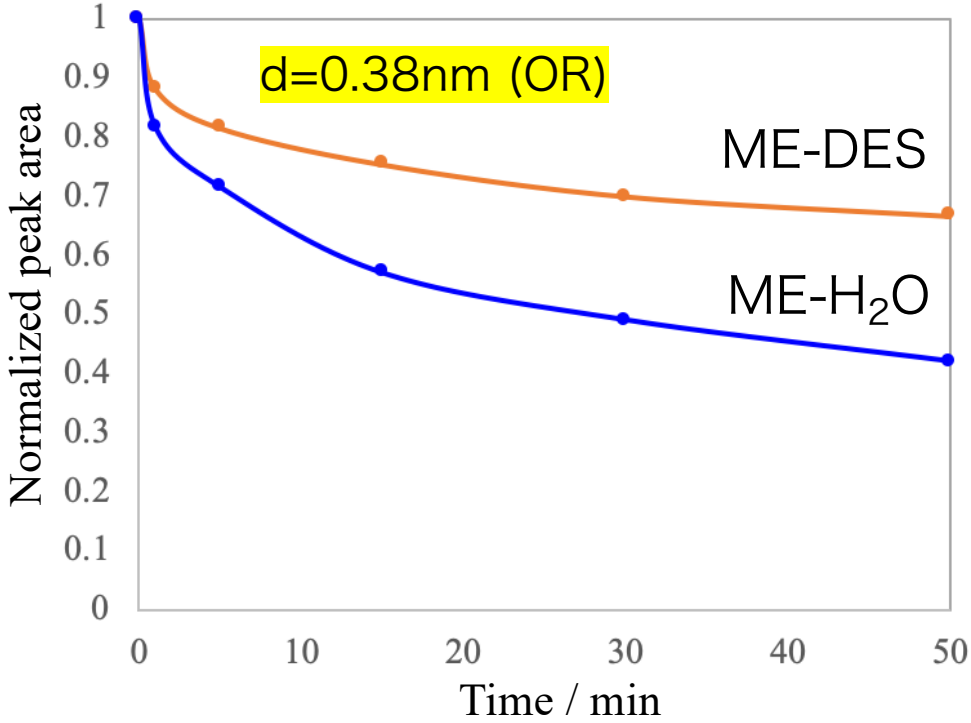
Hydrocarbon packing structures of lamellar





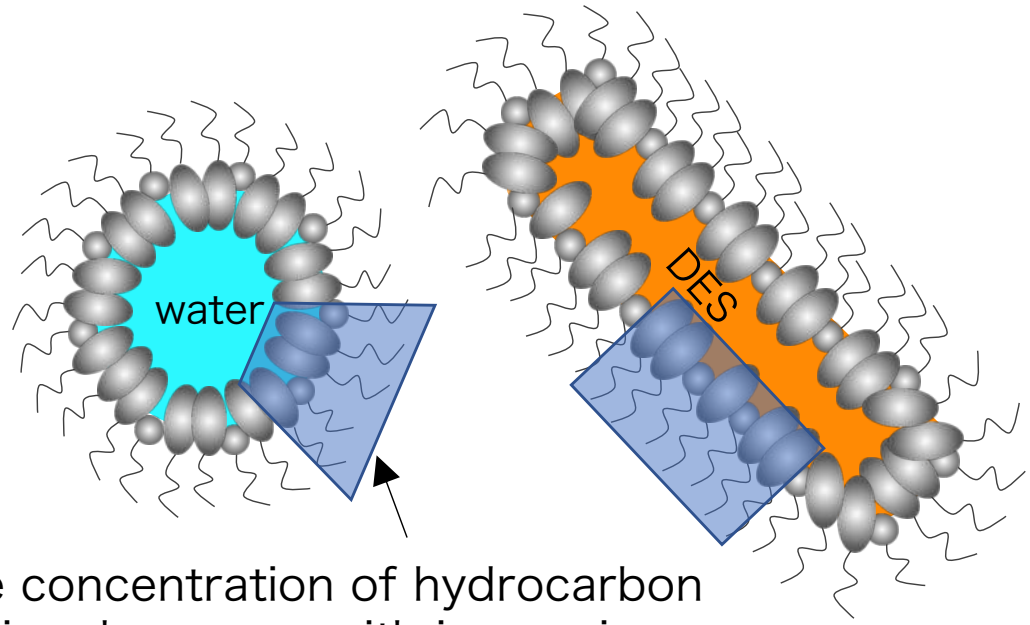
I Hatta et. al., *Biochim Biophys Acta* 2006, 1758 (11), 1830-1836.





