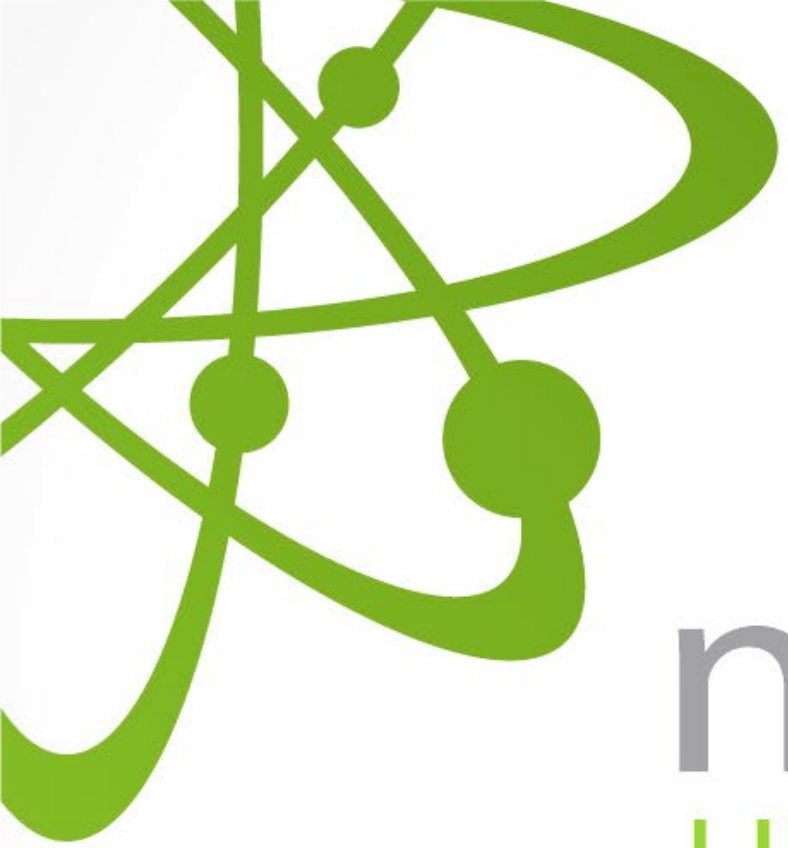

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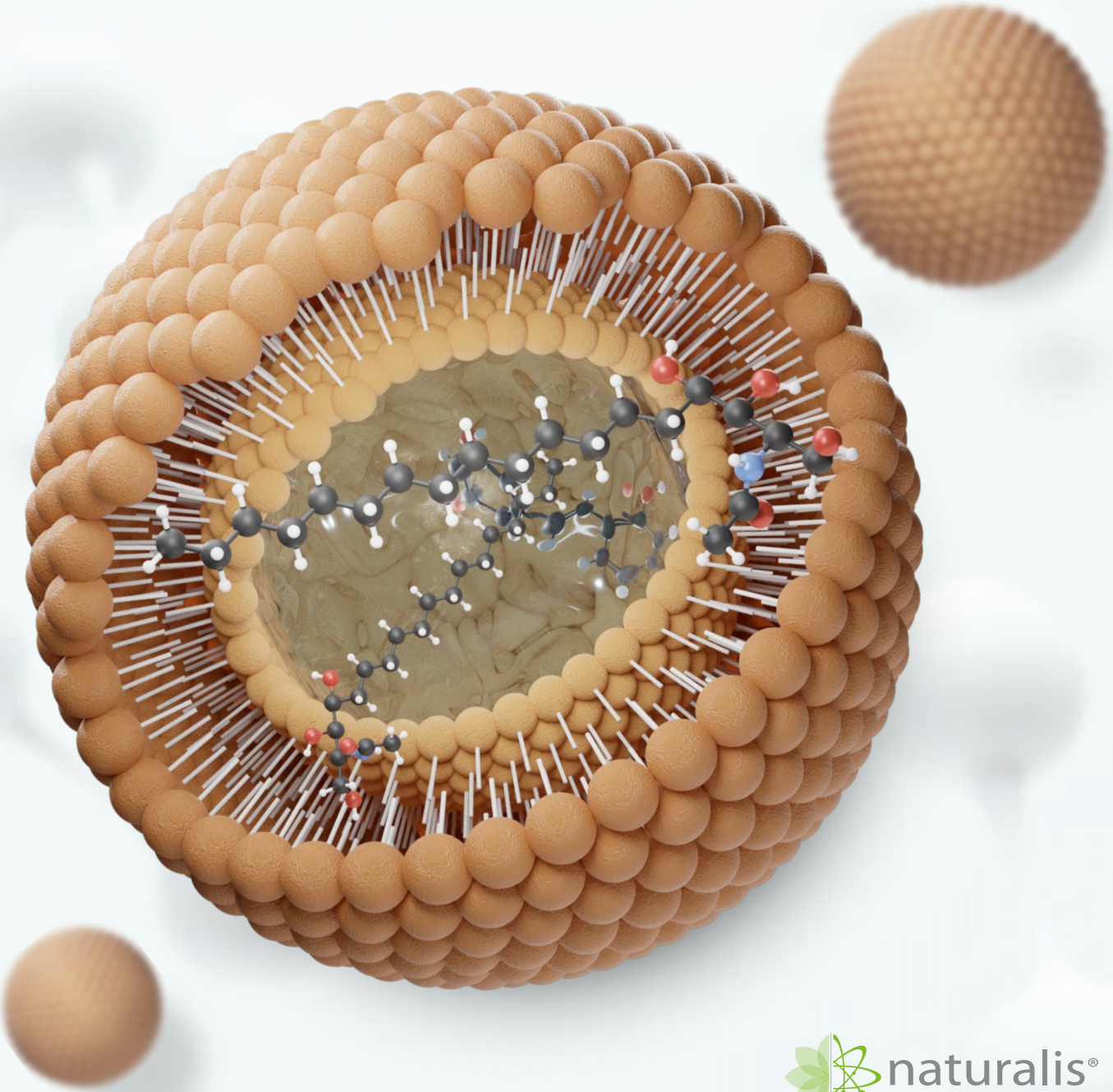
NIOSOME TECHNOLOGY



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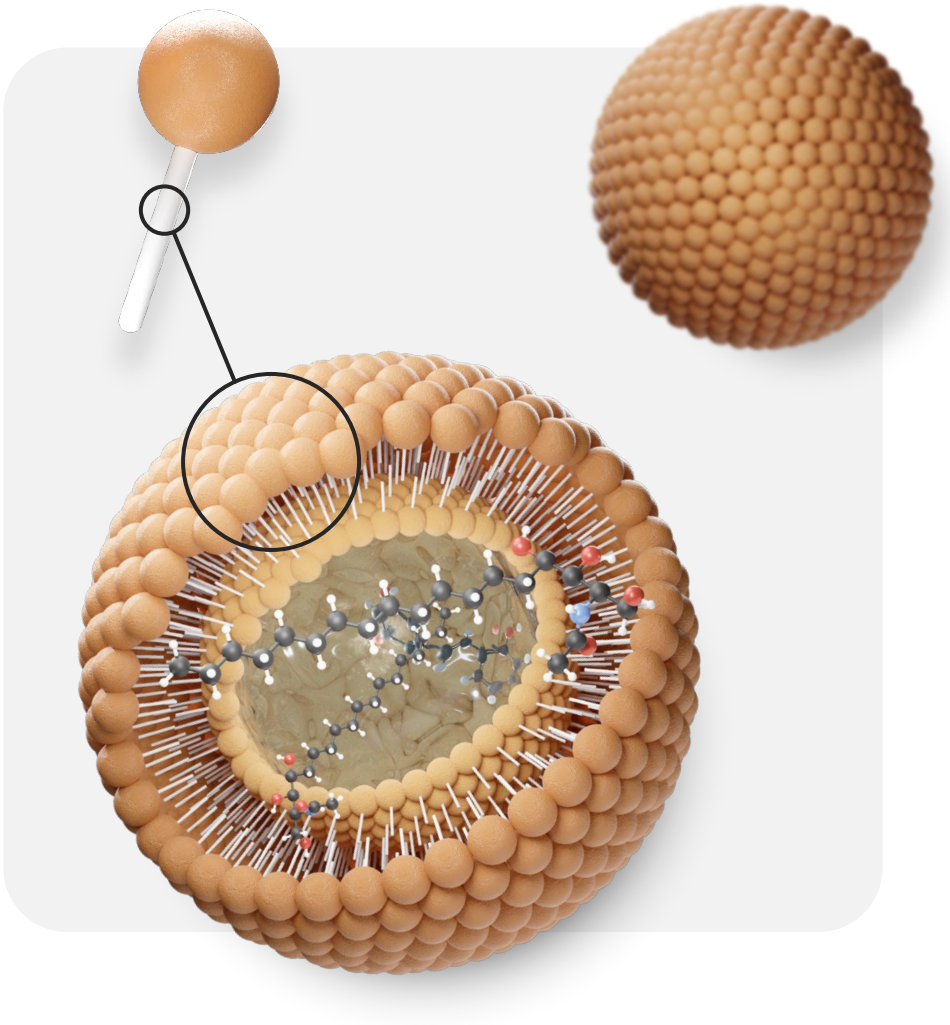
What is Niosome…

Is a delivery system, in which the active ingredient is encapsulated in vesicles structurally similar to liposomes but with a bilayer composed **of non-ionic surfactants rather than phospholipids**



Why to use a Delivery System?

….for attempting **to localize and concentrate the active ingredients in a skin compartment** of interest, leading to the maximum efficacy of cosmetic treatment.

What we do…

We select natural **pure molecules** that have a well-known biochemical mechanism of action in the target cell or tissue in the skin….and…
We encapsulate them into “**NIOSOME**” vesicles

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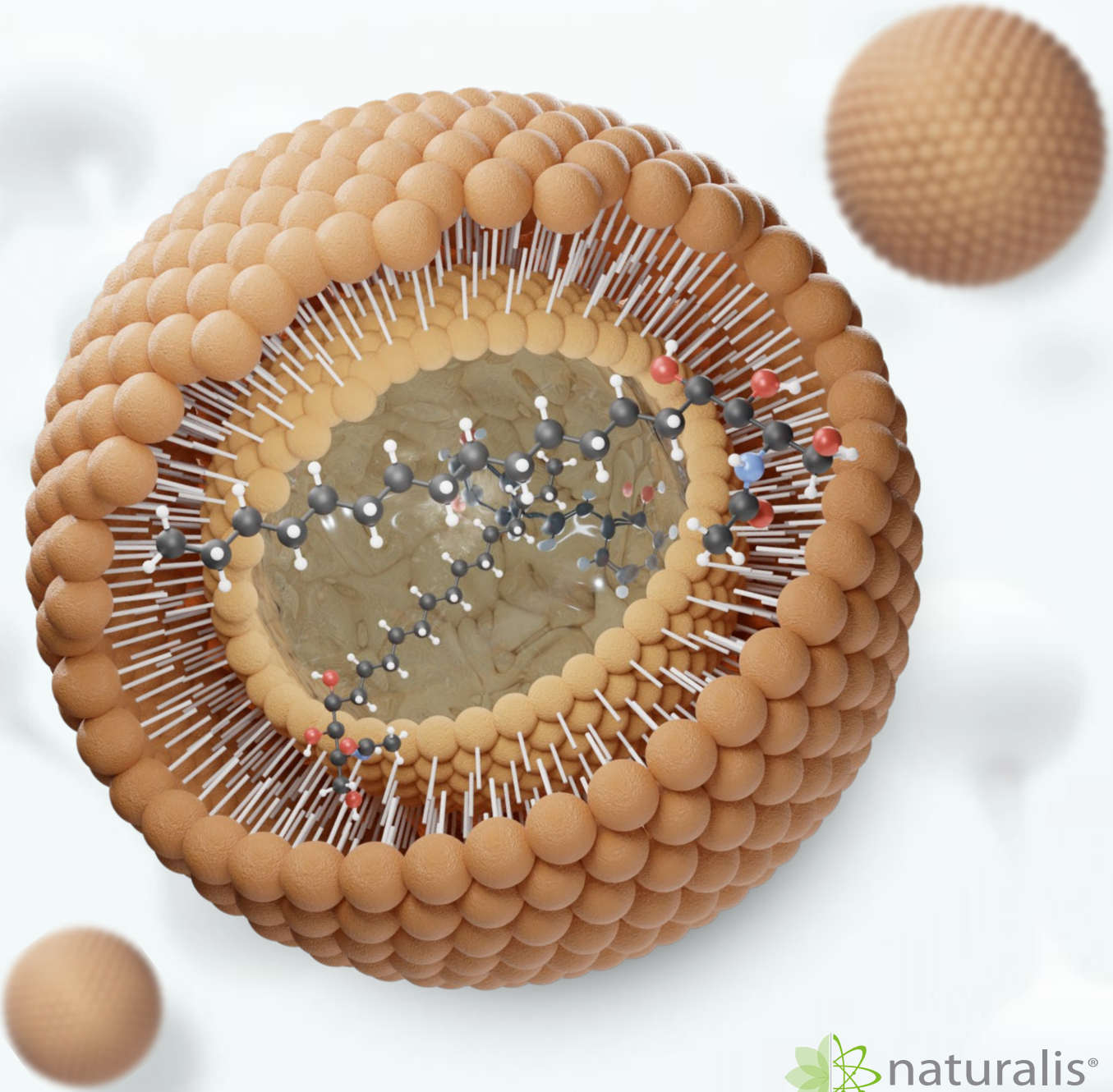
Why to use delivery system?



