Advance Research in Textile Engineering

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Austin Publishing Group

Review Article

Collagen Fibers: An Emerging Source for Medical Applications

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Received: March 09, 2022; **Accepted:** April 01, 2022; **Published:** April 08, 2022

Abstract

Collagen is a connective tissue protein that has piqued the interest of scientists for quite some time. Collagen is important for the organism's survival as well as the pathophysiology of sclerosis, scarring, inflammatory disorders, and regeneration. Low immunogenicity, regulated biodegradation and bioresorptivity during organism implantation, absence of toxicity, biocompatibility, and good plasticity are just a few of the practical qualities that make it appealing for medical and cosmetic materials. Collagen fiber, its extraction, and production method have all been examined in this review. The application is also discussed in this review.

Keywords: Collagen fiber; Inflammatory disorders; Organism

Introduction

In vertebrates, type I collagen fiber (CF) is one of the most abundant structural proteins. It is found in animal bones, tendons, cartilage, interosseous membrane, skin, ligaments, and other connective tissue, where it makes up 25% to 35% of total protein [1]. Individual collagen triple helices, as the basic unit of collagen fibers, assemble in a complex and hierarchical manner, resulting in macroscopic fibers and networks. The diameter of a collagen fibril is typically 10-500 nm. Glycoproteins and proteoglycans then collect it into a tiny fibril bundle with a diameter of 1-2 μm [2]. Collagen fibrils can be converted to collagen fibers by covalent cross-linking [3].

Natural collagen fiber differs from standard fibers in that it has a shorter length and can be used in textile fields more easily. Regenerated collagen fibers with specific properties are obtained by spinning methods with collagen protein extracted from substrates to adapt to human demands. Collagen is recognized as a desirable material for bio-applications due to its great biocompatibility and biodegradability, as well as its low antigenicity. Furthermore, collagen fibers have an affinity for chemicals and mental ions, allowing them to be used in a variety of sectors (Figure 1).

Production

Collagen is typically derived from tissues like skin, tendons, and bones. Collagen dissolving is hampered by natural collagen's low solubility, which is caused by covalent cross-links such as Schiff base [5], which form a stable fiber network. As a result, chemical/biological agents are used to break the covalent bonds and dissolve the collagen fiber. To date, there are three common procedures for obtaining noncovalently linked collagen: acid extraction, alkali extraction, and enzyme extraction.

Enzyme

Pepsin can cleave the cross-linked regions at the telopeptide without compromising the integrity of the triple helix, allowing the collagen to be extracted through further treatment. In a nutshell, raw ingredients are suspended in 0.5mol/l acetic acid with pepsin. Enzyme extraction is highly efficient and nonpolluting due to the high activity of the enzyme. Because enzymes are temperature and pH sensitive, it's critical to keep the reaction under control.

Acid extraction

Acid extraction is frequently done with acetic acid, sulfuric acid, citric acid, and hydrochloric acid. Acid causes partial hydrolysis of collagen, resulting in tiny collagen molecules [6]. Collagen is often extracted with a 0.5M acetic acid solution, which has proven to be effective without causing too much harm to collagen's triple helix structure. Normally, the extraction is carried out for 16 hours with periodic stirring. After centrifugation, a solution of NaCl is used to salt out the collagen solution. Collagen can be redissolved in acetic acid and reprecipitated as described above to further purify it. Temperature should be kept as low as feasible [7], for example, 15^{0}C, to avoid collagen degradation.

Alkali extraction

Sodium hydroxide, calcium hydroxide, sodium carbonate, and lime are often employed in alkali extraction. Although the processes for alkali extraction of CFs are identical to those for acid extraction, the use of a high amount of alkali will pollute the environment. At 40°C, raw materials are agitated in 0.5M NaOH including 10% NaCl [8]. The collagen is recovered by salting out the CF, purified by redissolving in acid, dialyzed against 0.01M acetic acid, and lyophilized after the CF has been dissolved. In practice, multiple systems are integrated and employed to produce the optimum effect during the collagen preparation process. Acid extraction and alkali extraction, for example, can be used to improve the extraction efficiency.

