Artículo de Investigación. Revista Ciencia e Ingeniería. Vol. 44, No. 3 pp. 297--308, agosto-noviembre, 2023.
ISSN 1316-7081. ISSN Elect. 2244-8780 Universidad de los Andes (ULA)

Biomateriales utilizados en ingeniería de tejidos para la fabricación de andamios

Biomaterials used in tissue engineering for the manufacture of scaffolds

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Resumen

El surgimiento de tecnologías, técnicas y materiales recientes en el campo científico ha creado un conjunto diverso de mejoras para el tratamiento médico y aplicaciones en Ingeniería de Tejidos (IT). El desarrollo de biomateriales para IT ha incrementado las capacidades de biocompatibilidad, biodegradabilidad, adhesión celular, proliferación celular, retención de agua y actividad antimicrobiana de los biomateriales. Las mejoras del uso clínico incluyen: Tiempo de regeneración más corto que mejora el tiempo de recuperación del paciente. Menor riesgo de reacciones adversas, ya que es menos probable que el cuerpo rechace la matriz tridimensional. Reducción del riesgo de infección con y sin antibióticos, dado que los antibióticos afectan la proliferación celular, el uso de material antimicrobiano sin antibióticos reducirá la actividad microbiana sin afectar la proliferación celular. Tiempo de degradación controlado, debido a que el Biomaterial es diseñado con un tiempo de degradación específico dependiendo del tejido que sustituirá. Mayor y mejor resistencia mecánica del biomaterial en el entorno hostil del sistema biológico. Todo esto genera biomateriales con una capacidad óptima para funcionar como un buen tejido natural y para reemplazar el tejido dañado o de bajo rendimiento, lo que permite a los pacientes restaurar la funcionalidad de las partes del cuerpo afectadas.

Palabras claves: Biomaterial, Ingeniería de tejidos, matriz tridimensional, Aplicaciones biomédicas, Biocompatibilidad.

Abstract

The emergence of recent technologies, techniques, and materials in the scientific field has created diverse improvements for medical treatment and Tissue Engineering (TI) applications. The development of biomaterials for TI has increased the biocompatibility, biodegradability, cell adhesion, cell proliferation, water retention, and antimicrobial activity capabilities of biomaterials. Clinical use enhancements include: Shorter regeneration time improving patient recovery time. Lower risk of adverse reactions, as the body is less likely to reject the scaffold. Reduced risk of infection with and without antibiotics, since antibiotics affect cell proliferation, the use of antimicrobial material without antibiotics will reduce microbial activity without affecting cell proliferation. Controlled degradation time, because the Biomaterial is designed with a specific degradation time depending on the tissue it will replace. Greater and better mechanical resistance of the biomaterial in the hostile environment of the biological system. All of this generates biomaterials with optimal ability to function like good natural tissue and to replace poorly performing or damaged tissue, allowing patients to restore functionality to affected body parts.

Keywords: Biomaterial, Tissue engineering, Scaffolds, Biomedical Applications, Biocompatibility.

1 Introduction

Throughout history there has been an increase in the use of research, and implementation of biomaterials in Medical, Tissue Engineering, and pharmaceutical fields (Rondón 2020a). Historical data dates back biomaterials to antiquity, as Egyptians used animal sinew to make sutures (Datta y col., 2022). Biomaterials is a sub-category of materials that focuses on materials that are in constant and/or intermittent contact with bodily fluids or fluids of biological systems. These fluids will expose the materials to harsh environments that will

promote corrosion, friction wear, enzyme, proteins, oxidation, etc., when implemented in Tissue Engineering TI. To understand the discipline of tissue engineering and why biomaterials play a fundamental role in making the discipline effective, TI will be defined as the use of cell combinations, engineering materials, and biochemical factors to enhance and/or replace the biological functions in an effort to improve the clinical procedures for the regeneration of tissue and damaged organs (Vasco y col., 2016). In order for TI to function correctly it must comply with the tissue engineering triad: scaffolds, cells, growth factors. The scaffolds will be made of the biomaterials to promote cell proliferation and growth factors, the reason for this is that a biomaterial's type, composition, properties, mechanism of action, will affect a scaffolds surface properties, external geometry, pore density and size, biocompatibility, interface adherence, degradation and mechanical properties (Ciolacu y col., 2022; Naureen y col., 2021).

The World Economic Forum states that TI dates back 30 years ago, to 1988. When Joseph Vacanti (surgeon), and Robert Langer (Professor at MIT), were doing work on the field, but it was not recognized as TI at the time (Langer & Vacanti 2016).

As of today, research has found the application of biomaterials used as scaffolds for tissue engineering, providing structure and architecture. This is due to engineered tissue having problems with structure, biocompatibility, lack of a bed for nutrients, microbial infections. This study will present que development of a qualitative investigation of documentary exploration. In the search of presenting biomaterials in TI, being applied as scaffolds or structural supports, by five points of conceptualization composition, type, properties, action mechanism, and biomedical use.