＊ME-H_2O disturbed hydrocarbon packing structures more than ME-DES.

→ Hydrocarbon in lipid can insert the hydrocarbon of spherical ME easer than cylindrical ME.
As a result, ME-H_2O tends to remain in the SC.



The concentration of hydrocarbon chains decreases with increasing distance from the core

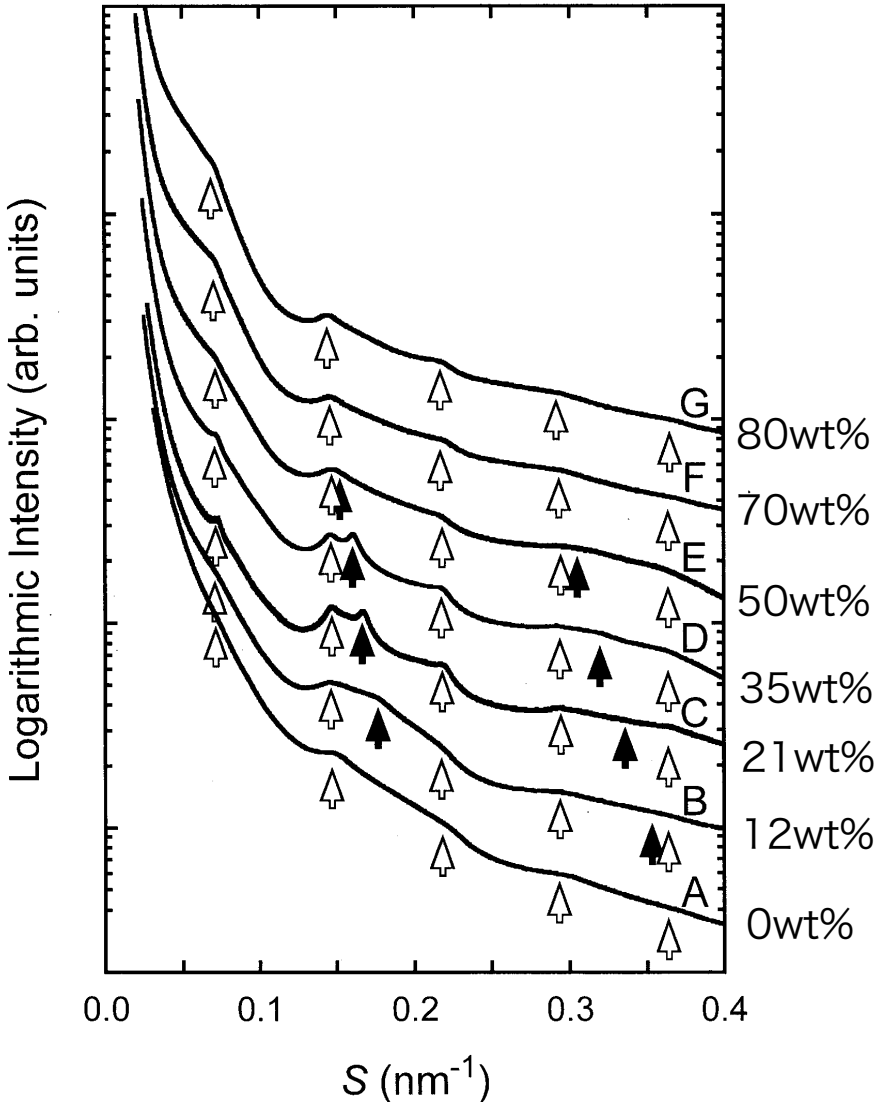
Conclusion 1

＊The penetration amount of ME-DES through the SC was higher than ME-H_2O.

＊ According to analysis of X-ray scattering, ME-DES mainly penetrates S-La.

＊ME-H_2O disturbed lipid lamellar structures soon after applying to the SC, and remained in hydrocarbon chains of the lipids.

