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A Review on Biomaterials and its Impact in Wound Healing

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Abstract

Wound is a rapid onset of injury and need to be delt with utmost care. Delay in wound healing is associated with several comorbidities and had led researcher to develop biomaterial for wound healing. Biomaterial are in use for wound healing therapies due to its versatile, highest degree of biocompatibility, antimicrobial, immune-modulatory, cell proliferative and angiogenic properties will create a microenvironment favorable for the healing process. Biomaterial has emerged into a major role player in various pharmaceutical and medical fields. The biopolymers such as cellulose, alginate, hyaluronic acid, collagen, chitosan was already been explored for its wound healing properties and available in market. This article discusses the current developments in the application of biomaterials for wound healing therapies, as well as their future course. This article aims to review the latest development in use of biomaterial in wound healing therapies.

Keywords: Biomaterials; Wound healing; Polymer; Skin; Injury

Introduction

European Society for Biomaterials (ESB) defined, a biomaterial as a 'material intended to interface with biological systems to evaluate, treat, augment or replace any tissue, organ or function of the body'. Biomaterial are employed in research and development in novel drug delivery technology since past for 60 years. A wide variety of materials are classified under synthetic and natural biomaterial. The market survey on biomaterials estimated at USD 135.4 billion in 2021 and from 2022 to 2030 it is expected to register a Compound Annual Growth Rate (CAGR) of 15.4%, due to the increased demand for medical implants, plastic surgery, regenerative medicine and wound healing applications [1]. Biomaterial had profound application in various fields which include medical neurology, orthopedics, ophthalmology, tissue engineering, dental carriers in NDDS, biomolecules implant are of them.

There are several criteria that a biomaterial should satisfy they should be Biocompatible, *i.e.,* non-toxic, non-allergenic, non-carcinogenic, should have suitable physical as well as chemical properties, should have suitable mechanical properties, should have acceptable shelf life, processing techniques should be easy, easily sterilizable, economical and readily available [2]. Upon implantation *in vivo* it should not cause a sustained inflammatory or toxic response, degradation time should be correspondent with healing or regeneration process, mechanical properties of material should match with the indicated application. Variation in mechanical properties due to degradation should be compatible with the healing or regeneration process and the product should be non-toxic, metabolism and clearance should be easy and the permeability and processibility should be appropriate with intended application [3].

Literature Review

Classification of bio materials

Based on tissues responses biomaterial classified into three:

- Bioinert biomaterials.
- Bioactive biomaterials.
- Bioresorbable biomaterials.

Regulatory in biomaterial

The Food and Drug Administration (FDA) provides regulatory guidance and approval for biomaterials and devices. There is regulatory situation for medical devices both in USA and in the European Union (EU) [4].

They classify the device in to three classes:

- Class 1 devices are those with the lowest risk to the patient.
- Class 2 devices offer intermediate risk.
- Class 3 devices are those that are life threatening if they fail.

Class 2 includes most of the implants, such as fracture fixation devices, and class 3 includes devices that replace or supplement the function of organs, such as artificial heart valves [5-8]. In Europe, biomaterials and medical devices are regulated by EU controls and must obtain a CE mark by satisfying the International Standards Organization (ISO) standards of manufacturing and record keeping.

Classification

From healthcare perspective, biomaterials can be divided in following categories: Synthetic (metals, polymers, ceramics, and composites), naturally derived (animal and plant derived, semi-synthetic or hybrid materials. Table 1 enlist biomaterial classification, their advantages, disadvantages and applications [9].

Type	Advantages	Disadvantages	Applications
Metals and metal alloys. E.g.: Gold, platinum, steel, titanium, cobalt, chromium.	• High material strength. • Easy to sterilize and fabricate.	• Corrosive • Excessive elastic modulus. • Aseptic loosening.	• Orthopedic implants, pins, screws and plates.
Ceramics and carbon compounds. E.g.: Glass, calcium phosphate salts (HA, titanium and oxides of aluminum.	• High material strength. • Corrosion Resistance. • Biocompatibility	• Difficult to mold. • Excessive elastic modulus.	• Bioactive orthopedic implants. • Artificial hearing aids. • Dental implants.
Polymers. e.g., PMMA*, Polycapro Lactone (PCL, PLA, polyurethanes, polycarbonates.	• Biodegradable • Biocompatible • Suitable mechanical strength. • Easily moldable and readily available.	• Leachable in body fluids. • Hard to sterilize.	• Orthopedic and dental implants. • Prostheses • Tissue engineering scaffolds. • Drug delivery systems.
Composites. E.g., Dental filling composites, carbon fiber reinforced methyl methacrylate bone cement+ultra-high molecular weight polyethylene	• Corrosive resistant. • Excellent mechanical properties.	• Laborious manufacturing methods. • Expensive	• Rubber catheters and glove. • Porous orthopedic implants. • Dental fillings.

Table 1: Biomaterials classification with their advantages, disadvantages, and applications.

