



Novel approach to peptide delivery to the skin

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CRS2026
ANNUAL MEETING & EXPOSITION
LISBON
— PORTUGAL —

MULTISECTOR
INNOVATION
for ADVANCING
DELIVERY SCIENCE
JULY 6-9, 2026

 **Avanti** Research
A CRODA BRAND

CRODA Pharma



Your Pharma solutions partner



High purity excipients

- Super Refined™ and High Purity (HP) polysorbates
- Super Refined™ PEGs, vegetable oils, esters and more
- Surfactants, solubilisers, and emulsifiers across prescription (Rx) and Consumer Health



Innovative lipids

- Cationic lipids
- Natural and synthetic phospholipids
- Functionalised lipids
- PEG lipids
- Sterols (plant-derived)
- Custom lipid synthesis



Vaccine adjuvants and systems

- Alhydrogel™ and Adju-Phos™ (aluminium-based)
- PHAD™ range: TLR4 agonist (MPLA analog)
- CAF®: Cationic Adjuvant Formulations
- Sustainably sourced Squalene (non-animal derived)
- QS 21 (saponin-based)
- Quil-A™ (saponin for veterinary)



Bioprocessing solutions

- Detergents for viral inactivation, cell lysis and endotoxin removal: Virodex™ range
- Ingredients for cell culture: Super Refined™ Poloxamer 188
- Super Refined™ Benzyl Alcohol
- Super Refined™ Polysorbates

PROVEN ANTI-AGING EFFICACY

Pal-KTTKS is a gold-standard anti-wrinkle peptide with well-established biological activity.



• STIMULATES ECM PRODUCTION

Promotes key extracellular matrix components.



• BOOSTS COLLAGEN SYNTHESIS

Enhances collagen I, III and IV expression in dermal fibroblasts.



• SUPPORTS DERMAL ARCHITECTURE

Improves dermal organization and tissue integrity.

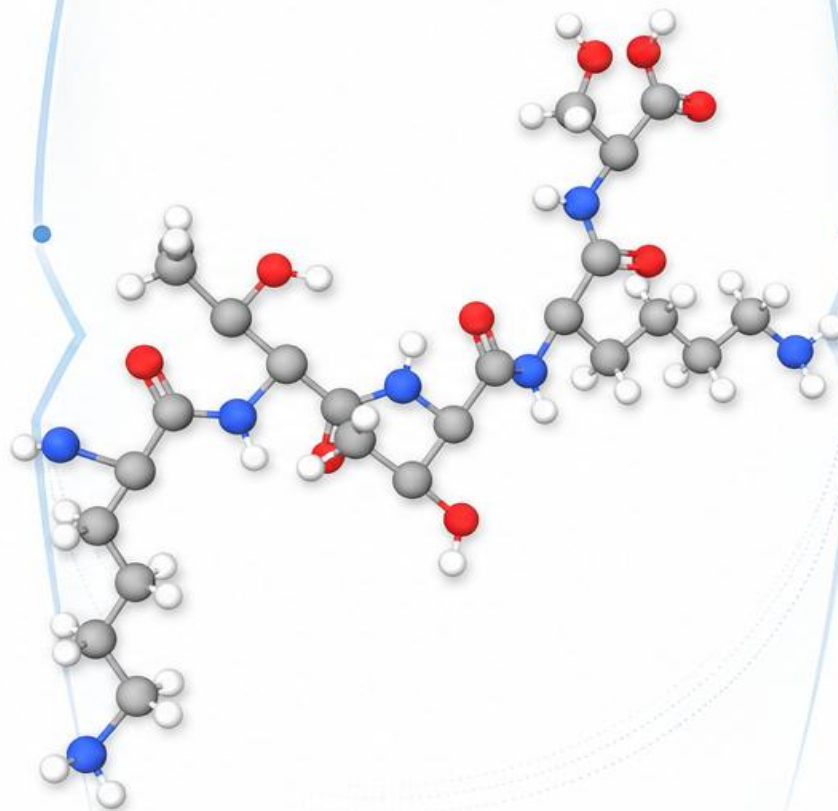


• CLINICALLY RELEVANT ANTI-WRINKLE ACTIVITY

Visible improvements in wrinkle appearance and skin quality.

Pal-KTTKS

(Palmitoyl-Lys-Thr-Thr-Lys-Ser)



INHERENT LIMITATIONS

Despite its efficacy, Pal-KTTKS faces intrinsic barriers that limit cutaneous performance.



• LIMITED SKIN PENETRATION

- Large molecular size
- Hydrophilic nature
- Restricted transport across the stratum corneum



• RAPID DEGRADATION

- Susceptible to proteolytic enzymes
- Leads to fast breakdown in the skin environment
- Short residence time

