PERSONAL CARE

ARLASOLVE™ DMI

ARLASOLVE DMI-PC

Dimethyl Isosorbide

Enhanced delivery of active ingredients

Ask consumers why they use a skin care product and chances are good they will purchase one they perceive to be effective, yet active ingredients for skin care formulations are only as effective as their delivery system. ARLASOLVE DMI and ARLASOLVE DMI-PC are skin adjuvants which boost the performance and enhance the delivery of actives within formulations for many personal care applications. The ability of these ingredients to penetrate deep layers of the stratum corneum enables effective delivery of actives in applications such as self-tanning, anti-acne, skin whitening and scalp treatment. They are especially effective in the delivery of DHA (dihydroxyacetone) for self-tanning applications. By increasing the level of DHA delivery and its depth of penetration, ARLASOLVE DMI and ARLASOLVE DMI-PC promote rapid color development and create a deeper, longer lasting tan. An improved distribution of DHA throughout the stratum corneum also results in a more even color and helps to minimize streaking.

Features / Benefits

- Optimizes delivery of skin care actives
- Improves spreadability of viscous materials
- Pleasant non-greasy skin feel
- Safe and easy to process
- Mild, non-irritant
- Broad formulation and application compatibility
- Soluble in water and many cosmetic oils
- Stable to hydrolysis and transesterification
- Ideal for use in acidic environments
- Reduces stickiness of polyol-rich water phase and thick emollient oils

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CRODA

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Applications

- Self-tanning
- Skin lightening
- Skin tone enhancing
- Scalp treatment
- Body countouring
- Anti-acne
- Anti-aging
- Nail polish remover

Structure and Composition

ARLASOLVE DMI and ARLASOLVE DMI-PC are clear, colorless, non-greasy liquids with the following chemical structure:

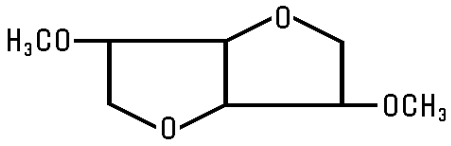

Figure 1:

Enhancing the performance of DHA in self-tanning formulations

Many self-tanning formulations are based on dihydroxyacetone (DHA), which reacts with proteins in the skin to form brown colored compounds, thus giving the appearance of a suntan. Clinical studies have been carried out, both internally (studies 1 & 2) and externally (study 3), in order to evaluate the performance enhancing benefits of ARLASOLVE DMI with DHA in self-tanning formulations.

Study 1

Color intensity of a cream formulation containing ARLASOLVE DMI

Two equal amounts of the cream formulation (shown below) with and without 5% ARLASOLVE DMI were applied to the upper legs. Photos and visual records were taken at 24 hours after application, in order to carry out a side-by-side comparison of the two formulations.

Visual results showed that the cream containing ARLASOLVE DMI resulted in a more intense and uniform artificial tan coloring (Figure 2).

Table 1: Cream formulation used in Study 1

Phase	Ingredient	%w/w
A	Water	qs to 100
	PRICERINE™ 9091 (Glycerin)	3.00
B	ARLACEL™ 165 (Glyceryl stearate (and) PEG-100 stearate)	4.00
	CRODAMOL™ GTCC (Caprylic/capric triglyceride)	7.00
	Dimethicone	3.00
	Cetearyl alcohol	5.00
C	Dihydroxyacetone	4.00
	ARLASOLVE DMI (Dimethyl isosorbide)	0 or 5.00
	Nipaguard BPX (Phenoxyethanol (and) methylparaben (and) propylparaben (and) 2-bromo-2-nitropropane-1,3-diol)	0.70
D	Citric Acid	to pH 5

