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Biomaterials in wound healing

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Angélica de Lima das Chagas
Graduate Program in Health Sciences, School of Medicine, Universidade Federal de Goiás, Goiânia, Goiás, 74605-50, Brazil.
ORCID: 0000-0003-3085-3955
E-mail: angelicalimac@gmail.com

ABSTRACT
Biocompatibility is the ability of biomaterials to promote and influence the tissue repair process, and to interact with tissues and organs without causing damage or compromising the biomaterial. The aim of this narrative review was to deepen the theoretical concept of the interaction between biomaterial and tissue. In addition to providing an accessible view of biocompatibility without ignoring the concepts. In this vein, the mechanisms of biocompatibility were analyzed, such as the systemic and local physiological response to biomaterials in order to improve clinical applicability. The interaction between biomaterials and the tissue interface is a complex chain of reactions between the organism and the device that can be modulated by the properties of the biomaterial. Understanding this interaction allows us to develop better applicability strategies with better clinical results.

Keywords: Biocompatibility, Biomaterials, Inflammatory response.

1 INTRODUCTION

Cutaneous wounds are one of the most important lesions in clinical surgery, which constantly requires research for new drugs, materials, and therapies for tissue repair. The normal wound healing process occurs in several overlapping phases, formed by a series of events that begin soon after the injury1,2 and the healing process is severely disrupted in cases of disease conditions, such as diabetes or accidents3. Extensive trauma resulting from accidents and burns results in significant tissue loss, hindering healing4,5, one strategy is to provide an artificial extracellular matrix in the form of a dressing or skin graft, provisionally assisting in the healing process6.

In the treatment of skin lesions, a range of skin substitutes, natural or synthetic, can be used in order to promote healing, which stimulates the production of cytokines, prevents dehydration, acting as a barrier to infectious agents, and must be biocompatible, in addition to having mechanical properties similar to native tissues7.

The use of natural products as a basis for the development of new devices to assist the tissue repair process is of interest to the pharmaceutical industry, as it offers the advantage of having a wide variety of chemical structures and also because they are a renewable biological source, from which their conscious obtaining does not promote harm to the environment. since the use of synthetic and biosynthetic materials is costly 8,9.

The aim of this review is to report the current biomaterials for the treatment of skin wound healing.

2 LITERATURE REVIEW

2.1 BIOMATERIALS: AN INTRODUCTION

2.1.1 Definition and History

Biomaterials are defined as devices that come into contact with biological systems, of synthetic or natural origin, which can be of temporary or permanent use, with the function of replacing or repairing a damaged tissue or organ10,11.

The interaction of non-biological materials in the human body dates back to prehistoric times. In an unintentional implant found in a 9000-year-old individual described by archaeologists who lived with a spear embedded in his hip, which apparently healed and did not significantly impede his activities12, illustrating the body's ability to handle material implants13.

There are still records of dental implants made by the Mayans as early as 600 B.C., linen sutures used by the early Egyptians, gold thread sutures by the Greeks as early as 200 B.C.13. However, the concept of biomaterial was only introduced in the twentieth century10.

The first generation of biomaterials developed between the 1960s and 1970s focused on the use of bioinert materials that promoted replacement of damaged tissue and mechanical support, with the principle of reducing the immune response, not causing foreign body reaction and preventing biological rejection, that is, they did not interact or interacted minimally with tissue. such as the use of gold and ivory to replace teeth, glass for eyeballs, and steel or wood to replace limbs10. Many of the first implants that were successful were accidental, where materials were designed for another application. The development of implant materials was based on trial and error, as little was known about biological interactions14.

With the development of foreign body response research in the 1980s and 1990s. "Passive" biomaterials have been replaced by second-generation biomaterials, bioactive biomaterials, which have been the target of studies focusing on the biological aspect, with the aim of inducing a specific biological response through active surfaces that could accelerate the regeneration and healing processes, developing together with new surgical techniques, allowing the development of more efficient and less invasive treatments10. 14.

However, bioabsorbable biomaterials with degradation rate and resorption properties have gained visibility, offering the opportunity to overcome the disadvantages of solid permanent implants without the need for surgical removal processes10. The association of the two models composing the third generation of biomaterials, characterized by the improvement of the biomaterial, composed of

adaptable systems, designed with biocompatibility and biofunctionality in mind and capable of stimulating specific cellular responses14.

In the present decade, fourth-generation biomaterials have emerged, intelligent or biomimetic biomaterials, developed to actively participate in the processes of healing, regeneration and recovery by acting in the biological environment in a specific way, associated with tissue engineering with stimulation at the molecular level 10, 14.

The application of biomaterials improves the quality of life, and the applications are vast, such as the replacement of joints and limbs, artificial arteries and skin, contact lenses and prosthetics, as well as a range of biomedical devices used for diagnosis and aid in recovery. Its applications can be for medical or purely aesthetic reasons, such as breast implants 4.