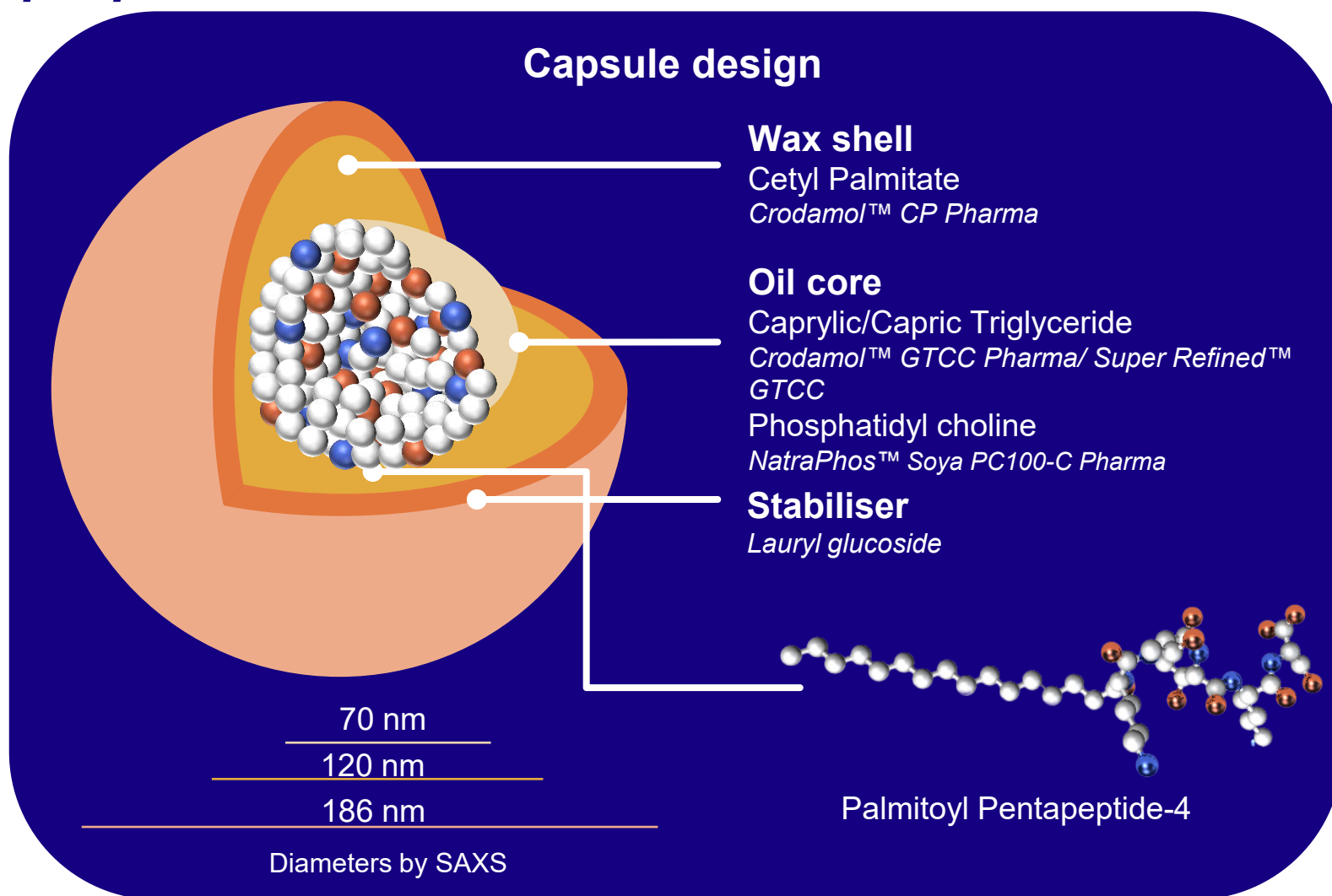


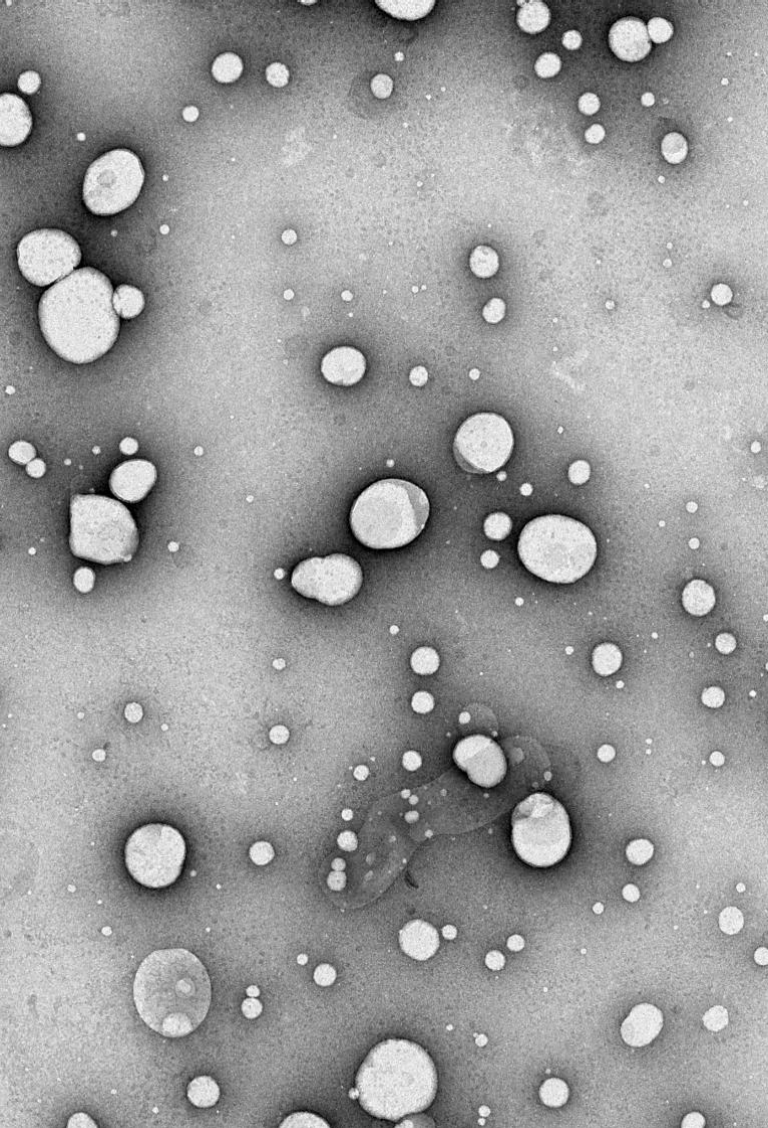
• REDUCED BIOAVAILABILITY

- Low delivery to target cells
- Suboptimal bioavailability
- Narrow therapeutic window

Encapsulating *the peptide*

- There are various formulation options to encapsulate peptides
- Delivery systems such as **lipid capsules** transport active ingredients through the skin barrier into targeted skin layers, thereby **increasing bioavailability** and **efficacy**.





