
Injectable Calcium Hydroxylapatite Implants: Biocompatibility

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Summary

Injectable Calcium Hydroxylapatite Implants (CaHA Implants) have been scientifically designed to provide biocompatibility, durability, efficacy, and ease of use in soft tissue augmentation.

The primary compound used in the implants is pure, synthetic calcium hydroxylapatite (CaHA) particles composed of calcium and phosphate ions. Calcium hydroxylapatite occur naturally in the body, therefore, synthetic CaHA is inherently biocompatible by chemical composition. It is identical in composition to the mineral portion of human bone and teeth. Therefore the synthetic CaHA particles are ultimately metabolized through normal homeostatic mechanisms. In addition, all of the ingredients in the implants' aqueous gel carrier are biocompatible and classified as "Generally Recognized as Safe" by the Food and Drug Administration.

Extensive safety studies have been conducted on the implant formulation, including toxicology assessments, standardized biocompatibility testing and long term animal studies. While the composition is inherently biocompatible by chemistry, specific testing of this CaHA Implant has validated the implant is biocompatible, non-toxic, non- antigenic, and non-allergenic. These results are consistent with those reported in literature and other clinical experiences with the many other calcium hydroxylapatite based implants.

CaHA Implant Formulation

The primary and durable component in the implant is calcium hydroxylapatite (CaHA), which has a clinically proven record of biocompatibility. It has been used for decades as an implant material in plastic and reconstructive surgery, orthopedics, otology, otolaryngology, neurosurgery, dentistry, maxillofacial surgery, and urology.

CaHA is a bioceramic, rather than a metal or polymer; it is by nature a non-irritant to the body. Should any CaHA become phagocytized, the particles degrade into calcium and phosphate ions, just as with small fragments of natural bone. Metabolism is handled through normal homeostatic mechanisms.

The other component of the implant is a gel carrier, which is an aqueous formulation of sodium carboxymethyl cellulose (NaCMC), glycerin, and sodium phosphate buffer. These excipients have extensive use in medical devices and are classified as "Generally Recognized as Safe" by the Food and Drug Administration (FDA). The synthetic formulation of the CaHA particles and the use of other historically compatible ingredients also removes any need for patient sensitization testing, allowing immediate treatment.

Biocompatibility Assessments

In vitro and *in vivo* biocompatibility testing conducted on the implants meet the requirements of the ISO 10993, *Biological Evaluation of Medical Devices*.

In vitro tests investigated cytotoxicity, blood interactions, and mutagenic responses (Table 1). Test results indicate the implants are nontoxic with no mutagenic response.

In vivo tests were performed to evaluate sensitization, irritation, systemic reactions, tissue reaction, and long-term safety. Results confirm the implants are non-antigenic, non-irritating, and nontoxic.

Table 1. Biocompatibility Testing

TEST	ADMINISTRATION	RESULTS
Acute Systemic Toxicity (mice)	Test article Intraperitoneal Injection	Non-Toxic
Intracutaneous Toxicity (rabbit)	Test article Intracutaneous Injection	Non-Toxic
Systemic Antigenicity (Guinea Pig)	<u>Induction Phase:</u> Test Article Intraperitoneal Injection <u>Challenge Phase:</u> Saline Extract IV injection	Non-Antigenic
7 Day Implantation (rabbit)	Test article Muscle implantation	Not Significant Non-Irritant
28 Day Implantation (rabbit)	Test article Muscle implantation	Not Significant Non-Irritant
Cytotoxicity (Agar Overlay)	Test article Direct Contact	Non-Toxic
Ames Mutagenicity	Saline extract	Non-Mutagenic
Clotting Time (Lee-White)	Test Article Direct Contact	No Significant Effect

Long-Term Safety Study

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Commercially available CaHA implants have an outstanding long term safety profile. Several commonly used CaHA based injectable products have been on the market for 10 plus years. The clinical records of use of these implants have demonstrated safety and efficacy to the patient. A number of technological advancements in recent years have spurred renewed interest in vocal fold injection augmentation. The present review discusses the characteristics of currently available short-term and long-term injection materials, and the advantages and disadvantages of each.

Recent findings: Many of the newer laryngeal injectable substances were originally used as dermal fillers born out of the plastic surgery and dermatologic literature. Clinical outcomes⁶⁻¹⁶ have improved as a result of exciting advancements in vocal fold injection material availability and design. New substances now closely mimic the native viscoelastic properties of the vocal folds.

Conclusions

Extensive biocompatibility studies reported here, which have been reviewed and accepted by the FDA, demonstrates that the implants are wholly biocompatible when injected into soft tissue. Since CaHA is natural to the body, there are no antigenic or inflammatory responses upon implantation. Long-term effects are equally benign. CaHA degrades through normal metabolic pathways in the same process as that seen with bone fragments, unlike implants made with silicone, polytetrafluorethylene (PTFE), carbon, and similar materials left behind from common fractures.

The primary cellular response to the implant material is an in growth of native tissue in and around the CaHA particles, which helps fix the particles at the implant site. The cellular response to the implant's gel carrier involves mononuclear macrophage phagocytosis and enzymatic biodegradation. This allows infiltration of the surrounding tissue to form a long-lasting implant of

CaHA particles and natural tissue.

The safety results seen in these studies of the implants are consistent with published data and other clinical experience with calcium hydroxylapatite.¹⁻¹⁷

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