Collagen is one of the most common biomaterials utilized in biological applications. To present, only three spinning methods have been documented for preparing CFs: wet spinning, electrospinning, and microfluidic spinning.

Electrospinning of collagen fibers

Electrospinning is a method of controlling the production and deposition of polymers using an electric field. This technique is highly

Citation: Zaki Mujahid SM, Abdul Alim M and Islam T. Collagen Fibers: An Emerging Source for Medical Applications. Adv Res Text Eng. 2022; 7(1): 1069.

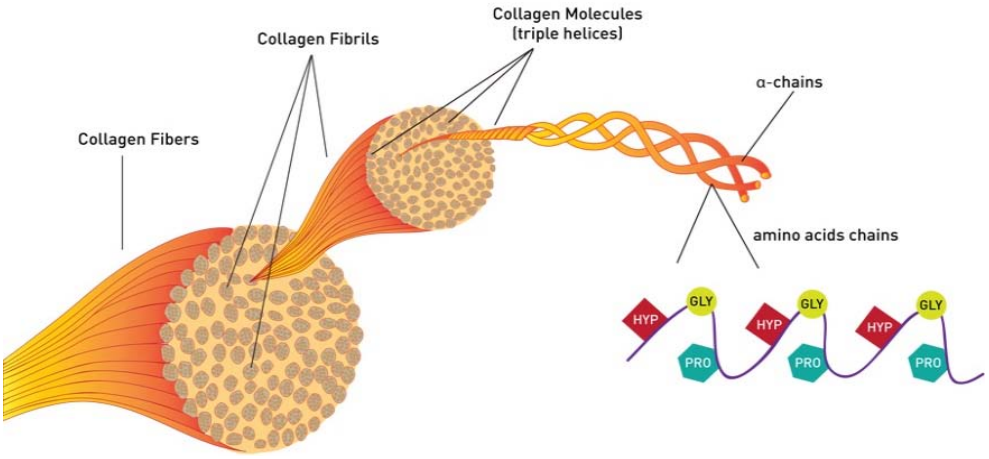

Figure 1: Molecular structure of collagen fiber [4].

efficient, quick, and affordable [9]. The collagen solution is usually supplied through a tiny needle opposite a collecting plate or target in electrospinning. As a result, the electrospinning process has the ability to create collagen fibrils that closely resemble, and in some cases, totally replicate, the structural and biological features of the natural polymer [10]. Matthews et al. [11] employed hexafluoro-2-propanol (HFP) as the solvent, and optimized the electrospinning conditions by adjusting the solution's viscosity and conductivity, as well as the spinning voltage, flow rate, and collecting distance in preliminary studies. Jet generation was initially detected at 12kV during electrospinning of an 8 percent w/v collagen solution in HFP. Increasing the voltage to between 19 and 21 kV provided electrospinning with stable operating conditions for more than three hours. With evaporation of HFP, dry CFs could be collected at a distance of 15cm on a grounded plate. The CFs produced by this approach with the aforementioned settings has dimensions that are close to native collagen fibrils and range in size from 100 to 600 nm (Figure 2).

Wet spinning

Among the different fiber manufacturing technologies available, wet spinning has the ability to convert biomolecules into fibers without the use of high voltage and is less likely to cause denaturation. Protein fibers, such as CF, are most often produced using traditional wet and dry spinning procedures. Wet spinning of chitosan-CFs from an aqueous 2 percent acetic acid-methanol solution spun into an aqueous 5 percent ammonia solution containing 40-43 percent ammonium sulfate was disclosed by Hirano et al. [13]. The continuous fibers generated had an average diameter of 36m. When the acid in the collagen is neutralized by contact with the neutralizing solution, CF can be produced [14]. After that, the fibers are dehydrated in acetone and ethanol baths. Fofonoff and Bell [15], as well as Furukawa et al. [16], described several other wet spinning processes for CFs.