2 Methodology

The methodology used in the development of this research was qualitative-documentary-exploratory, based on:

a. Search and data compilation: Pubmed, Frontiers, UP Coming, Wiley Online Library, Royal society of chemistry, MDPI, ACS Publications, ScienceDirect, SCOPUS, Cocinet, IEEE, SciELO, RedALyC and Google Scholar databases were used; following as premises and search criteria, the following key entries: "Biomaterials for support applications", and "Scaffolds in tissue engineering", during a period of one quarter of 2023, without language limitations.

b. Selection and refinement of information: the search period was 2019-2023. Zotero was used as a bibliographic manager to order the information by relevance on five bases that will be developed in this work. The bases were: types, composition, properties, mechanism of action, and biomedical use. The selected publications were relevant research papers and thematic reviews (Fig. 1).

c. Selection of subtopics: the refined information was focused on the distribution of the proposed research structure to identify the relationship and relevance of the selected topics for this research.

d. Analysis of results: it was carried out through a critical analysis of the compiled data, resulting in the orderly and understandable conclusions that are presented in this work.

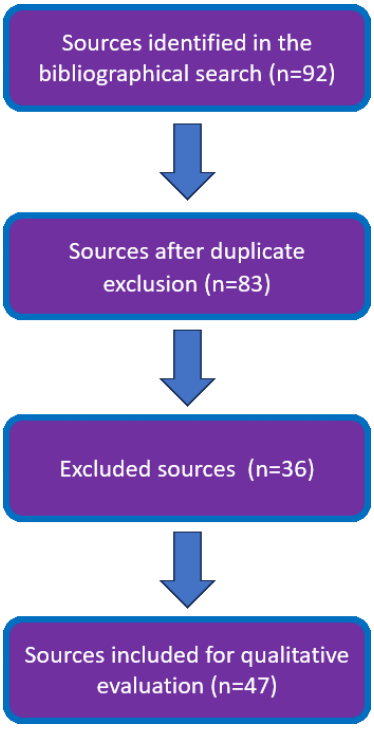

Fig. 1. Flowchart of the study selection methodology for this research.

3 Discussion and Results

To understand that biomaterials serve as the building blocks of a scaffold in tissue engineering, a scaffold must first be defined as an element that functions as a base structure or template for cell adhesion and cell interactions (proliferation and differentiation, etc.) that favor tissue formation (Liu y col., 2022). The implementation of scaffolds for clinical and structural use has generated critical importance in IT, since in this area it seeks to provide a chemically and mechanically appropriate environment for the introduced cells to proliferate and function as expected, and eventually to form. fully functional tissue (Mendoza 2022). When preparing the methodology for designing and manufacturing a new scaffold, an IT engineer must thoroughly investigate the problems, difficulties, and behavior of the environment for clinical use, since depending on the application that is going to be given, the scaffold will need , both specific physical-chemical properties (mechanical proper-

ties, biodegradability, etc.) and morphological (pore size, surface topology, distribution and interconnection of pores, etc.) to reproduce the cellular environment in vivo (Serrano-Aroca y col., 2022). For these definitions to be true, a scaffold must achieve biocompatibility, biodegradability, good mechanical and structural properties.

3.1 Biocompatibility

Biomaterial or biocompatible material is defined as any substance (Non-pharmaceutical) or mixture of substances, natural or synthetic, with the capacity to fulfill the desired function in a given period of time, without causing or considerably reducing adverse reactions in the biological environment, and generating an outstanding cellular or tissue response, and can be used independently or as part of a system that treats, augments or replaces any tissue, organ or function of the body (Kiradzhiyska y col., 2019; Liu y col., 2021). Some of the examples of biomaterial scaffolds that serve tissue engineering are tissue regeneration in regenerative endodontic procedures, heart tissue, bone tissue, and muscle tissue (Achilles tendon). Biocompatibility also aids the mechanical structure by providing the scaffold with a stronger anchorage. A specific study carried out on endodontic procedures, involved a tooth that had a periapical lesion, immature root and thin tooth walls, to fix the tooth they dried the root canal and temporized with calcium hydroxide, then rinsed with 17% EDTA to remove the calcium hydroxide and release growth factors from root dentin. Release of growth factors can be seen as material acceptance or biocompatibility generating bioactivity and actually doing the opposite of an adverse reaction.

3.2 Biodegradability

Biodegradability is defined as the ability of a material to be biodegraded, that is, the material by biological action decomposes into simpler and more stable substances, producing structural alterations in the initial molecule or molecules, and consequently, its original physicochemical properties change (Moreno 2020). Current biodegradable biomaterials focus on being able to be replaced in the biological system by biological material or native tissue. Taking this into account, the different types of biomaterials must have the ability to regenerate tissue by degrading a certain structure (scaffold), rapid biodegradability being viable, but in many cases if the degradability of the scaffold is slow, the system will cover the scaffold in a scar like tissue, but when it is the right speed, the system replaces the scaffold giving structure to the new tissue. Therefore, the degradation rate of the scaffold must be equal to the growth of new bone tissue (Gómez y col., 2022).

A good example of this can be seen with polycaprolactone (PCL), a highly biodegradable material that is widely used in tissue engineering, due to its biocompatibility, structural capacity, and mechanical properties combined with biodegradability. Because the nature of PCL is semi-crystalline and hydrophobic, PCL degrades in 2-4 years, which is too long for skin tissue regeneration, but is still applicable in many other areas of tissue engineering. However, when PCL is modified to electrospun PCL fibers (used in electrospun mesh), changes in the rate of degradation are evident. Dias y col., in their study on PCL Electrospun Degradation: An In Vitro and In Vivo Study, found that electrospun PCL fibers showed 97.11% enzymatic media in in vitro tests and clear biointegration of the meshes. electrospun, and the degradation of some parts, which demonstrated that PCL electrospun meshes are applicable or usable in short-term applications in skin regeneration (Dias y col., 2022).

