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Transcending the Limitation of Cosmetics: Ionic Liquids-Inspired Novel Skin Penetration System as an Alternative to Medical Beauty Treatments

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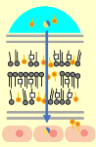
Introduction

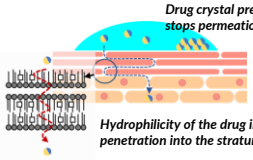
Hydrophilic drugs used in cosmetics have not fulfilled their potential owing to low skin penetration

Existing Solution #1
Chemical penetration enhancer



Making penetration pathway
- Penetration of stratum corneum intercellular lipids
- Disruption of their barrier structure

Safety issue



Existing Solution #2
Molecular modification: Prodrug

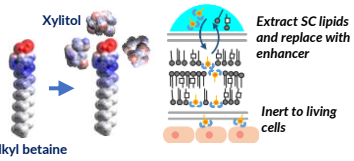
Molecular modification (acetylation, esterification, etc.)
- Improved diffusion in stratum corneum
- Inhibition of crystallization

Reassurance of drug efficacy and safety as a novel substance

Novel strategies to improve drug skin penetration are required

Molecular Modulation Strategies Inspired by Ionic Liquids (ILs)

Novel Enhancer:
Modulates the enhancer's mechanism through molecular interactions with coformer

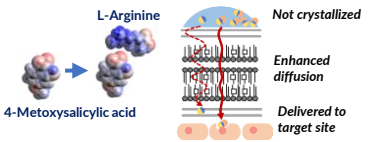


Focused on findings on ILs

ILs and deep eutectic solvents (DESs) can manipulate **physicochemical properties by specific intramolecular interactions.**

- Applicable to a variety of cosmetic active ingredients
- Capable of solving drug delivery problems
- Safe and compatible as cosmetics

Novel Drug Complex:
Modulates the drug's solubility and diffusivity through molecular interactions with coformer

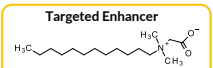


Result ❶ Novel Enhancer (AB/XY)

Enhancer IL Screening

Dissolved in 1:1 water/methanol solvent
Left overnight at 50 °C, then solvent removed

Targeted Enhancer



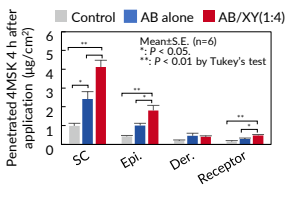
Visual images of Alkyl betaine/Xylitol (AB/XY)

	Coformer	Molar Ratio 0.5	1	2	3
Organic acid	Lactic acid	S	S	TL	TL
	Salicylic acid	S	S	S	S
	Citric acid	S	S	TL	TL
Amino acid	L-Lysin-HCl	S	S	S	S
	L-Arginine	S	S	S	S
	L-Arginine-HCl	S	TL	TL	-
	L-Alanine	S	S	S	-
	L-Hydroxyproline	S	S	S	S
	L-Glutamic acid	S	S	S	S
	L-Glycine	S	S	S	S
	L-Serine	S	S	S	S
	L-Aspartic acid	S	S	S	S
Polyol	Glycerol	S	S	S	TL
	Erythritol	S	S	NS	NS
	Xylitol	S	S	TL	TL
	Sorbitol	S	S	TL	TL
	1,3-Butylene glycol	S	TL	TL	TL

TL: Transparent liquid, S: Solid present, NS: Liquid with low stability

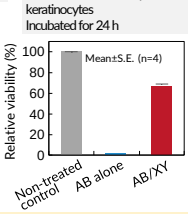
Skin Penetration Enhancement Effect of AB/XY

Model drug: Potassium 4-methoxysalicyliate (4MSK)
Diffusion cell (human skin)



Toxicity of AB/XY

Alamer Blue assay
Cells: Normal human epidermal keratinocytes
Incubated for 24 h

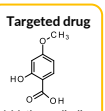


- AB became an ionic liquid with XY
- Suggests that the action of AB was enhanced by converting it to an IL
- Our strategy ensures penetration enhancers do not harm the consumer's skin

Result ❷ Novel Drug Complex

Drug Complex Screening

Targeted drug



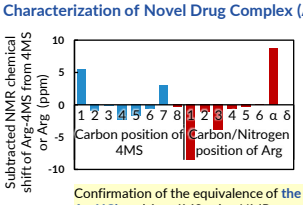
4-Methoxysalicylic acid (4MS)

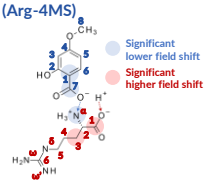
Coformer	Molar ratio	Visual
Choline	1:1	TL
Trimethylglycine	1:1	TL
L-Carnitine	1:1	TL
L-Citrulline	1:1	S
L-Arginine	1:1	TL
L-Lysine	1:1	S
L-Histidine	1:1	TL

TL: Transparent liquid, S: Solid present

Visual images of 4MS and Arg-4MS IL

Characterization of Novel Drug Complex (Arg-4MS)

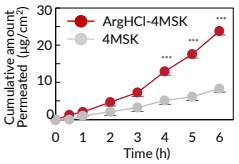




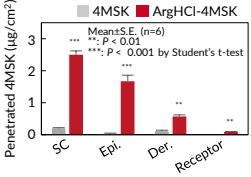
Confirmation of the equivalence of **the mixture of 4MSK and ArgHCl**, and Arg-4MS using NMR

Effect of Drug IL on Transdermal Penetration of Drug

Diffusion



Distribution at 1 h after application



- It was fully confirmed that 4MS forms ion-pairs with Arg
- Simply mixing 4MSK with ArgHCl increased the 4MSK-penetration speed by a factor of 2.5

Conclusion

- In the molecular modulation strategy, existing cosmetic ingredients with non-novel activities change their physicochemical properties by creating complexes (ILs) with new effects, such as improved penetration.
- Based on the molecular modulation strategy, two new ILs, i.e. a novel penetration enhancer IL (AB/XY) and a novel drug complex IL (Arg-4MS), which convert a skin brightening agent (4MS) to an IL, have been developed.
- These technologies have the potential to go beyond cosmetics and provide cosmeceuticals that help consumers stay healthy, beautiful, and age-free.