



Collagen as a substrate for biomaterials: Part 2

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Using biotechnology, it is possible to cut specific regions of the collagen molecule in order to solubilise collagen whilst, at the same time, retaining its helical nature. This new form of collagen can then be precipitated from solution, solubilised and moulded into any shape or form that may be required for medical purposes. This has been described in "Collagen as a substrate for biomaterials: Part 1", World Leather August/September 2007.

Most biomaterials are composed of collagen due to its low antigenicity and ability to integrate within the surrounding tissues. It is used as a scaffold for bioengineering purposes due to its inductive effect in being able to stimulate the cell response important for tissue repair. Another advantage is that the biomaterial may also be used as drug delivery systems by promoting the release of drugs, hormones and steroids to aid repair.

Applications of Collagen Matrices

Twenty to thirty years ago, the medical application of biomaterials grew due to improved knowledge of collagen processing. In turn this stimulated research into using collagen for technologies such as tissue engineering. An example of collagen utilisation occurs in the form of catgut, which has been used as sutures in many surgeries all over the world for the past thousand years.

Bio-based materials are available in different forms. The biomaterial may contain only native collagen (where the non-collagenic material has been removed), or solubilised collagen. In both cases the strength of the collagen may be reinforced by chemical and physical crosslinking depending on the application.

The utilisation of solubilised collagen for the purpose of biomaterial production is the most common since it is able to be manipulated into various forms such as membranes, sponges, gels and pellets to name a few examples. The purity of the collagen, chemical agents used to crosslink collagen, and surface morphology of the biomaterial, affect the body's ability to interact with the material. If the biomaterial triggers an inflammatory response the primary function of the material in aiding wound healing is negated.

Fibroblasts are cells which aid in repairing the extracellular matrix through the production of collagen. Studies have shown that fibroblast cells require a three-dimensional structure of a specific pore size to accelerate infiltration and thus growth of the cells in the sponge. This particular matrix is perhaps the most favoured for tissue engineering. Additives such as proteoglycans have been incorporated into collagen-based wound dressings. Other additives such as hyaluronic acid and fibronectin were found to alter the 3-D structure of the implant as well as attracting cells such as fibroblasts to proliferate and lay down collagen in an in vivo wound model.

Definitions

Biotic material: Biotic or biological materials originate from living organisms and represent the natural material in an essentially unmodified form, e.g., wood, straw, bark, bone, etc.

Bio-based materials: Processed biotic materials typically refer to materials that have undergone more extensive processing than is conventionally required to prepare biotic materials for use. They are commonly engineering materials made from substances derived from living matter.

Fibroblasts: A type of cell that synthesises and maintains the extra-cellular matrix of many animal tissues. They are the most common cells of connective tissue in animals. Fibroblasts provide a structural framework, for example, by providing collagens, glycosaminoglycans, elastin fibres and glycoproteins.

Antigenicity: Existence of antibodies.

There follows a few examples of the various forms of collagen-based matrices which are available:

FILMS, SHEETS AND DISCS

Collagen films, with a thickness of 0.01-0.5 mm, are prepared by pouring solubilised collagen onto plastic surfaces and allowed to dry. The main function of films is to provide a barrier against further infection and trauma. Drugs may be incorporated into the collagen matrix in various ways: chemically bonding the drug via hydrogen and covalent bonding to the collagen, or through encapsulation.

If the matrix is uncrosslinked, the material has a limited life-span as it is degraded by enzymes such as proteases and collagenases. The matrix may need to be strengthened using



crosslinking agents such as azides, aldehydes, epoxides, carbodiimides or diisocyanates.

Drugs that are currently utilised for treating infection are gentamicin, vancomycin and tobramycin. For a controlled release of drugs the membrane is crosslinked or another agent such as chitosan incorporated into the collagenic matrix. The material has shown promise as a treatment for infection.

It is well known that the addition of a collagenic film to polymer matrices aids the attachment and proliferation of fibroblasts to the biomaterial, which in turn aids the wound healing process. In order to strengthen the matrix physically, a nylon mesh may be added. This particular matrix was also found to improve wound healing.

SPONGES

This form is prepared by lyophilising (freeze-drying) collagen which has been swollen using acid or alkali. The concentration of collagen should be approximately 0.1-5% dry matter. The pore size is dependent on the concentration of the collagen as well as the rate of freezing.

These matrices have been used for a multitude of treatments from severe burns to wound ulcers. Sponges have the following desirable characteristics:

- Offers a moist environment.
- Provides a barrier from further trauma and infection.
- Soaks up wound exudate.
- Low adherence to the wound which prevents further trauma when removed.
- Easy absorbability into the body.

The matrix may also incorporate growth factors such as glucosaminoglycans, steroids and antibiotics to aid tissue repair. The sponge can also be crosslinked to achieve a durable material or to control the release of drugs to the required area.

Another important aspect is that the material promotes cellular growth and spreading. The collagen sponge is able to maintain its original structure due to the fibrous and porous nature. The porous nature allows the penetration and growth of the cell into the matrix. This is especially important for tissue engineering.

Sponges coated with basic fibroblast growth factor (BFGF) showed enhanced dermal and epidermal wound healing. Doillon showed in animal studies, that a matrix containing a pore size of approximately 50-300 μM , was optimal for the cellular penetration of fibroblasts into the material similar to the dermis layer of the skin. Once the cells are added to the sponge—where they are encouraged to grow—the cells differentiate forming structures which resemble tissue in the body.

GEL/HYDROGEL

The gel is usually applied in a solid form, the advantage being a large and constant surface area. However, this material does not possess the mechanical strength of the above-mentioned matrices, and thus sponges, scaffolds or fibres are far more widely used in areas where higher mechanical strength is required.

Blends which have been made with high and low molecular weight polymers such as dextran and maltose respectively, have aided in the penetration of the material into tissue. Hydrocolloids are used due to its ability to retain a large amount of wound exudate, as well as providing a moist wound environment which aids in the wound healing process.

Agents such as alginate or carboxymethylcellulose (AQUACEL® Hydrofiber®) are commonly being used. The

distribution of bacteria in the wound was found to be 20% lower as compared gauze dressings that are commonly in use. This may be due to micro-organisms being trapped within the gel network, which in turn restrict the flow of fluids or bacteria, and so limiting cross-contamination.

Other forms using collagen as a substrate, for purposes other than wound healing have been produced.

MINI-PELLETS

These are rods with a diameter of approximately 1-mm and 15 mm in length prepared from a collagen solution by a moulding press, drying and cutting. The pellet, which is cylindrical in shape, is usually injected into the patient and has been used as a delivery system for drugs with good results.

The residence time of the pellet in the body is much longer using this system than using intravenous and sub-cutaneous injections. The collagen concentration, density, compression of the matrix when extruded, all play a role in the drug release characteristics.

COLLAGEN COMPOSITES

In some cases, the development of the biomaterial may be application-specific and may be composed of collagen and other biopolymers such as cellulose, gelatin and dextran. Composites containing drugs have also been developed. Enzymes have also been attached to the collagen-based material and used for therapeutic purposes or drug delivery systems.

Collagen-based systems for tissue engineering

The focus at present appears mainly to be directed in the field of tissue engineering. The collagen-based implant has been used for variety of purposes:

- For culturing skin cells, and the resultant material used as a skin replacement.
- As a bone substitute due to its osteoinductive activity,
- The bioengineering of tissues such as blood vessels, heart valves and ligaments.

The biomaterials market is constantly improving and providing materials which significantly improve healing rates.

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