Examples of natural biomaterial includes collagen, coral and chitin obtained from insects and crustaceans, keratin obtained from hair, and cellulose obtained from plants [10]. Collagen and chitosan are being extensively studied for their use as a biomaterial. Implants of collagen sponges does not have any significant stiffness or mechanical strength. It is marketed as a treatment for wound healing and has showed good promise as a scaffold for neotissue formation [11]. For buildup or augmentation of dermal tissue injectable collagen is widely used in cosmetics.

Applications of biomaterials

Biomaterials play a key role in diagnosis as well as for the treatment of several diseases. The applications of biomaterials extent in various fields of pharmaceuticals as well as medicine which is listed in the Figure 1. In this review biomaterials in wound are given emphasis.

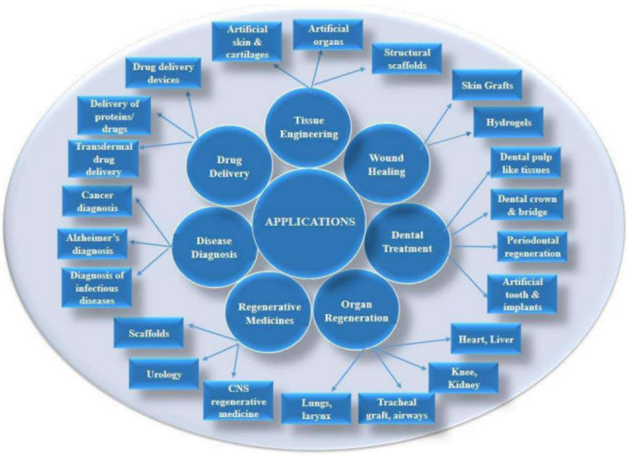

Figure 1: Applications of biomaterials.

Application of biomaterial in wound healing

Wound healing: Cutaneous wound healing is an essential physiological process consisting of the collaboration of many cell strains and their products [12]. Cell and biochemical events taking place in wound repair is divided into different stages: Inflammatory reaction, cell proliferation and synthesis of the elements which make up the extracellular matrix, and the posterior period, called remodeling. Mitchel, et al., illustrates the principles of repair for the majority of tissues in Figure 2. Tissue repair also involve growth factors, soluble mediators, blood cells, the production of the extracellular matrix, and the proliferation of parenchymal cells [13].

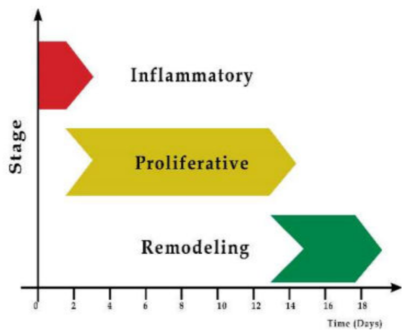

Figure 2: Stages of tissue repair.

Chitosan, cellulose, hyaluronic acid, alginate, elastin, dextran, fibrin, pectin and collagen are some examples of biopolymers that are extensively used for preparation of wound dressings [14]. Studies on silk graft found silk as a biomaterial for wound healing process. Due to the versatile property of biomaterials, they are extensively employed for formation of nano-fiber for wound dressing and wound repair by electro-spinning method. It has been found that antioxidant property of biomaterials accelerates the chronic wound healing property.

Bioactive glass composite biomaterials were also found to have wound healing process. Chitin and chitosan had wide range application as a biomaterial for the wound healing. Several studies were done over biomaterial for wound healing [15].

Forouzandehdel S, et al., developed magnetic composite hydrogel by graft copolymerization, for guaifenesin with the help of itaconic acid on starch and alginic acid in presence of grapheme sheets and Fe_3O_4 nanoparticles and this was useful for wound healing and drug delivery. Protease modulating matrix products have shown potential for the treatment of chronic wounds.

For wound healing, hydrogel acts as a great candidate as they can form a barrier from the hydrated environment and the pathogens. Polyvinyl alcohol is generally used for the fabrication of hydro gel and it shows application for wound healing. Calcium alginate hydrogel has provided as a drug carrier for protamine with neovascularization function in chronic wounds treatment [16]. Hyaluronan a polysaccharide is present in the skin and shows a great use as a hydrogel for wound healing. Hyaluronan with chitosan is used for the delivery of angiogenic promoting growth factor *i.e.,* vascular endothelial growth factor and its shows antibacterial and angiogenic activity and will show wound healing [17].

Chitosan: Mariana, et al., illustrated the antimicrobial properties of chitosan as well as the mechanisms of action toward microbial cells as well as the interactions with mammalian cells in wound healing process [18]. Chitosan is biocompatible, and non-toxic to living cells and tissue which was found by *in vitro* testing in different types of cells like keratinocytes, fibroblasts, hepatocytes, myocardial and endothelial cells. Diabetic patient needs long term treatment for chronic, non-healing wound which may cause distress, developing chitosan formulation would be more economical.

