



SOLVENT AND CRYSTALLIZATION EFFECTS ON SKIN ABSORPTION OF HYDROPHILIC AND LIPOPHILIC PERMEANTS

Lijing Xu
040123

OUTLINE

- ❖ Background

- ❖ Methods and results

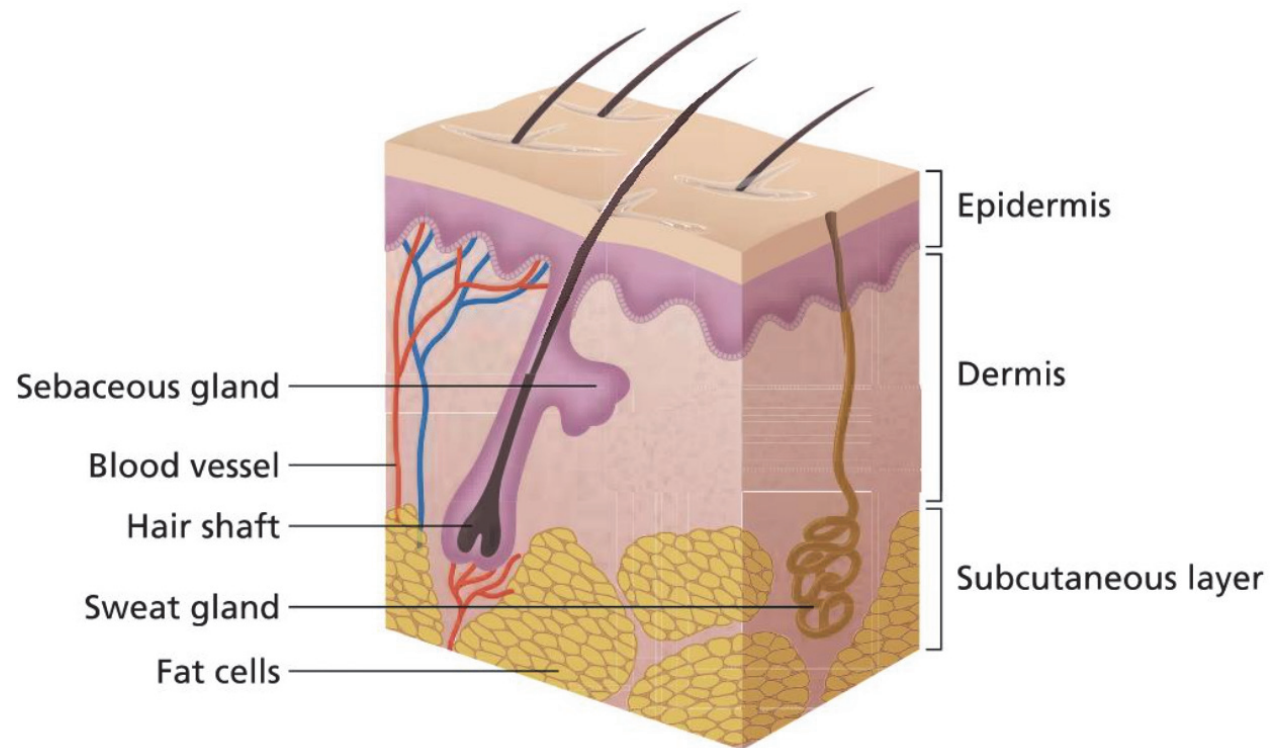
1. Solids deposition from solvents with a range of surface energies—light micrographs.
2. Skin penetration experiments – niacinamide, caffeine, testosterone and geraniol.

- ❖ Conclusion

BACKGROUND

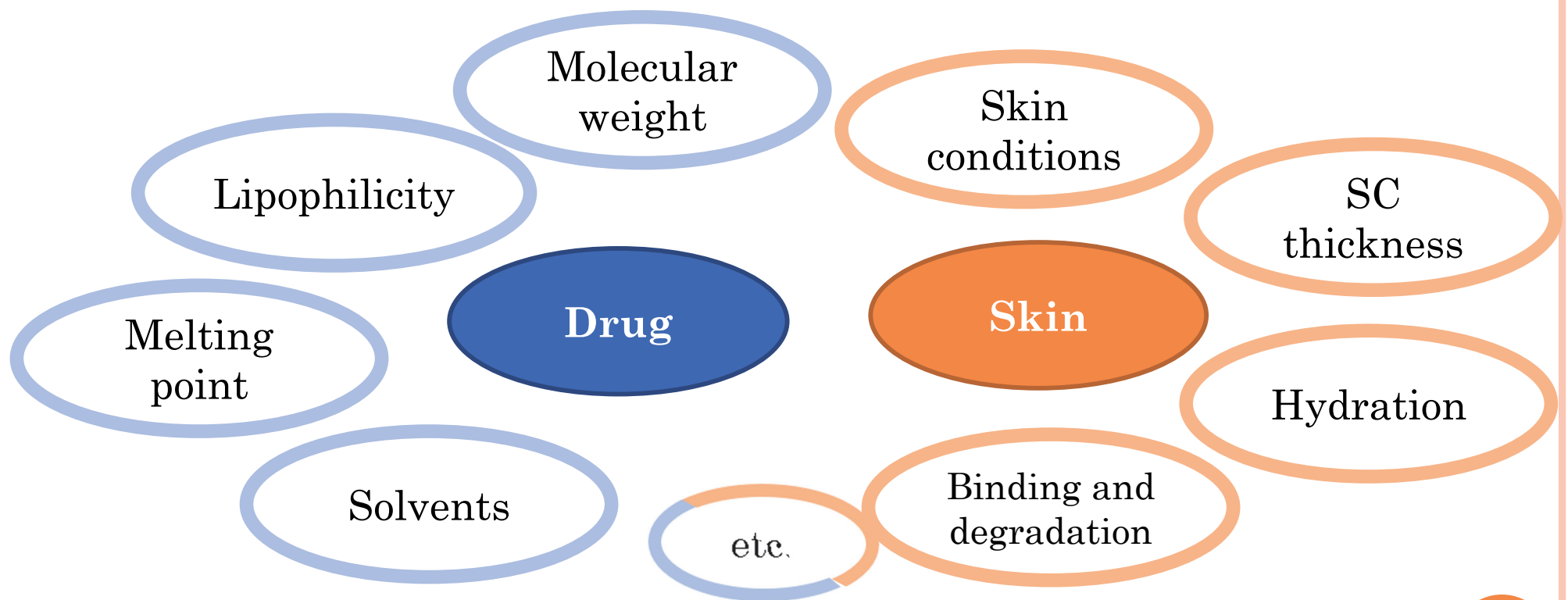
Skin absorption

Skin penetration
routes



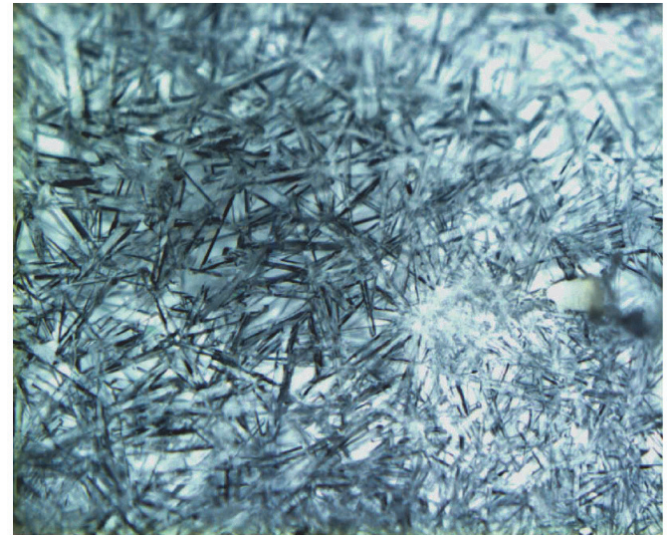
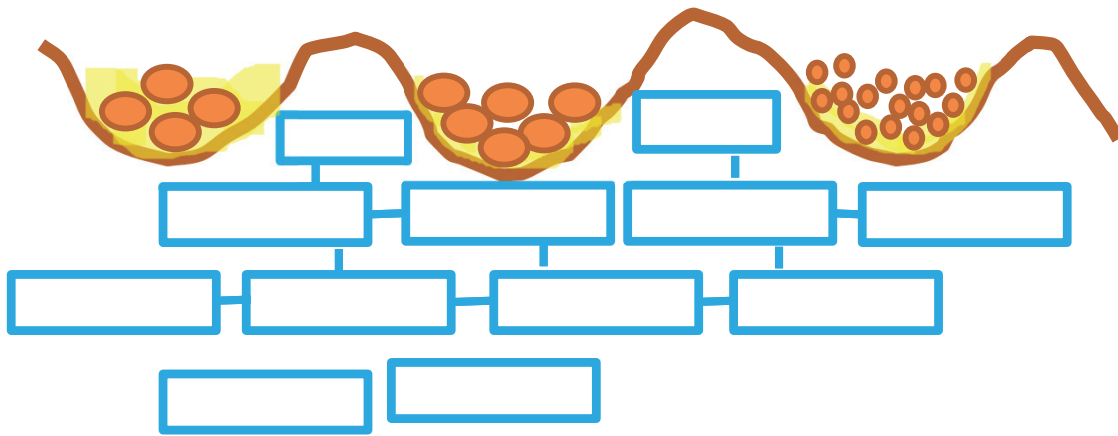
BACKGROUND

Skin absorption affecting factors



BACKGROUND

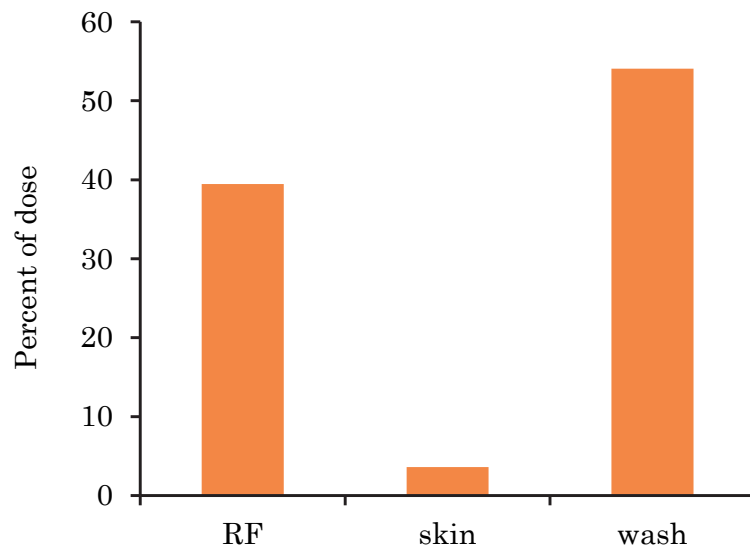
- Drug crystallization



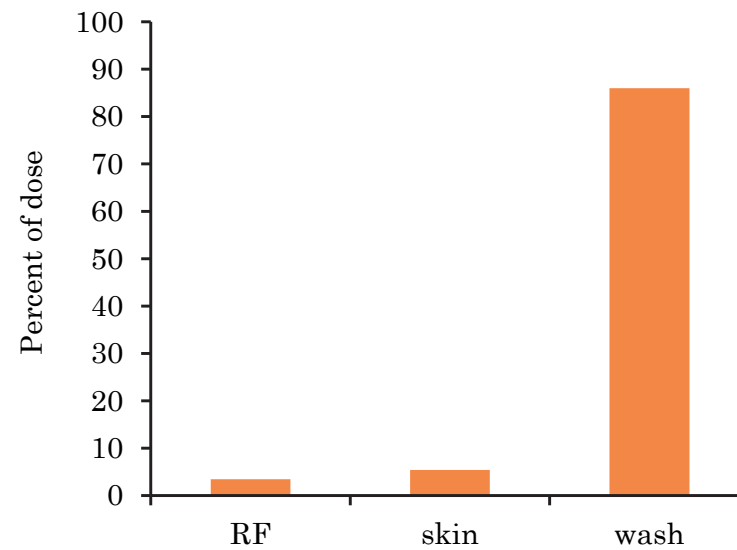
- Spreading capability

WHY ARE WE INTERESTED

CE data*: The majority of the materials were found in the wash, even when a small dose was applied.



1.08ug/cm² Caffeine
0.01M PBS



1.64ug/cm² Testosterone
EtoH

*Hewitt et al., J Appl Toxicol, 2019

TESTED COMPOUNDS

Table1 Physical properties of selected solutes

Permeant	MW (g/mol)	mp (°C)	log K _{oct}	P _{vp} (mmHg)	S _w (mg/ml)
Niacinamide	122.12	130	-0.37	8.07E-05	534
Caffeine	194.19	238	-0.07	7.33E-09	17.5
Testosterone	288.4	155	3.32	2.23E-08	0.133
Geraniol	152.2	-15	3.56	3.00E-02	0.35

TESTED COMPOUNDS

- Dose estimation

$$M_{\text{sat}} = \text{Best } C_{\text{sat}} * \text{deposition layer thickness}$$

Deposition layer thickness= 10% SC thickness

Fully hydrated 43.4um * 10% = 4.34um

Partially hydrated 43.4um * 10% = 4.34um

$$C_{\text{sat}} = K_{\text{sc/w}} * S_{\text{w}}$$

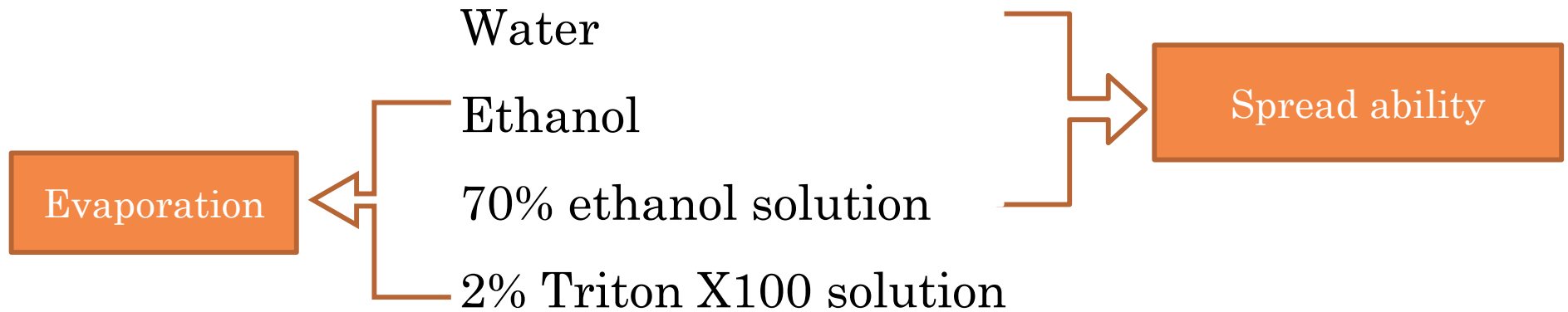
TESTED COMPOUNDS

- Target dose: estimated saturation dose*

Material	Dose (ug/cm ²)		CE
	Target	Actual	
Niacinamide	30.52	31.64	-
Caffeine	2.93	3.16	1.08
Testosterone	7.66	8.23	1.64
Geraniol	2.9	2.91	2.1

*Based on CE solubility and partition coefficient values

TESTED SOLVENTS



Solvent effect: niacinamide, caffeine, testosterone and geraniol.