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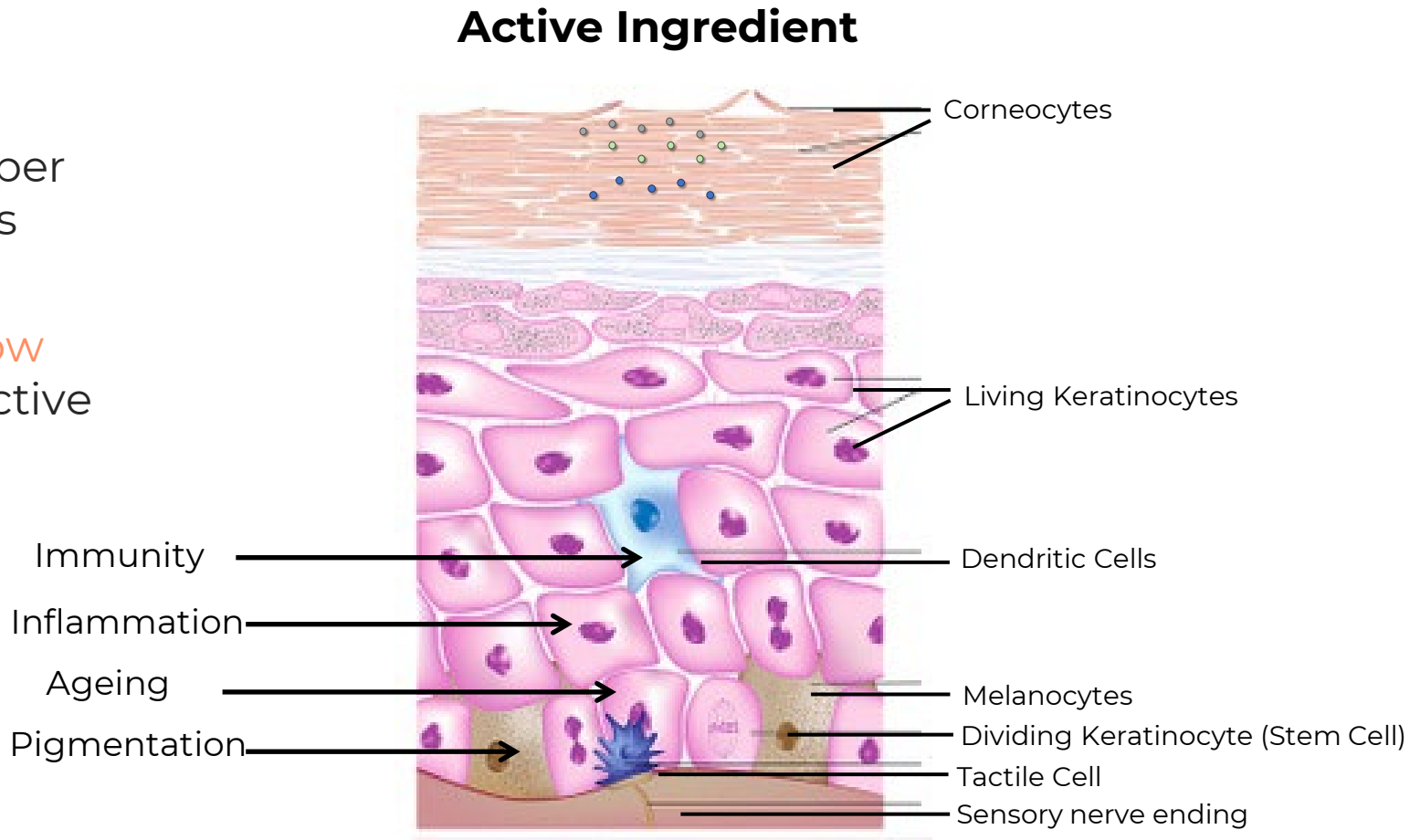
Why to use a Delivery System?

Active Ingredients must reach deeper layers, sites of living cutaneous cells

The stratum corneum has a very low permeation rate for conventional active ingredients



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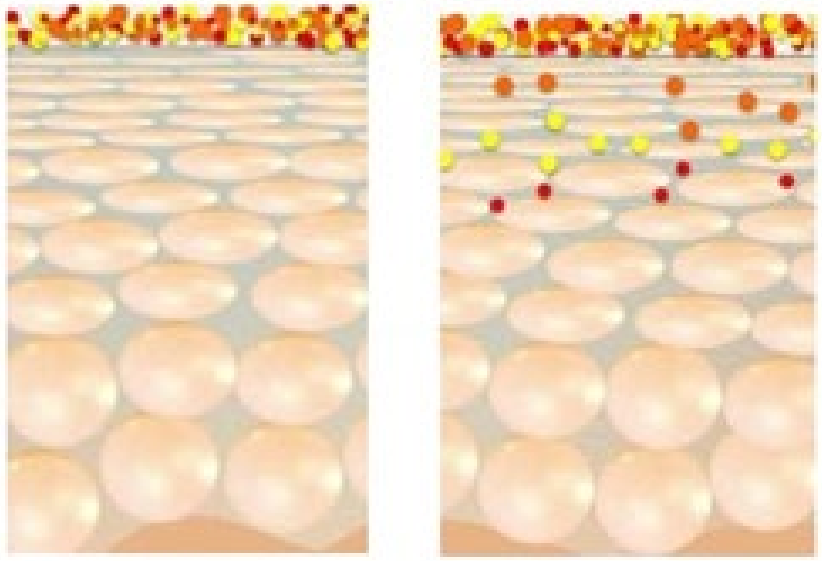
Why to use a Delivery System?

BUT in order to get it….

active ingredients must penetrate the **stratum corneum (the skin barrier)** and get its cellular target in the skin in sufficient concentrations

In other words the skin «barrier function» **must be overcome**

TRANSDERMAL AND DERMAL DELIVERY IS PROBLEMATIC BECAUSE THE STRATUM CORNEUM HAS A VERY LOW PERMEATION RATE



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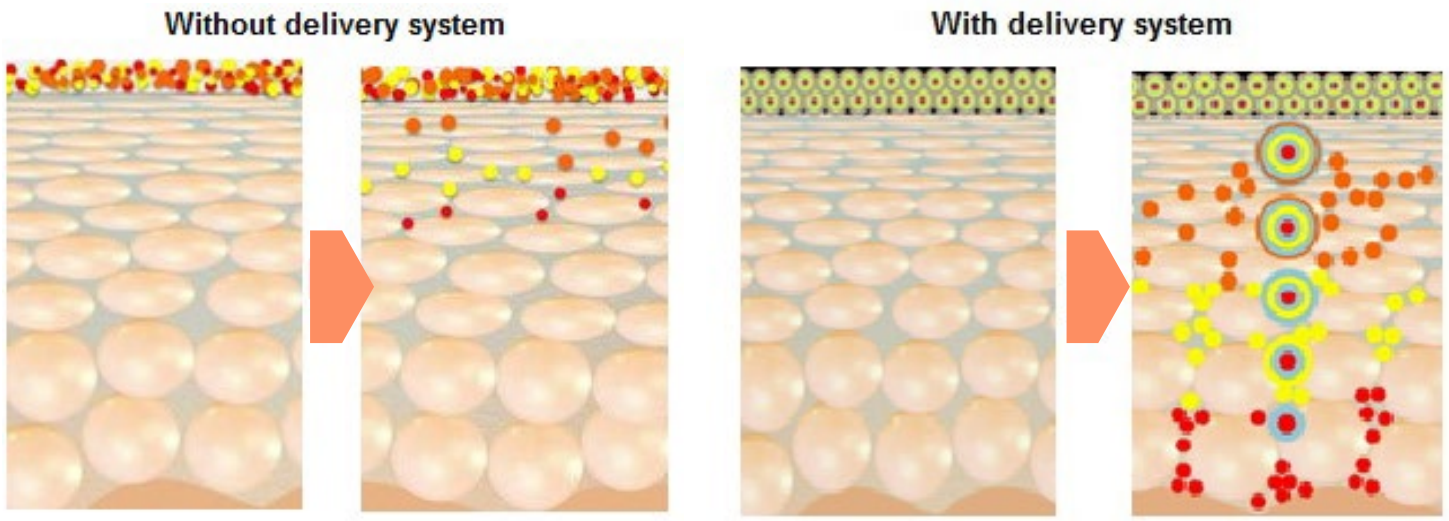
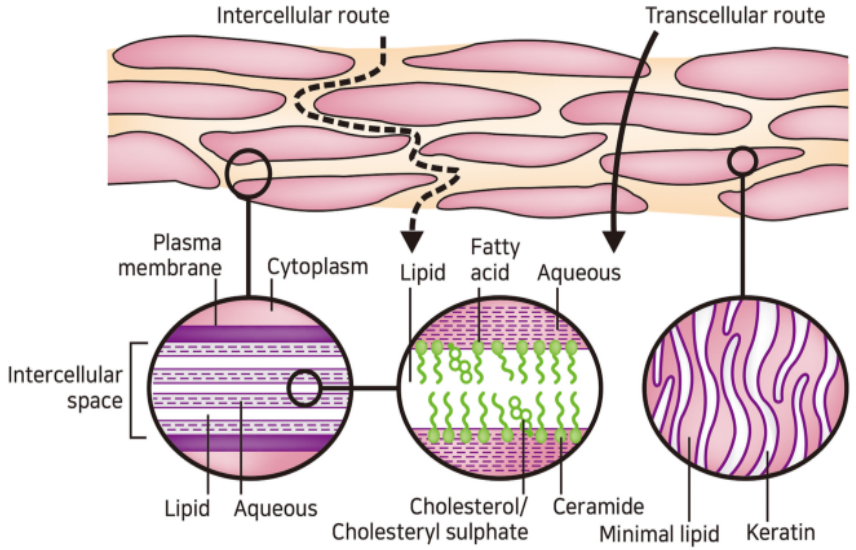
Why to use a Delivery System?

Skin care formulations **should incorporate specific elements** that improve the ability of active ingredients to overcome the stratum corneum

DELIVERY SYSTEM or PENETRATION ENHANCER

in order to partially and transiently disrupt and weaken the intercellular lipid lamellae in a reversible and safe manner





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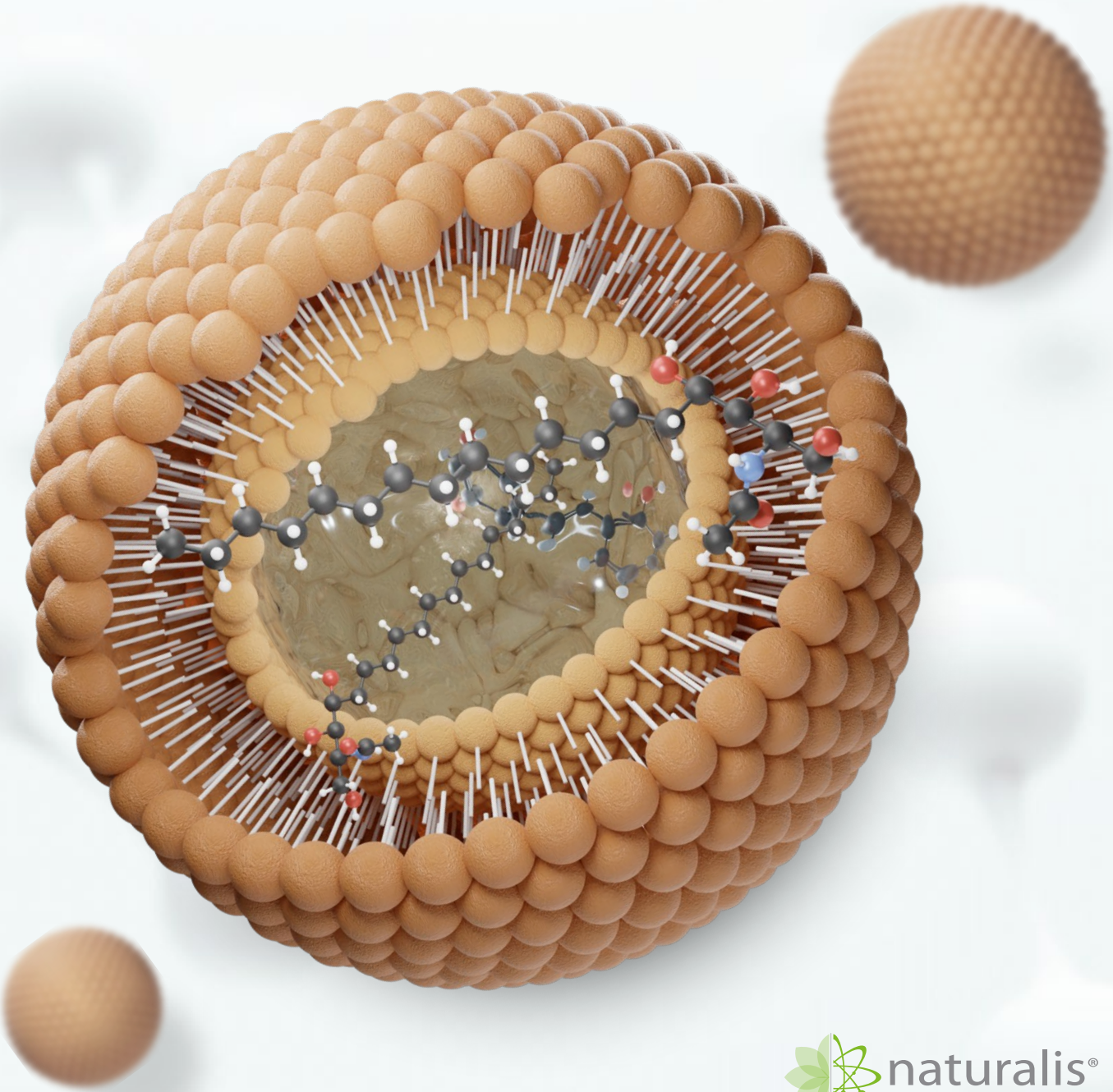
Vesicles as delivery system



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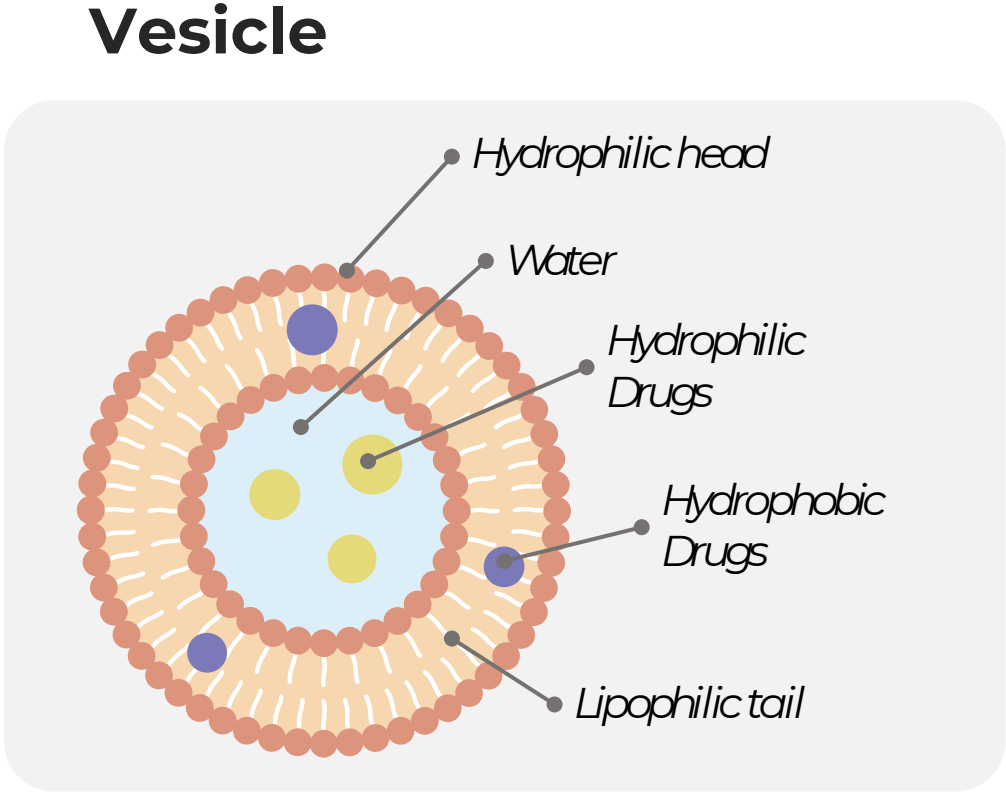
Vesicle as Tool for Transdermal and Dermal Delivery