Microfluidic spinning

The creation of fibers in a microchannel employing a coaxial flow of a pre-polymer and a cross-linking agent is known as microfluidic spinning. This is similar to wet pinning; however, the cross-linking agent is delivered straight from the coaxial flow rather than through the bath. To include CFs, microfluidic fiber spinning technologies were used. In compared to blended fibers, endless, plain CFs would be very desirable due to their superior performance, which includes stronger mechanical stability, better biocompatibility, and less processing complexity. Enomoto et al. [17] used a microfluidic spinning machine with phosphate buffer to create CF with diameters ranging from 8 to 30 m. The obtained CF had a high level of bioactivity.

Collagen composite fiber

By combining collagen with polymeric materials, mechanical and bioactive properties of spinning scaffolds can be tailored. Polylactic acid (PLA) [18], polyurethane (PU) [19], polycaprolactone (PCL) [20], polydioxanone (PDO) [21], hydroxyapatite (HAP) [22], chitosan [23], poly(N-isopropyl) acrylamide [24], and others are commonly used polymers for generating collagen composite fiber.

Medical Application of Collagen Fiber

Cardiac applications

The four heart valve rings are histologically, elastically, and uniquely connected to cardiac muscle *via* the collagenous cardiac muscle. The interventricular septum and the atrioventricular septum, which separate the heart chambers, are also part of the cardiac skeleton. Collagen's contribution to cardiac performance is essentially a constant torsional force opposing the fluid mechanics of blood pressure emitted from the heart. The collagenous tissue that separates the upper and lower chambers of the heart is an impermeable membrane that, through physiological reasons, excludes both blood and electrical impulses. Atrial fibrillation does not progress to ventricular fibrillation when collagen is present. Smooth muscular mass is coated with collagen in various densities. The compliance required to transfer blood back and forth is influenced by the mass, distribution, age, and density of collagen. Specialized collagen folds' individual heart valve leaflets into form under varying pressure. Gradual calcium deposition inside collagen is a normal part of the aging process. Calcified spots inside collagen matrices create contrast in a moving display of blood and muscle, allowing cardiac imaging technology to calculate ratios that are essentially blood in and blood out. The pathology of the heart's collagen underpinning falls under the heading of connective tissue illness [25].

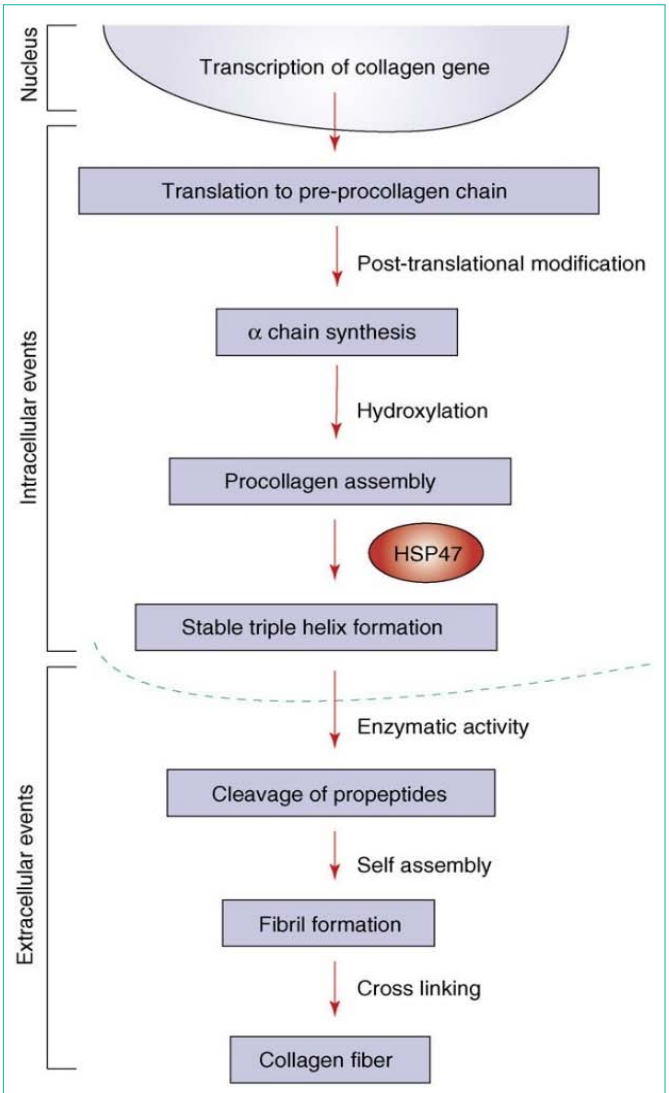

Figure 2: Process of collagen fiber formation [12].

