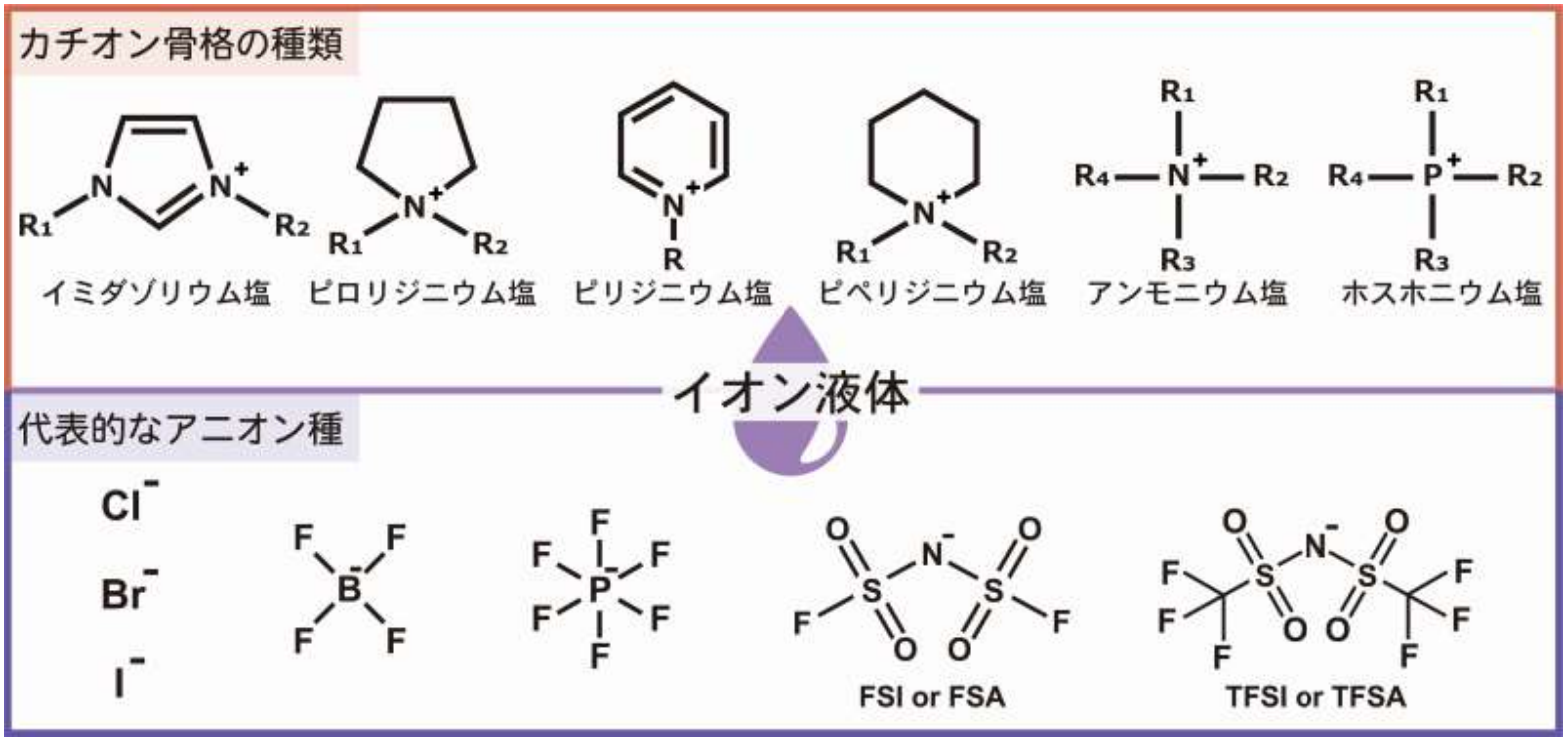
Ionic Liquid for Transdermal DDS

230907 Literature seminar #3

M2 Yuto Azumaya

Contents

Introduction : ionic liquid



関東化学HP：https://products.kanto.co.jp/web/index.cgi?c=t_product_table&pk=49

Introduction : application of Ion Liquid

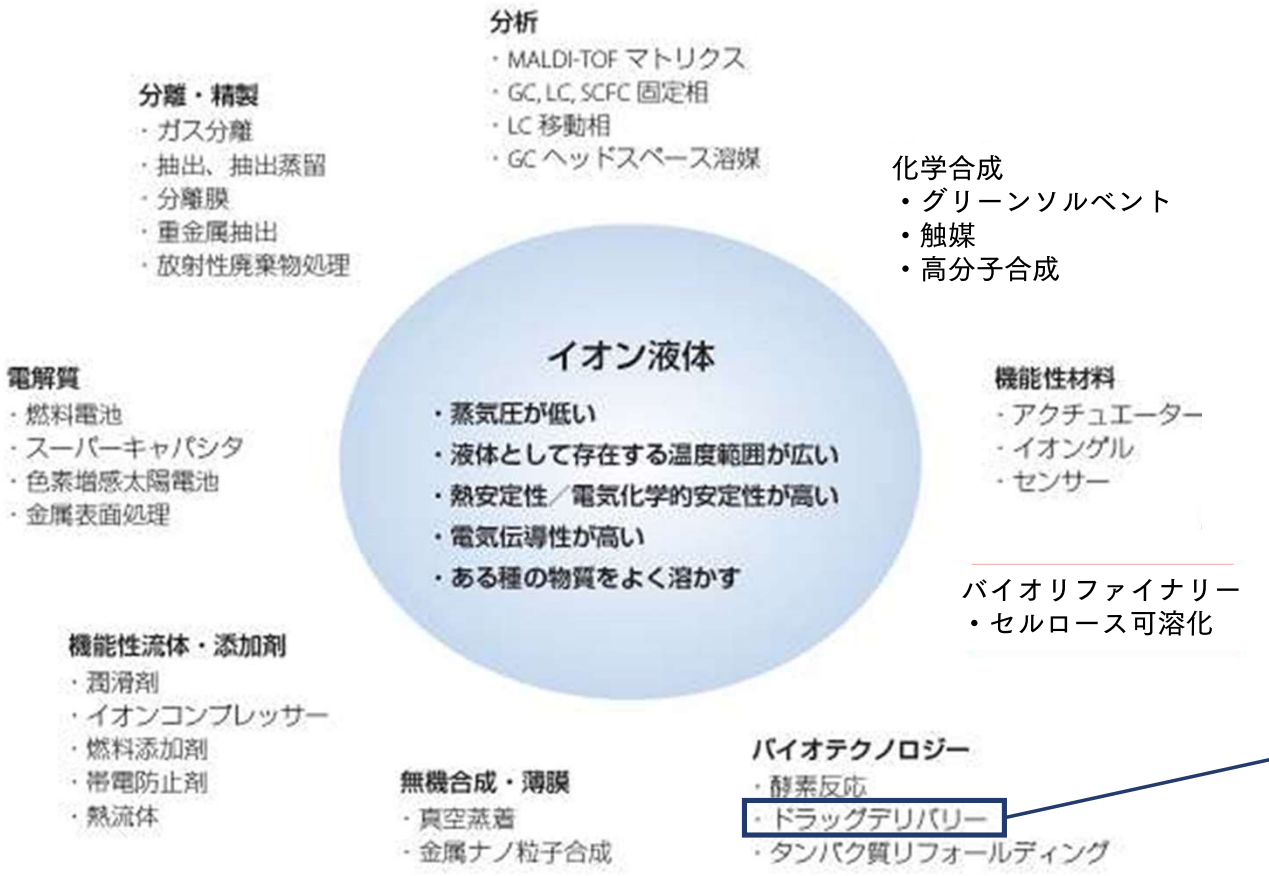
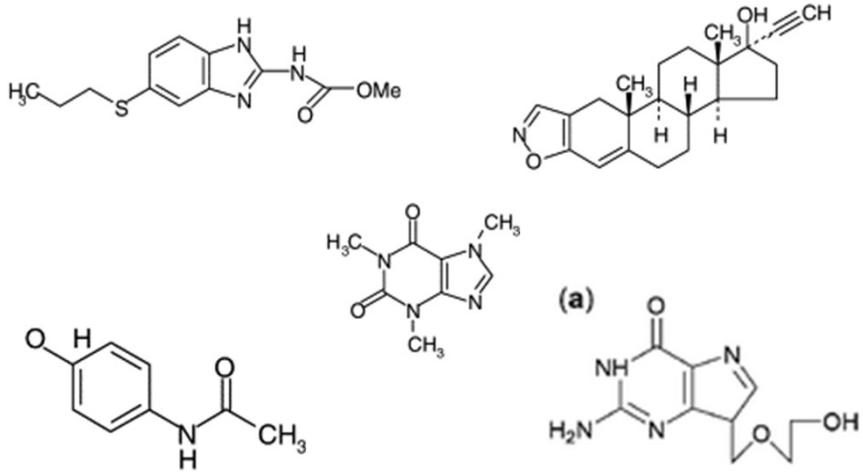