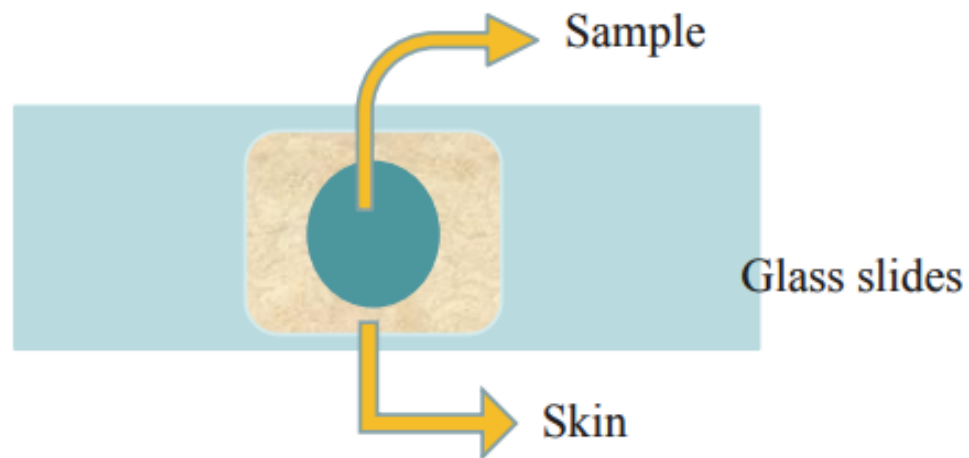
4 solvents

ethanol
/70% ethanol

4 solvents
/ethanol solutions

AIM 1: TEST COMPOUNDS SELECTION AND LIGHT MICROGRAPHS

METHOD

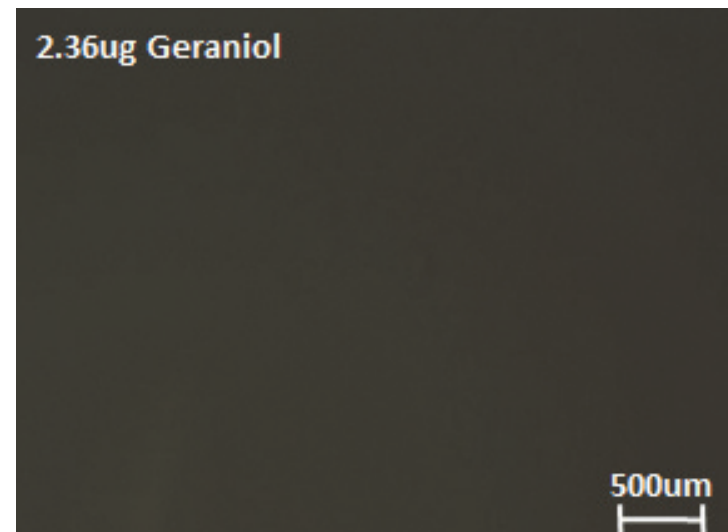
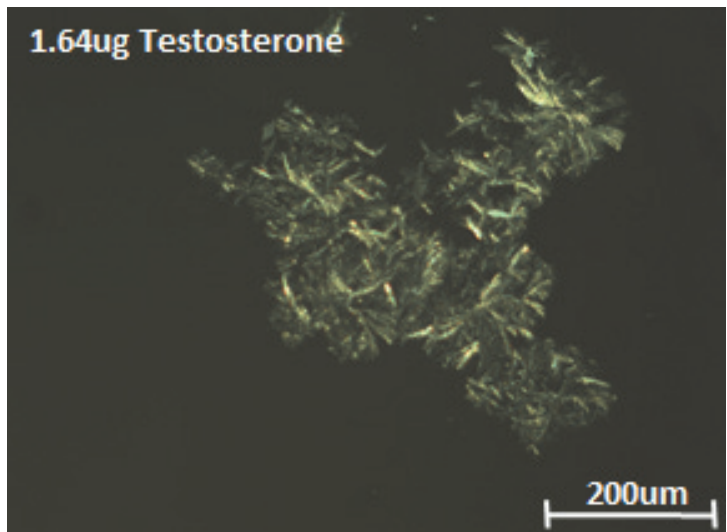
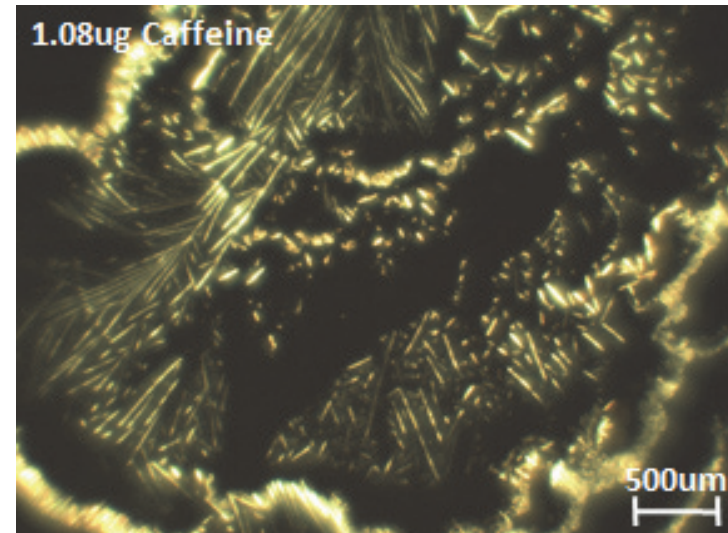
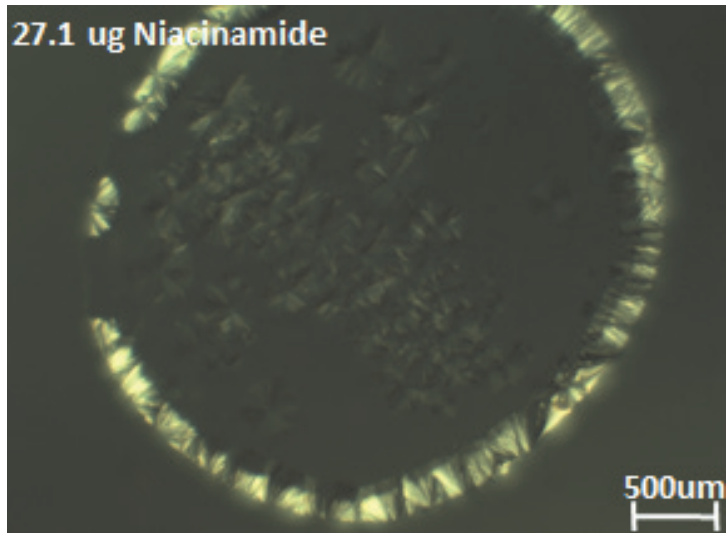


Sample preparation

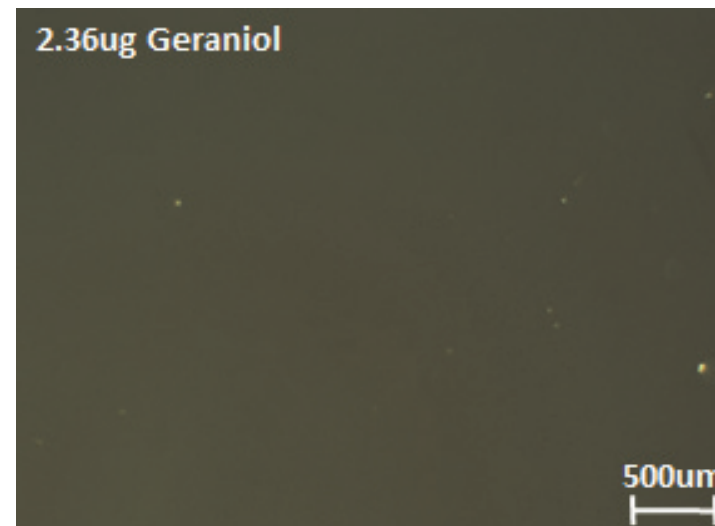
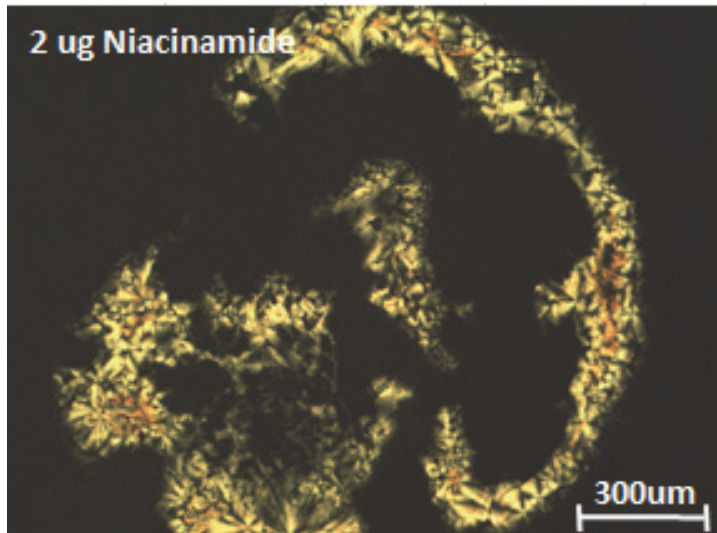
10uL of sample were pipetted onto substrates and allow to dry.

Glass slides and silanized slides: 1:1 ethanol and water;
Skin: four selected solvents