Transmission Electron Microscopy

Product *description*

Characterization



Composition

Water (Aqua) (and) Caprylic/Capric Triglyceride (and) Propanediol (and) Cetyl Palmitate (and) Lauryl Glucoside (and) Hydrogenated Phosphatidylcholine (and) Caprylyl Glycol (and) Palmitoyl Pentapeptide-4 + tocopherol, Helianthus Annuus seed Oil, Citric acid

Appearance

White opaque liquid

Naturalness

99.79 % natural origin content per ISO 16128

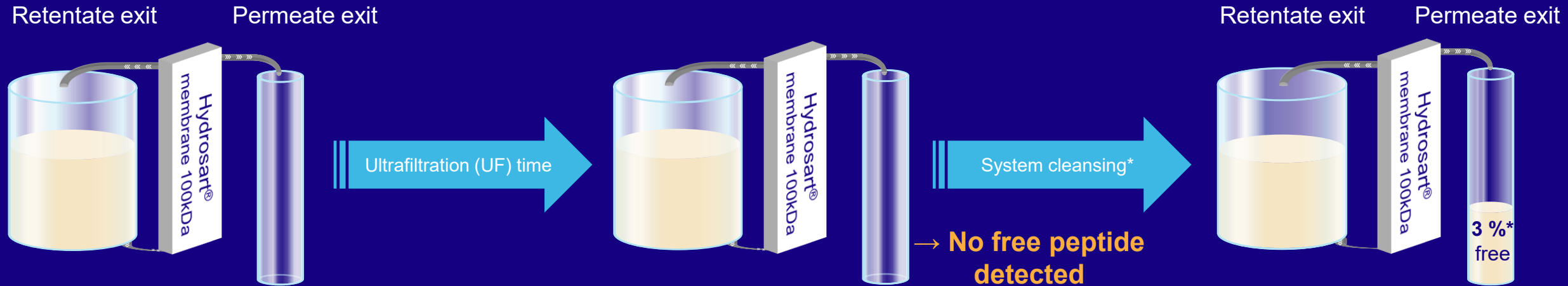
Biodegradability

92 % active ingredient readily biodegradable in 28 days

Particle size

$0.27 \pm 0.04 \mu\text{m}$

Encapsulation *performance*



The **tangential flow filtration (TFF)** generates a sweeping effect allowing to separate **encapsulated peptide** in the **retentate** (product retained by the membrane) from **non-encapsulated peptide** released in the **permeate** (product passing through the membrane).

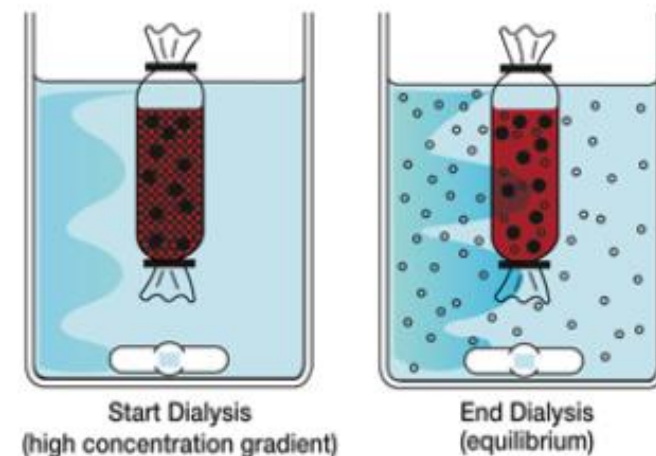
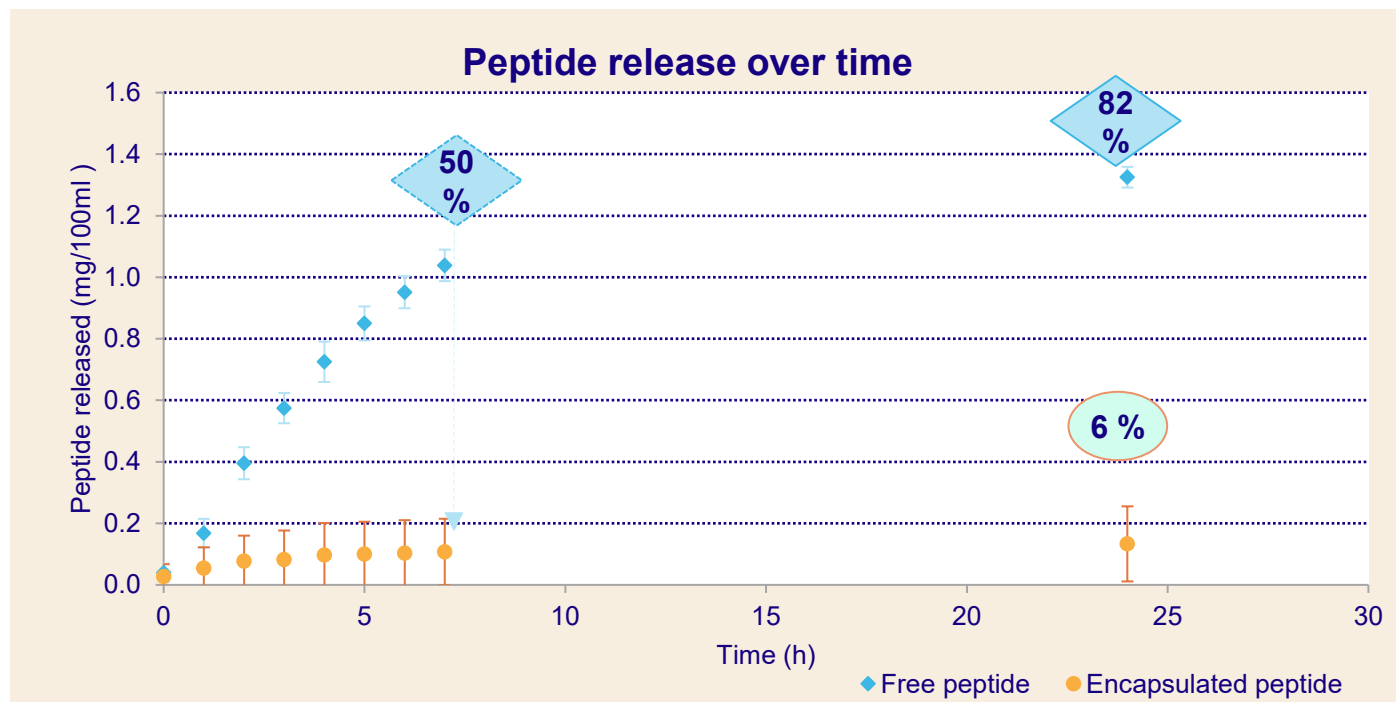
Only 3 % was found in the permeate after system cleansing confirming high encapsulation efficiency.