2.1.2 Classification of biomaterials

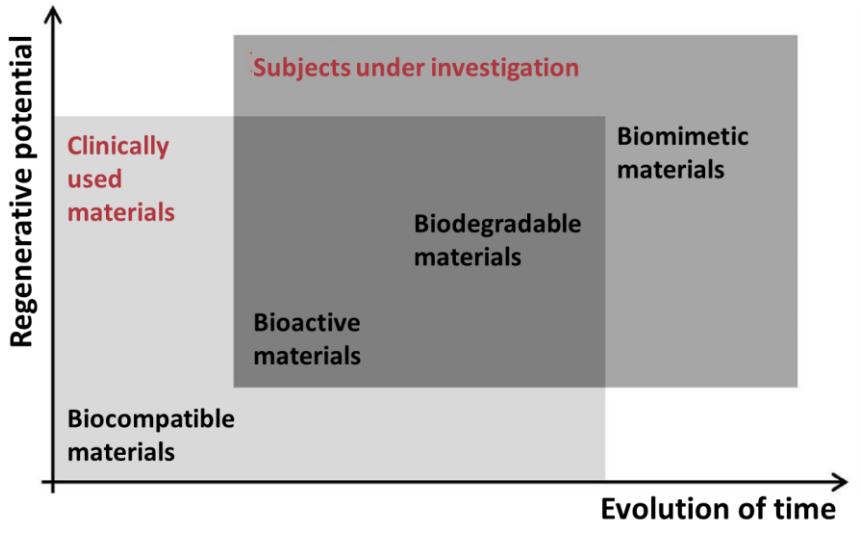
Biomaterials can be classified into three main types, described by the biological response they induce in the body, they can be bioinert, causing no or minimal tissue response; they can be bioactive, which stimulate the response of the host tissue, increase the interaction of the material and stimulate cell proliferation; while biodegradable or bioabsorbable materials are slowly decomposed by the body and gradually replaced14. (Figure 1)

Biomaterials can be classified into synthetic and natural. Some authors also classify biomaterials according to their chemical composition as ceramics, metallics, polymers and composites 10, 13, 14.

Ceramics have a diversity of composition and applications, they can work as a joint substitute, metal implant coating, drug delivery agent. They are inorganic compounds, have good dimensional stability, wear resistance and are stable in acidic environments15. Metals are widely used for orthopedic implants because they have excellent mechanical strength, good ability to

Deformation, ease of fabrication, low production cost, allow sterilization and are well tolerated by the body, with good application for plates and screws16.

FIGURE 1- Evolution of biomaterials. Classic biomaterials seeking to be biocompatible, with the action of replacing damaged tissues and providing structural support. The evolution of research to develop a biomaterial with bioactive components to increase the life of the implant by optimizing the tissue-material interphase. It is the development of smart biomaterials, seeking the biodegradability of the material together with active participation in the regeneration process, stimulating specific cellular responses at the molecular level.



Source: Pires et al. 10

Synthetic polymers offer attractive options for shape and architecture control, mechanical modulus, and degradation rate that can be adapted to each application, with biocompatibility and low immunogenicity. The most commonly used synthetic polymers are polylactic acid (PLA), polyglycolic acid (PGA) and poly(lactic-co-glycolic acid) (PLGA), polyacrylic acid (PAA), polyvinyl alcohol (PVA) and polyvinyl pyrrolidone (PVP) poly(methyl methacrylate) (PMMA)17. Although synthetic biomaterials can be molded into supports with interconnected pores, some can produce acid degradation products that can promote changes in the pH of the medium18. The pH change can affect the behavior and survival of cells and cause inflammatory tissue adverse reactions19. Composite materials are constituted by the association of biomaterials, where one phase configures the matrix while the other has a reinforcement or modifier component, used extensively for prostheses in which the reinforcement material

It can be added with the aim of improving mechanical property, increasing degradation rate, improving biocompatibility and bioactivity10. (Table 1)

TABLE 1 – Application of synthetic biomaterials 10

Biomaterial	Advantages	Disadvantages	Applications
Polymers Polyethylene Polyester Polyurethane PMMA Silicone	Elasticity, easy fabrication, low density	Low mechanical strength, weather-dependent degradation	Sutures, Vascular Grafts, Ligament Reconstruction, Implant Fixation, Drug Delivery Device, Contact Lenses

Metals & Alloys Stainless Steel Titanium Alloy Alloy from Cobalt-Chromium	High tensile strength, high wear resistance, high deformation energy	Low biocompatibility, corrosion in physiological environment, loss of mechanical properties with tissues Soft, high density	Orthopedic fixation, screws, pins, plates, dental implants
Ceramics & Glasses: Alumina Zirconia Carbon Calcium Phosphate Porcelain Bioactive glasses	Good biocompatibility, inert, corrosion resistance, high compressive strength	Low tensile strength, low mechanical strength, low elasticity, high density	Bones, joints, teeth, valves, blood vessels, and artificial tracheas
Composites Carbon Fibers – Thermosetting Resin, Carbon Fiber – Thermoplastic Carbon-Carbon Calcium Phosphate – collagen	Good biocompatibility, corrosion resistance, high tensile strength	Difficult to manufacture	Artificial heart valve (carbon or graphite), joint implant (carbon fiber reinforced with high-density polyethylene

Source: Pires et al.10

Biomaterials of natural origin can be divided into two groups: protein-based biomaterials, such as collagen, silk fiber, gelatin, fibronectin, keratin, and eggshell membrane, and are obtained from animal or plant sources, from bioactive molecules that mimic the extracellular environment, and polysaccharide-based biomaterials, such as hyaluronan, cellulose, Glucose, alginate, chondroitin, chitin and chitosan are obtained mainly from vegetable sources17. In vivo studies demonstrate that biomaterials of natural origin usually achieve greater biological advantages during biomedical applications 20, 21, 22.