One approach is the use of **vesicles** as drug delivery system

- **Ø 150-250 nm**
- **Composed of amphiphilic molecules**

Their centre consists of an aqueous cavity,
which is surrounded by one or more bimolecular sheets of amphiphilic molecules

- Hydrophilic drugs can be entrapped into the aqueous cavity
- Lipophilic drugs can be associated with the bilayer



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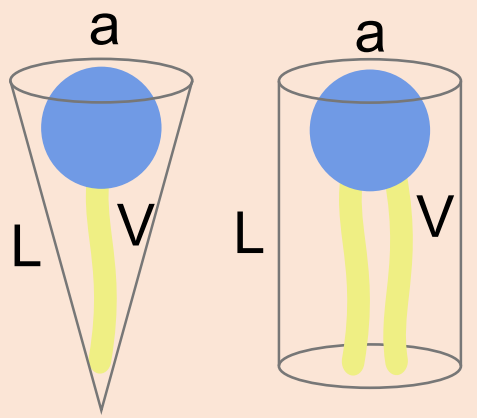
Vesicle as Tool for Transdermal and Dermal Delivery

A wide variety of amphiphilic molecules can be used to prepare vesicles

Molecular structure can influence the type of colloidal aggregate and the physico-chemical characteristics such as, **size, charge, lamellarity and bilayer elasticity** and consequently the behaviour of the vesicles

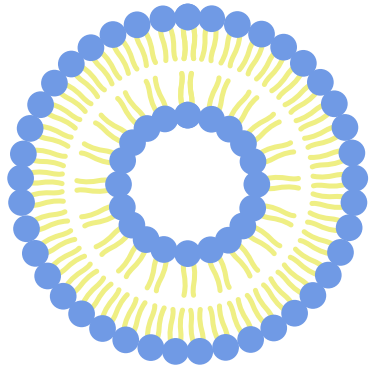


P=V/a L

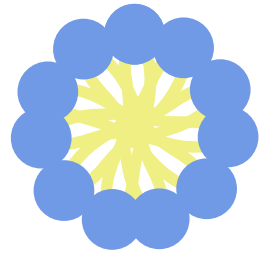
V=hydrocarbon volume
a=surface area of the head group
L=fully chain lenght

P<1/3 micelles (b)
1/3<P<1/2 vesicles (a)
1/2<P<1 planar bilayers (c)

Type of colloidal aggregates



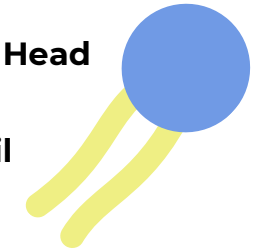
Vesicles

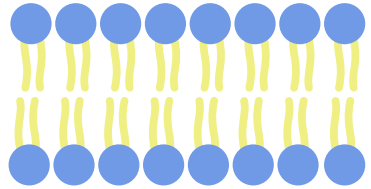


Micelle

Hydrophobic Head

Hydrophilic Tail





Sheet

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Vesicle as Tool for Transdermal and Dermal Delivery

In the last thirty years, many delivery systems have been developed

Liposome Derivates

- **Liposomes** - *Phospholipid bilayer (80' years)*
- **Conventional Niosome-** *Non-ionic surfactants bilayer (Span) (80'years)*
- **Ethosomes** - *Phospholipid bilayer + ethanol (90'years)*

Elastic Vesicles

- **Elastic Trasferosomes** - *Hybrid bilayer (90' years)*
- **Ultra-deformable Niosomes-** *Polyglycerol esters bilayer* (2008)

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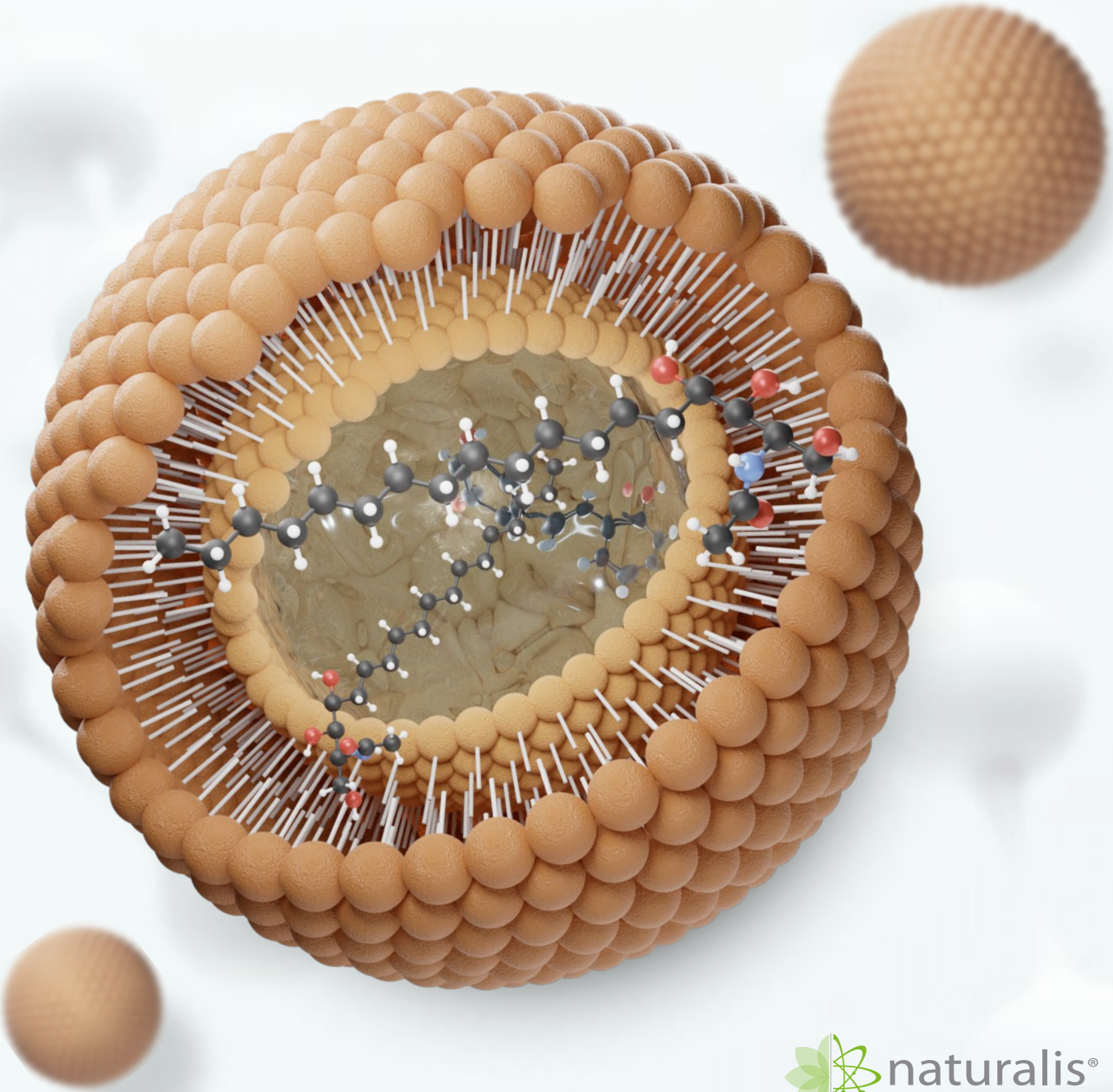
LIPOSOME
and DERIVATES



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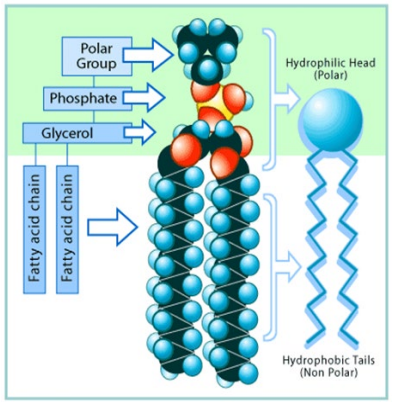
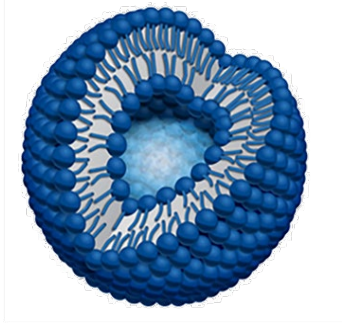
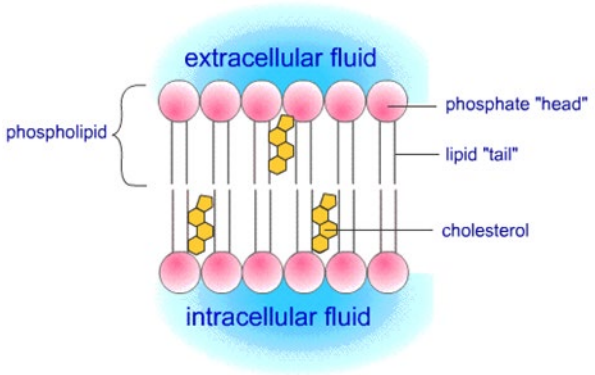
Delivery System: Liposome



Phospholipids



Liposome



- Amphiphilic molecules are Phospholipids + Cholesterol
- Cholesterol regulates the stability of the bilayer
- Shape, size and other properties depend by the ratio chol: phos.

Liposomes and derivates:

- **Liposomes** - *Phospholipid Bilayer (80' years)*
- **Ethosomes** - *Phospholipid Bilayer + Ethanol (90' years)*
- **Phytosome –** *Phospholipid interaction with the active ingredient (1996)*

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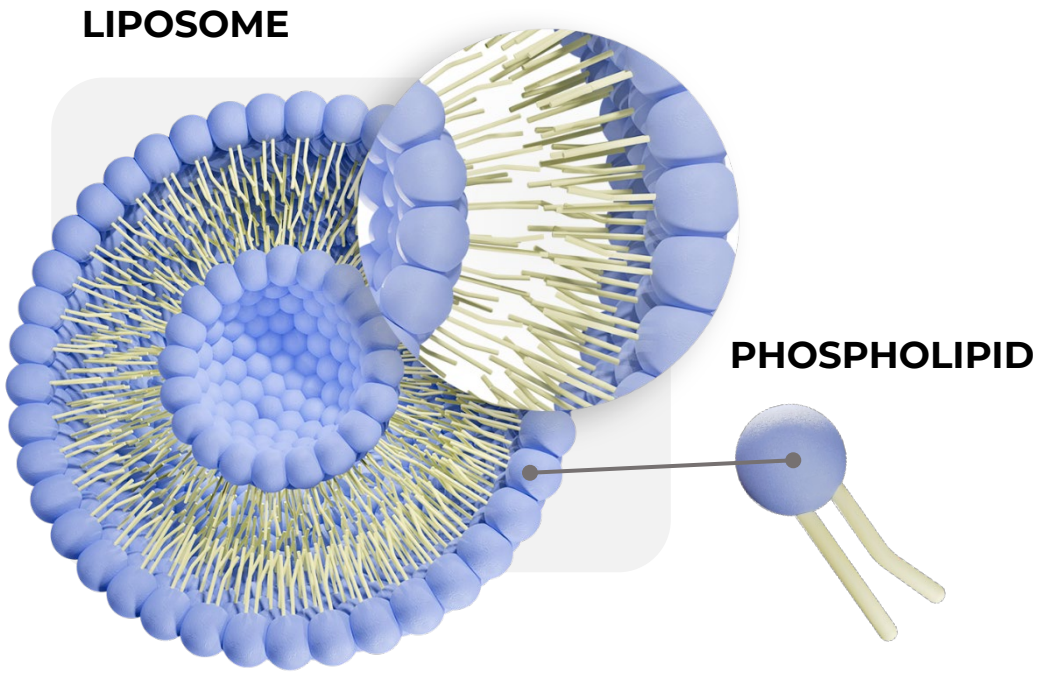
Liposome Delivery System

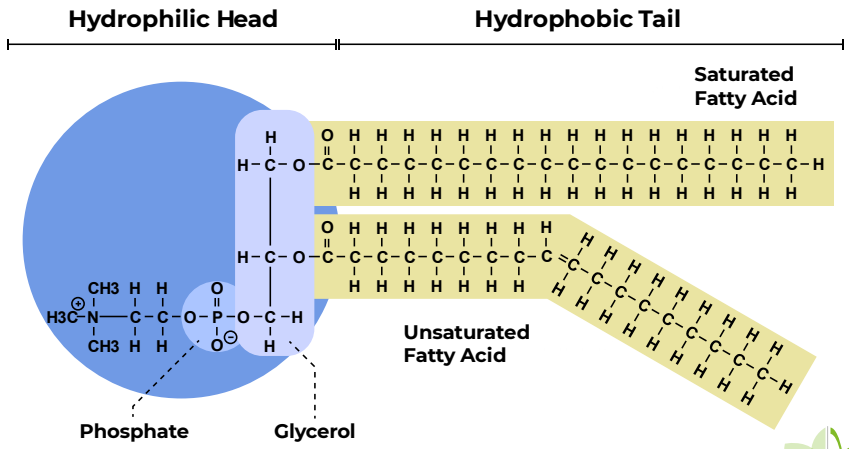
Advantages

- Reduce toxicity or irritation
- Increase drug stability
- Increase **deposition** of drug ***in Stratum Corneum***

Disadvantages

- Instability to **hydrolysis** of phospholipid molecules
- Instability to **oxidation** of phospholipid molecules
- Instability to **enzymatic degradation**





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Liposome Delivery System

Liposomes don't penetrate skin, but they may kick-start active ingredient delivery

By Andrew MCDOUGALL
09-Mar-2016 - Last updated on 09-Mar-2016 at 11:23 GMT

RELATED TAGS: Chemistry

Researchers in Denmark say that the way liposomes are perceived in beauty needs to change after showing that the vesicles, often praised by cosmetics companies for their alleged ability to transport active ingredients into the skin, cannot actually penetrate; but rather help the process get underway.