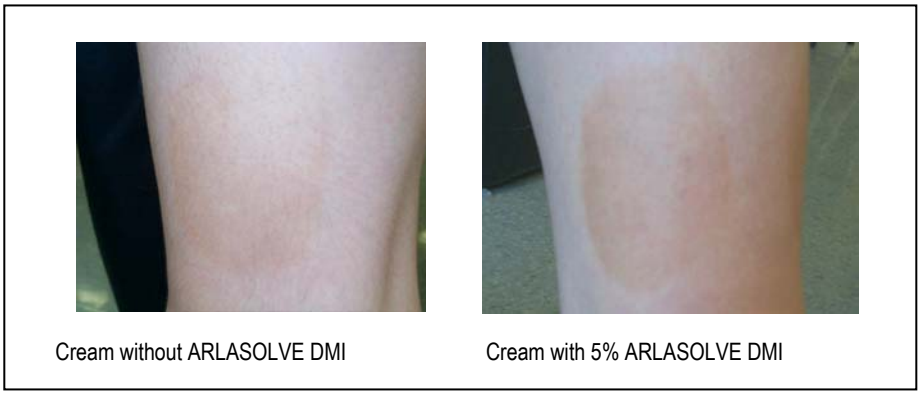

Figure 2: Enhanced color intensity development and skin color uniformity with the inclusion of ARLASOLVE DMI to a DHA-containing cream formulation.

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Study 2

Color intensity of a foam formulation containing ARLASOLVE DMI

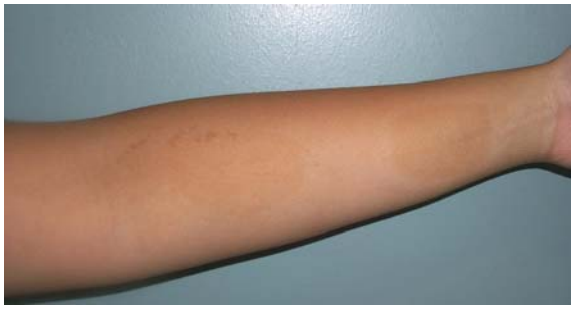
Table 2: Foam formulation used in Study 2

Ingredient	%w/w
Water	qs to 100
Dihydroxyacetone	4.00
Propylene glycol	2.00
PRICERINE 9091 (Glycerin)	2.00
RENEX™ S30 (Sorbeth-30)	2.00
PROMIDIUM™ CO (PPG-2 hydroxyethyl cocamide)	2.00
CRODAFOS™ M915A (C9-15 Alkyl Phosphate)	1.00
ARLASOLVE DMI (Dimethyl isosorbide)	0 or 3.00
Germaben II (Propylene glycol (and) diazolidinyl urea (and) methylparaben (and) propylparaben)	0.50

Study 1 was repeated, but instead using a foam formulation (shown below) on the inside lower arm. Two equal amounts of the foam were applied to the inside arm; lower arm with the foam containing 3% ARLASOLVE DMI and the upper lower arm with the foam without the ARLASOLVE DMI. Photos and visual records were taken at 24 hours after application.

Visual results (*Figure 3)* showed that the foam containing 3% ARLASOLVE DMI resulted in a more intense and uniform artificial tan coloring.

Left
Foam without
ARLASOLVE DMI



Right
Foam with 3%
ARLASOLVE DMI

Figure 3: Enhanced color intensity development and skin color uniformity with the inclusion of ARLASOLVE DMI to a DHA-containing foam formulation.

Study 3

Clinical study investigating color enhancing effects of ARLASOLVE DMI-PC with DHA in a self-tanning cream formulation

This clinical study was carried out externally by Hill-Top Research (St. Petersburg, FL, USA)[1], in order to establish the color uniformity enhancing effects of ARLASOLVE DMI-PC with dihydroxyacetone (DHA) contained within self-tanning cream formulations.

Thirty-six female volunteers were involved in a single application study. Washing, shaving and bathing were all standardized prior to and during the study to prevent interference with the results. Equal amounts of two test creams, identical in composition apart from one containing ARLASOLVE DMI-PC at 3.5%, were applied to two of three sites located on the lower leg. The third, untreated site was used as the control. Treatments were randomized over the sites and the trained evaluator was only made aware of the position of the control site.