Biomaterials have different applications, their properties are fundamentally evaluated for their application. For some tissues, a biomaterial may be more appropriate than others, depending on mechanical stress or resistance to corrosion, such as in cases of bone replacement10.

2.2 BIOCOMPATIBILITY

Biocompatibility is the fundamental requirement of a biomaterial. A biocompatible material promotes an appropriate response of the organism with minimal damage to normal tissue function, in a specific application; In addition, it does not generate a toxic, thrombogenic or allergic reaction. The main factors that determine biocompatibility are the reaction induced by the material in the host tissue and its degradation capacity23.

Any material after implantation in the body triggers some kind of response. This response is observed at the tissue-implant interface where the response can be toxic, damaging the cells surrounding the implant and causing systemic damage to the patient. The tissue response can be nearly

inert, which can generate a non-adherent fibrous capsule designed to isolate the host from the implant. The response may be bioactive, where there is implant-tissue bonding, and the response may also be implant degradation, where the implant, after degradation, is replaced by the host tissue16.

Evaluating the biological performance of the biomaterial is the main field of biocompatibility study. The evaluation of biocompatibility is important for the development of materials intended for implantation, not only involving criteria for acceptance or rejection of a material or device, but a set of processes that allow the evaluation of the biological performance of the material and the determination of parameters to identify, eliminate or determine tolerable limits of adverse reactions24, since being compatible with living organs or tissues does not mean that the material is totally inert. On the contrary, it is more possible that a degree of interaction is important for greater material efficiency25.

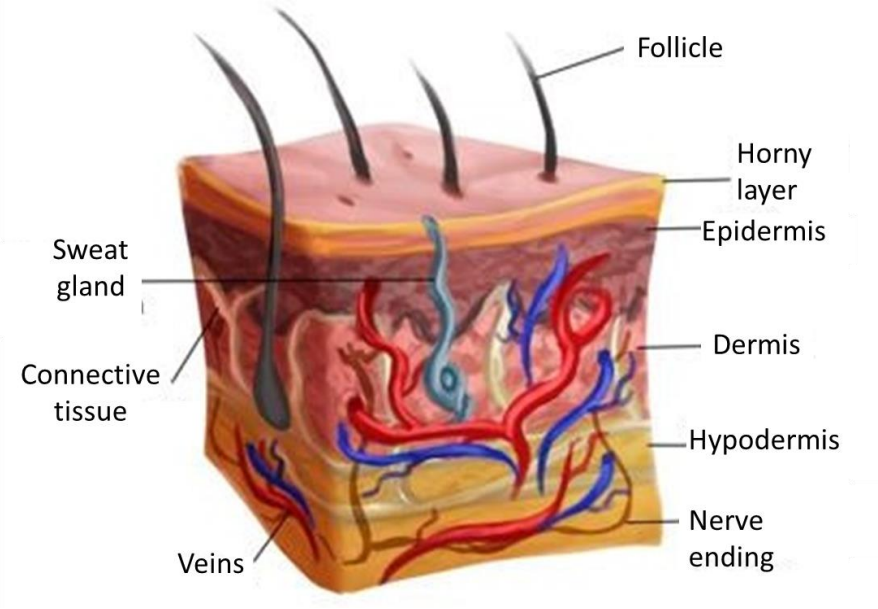
Combined with biocompatibility, a biomaterial needs to exhibit biofunctionality, which is the ability to behave appropriately for the function it was designed to perform. The choice of biomaterial for a given application is related to the effect of the material on the body, evaluating at the cellular and systemic level, and the effect of the body on the implant, it is not yet possible to affirm that a biomaterial is biocompatible and biofunctional for one application will behave the same for another application area24.

2.3 BIOMATERIALS IN THE HEALING OF SKIN WOUNDS

2.3.1 Principle of wound healing

The skin is the largest organ in the body, comprises 15% of the total adult weight and provides protection against external, chemical and biological agents in addition to promoting body thermoregulation. The skin is capable of stimulating self-regeneration, however, this process is dysregulated in cases of deep lesions, burns, diseases such as diabetes mellitus, together with compromised nutritional or immunological status, which can lead to a chronic injury, and many chronic lesions do not heal and can lead to limb amputation and mortality3,4,5,26. The skin is made up of three layers: epidermis, dermis, and hypodermis (subcutaneous layer) (Figure 2). The stratum corneum is the least permeable layer of the epidermis, which provides protection against pathogens and foreign substances in the body, the basement membrane has cells that differentiate into keratinocytes, which in turn differentiate and migrate towards the surface, and the keratinized layer has tissue barrier properties26.

