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Inflammasomes: key to the engine of skin inflammaging
Using natural oils in fragrance: its role in clean beauty
Enhancing nocturnal processes for beautiful skin

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Analysis of 'The trilogy of lifting'

■ Stefan Hettwer, Emina Besic Gyenge, Barbara Obermayer – Rahn, Switzerland

Wrinkle minimisation is the Holy Grail of cosmetic actives development. Since the creation of the first anti-aging formulations, the topic has been explored from every angle. The easiest way is of course to cover the skin with foundations to hide those unattractive features of skin ageing. But besides this use of camouflage, there is more which can be done. To understand how to improve or preserve the youthful appearance of the skin we need to know about its underlying biology.

The skin is composed basically of three layers: the subcutaneous adipose tissue, the dermis and the epidermis, which protects the body from the environment. Wrinkles only develop in the dermis and epidermis. Because of this, it is important to keep these tissues in a juvenile state.

The dermis is a very strong and resilient tissue, which is responsible for the skin's firmness and elasticity as well as its hydration. You can think of it in terms of a piece of leather as that is what it actually is; a tightly packed protein mesh consisting mainly of collagen,¹ which is responsible for the firmness together with elastin, which is responsible for the elasticity. This tissue is supplemented by moisture-retaining molecules such as hyaluronic acid and proteoglycans.

The epidermis is even stronger than the dermis and is held together by a huge network of keratin that forms interconnections between the cells of the upper epidermis.

It is easy to understand that the firm and elastic skin we had in our childhood

requires sufficient quantities of the important components and that any decrease in these, e.g. in collagen and elastin, will affect the restoring potential of the skin. You can readily observe this in real life: if you pinch the skin of a child on the back of their hand, you will see that the skin retracts immediately when you let it go. In contrast, when you do the same to a person aged 80 years and older, this can take up to a minute or even longer.

Wrinkles appear at regions where the dermal proteins collagen and elastin are less dense and where the connectivity of the dermis with the epidermis is weakened. This does not happen by chance but is the result of continuous repeated mechanical forces acting on the skin. The first mechanical forces that do this are involved in movement and as a result, the very first wrinkles we have are on the joints of our fingers and palms that are already there when we are born. So, whatever moves will cause wrinkles to develop and therefore our facial expressions will make wrinkles appear on our face sooner or later.

Rahn has developed three solutions in its Liftonin® range to fight wrinkles using completely different approaches:

1. Liftonin-Xpress, the instant wrinkle minimiser that employs a surface-acting biopolymer blend.
2. Liftonin for alabaster-like skin is an epidermal astringent thanks to the tannins it contains while it also stabilises the dermal

structure by providing bioavailable silicon. 3. Liftonin-Xpert Eco, the smart and ecological collagen manager improves dermal density by delivering the perfect amount of additional youth collagen.

Instant wrinkle minimiser

Instant cosmetic lifting is an attractive way of achieving fast and visible results. Liftonin-Xpress (now referred to as 'the wrinkle minimiser') acts on the epidermis, the outer cell layers of the skin, where wrinkles become apparent. The active ingredients are hydroxypropyl methylcellulose, pullulan and *Porphyridium Cruentum* Extract. The carefully adjusted blend of these polymers in the wrinkle minimiser generates a physical tightening and smoothing effect. The polymers form a three-dimensional network on the skin with powerful adhesion and cohesion effects. The result is an immediately noticeable tightening effect that lasts for hours as well as a quick and significant smoothing of wrinkles (Fig 1).² Application of the wrinkle minimiser resulted in a significant reduction of nearly all types of wrinkles in tests. The microrelief of the skin of the hands and arms is markedly improved, the prominence of fine lines on the face is reduced and the wrinkles in the eye area and forehead are significantly minimised.

Functional ingredients and efficacy

Hydroxypropyl methylcellulose (HPMC)
HPMC is used in the cosmetics industry in emulsions, toothpastes, shampoos, soaps, creams and lotions. During the development of the wrinkle minimiser, it was a particular challenge to select the type with the best tightening properties from the various kinds of HPMCs.³ The variant employed in the polymer matrix provides the wrinkle minimiser with outstanding performance as a wrinkle-smoothing rapid dermo-tensor.