Mohammad A. S. Abourehab investigated the bio-adhesive property of alginate makes it significant in the pharmaceutical industry. Alginate has shown immense potential in wound healing and drug delivery applications to date because its gel-forming ability maintains the structural resemblance to the extracellular matrices in tissues and the bioactive that loaded into ALG based gels will maintain local cone. Of biological factors (for example, proteins) for a prolonged period [19].

Chih-Hsin Wang, et al., investigated the effectiveness of chitosan dressing when compared with that of regular gauze dressing, and found that chitosan dressing will accelerate platelet aggregation and lower prothrombin time and activated partial thromboplastin time also possess blood absorption ability. Adenosine triphosphate assay results revealed that the chitosan dressing inhibited bacterial growth up to 8 d post-surgery and 16S rRNA based sequencing revealed that the chitosan dressing effectively protected the wound from microbial infection. They also promot the growth of probiotic microbes, as a result skin immunity and wound healing increases. They found chitosan dressing as an effective antimicrobial and procoagulant and promotes wound repair by providing a suitable environment for beneficial microbiota [20].

Discussion

A number of studies have demonstrated that chitin and chitosan accelerated wound healing in clinical and veterinary cases, and remedies using chitin and chitosan for treatment of wounds are being marketed. Chitin and chitosan have been used as filaments, powders, granules, sponges or as a composite with cotton or polyester. The main biochemical activities of chitin and chitosan based materials in wound healing are polymorphonuclear cell activation, fibroblast activation, cytokine production, giant cell migration and stimulation of type IV collagen synthesis.

The increasing interest in chitin and its deacetylated forms is due to the biological activity resulting from its susceptibility to degradation under the influence of enzymes present in body fluids, such as lysozyme and n-acetyl glucosoaminidase. The degradation products, called chito-oligomers, are able to stimulate macrophages and positively influence collagen deposition, thus accelerating the wound healing process.

Mei-Yin Chien, et al., investigated the rhizochitin being biocompatible, biodegradable and had a profound effect in wound healing by possible mechanisms like decreasing the expression of PDGF in the proliferation stage, increasing the expression of TGF in the inflammation and proliferation stages, and increasing the expression of VEGF in the inflammation and proliferation stages. Rhizochitin also inhibited secretion of MMP-9 and MMP-2.

Some ideal composite biomaterials based on biopolymers have been reported as a better option for the potential tissue engineering system. Table 2 explains some polymeric composite materials in tissue engineering. All the biomaterials discussed are used in tissue engineering as scaffold which either in single or combination works towards ideality.

SL No	Polymers	Salient features
1	Chitosan	Biodegradable, biocompatible, antibacterial, cytocompatible, bioactive.
2	Gelatin	Bioactive, biocompatible, hemocompatible, cell adherence, anti-thrombogenic.
3	Arabinoxylan	Biocompatible, antibacterial, cell adherence, bioactive, cell proliferation.
4	Collagen	Biodegradable, fibrous, biodegradable, cell proliferation

5	Xyloglucan	Cell proliferation, biodegradable, cell differentiation, biocompatible.
6	Fibrinogen	Biocompatible, hemocompatibility, cell proliferation, biodegradable, cytocompatible.
7	Hyaluronic acid	Bioactive, cell adherence, cell proliferation, cell differentiation, biocompatible.
8	Beta-glucan	Biocompatible, bioactive, biodegradable, antibacterial, mechanical.

Table 2: Polymeric composite materials in tissue engineering.

Conclusion

Biomaterials own multidisciplinary application in medical and pharmaceutical field. Several biomaterials have specific purpose in the body, used as implants to mimic the structure and function of tissues/ organs, organ regeneration, tissue engineering, wound healing, diagnosis of diseases and treatment, and delivery of drugs. Biomaterial and advanced technologies in drug delivery like scaffolds, nanofiber, nanocarriers are exhibiting a great role for the delivery of drugs.

From several studies chitosan demonstrated excellent features for wound healing. Chitosan had application in various areas of interest such as biomedicine, pharmaceutical, cosmetic, and food industries, wastewater treatment, and agricultural pest management. Chitosan may be one of the most important biopolymers that can be used to produce wound dressings that not only accelerate the wound healing process but also prevent infection of the wound, a necessary step in the wound healing process. The mechanism of action against microbial cells is not entirely defined, but numerous studies have presented similar results; therefore, researchers have formulated some hypotheses by which chitosan can inhibit microbial growth: Used as a wound dressing, chitosan stimulates the natural healing process and has no toxicity to the mammalian cell. Being biocompatible, chitosan has a known metabolic pathway. Once it enters the human body, it can be hydrolyzed by enzymes, such as lysozyme, present in mucus, tears, and saliva, to an important sugar, glucosamine, that it is already present in the human body. The existence of numerous chitosan-based wound dressings on the market shows the importance of this biopolymer in accelerating the wound healing process, and we may consider chitosan as a cost-effective solution not only for the treatment of acute wounds but also in the case of severe chronic wounds, such as diabetic ulcers.

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