FIGURE 2 – Normal skin structure. Source: Adapted from Vig et al 26



The dermis is composed of extracellular matrix connective tissue, fibroblasts, vascular endothelial cells, nerve endings, and blood vessels. The hypodermis is located just below the dermis, provides insulation and cushioning between skeletal structures, and promotes energy storage26.

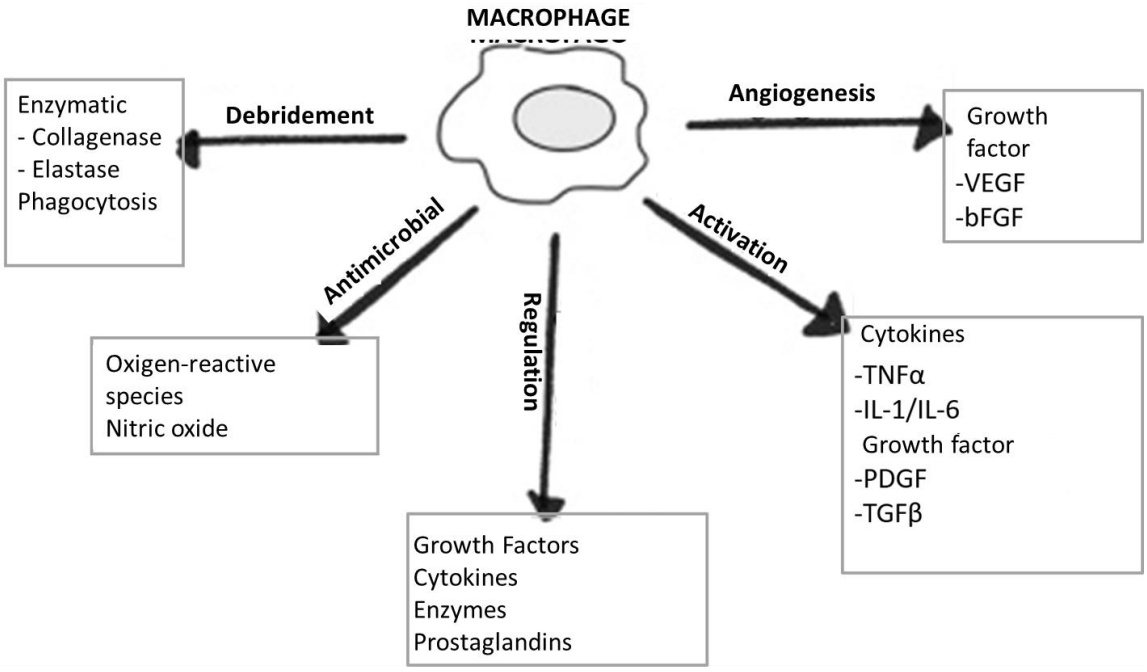
After a trauma, the injured tissue is healed through a series of events that begin shortly after the injury, and consist of hemostasis, inflammation, proliferation, and remodeling. Each phase involves the interaction of several cell types, bioactive factors, and a support platform formed by the extracellular matrix10.

Resolution of the lesion begins with hemostasis, through vasoconstriction, platelet activation and cytokine signaling, which activates the coagulation cascade and recruits cells to the site of injury, fibrinogen leads to coagulation of exudates (cellless blood and platelets), together with the formation of a fibrin network, resulting in a clot that stops bleeding27. The inflammatory phase occurs simultaneously with the hemostatic phase, observed through physical signs of flushing, heat, edema, and pain, and is characterized by decreased vasoconstriction, initiating vasodilation in response to histamines released by circulating mast cells, in addition to increased vascular permeability and the recruitment of inflammatory cells2, predominantly neutrophils and macrophages, which have the function of wound debridement4, It usually takes more than 24 hours. Neutrophils phagocytose dead cells and bacterial particles, and release reactive oxygen species that promote a hostile environment for bacteria. In the period of 24 to 72 hours, macrophages are the dominant cells, play a central role in the wound healing process, remove cellular debris and promote recruitment and activation of fibroblasts and myofibroblasts necessary for the subsequent phases of healing27 (Figure 3).

Then there is the proliferative phase that begins with the migration of fibroblasts, endothelial and epithelial cells coordinated with angiogenesis to produce granulation, which occurs about four

days after the injury. Consecutively, the remodeling phase occurs three weeks after the injury, and is the final stage of wound healing, composed mainly of fibroblasts and myofibroblasts, characterized by the replacement of immature type III collagen, formed during the proliferation phase, by mature type I collagen, concomitantly with wound contraction and promoting lesion closure2, 27.

FIGURE 3 – Macrophage performs multiple actions, such as cell activation via cytokines, angiogenesis via growth factors, antimicrobial action, and debridement.



Source: Adapted from Childs et al 27

2.3.2 Biomaterial-Host Tissue Interaction

The interaction between the biomaterial and the damaged tissue occurs at various scales, from centimeters and millimeters at the organ level, to individual scales such as cells (micrometer) and proteins (nanometers). A tissue or organ can be in contact with biomaterial for weeks, such as bandages, months, or years for organs. The interaction consists of physical contact, tissue growth, and chemical bonds. The interaction time is proportional to the size of the tissue component, cells interact with a biomaterial via integrins, while proteins interact through secondary bonds and hydrophobic interactions. Chemical interactions are: ionic, covalent or metallic, and may be associated with hydrogen bonds, van der waals and hydrophobic interactions28.