Pullulan

Pullulan is a natural polysaccharide made of maltotriose units.⁴ Its chemical structure with the α -(1→6) bonds provides pullulan

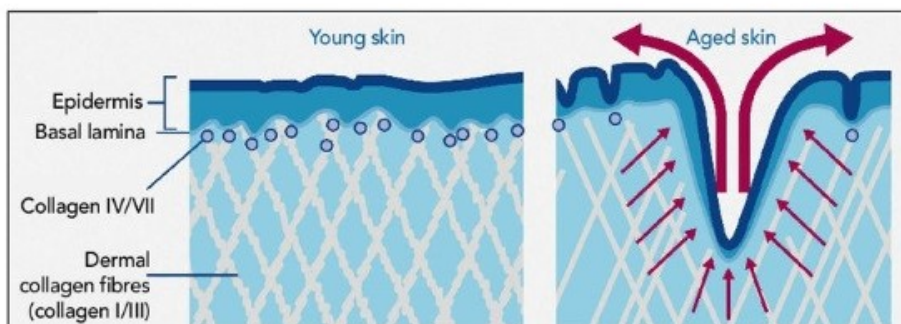


Figure 1: Liftonin-Xpress gives uplift to wrinkled skin using tensile forces created by a sophisticated polysaccharide film composed of hydroxypropyl methylcellulose, pullulan and phycocolloids obtained from red algae. Wrinkles disappear within seconds. As this is a mechanical effect, signs of visible rejuvenation are not permanent but do last for a couple of hours.

with outstanding flexibility and gives it special physical properties, such as powerful adhesion/cohesion to skin while it can also form thin, transparent films or networks with perfect mechanical characteristics leading to shrinkage when water is released.

Porphyridium Cruentum Extract

Porphyridium cruentum is a unicellular red alga. The alga continuously secretes a mucus made of polysaccharides called phycocolloids, which protectively surround the cells like a gel capsule. The key monomers are sulphated, uronic acid-containing sugars capable of retaining a high amount of water.⁶ The secondary alga metabolites may also contribute to a long term cosmetic function in the skin.

All these three ingredients deliver film-forming polysaccharide polymers that have a synergistic tightening effect and at the same time have moisturising properties. The polymer matrix blend in the wrinkle minimiser has been optimised to give a tightening effect that is intense and immediately perceivable but at the same time keeps the film flexible, ensuring a long-lasting effect for several hours. Incorporated in a marketable formulation (700338.0006, Ageless Eye Serum), the immediate effect is readily visible to the naked eye, as Figure 2 shows.

For alabaster-like skin

Liftonin (now referred to as 'the epidermal astringent') was designed to re-establish and protect the organization of the fiber network with regards to the dermal extracellular matrix. It can be seen as a dual-component glue for the dermal network (see Figure 3). Compression of loose and weak dermal fibres leads to a re-establishment of strong collagen bundles and creates a robust dermal fibre network. Both orthosilicic acid and tannic acid are capable of binding to and gripping extracellular matrix fibres due to their high content of hydroxyl groups. Orthosilicic acid strengthens the existing collagen network⁸ and tannic acid contributes to stable tightening of the fibre network. By these means, it reorganises the bundles of collagen in a way that promotes the infiltration of vital fibroblasts.⁷ Furthermore, the fixation of the collagen matrix to the basal lamina strengthens the dermo-epidermal junction, counteracting the formation of fine lines and exacerbation of fine lines to form deeper wrinkles.

