

The Resilient Hyaluronic Acid™ Technology

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OBJECTIVES

This document gives an overview of the **Resilient Hyaluronic Acid™** technology, patented by the Research & Development department of Teoxane Laboratories, and intended to the manufacturing of cross-linked hyaluronic acid (HA) gels. ^[1]

All Teosyal® cross-linked hyaluronic acid gels are processed according to the **Resilient Hyaluronic Acid™** technology, which optimizes their properties of **HIGH PURITY, HIGH ELASTICITY** and **HIGH RESISTANCE**.

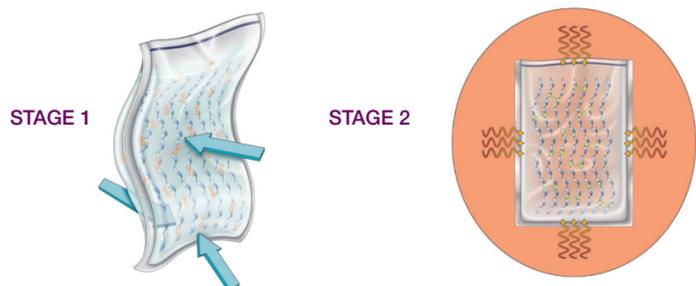
TECHNOLOGY

Resilient Hyaluronic Acid™ achieves a challenging goal: to optimize the cross-linking reaction of hyaluronic acid by BDDE (1,4-butanediol diglycidyl ether).

This patented process uses an original device: a sterile, malleable and hermetic pouch whereas standard processes use a rigid reactor equipped with a paddle or a mechanical accessory.

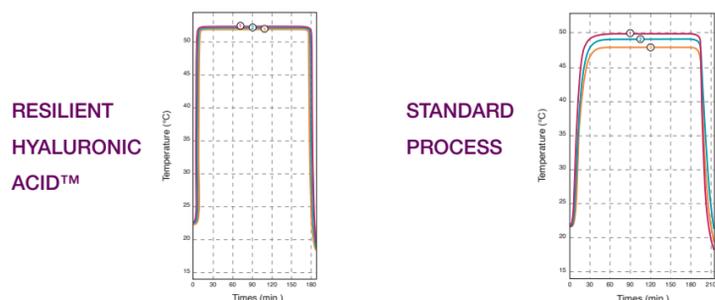


HA cross-linking reaction includes 2 stages. During the 1st stage, highly-concentrated HA water-solution is blended with BDDE, the cross-linking agent. Although the environment is extremely viscous (such as liquid honey), the most homogenous solution as possible has to be prepared. According to Resilient Hyaluronic Acid™ process, the pouch is deformed by applying gentle pressure on the outer walls thanks to specific equipments. This operation creates a homogeneous blend of HA and BDDE twice faster than with the conventional procedure by mixing with a paddle or a mechanical accessory in a rigid reactor. Thanks to our original device using soft but efficient mixing conditions, **HA chains are better preserved. In addition, risks of biological contamination are minimized** since the blend is preserved from any contact with the external environment.



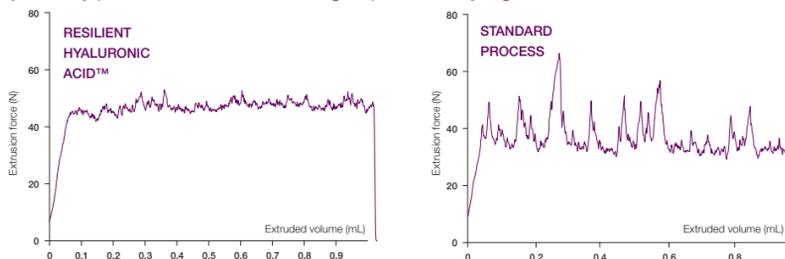
During the 2nd stage, a very precise temperature is applied in order to activate BDDE and make it interact with HA. BDDE molecules then create bridges that link 2 adjacent HA chains. The specific composition of the pouch walls allows an excellent heat conduction and a perfect homogeneity of the temperature. In the entire volume of the gel, the target temperature is reached at $\pm 0,2^\circ\text{C}$ compared to $\pm 2^\circ\text{C}$ in the conventional process.

Temperature curves as a function of time recorded at 3 different locations in the gel.



Therefore, the **Resilient Hyaluronic Acid™** technology enables to obtain a very regular cross-linking pattern. This is demonstrated on the gels obtained by their exceptionally smooth injectability profile through fine gauge needles as compared to cross-linked HA yielded by a conventional process, right after cross-linking with no mechanical homogenization applied. The absence of peak in the graph on the left below shows the gel's homogeneity.

Injectability profiles of the cross-linked gels packed in syringes



Outcomes: **Resilient Hyaluronic Acid™** affords a better control over the cross-linking conditions compared with a conventional process: a better preservation of HA quality and an isotropic cross-linking pattern yielding perfectly homogeneous monophasic gels.

