New plant-based nanovesicles based on alkyl polyglucosides surfactants and β-sitosterol as topical delivery systems

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CONTROLLED RELEASE SOCIETY
CRS 2023 ANNUAL MEETING & EXPOSITION
JULY 24-28, 2023 Paris Hotel » Las Vegas, NV, USA
THE FUTURE OF DELIVERY SCIENCE

New plant-based nanovesicles based on alkyl polyglucosides surfactants and β-sitosterol as topical delivery systems

Marta Alcaina-Hernando, Ivana Malvacio, Ilaria Ferraboschi, Annalisa Bianchera, Silvia Pescina, Lidia Ferrer-Tasies, Santiago Sala, Cristina Sissa, Nora Ventosa and Alba Córdoba

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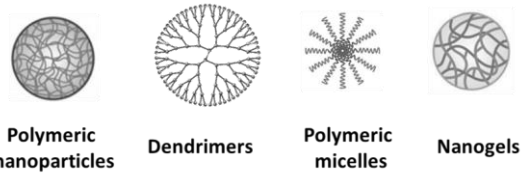
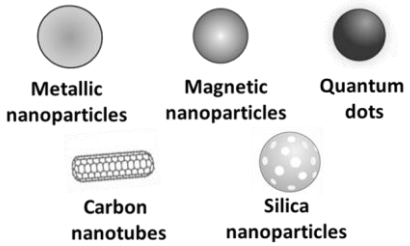
THERMODYNAMICALLY STABLE DELOS NANOVESICLES

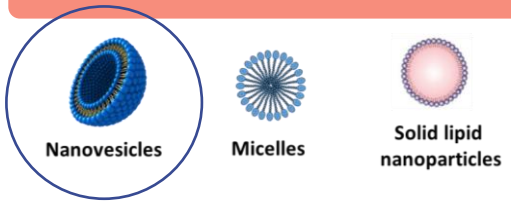
POLYMERIC-BASED NANOPARTICLES



INORGANIC-BASED NANOPARTICLES

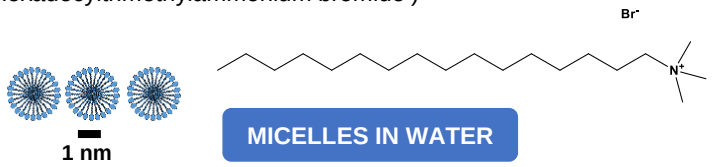


LIPID-BASED NANOPARTICLES

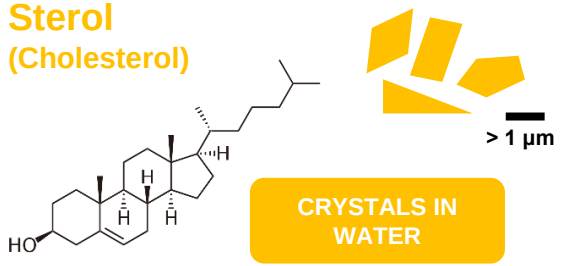


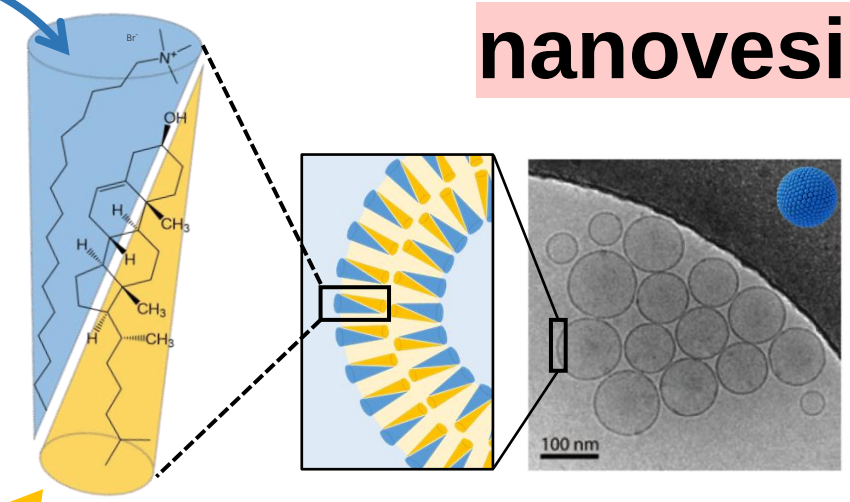
PROTEIN-BASED NANOPARTICLES

Quaternary ammonium surfactants
(CTAB)
(hexadecyltrimethylammonium bromide)