Figure 1. イオン液体の特徴とアプリケーション

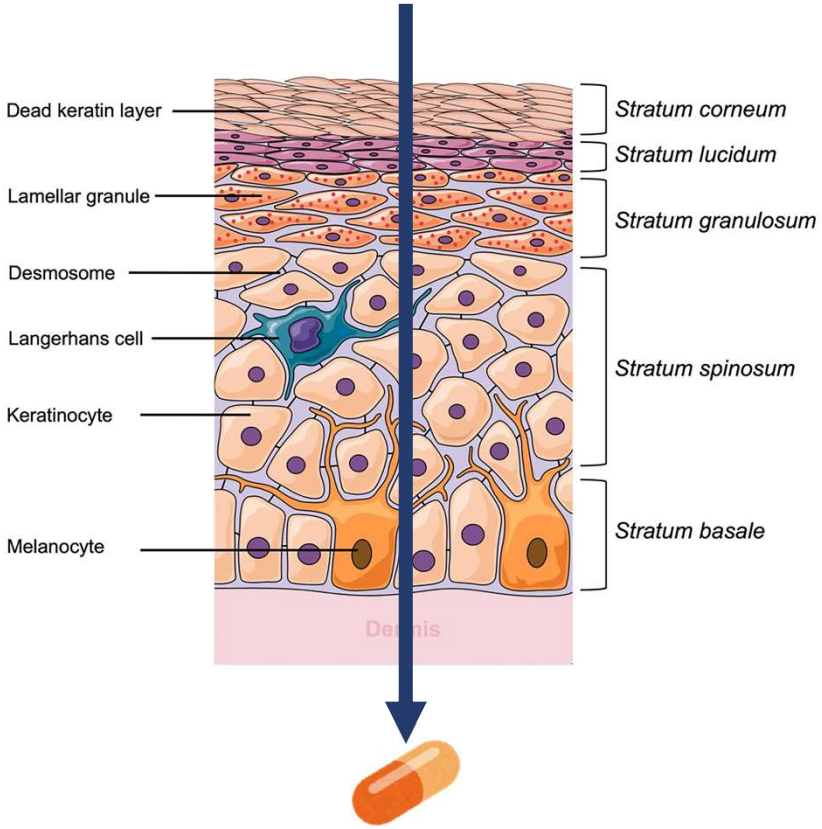
Introduction : Ion Liquid for pharmaceutical use

①solubilize poorly soluble drug molecules



- Avoidance of crystal polymorphism
- Improvement of drug efficacy and stability
- Application to other DDS systems

②Transdermal permeation enhancer (today's topic)



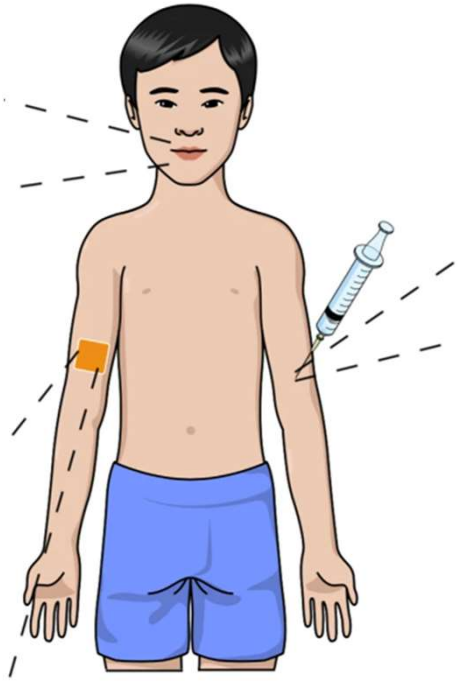
Eur J Pharm Sci ,**2008**,*33*,326

Introduction : Comparison of three different routes of drug administration

- Transdermal

○not or less invasive
○ease on application
○avoid first pass netabolism

×Skin irritation
×Limited to Suitable drug
  - MW<600 Da
  - a water/octanol partition coefficient in the range of 1−3
  - a low melting point



- oral

○Easy to swallow and convenient
○Various dosage form
×Degradation by digestive system or liver