97 %
encapsulation
efficiency

*System cleansing = worst case scenario

Release profile using dialysis bags

- Encapsulated peptide and free peptides were added to dialysis bags
- Samples from release medium withdrawn for 24h
- Mathematical modelling shows 15 x slower release than free active

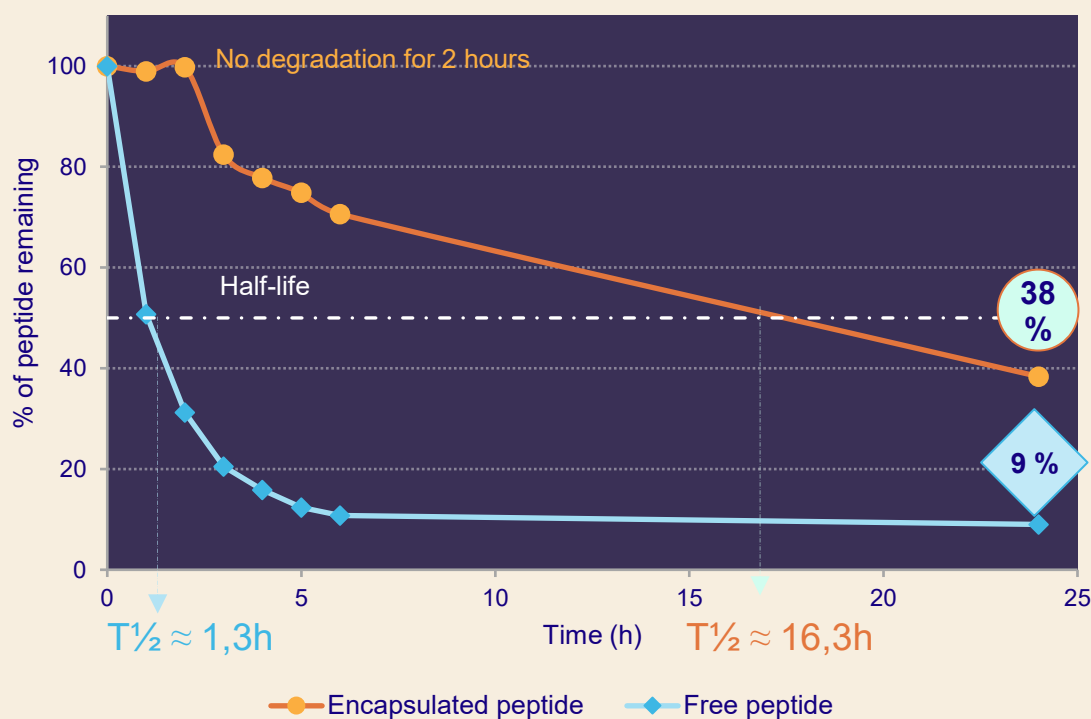


**Fast initial release
+ slow steady diffusion**

Stability Against Enzyme Attack

- Any unmodified linear peptide is susceptible to rapid cleavage at vulnerable bond positions by skin enzymes.

Enzyme digestion kinetics



Solution containing:

Free and Encapsulated peptide
(both, 100 ppm pKTTKS)