Sterol
(Cholesterol)





DELOS nanovesicles

- Nanosized and highly homogeneous
- Thermodynamically stable
- Targeted delivery
- Integrate large range of active molecules

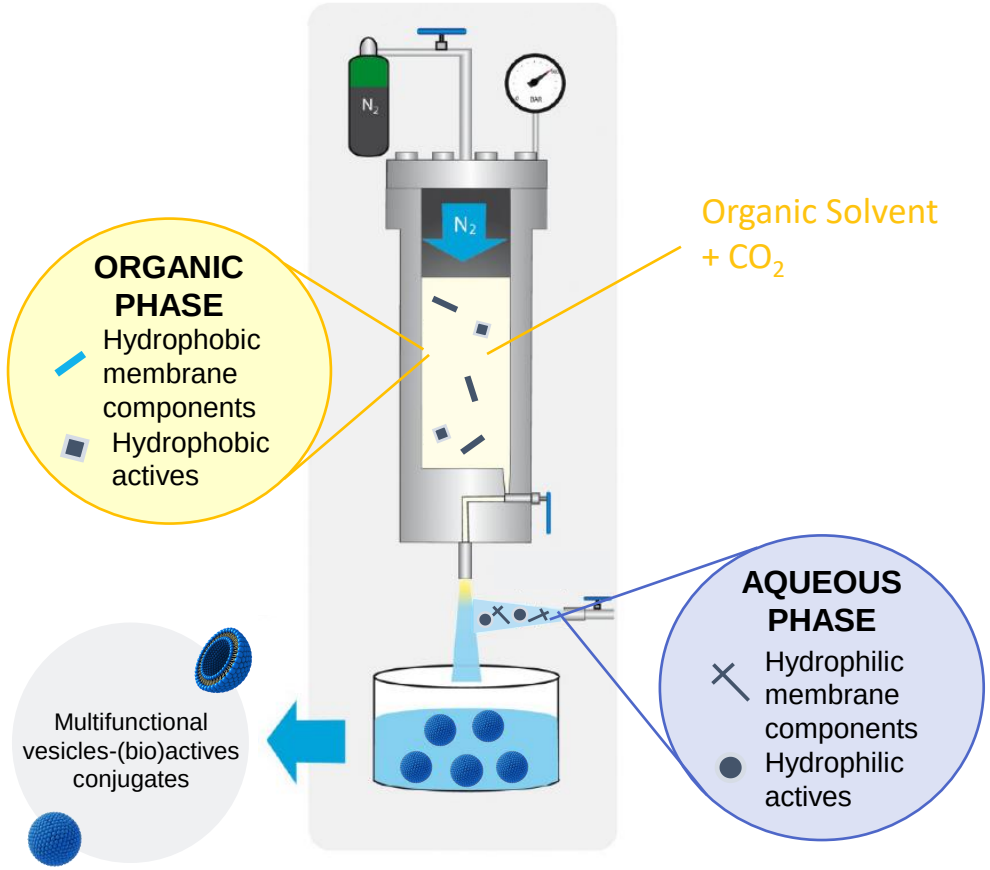
*N. Grimaldi, et al., Chem. Soc. Rev., **2016**, 45 (23), pp. 6520–6545.*
*M. Mitchell, et al.., Nature Reviews Drug Discovery, **2021**, 20(2), pp. 101-124.*
*L. Ferrer-Tasies et al., Langmuir, **2013**, 29, pp. 6519–6528*

ICMAB INSTITUT DE CIÈNCIA DE MATERIALS DE BARCELONA
EXCELENCIA SEVERO OCHOA CSIC

DELOS METHODOLOGY AS NANOVESICLE MANUFACTURING TECHNOLOGY

DELOS= Depressurization of an Expanded Liquid Organic Solution into aqueous solution