Table 3: Self-tanning cream formulation used in Study 3

Ingredient	%w/w
Water	Qs to 100
PRICERINE 9091 (Glycerin)	3.00
BRIJ™ S721 (Steareth-21)	1.60
BRIJ S2 (Steareth-2)	2.40
CRODAMOL GTCC (Caprylic/capric triglyceride)	7.00
Dimethicone	3.00
Cetyl stearyl alcohol	5.00
Ethoxydiglycol	5.00
Dihydroxyacetone	4.00
ARLASOLVE DMI-PC (Dimethyl isosorbide)	3.50
Nipaguard BPX (Phenoxyethanol (and) methylparaben (and) propylparaben (and) 2-bromo-2-nitropropane-1,3-diol)	0.70
Citric Acid	to pH 5.5

Skin color development was measured using a chromametric evaluation for intensity, clinical photography for uniformity and trained assessors used a relative visual scoring scale for both intensity and uniformity. These visual and instrumental assessments were carried out after one hour and at regular intervals over a 10 day period. All measurements took place after a 30 minute acclimatization period within a controlled environment.

Instrumental evaluation

Skin color development was measured for intensity using a Minolta Chromameter CR-300 ($\Delta E^*=[(\Delta L^*)^2+(\Delta a^*)^2+(\Delta b^*)^2]^{0.5}$), based on total color difference of the treated sites relative to the control (untreated site).

Figure 4 illustrates that while both formulation creams resulted in a significant color change on the skin, the cream containing ARLASOLVE DMI-PC resulted in significantly more color formation at 48 and 96 hours. This shows that ARLASOLVE DMI-PC improved the color intensity, for a deeper, longer lasting tan effect.

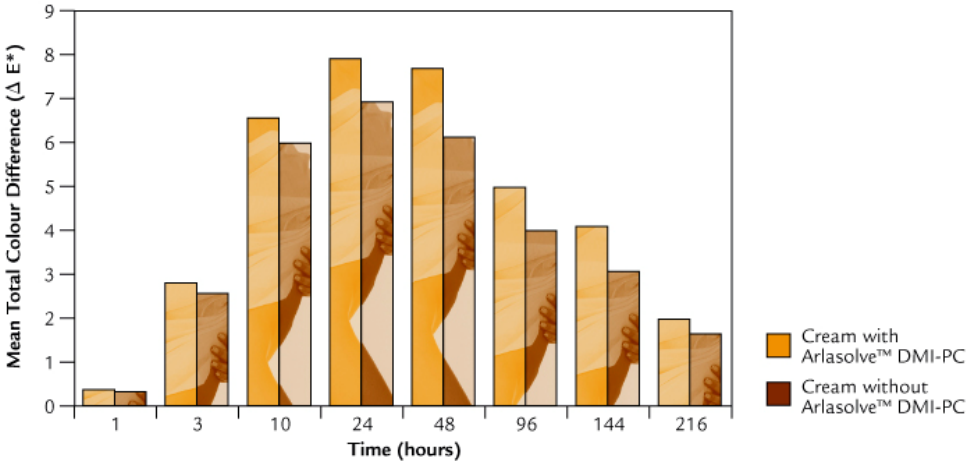


Figure 4: Mean total color difference demonstrates that ARLASOLVE DMI-PC maintains a significantly deeper tan for longer.

Visual evaluation

Throughout the 10 day study, trained visual evaluators carried out comparative evaluations between the treated and untreated control sites. These were performed using standardized conditions and a 5-point scoring system for color intensity and 4-point scoring system for color uniformity.

The color intensity developed with the cream containing ARLASOLVE DMI-PC was significantly more than the cream without ARLASOLVE DMI-PC from the 8-19 hours time-point onwards until the end of the study (Figure 5). This aids to further demonstrate the ability of ARLASOLVE DMI-PC to prolong the tanning effect.