The effects of water content of the SC on the penetration of MEs



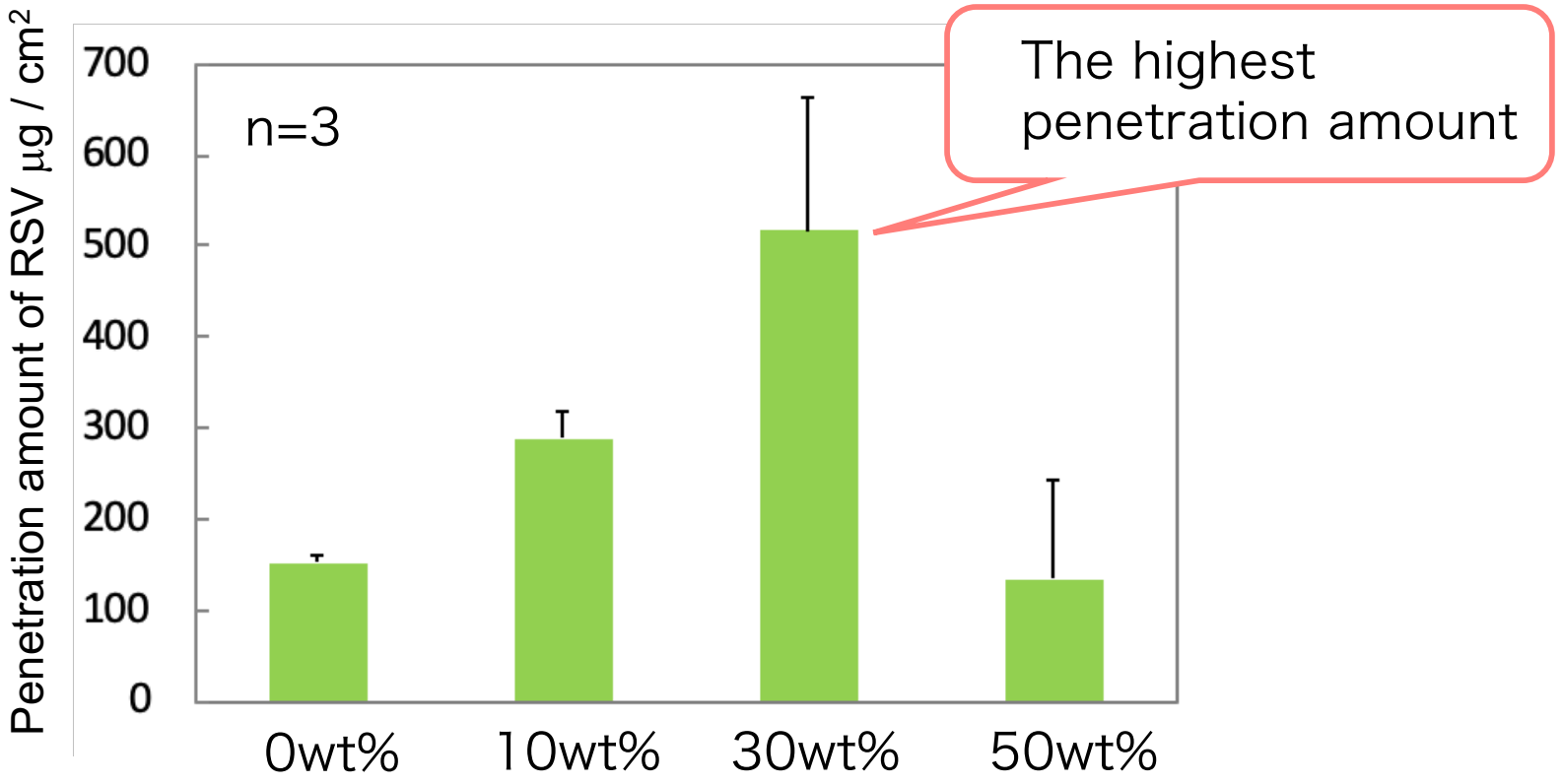
N. Ohta et al., *chemistry and physics of lipids* 123 (2003) 1-8.

The water content of the SC affected the structure of S-La.

The penetration route of ME-DES was S-La.

We investigated about the effects of water content of the SC on the penetration of ME-DES.