- ✓ **Green and sustainable platform**, based on compressed CO_2 as solvent.
- ✓ **One-step preparation** of vesicle-based conjugates.
- ✓ Obtention of **nanoscopic size** vesicles and with **great degree of unilamelarity**.
- ✓ **Scalable process**, demonstrated from lab (ml) to pilot plant (L).
- ✓ GMP pilot manufacturing under implementation
- ✓ Tested with success for **+50 actives:**



*M. Cano-Sarabia et al., Langmuir, **2008**, 24 (6), pp. 2433–2437*
*L. Ferrer-Tasies et al., Langmuir, **2013**, 29, pp. 6519–6528*

*N. Grimaldi, et al., Chem. Soc. Rev., **2016**, 45 (23), pp. 6520–6545.*
Granted patents: EP 1843836 ; US7754777 ; CA2566960 owned by Nanomol Technologies SL

NANOMOL TECHNOLOGIES

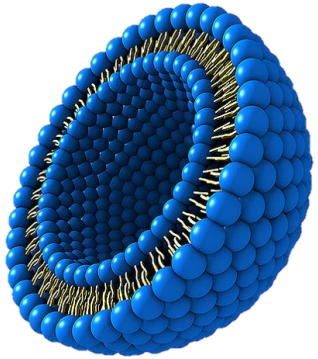
OBJECTIVE

Highly experienced in **pharmaceutical applications** using DELOS-NVs composed by *cholesterol* and *quaternary ammonium surfactants*

DESIRE TO INTRODUCE **DELOS TECHNOLOGY** TO **NEW MARKETS**

HEALTHCARE AND COSMETIC MARKET

DELOS Nanovesicles



Cholesterol : CTAB

Quaternary ammonium surfactants

× Limited use in cosmetics due to irritation effects

Cholesterol

✓ Totally allowed for cosmetic and pharmaceutical use

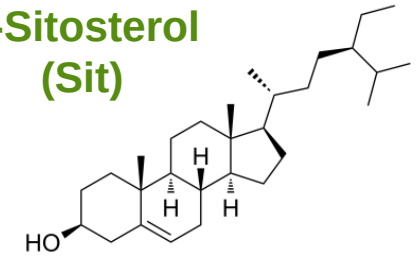
× Not accepted by vegan consumers (dermocosmetics) and patients (pharma)

OBJECTIVE

To develop novel plant-based DELOS vesicles using membrane components according to market needs, and to evaluate their potential as new delivery systems, loading actives of interest for topical administration

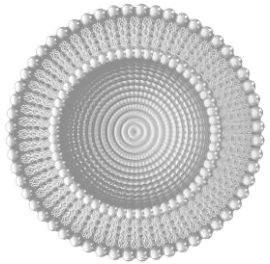
NEW SIT:LGL VESICLES USING COMPONENTS FROM VEGETAL ORIGIN

β-Sitosterol (Sit)

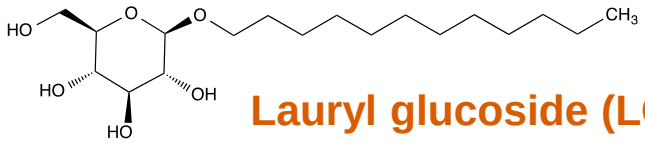


Sterol from vegetal origin

✓ Biocompatible ✓ Biodegradable



Neutral vesicles
Sit:LGL



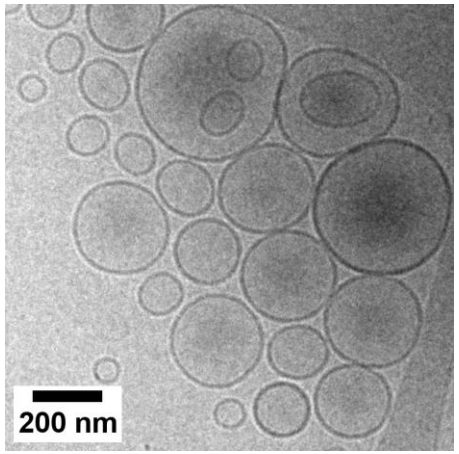
Lauryl glucoside (LGL)

