Hyaluronic acid - a legendary agent

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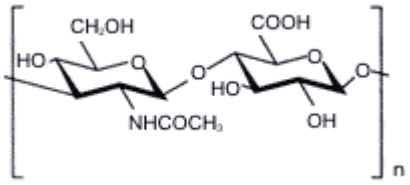
Hyaluronic acid is a legendary agent in the true sense of the word and it is almost impossible to imagine basic skin care and the treatment of wrinkles and dry eye syndrome without it. However where there is light there is also shadow and more and more treatment procedures with hyaluronic acid become known that rather belong into the category of wheeling and dealing than into scientifically based concepts. Read more about this agent in the following.

Hyaluronic acid is a natural and sugar-like biopolymer in the human body that alternately consists of D-glucuronic acid and N-acetyl-D-glucosamine-units.



Hyaluronic acid is an essential component of the vitreous body, ubiquitous lubricant in joints and a significant element of the extracellular matrix and the connective tissue in the skin. In terms of quantity it is the skin that contains the largest portion of it. With advancing age the content of hyaluronic acid in the joints decreases continuously. The term hyaluronic acid derives from the Greek expression for "vitreous" and refers to the fact that it is found in the vitreous body of the human eye. If hyaluronic acid in a cosmetic context is concerned it almost exclusively relates to sodium hyaluronate.

Retains enormous quantities of water

Hyaluronic acid can retain vast amounts of water. There are however dissenting opinions about the actual quantities retained by the different products on the market. An excellent comparison here is the formerly very popular dessert "jelly" or "jello" which is based on a related substance called xanthan. Only a very small amount of powder is required to produce a large quantity of stiff gel.
Due to the high water binding capacity the gel is rather interesting for cosmetic applications. However, there is an additional feature that gives the winning edge over other polysaccharides: hyaluronic acid creates films that stay on the skin surface other than modified polysaccharides like carboxymethyl cellulose or hydroxymethyl cellulose etc. which peel off like parchment foil after the water in the preparation has evaporated. That is why it can also be used in pure form as active agent concentrate.
An interesting dermatological indication is the dry eye syndrome. By taking advantage of the water retaining features of hyaluronic acid hyaluronic acid solutions are sprayed on the closed eye to impede the typical symptoms of eye redness and inflammations caused by low room humidity and deficient lachrymal secretion. Also liposomal combinations have proved successful for this purpose.

Spiriting away the wrinkles

Hyaluronic acid combines with the keratin of the skin via hydrogen bridges in a way that the evaporating water leaves a light tension on the skin which can spirit away minor wrinkles. An additional effect is a slight plumping on the wrinkle basis. Hence hyaluronic acid is an integral part of anti-aging products. Talking about xanthan: combinations of hyaluronic acid and xanthan perfectly complement one another.
Water binding as well as plumping effect is taken advantage of for the anti-wrinkle injection and lip enlargement. Today, cosmetic therapy as well as aesthetic dermatology use biotechnologically produced hyaluronic acid, and those times when it was gained from cockscombs are gone and over. Streptococcus zooepidemicus e.g. forms an excellent product with perfect compatibility and no tolerance problems.

Percentage shares: not necessarily comparable

If hyaluronic acid solutions (gels) are dehydrated by freeze drying a whitish and powdery dry matter is left which tends to attract water, or to use another term, which is hygroscopic.
Commerce preferably advertises with high concentrations of hyaluronic acid and in this context the truth is frequently bent. So con-

centrations of 10 to 20 per cent can be found in this connection. The consumer should not be deceived here as the content of hyaluronic acid gel in the product is referred to, or in other words, the content of hyaluronic acid plus water. The gels in general contain no more than 1 per cent of dry matter which in reality amounts to a hyaluronic acid concentration of 0.1 respectively 0.2 percent, just to apply the above mentioned figures of 10 to 20 per cent. This kind of jugglery with figures is also very popular in connection with extract concentrations.
The hygroscopic behaviour of the pure substance also determines its susceptibility towards microorganisms that depend on the presence of water. Hence the substance can only be stored in tightly closed containers.

Does it penetrate into the skin?