Buffer + 0.003 % trypsin

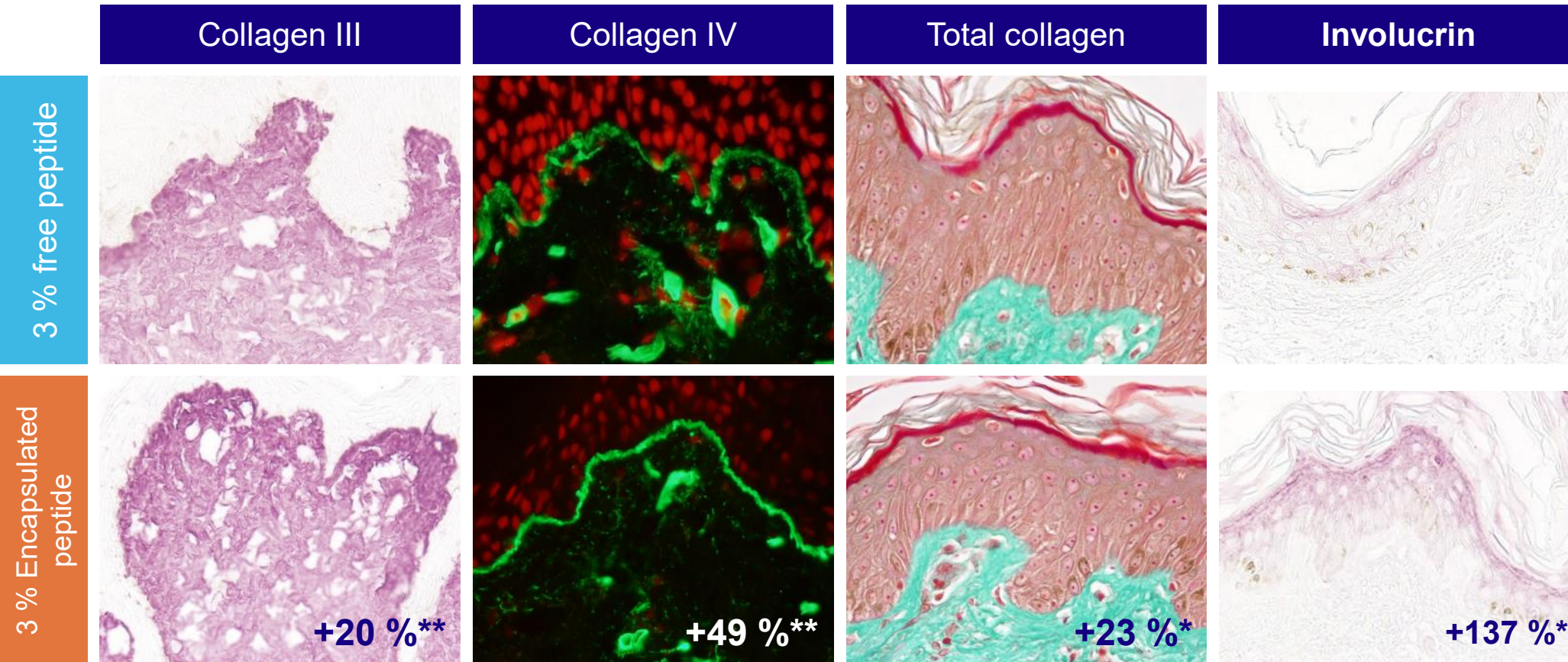


Samples withdrawn during 24h

x13 protection against enzymatic attack

Encapsulation → Better cellular metabolism

* $p < 0.05$, ** $p < 0.01$

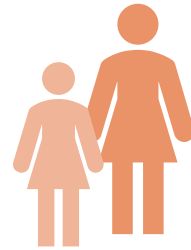


Encapsulation further increases collagen and involucrin , thanks to its smart peptide delivery system that promotes skin bioavailability.

Technology: Skin explants (female donor, phototype III, 58 years) + immunostaining (collagen III, collagen IV, involucrin) or Masson's trichrome staining (total collagen), application of a cream containing 3 % of peptide

Fast clinical *performance*

1 comparative clinical study – half face, double blind protocol



33

Caucasian
volunteers



Twice a day
1 month
Results from **15 days**

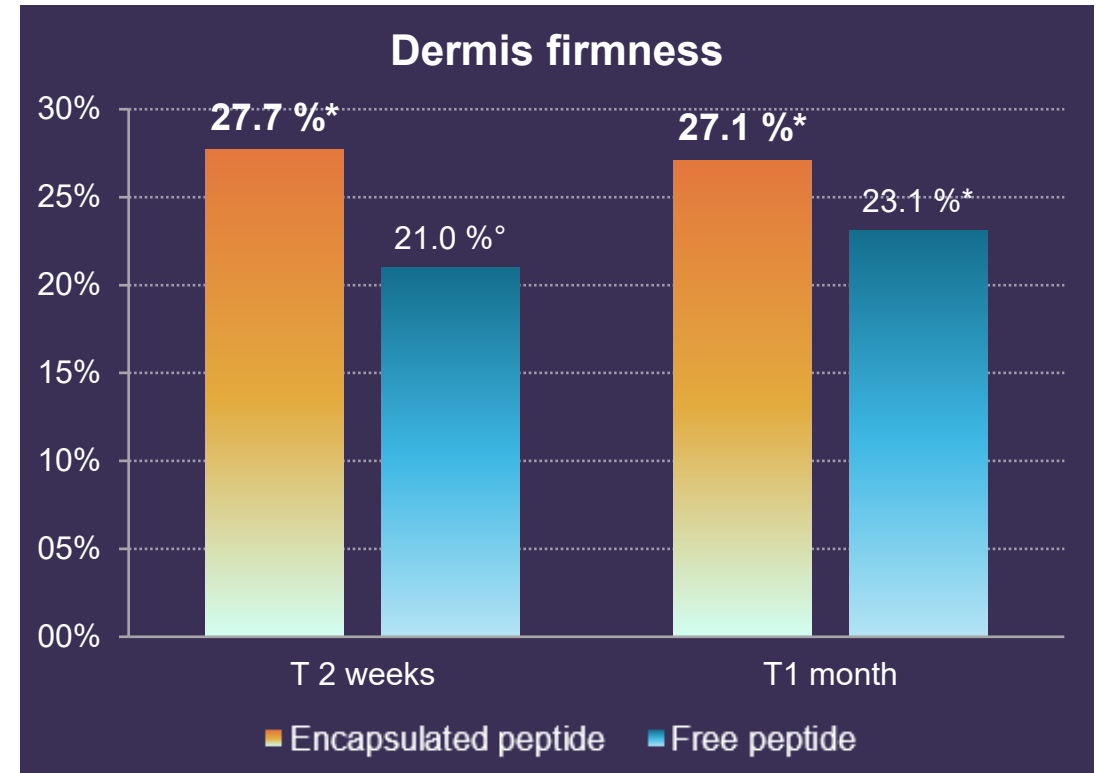
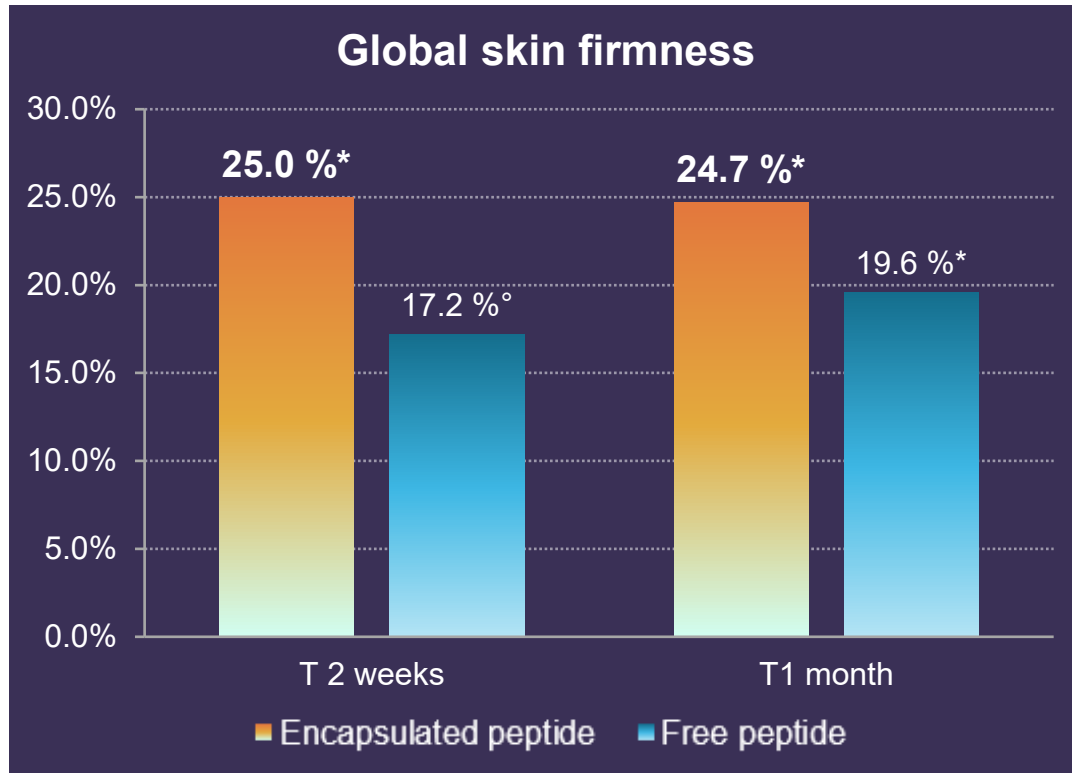
mean age: 56
[44-64]