GLASS SLIDES

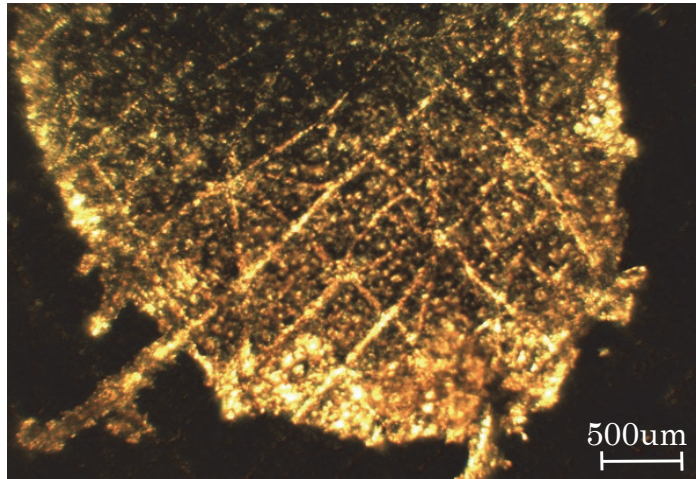


SILANIZED SLIDES

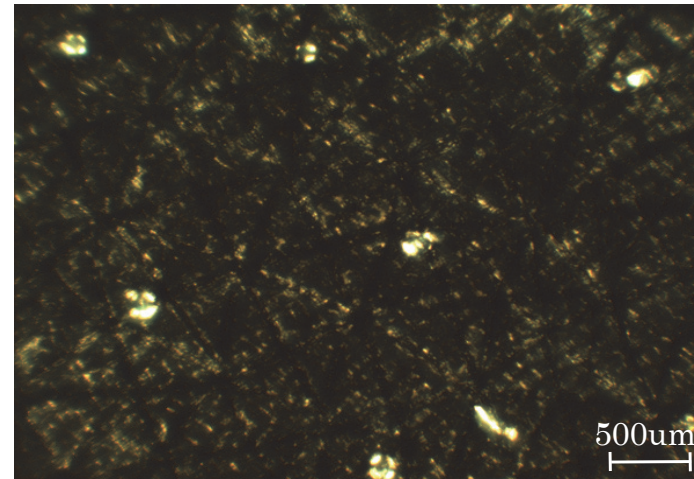


HEM – 50UG NA

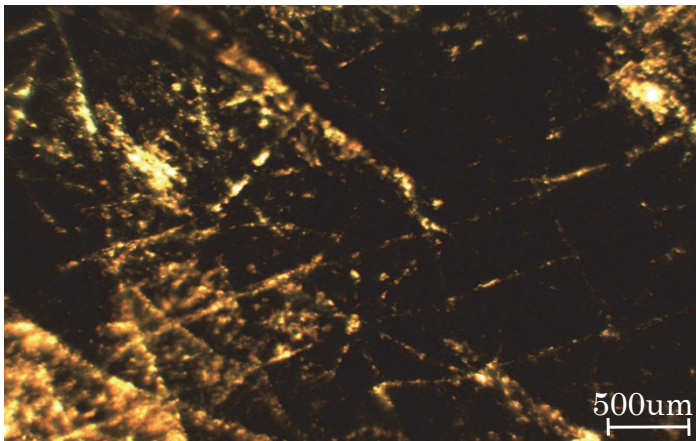
Water



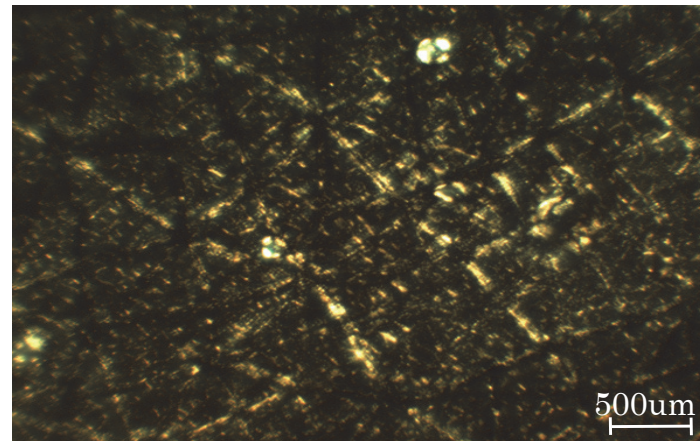
70% EtoH



EtoH

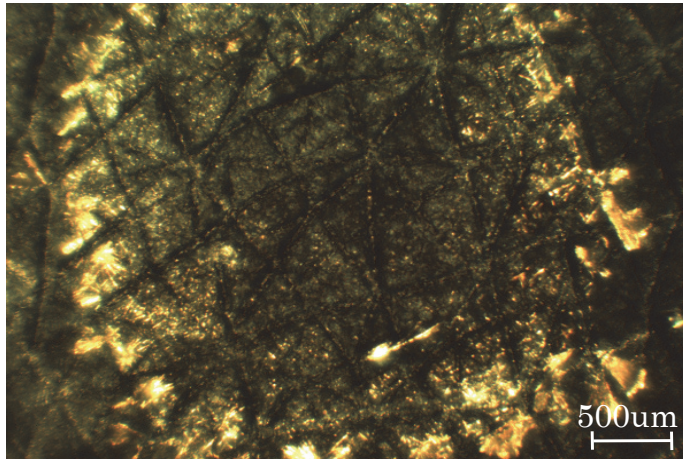


2% Triton solution

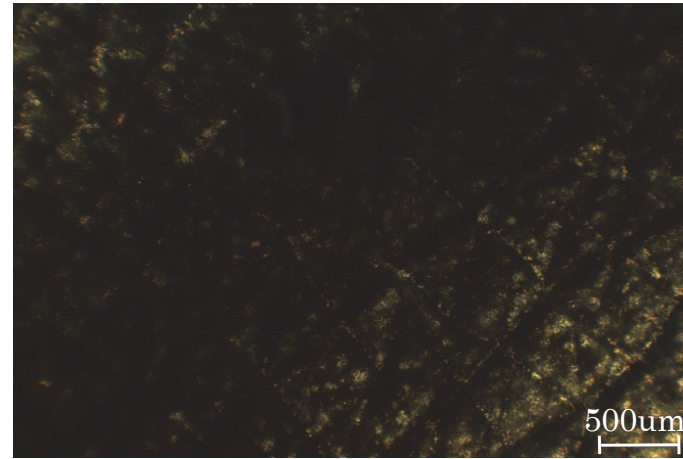


HEM – 10UG CAFFEINE

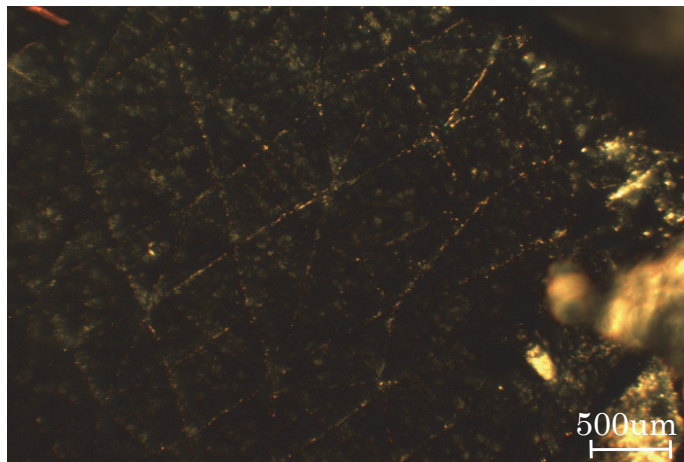
Water



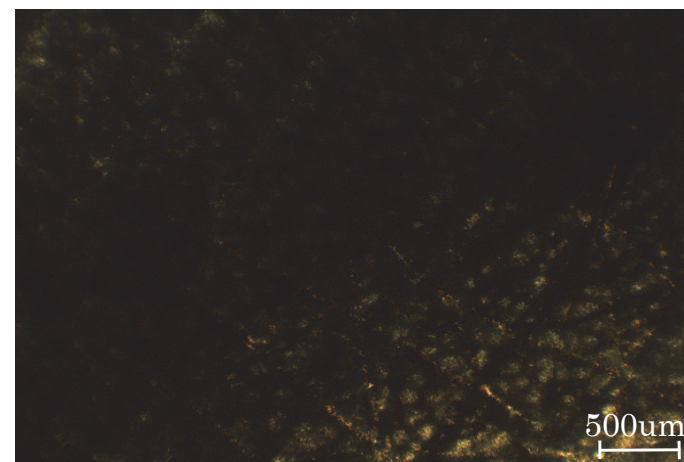
70% EtoH



EtoH

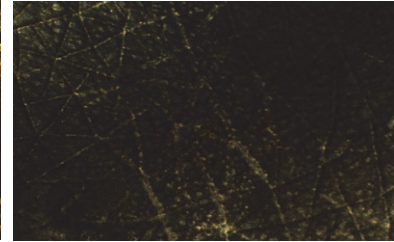
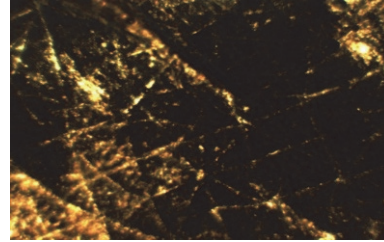
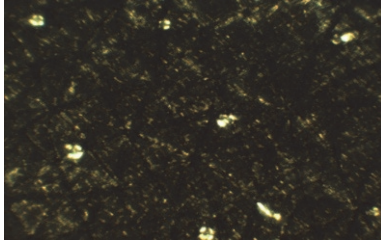
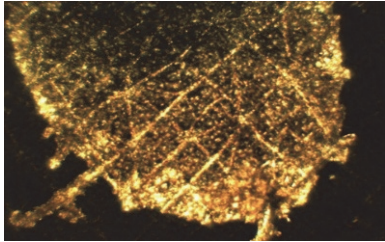


2% Triton solution

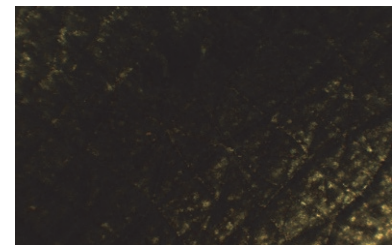
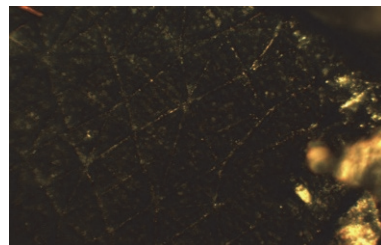
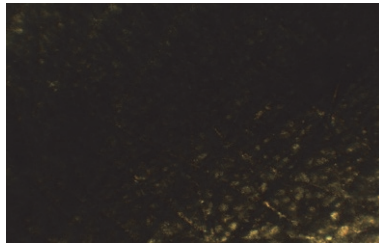
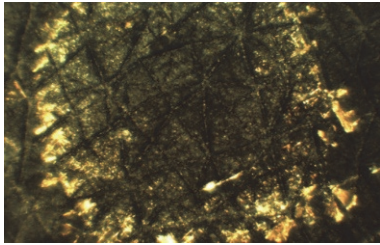


HEM

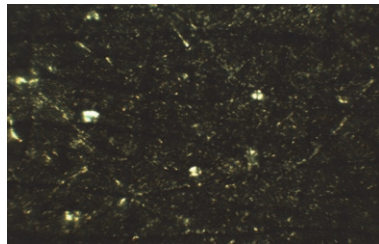
NA



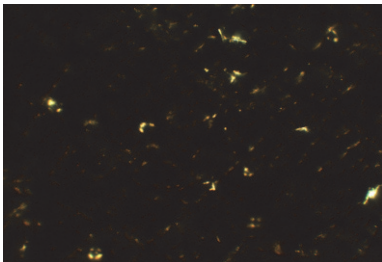
Caffeine



Testosterone



Geraniol



Water

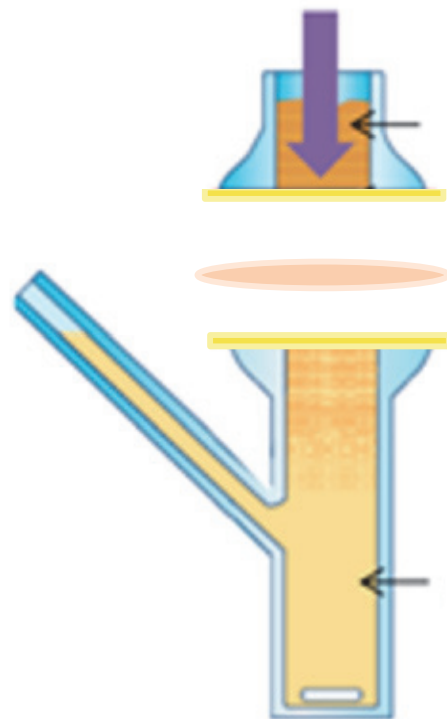
70% EtoH

EtoH

2% Triton solution

**AIM 2: DETERMINE THE EFFECT OF
SPREADING CAPABILITY OF SOLVENTS IN
SKIN PERMEABILITY**

EXPERIMENTAL DESIGN



Donor chamber

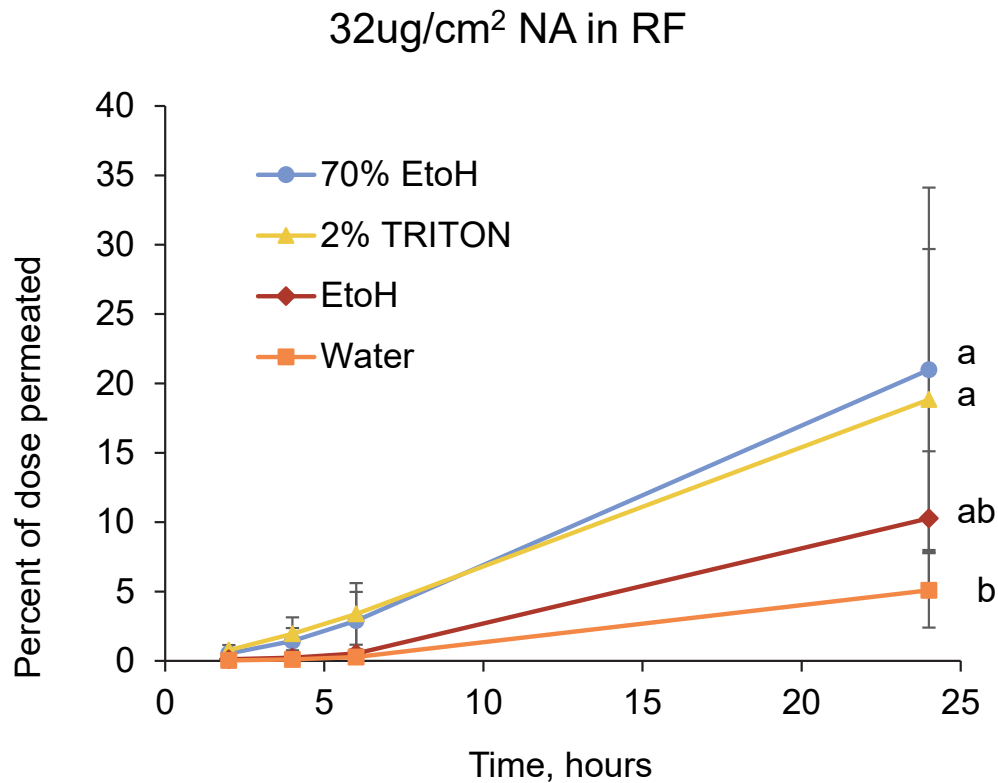
Skin

Receptor chamber

Randomized complete block
(RCB) design.

3 donors, 4-6 replicates per
donor

NIACINAMIDE



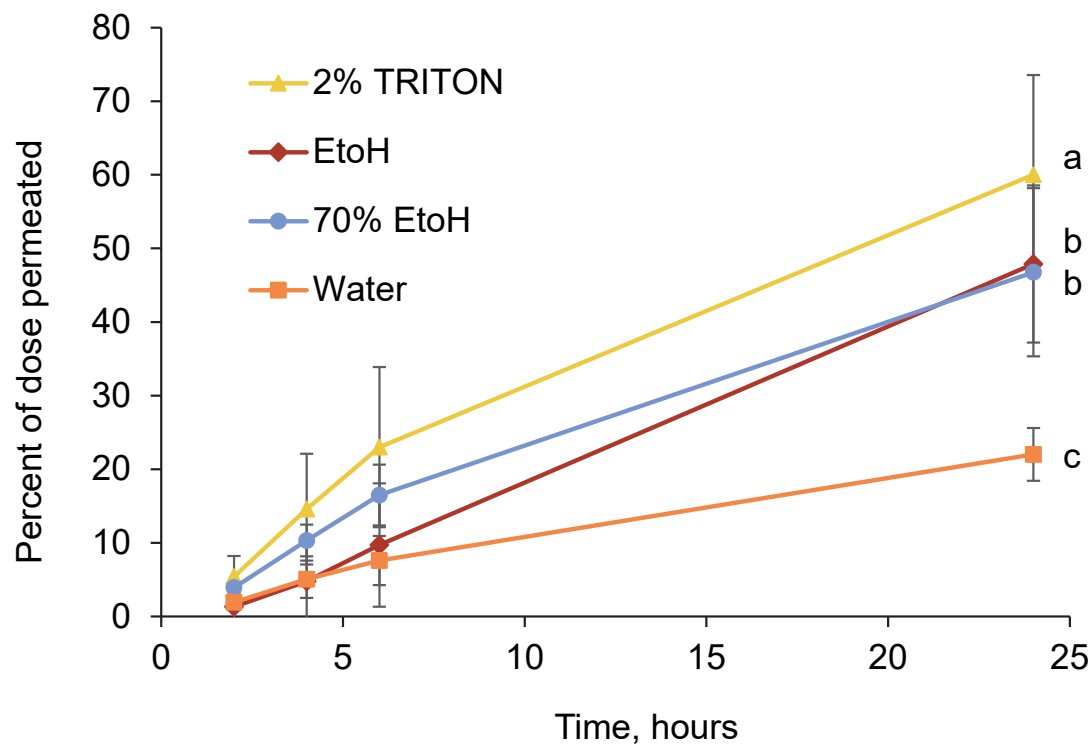
Treatments sharing the same letter are not significantly different.

There is no significant difference between triton solution, 70% ethanol and ethanol.

Water formulation is significantly lower than 70% ethanol solution and 2% Triton solution.

