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Biopolymers for Wound Healing

Dr. Kakuli Chowdhary

Lecturer, Chemistry, Govt. P.G. College, Kotputli, Jaipur (Rajasthan)

Dr. S.P.S. Rathore

Lecturer, Botany, Govt. P.G. College, Kotputli, Jaipur (Rajasthan)

Abstract

Wound healing is a multifactorial physiological process. Nature has provided us with ample resources to cure and heal wounds and burns. Cellulose and chitin have been used since ancient times for wound and burns healing. Various biopolymers from plant and animal origin have been used for this purpose, in addition to gels from arid zone plants, which have soothing and healing powers. Recently many polymers, both of natural and synthetic types have been engineered to bring about protection, soothing and healing of wounds. Apart from cellular and biochemical components, various enzymatic pathways also become active during repair and help the tissue to heal. Natural and synthetic get like materials, films/membranes, composites, micro/nano particulate systems have featured heavily in the development of biomaterials for wound healing and other tissue engineering purposes. Bio-compatible and biodegradable polymer scaffolds combined with cell's biological signals are being investigated as alternatives' to traditional options for tissue reconstruction and transplantation. The aim of this paper is to introduce the biomaterial community to the emerging field of self-healing materials and modified self-healing materials which may lead to the development of new classes of biomaterials.

Keywords: *Biopolymers, Wounds, Burns, Treatment, Dressing*

A wound is a disruption of the integrity of anatomical tissues caused by exposure to any factor. wounds are basically of two types:

1. Closed Wounds: This group includes contusion, hematoma and abrasion. Contusions type injuries involve damage to soft tissues, small blood vessels and deep tissue layers, resulting in their separation, but the anatomy of the skin remains intact. Oedema, and in later periods, atrophy and defective pigmentation are observed in wound and the healing is delayed. Vessel rupture or hyperemia due t vessel damage is called hematoma and wounds such as scraps are termed abrasions. The healing process is very painful because this type of wound involves damage to sensory nerves and the wound can easily become infected.

2. Open wounds: This group includes lacerations, cutting-pricking tool wounds, gunshot wounds, surgical wounds, insect bites and stings, radionacrosis, vascular neurological and metabolic wounds. Wounds except for lacerations cause serious damage to tissues beneath the skin. In laceration- type wounds, skin and subcutaneous tissues have been destroyed, but deep tissues remain healthy. The anatomical integrity of tissues is damaged in cutting- pricking tool wounds without any tissue damage at the edges of the wounds (Kapoor and Appleton, 2005) Also, wounds my be with tissue loss or without tissue loss.

Burns

Burn is a kind of wound that occur when skin or organs are damaged by an electrical current,

heat, chemical or inflammable agent effect. Burn causes changes of vascular permeability, extravasations of plasma proteins, aggregation of platelets and increased fibrinolysis (Yenerman 1986- Madri 1990, Atiyeh etal, 2005)

Burns are divided into four groups

(i) First degree burns: Only the outer layer of the epidermis and stratum corneun are damaged in this type of burn and there is no damage to the dermis. (Whitney & Wickline 2003)

(ii) Second degree burns : These type of burns are deeper than the first degree burns. Damage covers the entire epidermis and some part of dermis. Second degree burns may be superficial or deep (Sparkes 1997, Whitney and Wickline 2003)

(iii) Third degree burn: These types of burns result from hot water, fire and prolonged contact with electrical current. The wound area exhibits tautness & brightness as the elasticity of the skin is lost causing abnormal shrinkage. In such cases, all structures within the skin sustain damage. The dermis and subcutaneous fat are destroyed as a result of coagulation necrosis. Thrombosis occurs in vessels under the skin. Skin is damaged in all layers and is characterized by autolysis and leukocytoclastic infiltration for 2-3 weeks. Permanent deep scare in the skin occur following healing in these kinds of wounds and surgical intervention is usually required to restore normal appearance (Moulin et. al 2000, Shakespeare, 2001)

(iv) Fourth degree burns: These refer to the carbonization of burned tissues.

Wound And Burn Treatment

A wide range of methods have been used to treat wounds, since ancient times. One of the earliest information on wound treatment is found in Egyption medical documents, called the Ebern Papyrus. It is known that Egyptians treated wounds by covering them with frog skin and castor oil. The results have been limited. Throughout history, humans have used many materials of biological origin in wound and burn treatment. Although various experiments have been conducted on animals for wound and burn healing, it has been ultimately concluded that, as the histology of skin and the wound healing mechanism differs between animals and humans, so animal models or experiments can only provide a general identification of wound healing phases.

