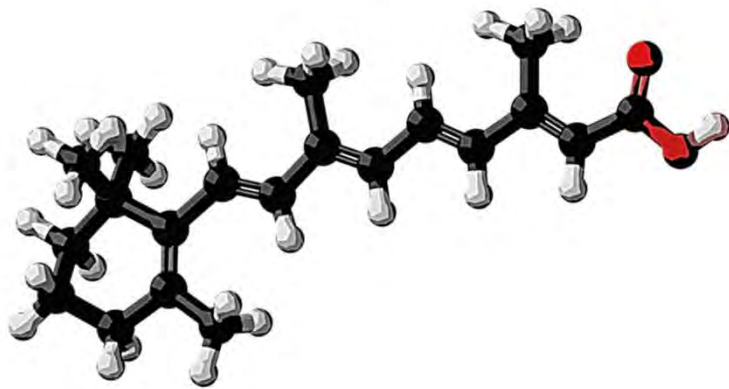


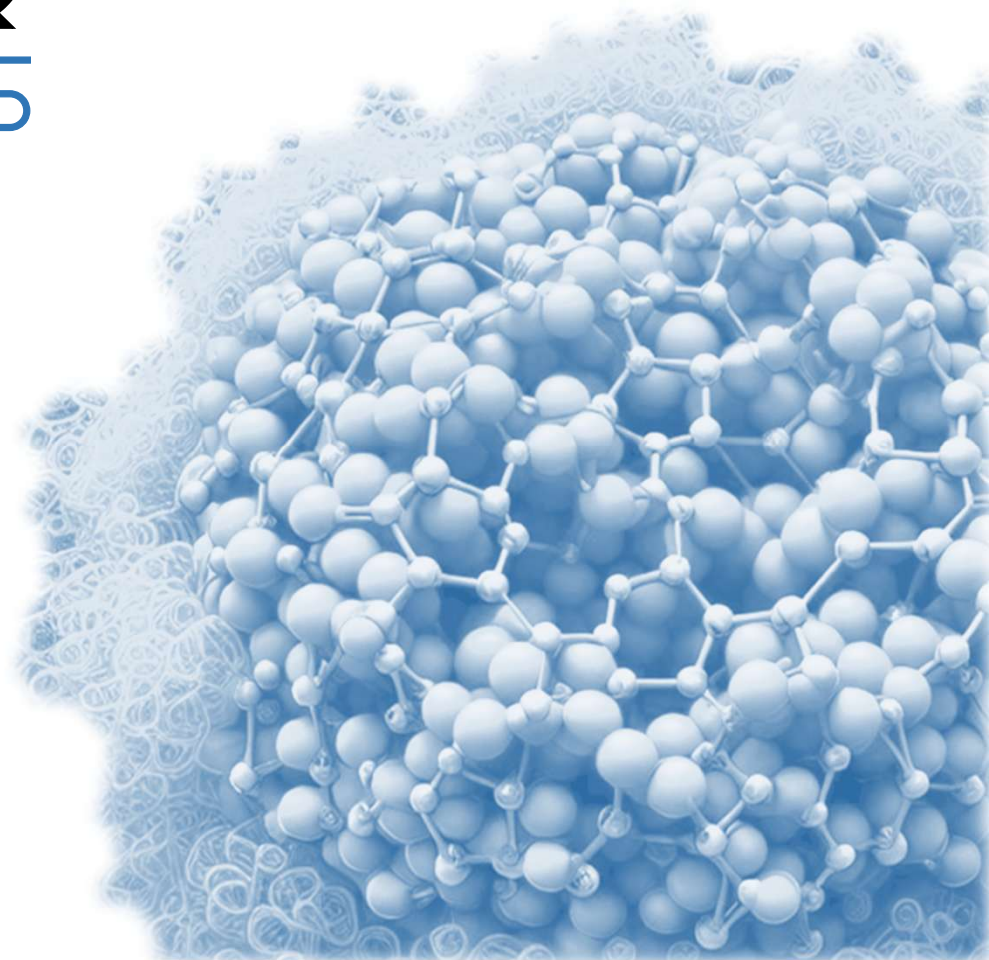
LIPODISQ[®]

RETINOLIDS



Curiosity, Innovation.