3.3 Mechanical properties

The mechanical properties provide scaffolds with mechanical resistance, resist load forces, corrosion, and permeability, and reduce friction in the support area of the biological system. Scaffolds must have an architecture that has mechanical properties like natural tissues or biological systems. For example, 3D-printed PCL scaffolds with large pores facilitate viability, proliferation, and cell adhering. When pore size in PCL scaffolds was increased from 245 to 433µm the compressive modulus and maximum allowable stress before failure decreased by approx. 50 to 75%, making it easier to deform. At the same time, small pores had greater load-carrying capacity. PCL scaffolds developed using B-TCP (Beta-tricalcium phosphate) with a 50 to 100% interlayer offset showed a higher bending modulus than those without. Other studies showed that PCL scaffolds that were developed in combination with hydroxyapatite (HAp) are a complex ceramic material and an offset, the scaffold had lower elastic moduli than PCL/HAp scaffolds without the balance (Yazdanpanah y col., 2022). HAp has high compressive strength and hardness. And is combined with other materials to enhance that material's properties (Malidarreh y col., 2022). Also, biomaterials properties help scaffolds serve as the base of new tissue. In the case of HAp, his bioactivity supports regeneration, as shown in bone and tooth enamel repair.

3.4 Architecture (structure)

To give strength and structure to the microstructure of a scaffold, matrices are used. The extracellular matrix (ECM) in mammals is made up of a wide and complex union of proteins and other molecules, it also has active ingredients for the union of specific cells. Amid the process of forming three-dimensional tissues, cells establish intercellular-like connections with nearby cells and bind specifically to the ECM. These cell-cell and cell-matrix interactions shape and regulate tissue function, allowing for variations in the physiological state of the tissue. In cell-matrix interactions, the binding of cell surface receptors to specific do-

mains on ECM molecules occurs, which releases a stream of intracellular signaling events, producing changes in cell behavior and/or organization of cells. tissues. The ECM is essential for the selective exchange of material between cells and blood, in addition to the delivery of nutrients and metabolic products (Rondón 2020b).

It has recently been discovered that a scaffold can be structured using 3D printing. Gómez y col., in their research on the design of parametric scaffolds with variable and interconnected porosity for bone tissue engineering, and knowing that the scaffolds must have the correct pore space to achieve gas and nutrient exchange, studied the feasibility of designing scaffolds with variable (irregular) and interconnected (open porosity) porosity, trying to emulate the conditions of trabecular bone tissue supported by software (Rhinoceros 3D Grasshopper). The tissues were designed with microstructural specifications to serve as a substitute for natural bone tissue. This meant that the algorithm allowed the measurement of previously defined structures using tomography, microtomography, or magnetic resonance, which yielded the measurements of the three-dimensional volumes of bone tissue, which were filled with a pattern of variable porosity. This advance made it possible to use this algorithm with the indicated biomaterials and create scaffolds with the correct porosity and structure (Gómez y col., 2022). This new technique used developed in 3D printing can be extremely useful in combination with polymers. When using polymers such as "Poly(L-lactide)" polylactic acid (PLA), since PLA has excellent biodegradable properties and is non-toxic to the body, printing a design with a porosity equivalent to the proliferation of cells in the host tissue will increase tissue regeneration. PLA is an aliphatic thermoplastic polymer, whose specific properties make it hydrophobic, and biocompatible, with thermal processability, poor toughness, slow degradation rate, and lack of reactive side chain groups. Furthermore, by increasing the temperature of PLA, the crystalline structures of PLA will provide greater mechanical resistance and its degradation half-life will depend on its stereochemistry and molecular weight (Taib y col., 2022).

The ECM is also called intercellular substance and it is constituted mainly of fibrillar proteins, capable of producing fibrous structures that involve various collagen, reticular and elastic fibers through various types of synthesis. An example of a biomaterial used as a matrix is illustrated in the article Biomaterial scaffolds for clinical procedures in endodontic regeneration, where the authors placed a collagen sponge "CollaCote" over the blood clot as a matrix, and a bioceramic called "iRoot BP". Plus" was placed against the matrix to give structure and better biocompatibility for the blood clot scaffold. Since collagen is a family of extracellular matrix proteins, it has great biodegradable and biocompatible properties. Once the blood reached the channel space, the cross-linked fibrin network was formed, which served as a scaffold for stem cell housing (Liu y col., 2021). "iRoot BP Plus" is a premixed bioceramic, composed of tricalcium silicate, zirconium oxide, tantalum pentoxide, dicalcium silicate, calcium sulfate, monobasic calcium phosphate, and fillers used for root repair (Mahgoub y col., 2022).

3.5 Bone Tissue engineering

Porous three-dimensional structures are essentially the surrogate materials for the extracellular matrix in this field. They act as templates for the generation of tissue, and depending on the need, they serve as support for cell culture, growth factors, signaling molecules, or biophysical stimuli (bioreactor). This combination of cells, signals (bioactive molecules), and biomaterials is often referred to as the tissue engineering triad (Ospina y col., 2023). These scaffolds are biodegradable and are cultivated in vitro so that once they are implanted in the region where the pathology exists, they induce regeneration and direct the growth of new tissue.