PLOS ONE

RESEARCH ARTICLE

Superresolution and Fluorescence Dynamics Evidence Reveal That Intact Liposomes Do Not Cross the Human Skin Barrier

Jes Dreier[1], Jens A. Sørensen[2], Jonathan R. Brewer[1]*

1 Advanced bioimaging group/MEMPHYS Center for membrane biophysics, Department of Biochemistry and Molecular Biology, University of Southern Denmark, Odense, Denmark, **2** Department of reconstructive surgery, Odense University Hospital, Odense, Denmark

From this study, published in the journal PLOS One, they add that liposomes cannot penetrate the skin's barrier without breaking.

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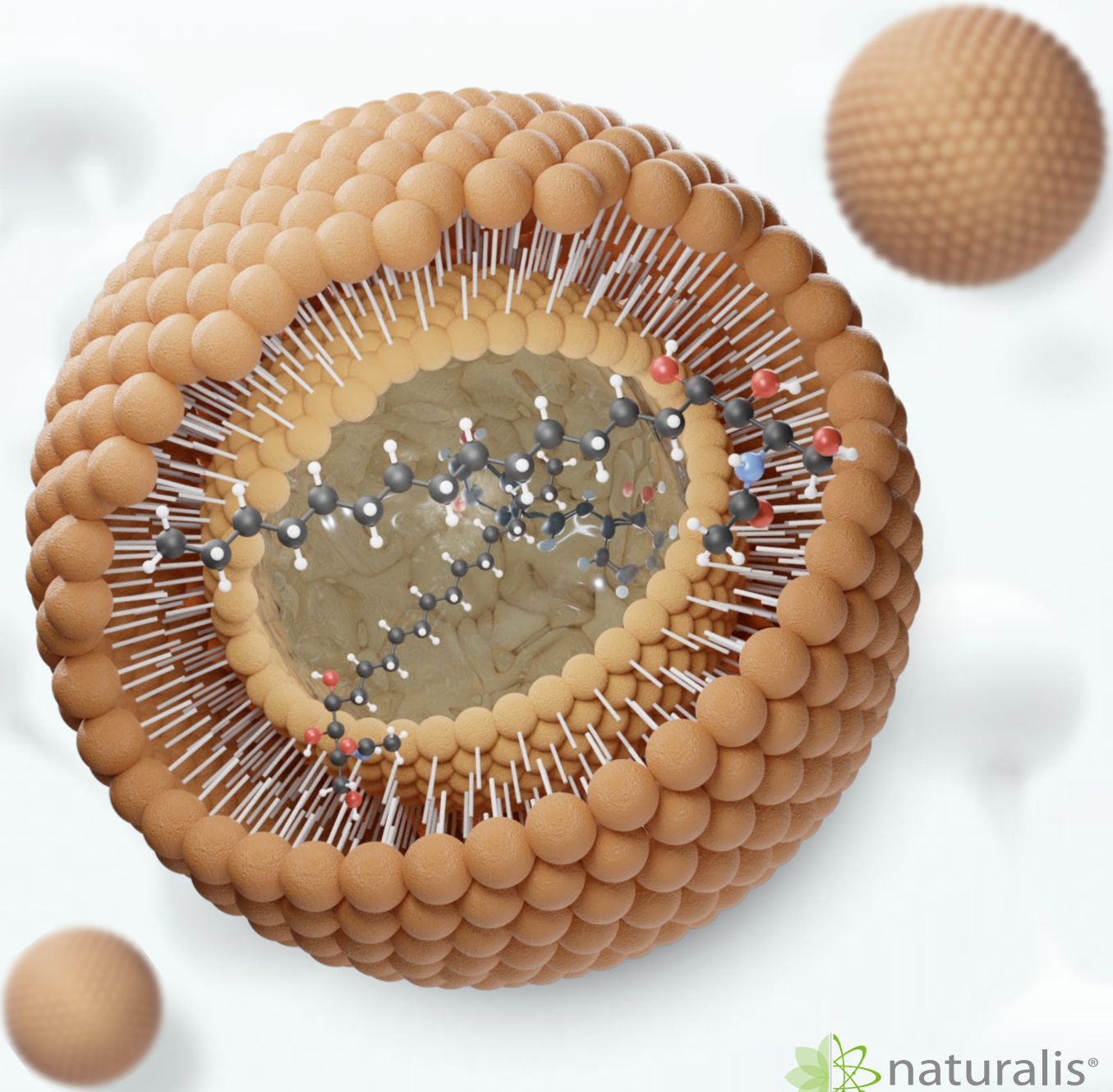
ELASTIC VESICLES



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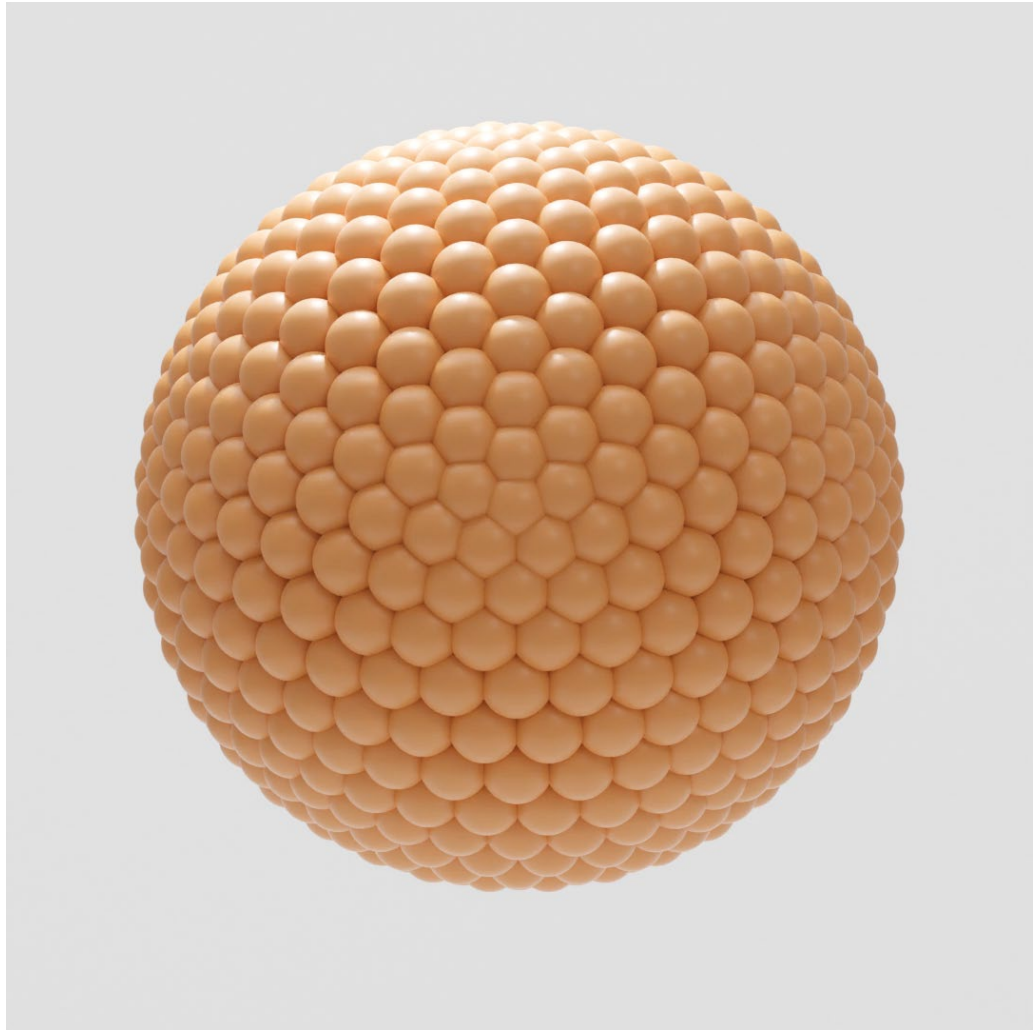
Elastic Delivery System

Based on single-chain surfactants. In the bilayer the molecules are more free to move. The result is a vesicle deformable, capable of easily overpassing the stratum corneum and increasing the bioavailability of the actives encapsulated within it.



- **Trasferosome** - *(90' years)*
- **Ultra-deformable niosome** – *(2006)*

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Bilayer Elasticity: Deformable Vesicles

At the end of the 90s, Gregor Cevc demonstrated

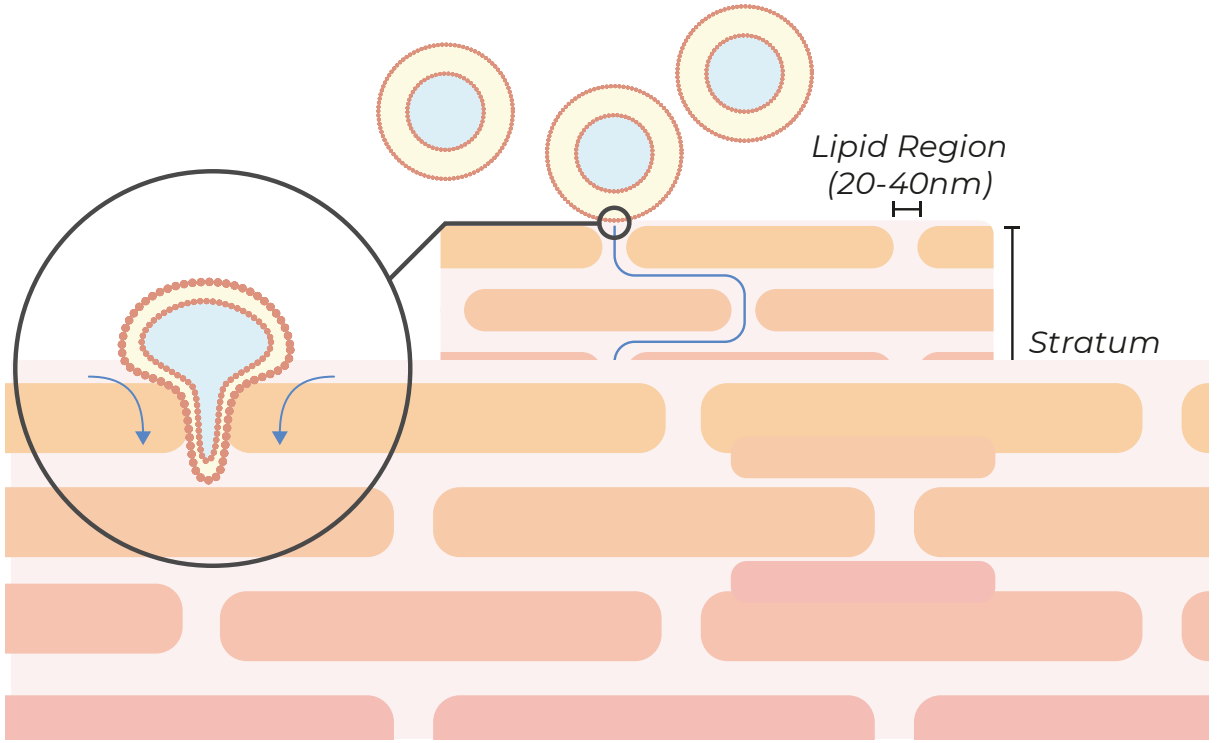
1) **Bilayer elasticity represents a crucial factor in determining its ability to penetrate the skin**
2) **The liposome does not penetrate the skin as it has a bilayer too rigid and not deformable**

Bilayer ELASTICITY is the most important factor for a vesicular delivery system

If the vesicles are elastic, they can squeeze through the pores (**20nm**) in Stratum Corneum (these pores are less than one-tenth of the diameter of vesicles **200 nm**)

Two main limitations of the liposome

- Instability into the Stratum Corneum
- Liposomes **are rigid vesicles**



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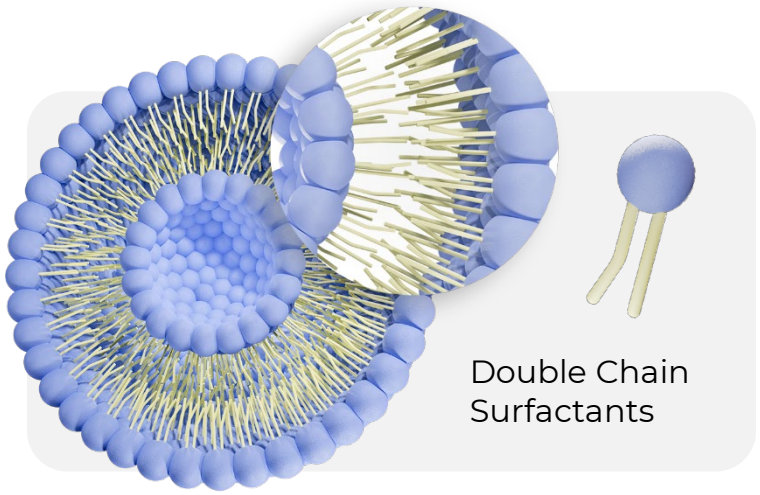
Bilayer Elasticity: Deformable Vesicles

Why do phospholipids form very rigid liposome vesicles?
The presence of two fatty chains in the phospholipid structure creates a very crowded molecular double layer of alkyl chains which imparts a high surface tension to the vesicle and consequently a **high rigidity** (due to repulsion force of Wan der Waals interaction between alkyl chains in the bilayer)



Crowded molecular double layer of alkyl chains

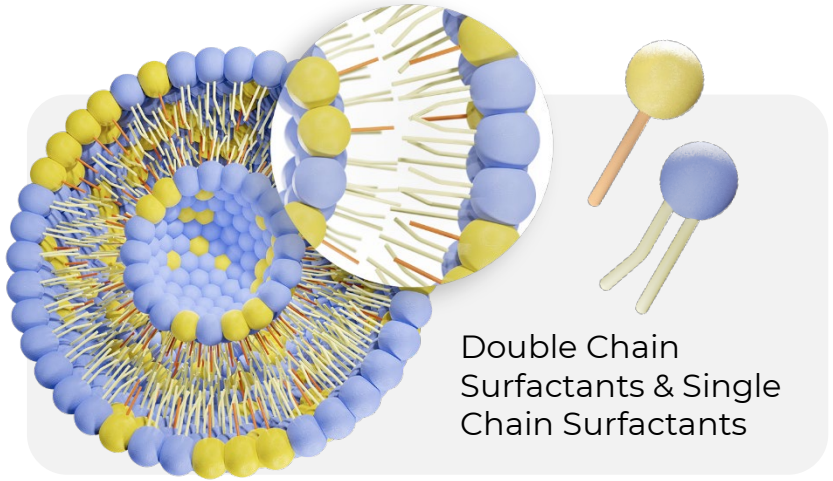
↓

High surface tension

↓

Rigidity

In Transferosomes phospholipids component are mixed with a single chain surfactants. These molecules reduce the number of alkyl chains inside the double layer imparting lower surface tension and increasing the **flexibility of the vesicle**