- injection

○100% bioavailability
○accurate dose
×Invasive ×painful
×expert personnel needed

Drug Deliv. and Transl. Res. **2022**,*12*, 758

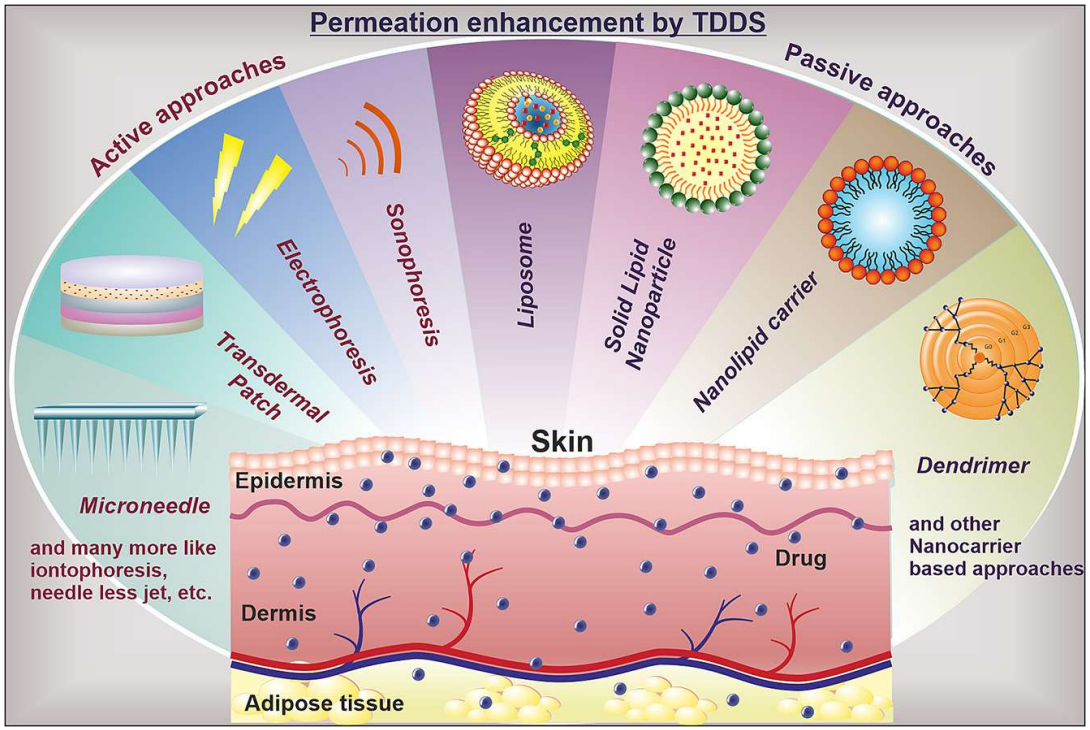
Introduction : transdermal drug delivery

- Transdermal

○not or less invasive
○ease on application
○avoid first pass netabolism

×Skin irritation
×Limited to Suitable drug
- MW<600 Da
- a water/octanol partition coefficient in the range of 1−3
- a low melting point

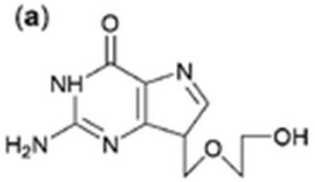
- Other method



J Control Release,**2022**,*351*,361

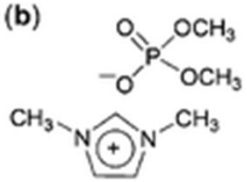
- There is a need to develop more hypoallergenic and efficient transdermal delivery methods.

Introduction : the first application of IL to TDDS



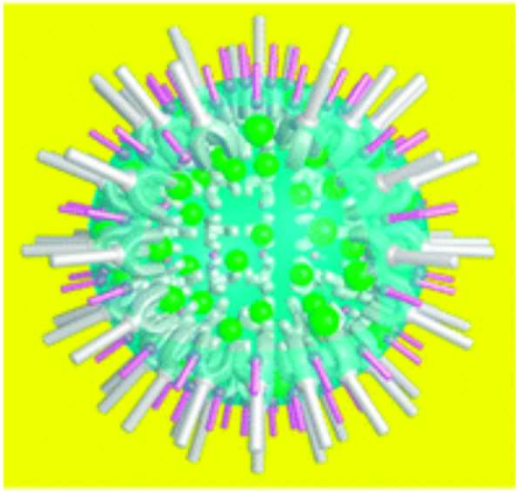
acyclovir
Sparcely soluble

+

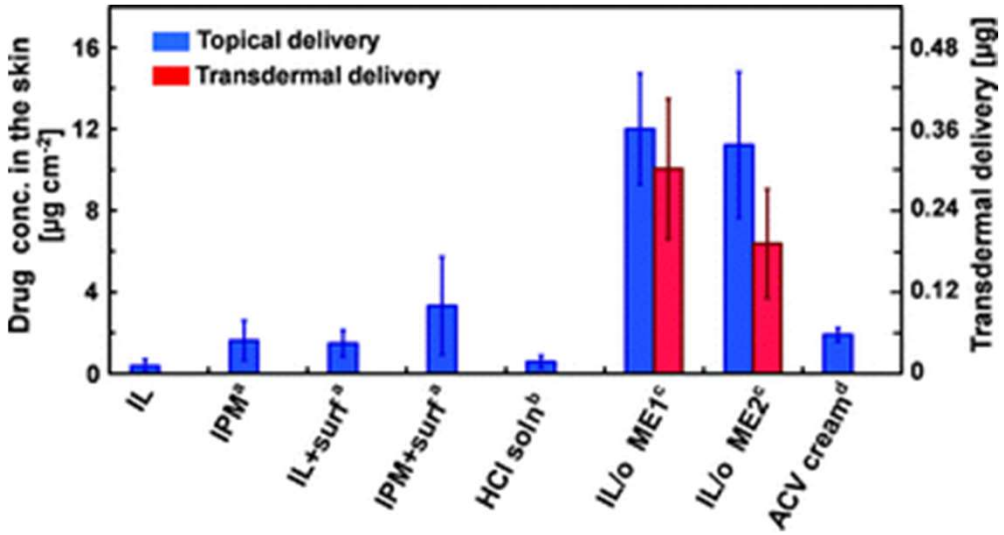


Ionic liquid

↓ Tween-80
Span20
(surfactant)



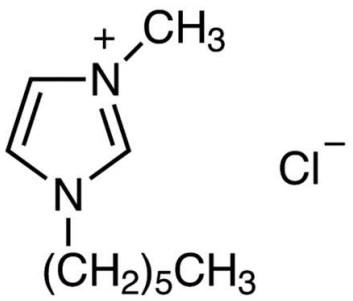
MicroEmulsion



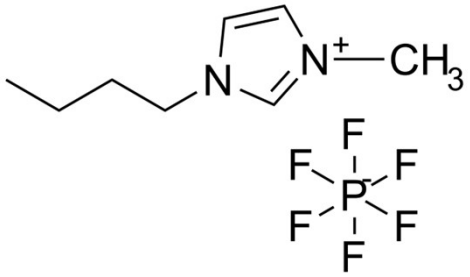
• Solubilization with IL → ME formulation improves delivery efficiency
※Transdermal delivery enhancement of IL was not clear