CAFFEINE

3.2ug/cm² CA in RF

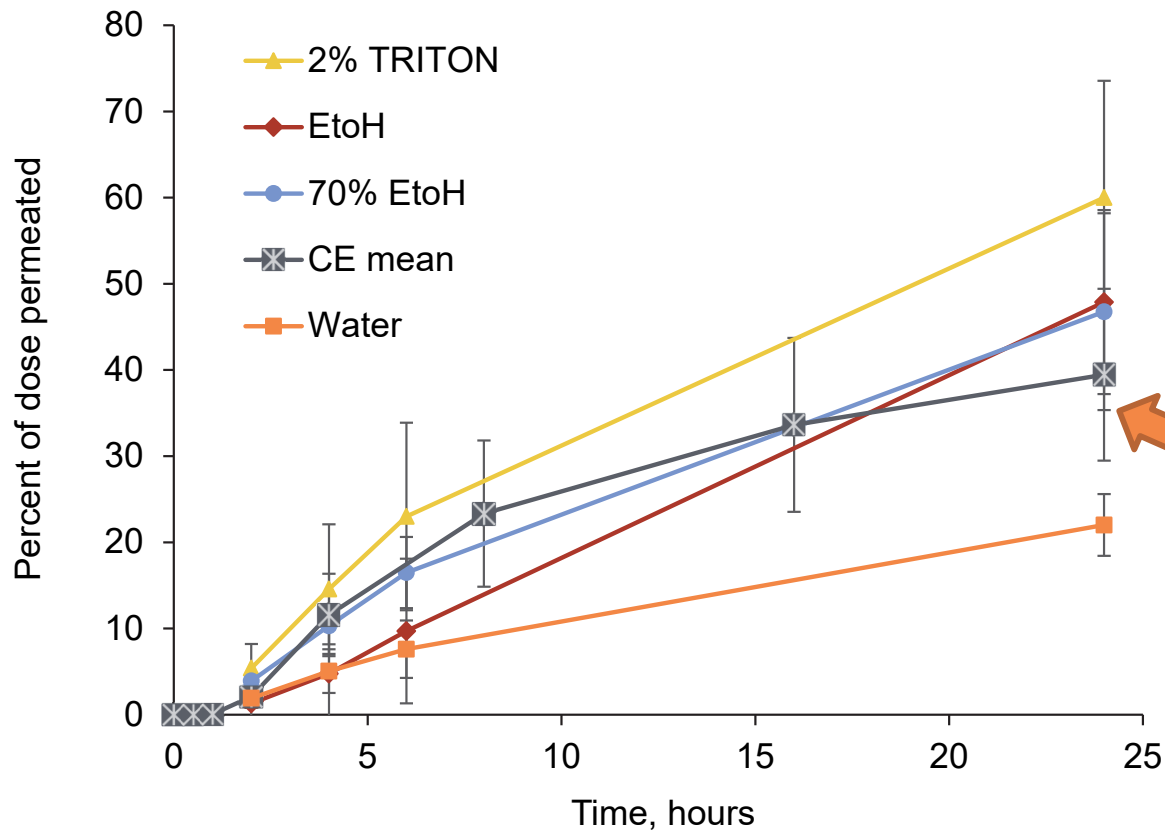


Water formulation is significantly lower than the other three groups.

There is no significant difference between ethanol and 70% ethanol.

Enhancer effect is not significant in this finite dose study.

CAFFEINE

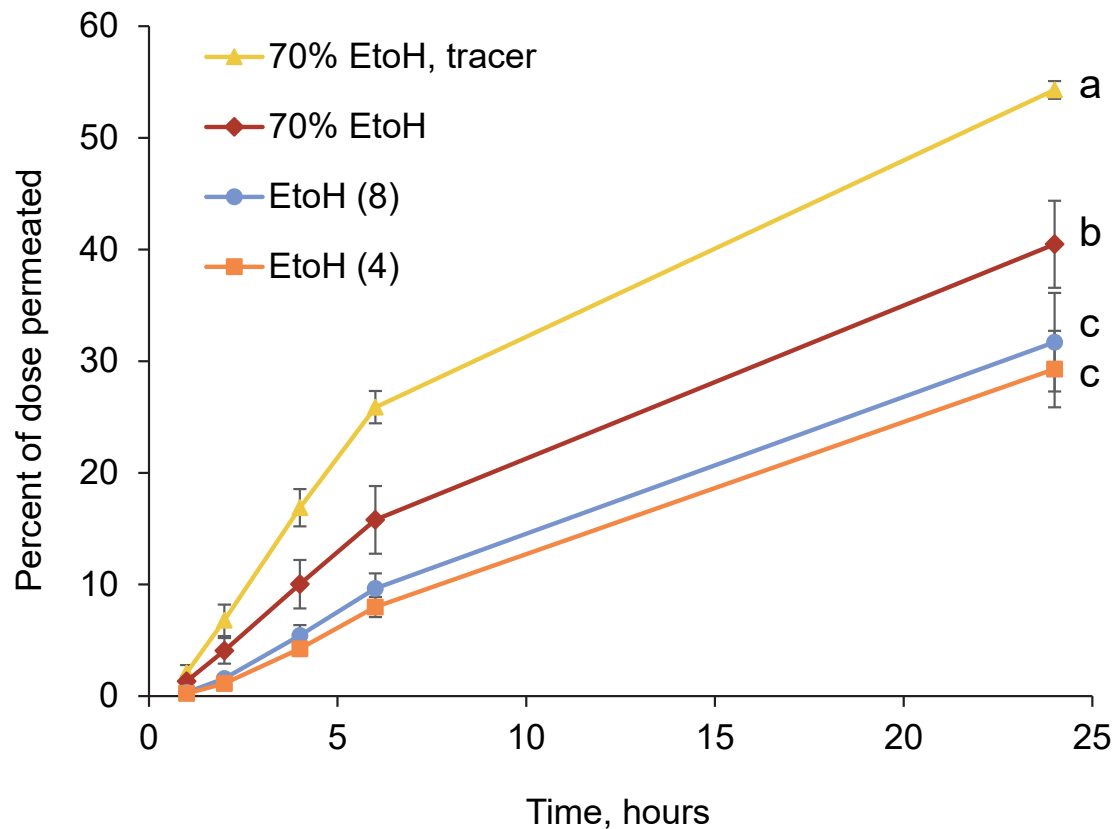


The permeated percent of dose from 0.01M PBS (CE experiment) was higher than water.

Other formulations contribute to higher permeation.

TESTOSTERONE

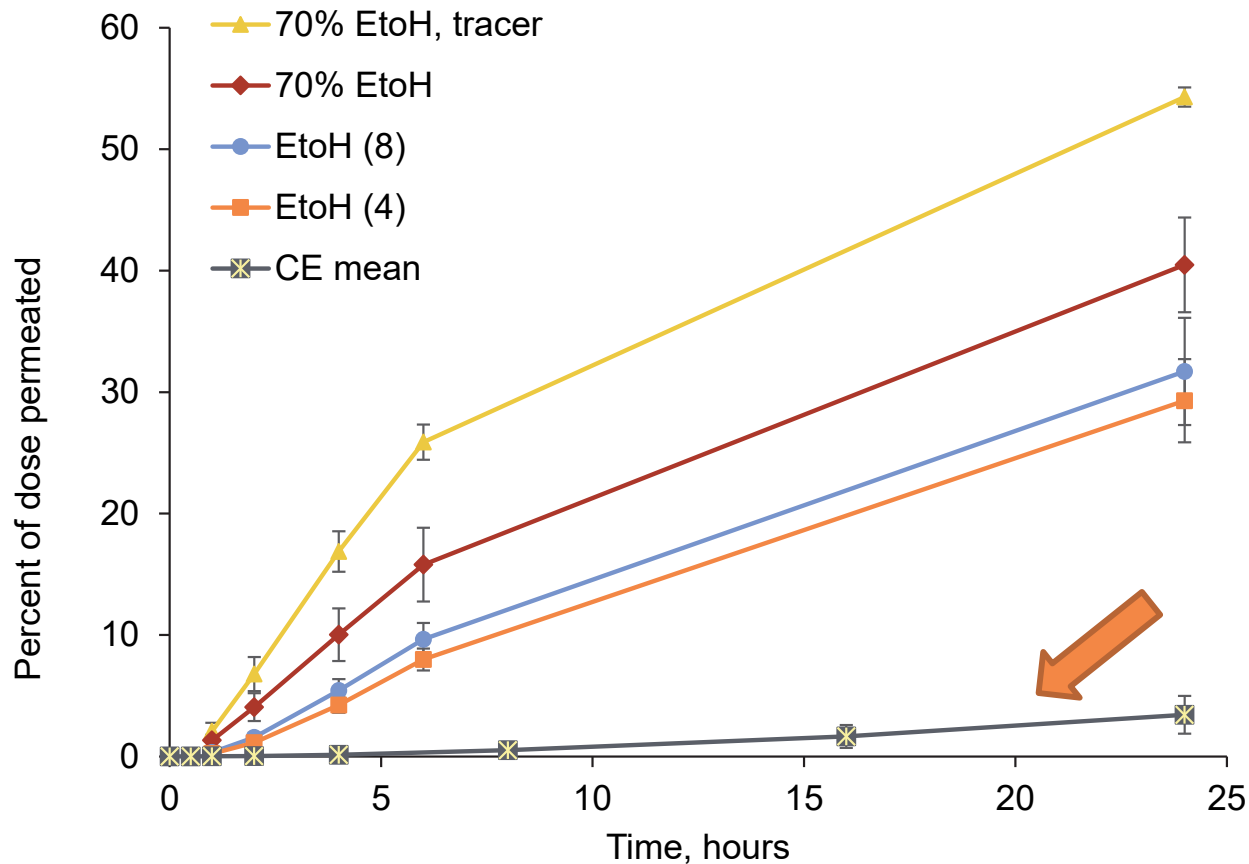
8.2ug/cm² Testosterone in RF



Tracer level testosterone yielded the highest permeation percent.

Permeated amount from ethanol group is different with 70% ethanol group. Evaporation effects is significant.

TESTOSTERONE

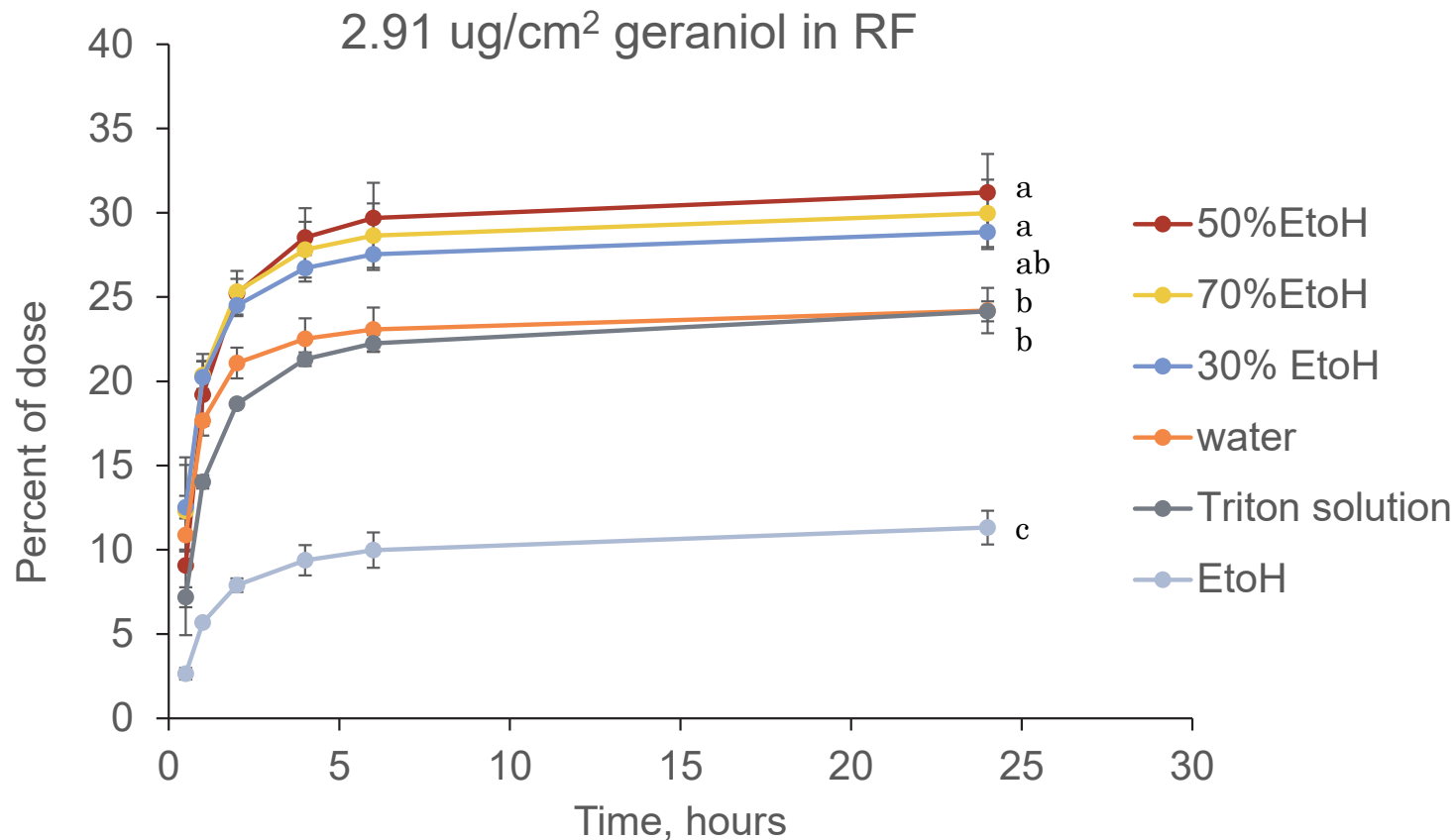


Both CE and our study use ethanol for testosterone.

The skin penetration study showed a significant different between two groups.