Less alkyl chains

↓

Lower surface tension

↓

Deformability

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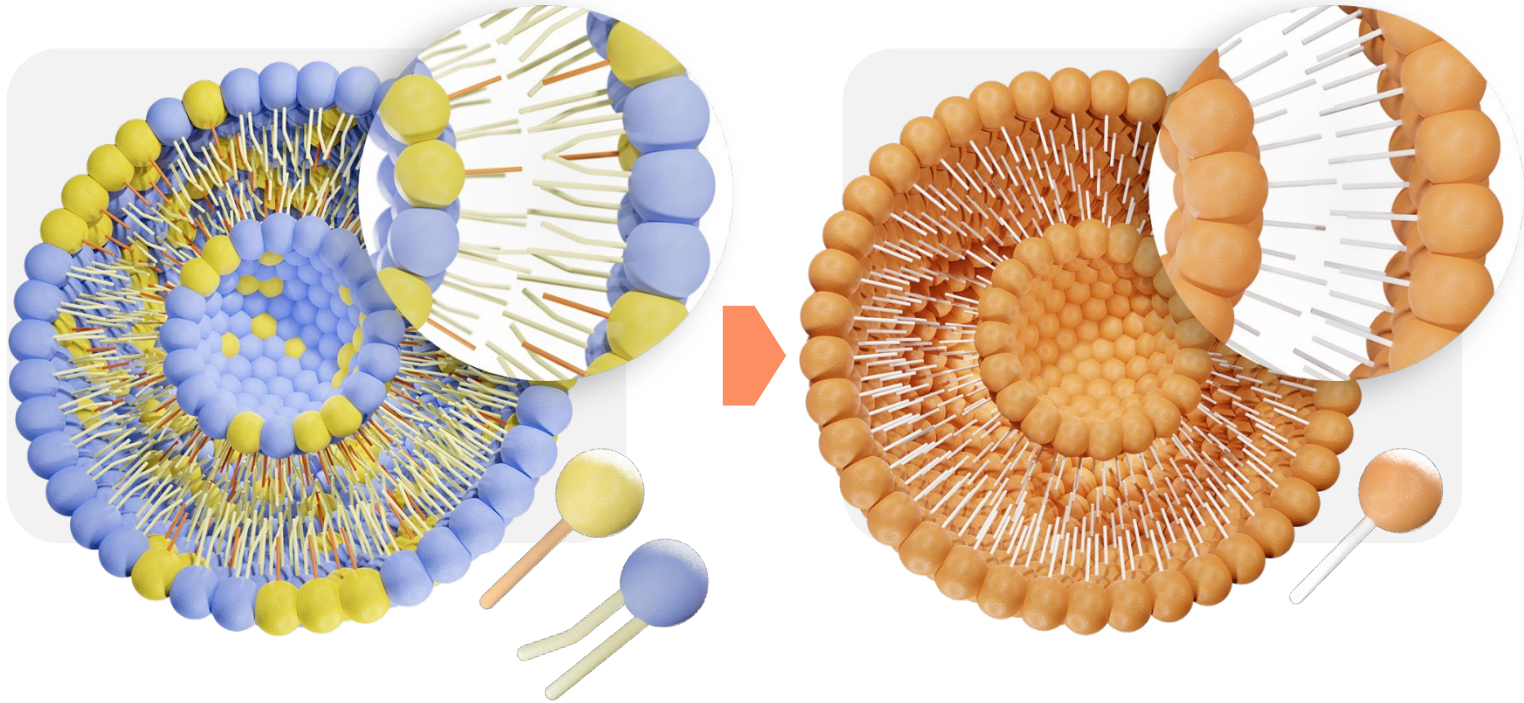
NIOSOME: Ultra-Deformable Vesicles

In Transferosomes phospholipids component are mixed with a surfactant mixture. The ratio of individual surfactants and **total amount of single chain surfactants control the flexibility of the vesicle**

Prof. Honeywell and Prof. Bouwstra introduced in 2006 the Ultra-deformable Niosome in wich bilayer is completely without phospholipids and is made only with single-chain surfactants. This bilayer structure get **the most of elasticity / deformability and therefore the maximum ability to penetrate the skin**

Transferosome

Niosome



Double Chain Surfactants & Single Chain Surfactants

Single Chain Surfactants

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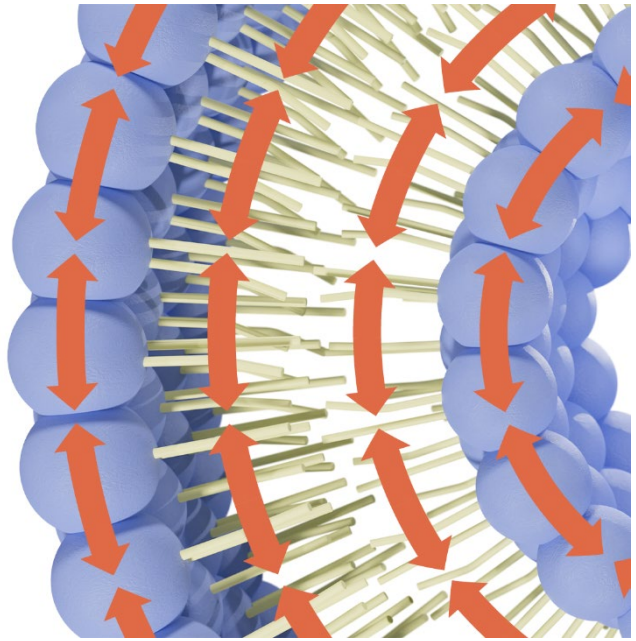
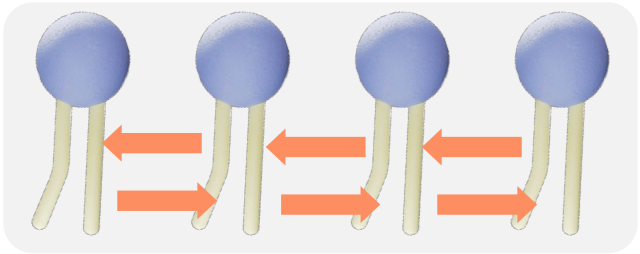
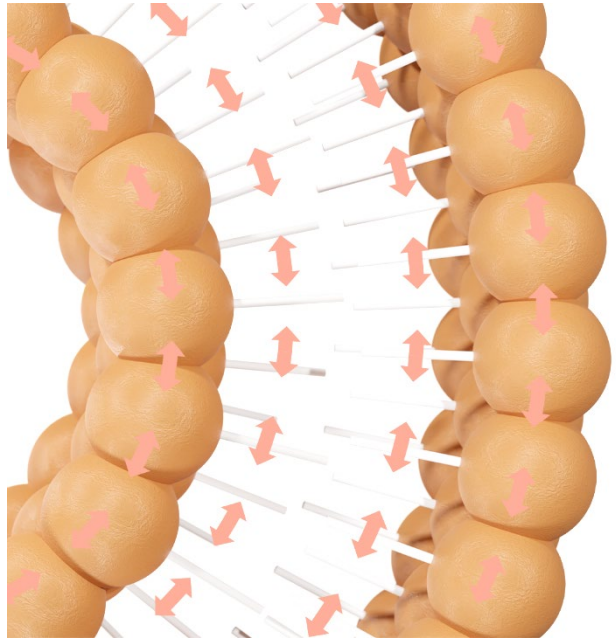
Single & Double Chain Surfactants

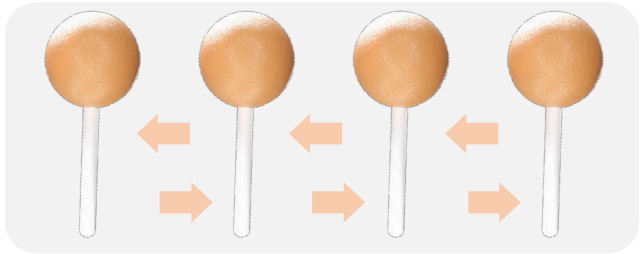
Because of their structure, **single-chain surfactants** undergo a lower repulsion force (*Van Der Waals force*), making the vesicle **less rigid and therefore more elastic and deformable**. This is a key concept that allows the **Niosome to be a very effective delivery system.**

High Van Der Waals force









Very low Van Der Waals force

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NIOSOME: Ultra-Deformable Vesicles

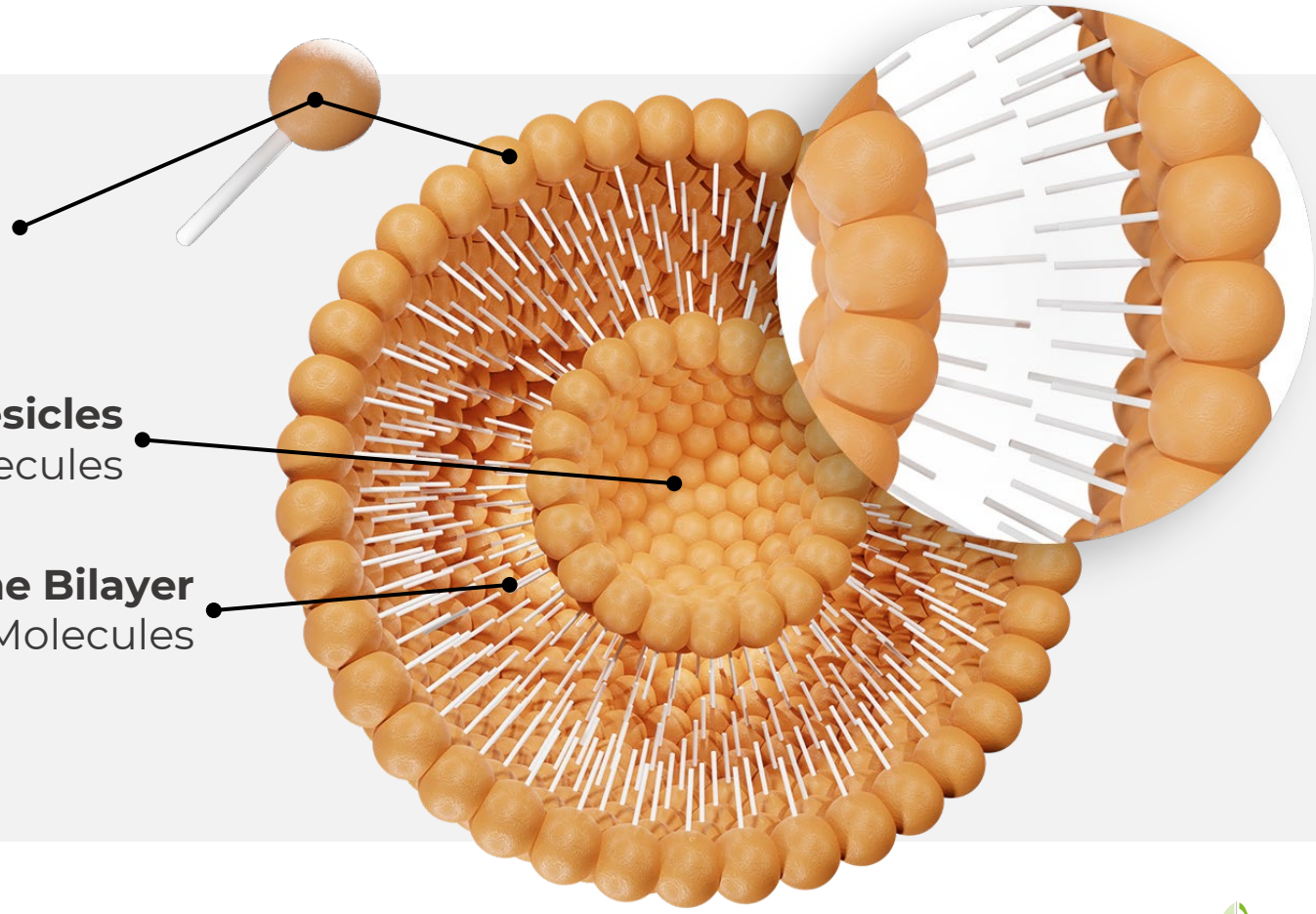
The Bilayer Composition of Single Alkyl Chains Guarantees the **Elastic Properties of the Vesicles**

Ø Diameter ~ 150 – 250 nm
Bilayer composition:

- **Polyglycerol Ester**

Core of the Vesicles
For Hydrophilic Molecules

Membrane Bilayer
For Lipophilic Molecules



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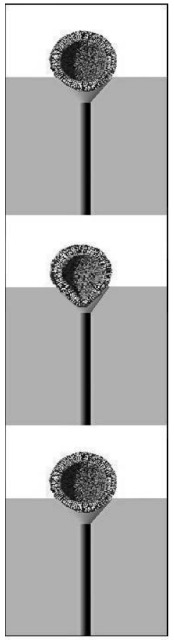
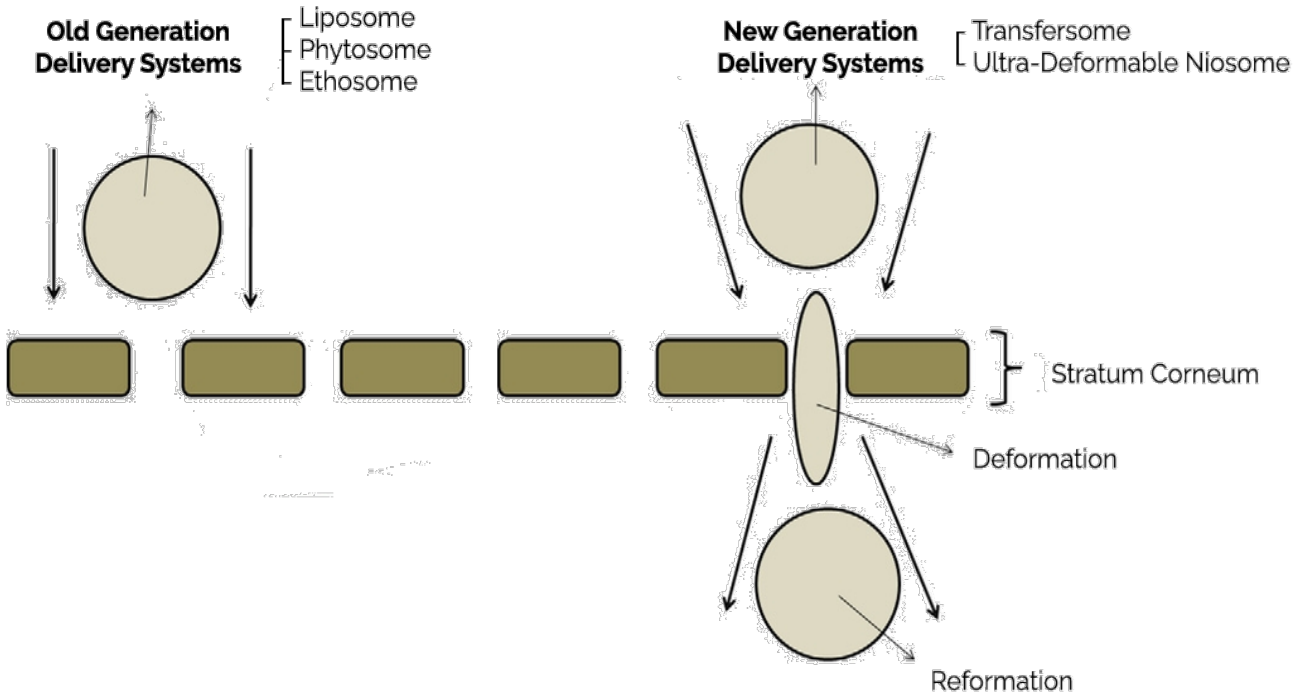
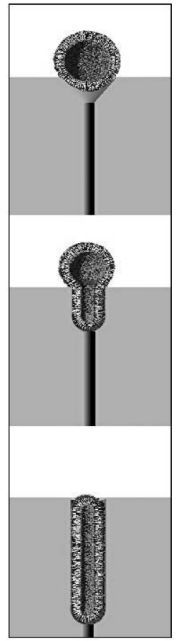
NIOSOME: Ultra-Deformable Vesicles