✓ Biocompatible
✓ Biodegradable

Sugar-based surfactant of the alkyl polyglucosides (APGs) family

Sit:LGL

Membrane components molar ratio = 1:1
[membrane components] = 5 mg/mL
Dispersant media = H_2O/EtOH 15% (v/v)



Technique: Cryo TEM

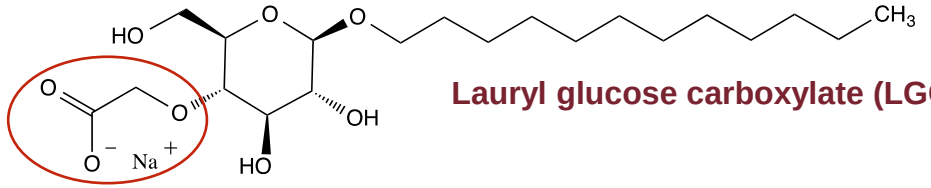
Size = 217 ± 11 nm
PdI = 0.22 ± 0.01
ζ-Pot = -42 ± 3 mV

Technique: Dynamic Light Scattering (n=3)

Long colloidal stability (> 2 years)

USE OF **ADDITIVES**

TUNING OF THE SURFACE CHARGE



Lauryl glucose carboxylate (LGC)

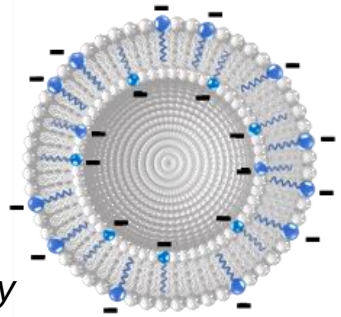
- Integrate a larger range of actives (by electrostatic interaction)
- Change the physicochemical properties of the vesicles

Patent application filed in August 2022 (EP22382751.0)

TUNING OF SIT:LGL VESICLES

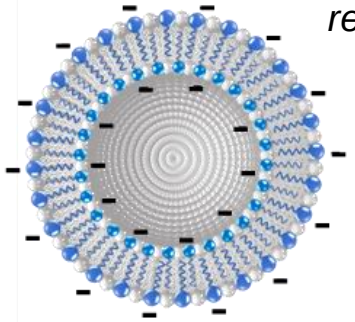
Screening of LGL:LGC molar ratio

Low quantity of LGC



1:0.8:0.2

Negative vesicles
Sit:LGL:LGC



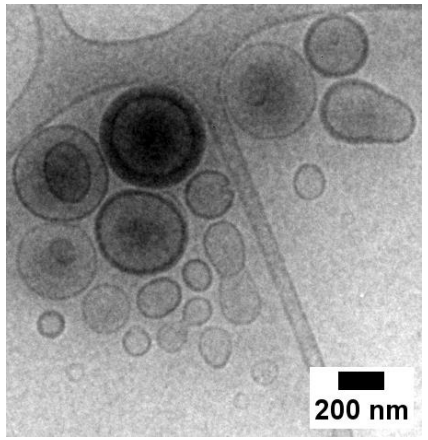
1:0:1

LGL completely replaced by LGC

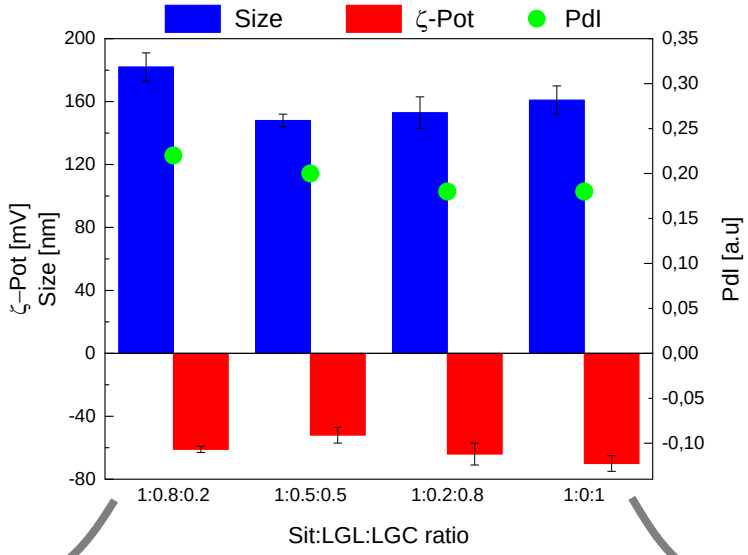
Sit:LGL:LGC

[membrane components] = 3 mg/mL
Dispersant media = H_2O/EtOH 15% (v/v)