Chem. Commun., **2010**,*46*, 1452

Introduction : Transdermal penetration promoting effect of IL



Hydrophilic IL



Hydrophobic IL

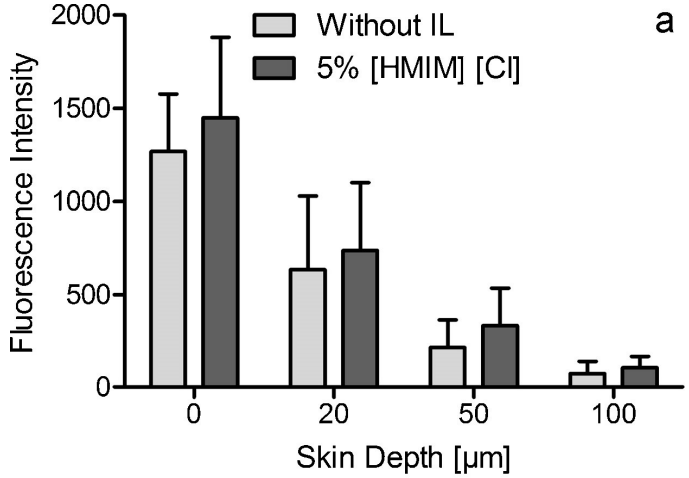
- In ME formulations incorporating hydrophobic ionic liquids
- Enhanced transdermal delivery capacity was observed

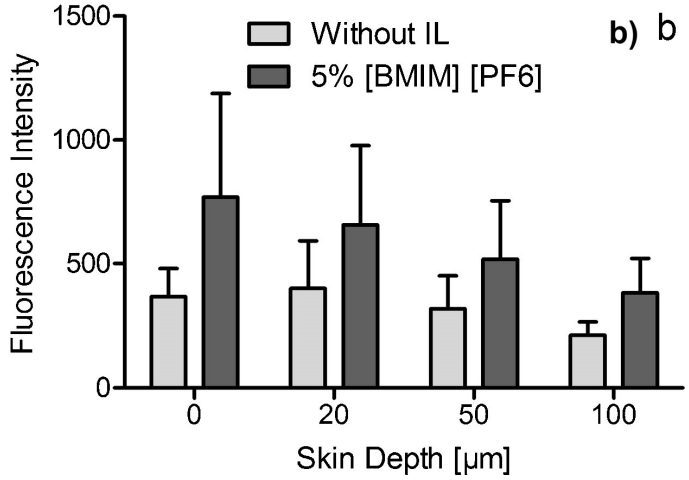
→Advance as a carrier for transdermal absorption enhancement

Considerations at that time on the effect of promoting transdermal delivery

- Ionic liquids are known to act as cationic surfactants
  - →Ionic surfactants penetrate the stratum corneum, extracting lipids from the stratum corneum and disrupting lipid bilayer packing in the tissue
- Anionic surfactants can enhance stratum corneum hydration in vivo

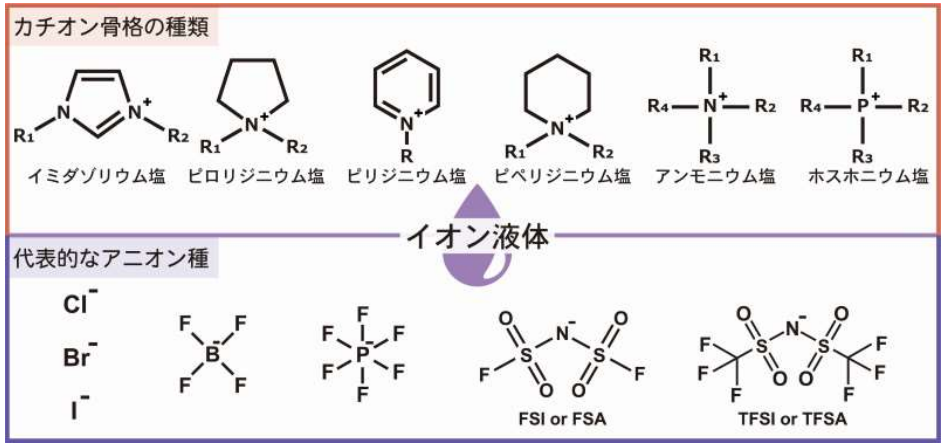
→These two actions were thought to improve skin penetration.





Int. J. Pharm.,**2013**,*441*,620

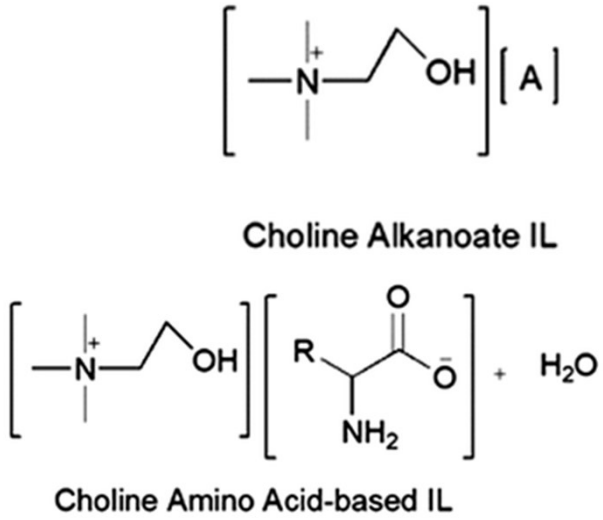
Introduction : Biocompatibility concerns and improvements



Biocompatibility concerns
Mainly membrane perturbation by cationic side chains and hydrophobic anions

- Bio-IL

ex)



- IL using biologically-derived molecules
→ Aiming to improve biocompatibility.
- Amino acids, fatty acids, choline, etc...

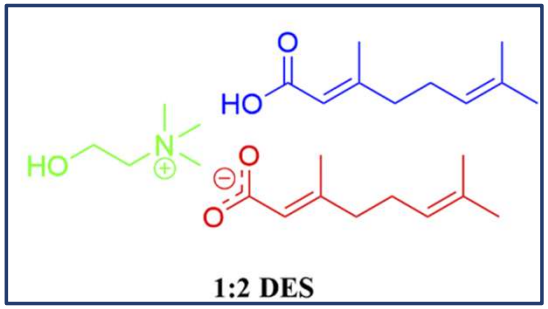
Introduction : today's main topics

- Request for IL-DDS

  - Transdermal delivery capacity
  - Biocompatibility (hypoallergenic, low toxicity, etc.)