Conventional Liposome





Ultra-Deformable Niosome



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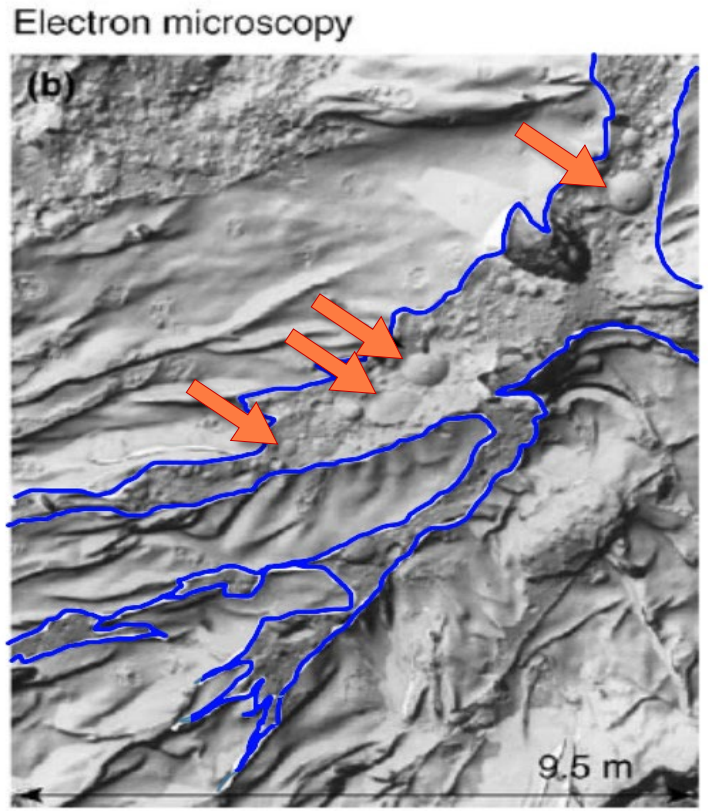
NIOSOME: Ultra-Deformable Vesicles

Vesicles visualized after 1h non –occlusive application using Freeze-Fracture Electron microscopy (FFEM)



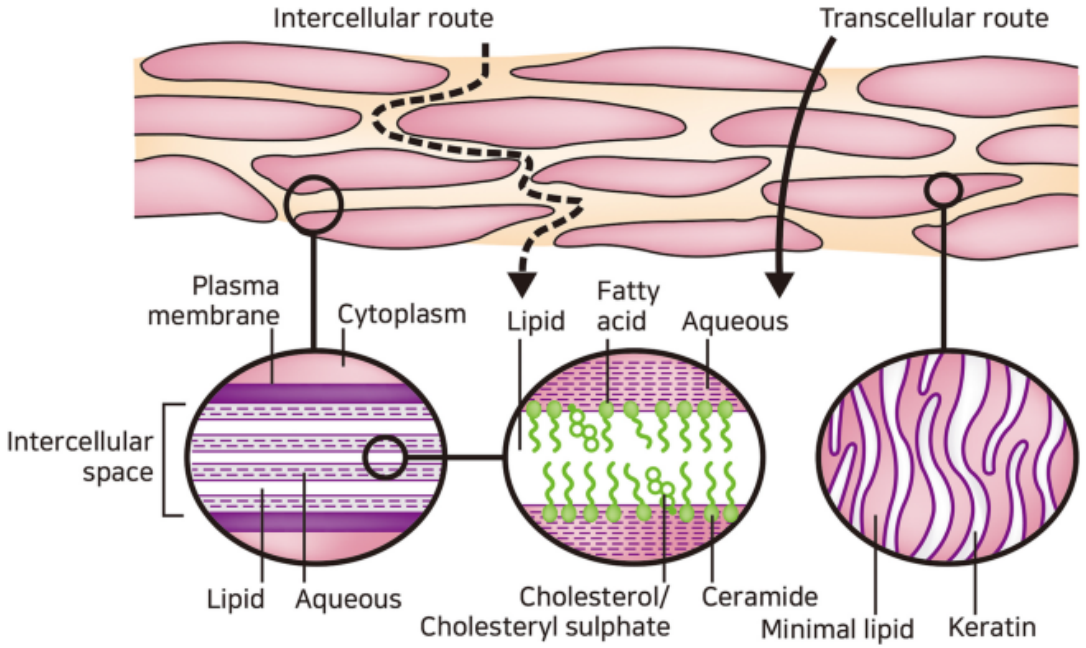


Image by courtesy of Prof. Honeywell-Nguyen PL

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NIOSOME: Ultra-Deformable Vesicles

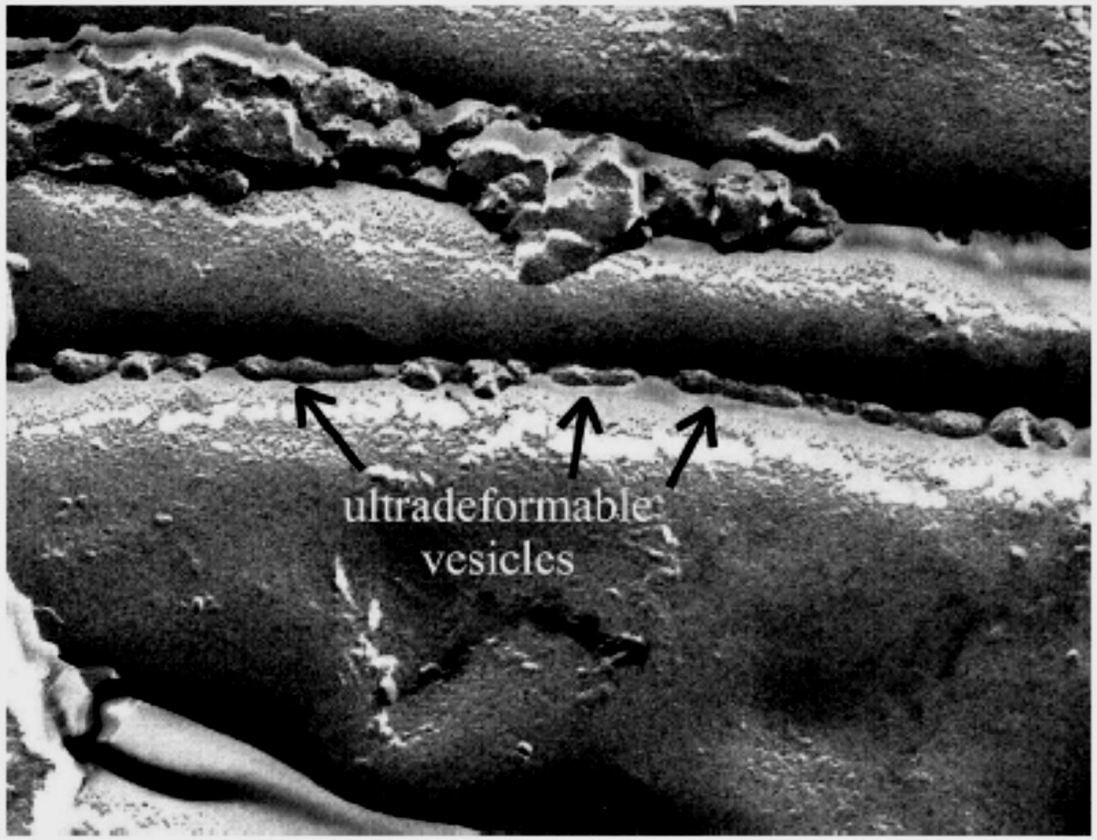

Figure 23: The skin: freeze fracture electron micrograph of ultradeformable vesicles in hydrophilic skin pores of the stratum corneum. (by courtesy of Prof. Dr. J. Bouwstra)

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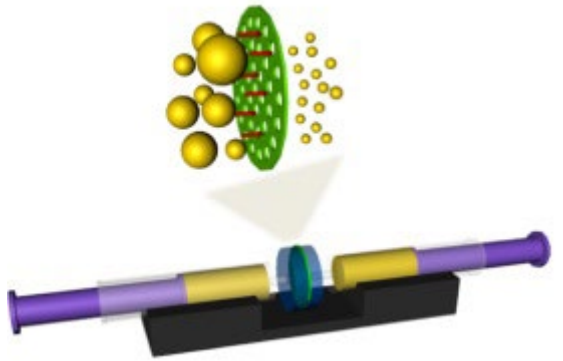
Deformability Index

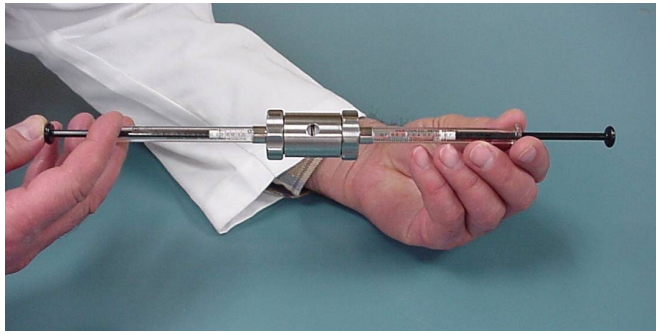
Evaluations of elasticity of deformable vesicles can be carried out by **extrusion measurement**. The vesicles are extruded through a polycarbonate membrane filter with a specific pore size at costant pressure.



The elasticity of the vesicles is expressed as in terms of deformability index according the following:

Deformability Index (DI)= $J(rv/rp)^2$

J= weight of dispersion extruded through the filter
rv= size of vesicles after extrusion
rp= pore size



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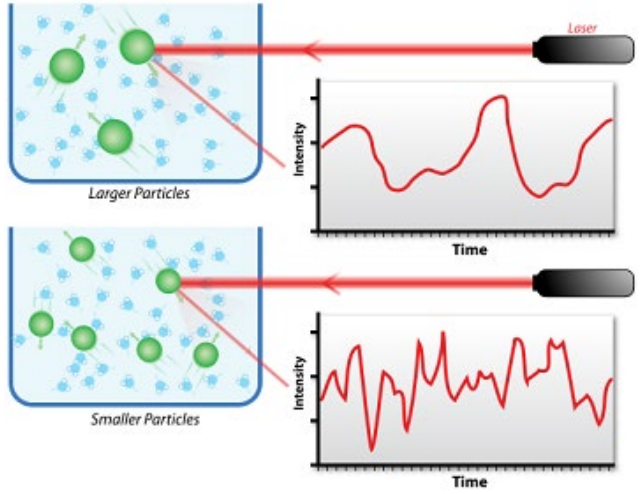
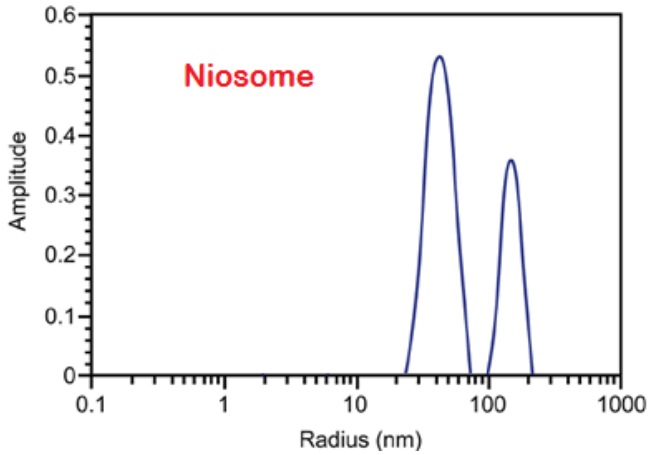
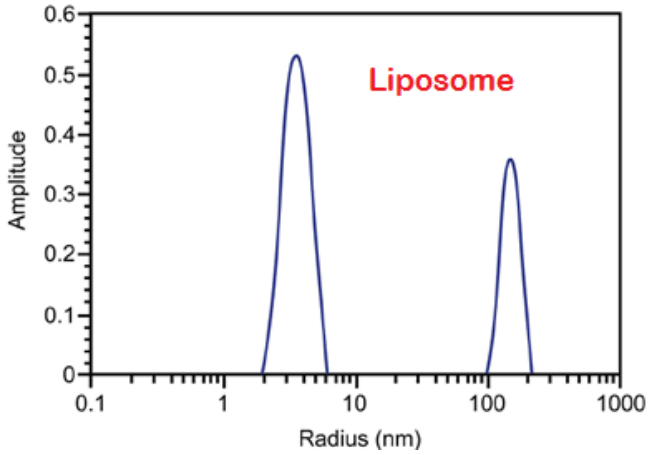
Deformability Index

As to determine the size of vesicles after extrusion (rv) ?

Particles suspended in liquids are in Brownian motion as a result of random collisions with solvent molecules. This motion causes particle diffusion through the medium. According to the Stokes-Einstein equation, the diffusion coefficient (D) is inversely proportional to the particle size (d). In this technique, the fluctuations in time of scattered light from the particles in Brownian motion are measured.