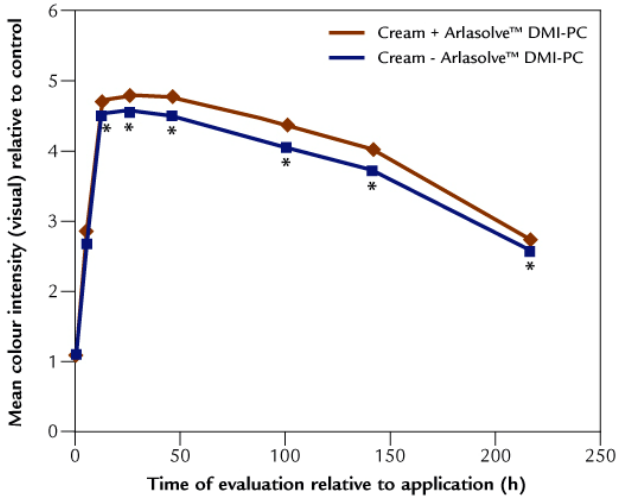


Figure 5: Mean color intensity (visual) relative to control

Visual evaluation of color uniformity by the trained assessors also showed that the cream containing ARLASOLVE DMI-PC was statistically more uniform than the cream without ARLASOLVE DMI-PC from 8-10 hours up to and including 48 hours (Figure 6). This demonstrates that ARLASOLVE DMI-PC helps to minimize the appearance of streaking during the period when the tanning effect is more intense.

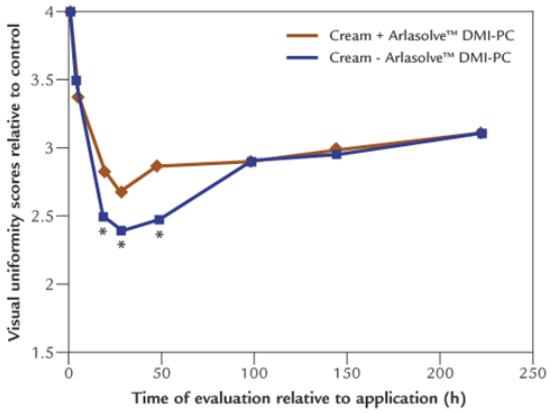


Figure 6: Visual uniformity relative to control

Correlation of results

Very good correlation exists between the mean visual data obtained through clinical assessment of relative color intensity and the instrumental data obtained through chromametric assessment of the total color difference (see Figure 6).

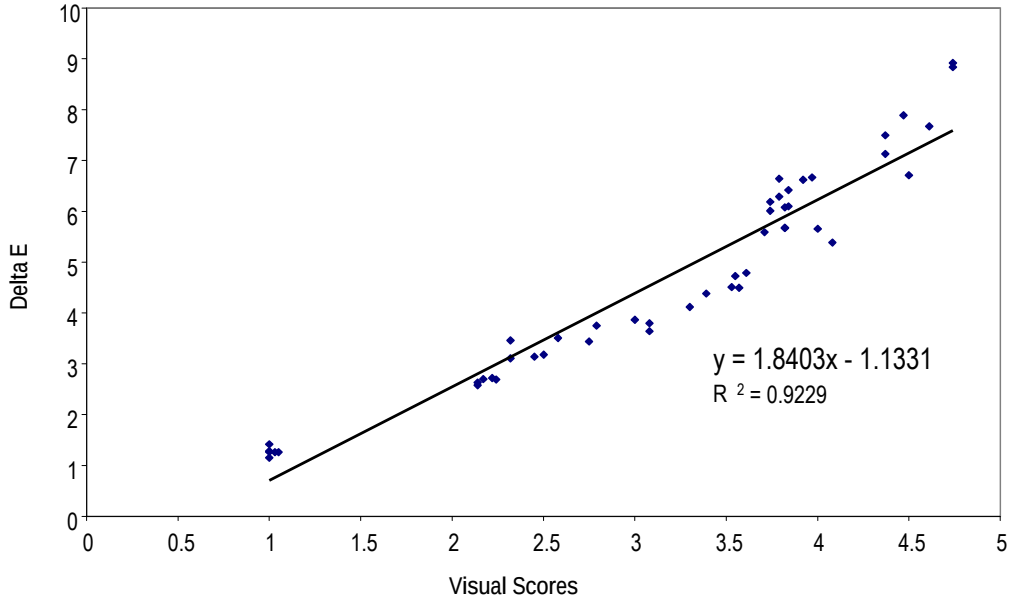


Figure 7: Correlation between visual and chromametric evaluations of the color development profiles

Improved spreadability

Color uniformity is, to a great extent, dependent upon uniform skin coverage. ARLASOLVE DMI-PC, as well as enhancing the delivery of DHA, can also be used to improve the spreading properties of oils within formulations to facilitate application. Improved spreadability with the inclusion of ARLASOLVE DMI-PC was noted by the trained evaluators used during the clinical trial[1].

