

Smart Galenics for Improved Bioavailability

SWSCC Chapter Meeting
October 5, 2017



Outline

Introduction

Penetration of lipophilic Actives

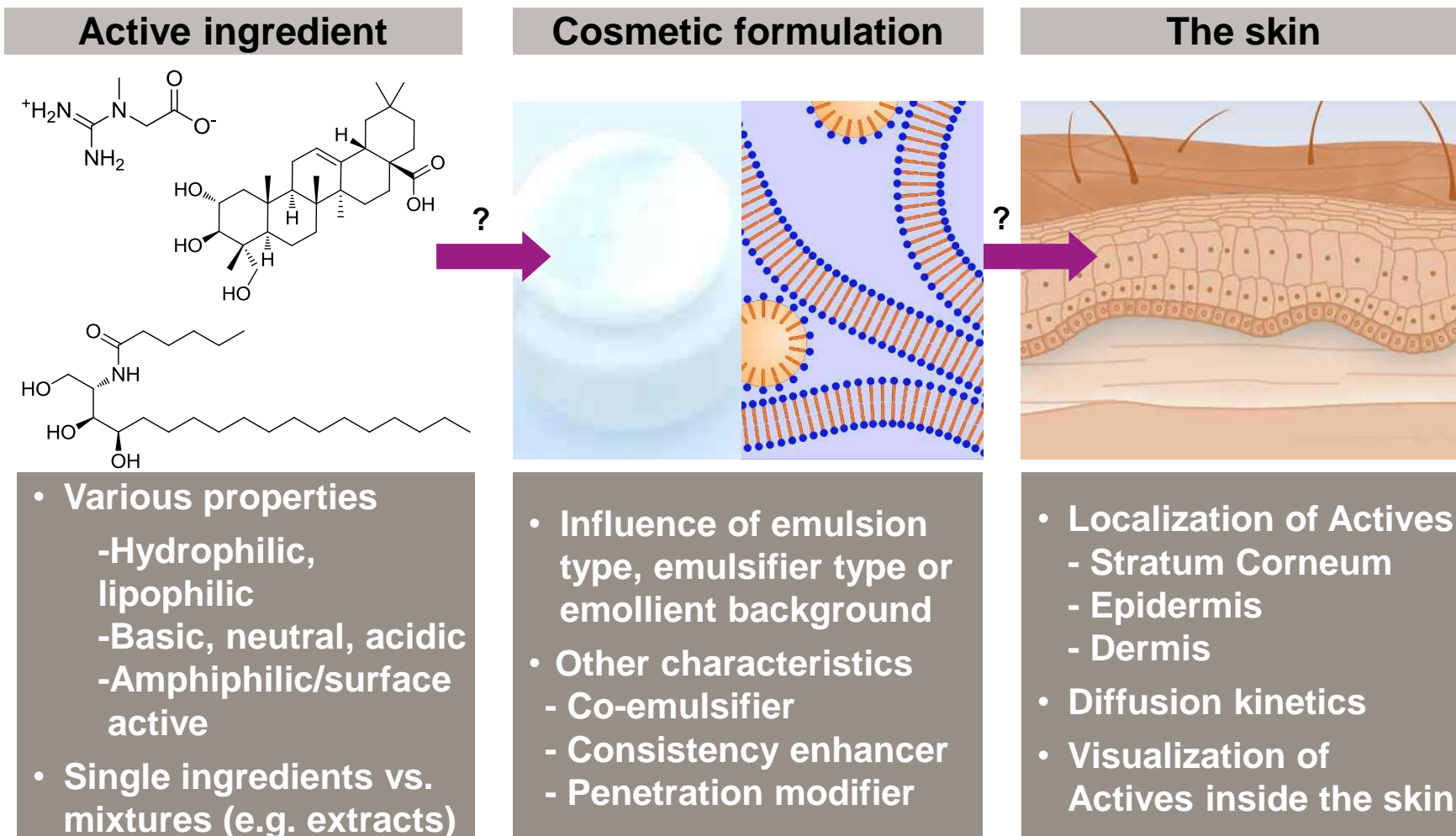
- Influence of emollient background
- Influence of solubilizer
- Influence of consistency enhancer

Penetration of hydrophilic Actives (peptides)

- Influence of lipophilic chemical modification
- Influence of emulsion type

Summary

Goal – Determination of delivery of Actives into skin



Test method

Based on OECD Test Guideline 428:

Skin Absorption: *in vitro* method

- 1) ***Ex vivo* pig skin (from food production); washing**
- 2) **Preparation of skin, removal of adipose tissue, shaving**
- 3) **Slicing into defined thickness layer with dermatome**
- 4) **Preparation of circular pieces**
- 5) **Mounting on Franz cell, application of test substance, incubation at 32 °C and 50% relative humidity**
- 6) **Skin sample preparation: Stratum corneum removal, epidermis-dermis separation**



Test method

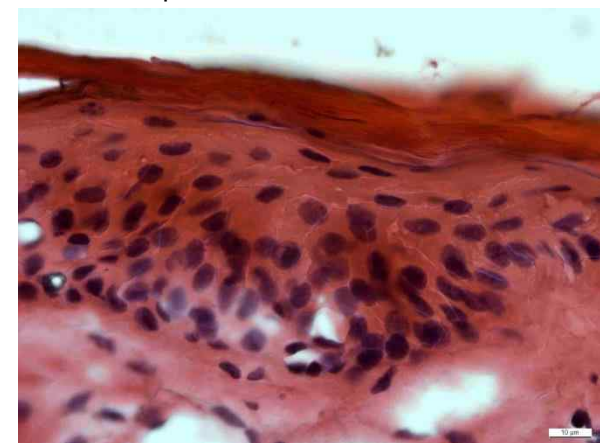
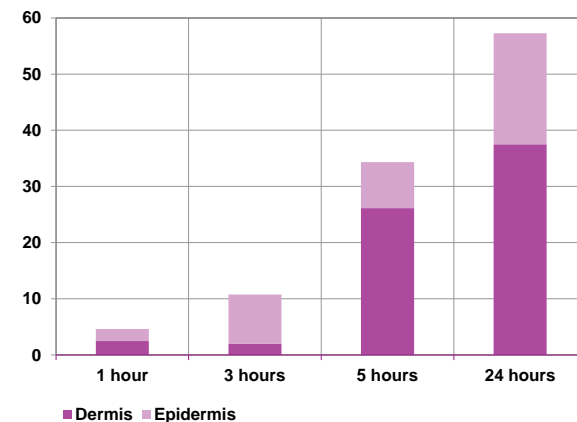
- Evaluation of bioavailability