An example of this type of application can be seen in the study on the design of a composite osteoinductive filament for osteoblast culture, which provided the basis for a new type of cell-matrix capable of allowing the growth, maturation, and proliferation of system cells. skeletal to regenerate acute and chronic bone defects. Providing more alternatives in tissue engineering. Considering the challenges involved in designing this scaffold, such as cell adhesion, proliferation, toxicity, adverse reactions, biodegradability, suitable mechanical properties, porosity, and size, it is imperative to choose the right materials to meet the challenges. Such materials were: biopolymers, PLA, Beta Tricalcium Phosphate, and biominerals (Ca^{+}, PO^{4-}, CO^{3-}). The authors, by continuing with the chemical bonding processes and the developed methodology, managed to manufacture a Beta-TCP scaffold of PLA and beta-tricalcium phosphate that can be printed on 3D machinery. After carrying out the mechanical and analysis tests on the biomaterial, it was confirmed that the material allows the proliferation of osteoblasts, and is biocompatible and non-toxic (Mendoza 2022).

Another scaffold with bold results is the Gelfoam sponge with autograft to treat nonunion. The Gel foam sponge is a collagen sponge. Nonunion occurs when the bone does not heal within the expected period. This can become problematic when trying to predict a precise time frame for repair. The problem remains a major concern, as it can be a complication of any fracture that is difficult to predict. Bone grafting from an external source of tissue is ideal because it has all the physiological and structural properties of autologous bone, as it is biocompatible, resorbable, osteoconductive, and osteoinductive, as well as safe and cost-effective. There are biomaterials with these same properties that accurately simulate the functions of the extracellular matrix, including cell proliferation, differentiation, and signaling, as well as being compatible with the transport of osteogenic growth factors. Within these biomaterials are gelatin sponges that have a highly porous

structure, which is effective for cell infiltration, giving way to oxygen, and growth factors, and the collagen it contains works as a natural scaffold. for osteoblast migration. Due to their good biocompatibility, low cost, and negative antigenicity, gelatin sponges are good transporter scaffolds for growth factors and osteogenic cells. Gelatin material has thermo-sensitivity as the material can be molded and change its state by changing the temperature at which it reacts making it a good material for shaping scaffolds (Kakarla y col., 2022; Alipal y col., 2021). "Gel-foam" is a sterile absorbable sponge and a hemostatic agent composed of gelatin of porcine origin, biodegradable, cheap, and easy to produce, all of the above, make "Gelfoam" an excellent candidate as a scaffold for bone grafts. Its use as a graft substitute has been ruled out, but its combination with bone marrow stem cells has been shown to promote better bone regeneration in large defects (Mazón y col., 2022).

3.6 Soft tissue regeneration:

The selection of a biomaterial for adequate replacement and regeneration of soft tissues depends on the ability of the material to emulate the properties of the extracellular matrix (ECM), generate cell viability and propagation, have degradation kinetics that can simply be controlled, or to preserve stability against physical, chemical and mechanical degradation that allows it to remain in the body until its extraction, in addition to having high biocompatibility when implanted in vivo.

The ECM of the connective tissues is constituted by a wide and complex union of proteins, mainly collagen and other soluble macromolecules such as elastin and proteoglycans, it also has active ingredients for the union of specific cells. The fundamental characteristic of the ECM is to serve as structural support during tissue function and to provide particular physiological and biomechanical properties. In soft biological tissues rich in collagen there is a correlation between their internal microstructure and their macroscopic mechanical properties. Today several biomaterials have these characteristics, and new and more effective biomaterials are being developed (Rondón 2021).

In a study called Advanced Nanofiber-Based Scaffolds for Achilles Tendon Regenerative Engineering. Using advanced nanofiber-based scaffolds, Zhu y col., created a way to enhance the repair, enhancement, and regeneration of Achilles tendon (AT) injuries. With this nanofiber, the aim is to imitate the mechanical and physiological properties of AT. The scaffold should provide biomechanical support, a bionic matrix for cell proliferation, differentiation, and migration, and promote AT integration and growth. Scaffolds AT-based nanofiber materials are materials used for tissue reconstruction such as silk fibroin protein, sodium alginate, and gelatin, which are degradable synthetic polymers like silk protein. The authors showed that the materials studied decreased peri tendinous adhesions and the effects associated with inflammation, vascular density, and fibrosis. The use of natural polymers is an advance because it is similar to natural tendons, which is a benefit for cell adhesion, proliferation, and differentiation. Natural materials have less mechanical resistance (Sahoo y col., 2021).

Vepari y col., define silk as a family of fibrous structural proteins with high mechanical properties, biodegradability, and biocompatibility, in addition to offering a wide variety of properties to the field of tissue engineering (Vepari y col., 2007, Sun y col., 2021). Likewise, silk fibroin polymers are easily inexpensive and widely available, have a relatively slow controlled degradation rate, and possess excellent mechanical properties for AT applications. On the other hand, insoluble collagen fibers are more suitable for the preparation of scaffolds than soluble collagen, since their mechanical properties are more similar to those of natural tendons. In addition, natural polymers mixed with synthetic polymers increase their mechanical resistance and promote tissue regeneration (Zhu y col., 2022a).