SC penetration amounts of ME-DES



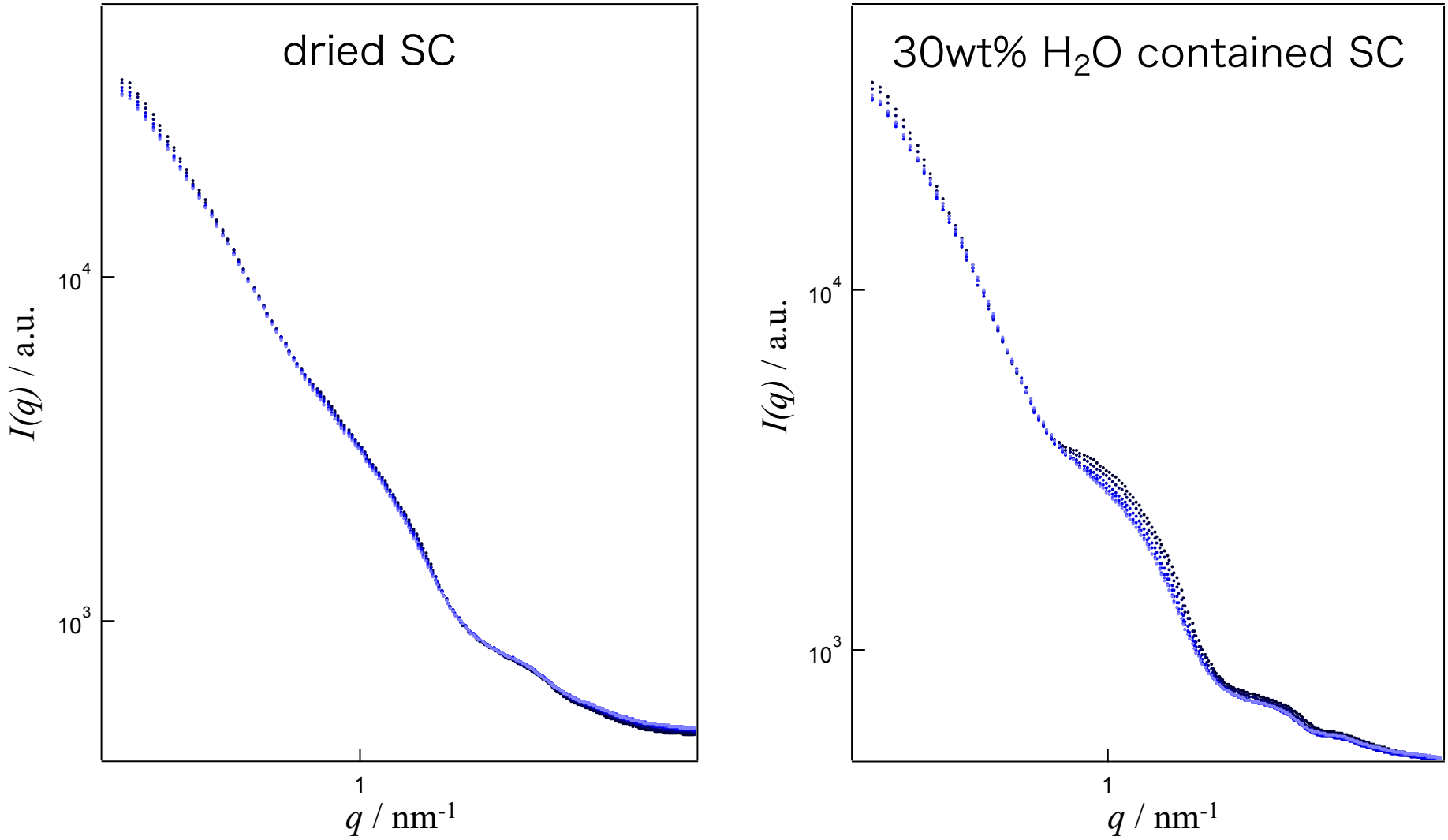
The highest penetration amount was achieved with 30wt% water contents

➡ The S-La spacing increases with increasing water contents of the SC.

When the SC contains excess water, ME cannot penetrate easily.