The following characteristics are required for ideal wound an burn dressing (Sheridan and Tompkins, 1999, Balasubramani et.al. 2001, Jones at.al. 2002)

(i) Ease of application
(ii) Bioadhesiveness of the wound surface
(iii) Sufficient water vapour permeability.
(iv) Easily sterilized
(v) Inhibition of bacterial invasion
(vi) Elasticity and high mechanical strength.
(vii) Compatibility with topical therapeutic agents
(viii) Optimum oxygen permeability
(ix) Biodegrability
(x) Non-toxic and non-antigenic properties
(xi) Long shelf life
(xii) Cost effective

Average water loss from normal human skin is $250g/m^2$/day. In wounded skin, the water loss can reach upto $5000g/m^2$/day.

Classification of dressing used in wound and burn treatment

Materials used to cover wounds and burns are also called artificial skin, as they fulfill the functions of normal skin within areas with wounds and partially destroyed skin. Wound and burn covering materials are classified as follows, (Stashak et. al. 2004)

(i) Traditional dressing

Traditional dressing is still most commonly used materials for wound and burn dressing (Balasubramani et. al 2001). The best sample for this group is gauge and soft cotton composites which have very high absorption capacity. They cause rapid dehydration. When they are being removed from the wound surface, they can

cause bleeding and damage of newly formed epithelium (Naimer and Chemla, 2000, Stashak it. al. 2004). Therefore, gauge composites with a non-adhesive inner surface are prepared to reduce the pain and trauma which can occur while removing traditional wound dressing from the wound surface.

Some of such traditional wound dressings used are-Paraffin gauge dressing,Petroleum gauge,Paraffin dressing containing 0.5% chlorhexadience acetate, Petroleum gange containing 3% bismuth tribromophenate, Sterile hydrogel dressing, Highly absorbent cotton wool pad and Highly absorbent rayon/cellulose blend sandwiched with a layer of anti shear high density polythene.

Antibacterial agents are added in to the dressings to eliminate the infection. Advantage of the traditional dressing is their low cost (Lim et. al. 2000, Price et.al 2001, Stashak et al. 2004). One of the most significant problems with these dressings is foreign body reaction in the wound caused by cotton fibers.

(ii) Biomaterial-based dressing

The most convenient method used in complete closure of wounds and burns is auto grafting. But, inadequate donor areas led to search for new tissue source (Sheridon et.al. 2001). Biological dressings are natural dressings with collagen type structure, which generally include elastic and lipid and these may be categorized as follows:

Type of dressing	**Dressing Material**	**Most common source**
Allograft	Scalp tissue Amniotic membrane.	Fresh or freeze-dried skin Fragments from patients relatives or cadavers
Xsenograft	Porcine tissue, Silver impregnated porcine tissue.	From Pig skin
Skin derivatives	Highly purified borine collagen. Formalin fixed skin	From different forms of collagen.

Disadvantage of biomaterial based dressing is their stability problems and risk of infection. This lead to the need for artificial dressing material which was cheaper, more effective and has long shelf life.

(iii) Artificial Dressing

Due to variations between path physiology of the wound and burn, it is difficult to develop an artificial dressing material that meets all the criteria for optimum healing. Much research is currently being undertaken to develop wound dressing materials that can provide optimum healing conditions, taking into account all of these inflammation, tissue replacement, fibrosis, coagulation etc. (Still et.al, 2003, Stashak et. al. 2004). Some of the artificial wound and burn dressing materials are enlisted below:

Type of dressing	Dressing Material	Brand Name
Film/memberane	Polyurethare Polyvinyl chloride Nylon velour Polyvinylidene chloride Polyurethane hydrocolloid Synthetic fibre+ aluminium Synthetic fibre emetal Activated charcoal	Opiderm Opsite Broclusive Gegaderm Stretch Neal capran 77C saran wrap Gram flex aluderm Scanpore tape Carbopad

Type of dressing	Dressing Material	Brand Name
Foam	Formalinised polyvinyl alcohol Polyurethane Poly dimethyl Siloxane	Ivalon Lyofoam Silastic
Gel	Calcium alginate Polyurethane with grafted acrylamide and hydroxyethylmethacxylate	Ivalon Lyofoam Silastic
Composite	Polyprophylene film and polyurethane Silicone film with a nylon fabric foam	Epigard Biobrase
Spray	Methacnflic acid ethoxyethyl ester Polyhydraxyethylmethacrylate and polyethylene glycol 400	Nobecutane Hydron

Polymers used for Artificial Dressings

Many natural and synthetic polymers are being used in the preparation of artificial dressing materials.