The variety of biomaterials that are used as scaffolds for tendon tissues has advantages and disadvantages. The advantages of synthetic polymer scaffolds are that they can be easily modified to meet requirements and their degradation is slower. At the same time, adverse effects can be degradation of the products in vivo such as inflammatory reactions and poor integration with host tissues. Although other components such as PGA (poly(glycolic acid), PLA, and PLGA Poly(lactic-co-glycolic acid) are biocompatible and cause minimal or no body reactions, since their degradation by hydrolysis (glycolate lactate) is present in the metabolic pathway of the human body (Su y col., 2021). Occasionally this can cause inflammation, as acid breakdown products are difficult to remove, yet it is the copolymer used in most FDA (United States Food and Drug Administration) therapeutic devices.

3. 8 Antimicrobial fillers:

These scaffolds contain fillers such as antibiotics, antiseptics, powders, peptides, carbon nanomaterials, metals, ceramics and combinations between them that prevent and/or treat infections. An example of this is polyhydroxyalkanoate/chitosan scaffold and 2D molybdenum disulfide (MoS_2) doped scaffold, this scaffold is used for skin infections because it treats recovery and is antibacterial because of methicillin-resistant *Staphylococcus aureus*. MoS_2 has properties such as ease of synthesis, high catalytic properties, exceptional on/off ratio, satisfactory biocompatibility, and enormous direct band gap of 1.8 eV for the monolayer (Kumar y col., 2022; Rondón y col., 2021). This type of material is biocompatible. Others that have been suggested are PCL nanofiber scaffolds containing Ag nanoparticles, formed with electrospinning. Biocompatible Boron Nitride doped poly-hydroxyalkanoate/chitosan (PHA/Ch-hBN) nanocomposite scaffolds have been successfully designed and manufactured with superior antibacterial activity by means of the solvent casting technique.

Boron nitride has great mechanical, electrical, thermal properties, and adequate cell proliferation, mineralism, and cell viability. But when used for scaffolds it showed less toxicity and a slower degradation rate (Kakarla y col., 2022). These makes Boron nitride an excellent material for TI. Scaffolds of Cs-Blended PLA nanofibers created with electrospinning showed great resistance to *E. coli* and no traces of cytotoxins. Among others (Serrano-Aroca y col., 2022)

3.9 Anti-bacterial scaffolds for bone regeneration:

This type of scaffold aims to impact large bone defects, using 3D scaffolds. Scaffolds used in bone regeneration include for example arabinoxylan-co-acrylic acid/Hap/TiO_2 nanocomposite, which is a scaffold that has demonstrated high porosity, biocompatibility, substantial mechanical strength, and cell growth in in vitro studies. Its porosity supports cell infiltration, adhesion, and extracellular matrix secretion, since its pore size is 110-125 nm. The mechanical resistance is between 3.5 MPa and 6.7 MPa, depending on the amount of TiO_2 and HAp in the sample, with 6.5 MPa being the optimum amount of resistance/porosity. The absorbance of the distilled or swelling water, once determined by the concentration of ceramic material, indicates that the porosity of the scaffold manages to balance the osmotic pressure. Non-toxic and interconnected properties provide good cell sustainability and increased cell count. The uniformly interconnected porosity allows the adhesion and proliferation of osteoblast cells (Khan y col., 2021).

Another example of these scaffolds is the carrageenan/acrylic/graphene oxide/hydroxyapatite hybrid nanocomposite with interconnected porosity. In their study Khan y col., I present that graphene oxide regulated pore size and uniformity, determined hydrophilicity, and enabled cell adhesion, cell proliferation, and osteogenesis migration of osteoblasts and osteoclasts. Additionally, the swelling and water retention offered by graphene oxide has hydrogen bonding that enhanced cells for bone regeneration. Which, in turn improves nutrient transfer and cell migration, differentiation and proliferation for tissue engineering. This scaffold is biodegradable and biocompatible, promoted by the amount of graphene oxide (Khan y col., 2021) and was composed by the lyophilization technique (Serrano-Aroca y col., 2022).

Following the same order of ideas, we have that the antibacterial scaffolds with antibiotics are scaffolds with localized controlled release of drugs. Because some antimicrobial materials can be toxic, antibiotic scaffolds aim to reduce that risk and generate microbial resistance. This implies that the use of non-toxic biomaterials for the scaffold, and then coating with antibiotics can achieve the same antimicrobial results for the scaffold. In these scaffolds, bioglasses are present and function in the repair of large tissues such as teeth and bones. Bioglasses have properties that allow growth factor secretion into cells and soft tissue healing. The bioactive ions released by Bioglass allow these biological reactions (Ma y col., 2022).