Malvern Cosmeceutics Ltd, December 2024

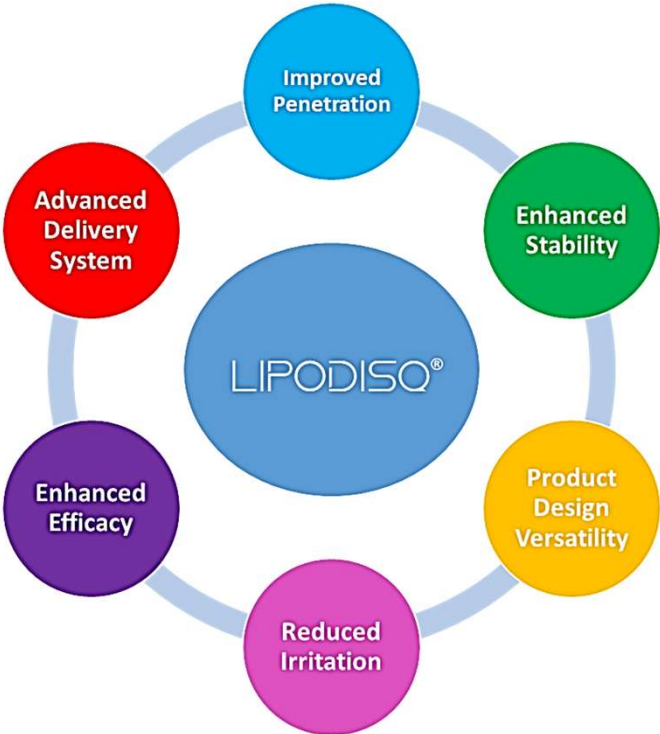


LIPODISQ[®] RETINOIDS

Introduction

Retinoids, particularly **Retinol**, are among the most extensively studied ingredients within personal care and dermatology. Clinical evaluations consistently demonstrate their effectiveness in reducing fine lines and wrinkles, boosting collagen and elastin production, and diminishing hyperpigmentation and photo-damage. Despite these benefits, formulation challenges often arise due to Retinol's instability, as it degrades when exposed to light and air. Additionally, its poor water solubility confines its use primarily to oily, non-aqueous formulations.

Lipodisq[®] **Retinoids** represent a significant step forward in skincare technology, addressing the key limitations of traditional retinol while enhancing its performance and user experience. These attributes make Lipodisq[®] based retinoids a preferred choice for individuals seeking effective, gentle, and scientifically advanced skincare solutions.



Curiosity, Innovation.

LIPODISQ[®] RETINOIDS

Retinoids are a class of compounds related to vitamin A and its metabolites, in addition to synthetic derivatives, that are characterised by their binding to nuclear receptors (retinoic acid receptors [RARs], and retinoid X receptors [RXRs]), which in-turn regulate gene transcription.

This affects:

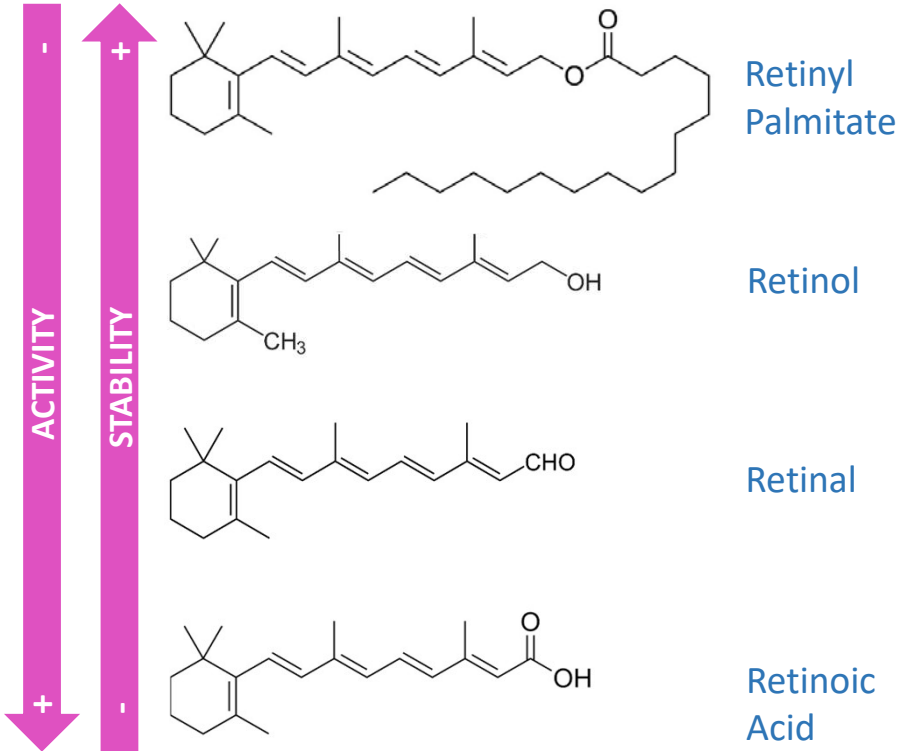
- Keratinocyte differentiation
- Collagen production
- Regulation of sebum production

Leading to:

- Inhibition of matrix metalloproteinases (MMPs), reducing skin aging
- Anti-inflammatory effects, beneficial for conditions like acne and psoriasis

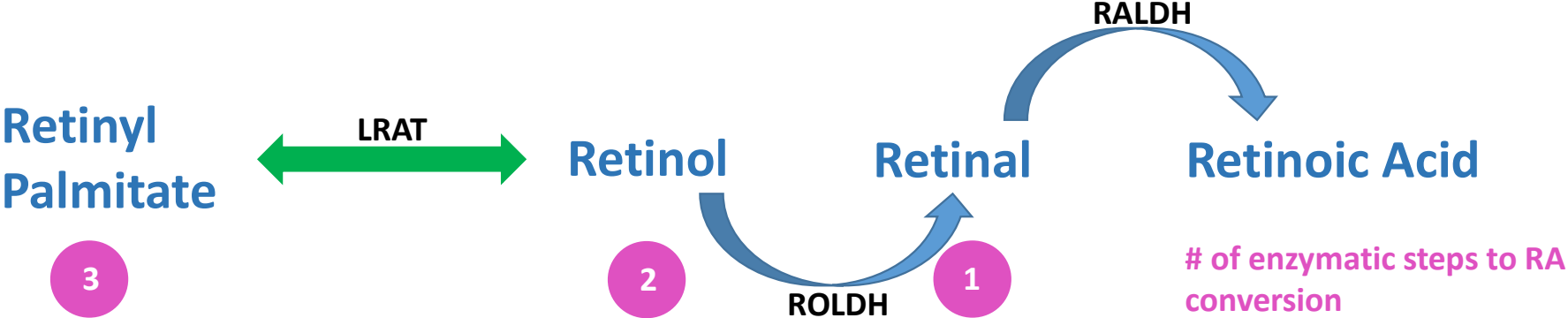
The main retinoids involved in the metabolic pathway are: **retinol**, **retinal** (retinaldehyde), **retinoic acid** (tretinoin), and associated ester, **retinyl palmitate**.