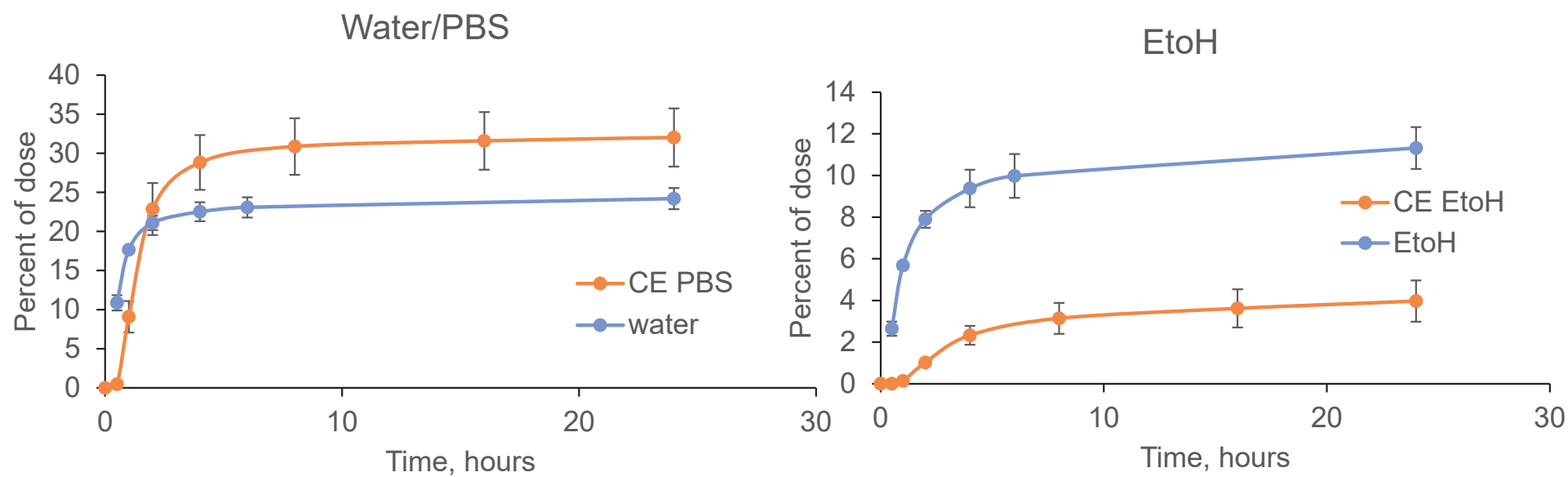
70% ethanol contribute to a higher permeation

GERANIOL



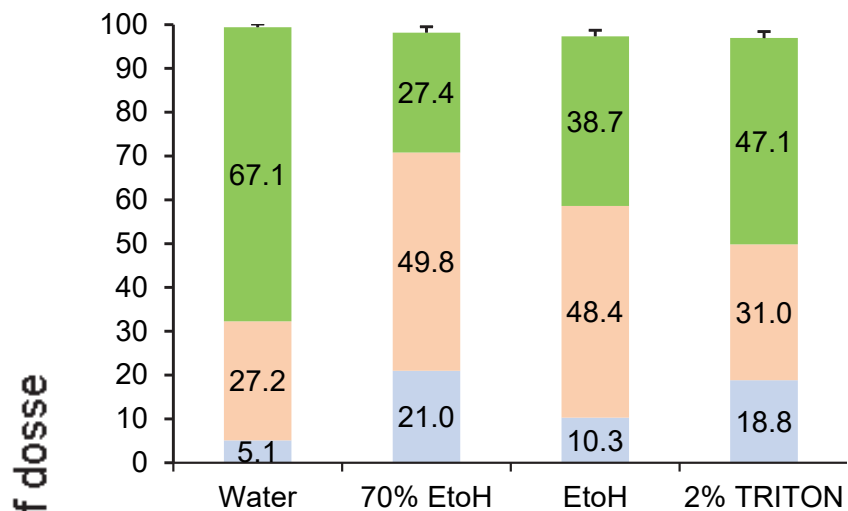
Ethanol solution contribute to the highest permeation amount followed by aqueous solutions. Ethanol is significantly lower than all the other groups.