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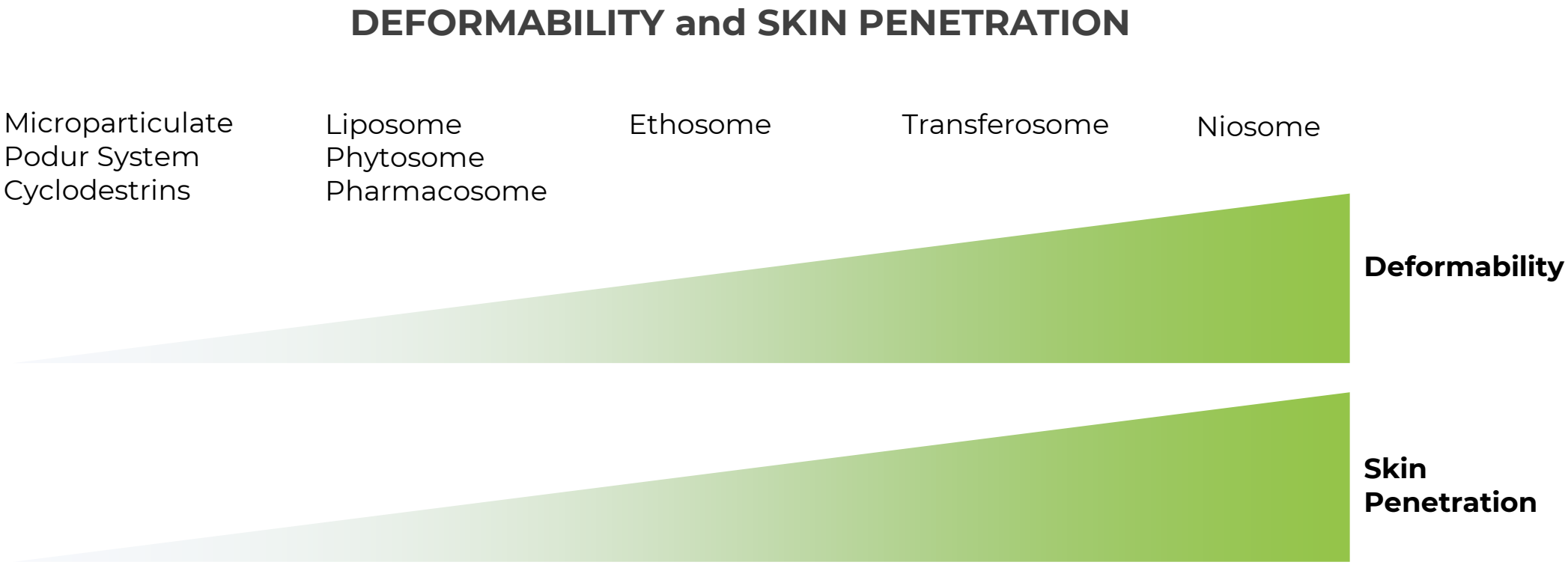
NIOSOME: Bilayer Elasticity



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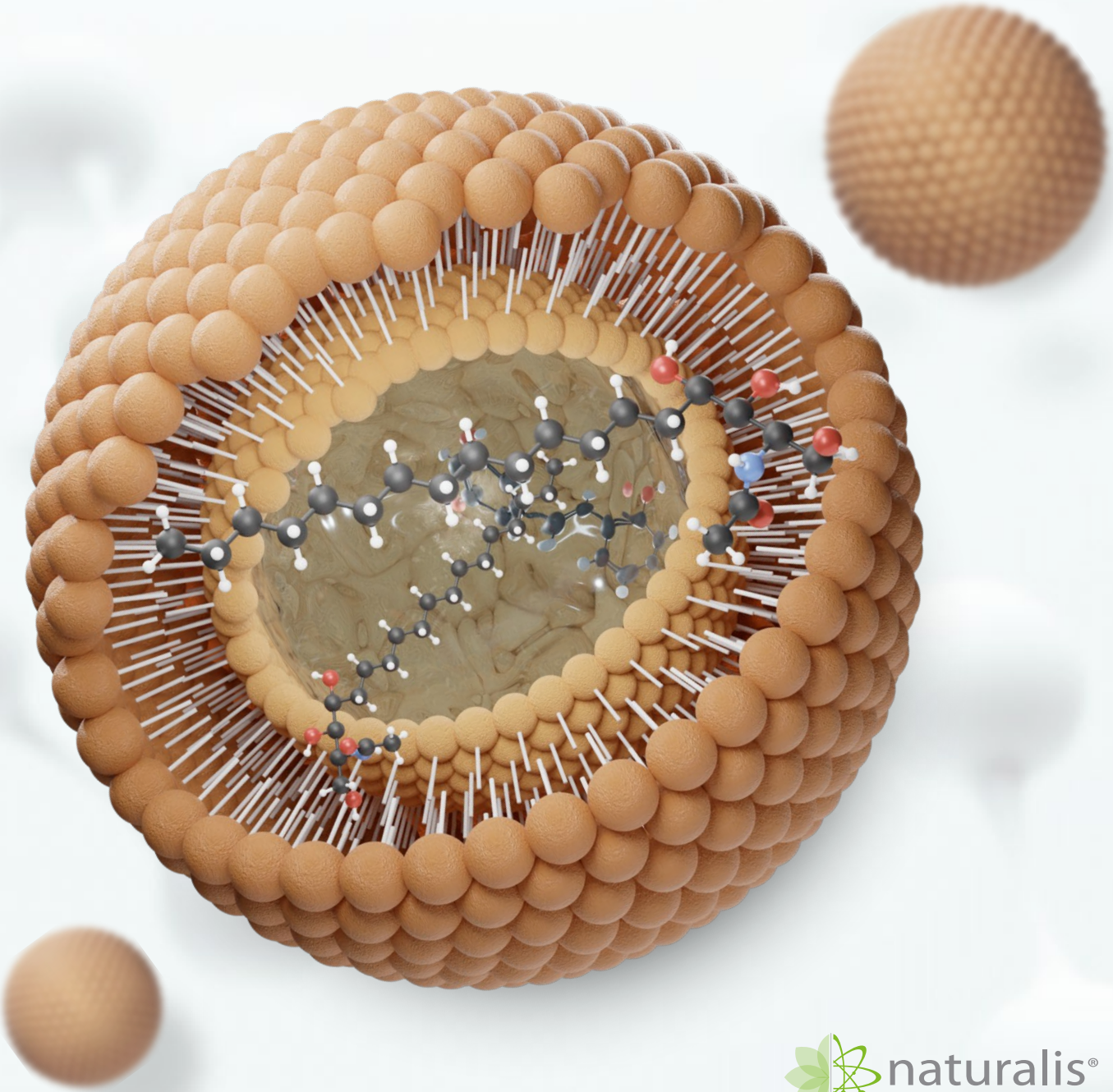
Mecchanism of skin penetration



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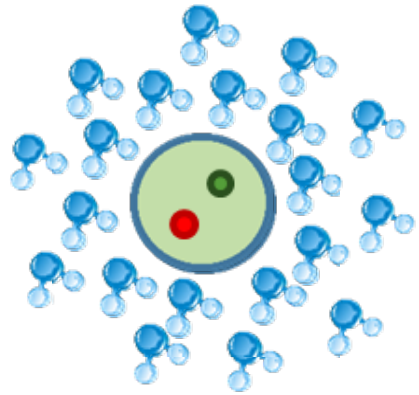
NIOSOME: Mechanism of skin penetration

The deformability of the vesicle is a **necessary but not sufficient condition** to ensure optimal penetration through the skin

The polarity and the ability of the vesicle to be solvated by a shell of water molecules is another important condition.



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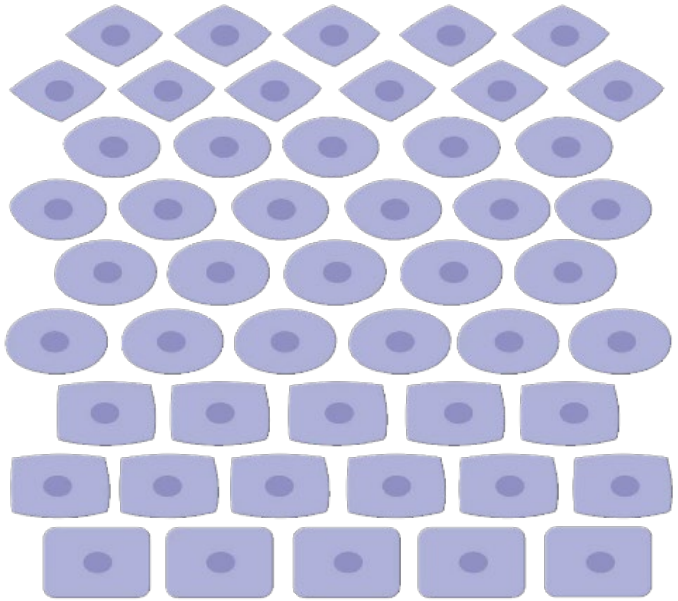
NIOSOME: Mechanism of skin penetration

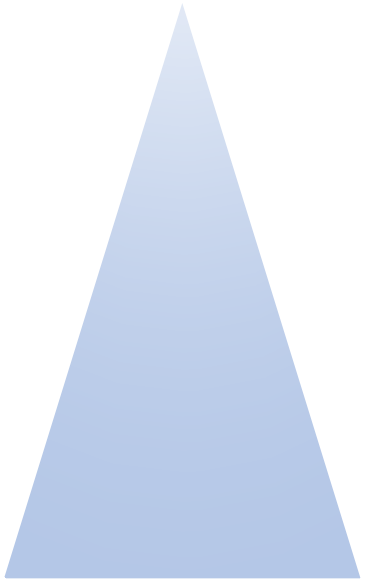
TEWL creates a decreasing gradient of water as we reach the superficial layers of the skin

Skin Upper Layers



Skin Deeper Layers

Low Water %



High Water %

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NIOSOME: The Osmotic Gradient

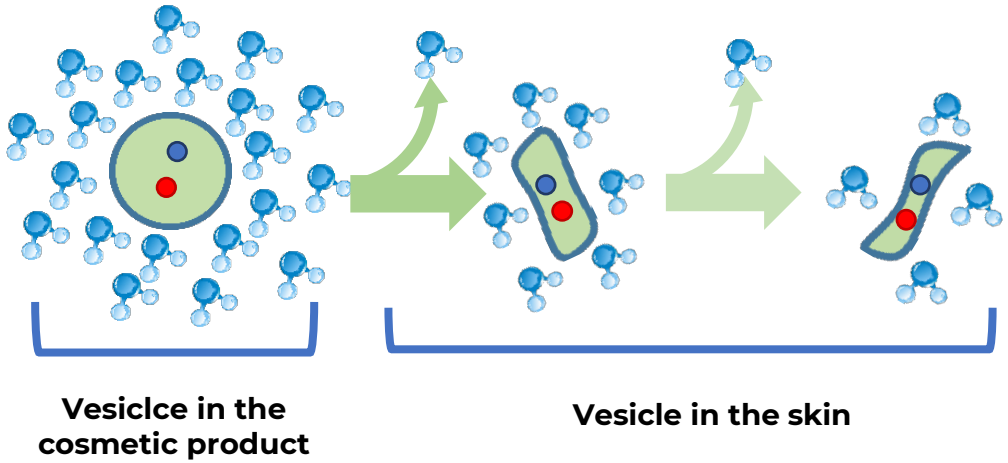
As **Niosome** vesicle **always seek to avoid dehydration.**

Vesicles applied on skin loses part of the water shell and for that tends to penetrate skin, squeezing through minute pores, and **migrate into the water-rich deeper layers to secure its adequate hydration.**

From the horny layer surface (relatively dry) to the wet viable tissues

Skin Penetration is driven by the water concentration gradient.

The transport of these elastic vesicles is thus **independent of concentration**



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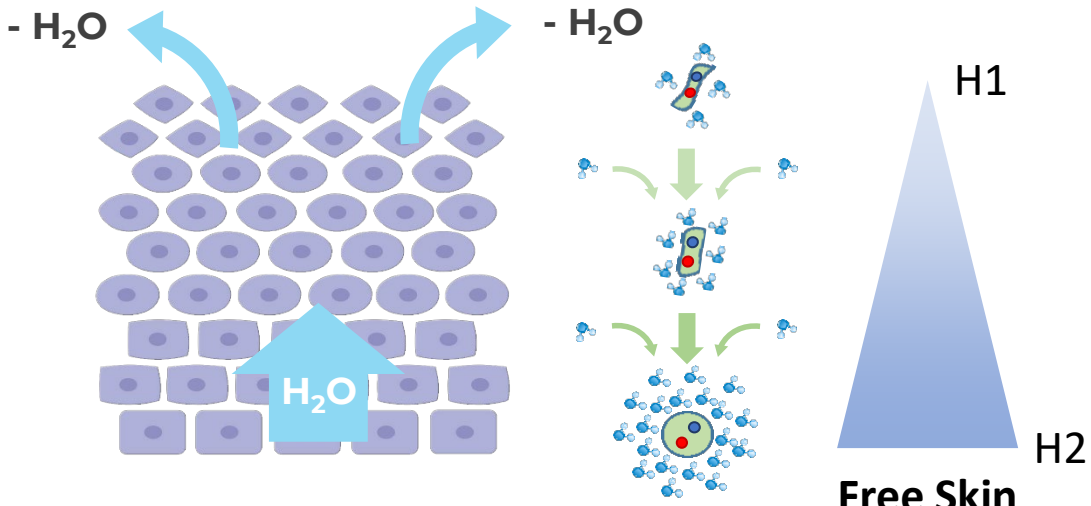
NIOSOME: The Osmotic Gradient