- A) Quantitative analysis via appropriate analytical method

- HPLC-UV/MS
 - GC-MS
 - Liquid scintillation counting

- Donor chamber & skin surface rinsing (**Rinse off**)
 - Skin preparation, total or fractionated (**Skin, Stratum Corneum, Epidermis, Dermis**)
 - Receptor fluid (**Receptor**)

- B) Histological preparation and histochemical (fluorescent) identification and visualization



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Penetration of lipophilic Actives

- **Influence of emollient background**
- **Influence of solubilizer**
- **Influence of consistency enhancer**

Penetration of hydrophilic Actives (peptides)

- Influence of lipophilic chemical modification
- Influence of emulsion type

Summary

Salicyloyl Phytosphingosine – Skin penetration test design

Test substance: Salicyloyl Phytosphingosine

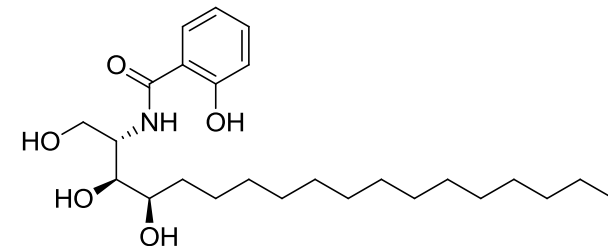
Skin model: *Ex vivo* pig skin, 1 mm thickness

Test setup: 15-20 mg/cm² test formulation,
6 replicates per test
Incubation time 24 h

Analysis: High performance liquid
chromatography-ultraviolet
spectroscopy (HPLC-UV)

Test vehicle: O/W cosmetic formulation based on emulsifiers
and systematic combination with emollients

- a) Octyldodecanol
- b) PPG-3 Myristyl Ether
- c) Caprylic/Capric Triglyceride
- d) Mineral Oil



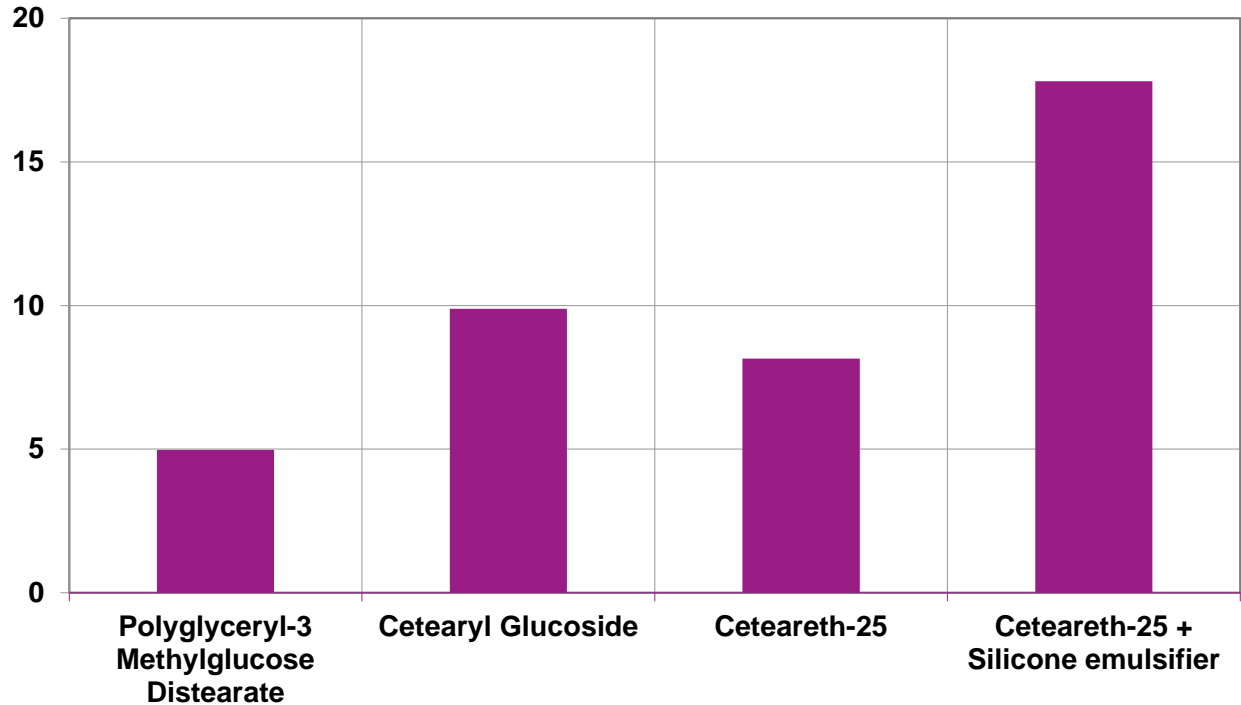
Salicyloyl Phytosphingosine
MW: 438; $c_{\log P}$: 7.8*