ARLASOLVE DMI-PC is sufficiently miscible with many substances, enabling it to facilitate and accelerate the spreading of substances onto a surface. In order to demonstrate this, dynamic contact angle measurements were taken for a very poorly spreading, strong water-repelling and substantive dimer acid. Upon mixing the dimer acid with ARLASOLVE DMI-PC, the contact angle was significantly reduced and spreadability improved (Figure 8).

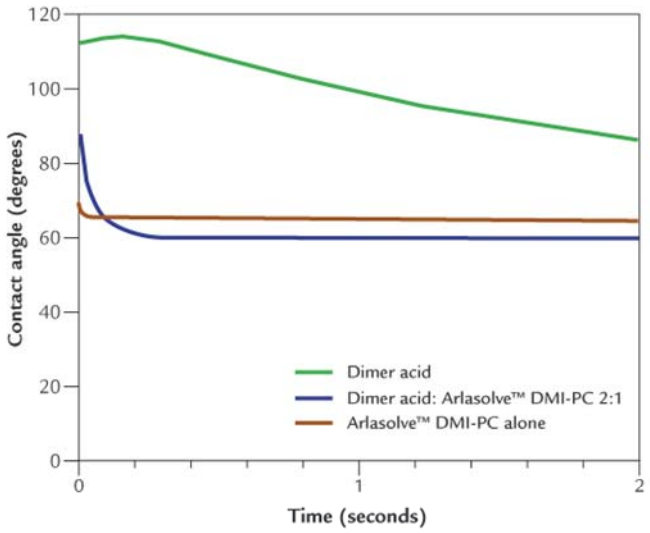


Figure 8: Dynamic contact angle measurements for Dimer acid; Dimer acid with ARLASOLVE DMI-PC (2:1); ARLASOLVE DMI-PC

Skin delivery enhancement

The functionality of an active ingredient depends on its intrinsic biological activity, which is typically obtained from in-vitro testing, and the concentration needed to achieve that biological effect.

Once the minimum concentration needed is known, the challenge is to get this functional concentration delivered from a formulation to its biological target. Thus the formulation should contain a sufficient starting concentration, it should be released from the formulation after deposition on the target surface, and it should penetrate through a variety of biological barriers. ARLASOLVE DMI and ARLASOLVE DMI-PC can help at each of these stages. They can increase the concentration of both lipophilic and hydrophilic actives in the formulation, or can bring them to their maximum thermodynamic activity.

These mechanisms of delivery enhancement cannot be viewed independently from other key formulation components (in emulsions: emollients and emulsifiers). Specifically to ARLASOLVE DMI and ARLASOLVE DMI-PC, care has to

be taken that they do not increase the solubility of actives in both the oil and the water phase and dilute the active below its thermodynamic activity, thereby reducing the biological functionality!

ARLASOLVE DMI and ARLASOLVE DMI-PC are non-volatile medium polarity solvents which are at the same time miscible with water and organic media. Once deposited on the skin surface, they can modify (increase) the polarity of the surface skin layers and help to carry the biologically active material through layers of variable polarity. The latter delivery enhancement effect will possibly be more apparent for hydrophilic active ingredients than for lipophilic actives, especially in emulsions.

Propagermanium case studies

Several studies have been conducted investigating the sparingly water-soluble multi-functional active ingredient Propagermanium, as its high cost and limited supply resulted in a need to maximize its effectiveness and minimize waste. It was discovered that ARLASOLVE DMI significantly enhanced the in-vivo functionality (UV-damage protection, skin whitening) of Propagermanium [5b, 5c].

Experiment 1

An experiment focusing around in-vitro skin delivery of polar (propagermanium), medium-polarity (caffeine) and low-polarity (Vitamin E acetate) substances in the presence of ARLASOLVE DMI was carried out at Catania University (Italy) [5a].

