



# HA Crosslinking in as little as One Minute

*How Studio Bioscience Unlocked a New Generation of Dermal Fillers and Injectable Products with ResonantAcoustic® Mixing*

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## OVERVIEW

Hyaluronic acid (HA) is the active ingredient in the world's most widely used dermal fillers and joint injection products. Crosslinking HA to improve its stability, durability, and rheological properties is the critical chemical step that makes those products possible. For decades, that step has required hours of processing at elevated temperatures, with results that are difficult to tune and prone to polymer degradation.

Dr. Felix Polyak, President of Studio

Bioscience, discovered that by applying ResonantAcoustic® Mixing to HA crosslinking, they achieved rheological properties that exceed those of leading commercial dermal fillers in as little as one minute at room temperature. [1][2]

The finding was presented at the International Society for Hyaluronan Sciences (ISHAS 2023) and is now the subject of an international patent portfolio spanning the United States, European Union, Canada, and Mexico. [2][3]



### Solution

- ResonantAcoustic® Technology
- Low Heat Reactive Chemistry
- Tunable Rheological Properties via Mixing Parameters



### Achievement

- BDDE Crosslinking of HA Gels in as Little as One Minute [1][2]
- Room-Temperature Processing — No Polymer Degradation [2]
- Rheological Properties Above Commercial Fillers [2]

# CHALLENGES

Crosslinking hyaluronic acid is central to making it stable enough for medical and cosmetic use. In its natural state, HA has a half-life of no longer than one and a half days after injection into skin or joints. Crosslinking — typically achieved using BDDE (1,4-butanediol diglycidyl ether) — extends that half-life significantly, making crosslinked HA the primary ingredient in the world’s most widely used dermal fillers and joint injection products. [2][4]

But conventional crosslinking has well-documented limitations. Most available methods require reaction times of several hours at approximately 50°C — temperatures that can cause mild to moderate degradation

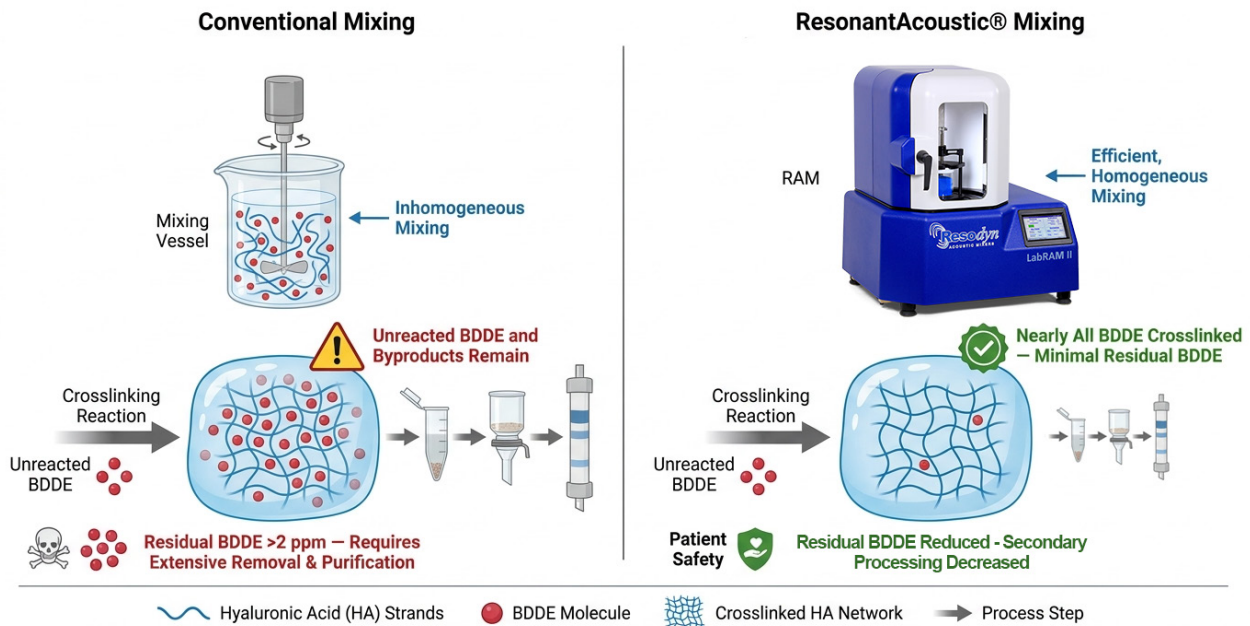
of the very polymer being crosslinked. [2] Additionally, independent peer-reviewed research has established that crosslinking efficiency is directly dependent on the mixing process, and that unreacted chemical cross-linker (BDDE) is hazardous to human health, requiring removal. Achieving both efficient crosslinking without unreacted chemicals is “one of the major challenging issues in hydrogel manufacturing.” [4]

The result is a market of products clustered within a narrow band of achievable and economically viable rheological properties — not because the chemistry cannot deliver more, but because the mixing process has always been the limiting factor.