Sit:LGL:LGC (1:0.8:0.2)

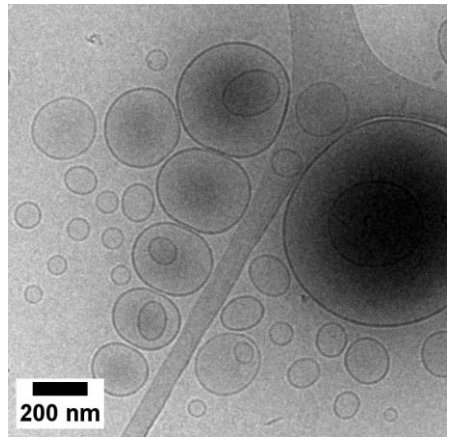


Technique: Cryo TEM



Technique: Dynamic Light Scattering (n=3)

Sit:LGL:LGC (1:0:1)

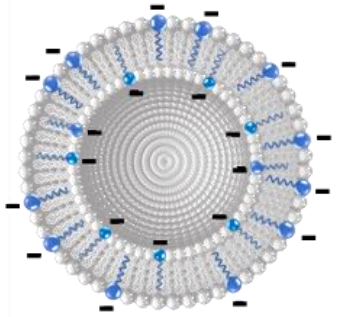


Technique: Cryo TEM

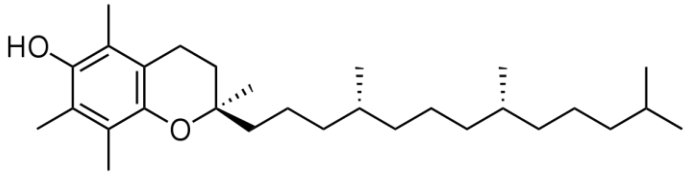
Patent application filed in August 2022 (EP22382751.0)

INTEGRATION OF α-TOCOPHEROL IN SIT:LGL:LGC vesicles

Negative vesicle
Sit:LGL:LGC
(1:0.8:0.2)



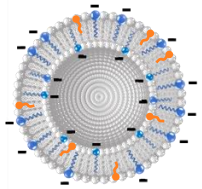
α-Tocopherol (TCP)



- Type of Vitamine E
- Antioxidant (free-radical scavenger)
- Lipophilic molecule

Sit:LGL:LGC

Membrane components molar ratio = 1:0.8:0.2
[membrane components] = 3 mg/mL
Dispersant media = H_2O/EtOH 15% (v/v)
[TCP] = 0.75 mg/mL



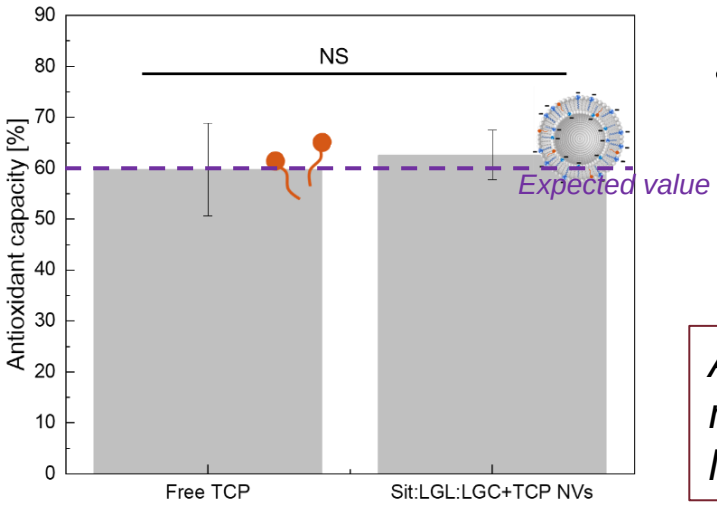
Size = 131 ± 4 nm
PdI = 0.19 ± 0.01
ζ-Pot = -41 ± 1 mV