On the other hand, one of the most widely used antibiotics is Vancomy-cin (VAN). Because of this, VAN-loaded mesoporous bioglass/PLGA composite scaffolds are presented as an example. This scaffold maintains its antimicrobial drug release for 8 weeks by inhibiting *S. aureus* and promoting biofilm formation, making it of great interest for bone tissue engineering, by promoting osteoinduction. Polymer scaffolds like PCL also use gentamicin and cyclin hydrochloride as antibiotics, but need more research on their toxicity and animal testing. In another study with a Bioactive Nano-Hap/polyurethane scaffold results of high resistance against *S. aureus* and *E. coli* were seen with a drug release time of 42 days. Polyurethane is a copolymer with a carbamate group, which has biocompatibility, hemocompatibility, hydrolytic resistance, and oxidative resistance. Scaffolds using nanocomposite bioceramics with three antibiotics: rifampicin, levofloxacin and vancomycin (Fathi-Karkan y col., 2022; Nakhaei y col., 2023). This showed good bioactivity in preosteoblasts and was able to inhibit bacterial growth and destroy biofilms of Gram-positive and Gram-negative bacteria (Serrano-Aroca y col., 2022).

3.10 Scaffolds with antibacterial polymer peptides:

Peptides are the basis of these scaffolds and are defined as a small chain of amino acids that has a specific order and is linked by peptide bonds, which when dealing with long chains, are called polypeptides (Rondón 2020c). The scaffolds with antibacterial polymeric peptides in this application stand out. After all, their mechanical properties are similar to the tissue to be regenerated, because they are porous, with high permeability to facilitate the transfer of nutrients to cells, and have an ideal surface structure to favor cell adhesion and present antibacterial characteristics. The biomaterials used in these scaffolds are both natural (gelatin, collagen) and synthetic polymers (polycaprolactone (PCL), poly(lactic-coglycolic) acid (PLGA), among others, which promote cell adhesion, migration, proliferation, and differentiation (Echeverría 2020).

An example of these types of scaffolds is the vanillin-bioglass crosslinked compound (Hu y col., 2021) which showed good biocompatibility results, strong antibacterial activity, and promotion of osteoblast differentiation. Being a scaffold designed for tissue engineering, it showed compatible mouse osteoblast attachment and proliferation in vitro to the point where cells spread throughout the scaffold and cell junction. When incubated in a biometric (Simulated Body Fluid) SFB solution, it showed the presence of minerals in crystalline morphology, in the form of a sphere, and a Ca/P ratio of 1.67 which is close to natural HAp. Its pore size ranged between 115.38 ± 58.52 and its porosity between 94.64 ± 0.71, which gives it excellent bioactivity. The scaffold showed strong osteoconductivity, which is reflected in good osteoblastic differentiation. Scaffolds based

on nano-HA, starch, gelatin, chitosan (CS), alginate (Kakarla y col., 2022), and S-nitroso-N-acetyl-penicillamine and manufactured by lyophilization to obtain a porous environment showed good antibacterial activity against *S. aureus* and *E.coli*. PCL/Hap scaffolds 3D printed with an antimicrobial polypeptide provided good biocompatibility, osteoconductivity, and antibacterial activity. Another mineralized collagen scaffold containing PLGA microspheres loaded with two synthetic antibacterial peptides (Vanzolini y col., 2022) had results showing the promotion of osteogenetic and antibacterial properties. On the other hand, a 3D-printed hybrid airgel-based scaffold using antibacterial peptide-modified silk fibroin with silicon showed bactericidal results for Gram pos. and Gram Neg bacteria, biocompatible with mouse embryonic preosteoblasts. Another 3D-printed scaffold composed of hydroxypropyl trimethylammonium chloride and chitosan (Wang y col., 2022) grafted with PLGA/Hap had results of antibacterial activity for *S. aureus* and bone regeneration in infected bone defects. A new flax/silk protein-based nanofibrous scaffold showed results of long-term antibacterial activity against *E.coli* and *S. aureus*, and flax contained bioactive peptides that promoted antioxidant, antibacterial, and anti-inflammatory capacity (Serrano-Aroca y col., 2022).

3.11 Scaffolds with carbon nanomaterials:

These materials have unique properties such as antibacterial activity and the ability to express many genes. Carbon nanomaterials in small amounts can improve the physical and biological properties of polymers, including mechanical performance, wettability, thermal and electrical behavior, water diffusion, growth, antimicrobial activity, and degradation.

As an example of scaffolds with carbon nanomaterials, the 3D printed scaffold with electroactive properties composed of PCL compounds percolated with thermally reduced graphite oxide is presented, which resulted in the complete eradication of bacterial growth (*S. aureus*) on the surface. of the scaffold and increased cell viability (Serrano-arocca y col., 2022)

3.13 Scaffolds with metals/ceramics/glass:

A 3D scaffolds composed of TiO_2 nano tubes or titanium oxide nanotubes. These function as good as metal oxide nano particles, which will be imbedded in composites (Ma y col., 2022) with silver ions only supported antimicrobial properties against *S. aureus* for 2 weeks. TiO_2 also helps evenly distribute the porosity in a nanocomposite scaffold (Khan y col., 2021). Another developed scaffold was composed of triacrylate-co-trimethylopropanetris (3-mercaptopropionate) (beta) and HAp, had results of osteo inductive and degradable properties that are capable of stimulating the proliferation of the bone progenitor cells, inhibited the proliferation of *S. aureus* and *E.coli* (Serrano-Aroca y col., 2022; Barragán 2022).

Table 1 presents a review of the biomaterials used in tissue engineering for the fabrication of evaluated scaffolds, as well as their types, composition, properties, mechanism of action, and biomedical use.