CHARACTERISTICS OF RESILIENT HYALURONIC ACID™ GELS

■ HIGH PURITY

The **Resilient Hyaluronic Acid™** cross-linking process, protected from any contact with external environment, associated with a thorough purification of the gels under cleanroom environment conditions above the standards required, guarantee very high levels of purity. **For each manufactured batch, levels of BDDE and bacterial endotoxins residues are even lower than the levels recognized as totally safe** (see the table below with the limit values validated by regulatory and health authorities and data from Teosyal® batches). ^[2-3]

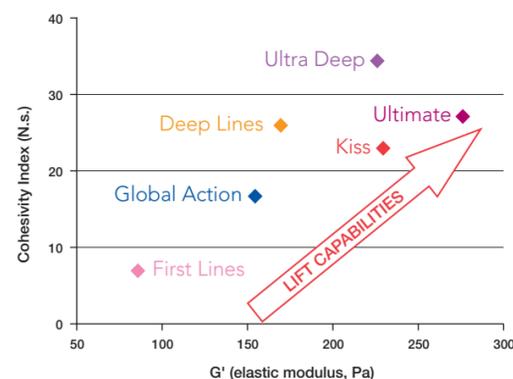
Teosyal® products and batch numbers	BDDE content [2]	Endotoxins LAL (EU/g) [3]
Maximum level validated by regulatory and health authorities	< 2 ppm	< 12.5 EU/g
Maximum level tolerable for a Teosyal® batch release	< 1 ppm	< 0.5 EU/g
Highest recorded value	0.43 ppm *	0.31 EU/g **
90% of the recorded values are :	< Limit of quantification (0.41 ppm)	< Limit of quantification (0.1 to 0.2 EU/g)

*: Annual Sampling Plan (2011) applied on all Teosyal® batches, and all formulations, according to ISO 2859-1.
**: Among about 350 batches released in 2011.

■ HIGH ELASTICITY

By creating a cross-linked HA network, perfectly monophasic and homogeneous, Resilient Hyaluronic Acid™ forms a tissue that is both cohesive and elastic. Its use in all Teosyal® dermal fillers enables to equilibrate the elastic modulus G' and the cohesivity index in order to adapt to each indication.

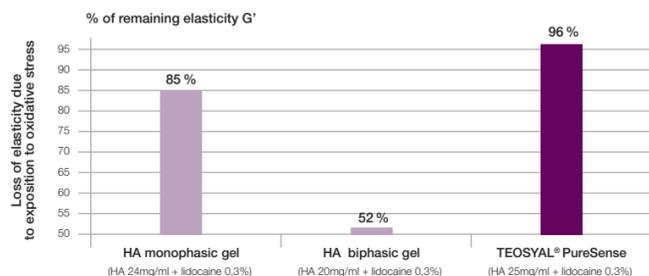
Especially, the most volumizing Teosyal® gels were shown to display the highest Lift Capabilities values compared to competitors. ^[4]



■ HIGH RESISTANCE

In vivo degradation of HA dermal fillers occurs over time through hyaluronidases, oxidative stress and mechanical stress. Thanks to high cohesivities and to very regular cross-linked networks, **Resilient Hyaluronic Acid™ gels allow to slowdown the natural degradation and thus to improve the durability of dermal fillers in the dermis.** This is demonstrated in vitro by applying an oxidative stress on a Teosyal® PureSense gel and on 2 competitors: we can observe that Teosyal® PureSense, including Resilient Hyaluronic Acid™, displays a better resistance by keeping a larger part of its initial elastic modulus G' after oxidation.

In-vitro test reproducing the action of oxidative stress in the skin



CONCLUSION

The **Resilient Hyaluronic Acid™** patented technology, by using a sterile malleable and hermetic pouch for the cross-linking reaction, leads to real and measurable benefits on the mechanical properties of Teosyal® dermal fillers. These essential advantages give Teoxane Laboratories' products their exclusive properties of **HIGH PURITY, HIGH ELASTICITY** and **HIGH RESISTANCE**.

REFERENCES AND NOTES

1- «Process for Preparing a Crosslinked Gel» Patent WO 2010131175; FR 2945293. 2- **Analysis performed by an Independent Laboratory.** A 2 ppm content of BDDE is considered as safe: the cancer risk from exposure of patient to BDDE is considered as minimal by the FDA. Source: U.S. Food and Drug Administration (FDA) Cancer Risk Assessment, Advisory Panel Briefing Information, PMA P020023, Nov. 2003. 3- Endotoxins can lead to general inflammation or systemic inflammation and septic shock, if the immune response is severely pronounced. 4- «Lift Capabilities evaluation of Hyaluronic Acid Fillers», Poster 10th AMWC 2012 - 10th Anti-Aging Medicine World Congress & Medispa.

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