The most widely used of these includes:

I. Natural Polymers

(a) Collagen: Collagen is a biodegradabic and biocompatible protein mostly found in connective tissue. The first medical usage of collagen in humans was reported by Knapp et. al (1977). Bovine collagen was also used as stuture and haemostatic agents. Today collagen is used in numerous biomedical applications (Hafemann et.al. 1999, Ortega & Milnev, 2000). These include collagen suspensions for dermal injection, topical nemostatre agents, wound dressing material, collagen stature and catguts, collagen gels for periodontal reconstruction, collagen sponges for the hemostasis and coating of joint and collagen rich pig skin wound dressing materials (Park et.al., 2004)

(b) Alginic acids and its salts: It is a natural polysaccharide derived from brown algae such as Laminaria and Ascophyllum species. Alginic acid are formed by linear block copolymerization of D-mannuronic acid and L-guluronic acid. Alginic acid and its salts are used for treatment of wound and burn due to their haemostatic properties.

(c) Hyaluronic acid and its derivatives: It is a natural biopolymer that alternatively consists of D-glucuronic acid and 2-acetamido-deoxy-D-glucose and is generally found in mammals bone tissues and synovial fluids (Kirker et.al 2002). Hylauronic acid interacts with proteins, proteoglycans, growth factors and tissue components called bimolecular which has vital importance in healing of various types of wounds (Park et al 2003) and it also protects wounds from micro organisms (Miller et. al. 2003)

(d) Chitosan: It is a linear polysaccharide composed of randomly distriuted β-(1-4)-linked -D- glucosamine (deacetylated unit) and N-acetyl-D-glucosamine (Muzzareli and Muzzarali, 2002). Chitosan has haemostatic effect (Ueno et. al. 1999, Khor and Lim 2003). Chitosan accelerates the formation of fibroblasts and increases early phase reactions related to healing (Paul & Sharma, 2004). Chitosan can be prepared in variety of forms such as gel, film, spray. Powder and micro and nanoparticles. This biopolymer is important for wound nealing due to low toxicity of chitosan and its biodegradation products, and its biocompatibility with blood and tissues Kim et.al, 2002)

(e) Fucoidan: It is a sulphated polyfucose polysaccharide and it has attracted considerable biotechnological research interest as it possesses anti-coagulant activity similar to heparin and has anti-thrombotic, anti-inflammatory, antitumorial and antiviral effets (Patankar et.al.1993) It may be able to modulate growth factor- dependent pathways in the cell biology of tissue repair (O'Leary et. al. 2004) as it interacts with growth factors such as basic fibroblast growth factor (BFGF) and transforming growth factor-β (TGF-B)

(f) Poly-N-acetyl-glucosamine: It is produced from marine microalgae an has haemostatic activity. It is used as support material for treatment of wound and burns (Pietramaggiori et.al.2008)

II. Synthetic Polymers

(a) Polyurethane and its derivatives: These are copolymers containing urethane group in their structures. They are formed by conjugation of diol groups and diisocyanate groups with polymerization reaction (Trumble et.al. 2002). A large number of polyurethanes are synthesized and used in treatment of burns and wounds due to their non-toxic properties

(b) Teflon: It is synthesized by polymerization of tetrafluoroethylene at high temperature and pressure. Teflon is an inert material which is non-carcinogenic, insoluble in polar and non-polar solvents and which can be sterilized. It can take desired shape by applying low pressure and can be easily applied to injured area (Lee & Worthington 1999)

(c) Proplast: It is the first synthetic-bio-material specially developed for implant applications. It has high biocompatibility with tissue, that is why it is particularly preferred material in wound, burn and surgical applications (Senyua et.al.1997)

(d) Methyl methacrylate: It is a non-biodegradable synthetic polymer that is resistant to heat and UV. It is used as a dressing supporting material in plastic surgery and the treatment of injuries (Nakabayashi, 2003)

(e) Silicon: Silicon has low toxicity, low allergic properties and high biocompatibility in the body (Jansson and Tengrak 2001). This polymer is resistant to biodegradation and is used in preparation of implant elastomers used in soft tissue repair and in the production of hypodermic needles and syringes (Park el.al. 2004) It is also used as wound support material in serve wounds and burns due to its high tissue compatibility. (Losi et.al., 2004)

Pharmaceutical formulations used as dressings for wounds and burns

Various pharmaceutical formulations have been developed as synthetic dressing materials for wound and burn treatment.