Biomaterials can induce cell change, with dressings in mind can be designed to aid tissue regeneration, such as the pore size of a scaffold, which can regulate the speed of cell migration. The smaller the pore diameter, the lower the speed of cell migration, the decrease in the pore is also related to an increase in the surface of the biomaterial, which promotes more binding sites for the cells. It is also possible to slow down the degradation of the polymeric biomaterial by adjusting the degree of cross-linking, or slowing down the natural degradation of collagen by grafting glycosaminoglycans

onto collagen fibers, has also been shown that changing the structure of collagen can reduce thrombosis, inhibiting platelet clotting and inflammatory response28.

2.3.3 Use of biomaterials in wound healing

There are reports of the use of biomaterials for wound healing in early medical-related writings. The ancient Egyptians recorded the use of grease, plant fibers, and honey to aid healing. Biomaterials are of great importance in the wound care industry, such as dressings, cell encapsulation mechanisms, and nanoparticle encapsulation therapies 29.

The ideal dressing should promote a rapid cure at a reasonable cost with minimal inconvenience to the patient30. In the early stages of healing, the injured tissue is very active and produces several metabolites, such as proteins, dead cells and tissue fluids, where the removal of metabolites helps to reduce the probability of infection31,32.

The dressings have the function of containing bleeding, absorbing exudate, debrideing the wound to remove foreign bodies, protecting the area from pathogens, helping granulation and improving re-epithelialization. In addition, they can be designed to control the microenvironment such as temperature and pH28.

An effective dressing combines some important chemical and physical properties, such as acting as a physical barrier to protect the wound. A porous material is important to allow gas exchange33, in particular the transfer of oxygen, which is essential for tissue recovery34, and to promote drainage of exudate. The maintenance of a moist wound environment facilitates the wound healing process, preventing tissue dehydration and cell death, and accelerating angiogenesis35, being non-adherent to the wound and easily removable without trauma, as well as being non-allergic and non-toxic36.

The therapeutic purpose defines the design criteria of the dressing, which can be hydrophilic or hydrophobic to control lesion fluids, porosity or swelling, to allow encapsulated drugs to penetrate the wound, and degradation of the biomaterial, which can be designed to aid regeneration28.

Wound dressings are manufactured with different types of materials, such as hydrocolloid, alginate, collagen, with a specific function of debridement, antibacterial, occlusive, absorbent, adherent and of varied physical form such as, solutions, emulsions, ointment, film, foam and gel. They may also contain biological products capable of stimulating or promoting healing events, from cell migration to the production of extracellular matrix (ECM) components30,37.

They can also be classified as primary, secondary, and island dressing, where the primary dressings make direct contact with the wound, the secondary dressings cover the primary dressings, and the island dressings have an absorbent central area surrounded by an adhesive edge30.

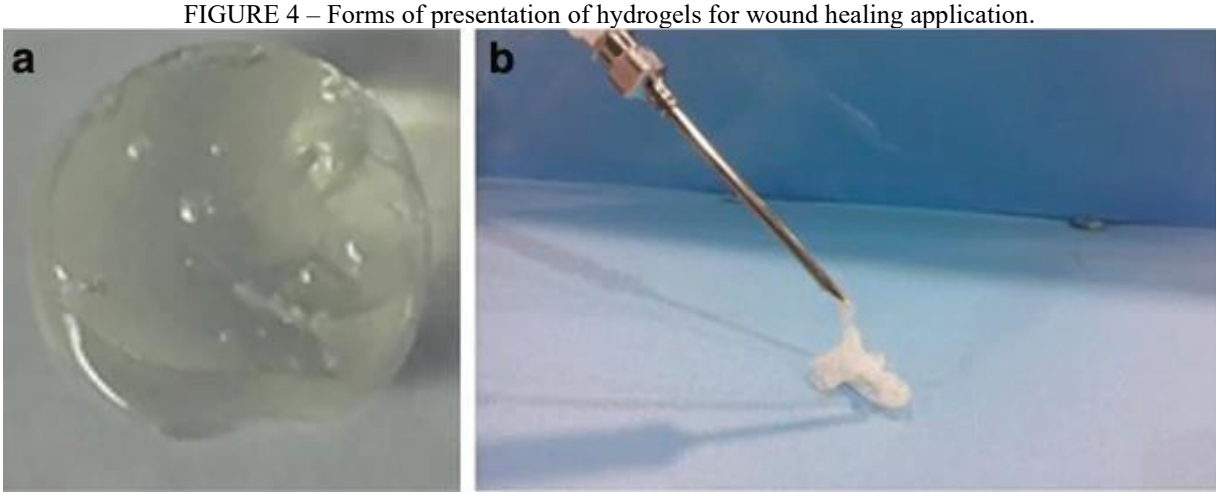
Solutions and emulsions are effective in the early stages of healing, with bactericidal or debridement action, however, they remain at the wound site for a short time. And semi-solid formulations such as ointment and creams can remain for a long period in the wound, such as silver sulfadiazine cream and silver nitrate, however, they are not effective in highly exudative lesions, due to the rapid absorption of liquids, they lose their rheological characteristics becoming mobile. Traditional dressings include cotton, bandages, natural or synthetic gauze, are dry, do not provide a moist environment to the wound and can be used as primary or secondary dressings. They provide bacterial protection, but it is lost when the external surface of the dressing is moistened by wound exudate or external fluids30.