FREE SKIN

Water gradient is created by TEWL

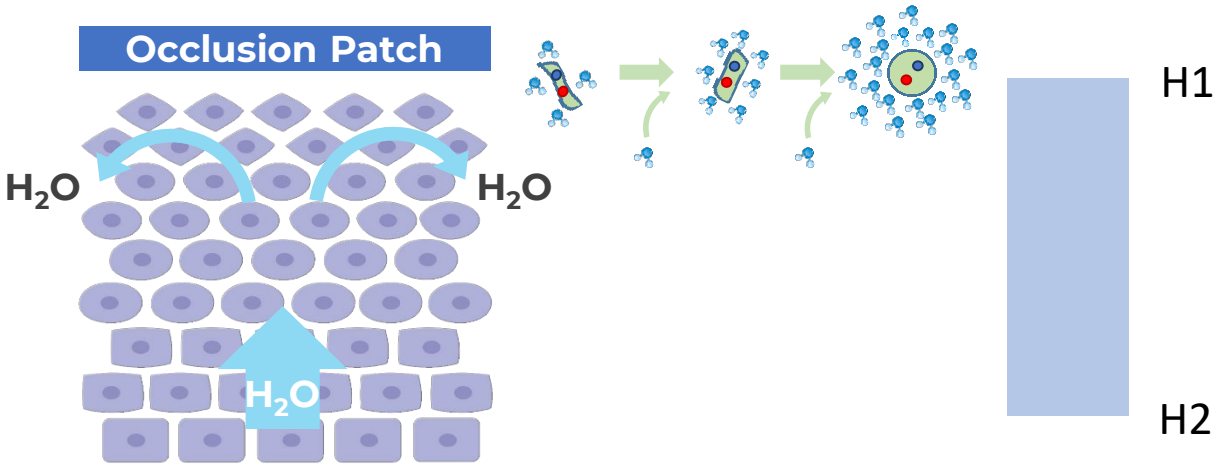


Dehydrated vesicles can squeeze between Stratum Corneum Gaps and penetrate deep in the skin actively attracted by the water gradien

Free Skin
Water Gradient
H2 >> H1

OCCLUDED SKIN

Penetration is blocked by Rapid Re-Hydration



Occluded Skin
Water Gradient
H2 = H1

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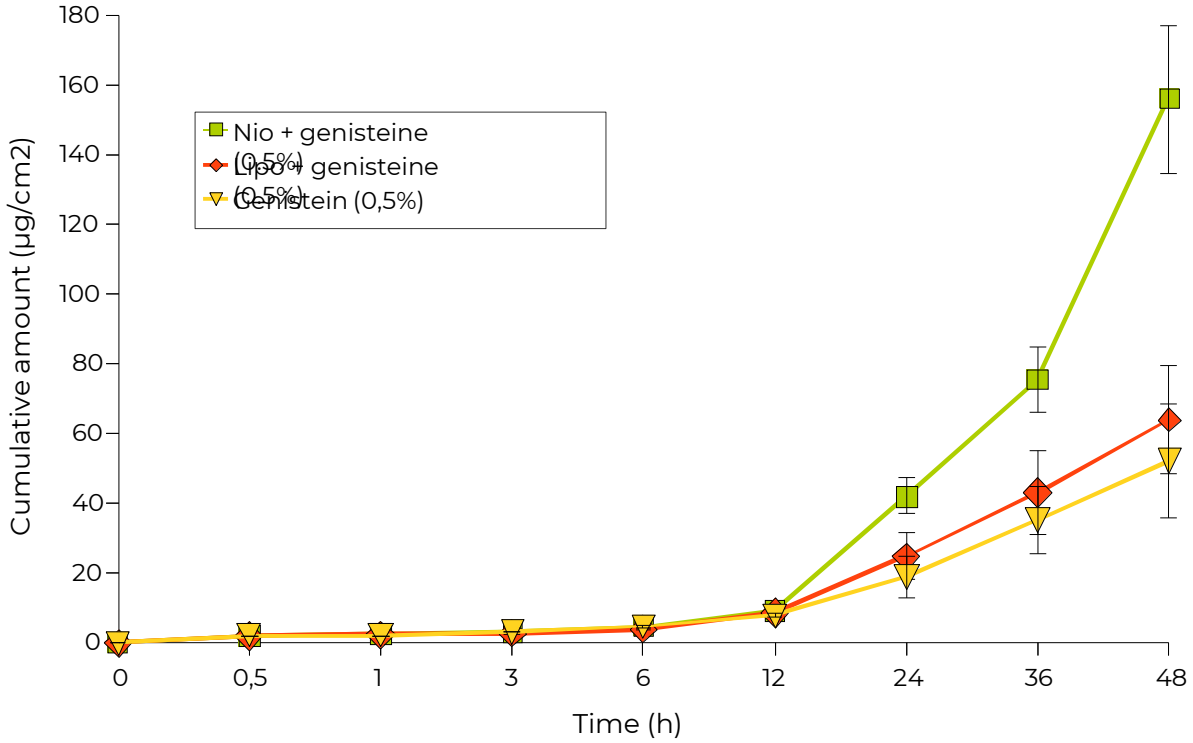
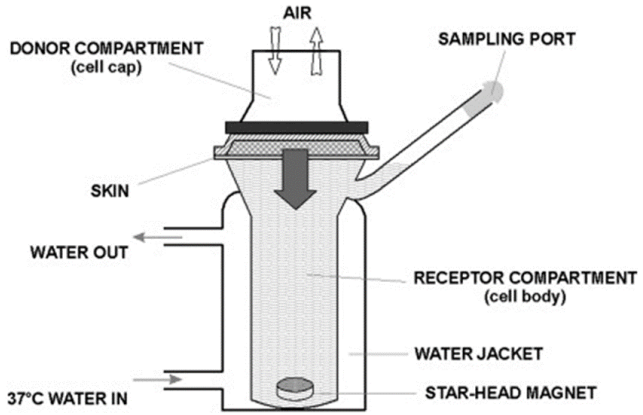
Skin Penetration Study

by Franz Diffusion Cell





Both Liposome and Niosome permeate Stratum Corneum

Formulation with Niosome demonstrated a higher skin permeation and stability after 48 h incubation compared to Liposomes

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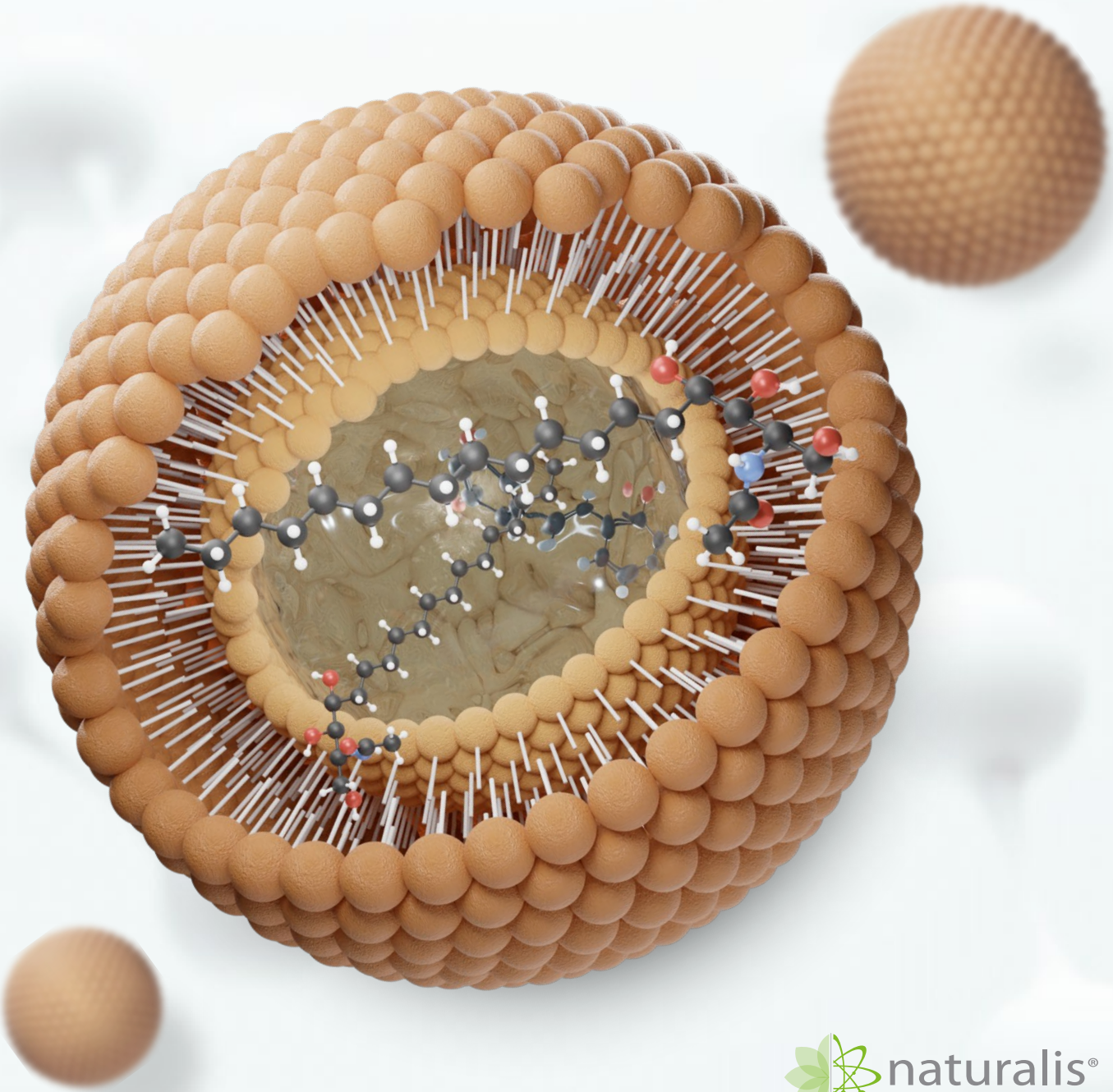
NIOSOME
Composition



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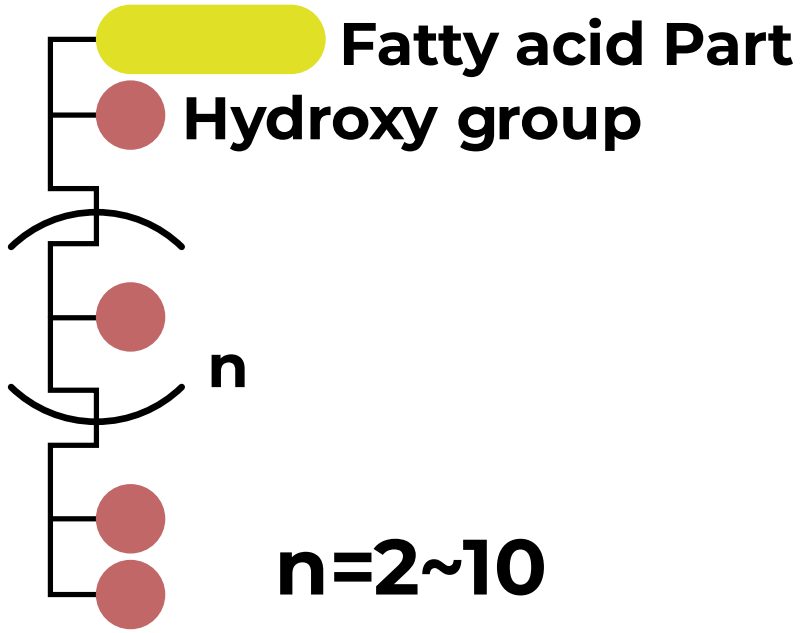
Elastic Niosome

Materials used in the preparation:

1) Polyglycerol esters
by chemical synthesis starting from glycerin and natural oils are used to form the bilayer

Polyglycerols-10
- Polyglyceryl-10 Palmitate (coconut oil)
- Polyglyceryl-10 Laurate (coconut oil)
- Polyglyceryl-10 Oleate (olive oil)

Polyglycerols-6
- Polyglyceryl-6 Esters (Oleate and Laurate)



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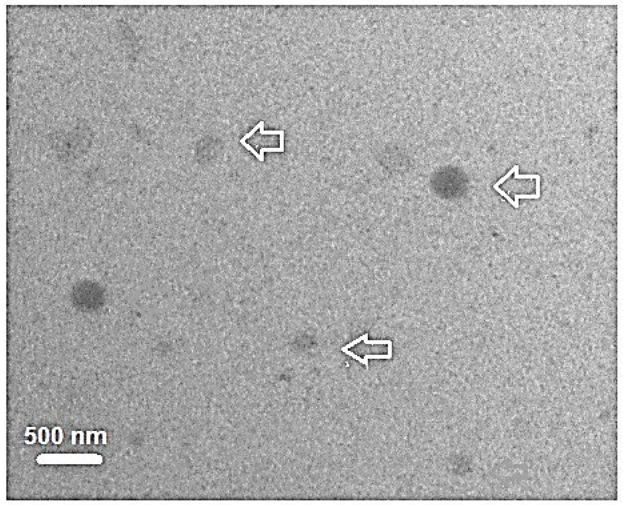
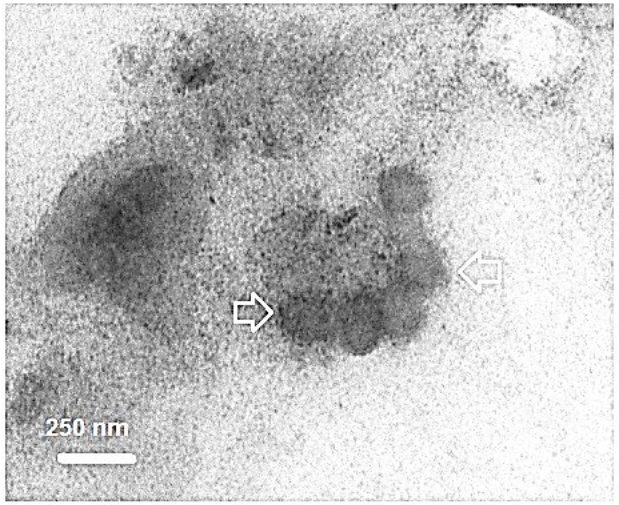
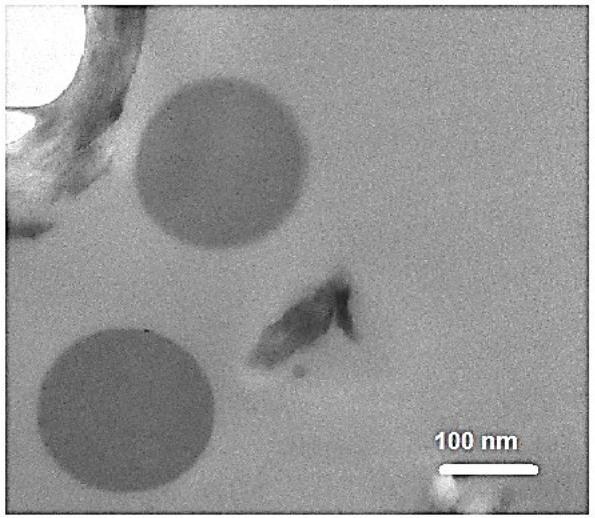
Elastic Niosome Observed by TEM Transmission Electron Microscopy







NIO-HMR vesicles dil. 1,00 % in water

Staining: Uranyl Acetate 1,0%

JEM-1200EX, JEOL Co., Tokyo, Japan
80000 x

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Thank you