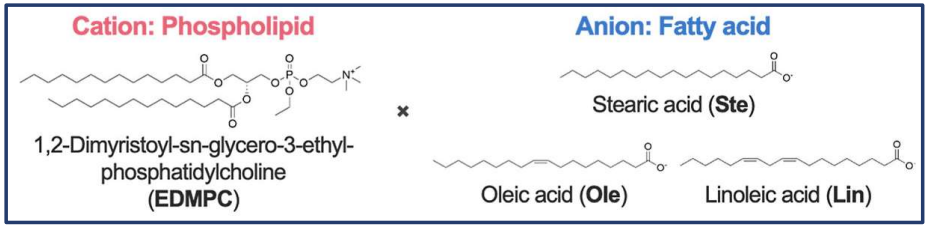
- Main Topic

①CAGE system



Choline + Geranic acid

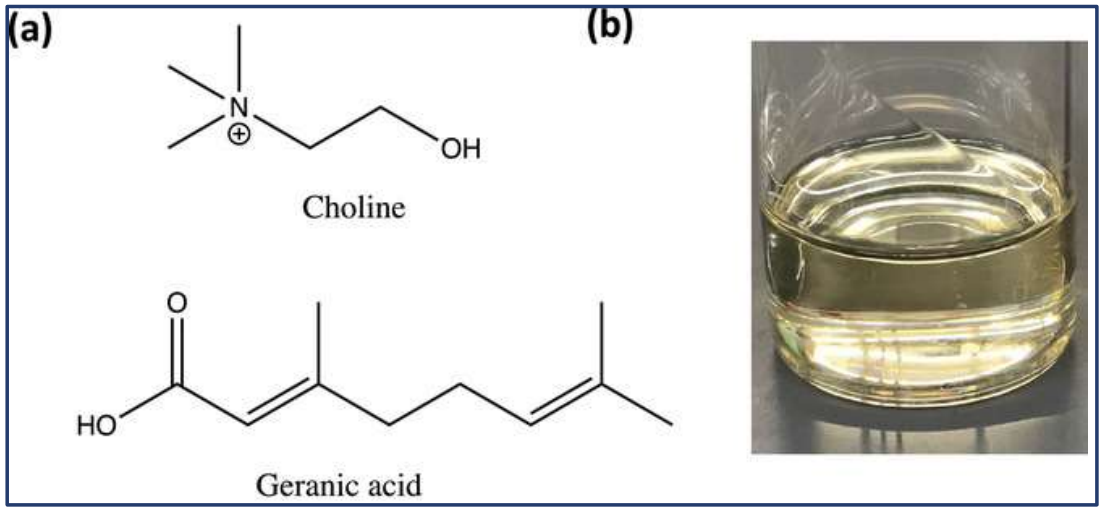
②LBIL system

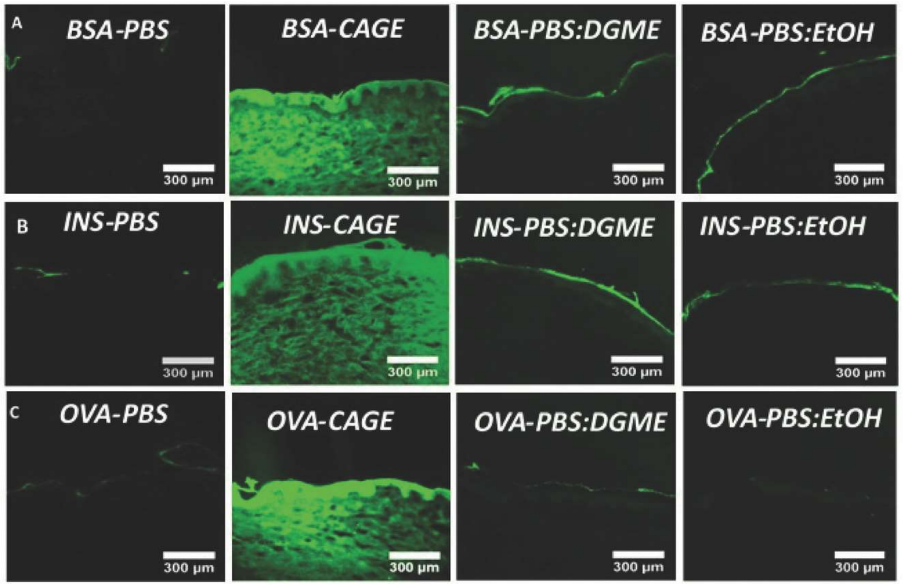


Cationic phospholipid + Fatty acid

Contents

Application① : What is CAGE system?





- An ionic liquid (or deep eutectic solvent) composed of choline and geranic acid
- Has a transdermal penetration enhancing effect
- low cytotoxicity

- First released in 2014, used for deep skin DDS of antibiotics
- 2017: applied for protein delivery

S., *Adv. Healthcare Mater.* 2017, 6, 1601411.

Application① : CAGE system mechanism study

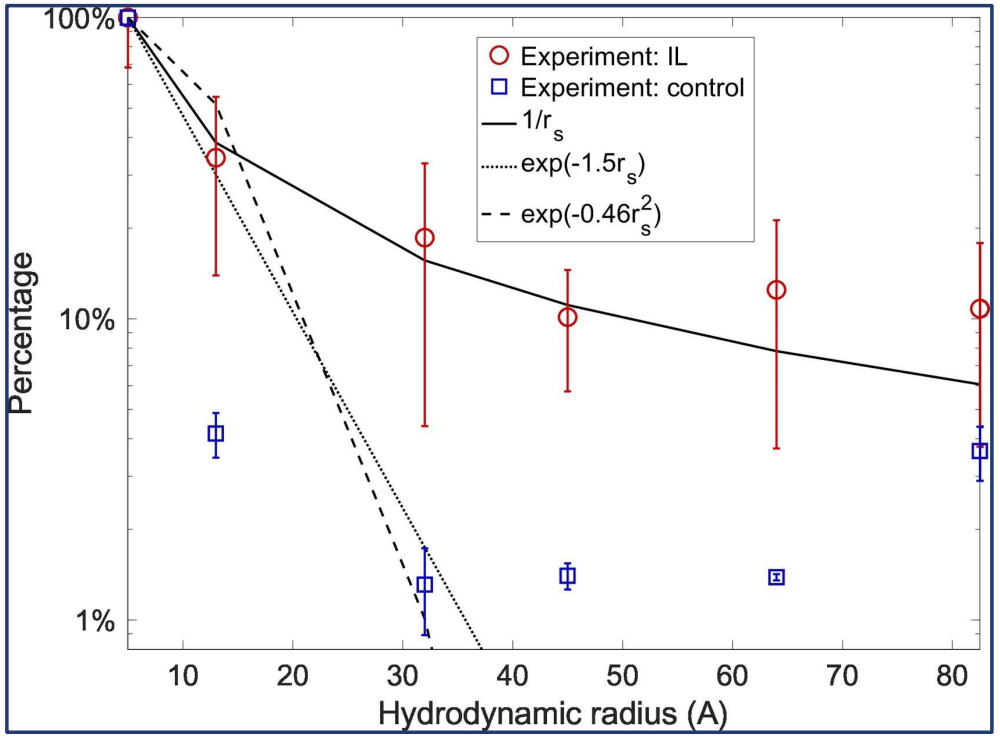
Evaluate delivery efficiency of dextrins of various molecular weights