Structure = Activity



The metabolism of retinoids in the skin is a complex process involving multiple steps, enzymes and binding proteins. Following topical application and transdermal absorption a homeostatic balance is maintained within the epidermis by activation of the enzymes involved in the metabolic pathway. **Retinol** is enzymatically oxidised (through the removal of hydrogen) by a specific isoenzyme: alcohol dehydrogenase (ROLDH), to produce **retinal** (retinaldehyde); this is subsequently oxidised (addition of oxygen) by the retinal-specific enzyme: aldehyde dehydrogenase (RALDH), to produce **retinoic acid**. Retinoic acid can then be transported intracellularly to induce cellular activation.

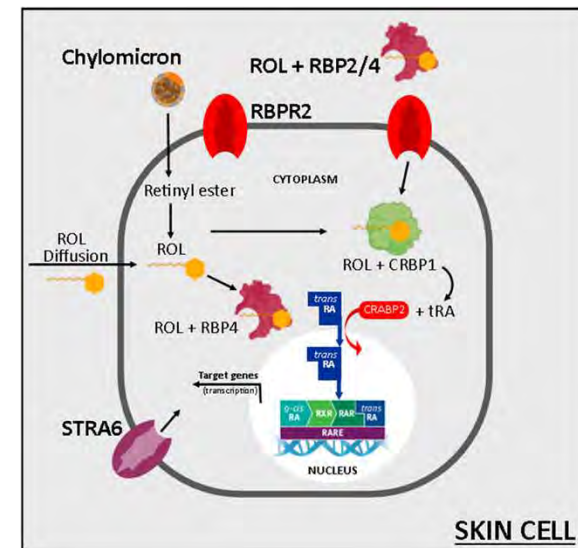
Retinol can also be converted by localised lecithin retinol acyltransferase (LRAT) to **retinyl esters**. These can then be mobilised systemically and form part of a retinol homeostasis mechanism; while retinol esters from the systemic circulation can also feed back into the dermal pathways to effect cellular differentiation and skin health.



Intracellular activation:

Retinoids do not exist independently in the body and are always bound to specific carrier proteins for stability and transport. In circulation, retinoids are primarily bound to retinol-binding proteins, RBP2 and RBP4. These complexes allow retinoids to enter cells by binding to transmembrane receptors e.g. retinol-binding protein 4 receptor 2 (RBPR2) or stimulated by retinoic acid receptor 6 (STRA6), facilitating the internalization of retinol. Intracellularly, retinol transport relies on the carrier protein: cellular retinol-binding protein 2 (CRBP2), which helps mobilize retinol from extra-dermal sources. Once inside the cell, retinol can be enzymatically converted into retinyl esters by lecithin retinol acyltransferase (LRAT) in the endoplasmic reticulum. These esters are then packaged into chylomicrons, enabling their release into the bloodstream for storage or use in other tissues.

Intracellular retinol binds to cellular retinol-binding protein 1 (CRBP1) and is converted into either 11-cis retinal (for visual function) or all-trans retinoic acid (t-RA). The t-RA, crucial for cosmetic applications, is carried by cellular retinoic acid-binding protein 2 (CRABP2) into the nucleus. There, it binds to retinoic acid receptors (RAR) and retinoid X receptors (RXR), which interact with retinoic acid response elements (RAREs) to activate gene transcription. This process promotes cellular activation and dermal improvements observed in clinical applications.



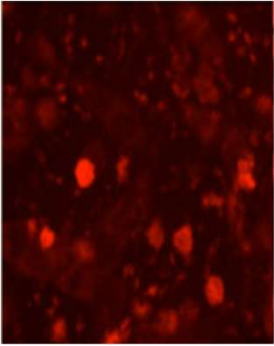
*Graphic: Intracellular metabolism of retinoids. Adapted from Ask *et al.*, Nutrients 202115

Delivery System: Lipodisq[®]

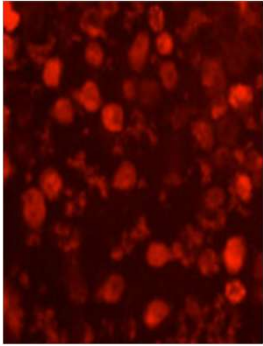
For this complex homeostatic process to be influenced by topical application of retinoids it is imperative to ensure stable and sustained delivery. Retinoids are never unbound in the body due to their high activity and instability; they are always transported by protein chaperones, which ensure their targeted delivery into cells and subsequently into the nucleus where they exert their effect. Similarly, **Lipodisq[®]** functions as a stabilising carrier structure, enhancing cellular delivery and achieving an effective dosage at the site of action.