GERANIOL

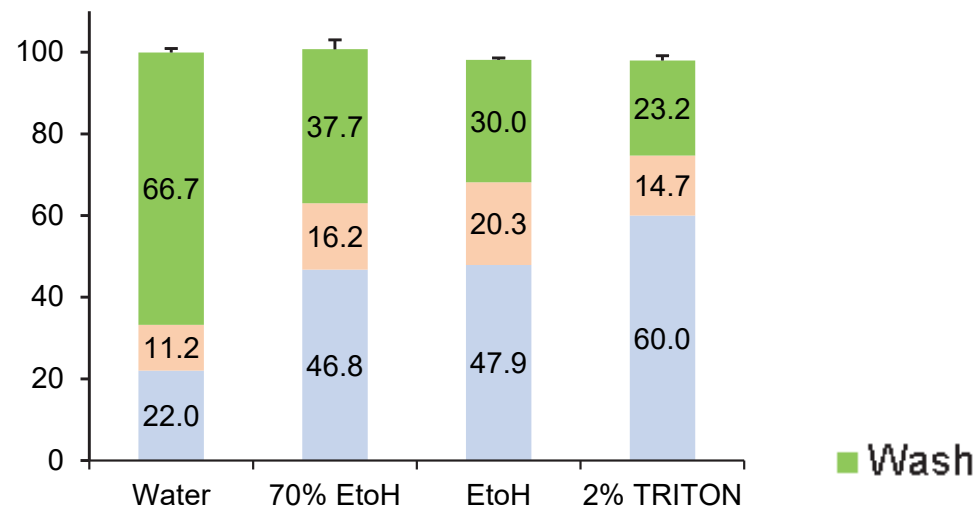


MASS BALANCE

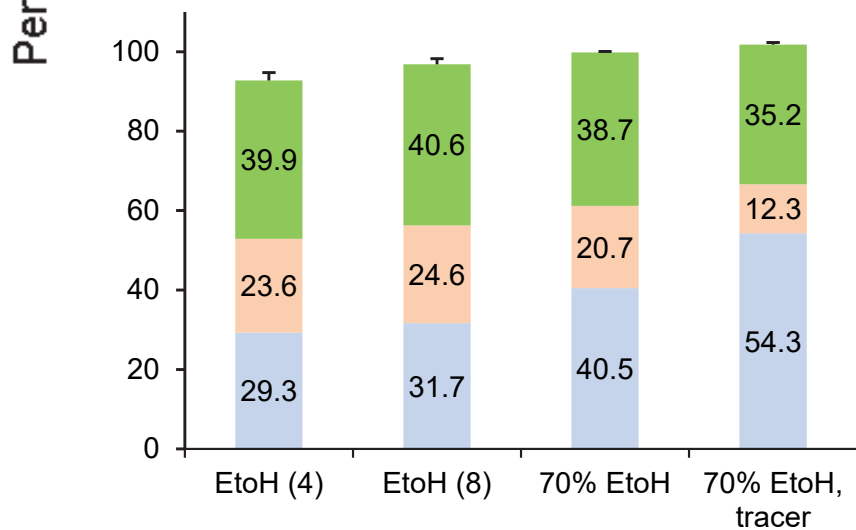
Niacinamide



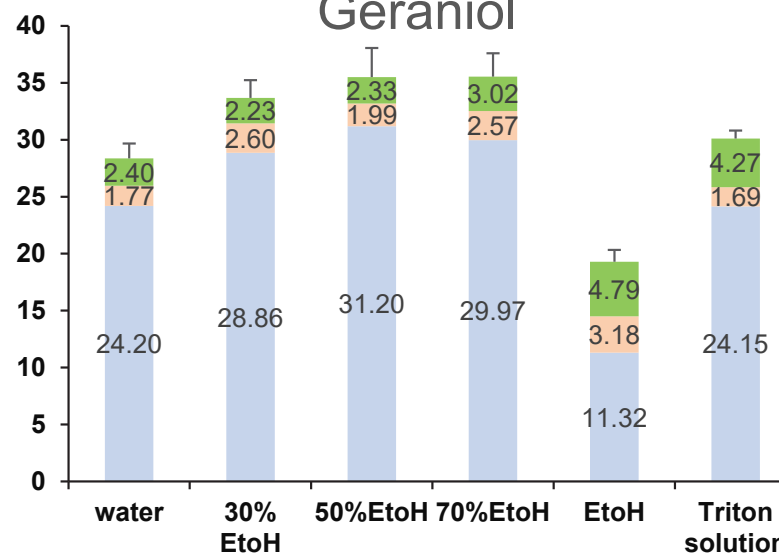
Caffeine



Testosterone



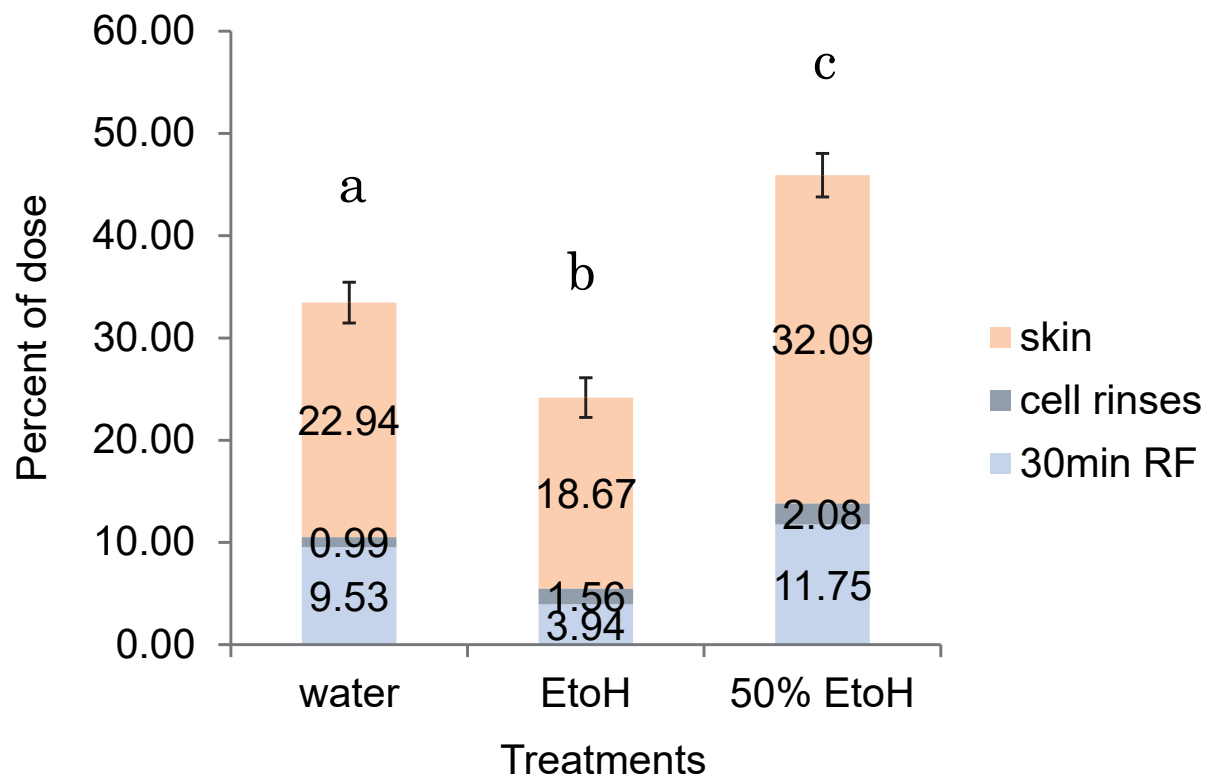
Geraniol



Treatments

EVAPORATION TEST

Totally mass balance for 2.91 ug/cm² geraniol after 30mins

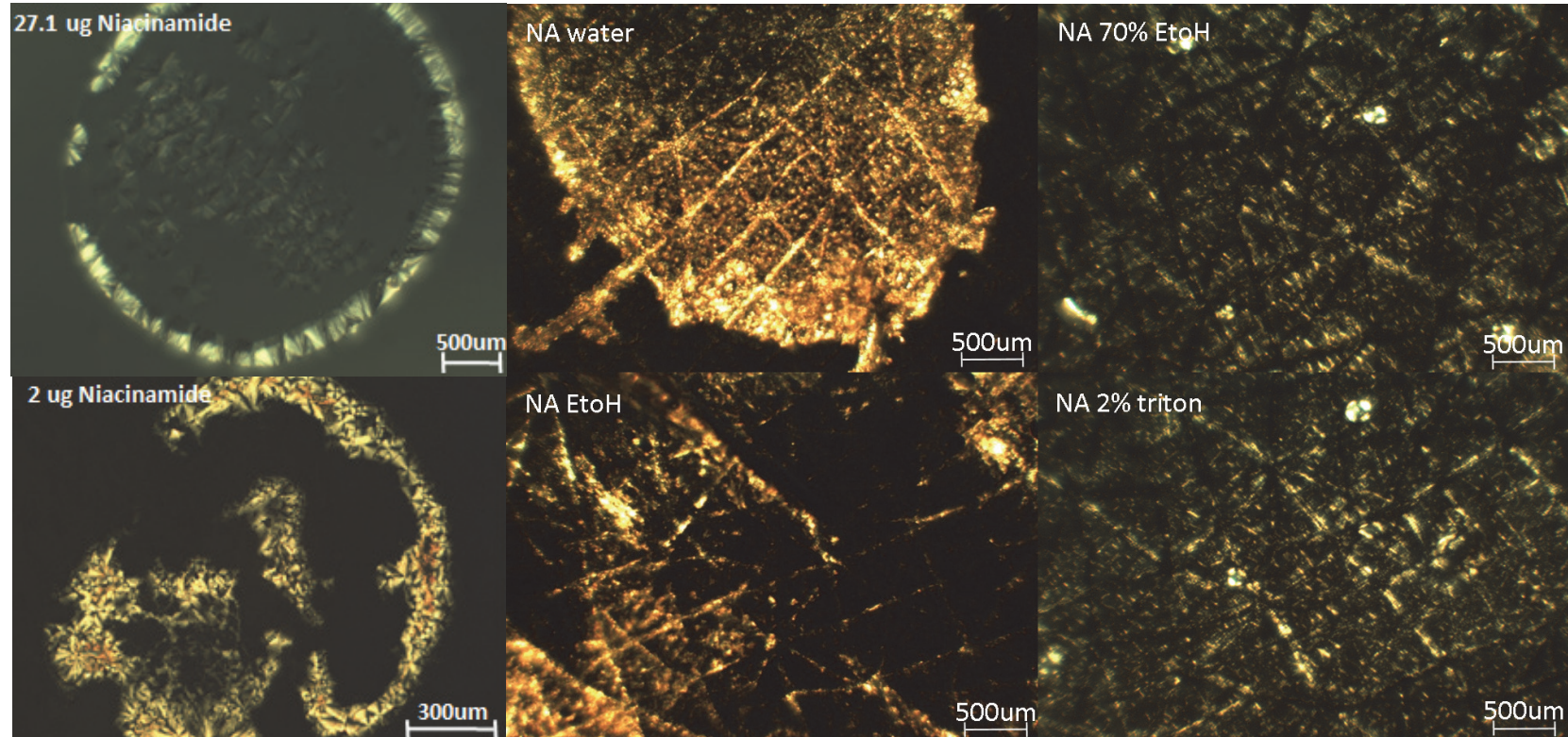


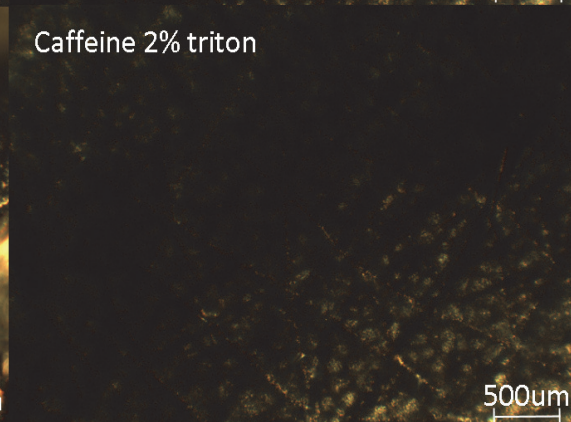
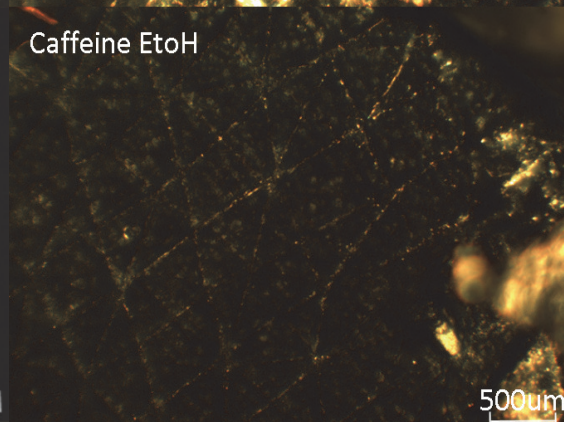
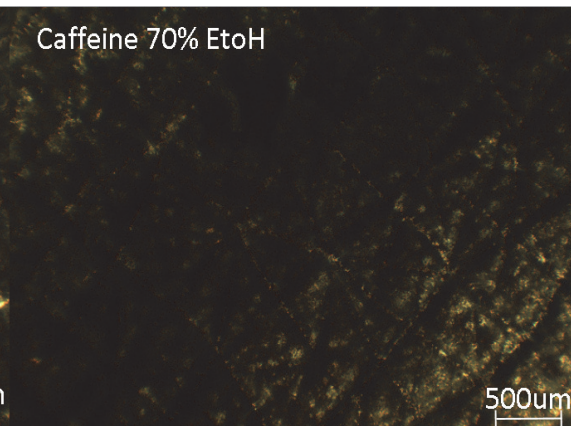
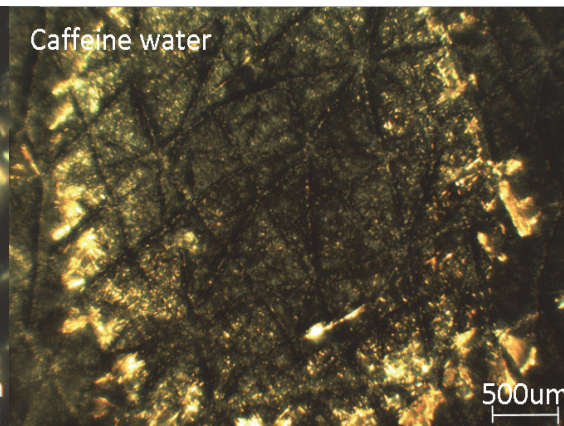
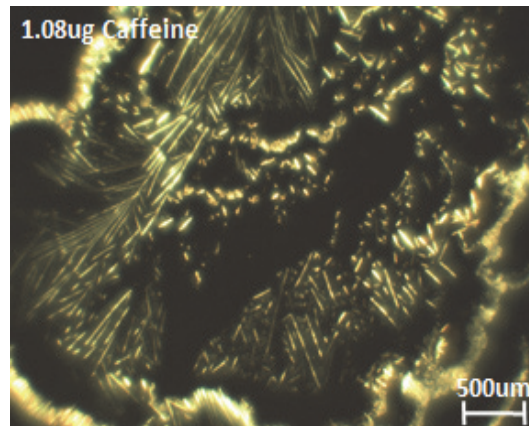
>50% of geraniol was evaporated at 30 mins after dosing.

CONCLUSION

- Water is the poorest deliver system for hydrophilic compounds. Solvents with lower surface energies are better deliver agents.
- Ethanol and water mixtures are the best delivery systems for lipophilic permeants.
- Solvents evaporation rate affects lipophilic permeants more.
- Ethanol is the poorest vehicle for geraniol.
- Delivery rate and crystallinity are inversely related for hydrophilic compounds.

THANK YOU





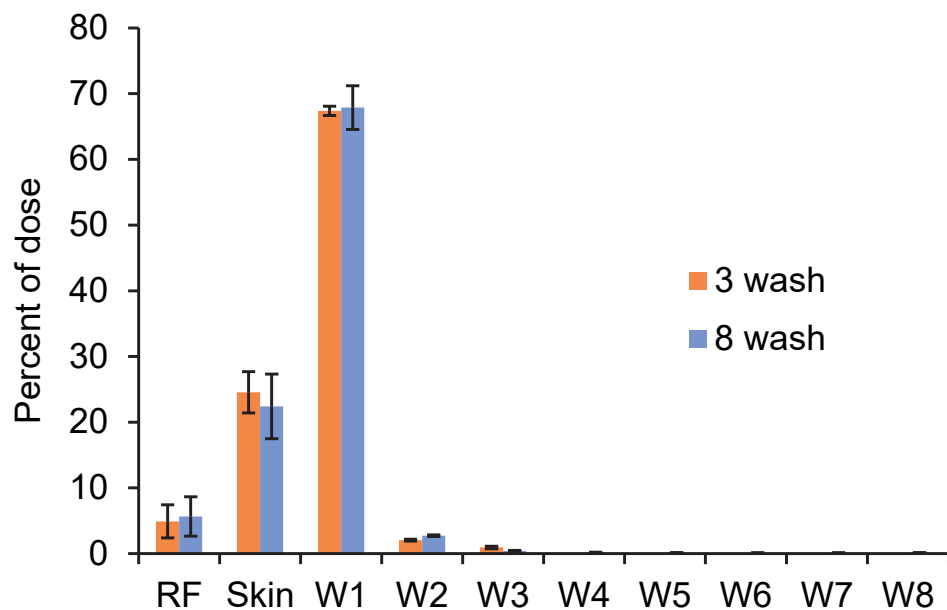
RINSING EXPERIMENT

RINSING EXPERIMENT

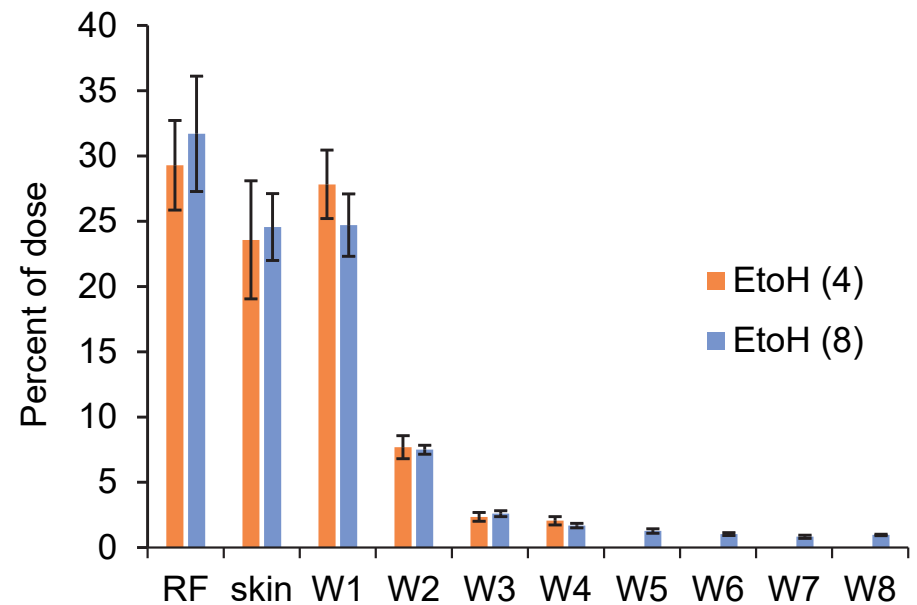
- Two permeants were studied – niacinamide and testosterone.
- Two skin rinsing protocols were employed.
- Niacinamide: 3 rinses (water only) and 8 rinses (hand soap and water) .
- Testosterone: 4 rinses and 8 rinses, first rinse with 2% mild hand soap, the rest with water.

RINSING EXPERIMENT

There is no significant difference between two rinsing protocol for both hydrophilic and lipophilic compounds.