The epidermal astringent not only provides mechanical support to the dermal structure but also promotes healthy cell function: Valuable nutrients and vitamins present in the millet extract promote the viability of keratinocytes and fibroblasts. Orthosilicic acid stimulates the collagen production of dermal fibroblasts.⁸ By

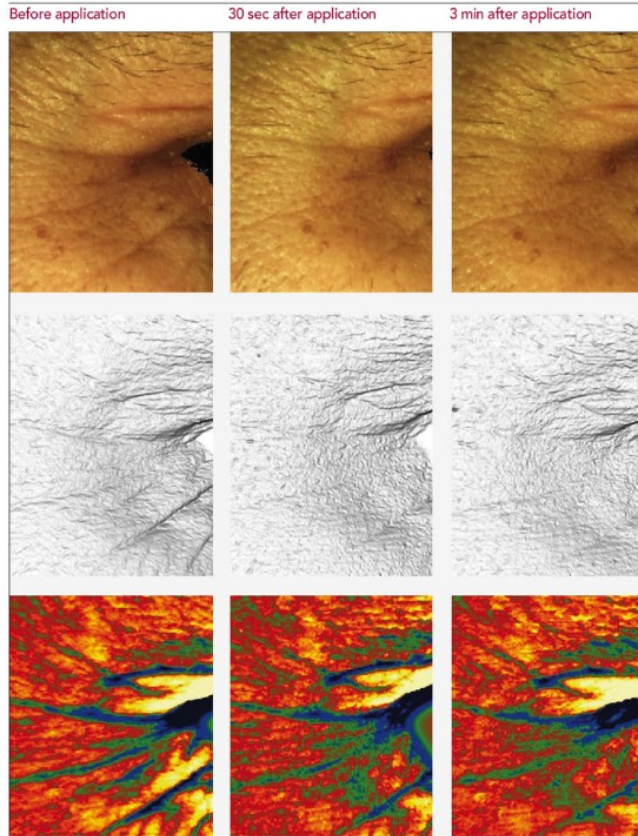


Figure 2: Liftonin-Xpress provides immediately visible results following application of a small amount of Ageless Eye Serum containing 2% Liftonin-Xpress. Within 30 seconds, the lifting effect is almost fully completed as demonstrated by the readout of a PRIMOS 5.1. device. Male volunteer, aged 45. Top panels: optical view, middle panels: relief projection, lower panels: false colour representation of wrinkle depth.

providing an attractive environment for the recruitment of fibroblasts to the affected collagen structures using tannins, the required fresh collagen is supplied where it is needed most. In addition, by inhibiting dermis-decomposing enzymes, tannins can help to maintain a fully functional dermis.⁹ As a result, the epidermal astringent perfectly combines physical properties and biological effects in one active ingredient.¹⁰

Functional ingredients and efficacy
Tannins and tannic acid: natural astringents derived from oak gallnut

Tannins are excellent astringents: they are extremely rich in hydrogen donors and acceptors, which allows them to form multiple hydrogen links and bond tightly with proteins. This very well-known intrinsic property of tannins can be employed to

generate a tightening effect on the skin surface. However, recent research has revealed another structural benefit to the skin: tannins contribute to tight crosslinking and stabilisation of the fiber network of the extracellular matrix of the dermis and reorganise the collagen bundles in a way that promotes the infiltration of fibroblasts.⁷ An *in vitro* experiment using collagen disks supplemented with fibroblasts, the presence of tannins delayed the contraction significantly by several days due to fixing of the collagen structure (Fig 4).

Millet Seed Extract: bioavailable silicon for strong connective tissue
For decades, millet has been widely

appreciated as a food supplement that beautifies the skin from the inside. However, cosmetic formulations also use millet to supply the skin with valuable vitamins and minerals. It contains important amino acids, folate and niacin and is rich in iron, magnesium, potassium, but most importantly silicon as the bioavailable orthosilicic acid. Orthosilicic acid, as the body's main silicon-containing compound, comprises four reactive hydroxyl groups. It can bind collagen and glucosaminoglycans and in this way stabilise the dermal networks. Several investigations in the field of material science have demonstrated the very high capacity of orthosilicic acid for binding collagen. It can very readily interlink various collagen fibres to form the required bundles, which will strengthen the existing collagen network.⁶

Application of the epidermal astringent improves the evenness of the skin microstructure and reduces fine lines, measurably (Fig 5) as well as visibly (Fig 6).