Cream containing
3 % Encapsulated peptide
or **3 % peptide**

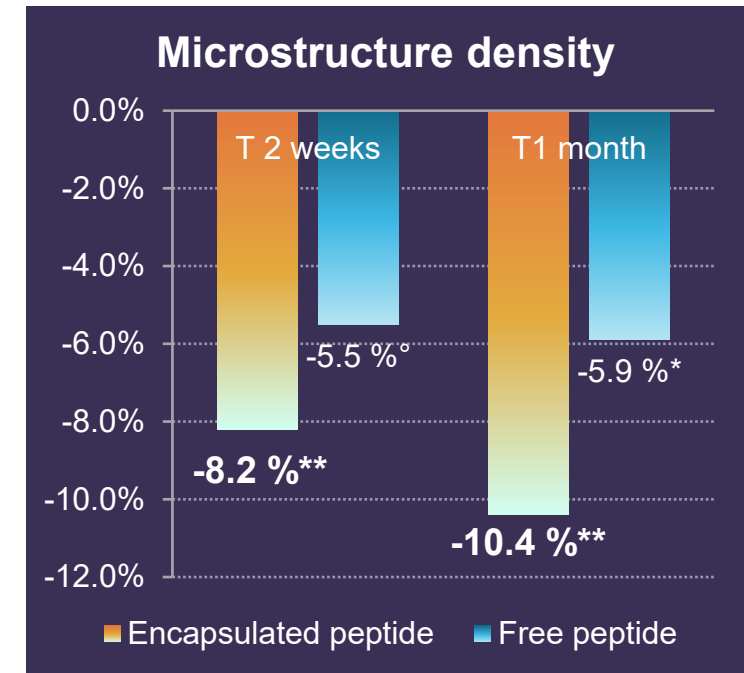
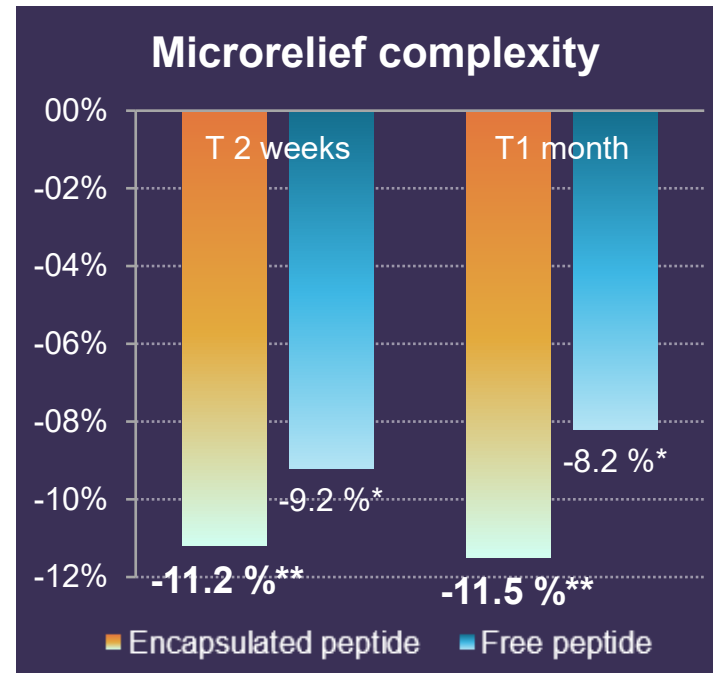
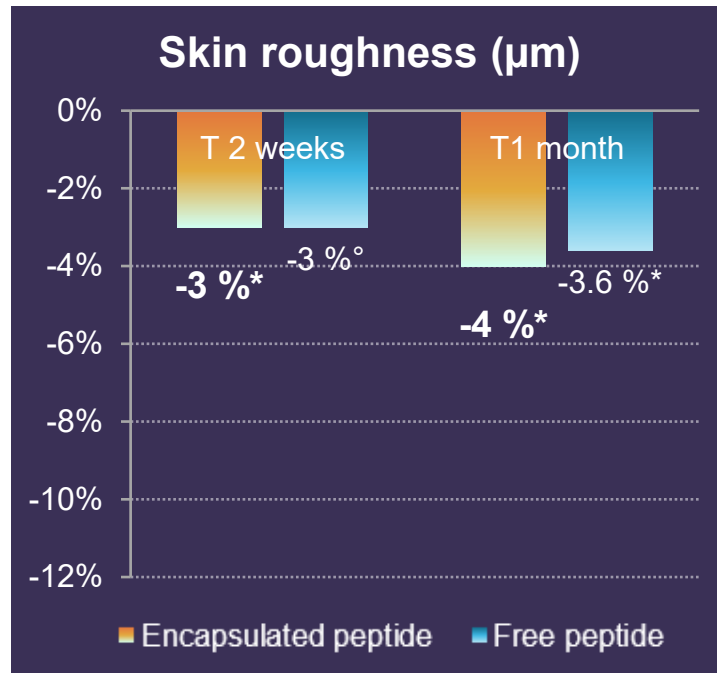
Performance evaluation by fringe projection (AEVA) and by indentometer (EasyStiff®)