Lipodisq[®]: Enhanced Intracellular Delivery

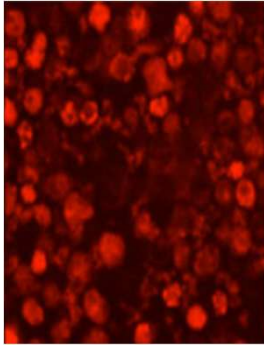
In vitro study, University of Oxford (2014), assessing intracellular uptake and nuclear targeting of anti-cancer agent, Doxorubicin. Study carried out over a 24hr incubation period, 200x below IC50 of Doxorubicin (DOX). Lipodisq[®] formulations demonstrated superior cellular uptake, including nuclear delivery.



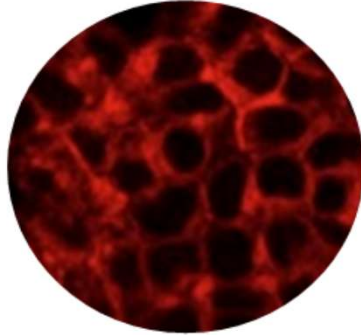
DOX Control Solution



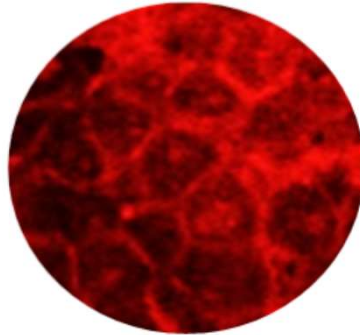
DOX Lipodisq[®] (Membrane 1)



DOX Lipodisq[®] (Membrane 2)



DOX Control Solution



DOX Lipodisq[®] (Membrane 2)

LIPODISQ® RETINOIDS

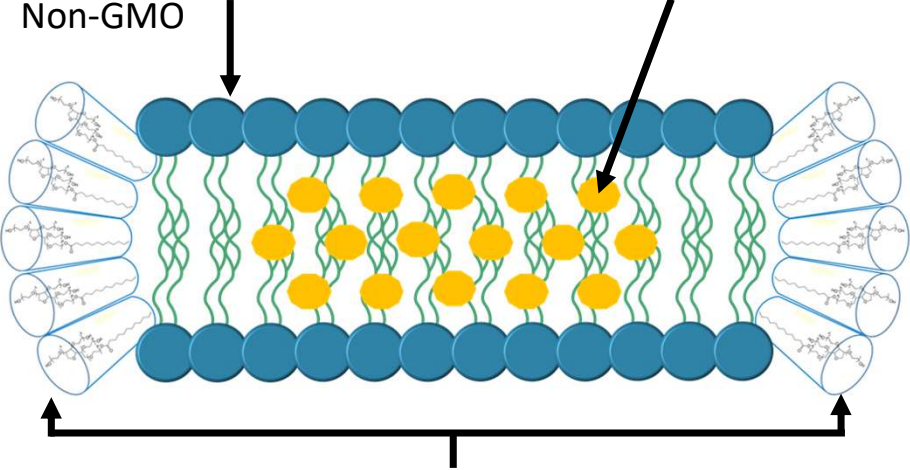
Personal Care Active Delivery:

The centre of a Lipodisq® is composed of a phospholipid bilayer with a defined high content of phosphatidylcholine. The lipophilic area is primarily made up of fatty acid tails of phospholipids, which typically have a high log P value, ranging from 3 to 8 or higher, reflecting strong lipophilicity. This provides an optimal environment in which to solubilise and encapsulate **lipophilic/hydrophobic active agents**, such as **Retinol**, **Retinal** and **Retinoic Acid**, rendering them **water soluble** and isolating them from the surrounding aqueous environment.

Lipodisq®: Active Delivery

Phospholipid Membrane:
Phosphatidylcholine rich,
sourced from Soy.
Non-GMO

Retinoid Active:
Encapsulated within
hydrophobic core



Surfactant Chaperone

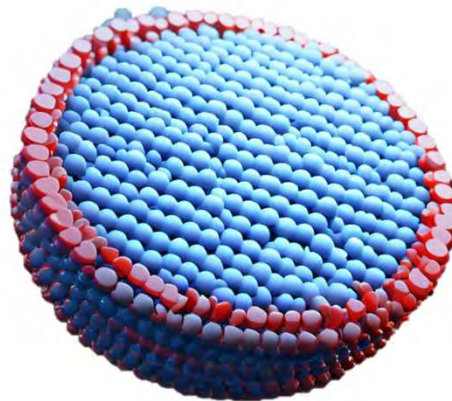
Standard Grade: Polysorbate 20, RSPO MBAL Source