Smart collagen management

Wrinkles that have appeared in the collagen-rich tissue of the dermis over the years can only be reversed with difficulty. The consequence is thin, wrinkled and inelastic skin. The collagen remodelling processes are very slow, and undergo complex biochemical reactions, which ensure a subtle balance between the degradation and reconstruction of collagen. Since with increasing age the balance shifts towards degradation, it is important to counteract this at an early stage, but in a regulated manner, with a suitable boost of collagen. This can be achieved by means of a controlled increase in collagen synthesis by means of the stimulation of fibroblasts without interference by inflammatory subsidiary processes. To maintain as youthful a dermis structure as possible, the processes that occur during the integration of new collagen fibres must be given sufficient time to develop a strong network.

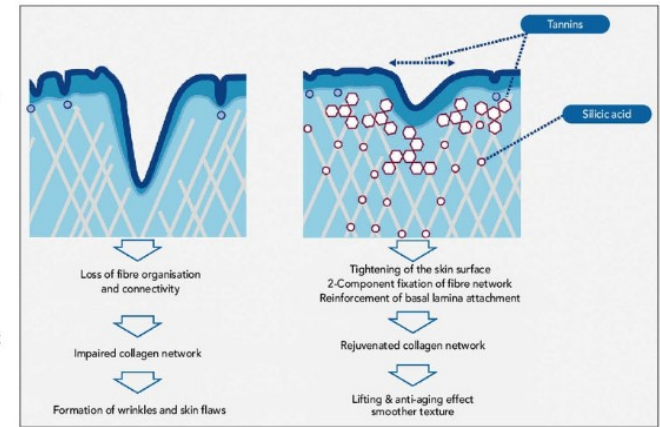


Figure 3: Liftonin tightens loose collagen fibers. Orthosilicic acid and tannins possess multiple hydrogen bond donor groups which will reorganise a loose collagen network. In addition, tannins have astringent properties that help smooth micro wrinkles and the skin microrelief.

But at the same time, the activation of the immune cells must be disabled to prevent overmodulation of the system, and thus an unwanted development with the collagen fibers arranged in parallel, as is the case in scar tissue.

Liftonin-Xpert Eco (now referred to as 'the collagen manager') offers an innovative mechanism that can compensate for an imbalance in the collagen metabolism of the dermis in a controlled manner (Fig 7). The unique combination of acetylated polymannose, which has a stimulating effect on the fibroblasts, and compounds such as kniphofone, which suppress the development of inflammatory responses by inhibiting leukotriene synthesis, makes the collagen manager a smart manager of the dermal structure.¹¹ The effects mean that the formation of wrinkles can be delayed for a long time, and old skin can be restored to a more youthful condition. The collagen manager helps everywhere that

the long-term quality of collagen is important: providing anti-ageing effects as well as helping deal with stretch marks and tattoos.

Functional ingredients and efficacy

Mannan from *Bulbine frutescens* leaf juice Like the *Aloe vera*, *Bulbine frutescens* is a succulent plant and contains a gel-like sap in its leaves. For the manufacture of the collagen manager, pure sap is obtained by means of non-aggressive cold pressing of the leaves. The mannan-containing fraction is obtained using a special refinement concept with a sophisticated filtration system. This technique makes it possible to offer a natural, COSMOS-listed, sustainable product. *Bulbine frutescens* has long been used in traditional medicine for the healing of skin injuries, burns, sunburn and insect bites¹² due to the soothing, anti-inflammatory effect of the sap. However, the results of scientific studies of *Bulbine*