Mechanical resilience *in only 15 days*



* $p < 0.01$ vs T0, for 32 volunteers

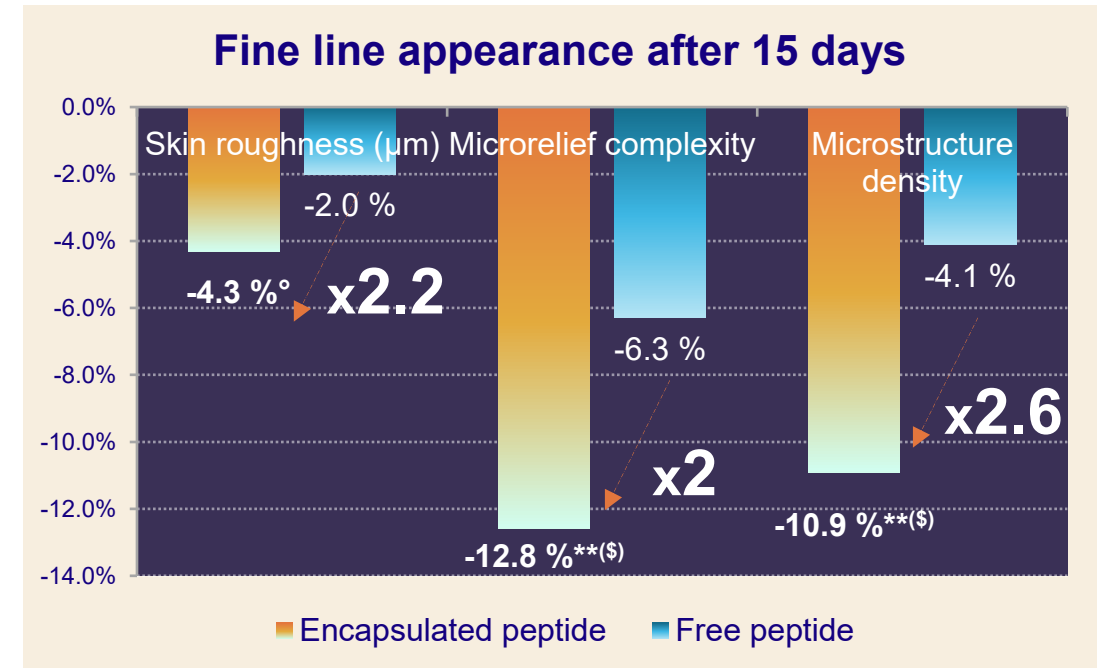
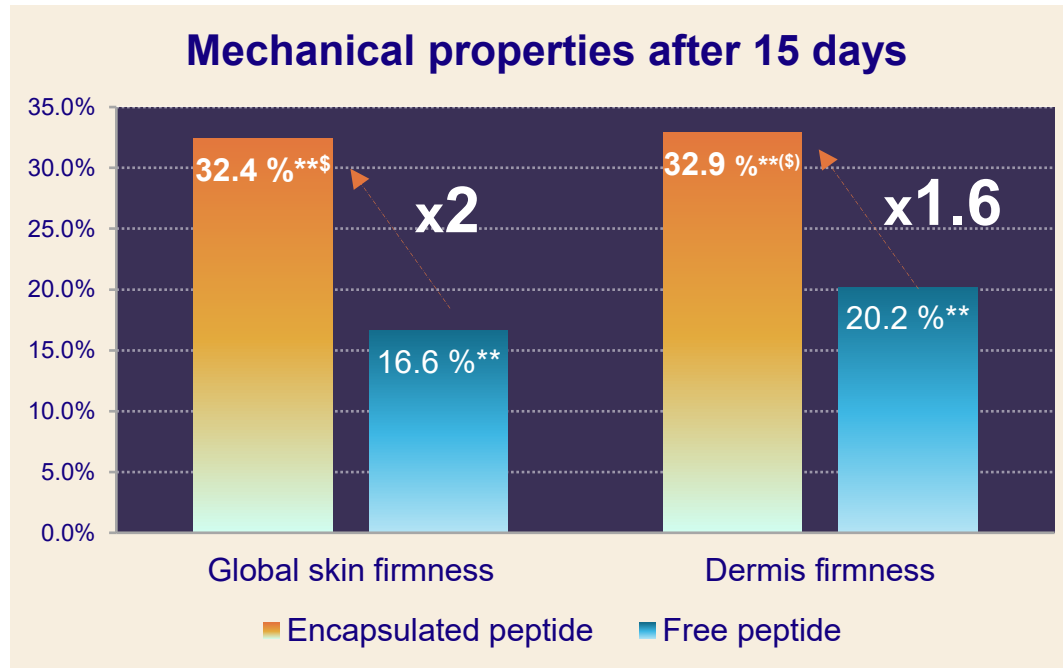
Anti-wrinkle benefits *in only 15 days*



- At the same peptide concentration, encapsulated peptide outperforms free-form.
- It rapidly smoothes the skin, improves skin texture and reduces wrinkle & fine line density in as little as 15 days.