Technique: Dynamic Light Scattering (n=3)

Entrapment Efficiency = 49 ± 12 %

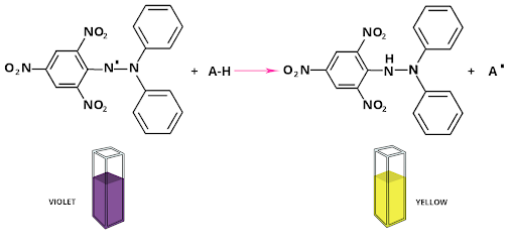
Technique: UV-Vis spectroscopy (n=3)
*EE% = (TCP in filtered sample/TCP total)*100*

Antioxidant capacity: DPPH assay



Technique: UV-Vis spectroscopy (n=2)

2,2-Diphenyl-1-picrylhydrazyl



Antioxidant capacity is maintained after TCP loading in DELOS vesicles

✓ Additional actives have been successfully integrated.

Patent application filed in August 2022 (EP22382751.0)

IN VITRO SKIN COMPATIBILITY: NON-IRRITANT DELIVERY SYSTEMS

How to validate the safety of nanoformulations for topical administration?

SKIN IRRITATION TESTS → **Reconstructed Human Epidermis (RHE)**, 3D *in vitro* models of human skin (commercially available)

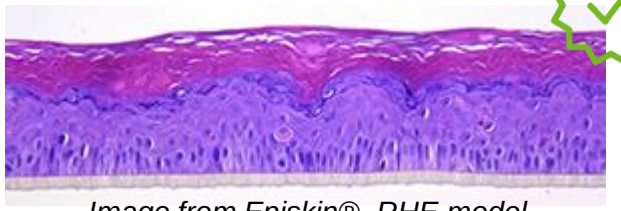
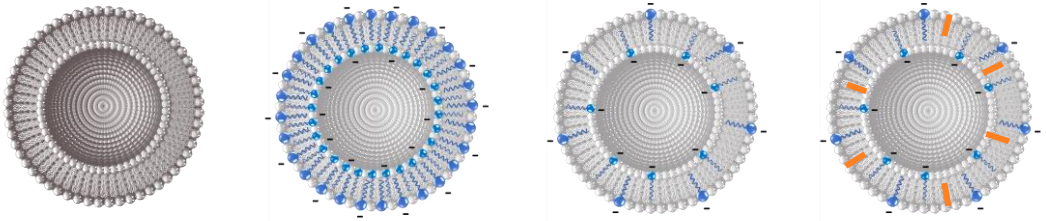


Image from Episkin®, RHE model

Samples analyzed:

4 DELOS nanoformulations



Sit:LGL (1:1)

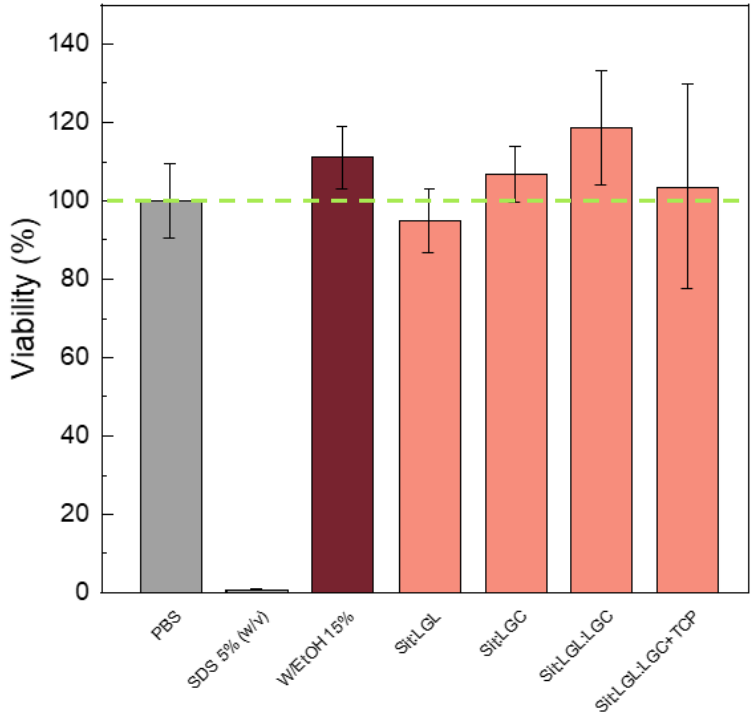
Sit:LGC (1:1)