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* ChemBioDraw Ultra 12

Skin penetration test results – Emulsifier series

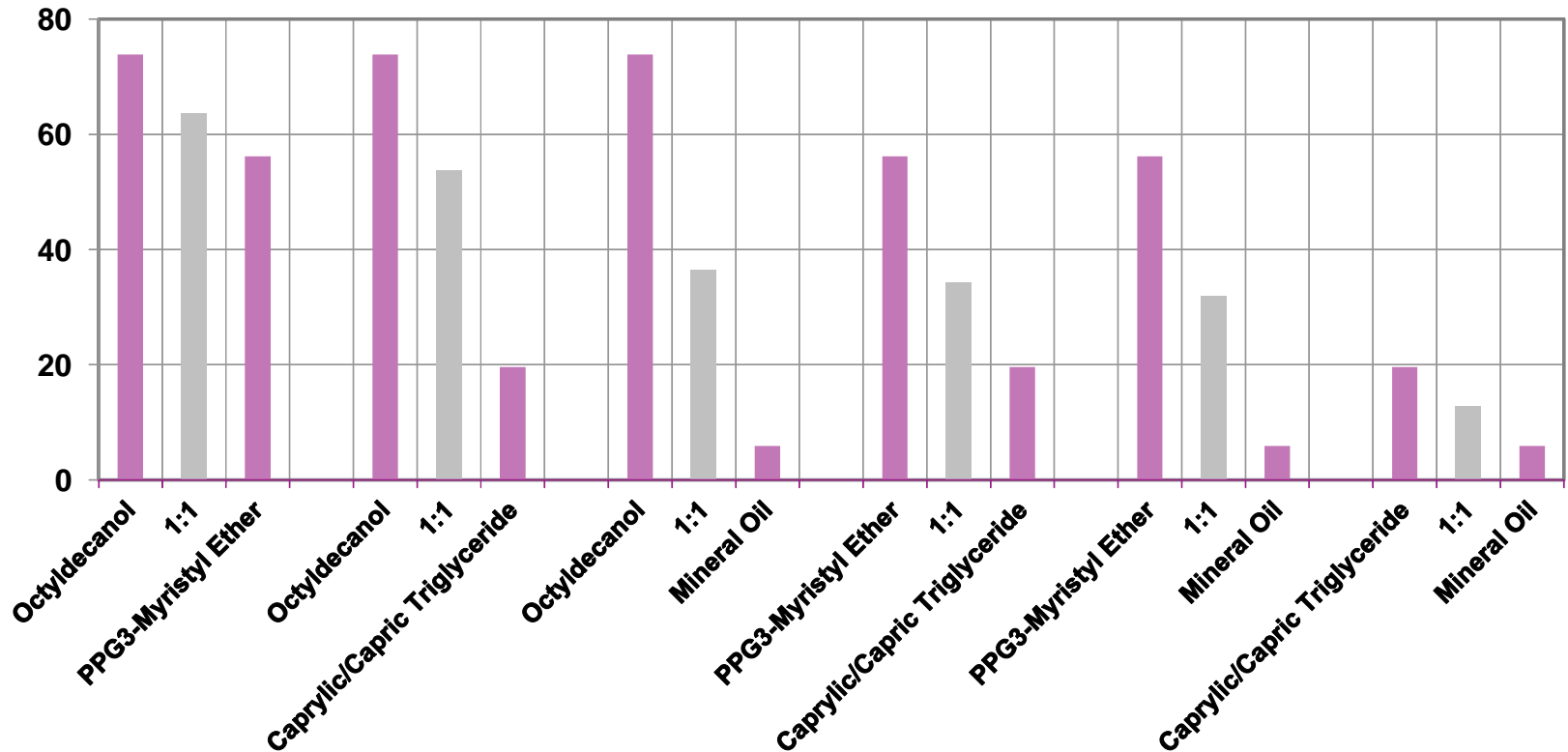
Bioavailability of Salicyloyl Phytosphingosine from formulations with various emulsifiers [%]



- High molecular weight emulsifiers enhance bioavailability
- Lamellar structures can potentially retain the Active

Salicyloyl Phytosphingosine – Skin penetration test results

Bioavailability of Salicyloyl Phytosphingosine in the presence of varying emollients [%]



A well balanced combination of polar and non-polar emollients will result in an optimized penetration profile of **Salicyloyl Phytosphingosine**

Tocopheryl Acetate – Benefits & Claims

- **Natural antioxidant**
- **Skin-conditioning agent**
- **Anti-inflammatory properties**
- **Strengthens the skin's barrier function**
- **Increases skin moisture**
- **Improves skin surface properties**
- **Prevents skin damage, reduces sunburn cell formation**
- **Protects against UV light / reactive oxygen species**
- **Promotes wound healing**
- **INCI: Tocopheryl Acetate**



Tocopheryl Acetate penetration – Test design

Test substance: Tocopheryl Acetate
(DL- α -Tocopheryl acetate)

Skin model: *Ex vivo* pig skin, 1 mm thickness

Test setup: 15-20 mg/cm² test formulation,
6 replicates per test
Incubation time 24 h

Analysis: High performance liquid chromatography (HPLC)

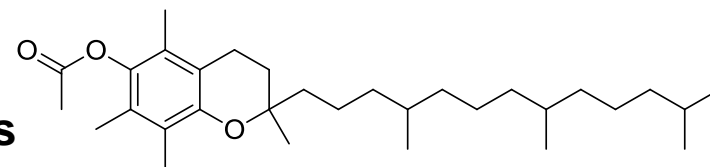
Test vehicle: O/W cosmetic formulation based on Polyglyceryl-3
Dicitrate/Stearate &

A) lamellar structure building consistency enhancer

- Influence of emollients
- Influence of absorption enhancer

B) acrylate thickener (Carbomer)

