Characteristics and Uses of Collagen

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Collagen products are used in medicine and dentistry for many purposes, including wound dressings and as matrices for tissue growth. As the chief structural protein of the body, the properties of collagen that make it suitable for use in dentistry are dependent upon characteristics of amino acid composition and sequence. Their are many physical, chemical, and biological properties of collagen that favor the use of collagen as a biomaterial of the nineties; they are: high tensile strength, orientation of fibers, semipermeability of membranes, low-antigenicity, its positive effect on wound healing rates and hemostatic properties.

Hydrolyzed collagen is defined as a collagen hydrolysate polypeptide derived by hydrolysis having a molecular weight of 1,000 to 10,000. A typical amino acid composition is shown in Exhibit I.[1]

Exhibit I - Typical Amino Acid Composition of Hydrolyzed Collagen

Amino Acid	Typical Composition (%)
Glycine	20.0-30.5
Alanine	8.0-11.0
Serine	2.9-4.1
*Threonine	1.8-2.6
Proline	13.7-18.0
Hydroxyproline (only found in collagen)	12.1-14.5
*Valine	2.1-3.4
*Isoleucine	1.3-1.8
*Leucine	2.8-3.5
*Phenylalanine	1.1-2.6
Tyrosine	0.2-1.0
Cystine/cysteine	0.0-0.9
*Methionine	0.7-0.9
Aspartic acid	5.7-9.0
Glutamic acid	10.0-11.7
Arginine	7.3-9.0
*Histidine	0.7-1.0
*Lysine	3.9-5.2
Hydroxylysine(only found in collagen)	0.7-1.2

Hydrolyzed collagen is available as a viscous, amber aqueous solution or most commonly, as an off-white to white hygroscopic powder. It will absorb up to 30 times its own weight in water. It is commercially prepared by any one of three methods: alkaline hydrolysis, enzymatic hydrolysis or acid hydrolysis; and it is commercially derived from either bovine or porcine sources.[2]

* essential amino acids

The spectrum of amino acids resulting from the hydrolysis of collagen differs greatly from that of other proteins by its high content of glycine and proline and low content of histidine, tryptophan and cystine (see Exhibit I). Collagen also contains two amino acids not found in other proteins, hydroxyproline and hydroxylysine. These two acids allow for differentiation between collagen hydrolysates and other protein hydrolysates.[3]

Acute toxicity studies have found *hydrolyzed collagen* nontoxic when administered orally to mice and rats.[4-5-] Dermal studies, when applied to rabbits and guinea pigs, gave no indication of systemic toxicity.[7-8] *Hydrolyzed collagen* was minimally irritating when evaluated for ocular irritation by a modified Draize eye test in rabbit eyes.[9-10] In sensitization studies utilizing white guinea pigs, *hydrolyzed collagen* was found to be nonsensitizing.[3] In phototoxicity/photosensitization studies, hydrolyzed collagen was used to decrease UV-induced erythema.[11] On the basis of the available animal and clinical data, it can be concluded that hydrolyzed collagen is safe in the present practice of use.

Collagen has many unique biological characteristics for which no synthetic substitute exists. Type I collagen is used in many applications because of its minimal antigenicity,[12] its hemostatic capability,[13-14] its chemotactic properties,[15] and it is readily available from many natural sources[16].

Collagen, the principal structural protein, is the main component of connective tissue, while Type I collagen is the dominant constituent occupying over 90% of the tissue. The use of Type I collagen as a wound dressing dates back nearly 85 years.[17-18] Collagen has been prepared in various forms such as films, powders, sponges and gels. The commercialization process of collagen to date has been very slow primarily because of the high cost of preparation, difficulties of handling and storage, and its cost-effectiveness during application.

In a number of reports collagen has been shown to be beneficial by 1) Controlling the evaporation of fluid, keeping the wound pliable and flexible, 2) promoting the development of granulation tissue, 3) diminishing pain, 4) providing mechanical protection against physical and bacterial insult.[19-20-21] Other clinical reports have indicated that collagen powders exhibit excellent adhesion to the wound, hemostatic properties, tissue fluid (exudate) binding and adequate stimulation of cell reactivity with the formation of a highly vascularized granulation bed.[22]

Films made from *hydrolyzed collagen* have been used to prevent postoperative adhesions.[23] Operation often induces the fibrous tissue adhesions found frequently in operations in the abdominal cavity and often in tendons and nerves. Undesired tissue damage results in most surgical procedures such as cutting, desiccation, ischemic and manipulative abrasions.

Reports indicate that *hydrolyzed collagen* was tested as a tissue adhesive for suture replacement.[24] *Hydrolyzed collagen* was tested because of its chemical resemblance to connective tissue and its adhesive properties. An ideal tissue adhesive is biodegradable, nontoxic, and readily absorbed so that it does not impose a hindrance to the healing process. *Hydrolyzed collagen* was found to be a useful biomaterial for this application.

Since Type I collagen is the most dominant protein in human connective tissue, including periodontal ligaments and gingiva tissue[25], collagen products possess many of the biologic qualities which enhance

the type of wound healing desired following dental therapy involving the oral mucosa, gingiva and periodontal ligament.

The desirable characteristics that are sought following periodontal and gingiva therapy include: clot formation and stabilization, neovascularization and epithelial cell rejuvenation.[26] In order for regeneration to occur, a well-organized clot must form shortly after wound closure.[27] Collagen is known to be a natural hemostatic agent. It is this characteristic that may facilitate early wound stabilization by enhancing the initial blood clot formation. Collagen may also serve as a biologic scaffold for ingrowth of endothelial cells and progenitor cells from the periodontal ligament.[28] Collagen, has been demonstrated to be chemotactic for fibroblasts in vitro. [29]

Studies employing peptide mapping for collagen composition provide evidence for the presence of both Type I and Type III collagen.[30] The fibers of the periodontal ligament are predominantly composed of collagen. Studies in vitro in a number of connective tissues, have confirmed that there is a rapid conversion of Type I procollagen to collagen Type I. The use of collagen in the management of tissue regeneration is a natural selection as an aid to enhanced healing.

The gingival is made up of soft connective tissue (the gingival corium) and the connective tissues of the periodontal ligament and the overlying epithelium. The gingival extends from its limiting margin in the cervical region of a tooth to the alveolar mucosa covering the bony alveolar processes of the jaws. The gingival corium attaches to both the alveolar bone and the cervical bone and the cervical region of the tooth protects and maintains the integrity of the periodontal ligament.[32] Biochemical studies show that the main components of gingival connective tissue are Type I and Type III collagen, Type I collagen being the principal constituent.[31] The main fibrillar component of the gingiva is Type I collagen; a heavier concentration of Type I collagen is also found in the deeper layers of the gingival corium.[33]

Inflammation of the gingiva or gingivitis is one of the most common dental diseases for humans. If not controlled or treated, it will lead to periodontal disease with a slow progressive destruction of the ligament and alveolar bone.[34]

The mouth or oral mucosa is lined by a mucous membrane whose structure resembles that of the skin. It is composed of two layers, the overlying epithelium and an underlying connective tissue. The structure of this membrane varies with the functional requirements of the different regions of the oral cavity; for example, areas involved in the mastication of food such as the gingivae and tongue have a much different structure than that of the floor of the mouth.[35] The oral mucosa is made up of mainly Type I collagen, representing approximately 80-90% of the total collagen content.[36]

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