Cosmetic surgery

Collagen is frequently utilized in aesthetic surgery, as a healing aid for burn patients, for bone rebuilding, and in a range of dental, orthopedic, and surgical procedures. Dermal fillers, both human and bovine collagen, are frequently utilized to alleviate wrinkles and skin aging. The following are some points of interest:

- There is a risk of allergic reactions resulting in extended redness when used cosmetically; however, this can be almost minimized by employing a simple and unobtrusive patch prior to cosmetic use [27].
- The majority of medicinal collagen comes from young beef cattle (bovine) that have been confirmed BSE-free. The majority of manufacturers utilize animals from "closed herds" or countries where BSE has never been reported, such as Australia, Brazil, and New Zealand [27].

Bone grafts

Because the skeleton is the body's structural foundation, it's critical that it stays strong even after breaks and injuries. Collagen is employed in bone grafting because it is an extremely strong molecule with a triple helix shape. It is ideal for usage in bones since it does not damage the skeleton's structural integrity. Collagen's triple helix shape protects it from enzyme degradation, allows cells to stick together, and is essential for the efficient formation of the extracellular matrix [28].

Tissue regeneration

Collagen scaffolds, whether in sponges [29], thin sheets [30], gels [31], or fibers [32], are utilized in tissue regeneration. Pore structure, permeability, hydrophilicity, and in vivo stability are all beneficial features of collagen for tissue regeneration. Collagen scaffolds also enable the deposition of cells like osteoblasts and fibroblasts, and once placed, they allow normal growth to occur [33].

Reconstructive surgical uses

Collagens are commonly used in the development of artificial skin substitutes for the treatment of severe burns and wounds [34]. Collagens can come from bovine, equine, porcine, or even human sources, and they're often combined with silicones, glycosaminoglycans, fibroblasts, growth factors, and other materials [35].

Wound healing

Collagen is a vital natural resource in the body and a component of skin tissue that can help with wound healing at all stages [36]. Closure can occur when collagen is made available to the wound bed. It is therefore possible to avoid wound worsening, which might lead to treatments such as amputation. Collagen is a natural product that can be utilized as a natural wound dressing since it contains qualities that artificial wound dressings lack. It is bacteriostatically resistant, which is critical in a wound dressing. Because of its natural capacity to resist infection, it aids in keeping the wound clean. Collagen as a burn dressing allows healthy granulation tissue to grow fast over the burn, allowing it to heal more quickly [37].

Collagen performs the following tasks in wound healing throughout each of the four phases:

- **Guiding function:** Collagen Fibers serve as a guiding force for fibroblasts. Fibroblasts move along a matrix of connective tissue.
- **Chemotactic properties:** Collagen fibers have a vast surface area, which attracts fibrogenic cells.
- **Nucleation:** Collagen can operate as a nucleating agent in the presence of certain neutral salt molecules, causing fibrillar structures to form. A collagen wound dressing could be used as a guide to help new collagen and capillary growth grow in the right direction.
- **Hemostatic properties:** Blood platelets form a hemostatic clog when they interact with collagen.

Conclusion

Collagen is not a simple protein, and any substance based on collagen for biomedical, cosmetic, or biotechnological purposes requires a basic understanding of collagen biochemistry and processing technologies, as well as a comprehension of its physico-

chemical properties. Because of the diversity of extracted collagen induced by its age, crosslinking degree, and complicated features, even results obtained at the same time in various laboratories can differ. Nonetheless, due to its intriguing features, such as biocompatibility, low antigenicity, and film-forming properties, various novel materials based on collagen are expected to be developed in the near future. The development of new materials based on collagen is of interest to biomedical firms and the cosmetic industry because there are still numerous ways to modify this biopolymer.

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