- Influence of emollients
- Influence of absorption enhancer



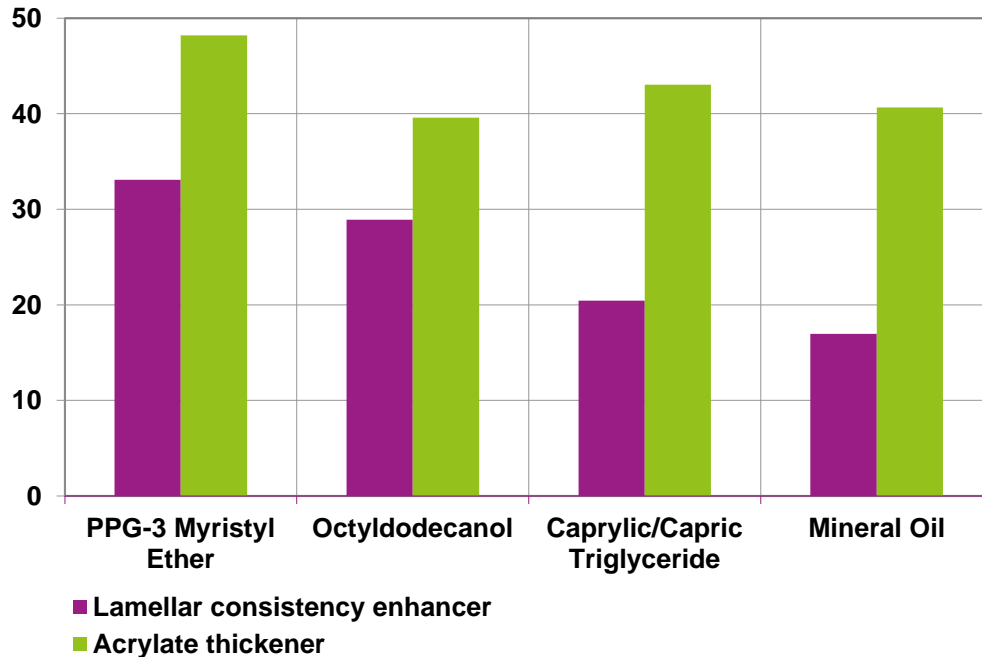
MW: 472.74

c logP: 12.2*

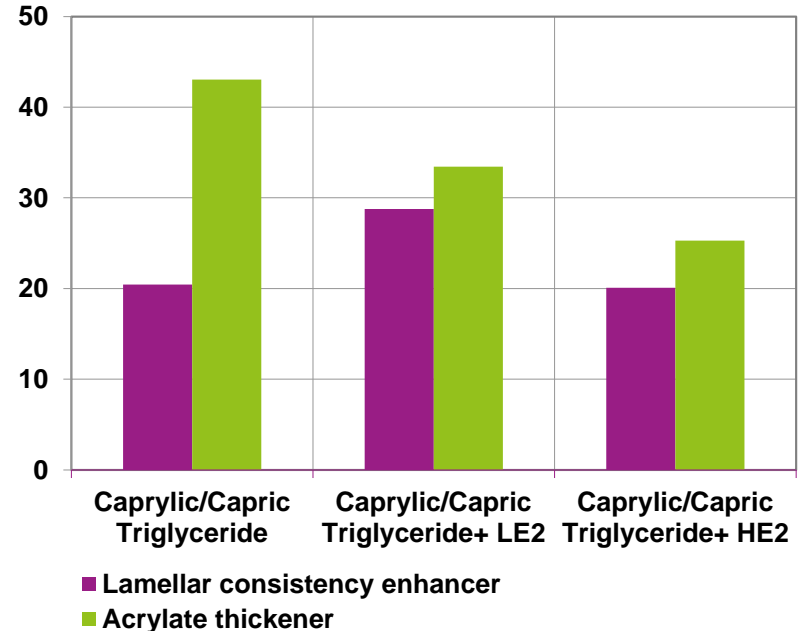
* ChemBioDraw Ultra 12

Tocopheryl Acetate penetration – Test results

Bioavailability of Tocopheryl Acetate from an O/W emulsion based on Polyglyceryl-3 Dicitrate/Stearate [%]



Bioavailability of Tocopheryl Acetate from an O/W emulsion based on Polyglyceryl-3 Dicitrate/Stearate - Influence of enhancer [%]



- Polar emollients improve bioavailability
- Lamellar structures can potentially trap lipophilic active ingredients
- Lipophilic enhancers minimize the trapping effect

Terminalia Arjuna Bark Extract – Skin penetration test design

Test substance: Terminalia Arjuna Bark Extract vs.
Terminalia Arjuna Bark Extract, Pentylene Glycol

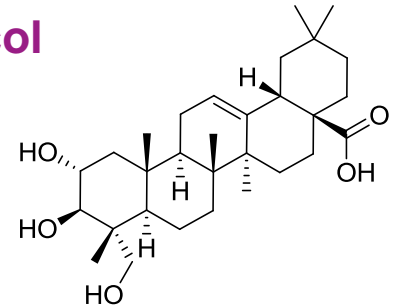
Skin model: *Ex vivo* pig skin, 1 mm thickness

Test setup: 15-20 mg/cm² test formulation,
6 replicates per test
Incubation time 24 h

Analysis: Gas chromatography-flame ionization
detection (GC-FID)

Test vehicle: O/W cosmetic formulation, based on Bis-
PEG/PPG-16/16 PEG/PPG-16/16 Dimethicone
(silicone emulsifier) / Cetareth-25 (ethoxylated
emulsifier), systematically exchanging the
emollient background

- a) PPG-3 Myristyl Ether
- b) Caprylic/Capric Triglyceride
- c) Mineral Oil



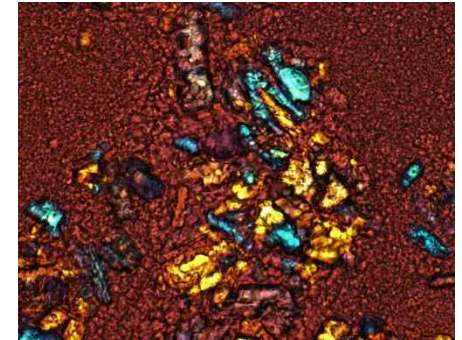
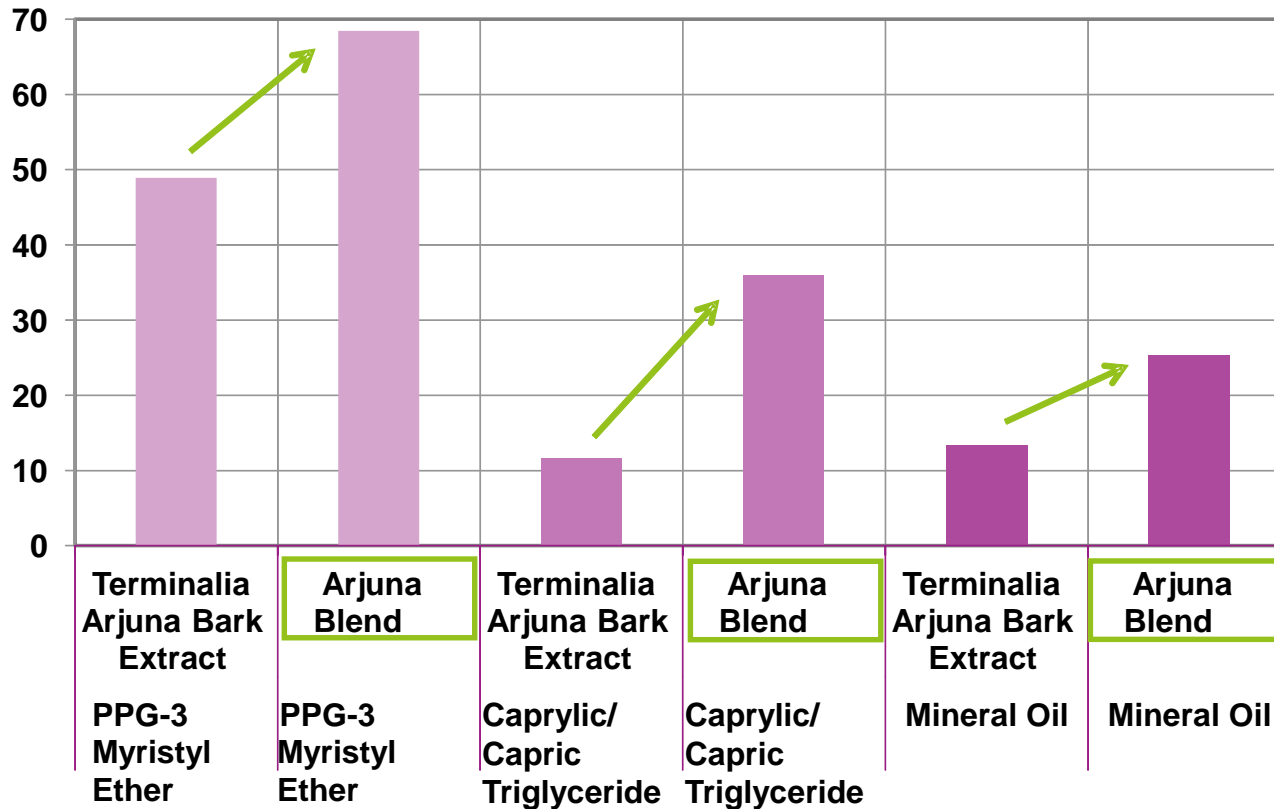
Arjunolic Acid
MW: 489; $\log P$: 3.3*