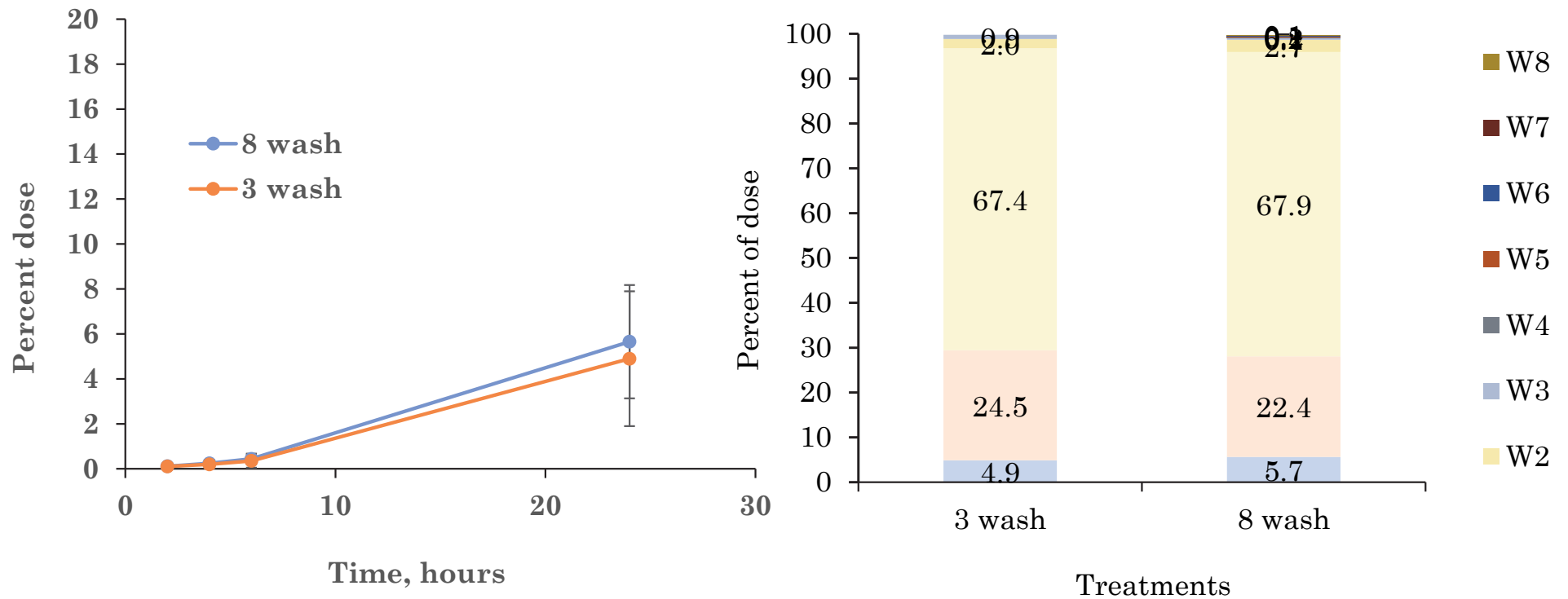


Niacinamide

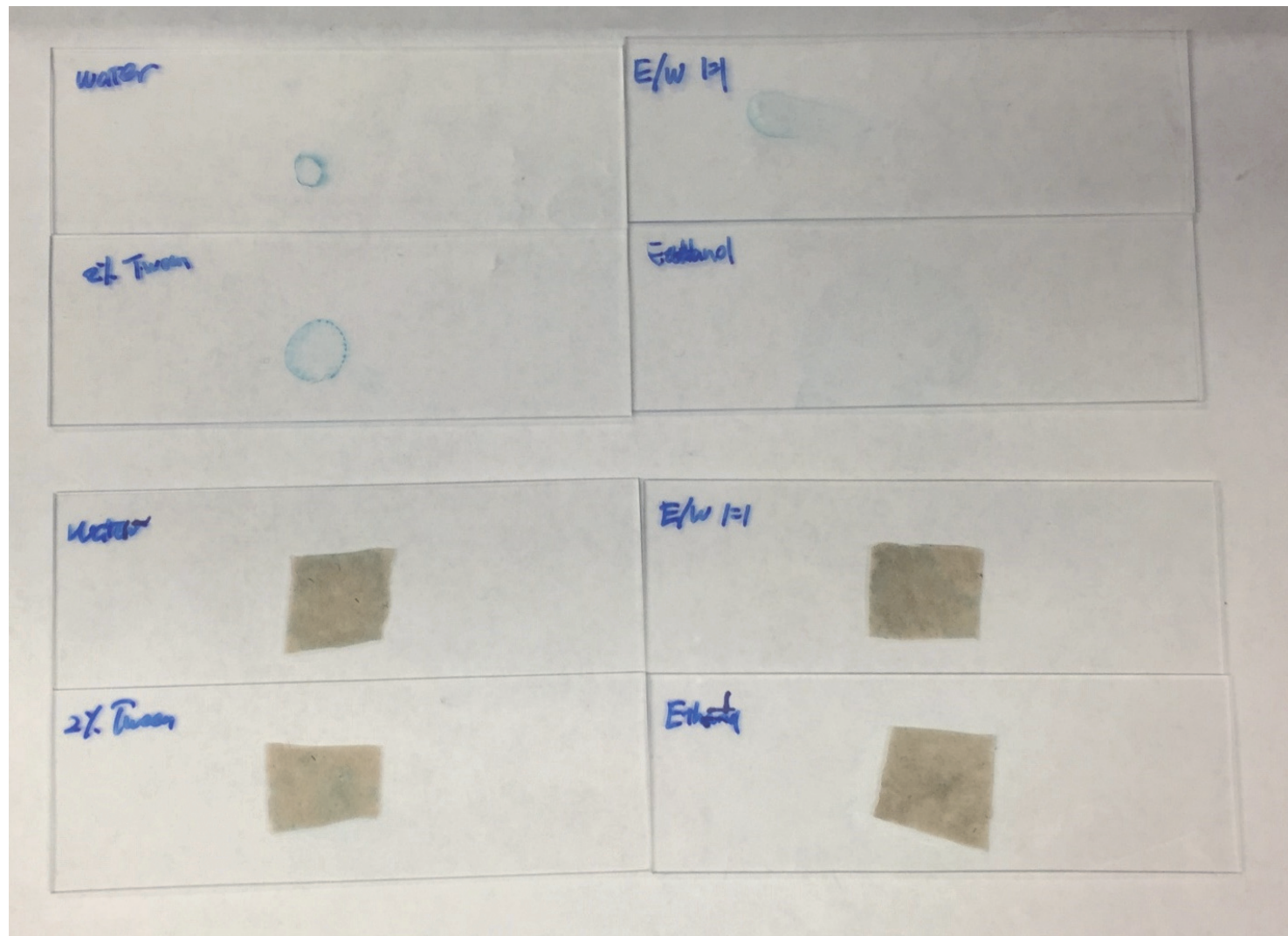


Testosterone

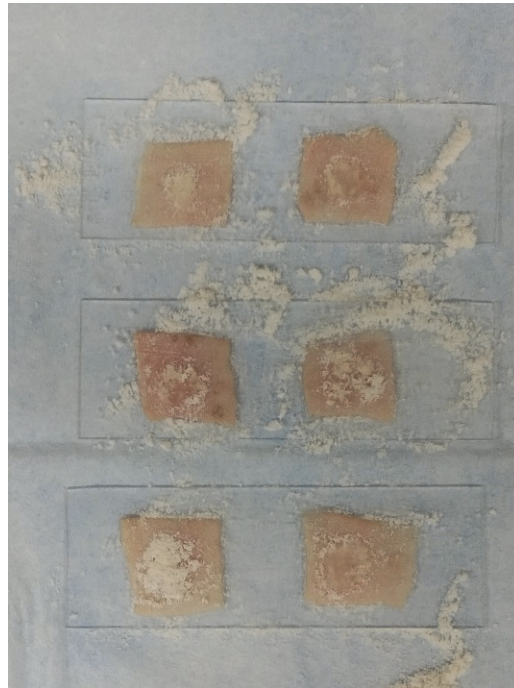
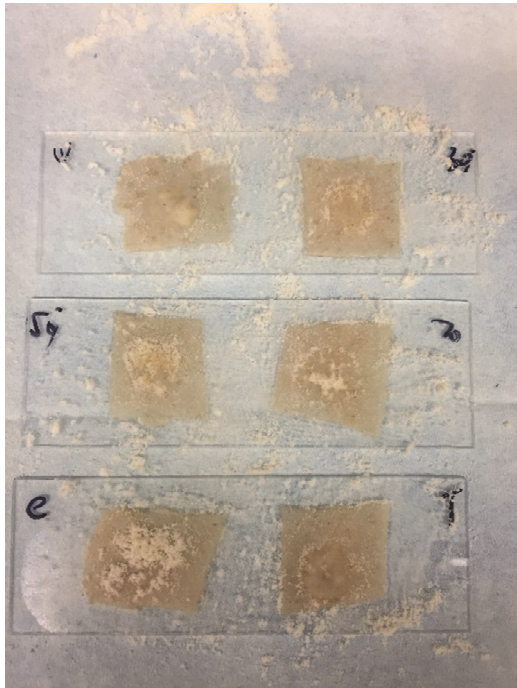
NIACINAMIDE RINSES



SOLVENTS SPREADING TEST



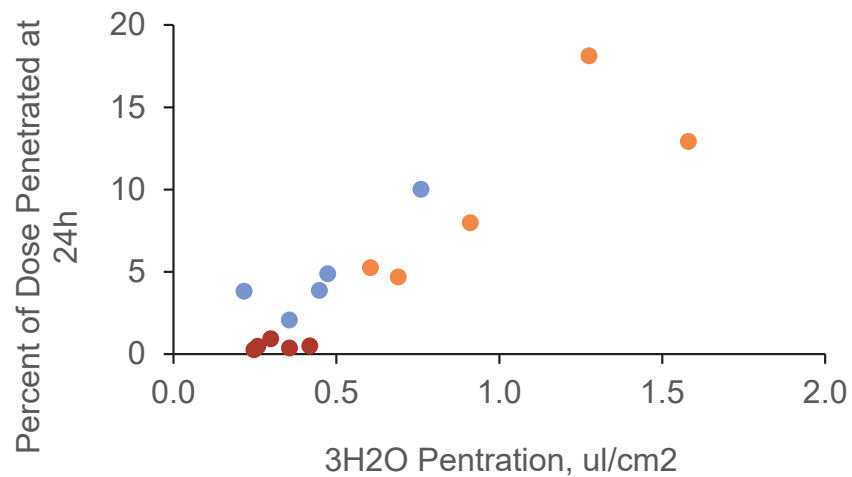
SOLVENTS SPREADING TEST



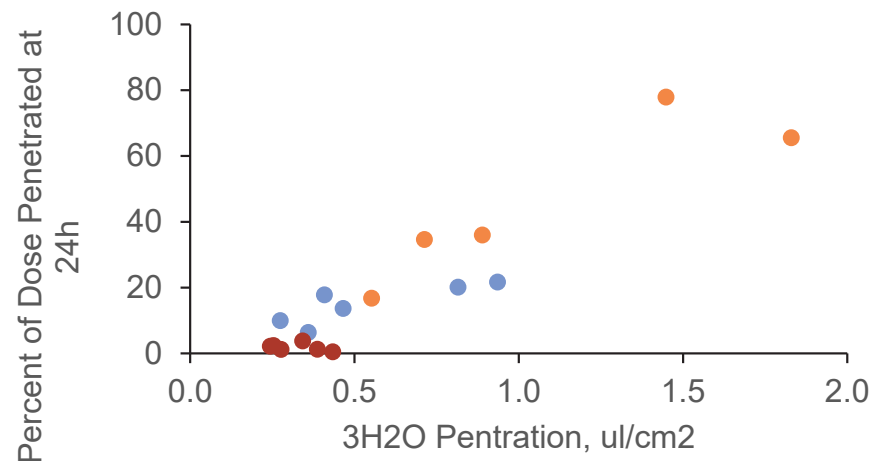
Sample	Averaged ratio	SD
water	1.00	0.00
30% ethanol	2.10	0.57
50% ethanol	2.44	0.55
70% ethanol	2.99	0.58
ethanol	4.18	1.37
2% triton	3.06	0.68

NA

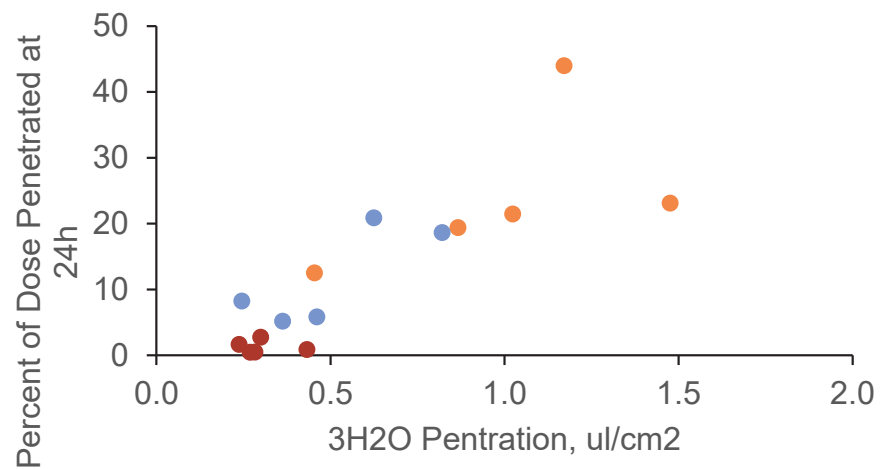
NA from water



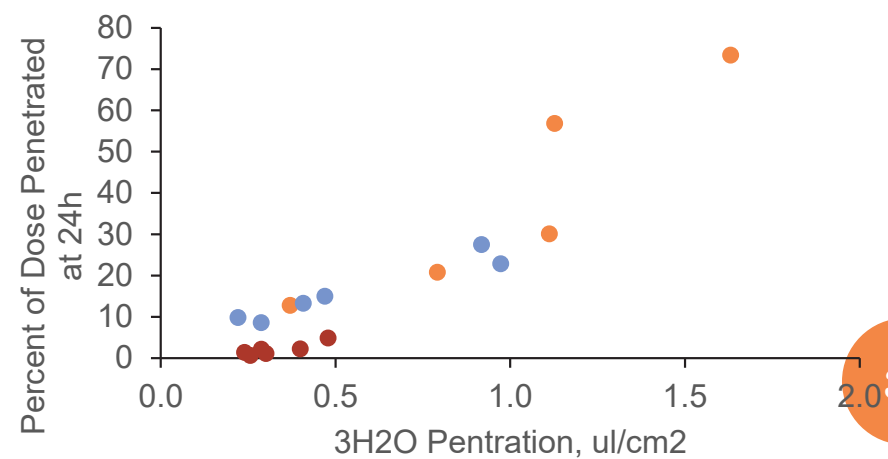
NA from 70% EtoH



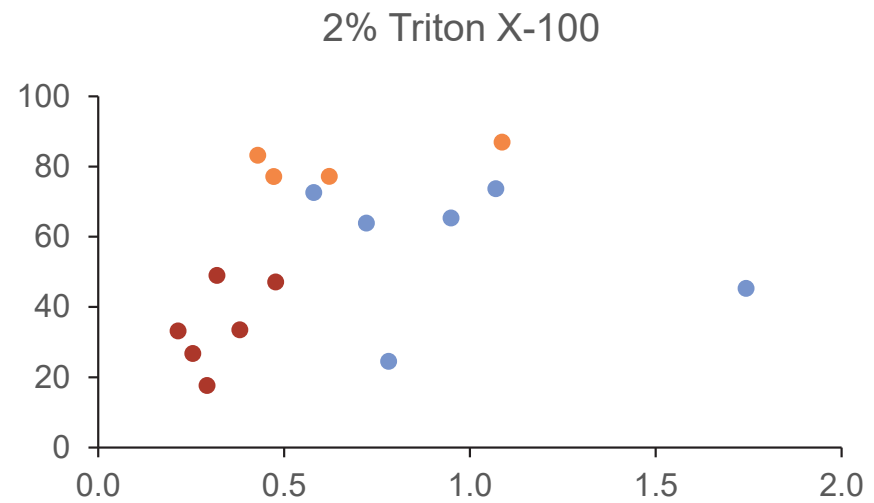
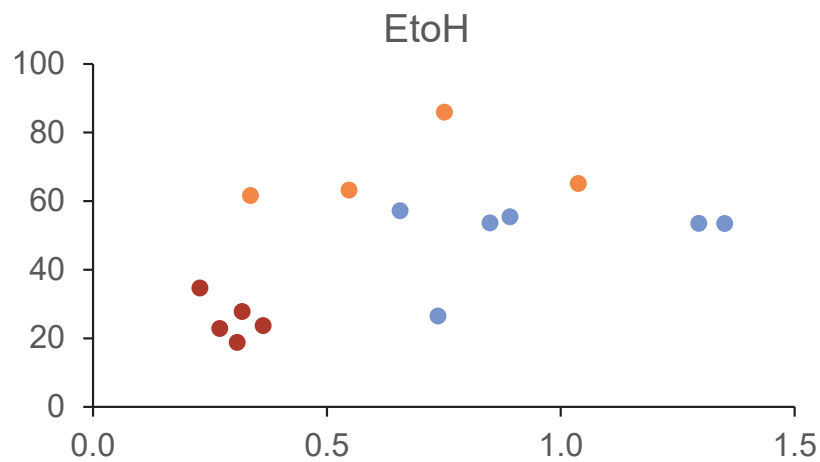
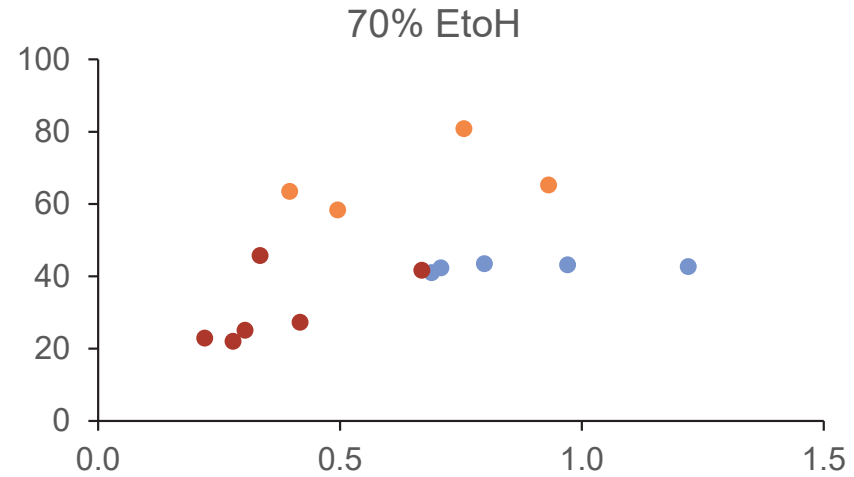
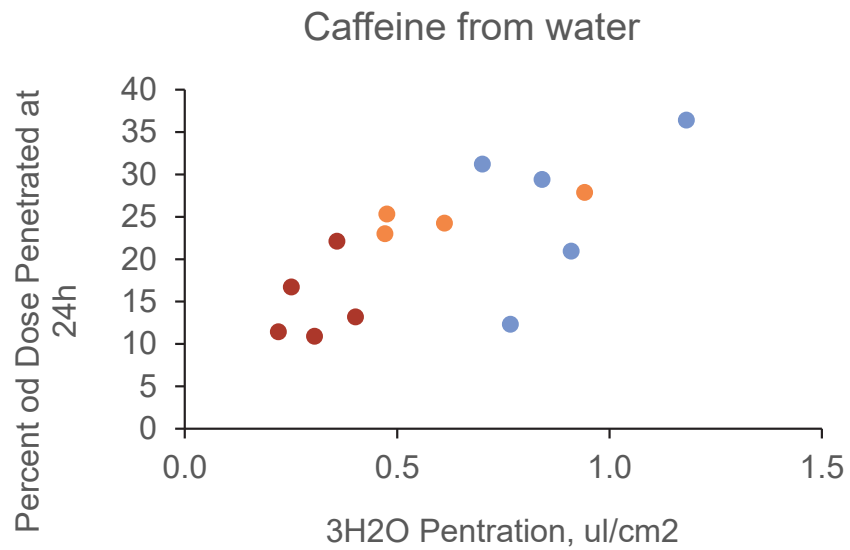
NA from EtoH