Name	Type	Composition	Properties	Action mechanism	Biomedical use	Bibliography
Collagen	Bio polymer	Blends with sintetic polymers.	Biocompatible; Biodegradable; Blend with synthetic polymers.	Collagen hydrolysate induced unidirectional changes in cyclic nucleotides.	Dental regeneration.	(Collins y col., 2021).
Blood clot	Bio polymer	Platelets and meshwork of propein strands “fibrin”.	Biocompatible.	Platelets and proteins bind to stop bleeding.	Dental regeneration.	(Liu y col., 2022; Mahlangu y col., 2023).
Chitosan	Bio polymer	β-(1-4)-2-acetamida-d-glucosa y β-(1-4)-2-amino-d-glucosa6	Biodegradable; Non-toxic; Antimicrobial.	Binding to the negatively charged bacterial cell wall causing disruption of the cell, thus altering the membrane permeability, followed by attachment to DNA causing inhibition of DNA replication and subsequently cell death.	Tissue regeneration.	(Cavazos y col, 2020; Yilmaz y col., 2020).
Poly-hydroxyalkanoate	Bio polymer	poly(3-hydroxybutyrate-co-3-hydroxyvalerate	Biodegradable; Thermoplastic; Biocompatibility; Non-toxic.	Poly esters of hydroxyalkane synthesized by bacteria as carbon and energy storage compounds.	Tissue regeneration.	(Kumar y col., 2022).
Starch	Bio polymer	$(C_6H_{10}O_5)_n$ Polysaccharide made up of 1,4 linkages between glucose monomers.	Biocompatible; Biodegradable; Water absorbance.	The starch granules retain water.	Tissue regeneration.	(Bikila y col., 2021).
Cross-linked	Bio polymer	Insoluble protein polymer that stabilizes the platelet	Biocompatible.	Thrombing activates the FXIII. This takes a CA^{2+} dependent	Tissue regeneration.	(Liu y col.,

fibrin	/protein polymer	plug.		transglutaminase and catalyzes forming covalent bonds between lysine and glutamine.		2021: Vilar y col., 2022).
Polylactic acid (PLA)	Polymer	Made of L-LA blocks with a semicrystalline and high structural regularity.	Biodegradable; Non-toxic; Hydrophobic.	When it comes to PLA degradation in the body , hydrolysis comes to action breaking the ester bond back bone. Yet tissue temperature, PLA composition, and chirality will affect PLA degradation rate in the body making it possible to tailor the regeneration of tissue capability.	Multiple applications in tissue engineering.	(Taib y col., 2022, Mendoza 2022).
Polycaprolactone (PCL)	Polymer	Polycaprolactone; Is a biodegradable polyester.	Biocompatible; Biodegradable.	The hydrolytic degradation of PCL takes place through the cleavage of the ester bonds in the structure through a complex process that depends on the molecular weight of the polymer, its crystallinity and the shape of the structure to be degraded, among other factors.	Control of cell growth and proliferation.	(Kumar y col., 2022; Yazdan-panah y col., 2022; Abdelfatah y col., 202).
Poly(lactic-co-glycolic acid) (PLGA)	Co-polymer	50% lactic acid and 50% glycolic acid.	Biodegradability; Biocompatibility; Low mechanical strength.	The PLGA polymer biodegrades into lactic and glycolic acids. Lactic acid enters the tricarboxylic acid cycle and is metabolized and subsequently eliminated from the body as carbon dioxide and water.	Tissue regeneration; Prolonged drug release.	(Wei y col 2022; Chen y col., 2022; Echeverría 2020; Su y col., 2021).
Polyurethane	Polymer	$C_3H_8N_2O$	Flexible; Biocompatible; Hemo-compatible; Hydrolytic; Oxidative resistance.	Fibrin(ogen) binds and surrounds cancer cells, forming a structure that protects tumors from immune cells, in a process that may be enhanced by attracted platelets.	Control of cell growth and proliferation.	(Fathi-Karkan y col., 2022; Nakhaei y col., 2023).
Sodium Alginate	Polymer	$NaC_6H_7O_6$ Linear polysaccharide derived of alginic acid comprised of 1,4-B-d-mannuronic (M) and a-I-guluronic (G) acids.	Increase viscosity of liquid solution.	Allows water solubility, in liquid gel form the monovalent ions can be exchanged for divalent ions, changings almost instantly from a low viscosity to gel structure.	Tissue regeneration.	(Kakarla y col., 2022; Sahoo y col., 2021).
Syntetic peptides	Polymers	Peptides developed by side-directe mutation (adding or deleting aa), novo design, template design, self assembly based desing.	Biocompatible; Antimicrobial.	Interact with eukaryotic cells by neutralizing, reducing activity or stabilizing the phospholipid bilayer.	Anti-microbial activity.	(Ding y col., 2020; Vanzolini y col., 2022).
Silk fibroin	Polymer	Family of extracellular proteins.	Biocompatible; Biodegradable.	Low inflammatory response by less adhesion to immuno-competent cells. No upregulation of inflammatory pathways and no migration of lymphocytes.	Tissue regeneration.	Sun y col., 2021; Zhu y col., 2022a).
Titanium dioxide (TiO_2)	Metal	Metal oxide.	Antimicrobial.	The generation of ROS (reactive oxygen species) destroys bacterias structure and function.	Anti-microbial activity.	(Ma y col., 2022; Serrano-arocca y col., 2022).
Vanillin	Organic composite	Membrane active compound.	Antimicrobial; Biocompatible.	The dissipation of ion gradients and the inhibition of respiration, the extent to which	Anti-microbial activity.	(Serrano-arocca y col.,