The test method involved using excised human skin of 4 donors, previously tested for integrity with tritiated water, for use in a Franz-cell diffusion cell experiment. The receptor contained saline solution for the propagermanium and caffeine experiment, and an ethanol: water mixture for vitamin E acetate. The skin samples were contacted with a 20% aqueous ARLASOLVE DMI solution and then wiped clean before 0.2 ml of the test-solutions (1% propagermanium, 0.1% caffeine, 2% vitamin E acetate) was applied. The results, which are shown in Figure 9, show a significant increase in skin delivery for the samples containing the aqueous ARLASOLVE DMI pre-treatment.

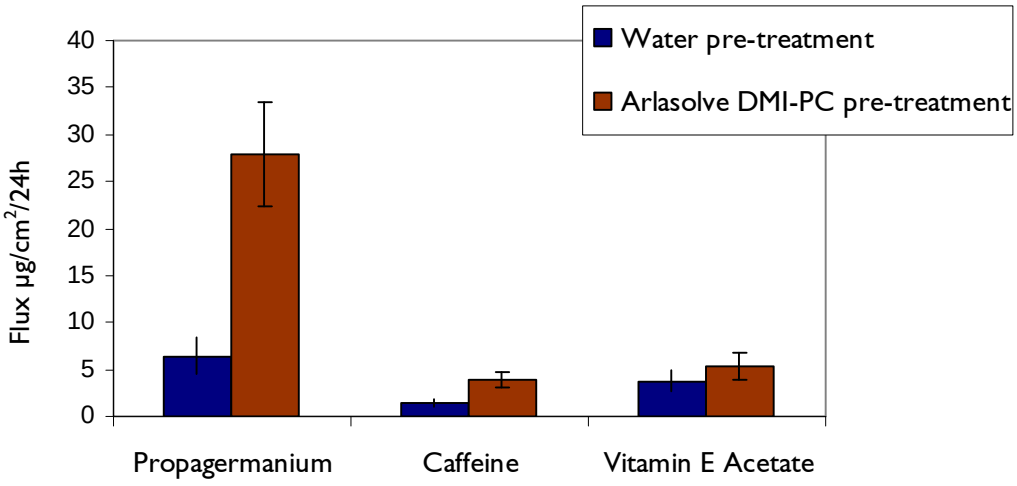


Figure: 9 Skin delivery evaluation of ARLASOLVE DMI

Experiment 2

A study at Dermscan (1997) on the effect of Propagermanium on the protection of Langerhans cells in skin explants by immuno-fluorescence spectroscopy confirmed the functionality of ARLASOLVE DMI. Liquid solutions of aqueous Propagermanium and Propagermanium in aqueous/ARLASOLVE DMI were placed on skin explants (4 explants) and compared to untreated, aqueous ARLASOLVE DMI treated and a positive control (Vitamin C + Glutathion solution). Two explants were irradiated with 1.5J/cm^2 UVB and compared to non-irradiated controls. The average of 12 cell-counts is taken for the calculation of cell viability. The results are shown in the table below.

$$\% \text{ viability} = \frac{\text{Number of cells on treated explants}}{\text{Number of cells on non-treated non-irradiated explants}} \times 100$$

Table 4: Viability test

Test product	% viability non-irradiated	% viability irradiated
Non-treated	100	0
positive control	97	81
0.9% Propagermanium in water	96	85
ARLASOLVE DMI : water, 1:1	93	4
0.25% Propagermanium in ARLASOLVE DMI:water	53	n.a. (*)
0.05% Propagermanium in ARLASOLVE DMI:water (*)	72	107

(*) product had to be diluted with water to acceptable level of cytotoxicity

From this experiment it appears that ARLASOLVE DMI enhances greatly the activity of propagermanium, to the point that it must be diluted to avoid cytotoxicity (in-vitro).

Experiment 3

A more recent study carried out by Syngenta CTL (UK)[2], looks more in detail to the skin delivery effect of ARLASOLVE DMI-PC on propagermanium. Using a Franz glass diffusion cell system, 25mg of the formulation shown below was applied to 2.5 cm^2 pig skin dermatomed to 400 µm. The dermal side was in contact with stirred aqueous ethanol at 32^{0}C. Following a 24hour contact time the excess formulation was wiped off, the epidermal side of the skin sample was tape-stripped 5 times and then tape strips, skin and receptor fluid analyzed for propagermanium by ICP-MS.