Green Grade: Sucrose Ester, Natural Origin & Enhanced Biodegradability

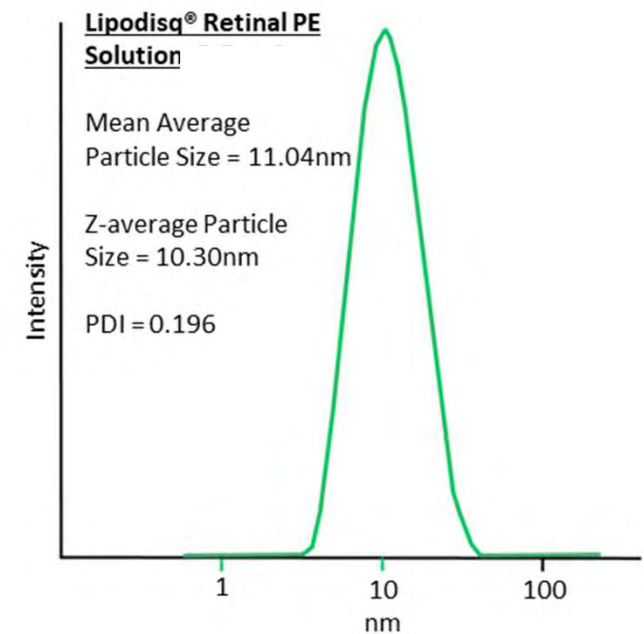
LIPODISQ[®] RETINOIDS

Key Features:

- Solubilises **Retinoids** in water
- Improves stability of **Retinoids**
- Small particle size (~10 – 40nm)
- Enables production of clear aqueous gels/solutions, suitable for inclusion in conventional creams/serums
- Stable in aqueous solution upon dilution
- Facilitates skin absorption
- Sustained release, avoiding 'dose dumping' of **Retinoids**, reducing irritation events



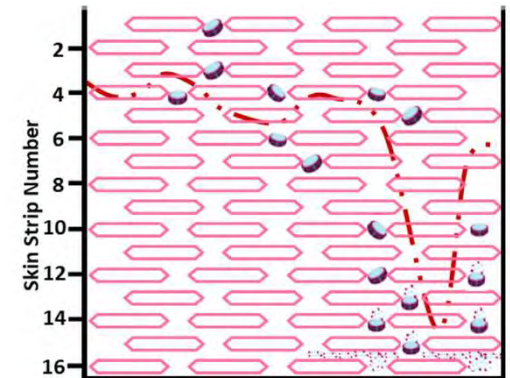
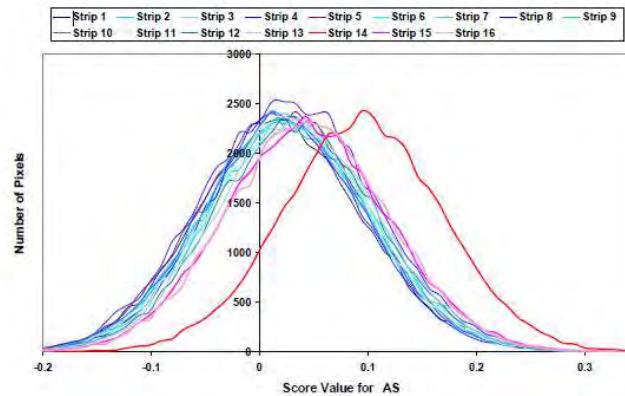
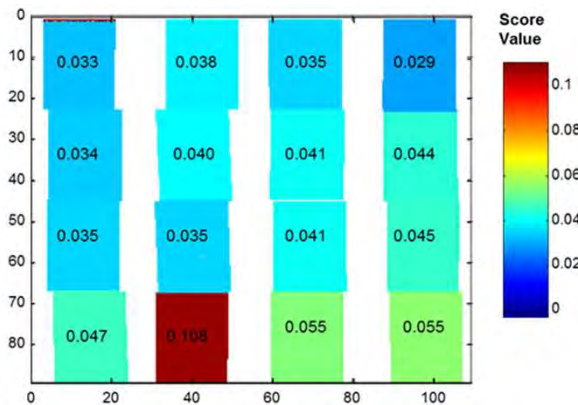
Lipodisq[®]: Active Delivery



Transdermal Penetration:

The small size of Lipodisq[®] particles enables them to penetrate the upper layer of the epidermis, the stratum corneum. As a result of a high loading capacity for oil soluble agents, Lipodisq[®] have a far greater potential for delivering significant amounts of active agents, as compared to much larger particle systems such as liposomes/niosomes.

In vivo study: Lipodisq[®] formulation containing a marker dye is applied to the outer layer of the skin for 20 minutes, the skin is washed and 20mm² adhesive tape used to repeatedly strip layers of *stratum corneum*, the dye removed on each strip is then analysed spectrophotometrically using a near-infrared technique to assess the presence of the marker dye.



Results: Lipodisq[®] formulation facilitates penetration of the dye to the lower layers of the stratum corneum >16 consecutive skin strips, effectively overcoming the barrier function of the skin.

LIPODISQ[®] RETINOIDS

Stabilising, Protection

Active Stabilisation:

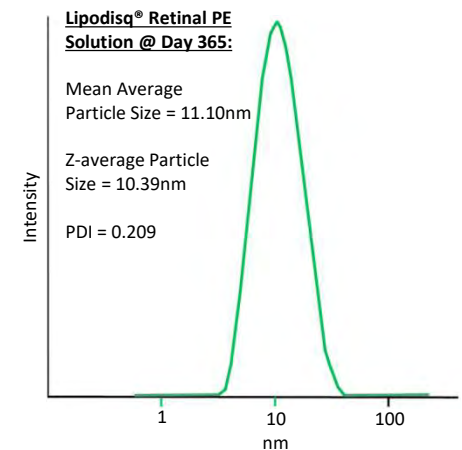
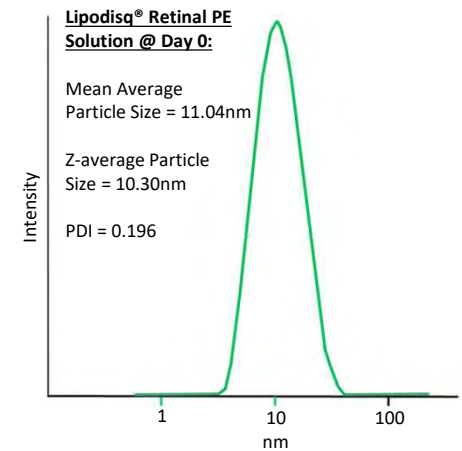
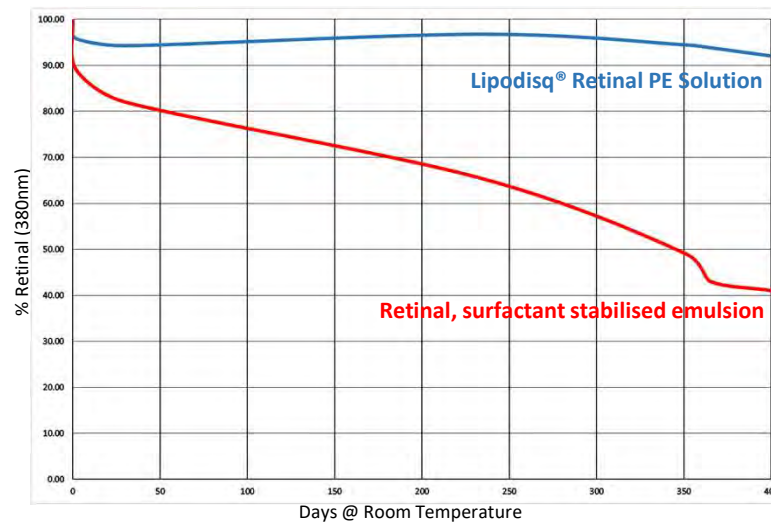
Lipodisq[®] constructs protect the active agent from oxidation and degradation by encapsulating hydrophobic or amphiphilic active agents within its phospholipid membrane and also renders them water soluble. Lipodisq[®] formulated actives exhibit superior stability, in concentrated formats as well as finished products, vs conventional product offerings. Providing both consumer and product manufacturers with stable and efficacious products for the duration of their use.

Case Study:

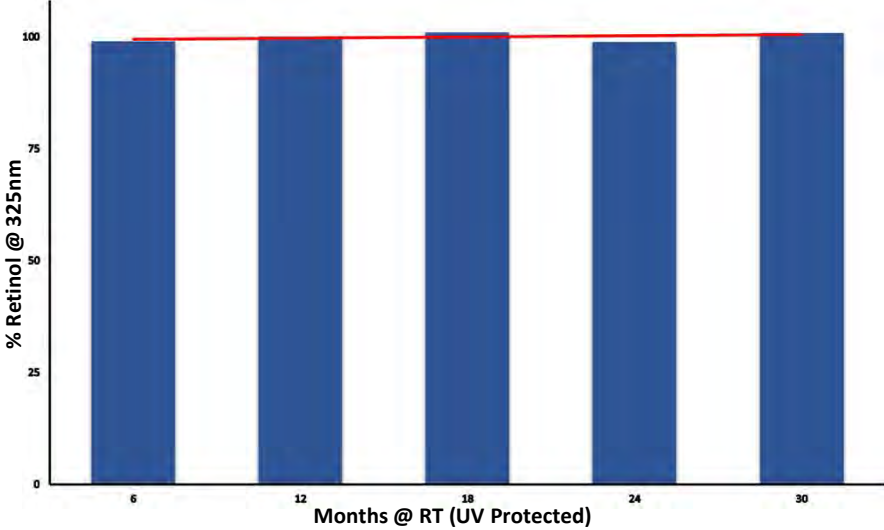
Lipodisq[®] Retinal PE Solution

After >365 days storage at room temperature, 93.80% Retinal content retained within Lipodisq[®] sample (UV-Vis Spectrophotometer measurement @ λ 380nm) compared to 40.00% Retinal content retained within a conventional formulation format.

Particle stability and size characteristics remain unchanged.



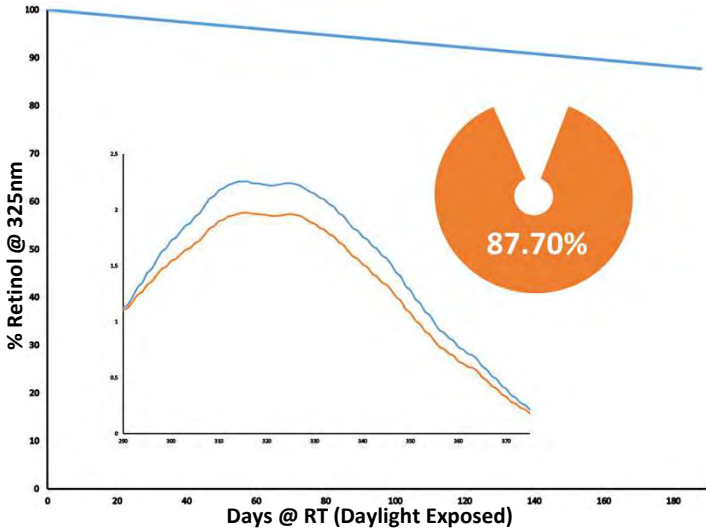
LIPODISQ® RETINOIDS



Case Study, Formulation Stability: Lipodisq® Retinol PE Solution

Real-time assessment (UV analytical method) of 5% Lipodisq® Retinol PE Solution in commercialised aqueous gel formulation demonstrates superior stabilising properties, **>95%** Retinol content retained after 30 months storage at room temperature (opaque packaging).