Modern biomaterials were developed as an improvement on traditional healing agents, promote a moist environment to aid healing while keeping the environment protected to prevent infection, have low adhesion, provide protection against trauma, absorb excess exudate and allow gas exchange, in addition to being associated with drug delivery therapies, growth factors, compounds that stimulate healing, with antibacterial action or that stimulate cells, providing specific proteins to the site of injury or promoting the synthesis of ECM via growth factors or proteins. Examples of modern biomaterials are; hydrogels, electrical matrices, films, membranes, sheets and scaffolds30,37.

a) Hydrogel

Hydrogels are widely used for repair and regeneration of damaged tissue, due to their viscoelastic properties, permeability, porosity, biodegradability, and biocompatibility, making them able to form a barrier against pathogens and keep the environment hydrated to aid healing. They can be presented in gel form, as a film or as an elastic solid film (Figure 4).

FIGURE 4 – Forms of presentation of hydrogels for wound healing application.



b) Gel form. Source: Murray et al37

In the preparation of the films, the polymeric components are cross-linked to retain water, and can absorb a significant amount of fluid in exuding wounds30. Hydrogels can serve as delivery

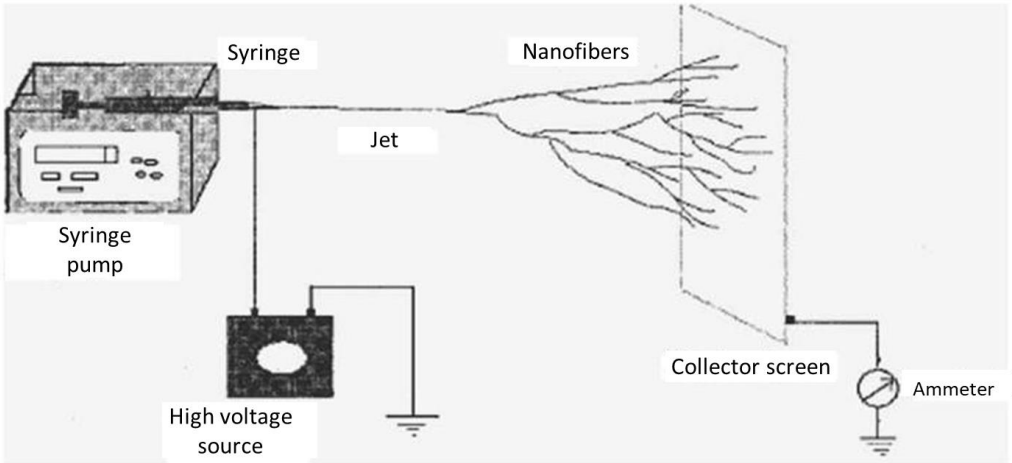
vehicles for drugs and other wound healing compounds, and can be manipulated to promote controlled release of compounds28. PVA is a polymer frequently used in the manufacture of hydrogels for wound healing37. And they can be combined with other compounds to stimulate healing, such as curcumin38 and zinc oxide39. When applied as a gel, they generally require a secondary coating and need to be changed frequently, while films do not require a secondary coating because they are made of semipermeable film, with or without adhesive edges, in addition to providing protection and allowing gas exchange through the film28.

Hyaluronic acid, naturally present in the skin, is a polysaccharide also used in the production of hydrogels37. Hydrogels composed of hyaluronic acid and chitosan are used to release vascular endothelial growth factor (VEGF) and have antibacterial and angiogenic action40. For tissue engineering applications, a spongy scaffold was developed from collagen aerogel with Tritticum eaestivum that showed good biocompatibility in vitro, associated with antimicrobial activity and pro-angiogenic property 41.

b) Electrical Matrix

The use of electric matrix in the preparation of dressings has a number of advantages, it allows the mixing of fibers with diameters varying in micro and nanometers, which are unite in a highly interconnected porous microstructure, resembling the natural extracellular matrix (ECM); create a lesion cover while having oxygen permeability; promote protection against infectious agents and keep the environment moist37. Obtained through the electrospinning method, the technique allows the production of nanofibers (Figure 5).