* ChemBioDraw Ultra 12

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Terminalia Arjuna Bark Extract – Skin penetration test results

Bioavailability [%]



O/W formulation with Terminalia Arjuna Bark Extract in the oil phase



O/W formulation with Arjuna Blend

Solution of Terminalia Arjuna Bark Extract exhibits

- improved bioavailability of pentacyclic triterpenes
- easy formulation properties

Turmeric Root Extract

The golden spice of India

- Manufactured from Curcuma Longa Roots by an environmentally friendly supercritical CO₂ extraction process
- Purified Turmeric Oil highly enriched in Turmerones (>65%) with improved color and odor
- Viscous liquid with 100% active matter
- NaTrue and COSMOS certified
- INCI: **Curcuma Longa (Turmeric) Root Extract** (CFDA: yes)

Curcuma Longa Root Extract induces endogenous cellular defense mechanisms against oxidative stress and thereby provides skin radiance, evenness of skin tone and reduction of wrinkles



M. Wegmann *et al.*, *Personal Care*, 2009, January issue, 37-40

Turmeric Root Extract skin penetration - Test design

▪ **Test substance:** **Curcuma Longa (Turmeric) Root Extract**

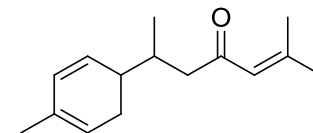
▪ **Skin model:** *Ex vivo* pig skin, 1 mm thickness

▪ **Test setup:** 15-20 mg/cm² test formulation, 6 replicates per test
Incubation time 24 h

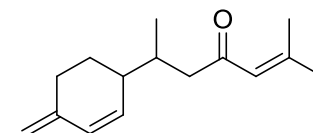
▪ **Analysis:** High performance liquid chromatography (HPLC)

Test vehicle: O/W cosmetic formulation based on **Polyglyceryl-3 Dicitrate/Stearate** (PEG-free, glycerin-based emulsifier), exchanging the

- emollient
 - a) **PPG-3 Myristyl Ether**
 - b) **Octyldodecanol**
 - c) **Caprylic/Capric Triglyceride**
 - d) **Mineral Oil**
- consistency enhancer
 - a) **Glyceryl Stearate / Stearyl Alcohol**
 - b) **Carbomer**

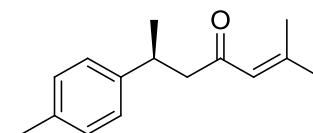


alpha-Turmerone



beta-Turmerone

MW: 218; _clogP: 4.1*



ar-Turmerone

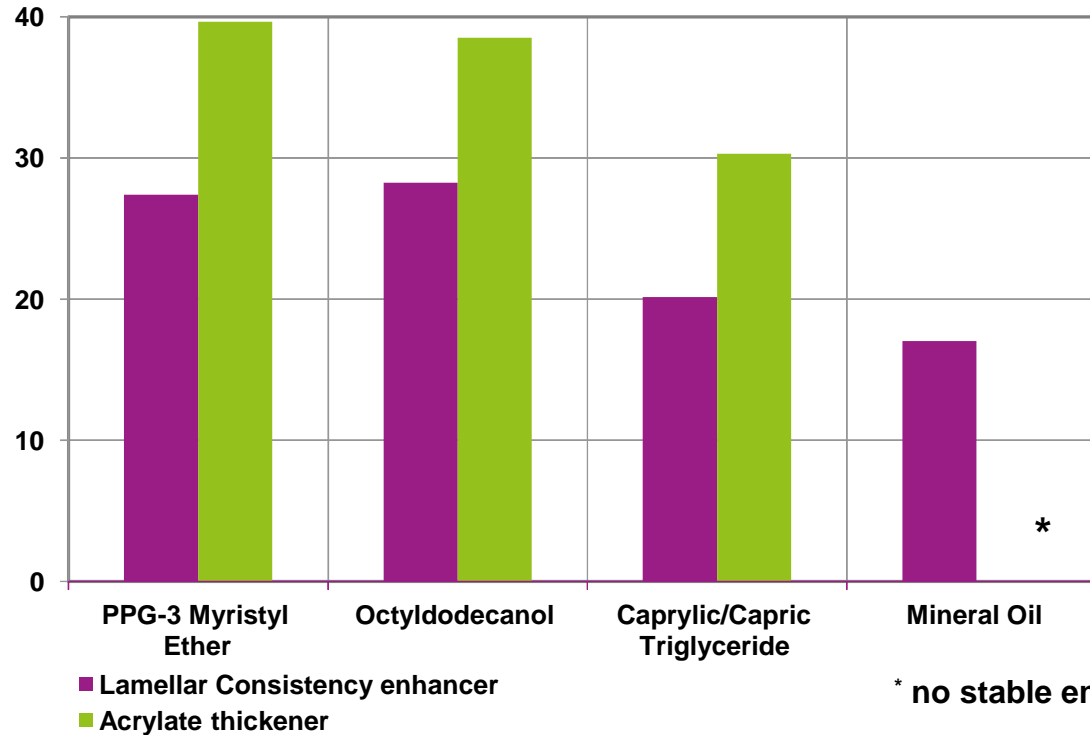
MW: 216; _clogP: 3.9*

* ChemBioDraw Ultra 12

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Turmeric Root Extract – Skin penetration test results

Bioavailability of Turmeric Root Extract from an O/W emulsion based on Polyglyceryl-3 Dicitrate/Stearate [%]