Stabilising, Protection



Case Study, UV Stability: Lipodisq® Retinol PE Solution

After **>180 days** storage at room temperature and **exposure to daylight**, **87.70%** Retinol content retained within Lipodisq® sample (UV-Vis Spectrophotometer measurement @ λ 325nm).

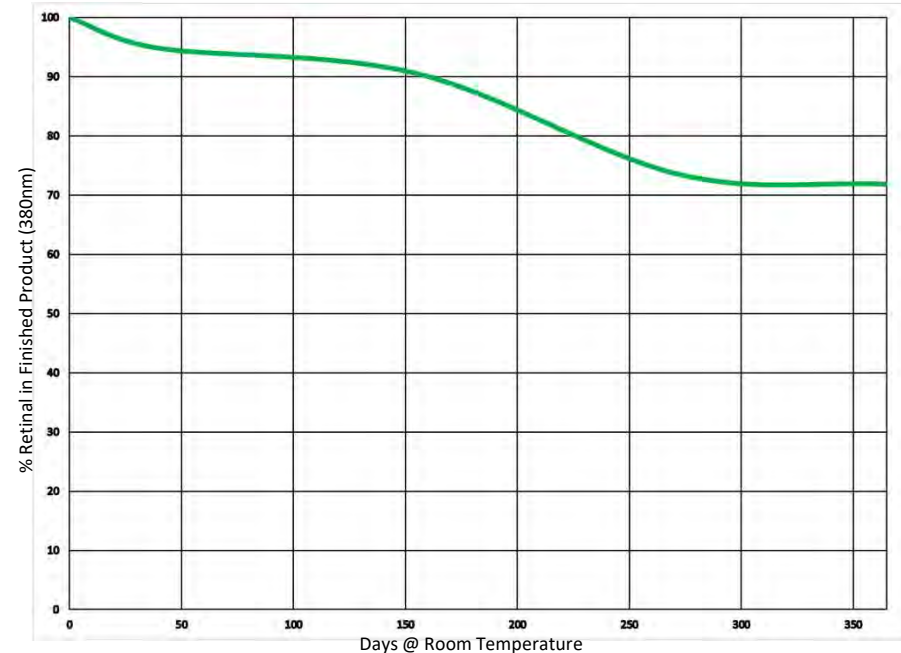
Formulation Stable:

Lipodisq[®] solutions for Personal Care, are compatible with most commonly used excipients. Lipodisq[®] are suitable for inclusion within aqueous gels, oil-in-water emulsion/creams, hydrogel patches and mask technologies. Stabilising performance of Lipodisq[®] encapsulated actives is retained during manufacturing and processing of finished products and throughout a product's shelf-life.

Case Study:

Aqueous gel containing Lipodisq[®] Retinal PE Solution (Retinal content 0.05%)

Post production processing and >365 days storage at room temperature, 72% Retinal content retained in the finished product (UV-Vis Spectrophotometer measurement @ λ 380nm). No Secondary anti-oxidants or stabilisers have been included.



LIPODISQ[®] RETINOIDS

Powerful Antioxidant Performance

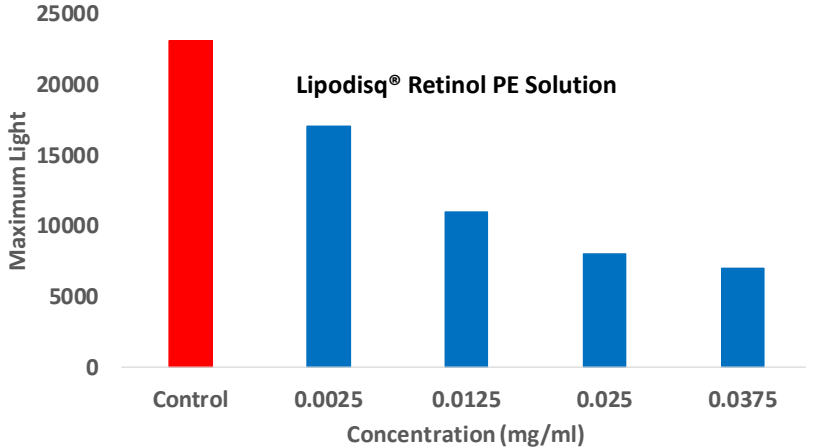
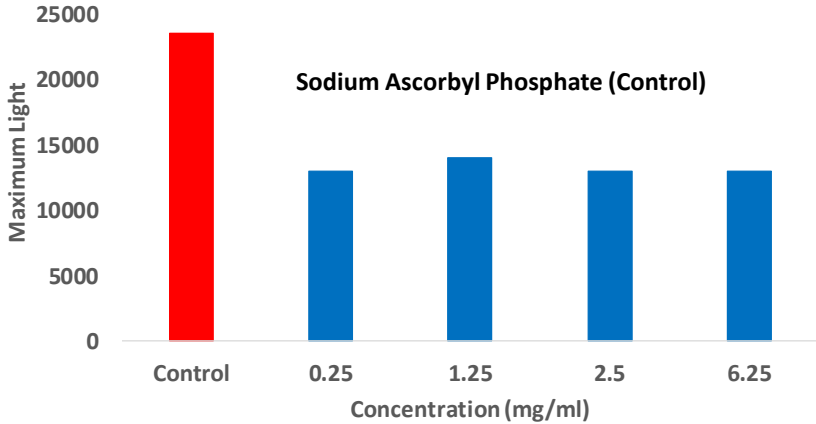
Antioxidant (AO) activity of a solution containing Lipodisq[®] Retinol PE Solution was assessed using ABEL[®] Antioxidant Assay and results compared directly to a reference solution containing sodium ascorbyl phosphate (SAP) which is regularly used in personal care products as an effective antioxidant.