°p<0.1, *p<0.05 or **p<0.01 vs T0, for 28 volunteers

Greater performance *on fine lines*



Encapsulation increases in 2x performance on fine lines in just 15 days.

Sub-group with fine lines (20 volunteers for mechanical properties and 18 volunteers for fine line appearance)

[°]p<0.1, ^{**}p<0.01 vs T0, ^(\$)p<0.1, ^{\$}p<0.05 vs Matrixyl®

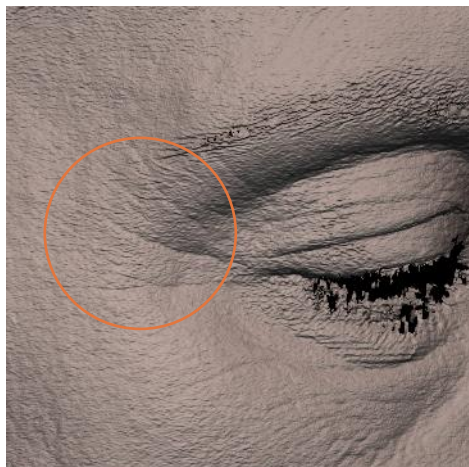
in vivo

Visible results *in just 15* *days*

- Encapsulated peptide
smoothes wrinkles,
delivers firmer skin and a
finer skin texture
in just 15 days.

Clinical study: 33 Caucasian female volunteers, mean age: 56 [44-64], with visible wrinkles or fine lines
Twice daily application on the hemiface of a cream containing 3 % of peptide for 1 month.
Performance evaluation by AEVA, HeadScan® photo bench.

Vol #12



Vol #12

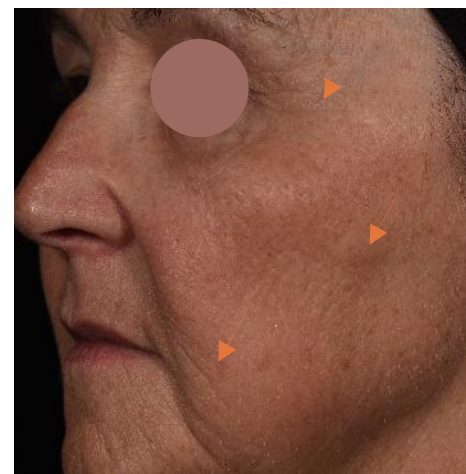


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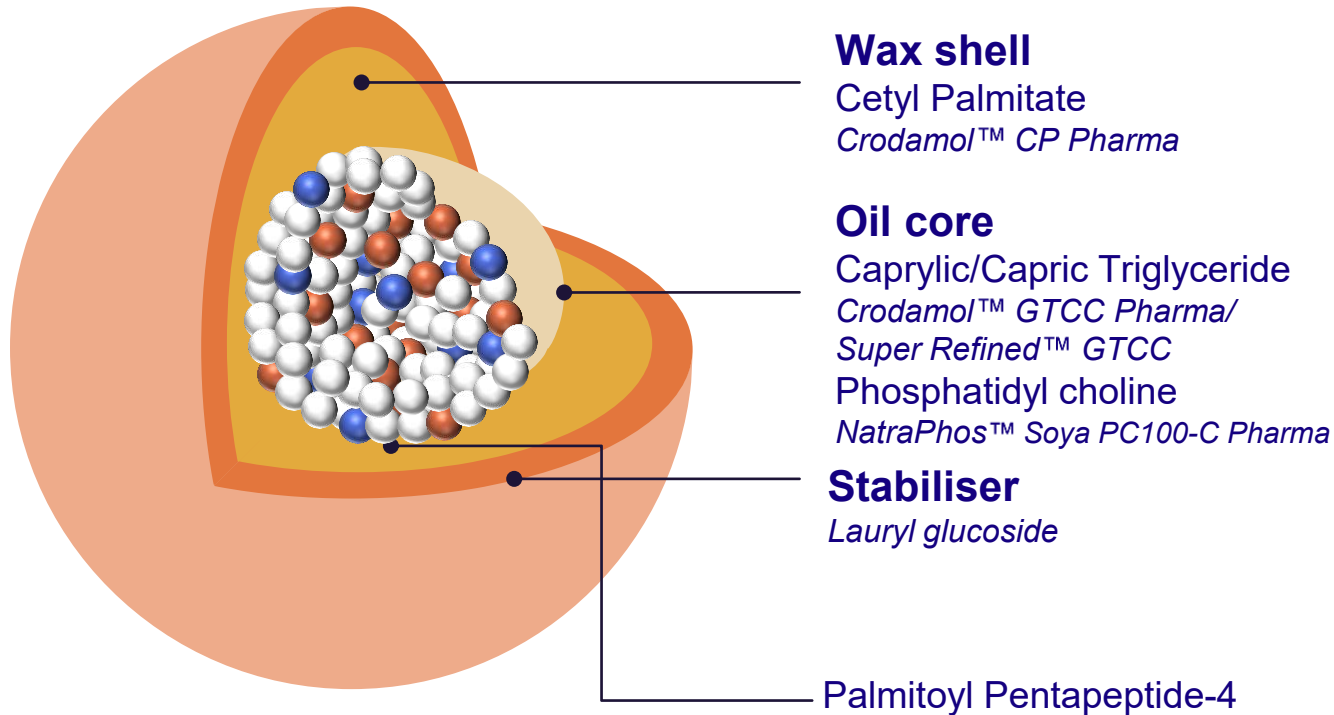


BEFORE

AFTER 15 DAYS



Summary



- **PAL-KTTKS is a gold standard anti-wrinkle peptide**
 - Stimulates ECM production
 - Boosts collagen synthesis
 - Supports dermal architecture
- **Nanoparticle overcomes the limitations of PAL-KTTKS**
 - Improved skin penetration
 - Reduced enzymatic degradation
 - Improved bioavailability
- **Croda offer a range of excipient and lipidic products to help improve solubility, stability and bioavailability of peptide active components**

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