FIGURE 5 - Diagram of the electrospinning process in the preparation of dressings. Source: Adapted from Zahedi et al36



The polymers are dissolved in specific solvents and inserted into a syringe, and subjected to a high potential difference between the head of a syringe needle with a flat end, the manifold. The electric field generates a jet of solution in the direction of the collector and within the space between the tip of the needle and the collector, the solvent evaporates, collecting only the polymer36. Gelatin nanofibers

containing Centella asiatica extract have been manufactured via electrospinning, and have been shown to exhibit dermal wound healing activity42. A dressing of starch nanofibers with gelatin loaded with Lawsonia inermis showed antibacterial activity, stimulation of fibroblast proliferation and collagen synthesis, improving healing in second-degree burn models43. In another study, collagen from the skin of marine fish was used as a coating to support polymeric nanofibers with Coccinia grandis extract, and showed cytocompatibility, increased collagen synthesis and accelerated wound healing in an animal model44.

c) Films, Membranes & Sheets

There is a range of skin substitutes for wound healing26. Most of them are transparent, which allows evaluation of the lesion, and they adjust easily, due to the elasticity and flexibility characteristics), such as in elbows and knees30. However, healing can present versatility depending on the patient, such as; nutritional status, presence of diseases, and wound conditions, requiring materials capable of maintaining adequate conditions specific to wound healing in each case26.

Aiming at these needs there are membranes of different natural and synthetic polymers, grouping the characteristics of ideal dressing, with new design and production techniques. They include the incorporation of bioactive molecules into the dressing material, such as; antimicrobial agents, vitamins, growth factors, minerals and others), which help and accelerate the healing process30. Herbicidal compounds with antimicrobial activity, help in coagulation, acting on inflammation, collagen synthesis and re-epithelialization steps in healing such as; tannins, terpenoids, phenolic compounds, volatile oils, flavonoids, alkaloids, saponins, etc.45, 46.

Membranes such as Talymed® are available on the market, which is a matrix of poly-N-acetylglucosamine (pGlcNac) fibers isolated from microalgae that stimulate cell migration by interacting with fibroblasts and endothelial cells 47. Hyalosafe® is a transparent membrane designed to maintain a humid environment, composed of benzyl ester, which during degradation provides hyaluronic acid to the lesion48. Actsorb TM Plus is an antimicrobial activated charcoal dressing with silver49. Most existing brands differ in terms of permeability, adhesiveness and shape30.

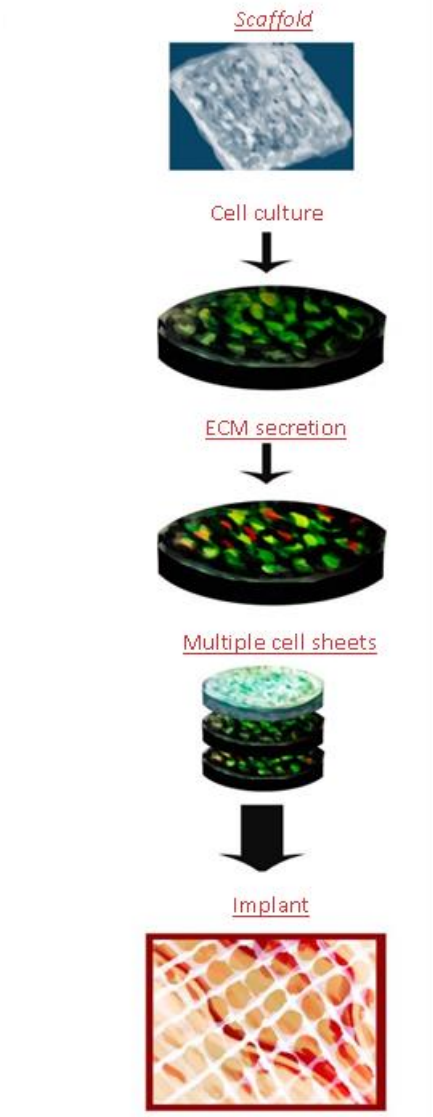
d) Scaffolds and tissue engineering

Tissue-modified skin substitutes are future alternatives to traditional wound healing and tissue regeneration strategies. Among tissue engineering organs, the skin was the first engineering organ that moved from laboratory research to patient care 26.

Scaffolds are key components in regenerative medicine and tissue engineering, being the best biomaterials for restoring, improving, and maintaining tissue function, as they provide a suitable medium that allows cells to survive, proliferate, and differentiate. Scaffolds can be produced from synthetic and natural polymeric materials, degradable or not50.

Scaffold preparation for tissue engineering involves cells and/or extracellular matrix. The porous nature of scaffolds allows for the inoculation of cells and the exchange of nutrients. They are used for the growth of tissue, organs and bones because the network of pores interconnected cells simulate the construction of ECM by providing a physical matrix where cells bind and produce their own ECM. At the same time, they deliver nutrients to the center of the device through the interconnections of the pores50. (Figure 6)

FIGURE 6- Cell scaffolds that secrete extracellular matrix (ECM). Cells are seeded and secrete MEC which facilitates growth and proliferation, multiple seeded cells capable of secreting ECM are used for implantation at the wound site.



Source: Adapted from chaudhari et al. 50th

With the development of materials and technologies for more economical production of the biomaterial for wound healing therapies, technologies for the manufacture of scaffolds have advanced in recent years. The ability to manufacture caffolds using 3D printing technologies has enabled the development of skin substitutes that can not only be produced to be specific to patient wounds, but

also in the use of bioinks that allow the printing of cell-laden scaffolds . In addition, advances in bioprinting and bioinks now allow for direct printing of scaffolds on body parts, opening up the ability to print scaffolds directly onto patient wounds in the future37.