Sit:LGL:LGC (1:0.8:0.2)

Sit:LGL:LGC + Tocopherol (VitE)

Negative control: PBS (100% of viability)
Positive control: SDS 5% w/v in PBS (no viability)

Dispersant media
Water/EtOH 15% (v/v)



Technique: MTT assay (n=3)

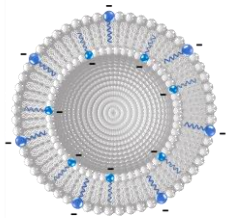
All formulations are biocompatible with the skin, non-irritant effects are seen.

SAFE FORMULATIONS FOR TOPICAL ADMINISTRATION

OECD (2015), Test Nº. 439: In Vitro Skin Irritation: Reconstructed Human Epidermis Test Method, OECD Publishing, Paris

EX VIVO SKIN PERMEATION: Fluorescent payload delivered to the EPIDERMIS

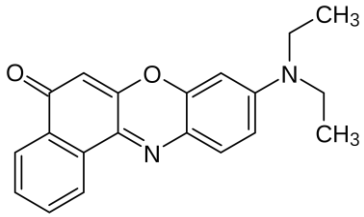
- Study permeation by fluorescence using Nile Red (NR) with Franz cells and multiphoton microscopy.



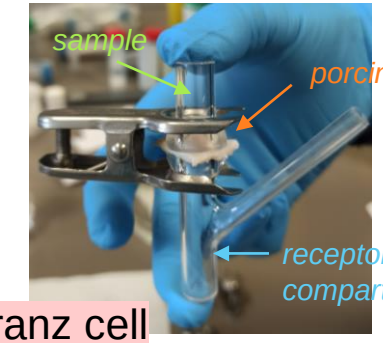
Sit:LGL:LGC
(1:0.8:0.2)

Dispersant media = Water/EtOH 15% (v/v)

Nile Red



Theoretical loading: 50 µM

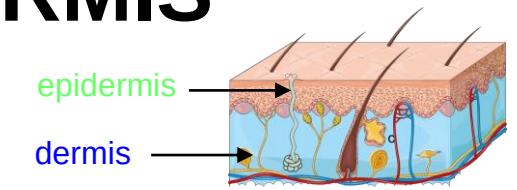


Franz cell

Analysis time = 6 h

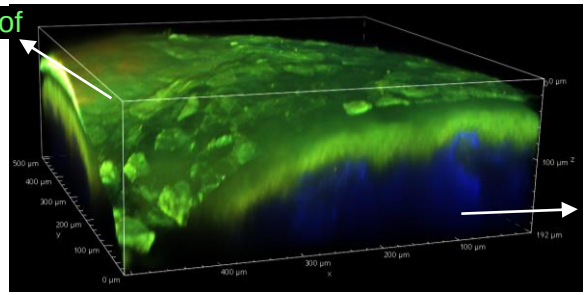
Permeation of NR to epidermis, without reaching dermis.

SUITABLE FOR LOCAL TOPICAL ADMINISTRATION



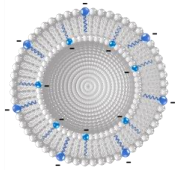
Autoflorescence of epidermis cells

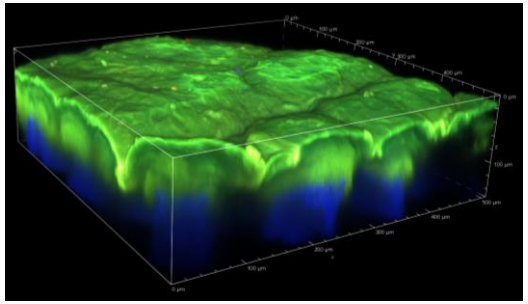
Dispersant media
Water/EtOH 15% (v/v)