				is species-specific. These effects initially do not halt the production of ATP.		2022; Hu y col., 2021).
Boron nitride	Metal or colorless crystal	BN, binary compound composed of the same number of nitrogen atoms (N) and boron atoms (B).	Biocompatible.	Boron nitride increases the swelling properties of the scaffold. Decreases cell viability.	Anti-microbial activity.	(Kakarla y col., 2022; Zhu y col., 2022b).
Hydroxiapatite (HAp)	Bioceramic	$Ca_{10}(PO_4)_6(OH)_2$	Nontoxic; Bioactivity; Osteoconductive.	Improves mechanical properties to other materials.	Filler for bone repair, tooth repair.	(Ma y col., 2022; Malida-rreh y col., 2022; Khan y col., 2021).
Bioglass	Bioceramic	Silicate-based glasses; Phosphate-based glasses; Borated-based glasses.	Biocompatible; Biodegradable.	Stimulates the secration growth factors of cells. Induces bioactivity with ions released from bio glasses	Anti-microbial activity.	(Ma y col., 2022; Serrano-arocca y col., 2022).
Molybdenum disulfide	Metal	MoS_2 2D layered structure with each layer of thickness of about 0.65 nm, which are heaped upon each other to form bulk. Weak van der Waals forces clasp these layers together.	Ease of synthesis, high catalytic properties, exceptional on/off ratio, satisfactory biocompatibility, and enormous direct band gap of 1.8 eV for the monolayer, anti bacterial , biodegradable	The severity of the mechanical interaction between the cellular membrane and MoS_2 nanostructures was assessed, which is accounted for the phospholipids extraction, which in turn destroys the integrity of the membrane, directing to cytoplasm leakage and finally cell death.	Anti-microbial activity.	(Kumar y col., 2022; Serrano-arocca y col., 2022)
N-2-hydroxypropyl trimethyl ammonium chloride chitosan	Polymer	Chitosan, B-glycerophosphate disodium, a-glycerophosphate, acetic acid, lactic acid.	Antibacterial Biocompatible	Shows skin healing, by the presence of N-2HACC Hydrogel freezes dried powder reach more than 80% in cells. The large portion of N-2HACC hydrogel caused a promotion of cell proliferation, and enhance cell migration.	Chitosan gauze.	(Wang y col., 2022).
Gelatin	Polymer	$C_{102}H_{151}N_{31}O_{39}$ Formed from collagen hydrolysis; It consist of glycine proline and 4-hydroxy proline residues.	Biocompatibility, Low cost, Thermosensitive, cell viability	Has strong interfacial interaction, and when paired with HAp, the gelatin influences the nucleation and formation of HAp nanocrystals.	Formulates hydrogels, prolonged drug release.	(Kakarla y col., 2022, Mazón y col., 2022 Alipal y col., 2021).
Arabinoxylan-co-acrylic acid/Hap/TiO_2 nanocomposite scaffold	Nanocomposite	2.0g arabinolaxan, 0.05g potassium persulfate, 0.50 ml AAc monomer, 0.2-0.8 TiO_2, 2g HAp powder	Biocompatible, Good mechanical strength, cell proliferation, adhesion, non toxic	The amount of ceramic material generates crosslink points in the polymer network. and the ceramics hydrophobicity affects the swelling behavior of the bioactivity.		(Khan y col., 2020; Serrano-arocca y col., 2022; EMBL-EBI 2019).
Carrageenan/acrylic/graphene/hydroxyapatite hybrid nano composite	Nanocomposite	Carrageenan (C_{1013}-$_{100}$G), acrylic acid (AAc) (C_3H_4O), N,N′-methylene-bis-acrylamide (NN-MBA) ($C_7H_{10}N_2O_2$), potassium persulfate ($K_2S_2O_8$), nano-hydroxyapatite (n-HAp)	Cell proliferation, cell migration, water retention, biodegradable , biocompatible	Water retention permitted the formation of hydrogen bonds enabling cell regeneration.	Tissue regeneration.	(Khan y col., 2021; Serrano-arocca y col., 2022), Abdelfata

		(<100 nm particle size, ≥95%), graphene oxide (GO) (763713-1G), Phosphate-Buffered Saline (PBS) solution and hydrochloric acid (HCl)		h y col., 2021).
Vanillin-bioglass crosslinked 3D CS	Ceramic composition		Tissue regeneration Anti-microbial activity	(Kakarla y col., 2022; Hu y col., 2021).

5 Conclusions

The increase in biomaterials and the combination of biomaterial scaffolds have become much more precise and efficient, generating new and more efficient clinical uses, with high bioactivity, biocompatibility, biodegradability and without losing the mechanical properties that strengthen the scaffold structure. This generation of tissue engineering scaffold biomaterials has the ability to provide 3D printed porous variability, antimicrobial properties to reduce infection, and improved regeneration due to its biodegradability.

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Recibido: *16 de enero de 2023*

Aceptado: *25 de mayo de 2023*

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