More recently, different types of skin constructs have been designed to mimic ECM using components such as collagen, hyaluronic acid, and some have skin cells incorporated into them. Such as Hyalomatrix® and three-dimensional (3D) Hyalograft, which are polymeric matrices with embedded fibroblasts, in which they secrete ECM into the lesion, with the advantage that the cells can be derived from the patient, which minimizes the immune response and possibility of rejection. Dermagraft ™, consists of a bioresorbable polyglycolic acid structure containing neonatal human fibroblasts, used both for burns and chronic wounds, presenting the advantage of not having to remove it from the patient, the scaffold cells are incorporated into the new skin, closing the lesion. Apligraf® and OrCel ™ use neonatal fibroblasts and keratinocytes in a collagen matrix that mimics the stratum corneum, and the matrix is absorbed during the healing process37.

There are several commercial biomaterials for wound healing, permanent or temporary, available on the market for use in specific clinical issues26. However, this is still a field under study, and Chart 2 shows the biomaterials currently under development29

TABLE 2 - Biomaterials currently under development.

Kind	Constituent	Therapeutic benefit
Solution	Siloxysilane (polymer)	Liquid bandage, spray, provides protection and prevents maceration
Higrogel	Dextran (polysaccharide) Urethane	Complete regeneration of skin and nerves in a pig model
Scaffold		*Scaffold* selectively degraded by reactive oxygen species (ROS) at the wound site in a mouse model guides the formation of new tissue
Construction artificial dermal	Collagen	Collagen-glycosaminoglycan matrix with UV has reduced toxicity compared to gluceraldehyde-based dermal substitutes
Hydrogel	Synthetic	Adhesive polypeptide with antibacterial activity for Escherichia coli and Staphylococcus aureaus
With bioactive components	Fibrin	Growth factor with affinity for ECM induces chronic wound repair in a diabetic model
	Hyaluronic acid	Hydrogel encapsulating amniotic fluid-derived stem cells release growth factors and cytokines improving re-epithelialization and vascularization
		Hyaluronic acid nanoparticles encapsulating vitamins E, embedded in polymeric film, with controlled release of vitamin E - reduction of water loss
Cell encapsulation	Poly **β**; Amino Ester	Modified stem cell with high VEGF implanted in *scaffod* in mouse, increased angiogenesis, reduced muscle degeneration
	Fibrin and PEG	Stem cells derived from adipose tissue with PEG-fibrin gel showed wound healing and angiogenesis
	PEG+RGD	Injectable cellular adhesive support leads to rapid skin regeneration in rodent model
Nucleic acid supply	Collagen	PDFG Gene Delivery in Collagen Hydrogel Accelerated Wound Healing in Dermal Ulcers
	Hyaluronic acid	Biodegradable hydrogel with VEGF plasmid – accelerates

		wound healing
Based on Animal product	Amniotic membrane Marine Collagen	Bovine lyophilized amniotic membrane extract tested in rabbit ear wound model, increased dermal and epidermal regeneration Collagen film – improved regeneration and angiogenesis
Loaded with drug or antibiotic	Chitosan and PEG Polyurethane and dextran	Chitosan microspheres loaded with silver sulfadiazine demonstrate bactericidal activity *PEG-Chitosan Scaffold* Loading Ciprofloxacin – Increased Healing Speed Nanofiber from polyurethane-dexterous-Bactericidal activity Gram – and Gram+

Source: Adapted from Das et al 29

2.4 LIMITATIONS OF COMMERCIALLY AVAILABLE DEVICES

There are several limitations to commercially available biomaterials for use in healing, as they have low mechanical integrity, failure to integrate into the recipient tissue, low induction of vascularization and scarring, and immunological rejection. Given the inability to revascularize, scaffold cells can die and detach from host tissue. Currently, the available skin substitutes consist mainly of fibroblasts and keratinocytes and therefore lack the ability to create differentiated structures such as hair and sweat glands. Therefore, there is a need to include additional cell types, such as endothelial cells. In order to meet the massive demand from hospitals for clinical applications, it is necessary to improve large-scale production, so there is also a need to reduce the cost of biomaterials with a healing function26.

Skin substitutes using scaffold with cell culture promise future tissue regeneration and wound healing therapies. There is also a need to improve the vascularization of these devices to increase their lifespan and provide better integration with host tissues. One way to increase vascularity is by using bioreactors to provide mechanical stimulation needed to develop mature blood vessels51.

3 FINAL THOUGHTS

This review details a variety of therapies that are currently available in patients for the treatment of wounds that incorporate a biomaterial component. These therapies range from polymeric hydrogel ointments to artificial dermal construction. Due to the heterogeneous nature of wounds, there is no one-size-fits-all therapy, although continued advancement in the technologies used to develop these therapies, such as 3D printing dressings directly onto a wound, may result in wound healing in the future.

An important step in the development of biomaterials for healing will be to standardize the production process and reduce manufacturing costs. In addition, standardization of storage and preservation is also important to extend its shelf life. Further research is also needed to assess the possibility of increased risk of future malignancies in these cells. It should be noted that better and more efficient products can be developed by a detailed understanding of the biomaterial-tissue mechanism of action.

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