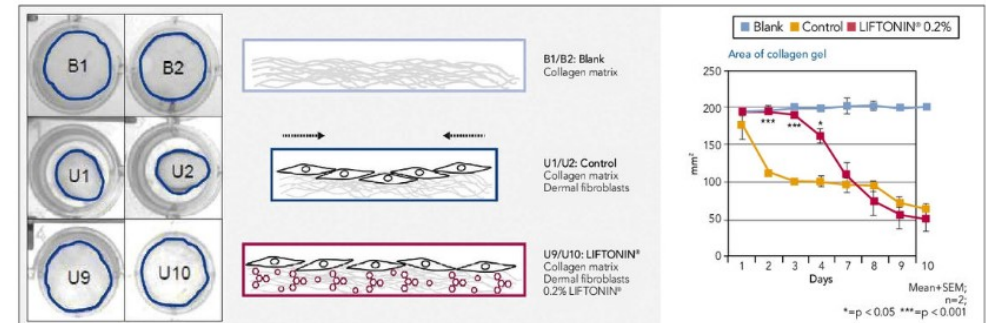


Figure 4: Tannins in Liftonin are able to stabilise the collagen network. Application of 0.2% Liftonin leads to a delayed gel contraction when fibroblasts are applied to the collagen matrix. This demonstrates the physical power of tannins to bind and reorganise a collagen network.

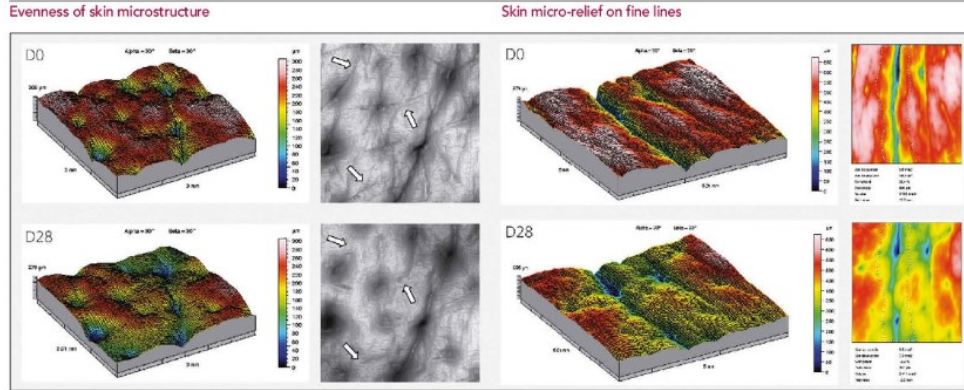


Figure 5: Improvement of microstructure and fine lines with use of Liftonin. After 28 days of treatment with 2 % Liftonin, the skin was markedly enhanced.

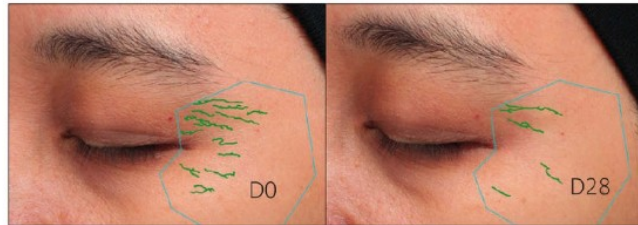


Figure 6: Improvement of visible wrinkles with use of Liftonin. After 28 days of treatment with 3 % Liftonin, wrinkles were markedly reduced.

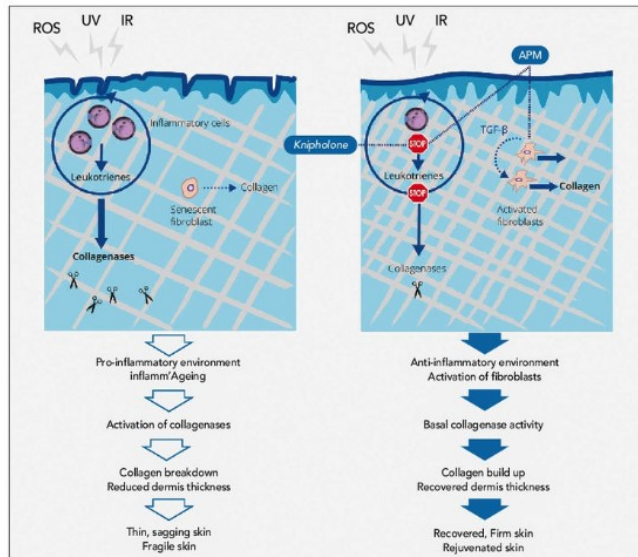


Figure 7: Smart collagen management with use of Liftonin-Xpert Eco leads to recalibrated levels of collagen in the dermis. Ageing alters the balance between collagen build-up and breakdown. Senescent fibroblasts produce too little collagen, while inflamm'ageing leads to increased degradation of existing collagen. Liftonin-Xpert Eco restores balance and normalises the collagen content of the dermis.