(i) Films/membranes

These films and membranes are available in various thickness, ranging from μm to mm, and are prepared using various natures and synthetic biopolymers. Films and membranes are used to protect and heal the wound or burn areas. Polyurethane, Polyvinylyrrolidene (Yoo and Kim 2008), Hyaluronic acid (Uppal et al, 2011) Collagen (Boa et.al 2008), chitosan and its derivatives (Tanigawa et.al. 2008), and fucoidan (Sezer et.al,2007) are some of the synthetic and natural polymers used to make films and membranes. In recent years, the use of polymers has gained priority in tissue engineering and biotechnology, both as dressing material and in enhancing treatment efficiency (Atiyeh et.al.2005)

(ii) Gels

Gels are various semisolids preparations formed by dispersion of inorganic or organic substances that have larger particle size than colloidal particles in a liquid phase. Hydrogels are semisolids systems which are formed by combination of one or more hydrophilic polymers. These are frequently used as dressing materials as they can absorb water more than their weight and cause less irritation when in contact with wounded or burnt tissue surface. They permit oxygen penetration .Hydrogels are preferred due to their patient compliance,treatment efficiency, ease of application and easy bioadhesion. They can be easily removed from application site when required.

Natural biopolymers such as chitosan and hyalouronan and their derivatives are used for hydrogel preparation and have shown satisfactory results in healing wounds and burns. Synthetic polymers such as polvinyl alcohols are also used to make hydrogels by combining them with natural biopolymers such as chitosan and

are used as wounds dressing material. These cross linked polymeric hydrogels are capable of ideal water absorption and swelling and provide an ideal moist environment necessary for wound healing, also such wound dressing materials is more elastic and flexible. Wound gels containing polyhexadiene, showed appreciable results in healing and treatment as they are non staining and so wound assessment can be done without painful wound cleaning, which is not so with iodine contining or silver sulfadiazine crome containing gels. The polyhexadiene containing gels are thermosensitive gels and they are easy to handle and bring about easy filling of wound cavities. Gelatin/alginate hydrogels also are effective wound and burn healers. Chitin is also used in place of chitosan.

(iii) Sprays and foams

Sprays contain solvent and polymers and form a film layer on the surface of the wound when sprayed. polyhydroxyethyl methacrylate powder and liquid polyethylene glycol are used in hydron sprays. Disadvantage of hydron is loss of integrity of the dressing and accumulation of submembrane fluid. Another example of aerosol spray is papain-pectin spray. Lyofoam, polyurethane foam are also used for aerosol sprays.

(iv) Composites

These involve an outer lager with high mechanical strength, which is resistant to the effects of environments and provides moisture by preventing evaporation. Chitin nanofibrils/ chitosan glycalate composites (Muzzarelli etal 2007), Salmon collegen comosites (Shen et.at. 2008), polymer-xerogel composites (Costache et. at. 2010) and autologus cellulose gel matrix systems (Weinsten-Oppenheimer et.at. 2010) are used for composties. Bilaminar composite membranes containing bovine collegen based dermal analogue and silastic epidermis has een developed for the treatment of wounds and burns. Biocompatible bovine collagen based dermal analogue slowly degrades and provides a suitable environment for development of patient's connective tissue, it is permeable to oxygen and water and protects the wound form trauma and microorganisms Synthetic composites are also effective and easily applicable and do not cause infection.

(v) Partiulate system

Greatest advantages of particulate systems are that they provide oxygen and water permeability have large contact surfaces, high bioadhesiveness and drug release is the wound area can be controlled leading to speedy wound healing (Kawaguchi 2000, Date and Patravale 2004), polyethylen-co-vinyl alcohol nanofibre (Xu et- at 2011), fucoidan micrpparticles (Sezer et. at. 2008) collagen sponges (Lee 2005) and liposome containing epidermal growth factor (Alemdaroglu et al 2008), have been used for this purpose.

Conclusion

The biopolymers are nore effective as wound heading accelerator than synthetic polymers. The wound treated with biopolymers and biomaterials shows accelcrated healing. Biopolymer stuctural arrangement is similar to that of normal skin. Consequently the biopolymcers are considered to be one of the ideal materials with biocompatibility, biodegradability and wound healing property as well as easy application.

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