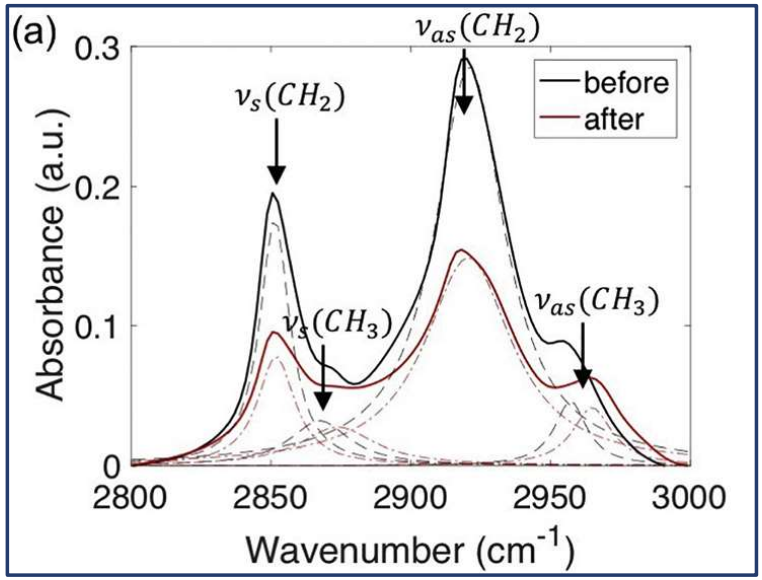
Transdermal Delivery Theoretical Modelling

$$P = \frac{\varepsilon/\tau}{\Delta x} DK$$

***P* vs. MW?**

modeling macromolecular drug delivery



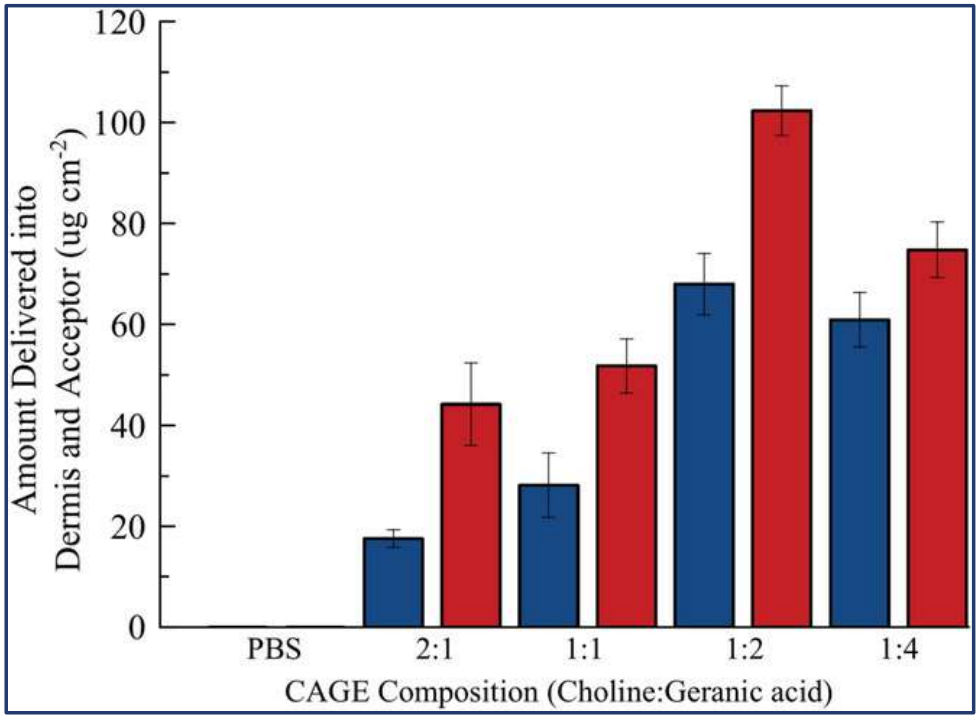


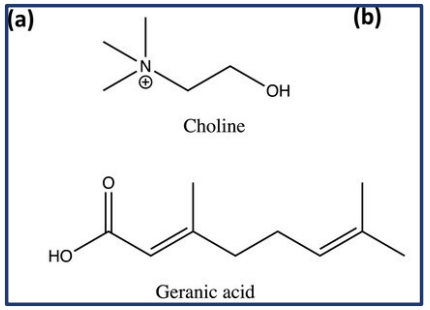
Confirmation of SC lipid migration into IL (FT-IR)→Extraction action of lipids

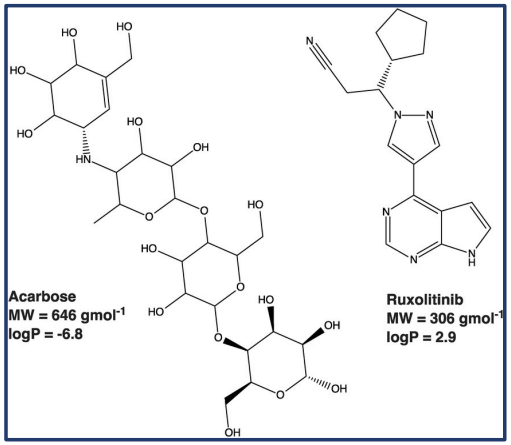
Smaller decrease in diffusion with increasing molecular weight
→Suggests a potentially more favorable mode of macromolecular delivery

J Control Release.,2019,311,162

Application① : systematic study





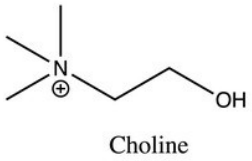


• Maximum efficiency when cation : fatty acid = 1:2 (Considered just the right balance between hydrophobicity and distribution to skin)

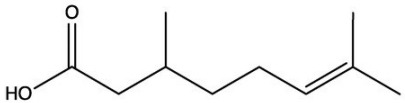
Adv. Mater. **2019**, *31*, 1901103.