- Polar emollients improve bioavailability
- Lamellar structures can potentially trap lipophilic active ingredients

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- Influence of solubilizer
- Influence of consistency enhancer

Penetration of hydrophilic Actives (peptides)

- **Influence of lipophilic chemical modification**
- **Influence of emulsion type**

Summary

Tetrapeptide-30 skin penetration – Lipidation and chassis variation

Test substance: **[³H]-PKEK**
[³H]-Palmitoyl-PKEK

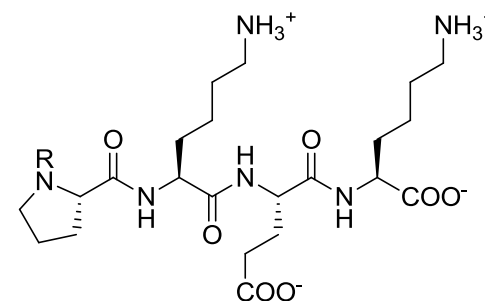
Skin model: *Ex vivo mamma skin*

Test setup: Franz diffusion cell
Incubation time 5 h

Analysis: HPLC-radiodetection

- Donor chamber & skin surface (**Rinse off**)
- Tape strips (**Stratum Corneum**)
- Epidermis, dermis & subcutaneous tissue (**Viable skin**)
- Filter gaze & receptor fluid (**Receptor**)

Test vehicle: O/W emulsion, pharmaceutical W/O microemulsion



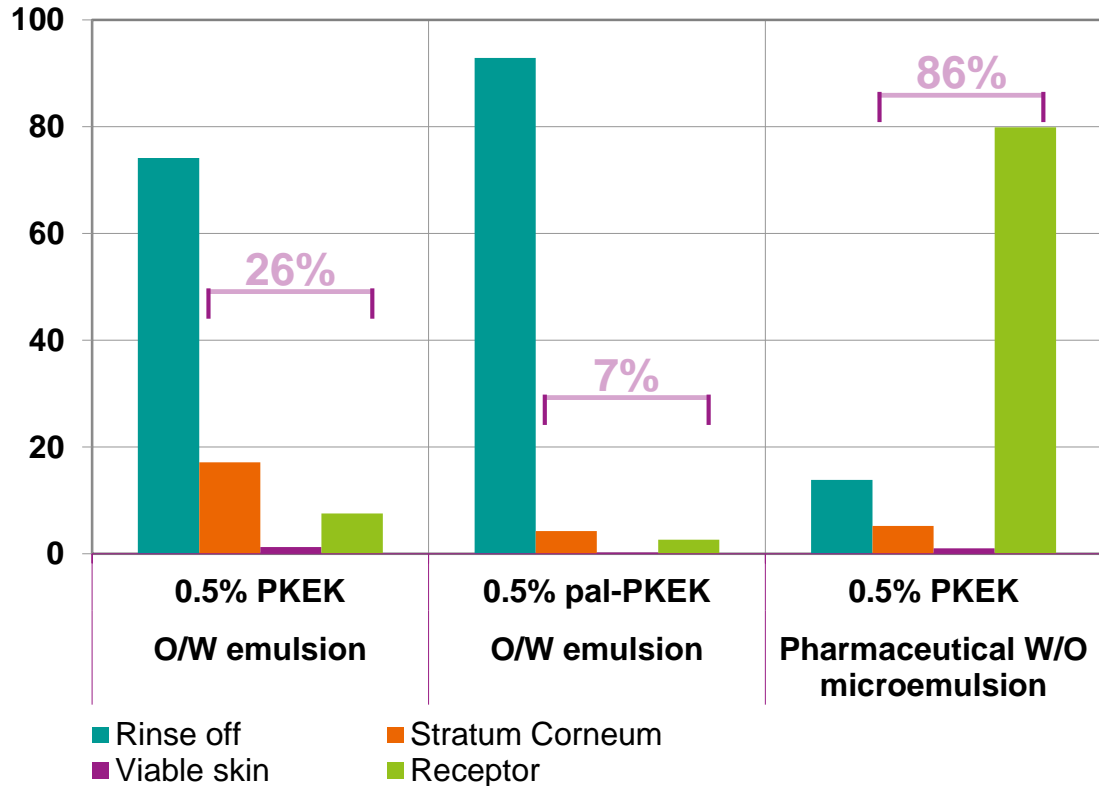
Pro-Lys-Gly-Lys
R= H₂⁺ **PKEK**
(MW: 501.60, _clogP: -9.0^{*})
R= C₁₅H₃₁CO **pal-PKEK**
(MW: 739.00, _clogP: -2.3^{*})

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* ChemBioDraw Ultra 12

Tetrapeptide-30 – Skin penetration test results

Bioavailability of PKEK peptides within 5 hours [%]



- Palmitoylation does not improve skin penetration properties of PKEK
- Formulation optimization, e.g. by incorporation into a colloidal W/O microemulsion, enhances PKEK skin penetration several fold

Tetrapeptide-21 skin penetration – Lipidation and chassis variation

Test substance: **[Gly-1-¹⁴C]-GEKG**
[³H]-Palmitoyl-GEKG

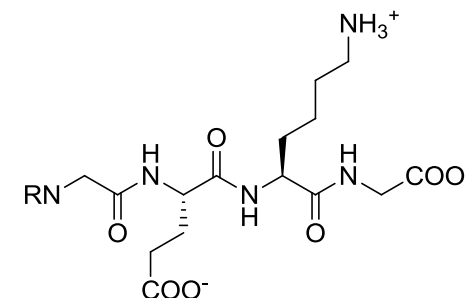
Skin model: *Ex vivo mamma skin*

Test setup: Franz diffusion cell
Incubation time 5 h

Analysis: HPLC-radiodetection

- Donor chamber & skin surface (**Rinse off**)
- Tape strips (**Stratum Corneum**)
- Epidermis, dermis & subcutaneous tissue (**Viable skin**)
- Filter gaze & receptor fluid (**Receptor**)