## Why Incomplete Crosslinking is a Patient Safety Issue

*When HA is not homogeneously mixed with BDDE before crosslinking, unreacted BDDE remains in the final product. Unreacted BDDE and its oxidized byproducts are toxic and can cause allergic reactions in patients. Residual BDDE in finished dermal fillers must remain below 2 parts per million to be considered safe for human use. [5][6]*

*ResonantAcoustic® Mixing addresses this at the source by driving efficient crosslinking. Dr. Polyak’s patent documents that RAM-based crosslinking “substantially does away with isolation and purification procedures”, saving significant cost for manufacturers. [2] Better mixing means more complete crosslinking, less residual crosslinker, and a cleaner, safer final product.*



## SOLUTION

ResonantAcoustic® Mixing, pioneered by Resodyn Acoustic Mixers, uses low-frequency, high-intensity acoustic energy to process materials without blades or impellers. At Studio Bioscience, Dr. Polyak applied it as a driver of reactive chemistry, using the acoustic energy to accelerate and control the BDDE crosslinking reaction itself.

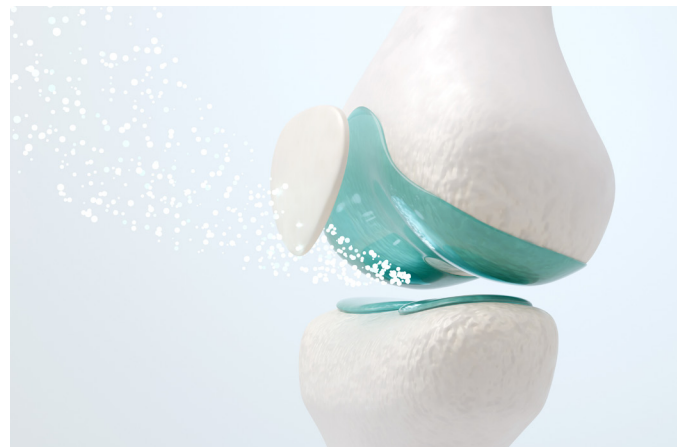
Presenting at ISHAS 2023, Dr. Polyak described the significance of what his team had discovered:

*“This is [an] example of utilizing a known physical technique, so called resonant acoustic mixing, for chemical reaction. In our case BDDE-HA crosslinking. Successful application of resonant acoustic technology to HA crosslinking leads to significant technological advantages and at the same time allows to create crosslinked HA gels with new... rheological properties.” [1]*

### From Hours at 50°C to Minutes at Room Temperature

The process documented in the patent replaces the conventional multi-hour, elevated-temperature crosslinking reaction with a two-step RAM process conducted entirely at room temperature. Hyaluronic acid is first mixed with an aqueous sodium hydroxide solution using RAM at 60g acceleration for three minutes, producing a homogeneous gel. BDDE is then added and the mixture subjected to a further six minutes of RAM at 80g, completing the crosslinking reaction. Crosslinking was achieved in as little as one minute. [2]

Performing the reaction at room temperature directly addresses the degradation problem inherent in conventional methods. As the patent states:



Injectable HA products benefit from precise tuning for performance attributes.

*“Performing the crosslinking at room temperature advantageously provides for preventing potential decomposition of the polymer at more elevated temperatures such as 50°C, especially when the crosslinking is performed over extended periods of time such as one or more hours. Decomposition may be especially problematic with carbohydrate polymers such as hyaluronic acid.” [2]*

### Superior and Tunable Rheological Properties

RAM produced measurably superior HA in key rheological properties. The patent documents that BDDE-crosslinked HA obtained using RAM exhibits high dynamic viscosities and a relatively high storage modulus  $G'$  and loss modulus  $G''$  compared directly to leading commercial dermal fillers, including Juvederm Ultra® XC, Juvederm Voluma® XC, Restylane Kysse®, Restylane Volyme®, and Belotero Balance®. [2]

A further and commercially significant advantage is that the rheological properties of the crosslinked material can be tuned by adjusting RAM mixing parameters, such as forcing energy and frequency, without changing the chemistry. This gives formulators a new

degree of control over the final product that conventional crosslinking methods cannot offer. [2]

## A New Platform for Dermal Fillers and Beyond

The applications documented in the patent extend well beyond dermal fillers. RAM-crosslinked HA is documented for therapeutic applications including joint injection products, stress urinary incontinence, vesicoureteral reflux, vocal fold insufficiency, and vocal fold medialization — anywhere that a crosslinked, injectable HA hydrogel with tunable properties is clinically useful. [2]

Dr. Polyak expressed his confidence in the technology's commercial trajectory directly:

*“We strongly believe that this technology will find its way for creation of new and highly valuable new dermal fillers and joint injection products.” [1]*

## CONCLUSION

Studio Bioscience's application of ResonantAcoustic® Mixing to HA crosslinking represents a genuine chemical process innovation and a documented use of acoustic mixing as the driver of a reactive chemistry process. Conventional crosslinking requires hours at elevated temperatures and produces materials within a constrained rheological range. RAM achieves crosslinking in as little as one minute at room temperature, with superior and tunable properties that existing commercial products do not match.

The international patent portfolio covering this process in the US, EU, Canada, and Mexico reflects the significance of the discovery. As ResonantAcoustic® Mixing continues to find new applications at the chemistry frontier, the Studio Bioscience work stands as a compelling proof of concept: acoustic energy is not just a mixing tool, but a reactive chemistry platform. [1][2][3]

**Contact Resodyn Acoustic Mixers, Inc. to discuss how we can transform your reactive chemistry process.**

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### CITATIONS

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