Application① : systematic study

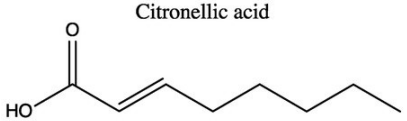
(a)



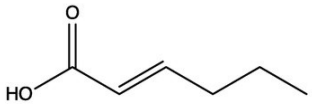
Choline



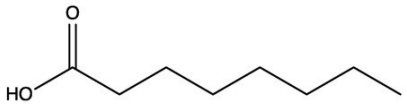
Citronellic acid



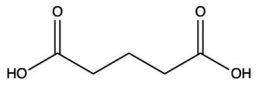
Octenoic acid



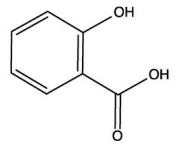
Hexenoic acid



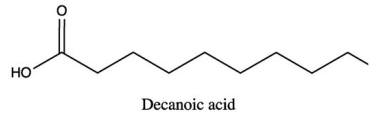
Octanoic acid



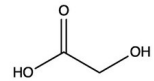
Glutaric acid



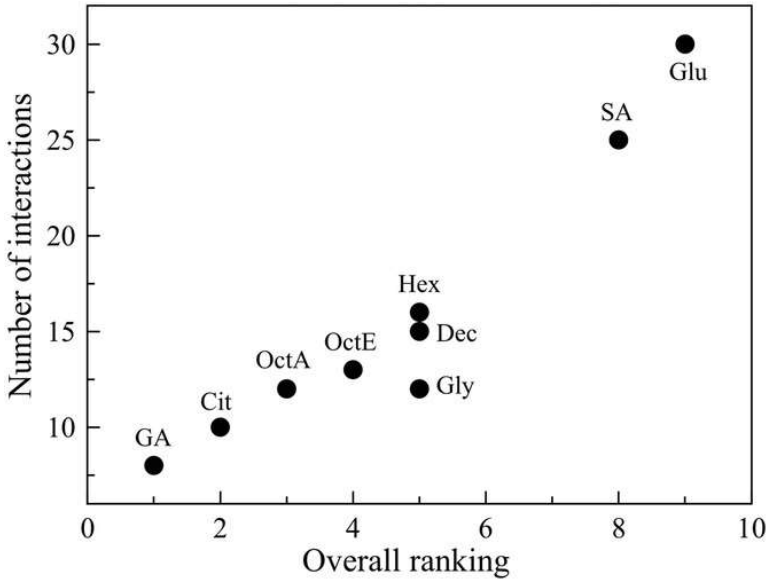
Salicylic acid



Decanoic acid



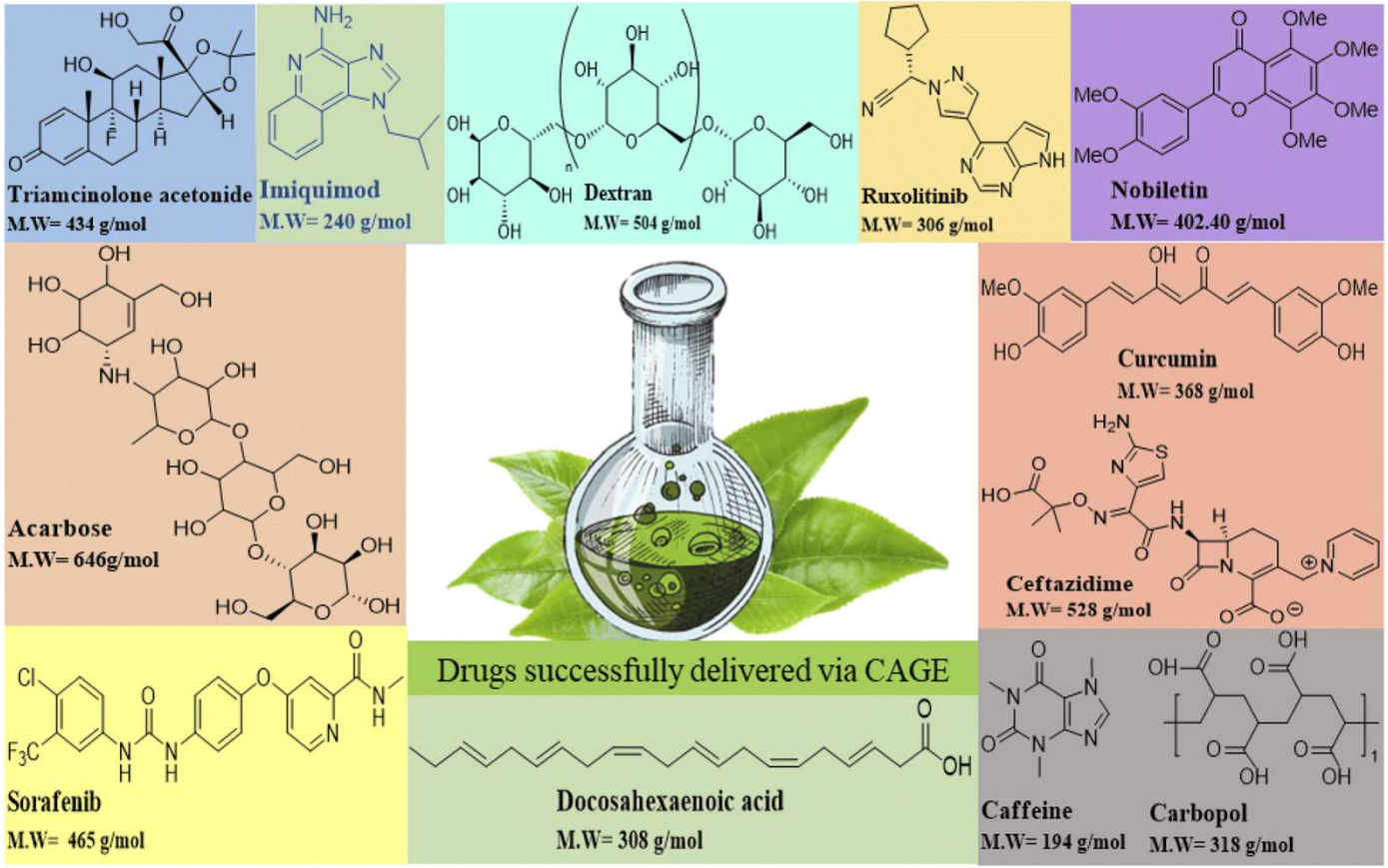
Glycolic acid



- Fatty acids: hydrophobic and highly unsaturated promote delivery more
- The smaller the interaction between ions, the higher the efficiency (NOESY)
- The number of cross peaks between alkyl chains was inversely correlated with the delivery efficiency rank.
  - Ability to penetrate stratum corneum depends on fatty acid anions
  - Strong interactions between ions inhibit distribution to the skin

Adv. Mater. **2019**, *31*, 1901103.