Test vehicle: O/W emulsion, pharmaceutical W/O microemulsion

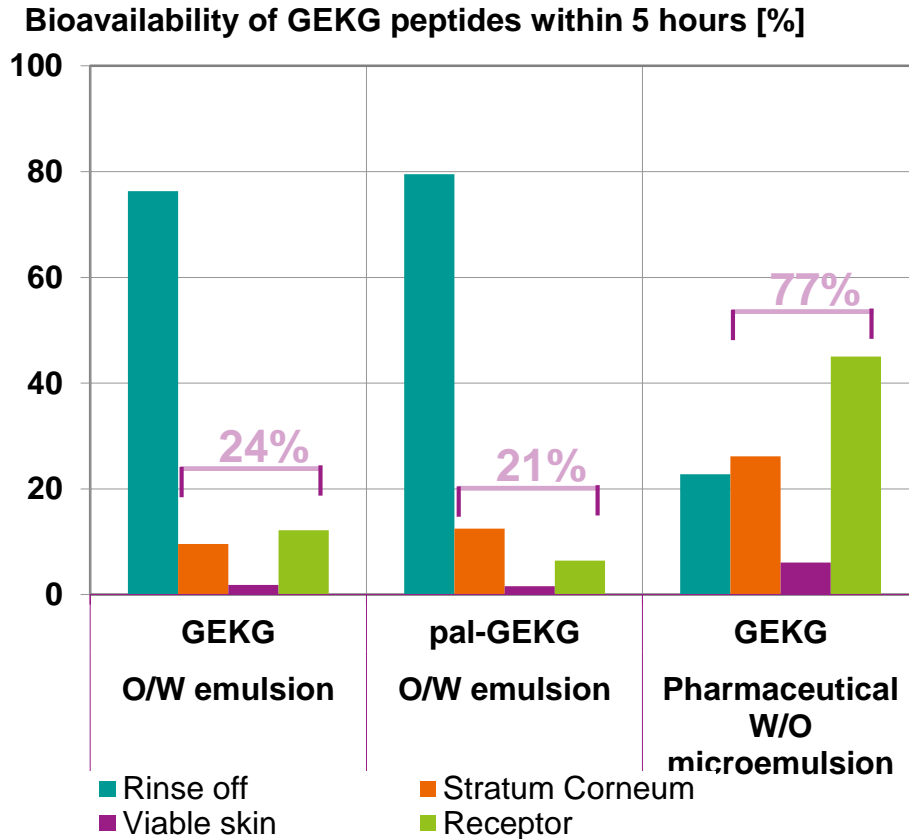


Gly-Glu-Lys-Gly
R= H₃⁺ **GEKG**
(MW: 389; _clogP: -10.4*)
R= C₁₅H₃₁CO **pal-GEKG**
(MW: 628, _clogP: 2.0*)

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* ChemBioDraw Ultra 12

Tetrapeptide-21 (GEKG) – Skin penetration test results



- Palmitoylation does not improve skin penetration properties of GEKG
- Formulation optimization, e.g. by incorporation into a colloidal W/O microemulsion, enhances GEKG skin penetration several fold

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Introduction

Penetration of lipophilic Actives

- Influence of emollient background
- Influence of solubilizer
- Influence of consistency enhancer

Penetration of hydrophilic Actives (peptides)

- Influence of lipophilic chemical modification
- Influence of emulsion type

Summary

Summary

- Careful selection of the *emollient* mixture, *solubilizer* and *consistency enhancer* is critical for optimal bioavailability of **lipophilic** Actives
- These factors have less effect in case of **hydrophilic** Actives, which require *different formulation strategies*
- Lipidation by chemical modification of **hydrophilic** Actives does not necessarily lead to improved bioavailability
- Change of *formulation type* can drastically influence penetration of **hydrophilic** Actives



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Salicyloyl Phytosphingosine skin penetration – Test formulations I

BT 191		1	2	3	5
A	Polyglyceryl-3 Methylglucose Distearate	3.00%			
	Ceteareth-25		2.00%	2.00%	
	Bis-PEG/PPG-16/16 PEG/PPG16/16 Dimethicone; Caprylic/Capric Triglyceride			1.00%	
	Stearyl Alcohol	1.00%	1.50%	3.00%	1.50%
	Glyceryl Stearate	2.00%	4.50%	3.00%	4.50%
	Caprylic/Capric Triglyceride	19.00%	17.00%	16.00%	18.00%
	Salicyloyl Phytosphingosine	0.20%	0.20%	0.20%	0.20%
B	Water	ad 100%	ad 100%	ad 100%	ad 100%
	Glycerin	3.00%	3.00%	3.00%	3.00%
	Cetearyl Glucoside				1.00%
C	Caprylic/Capric Triglyceride	0.60%	0.60%	0.60%	0.60%
	Carbomer	0.15%	0.15%	0.15%	0.15%
D	Sodium Hydroxide (10% in Water)	q.s.	q.s.	q.s.	q.s.
Z	Methylisothiazolinon, Ethylhexylglycerin, Water	0.12%	0.12%	0.12%	0.12%
	Viscosity (Brookfield LVDV I+, S96, 1.5 rpm) [Pa·s]	298	316	421	232

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Salicyloyl Phytosphingosine skin penetration – Test formulations II

BT 156		4	1	3	2	7	8	9	6	5	10
A	Ceteareth-25	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%	2.0%
	Bis-PEG/PPG-16/16 PEG/PPG16/16 Dimethicone; Caprylic/Capric Triglyceride	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%
	Cetearyl Alcohol	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%	5.0%
	Stearic Acid (and) Palmitic Acid	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
	Octyldodecanol	14.8%				7.4%	7.4%	7.4%			
	PPG-3 Myristyl Ether		14.8%			7.4%			7.4%	7.4%	
	Caprylic/Capric Triglyceride			14.8%			7.4%		7.4%		7.4%
	Mineral Oil (30 mPa*s)				14.8%			7.4%		7.4%	7.4%
	Salicyloyl Phytosphingosine	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%
B	Water	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%
	Glycerin	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%	3.0%
C	Respective emollient	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%	0.6%
	Carbomer	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%
D	Sodium Hydroxide (10% in Water)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Z	Methylisothiazolinon, Ethylhexylglycerin, Water	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%
	Viscosity (Brookfield LVDV I+, S96, 1.5 rpm) [Pa·s]			516	576						488

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Tocopheryl Acetate skin penetration – Test formulations I

JS15		1	2	3	4	5	7	8
A	Polyglyceryl-3 Dicitrate/Stearate	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%
	Glyceryl Stearate	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%	1.50%
	Stearyl Alcohol	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
	PPG-3 Myristyl Ether	20.0%						
	Octyldodecanol		20.0%					
	Caprylic/Capric Triglyceride			20.0%			17.0%	17.0%
	Mineral Oil (30 mPa*s)				20.0%			
	Lipophilic penetration enhancer (LPE2)					20.0%	3.00%	
	Hydrophilic penetration enhancer (HPE2)							3.00%
B	Water	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%
C	Tocopheryl Acetate (DL-α-Tocopheryl acetate)	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Z	Dipropylene Glycol; Methylparaben; Ethylparaben; Water; Methylisothiazolinone	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
	Viscosity (Brookfield RVDV I+, S93, 10 rpm) [Pa·s]	4.5	14	13.5	32.5	0	9	3