frutescens point in a new direction: thus *Bulbine frutescens* sap has been shown to stimulate collagen synthesis in fibroblasts^{13,14} an effect that has been confirmed by the results of our own *in vitro* studies. The acetylated polymannose (APM) is most likely responsible for this. It has been shown that purified APM significantly stimulates the proliferation of fibroblasts and significantly increases the rate of collagen synthesis.^{15,16} APM has been ascribed a whole series of other positive effects, for example anti-inflammatory, anti-bacterial and even anti-tumorigenic effects. APM also appears to regulate the immune response in a remarkable way, leading to faster healing of skin wounds.¹⁷ These combined features – stimulation of collagen expression as well as anti-inflamm'ageing properties – make smart collagen management possible, which means the skin is provided with exactly the amount of collagen needed to sufficiently suppress inflammatory processes and thus counteract natural skin ageing. The result is an extraordinary reduction of wrinkles and a noticeable lifting effect on sagging skin, e.g. in the neck area (Fig 8).

Although smart collagen management needs some time to provide visible results, it seems to be the most powerful solution when it comes to sustainable wrinkle minimisation and rejuvenation of the skin. Due to the collagen stimulating activity, the collagen manager can be used in a wide range of cosmetic applications designed for the care of stretch marks, tattoos as well as nail cuticles.

Conclusions

Liftonin-Xpress, Liftonin and Liftonin-Xpert Eco represent three generations of anti-wrinkle cosmetic actives that keep pace with our times. On the basis of cutting-edge scientific solutions, different concepts were developed to target ageing skin. Rahn

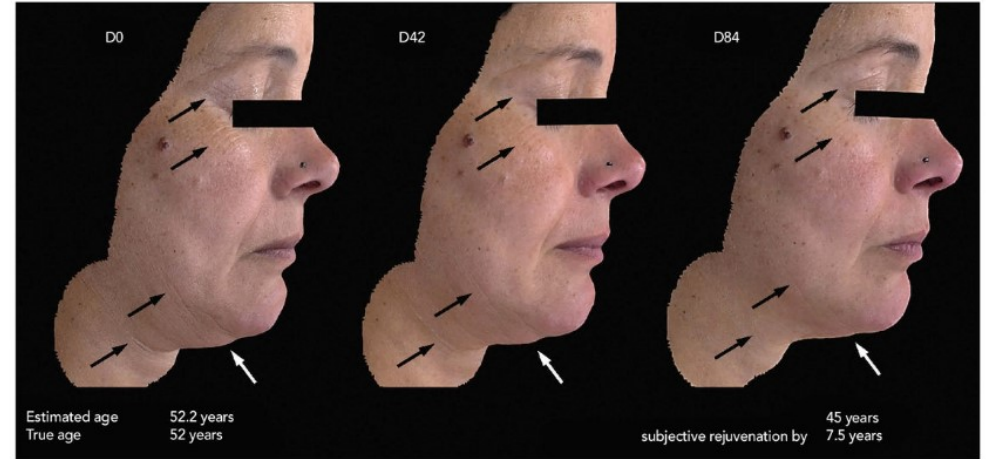


Figure 8: Liftonin-Xpert Eco visually reduces wrinkles. Deep expression wrinkles in the eye area are significantly reduced after just 6 weeks and almost vanish after 3 months treatment with 3 % Liftonin-Xpert Eco. The result was a highly significant subjective rejuvenation by 7.5 years as assessed by a collective of 67 persons asked to estimate the age of the subject from the study photographs.