Figure 10 reveals that the addition of 10% ARLASOLVE DMI-PC to a formulation resulted in a 2-fold increase of the propagermanium concentration delivered to the skin fraction without delivering it transdermally.

Table 5: Oil-in-water test emulsion

Ingredient	%w/w
Water	Qs to 100
CITHROL™ PGMIS (Propylene glycol isostearate)	15.00
CRODAMOL GTEH (Triethylhexanoin)	3.00
BRIJ S721 (Steareth-21)	5.00
BRIJ S2 (Steareth-2)	1.00
Propagermanium	0.50
ARLASOLVE DMI-PC (Dimethyl isosorbide)	0 or 10.00
PRICERINE 9091 (Glycerin)	4.00
Xanthum gum	0.40
Nipaguard BPX (Phenoxyethanol (and) methylparaben (and) propylparaben (and) 2-bromo-2-nitropropane-1,3-diol)	0.70

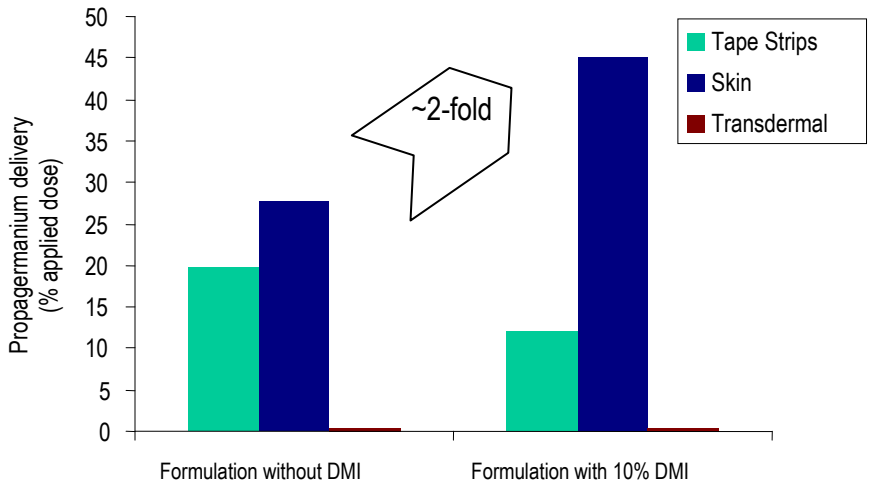


Figure 10: Delivery of Propagermanium formulation with and without ARLASOLVE DMI-PC

Mild, safe and easy to process

ARLASOLVE DMI and ARLASOLVE DMI-PC provide a safe and easy to handle alternative to using a high concentration of active ingredients. The high boiling point, low viscosity and low volatility ensures safe delivery during processing without the risk of recrystallization of the active. ARLASOLVE DMI and ARLASOLVE DMI-PC are an ideal alternative to materials that are currently under regulatory pressure such as glycol ethers, including ethoxydiglycol. Extensive safety data for this product already exists and has shown ARLASOLVE DMI and ARLASOLVE DMI-PC to be free of irritation and completely safe for use in both topical skin applications and oral drug delivery systems.

Broad compatibility

ARLASOLVE DMI and ARLASOLVE DMI-PC are miscible with a wide range of ingredients, including most organic solvents, nonionic surfactants and water (in all proportions). As a result, ARLASOLVE DMI and ARLASOLVE DMI-PC

can be formulated into a variety of formulations and is compatible with many delivery systems, including clear gels, foams, creams, lotions, sprays and ointments.