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Tocopheryl Acetate skin penetration – Test formulations II

JS19		1	2	3	4	5	6	7
A	Polyglyceryl-3 Dicitrate/Stearate	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%
	PPG-3 Myristyl Ether	22.0%						
	Octyldodecanol		22.0%					
	Caprylic/Capric Triglyceride			22.0%			19.0%	19.0%
	Mineral Oil (30 mPa*s)				22.0%			
	Lipophilic penetration enhancer (LPE2)					22.0%	3.00%	
	Hydrophilic penetration enhancer (HPE2)							3.00%
B	Water	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%
C	Respective emollient	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
	Carbomer	0.20%	0.20%	0.20%	0.20%	0.20%	0.20%	0.20%
D	Tocopheryl Acetate (DL-α-Tocopheryl acetate)	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
Z	Dipropylene Glycol; Methylparaben; Ethylparaben; Water; Methylisothiazolinone	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
	Viscosity (Brookfield RVDV I+, S93, 10 rpm) [Pa·s]	12	22	21	26	2	14.5	10

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Arjuna Bark Extract – Test formulations

BT 269		1	2	3	4	5	6
A	Cetareth-25	2.00%	2.00%	2.00%	2.00%	2.00%	2.00%
	Bis-PEG/PPG-16/16 PEG/PPG-16/16 Dimethicone; Caprylic/Capric Triglyceride	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%
	Cetearyl Alcohol	5.00%	5.00%	5.00%	5.00%	5.00%	5.00%
	Stearic Acid (and) Palmitic Acid (Edenor L2SM GS, Cognis)	0.50%	0.50%	0.50%	0.50%	0.50%	0.50%
	PPG-3 Myristyl Ether	14.50%	-	-	14.50%	-	-
	Caprylic/Capric Triglyceride	-	14.50%	-	-	14.50%	-
	Mineral Oil (30 mPa s)	-	-	14.50%	-	-	14.50%
	Terminalia Arjuna Bark Extract	0.25%	0.25%	0.25%	-	-	-
B	Water	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%
	Glycerin	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%
C	Carbomer	0.15%	0.15%	0.15%	0.15%	0.15%	0.15%
	PPG-3 Myristyl Ether	0.60%	-	-	0.60%	-	-
	Caprylic/Capric Triglyceride	-	0.60%	-	-	0.60%	-
	Mineral Oil (30 mPa s)	-	-	0.60%	-	-	0.60%
Z	Terminalia Arjuna Bark Extract, Pentylene Glycol				2.5%	2.5%	2.5%
	Methylisothiazolinone; Ethylhexylglycerin (Euxyl K 220, Schülke & Mayr)	0.12%	0.12%	0.12%	0.12%	0.12%	0.12%
	Sodium Hydroxide (10% in water) (pH 5.5)	0.43%	0.43%	0.43%	0.43%	0.43%	0.43%

Turmeric Root Extract – Test formulations

JS		21-1	21-2	21-3	21-4	22-1	22-2	22-3
A	Polyglyceryl-3 Dicitrate/Stearate	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%	3.00%
	Glyceryl Stearate	1.50%	1.50%	1.50%	1.50%			
	Stearyl Alcohol	0.50%	0.50%	0.50%	0.50%			
	PPG-3 Myristyl Ether	20.0%				22.0%		
	Octyldodecanol		20.0%				22.0%	
	Caprylic/Capric Triglyceride			20.0%				22.0%
	Mineral Oil (30mPa·s)				20.0%			
B	Water	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%	ad 100%
C	Carbomer					0.20%	0.20%	0.20%
	respective emollient					0.80%	0.80%	0.80%
D	Curcuma Longa (Turmeric) Root Extract	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%	1.00%
	Dipropylene Glycol; Methylparaben; Ethylparaben; Water; Methylisothiazolinone (Microcare® MEM, Thor GmbH)	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%	0.80%
	Viscosity (Brookfield RVDV I+, S93, 10 rpm) [Pa·s]	14.5	29	30	55	14	12.5	9
	pH	6.9	5.9	6.7	6.9	6.1	6.3	6.1

Tetrapeptide-30 (PKEK) – Test formulations

O/W cream (BT338)			
A	Polyglyceryl-3 Methylglucose Distearate	3.00%	3.00%
	Glyceryl Stearate	2.00%	2.00%
	Stearyl Alcohol	1.00%	1.00%
	C12-15 Alkyl Benzoate	9.50%	9.50%
	Caprylic/Capric Triglyceride	9.50%	9.50%
B	Water	ad 100%	ad 100%
	Butylene Glycol	1.50%	1.50%
	Glycerin	2.50%	2.50%
C	[³H]-PKEK (Tetrapeptide-30)	0.50%	
	[³H]-Palmitoyl-PKEK		0.50%
	Methylisothiazolinone, Methylparaben, Ethylparaben (Microcare® MEM, Thor Personal Care)	0.80%	0.80%

**Identical vehicle
formulation as in**

Tetrapeptide-30 (PKEK)
 • **Anti-age spot study**
 • **Study on Asian skin**

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Tetrapeptide-21 (GKEG) – Test formulations

O/W cream (BT330)			
A	Polyglyceryl-3 Methylglucose Distearate	3.00%	3.00%
	Glyceryl Stearate	2.00%	2.00%
	Stearyl Alcohol	1.00%	1.00%
	C12-15 Alkyl Benzoate	9.50%	9.50%
	Caprylic/Capric Triglyceride	9.50%	9.50%
B	Water	ad 100%	ad 100%
	Butylene Glycol	1.50%	1.50%
	Glycerin	2.50%	2.50%
C	[Gly-1-¹⁴C]-GEKG (Tetrapeptide-21)	50 ppm	
	[³H]-Palmitoyl-GEKG		50 ppm
	Methylisothiazolinone, Methylparaben, Ethylparaben (Microcare® MEM, Thor Personal Care)	0.80%	0.80%

Identical vehicle formulation as in

Tetrapeptide-21 (GKEG)
• **Facial anti-wrinkle study**

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