Results: ABEL[®] assessment confirmed the antioxidant activity of SAP over a concentration range of 0.25-6.25mg/ml.

Lipodisq[®] Retinol PE Solution tested over a concentration range of **0.0025-0.0375mg/ml** showed an approximate **20 fold increase in antioxidant activity as compared to SAP.**

Lipodisq[®] Retinol PE Solution is able to deliver powerful antioxidant performance at low concentrations of use.

20x AO Performance



LIPODISQ[®] RETINOIDS

In vivo Efficacy

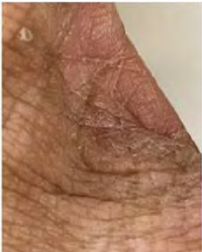
Example Consumer Product Efficacy:



Nip + Fab

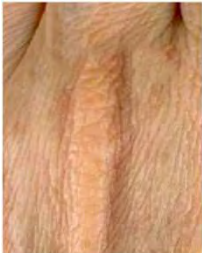
Retinol Fix Blemish Gel Treatment 10%

[10% Lipodisq[®] Retinol PE Solution] Acne Care



Before

After 30 Days



Before

After 30 Days

RE:ERTH Pte Ltd

RE:ERTH

Rejuvenating Hand Treatment

[Lipodisq[®] Retinol PE Solution] Hyperpigmentation, Anti-ageing

LIPODISQ[®] RETINOIDS

In vivo Efficacy

Example Consumer Product Efficacy:



Day 0



Day 28

Anti-wrinkle Gel Formulation
(Custom Finished Product, Malvern Cosmeceutics Ltd)
[5% Lipodisq Retinol PE Solution]

LIPODISQ® RETINOIDS

Lipodisq® Products

PERSONAL CARE

Product	INCI	Key Features
Lipodisq® Retinol PE Solution	<i>Aqua, Polysorbate 20, Retinol, Lecithin, Phenoxyethanol, Ethylhexylglycerin, BHT, BHA</i>	Anti-ageing, skin lightening/brightening, stimulates collagen production, thickens dermal layer and has a plumping effect.
Lipodisq® Green Retinol Solution	<i>Aqua, Sucrose ester, Retinol, Lecithin, Undecane, Pentylene glycol, Caprylyl glycol, Tridecane, Bioflavonoids, Tocopherol</i>	Anti-ageing, skin lightening/brightening, stimulates collagen production, thickens dermal layer and has a plumping effect. <u>99% Naturality Score!</u>
Lipodisq® Retinal PE Solution	<i>Aqua, Polysorbate 20, Retinal, Lecithin, Phenoxyethanol, Ethylhexylglycerin</i>	Anti-ageing, skin lightening/brightening, stimulates collagen production, thickens dermal layer and has a plumping effect. <u>Just one step metabolic conversion needed to form retinoic acid within the skin!</u>

Distribution (All Grades)

MALVERN COSMECEUTICS



NaturEx



LIPODISQ[®] RETINOIDS

Lipodisq[®] Products

PHARMACEUTICAL GRADE

Product	INCI
Lipodisq [®] Retinal Solution (PS20)	<i>Water, Polysorbate 20, Retinal, Lecithin (Synthetic) STERILE</i>
Lipodisq [®] Retinoic Acid Solution (PS20)	<i>Water, Polysorbate 20, Retinoic Acid, Lecithin (Synthetic) STERILE</i>
Lipodisq [®] Retinoic Acid Solution (P[SMA])	<i>Water, Poly(styrene-maleic acid), Retinoic Acid, Lecithin (Synthetic) STERILE</i>

Distribution (All Grades)

MALVERN COSMECEUTICS



LIPODISQ® RETINOLDS

e.g. Lipodisq® Retinoid Products



LIPODISQ® RETINOIDS

Licenseses, Distributors and Highlighted Partners/Customers:

VERITAS

Rodial

RE:ERTH



The Organic Pharmacy

NIP+ FAB

HAL SKIN

Mybestie® Skincare with Cosmeceuticals

SUPER FACIALIST



COWSHED

Dr.Anmytas

KUARAL

skin Chemists LONDON

Lipodisq[®] technology is covered by one or more of the following patents owned by Malvern Cosmeceutics Limited:

AU 2006253886
CA 2,611,144
CN ZL200680018957.2
EP 1890675
GB 2426703
JP 5142898
IN 261468
US 8623414
WO/2021/005340A1 pending

AU2007327054
CN ZL200780044148.3
GB2464393
JP6567575
JP5142989
SA2009/02939

LIPODISQ[®]

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Curiosity, Innovation.