Application① : recent development



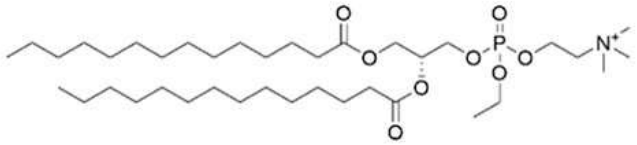
RSC Adv., 2022, 12, 25977

Application② : LBIL system

(a)

Lipid-based biocompatible ionic liquids

Cation: Phospholipid



1,2-Dimyristoyl-sn-glycero-3-ethyl-phosphatidylcholine (**EDMPC**)

×

Anion: Fatty acid

Stearic acid (**Ste**)

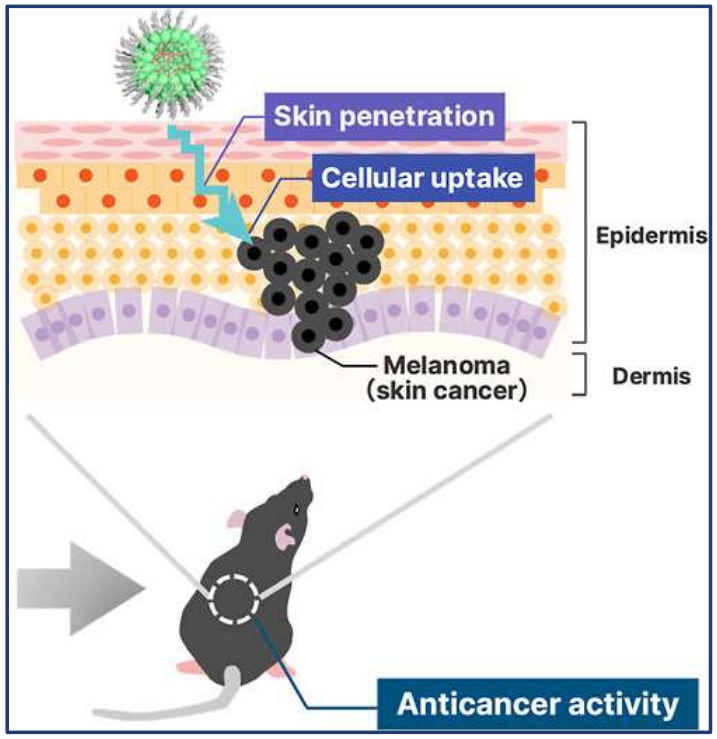
Oleic acid (**Ole**)

Linoleic acid (**Lin**)

Application② : LBIL – based TDDS

The merit of oligonucleotides TDDS

- Avoid severe injection site reactions and pain
- Avoid side effects from systemic drug exposure.



課題①：barrier of SC

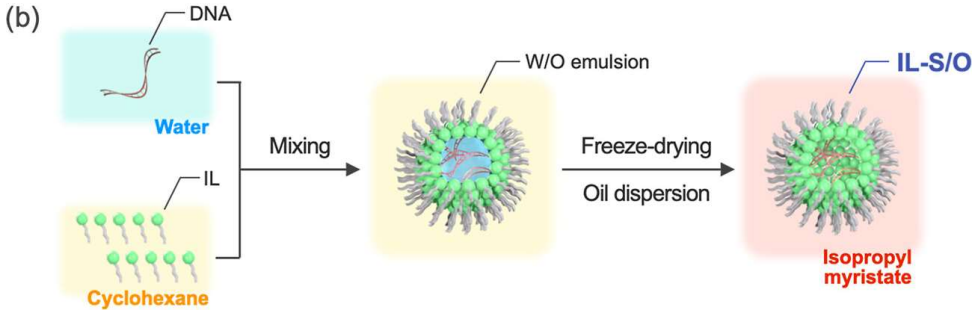
→ Transdermal delivery capability of IL

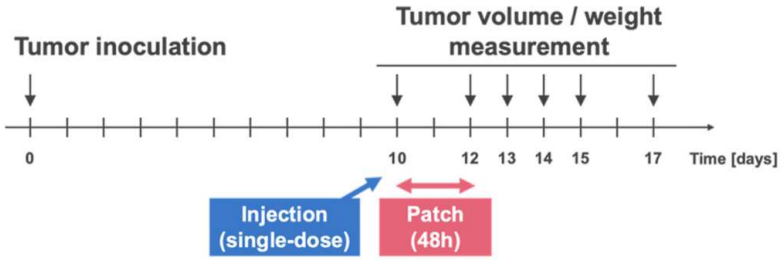
課題②：cell membrane

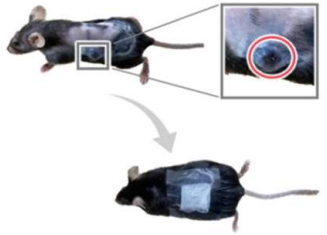
→ Ability of cationic qualities to be delivered intracellularly

ACS Appl. Mater. Interfaces 2023, 15, 28, 33299

Application② : LBIL – based TDDS of oligonucleotide



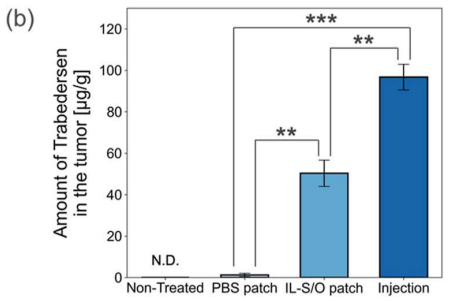


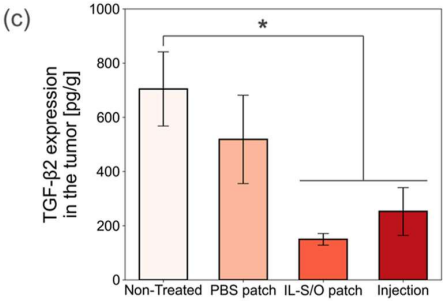


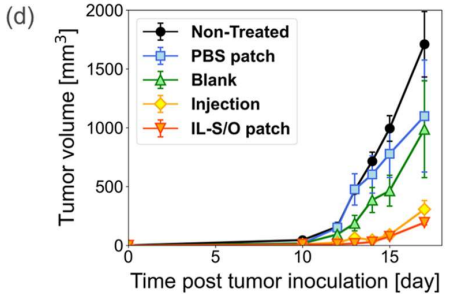
TDDS of trabedersen(α-TGFβ)

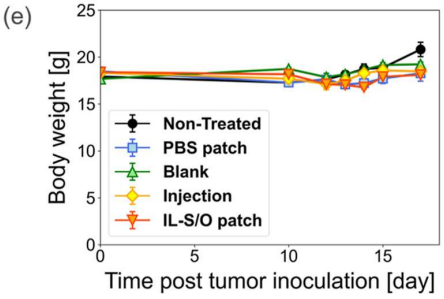
- Tumor shrinkage in model mice was confirmed.
- No side effects were observed.

→Expected to be developed as an alternative administration method to intravenous injection









ACS Appl. Mater. Interfaces 2023, 15, 28, 33299

Summary

- Summary

  - Ionic liquids: liquid salts at room temperature, which have been applied in various ways to date
  - Transdermal delivery enhancers
  - ILs can deliver various drug molecules transdermally

  →Expected to be developed as a transdermal delivery method in clinical practice

- problems

  - More detailed study of delivery mechanisms and biotoxicity
  - Further functionalization
  - Research for clinical application