AG is now able to supply the instant wrinkle minimizer Liftonin-Xpress for those needing their best looking moment of the day, stabilise the existing dermal network with Liftonin to preserve a youthful-looking

appearance and provide the optimal amount of collagen in situations where mature skin cannot accumulate the additional quantity required for dermal stability by itself.

From study data on wrinkle reduction, we can conclude that Liftonin-Xpress acts instantly for several hours but has no long term effect on the skin structure (light red line at 0, Fig 9). Liftonin develops its full efficacy

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after only 4 weeks although it has to be admitted that no later time points were investigated. Liftonin-Xpert Eco needs more time to manifest its efficacy as it influences skin biology at a deeper level to promote collagen expression, which obviously takes a while but gives the best results. In view of these results, it is apparent that a combination of these three active ingredients would serve as a powerful supplement in cosmetic formulations designed for the initiation of anti-wrinkle treatment that would provide impressive instant results combined with collagen stabilisation and a long-term collagen buildup. **PC**

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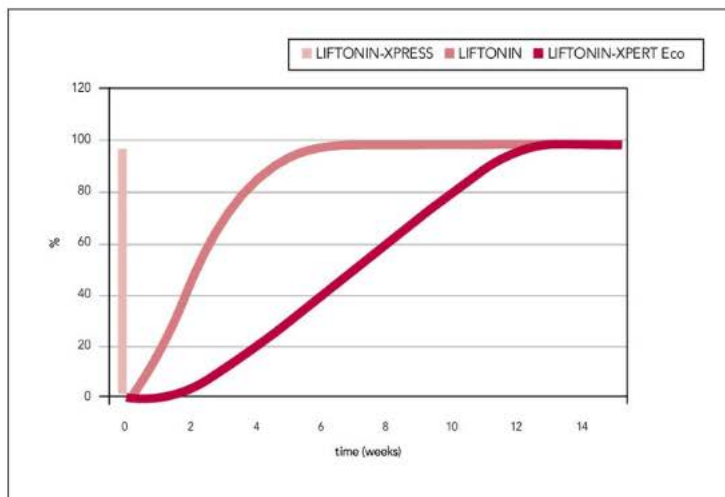


Figure 9: Progression of efficacy based on study results. By means of continuous use of the active ingredients, the anti-wrinkle effect of Liftonin-Xpress is manifested immediately, while the effects of Liftonin become apparent within 4 weeks and those of Liftonin-Xpert Eco within 3 months in accordance with their individual modes of action. Continuous use of the latter agents will maintain achieved benefits at a high level.

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Formulation 1: Ageless Eye Serum

Phase	Substance	INCI Name USA	% w/w
1	Water demin. ¹	Water	84.20
	LIFTONIN [®] -XPRESS ²	Hydroxypropyl Methylcellulose, Pullulan, Porphyridium Cruentum Extract	2.00
2	Optigel WX ³	Bentonite, Xanthan Gum	1.00
	Optigel CL ³	Magnesium Aluminum Silicate	4.00
3	Solagum AX ⁴	Acacia Senegal Gum, Xanthan Gum	0.30
	TEGO Pep 4-17 ⁵	Tetrapeptide-21, Glycerin, Butylene Glycol, Water	5.00
4	Verstatil PC ⁶	Phenoxyethanol, Caprylyl Glycol	1.10
	Eldew PS-203R ⁶	Phytosteryl/Octyldodecyl Lauroyl Glutamate	0.20
5	Citric Acid solution 10% ¹	Citric Acid, Water	2.20

Production: Prepare half of the water / Add LIFTONIN[®]-XPRESS while stirring; let it swell for about 10 minutes, the phase must be free of lumps / Take the other part of the water and add Optigel WX and CL while stirring / Homogenise for 10 minutes and add the whole gel to the water and LIFTONIN[®]-XPRESS mixture while stirring / Continue stirring till a homogenous gel appears / Add the remaining ingredients while stirring; homogenise

Properties:

Appearance Light brownish gel
pH-value 6.5-7.0

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