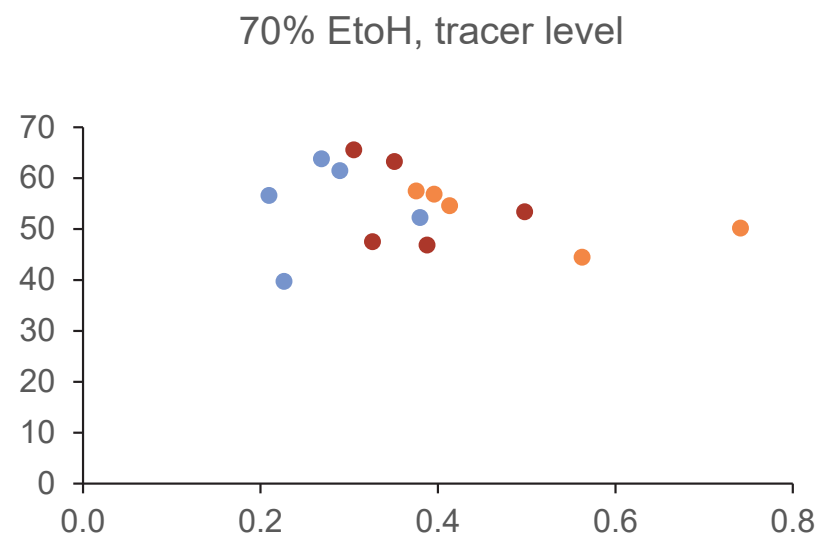
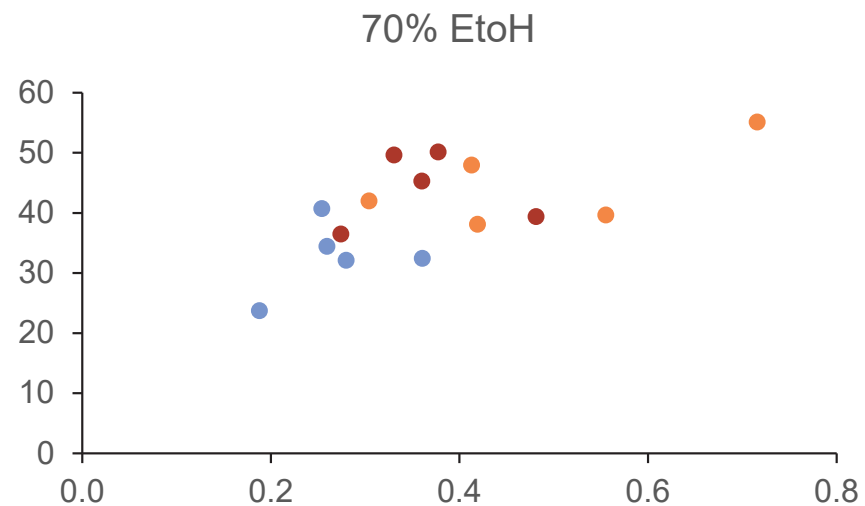
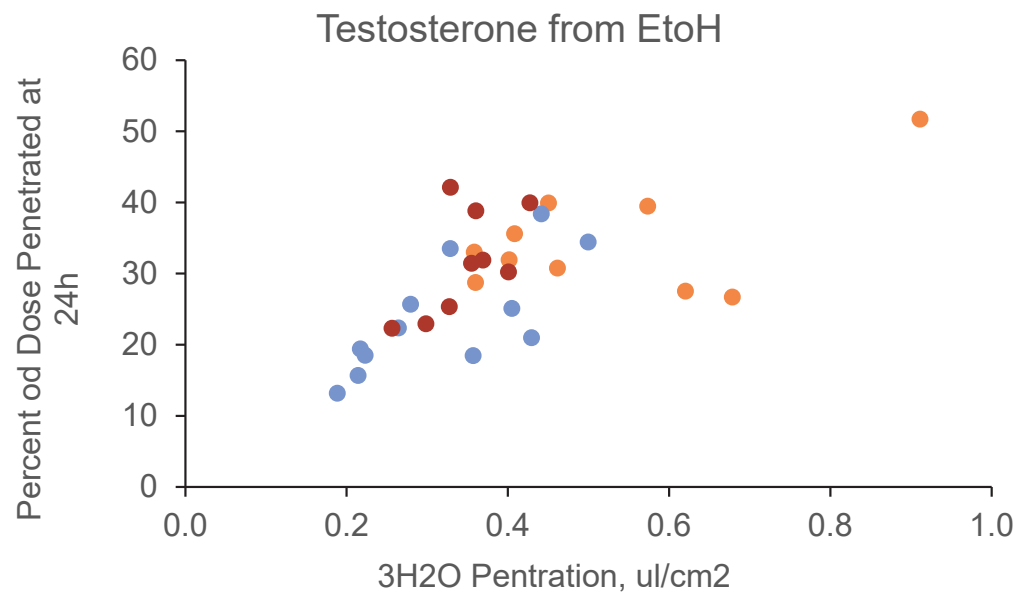
NA from 2% Triton X-100



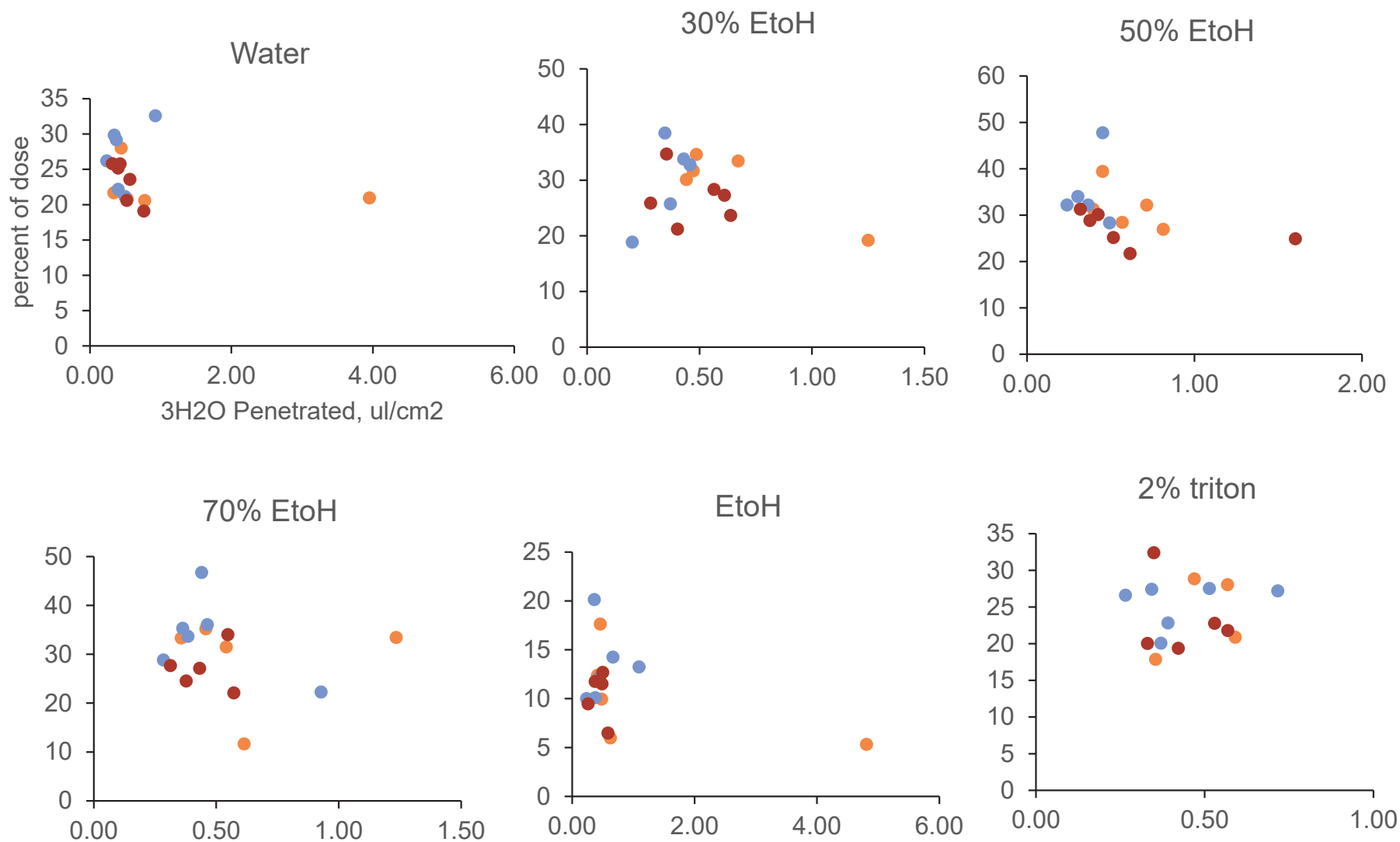
CAFFEINE



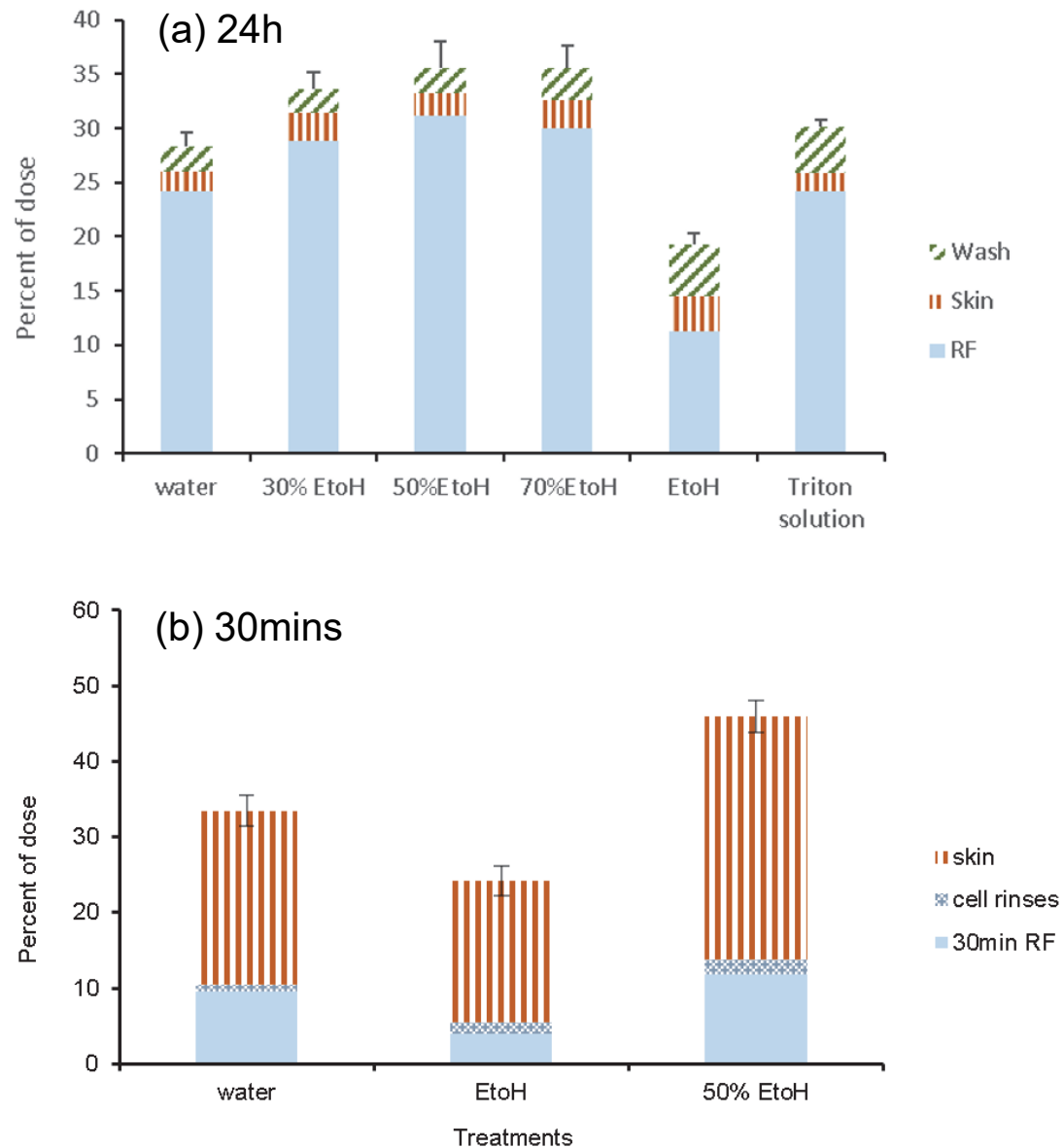
TESTOSTERONE



GERANIOL



EVAPORATION TEST



PERMEANT DIFFERENCE

Compound	Group	Mean	SEM	RSE, %
Niacinamide	Donor 1	29.72	2.53	
	Donor 2	11.96	2.42	
	Donor 3	1.29	2.47	
	Average	14.32	8.29	57.9
Caffeine	Donor 1	59.14	2.05	
	Donor 2	46.86	1.76	
	Donor 3	26.5	1.73	
	Average	44.17	9.52	21.6
Testosterone	Donor 1	42.22	1.71	
	Donor 2	33.78	1.59	
	Donor 3	40.82	1.71	
	Average	38.94	2.61	6.7
Geraniol	Donor1	24.51	1.012	
	Donor2	27.345	0.935	
	Donor3	22.987	0.949	
	Average	24.95	1.28	5.1

DONOR INFO

	Donor	Age	Sex	Donor site
Niacinamide	CC072020	33	MALE	RPL
	JC031421	59	MALE	RPL
	AF053021	37	FEMALE	RPL
Niacinamide rinse	JC031421	59	MALE	RPL
	AF053021	37	FEMALE	RPL
	CC072020	33	MALE	PT
Caffeine	CC072020	33	MALE	RPL
	JC031421	59	MALE	RPL
	AF053021	37	FEMALE	RPL
Testosterone	CC072020	33	MALE	PT
	CM113021	67	MALE	PT
	EH120420	54	MALE	RPL
Geraniol	CC072020	33	MALE	PT
	CM113021	67	MALE	PT
	EH120420	54	MALE	RPL