Hyaluronic acid is offered in different molar masses. A clue may be here the molar mass of 1,000,000 Dalton (corresponds to 1,000,000 g/mol). It is frequently claimed that hyaluronic acid with lower molar mass can easier penetrate into the skin and hyaluronic acid with high molar mass not at all. In this context also the term monomer hyaluronic acid is used. It can however be stated that externally applied hyaluronic acid in conventional form i.e. as gels or creams will not reach the deficient corium. Not to speak of passing through an intact skin barrier. Mechanical energy like ultrasound may support its anchoring in the keratin of the skin. On the other hand however it was observed that ultrasound application results in a formation of chain fragments. A penetration of the low molar substance as for instance lower than 25,000 g/mol no longer is excluded. Hyaluronic acid fragments of low molar mass are also released as messenger substances in case of inflammations.

Interlinking – when is it reasonable?

The disadvantage with hyaluronic acid is that it is easily removed during the washing process and therefore has to be re-applied over and over again. The enzymatic degradation process of the material used in anti-wrinkle injections also is seen as a disadvantage. In order to eliminate these negative factors, the chemical structure of hyaluronic acid has been modified again and again. The different hyaluronic acid strands are linked with each other by etherification of the free hydroxyl groups (**-OH**) and esterification of the carboxyl groups (**-COOH**) with polyfunctional substances that form an artificial bridge between the different strands. Also a deacetylation of the N-acetyl-D-glucosamine group and the subsequent condensation with interlinking aldehydes and carboxylic acid are reported. Crosslinking or even "double crosslinking" may be a useful procedure to deal with the enzymatic degradation of anti-wrinkle injections however with regard to external skin care it is not a good idea as the water binding capacity is impaired due to the fact that the number and availability of polar groups decreases. The tolerance of these interlinked products is reported to be excellent though.

In form of microparticles

A further alternative is to combine hyaluronic acid with a matrix of 2-(diethylaminoethyl)-dextran which is a chemically modified dextrin also known as sephadex **DEAE A25**, hypromellose i.e. a chemically modified cellulose (methyl-hydroxypropylcellulose) and crosslinked hyaluronic acid. The resulting microparticles also appear safe enough not to trigger irritations or inflammations in the long term. This combination is also supposed to have a longer shelf life than regular hyaluronic acid as it is less susceptible to degrading hyaluronidases. In product marketing and advertising it is also described with the term hyper twisted stabilized hyaluronic acid.

Combinations with laser?

Hyaluronic acid solutions modify with thermal ($\geq$ 100 ^{0}**C**) and mechanical strain as for instance high pressure homogenization and ultrasound applications, which means that the solutions increase their fluidity and contain more and more short chained fragments that may penetrate easier into the horny layer, as already is described above. It is however a disadvantage that also the water binding capacity decreases. In a patent application describing this already known process it is maintained that those fragments merge again into their original long chained polymer structure of the hyaluronic acid after their application on the skin (through massages) and their penetration with the help of infrared cold light laser therapy. Until today however there is no evidence for this statement. Hence the patent application may rather be related to a specific sales action for laser devices.

Stimulating the natural production

The following interesting alternatives to the external application of hyaluronic acid products are in progress

- an exogenic stimulation of the hyaluronic acid synthesis in the skin and

- **the inhibition of hyaluronic acid degrading enzymes (hyaluronidases)**

The penetration of appropriate active agents is easier and more elegant than the penetration of hyaluronic acid products. Based on the principles of corneotherapy the horny layer is prepared for the passage of active agents with liposomes or nanoparticles and then reconditioned with the help of adequate barrier creams. The advantage of this technique is that the effect may start right at the spot where it is needed.

The formation of hyaluronic acid can be stimulated with soybean extract e.g. which is rich in phytohormones (isoflavones) as well as in saponins. Alternatively a combination of liposomal red clover extract (phytohormones) and butcher's broom extract (ruscus aculeatus) may be used. Butcher's broom contains the saponins ruscin and ruscoside as well as their aglycons (the glycosidic agents without the sugar portion) ruscogenin respectively neo ruscogenin. Appropriate eye and wrinkle products may also be equipped with surface effective hyaluronic acid.

Inhibiting the degradation

Many substances with a polysaccharide-like structure as hyaluronic acid have inhibiting effects on the hyaluronic acid degradation. Among them are heparin and vegetable pectins that also form gels like hyaluronic acid and may be used e.g. as additives in the marmalade production. One of the most popular is the pectin contained in apples. The alginic acids of fucophyta also belong to this category. It should however be mentioned that these polysaccharide derivatives have the same unfavorable penetrating behavior as hyaluronic acid itself.

By contrast though, saponins (see above) like glycyrretic acid, glycyrrhizin (both gained from liquorice root) and aescin (gained from horse chestnut extract) show better results. Until now however their effect could only be proved in vitro. The same applies for the above mentioned flavonoids.

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