Formulating

From our experience in formulating with ARLASOLVE DMI and ARLASOLVE DMI-PC, we have produced the following guidelines:

- Typical usage level 3-5%
- ARLASOLVE DMI and ARLASOLVE DMI-PC can be considered as drop-in ingredients that will not affect emulsion stability at typical usage concentrations
- The ether-chemistry of ARLASOLVE DMI and ARLASOLVE DMI-PC and the typical concentration they are used at can result in pH drift of the formulation to lower values. This can be of benefit to the formulation (e.g. with acid stable actives). If not, the use of anti-oxidants or buffers may have to be considered.
- In order to optimize delivery enhancement, care must be taken to add ARLASOLVE DMI and ARLASOLVE DMI-PC at the appropriate level in order to maximize the thermodynamic activity of the active in the formulation after it has been deposited on the target surface and after all volatiles have evaporated from that surface.

Table 6: Physical characteristics

Molecular Weight	174.19
Refractive index	1.4601
Solubility Parameter	9.0 (Fedor), 10.1(Hansen), 10.2(Hoy) [1]
Freezing point	<-50^{0}C
Boiling point	>112.2^{0}C
Flash point	118^{0}C (closed cup)

Table 7: Regulatory Information

EINECS	226-159-8
CAS number	5306-85-4

References

1. Johann Wiechers, Pascale Rossi, Jeffrey Berg, Lorraine Harnish, *SÖFW-Journal*, 2006, 132(1/2), 52-56

5a. Dederen, J.C., *Research Disclosure* (1997), 399(July), 479-480

5b. Dederen, J.C., *Cosmetics and Toiletries Manufacture Worldwide* (1996), 170-173

5c .Montenegro, L.,Bonina, F., Dederen J.C., *J.Soc.Cosmet.Ch*em (1996), 47, 307-313

2. Pascale Rossi, Johann Wiechers, Caroline Kelly, *Cosmetics and Toiletries*, 2005, 120(3), 107-111

PERSONAL CARE

Amazing Neck and Face Cream with ESSENSKIN™ SC-502

For enhanced performance, this cream utilizes two of Sederma's ingredients, ESSENSKIN and RIGIN™, each specifically targeting needs of mature skin. ESSENSKIN recreates the calcium gradient lacking in mature skin and supplies nutrients essential for protein synthesis. Clinically tested, ESSENSKIN firms the skin, improves skin reflectance, enhances skin texture and visibly reduces the sagging neck line. RIGIN helps promote and protect macromolecules. Clinical studies demonstrate the ability of RIGIN to firm both the face and the neck. The ARLASOLVE™ DMI-PC promotes the delivery of these actives, while ARLACEL™ LC and CRODAMOL™ OP contribute to the emollient, dry, silky feel of the formula.

Ingredients	%
Part A	
ARLACEL LC (Sorbitan Stearate (and) Sorbityl Laurate)	4.00
Water	70.40
ARLASOLVE DMI-PC (Dimethyl Isosorbide)	5.00
Part B	
Glycerin	5.00
Potassium sorbate	0.10
PHENOVA™ (Phenoxyethanol (and) Methylparaben (and) Ethylparaben (and) Butylparaben (and) Propylparaben (and) Isobutylparaben)	0.80
Part C	
CRODAMOL OP (Ethylhexyl Palmitate)	4.00
Cetearyl Alcohol	0.50
Cyclomethicone[2]	2.00
Part D	
RIGIN (Aqua (and) Glycerin (and) Steareth-20 (and) Palmitoyl Tetrapeptide-7)	3.00
Hydroxypropyl Starch Phosphate[3]	2.00
ESSENSKIN (Water (aqua) (and) Pentylene Glycol (and) Polysorbate-20 (and) 3-Aminopropane Sulfonic Acid (and) Calcium Hydroxymethionine (and) Hydroxyethylcellulose)	3.00
Fragrance	0.20

Suppliers: 1. Croda/Sederma 2. Dow Corning 345 Fluid, Dow Corning 3. Structure XL, National Starch

pH: 5.5 ± 0.5; Viscosity 41,920 cp ± 10% (Spindle 63 @ 1.5 rpm)

Procedure

Part A, add ARLACEL LC to water and heat to 80°C with mixing. Heat and mix Part B, and add to Part A. Heat Part C with mixing to 80°C. Add Part C to Part A/B, mix for 10 minutes at 80°C. Homogenize. Continue to mix Part A/B/C while allowing to cool to 35°C. At 35°C add Part D and mix well until room temperature.

SCA#-0225
MCB# 0193-114