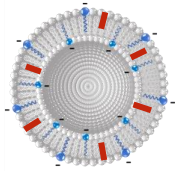
Collagen present in dermis

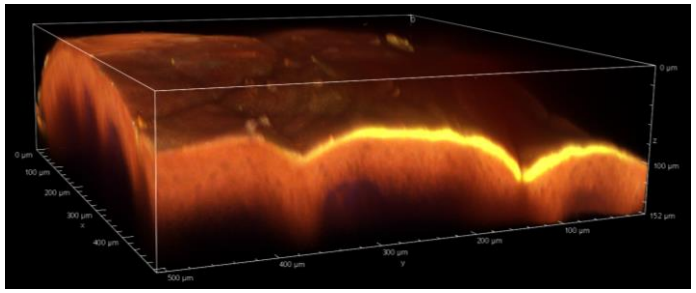
Blank vesicles
(Sit:LGL:LGC)





NR loaded vesicles
(Sit:LGL:LGC + NR)

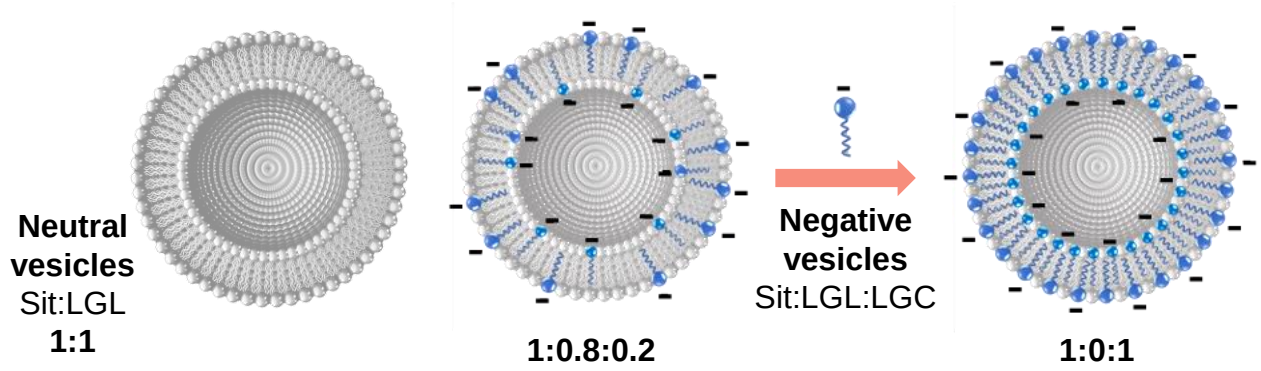




TAKE HOME MESSAGES

- ✓ We report for the first time a tunable **delivery platform** using **plant-based membrane ingredients that self-assemble in stable small vesicles**.

  (*Patent filed in August 2022)*



- ✓ Different kind of **actives, such as tocopherol, can be loaded in the Sit:LGL based vesicles** maintaining their function.

- ✓ The new delivery platform is **biocompatible and non-irritant** with the skin as demonstrated using an *in vitro 3D epidermal* model.

- ✓ These novel DELOS vesicles seem to help **actives to permeate through epidermis without reaching the dermis,** as shown in the *ex vivo* models using skin explants.

- ✓ Thus, this new delivery platform covers an unmet need for vegan patients and consumers in pharma and cosmetics.

Thank you for your attention!

Any questions?

NANOMOL TECHNOLOGIES

nanomol bio
NANOSTRUCTURED MOLECULAR MATERIALS FOR BIOMEDICINE

ICMAB
INSTITUT DE CIÈNCIA DE MATERIALS DE BARCELONA

EXCELENCIA SEVERO OCHOA · CSIC

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Bioingeniería, Biomateriales y Nanomedicina

UNIVERSITÀ DI PARMA

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ADDRes Lab, Department of Food and Drug

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Financial support

DOCTORATS INDUSTRIALS
Aliança de talent!

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DIN2019-010396
PID2019-105622RDB-100

Micro4Nano

European Commission

MARIE CURIE ACTIONS

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