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Thermoresponsive Hydrogels Based on Hyaluronan for Injectable Use in Dermatology

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Abstract

The majority of commercially available HA-based dermal fillers use chemical cross-linking to enhance their mechanical characteristics and prolong their shelf life in vivo; nevertheless, more rigid and elastic formulations need a stronger extrusion force for injection in clinical settings. We suggest a thermosensitive dermal filler, injectable as a low viscosity fluid that undergoes in-situ gelation upon injection, to balance longevity and injectability. In order to do this, "green chemistry" was used to combine HA with a linker and a thermosensitive polymer called poly(N-isopropylacrylamide) (pNIPAM). Water served as the solvent. At normal temperature, HA-L-pNIPAM hydrogels had a relatively low viscosity, but at body temperature, they spontaneously produced a stiffer gel with a submicron structure.

Keywords: Dermal fillers• Hyaluronic acid • Balance

Introduction

Due to its usage in treating issues related to ageing skin, such as reduced skin elasticity, face wrinkles, and collagen degradation, injectable biomaterials have gained popularity. Dermal fillers have been extensively studied for their ability to produce rapid face rejuvenation through easy and quick procedures. In 2020, there will be more than 2.6 million minimally invasive operations performed in the US alone using Hyaluronic Acid (HA)-based fillers, which make up the greatest percentage of products among the various materials. This is explained by HA's non-toxicity, biocompatibility and simplicity of reversal.

D-glucuronic acid and N-acetyl-D-glucosamine are alternately repeated and linked by "-linkages, GlcA, to form natural HA. Both the epidermis and the dermis synthesise it as a high-molecular-weight substance, but it degrades quickly as a result of oxidative stress and hyaluronidases. Unmodified HA in the skin has a half-life (t1/2) of around 12 hours. Lower molecular weight fragmented HA is a powerful inducer of angiogenesis and inflammation, which might have negative effects like erythema, mild oedema, hematoma, itching and pain. To enhance mechanical qualities and in vivo residence time, HA utilised in dermal fillers is frequently cross-linked [1].

Literature Review

Hyaluronic acid sodium salt (1500–1750 kDa) of laboratory quality was acquired from Contipro a.s. in Doln Dobrou, Czech Republic. Click Chemistry Tools (Scottsdale, AZ) supplied the sulfur-dibenzocyclooctyne-PEG4-amine (Sulfo DBCO-PEG4-NH2) that was purchased. Hyaluronidase from bovine testes (Type VI-S), hydrogen peroxide (30% w/w), toluidine blue, Dulbecco's Modified Eagle's Medium-High Glucose (DMEM), embryoMax L-glutamine solution (100X), Foetal Bovine Serum (FBS), and the antibiotic-antimycotic solution (100X) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Dialysis membranes were purchased from Repligen (Waltham, Massachusetts, USA) in the form of Biotech CE Dialysis Tubing 300 kDa. I got the Alcian blue PAS stain kit from ABC. The reference products Belotero Balance and Belotero Volume were obtained from Merz Pharma (Geneva, Switzerland) and used [2].

On a Peltier cone-plate C35 2°/Ti rotor-equipped HAAKE Mars RheometerTM (Thermo Scientific, Waltham, MA, USA), rheological behaviours were assessed. A sample hood was used during measurements on 420 L samples to lessen evaporation. The artificial HA-L-pNIPAM copolymers were first dispersed in agitated PBS for a whole night, after which centrifugation was carried out at 10,000 rpm for 20 min at 4 °C. In order to simulate the forces to which a filler is exposed in vivo from gravity and muscular movements, the storage modulus (G′) and loss modulus (G″) of the obtained formulations (3%, w/v) were evaluated as a function of temperature using a ramp from 22 °C to 37 °C with a heating rate of 0.04 °C/s and a constant oscillatory frequency of 0.7 Hz [3].

Hyaluronan (HA), a naturally occurring polysaccharide found in the extracellular matrix of various tissues, has emerged as a promising candidate for the development of injectable hydrogels. HA exhibits excellent biocompatibility, biodegradability, and viscoelasticity, making it well-suited for dermatological applications. Additionally, HA possesses the ability to retain water, providing hydration and lubrication to the surrounding tissues. To confer thermoresponsive properties to HA hydrogels, molecular modifications are necessary. Various approaches have been explored, including the introduction of hydrophobic moieties or grafting of thermoresponsive polymers onto HA backbones. These modifications allow for the modulation of gelation behavior, injectability and mechanical properties of the resulting hydrogels [4-6].

Discussion

According to conventional wisdom, oxidative stress, hyaluronidases, and mechanical stress are the principal in vivo degraders of dermal filler products. Therefore, we evaluated the enzymatic digestion and oxidative degradation of HA-L-pNIPAM hydrogels at 37 °C *in vitro* and compared them to Belotero Balance. Hyaluronidases were added, and the results were considerably more noticeable. Candidates 1 and 2 and Belotero Balance adhered to the same declinating tendencies in both moduli. Candidate 3 once more exhibited a viscoelastic behaviour with significant G′ and G″ standard deviations. thermoresponsive hydrogels have attracted considerable interest due to their ability to undergo reversible sol-gel transitions in response to temperature changes. This unique behavior enables them to be injected as a liquid and form a gel in situ at physiological temperatures, making them attractive for use in dermatological procedures.

The applications of thermoresponsive HA hydrogels in dermatology are diverse. One significant application is the delivery of bioactive molecules,

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such as growth factors, peptides and drugs, to enhance wound healing, tissue regeneration and aesthetic procedures. The injectable nature of these hydrogels enables precise and targeted delivery, minimizing invasiveness and promoting controlled release of therapeutic agents. Despite the promising potential of thermoresponsive HA hydrogels, certain challenges need to be addressed. The gelation kinetics, mechanical properties and long-term stability of these hydrogels require optimization. Strategies such as the incorporation of crosslinking agents or the combination of HA with other materials in hybrid systems have been explored to overcome these challenges and enhance the performance of injectable formulations.

Conclusion

The benefits of HA-based thermosensitive fillers in terms of hydrogel injectability, resistance to enzymatic degradation, and tissue integration were highlighted in this study and contrasted to those of commercially available reference materials. Water was used for the copolymer syntheses; because of the water-based, reliable scheme of the EDC/NHS amidation and the effectiveness of the click chemistry method, it should be viable to scale up the production process. At body temperature, three distinct HA-L-pNIPAM-based fillers were developed that have a high storage modulus G′ while still being injectable with 34G needles.

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Conflict of Interest

There are no conflicts of interest by author.

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