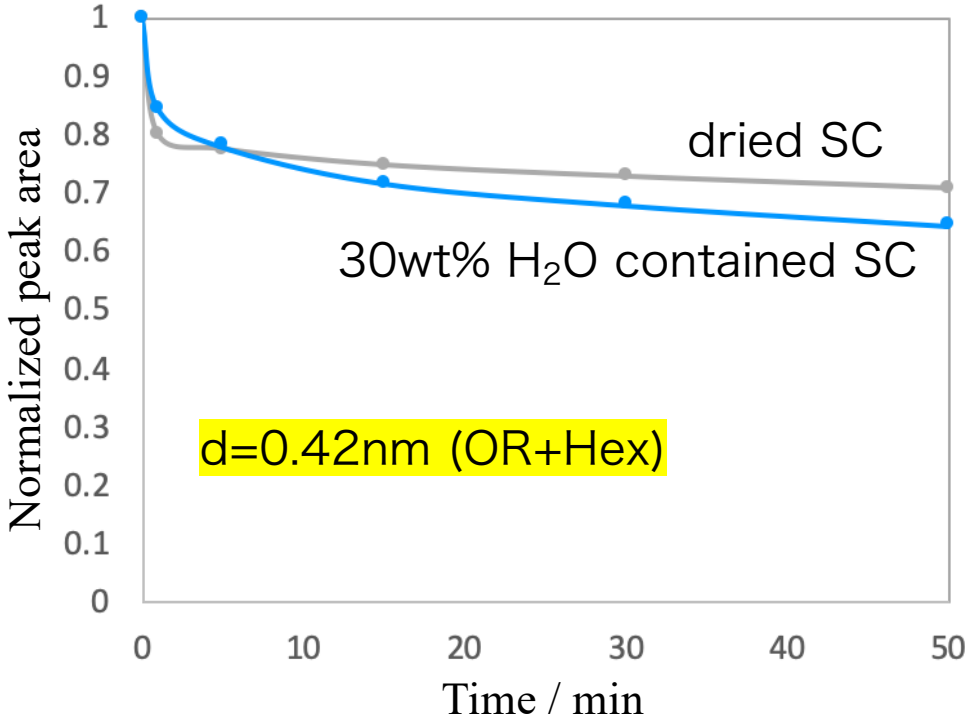
➡ Few affinity of the ME dispersing solvent with the water in the SC.

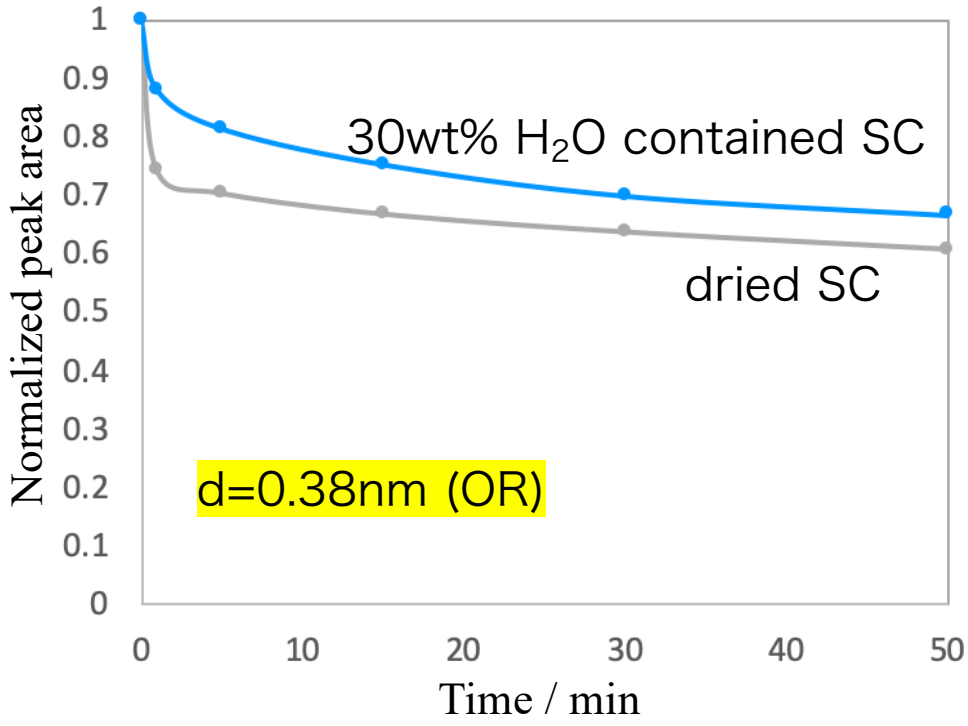
Structural transition of lipid lamellar structures from 1 to 60 min after applying ME-DES



ME-DES did not disrupt the lamellar structures for the dried SC while ME-DES disrupt S-La with time for 30 wt% H_2O contained SC.

Hydrocarbon packing structures of lamellar





MEs disturbed hydrocarbon packing structures for both SC.

For dried SC, MEs may remain in hydrocarbon chains in the SC because the structural change of the lamellar in SC in the SAXS region was not occurred.

For 30wt% H_2O SC, MEs may penetrate S-La while disordering chain packing structures.

Conclusion 2

＊The highest penetration of ME-DES was achieved with the SC containing 30 wt% H_2O.

＊For dried SC, the structural change of the lamellar in SC was not occurred while the hydrocarbon chain packing in SC was disordered.
→ MEs mainly remained in hydrocarbon chains of the lipids.

＊For the SC containing 30 wt% H_2O, MEs seem to penetrate S-La while disordering chain packing structures.