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by Nishika Sharma

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NANOPARTICLE APPLICATIONS IN SCAFFOLD-BASED TISSUE ENGINEERING

Nishika Sharma

Delhi Technological University

Email - -nishikasharma1011@gmail.com

ABSTRACT

Tissue engineering is an emerging multi-disciplinary area that seeks to reconstruct or regenerate damaged tissues and organs by employing cells, biomaterials and bioactive molecules. Most of the traditional scaffold materials, however, are not capable of mimicking the functional and structural properties of Native Tissues., limiting their clinical applications. In this context, nanotechnology has attracted significant attention for its ability to overcome these limitations and produce new and improved biomaterials. This review provides an extensive analysis of the use, of important NPs in tissue engineering, include ceramic, Metallic and Metal oxides, carbon-based & polymer-derived nanoparticles. These materials have unique nanoscale size and large-surface area, it can induce various cellular responses such as adhesion, proliferation, and differentiation, and facilitate the sustained delivery of therapeutic agents. The hydroxyapatite and calcium phosphates used in the ceramic nanoparticles help to impart bone-like properties and mechanical strength. Gold, silver, and Fe-based nanoparticles possess a multifunctional therapeutic action and antimicrobial property. Carbon-based nanomaterials enhance the mechanical properties of the structures, as well as their interactions with cells, while polymeric nanoparticles are used to adjust the degradation rates and to efficiently deliver bioactive compounds. However, their potential benefits have not been fully realized due to their toxicity, long-term safety, and regulatory issues. There is a need for easier and safer nanoparticle systems development along with the incorporation of new manufacturing methods in future studies. Taken together, strategies based on nanoparticles could be a encouraging direction for the (TE) tissue engineering and regenerative medicine fields.

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LIST OF SYMBOLS, ABBREVIATIONS

NPs: Nanoparticles

TE: Tissue Engineering

IONPs: Iron Oxide Nanoparticles

NDs: Nanodiamonds

CU: Copper

ECM: Extracellular Matrix

Au: Gold

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CHAPTER 1

INTRODUCTION

Tissue engineering (TE) involves the development of new tissues and organs. using a combination of cells and. biomaterial scaffold. These scaffolds function as three-dimensional frameworks in three dimensions that facilitate cell adhesion, growth, and differentiation. specific cell types. Growth factors are incorporated within these structures to regulate cellular activities and guide them toward desired outcomes, with the aim of producing functional tissues or organs capable of regeneration and suitable for implantation.
Although TE is a powerful tool, there are a number of challenges, and it can be difficult to apply the concepts clinically. A significant challenge is the lack of engineered materials with the same properties as native tissues. The development of nanotechnology, especially using engineered nanoparticles, may be a possible answer to the challenges. Nanoparticles are particles with the size of nanoscale which have the properties of nanoscale.
Chemical properties which improve their suitability for use in different applications. Nanoparticles have been extensively used in the biomedical field, such as controlled drug delivery. Targeted imaging, DNA analysis, photothermal therapy, gene transfer, and biosensing. Later, they were introduced into tissue engineering applications. In addition, nanoparticles are being examined for therapeutic applications in various diseases including cancer, diabetes, allergies, infections, and inflammatory diseases.

Recently, nanoparticles have been of high interest in the field of TE due to their improvement in increasing both mechanical strength and biological performance. Various types of nanoparticles have their own properties which makes them highly appropriate for TE applications. For example, gold nanoparticles (GNPs) have a very good surface functionality and electrical conductivity, and silver and other metallic nanoparticles, such as metal oxides, are known to have a high antimicrobial activity. The two materials of interest are quantum dots for their fluorescence properties, and carbon nanotubes (CNTs) have outstanding electromechanical properties. In addition, magnetic nanoparticles have been widely used across several fields, including cell mechanotransduction studies, gene delivery, controlling organization, and creation of complex three-dimensional tissue structures.

The benefits of nanoparticles as a tool for tissue engineering are primarily attributed to their nanoscopic size and to their large surface-to-volume ratio, like peptides and small proteins.. They are able to cross biological membranes with ease and have properties that promote their internalization into cells. Furthermore, nanoparticles are very versatile in their design and can have a wide range of surface characteristics and sizes to suit the application. Notably, their nanoscale properties closely mimic the size of components within the naturally occurring extracellular matrix (ECM) which makes them ideal to mimic natural tissue environments.

Nanomaterials can be used to enhance cell adhesion, provide appropriate mechanical properties, increase bioactivity, and allow controlled release of bioactive components to improve tissue interfaces.

This means that they have a greater potential for tissue integration and regenerate compared to conventional polymeric biomaterials. Engineered biocompatible nanomaterials allow for further enhancement of orthopedic tissue repair by strengthening the bone–ligament interface, improving cell adhesion, and demonstrating antimicrobial properties. Furthermore, high throughput genetic screening and 3-D bioprinting technologies allow the optimization of biomaterial formulas for sensing and diagnostic purposes.

Nanoparticles can also help in the reconstruction of tissues, allowing the controlled and stable delivery of therapeutic agents, enhancing interactions with biological tissues, and shielding the agent from degradation. They can be used to mimic the extracellular matrix, to support the growth of cells, and to be customized for targeted drug delivery; they can be employed as versatile and biocompatible carriers in tissue engineering and regenerative medicine.

The aim of this review is to provide a general overview of the different applications of different types of nanoparticles in tissue engineering. It emphasizes the roles of nanoparticles of magnetic, metallic, ceramic, polymeric, carbon-based and metal oxide materials, and their relevance in this context, field. The biocompatibility and immunogenic response of these materials is generally good, which makes them especially useful. Moreover, the intrinsic properties of each type of nanoparticle are highly useful to solve the current problems in tissue engineering, particularly in tissue-based applications where material-based approaches are still the primary approaches. underutilized. The ideas presented in this review are meant to help material scientists and tissue engineers to identify and select the most appropriate nanoparticle systems for their applications.

CHAPTER 2

REVIEW OF LITERATURE

Tissue engineering is an interdisciplinary research area whose goal is to fix, replace or regenerate damaged tissues through the blending of cells, bioactive molecules, and biomaterials. The paper shows that the concept has great potential, but a major problem with conventional scaffolds is that they do not mimic the complexity of the native tissues, and so are not useful in clinical applications. That has led the researchers to look at ways to improve the design and biological activity of scaffolds, using nanotechnology. The very small size and large surface area of the (NPs) nanoparticles in combination with their surface chemistry, which can be tailored, make them more effective in interacting with cells and biological matrices in particular. They can enhance cell adhesion, proliferation, differentiation, and/or controlled release of therapeutic agents in tissue engineering. The paper presents a vision of the potential of nanoparticle scaffold technology in regenerative medicine, given its ability to give structural integrity and biological activity.

2.1 Nanoparticles in tissue engineering

The literature surveyed in the paper. It can be concluded that great interest has been paid to nanoparticles in the field of tissue engineering due to their ability to enhance the mechanical and biological properties of scaffolds. They are the nanoscale size, which is comparable to components of the extracellular matrix, and therefore suitable to emulate native tissue environments.. Their biomimetic characteristic is one of the principal reasons for their extensive research in bone, dental, neural, and skin tissue engineering. The paper also mentions that the versatility of nanoparticles allows them to be customized for various applications, including antimicrobial properties, electrical conductivity, magnetic properties, and drug delivery systems. They are very useful in complex scaffold systems where a scaffold material may not meet all the clinical needs. Consequently, much research has been undertaken on a composite or hybrid scaffold as opposed to a single component scaffold.

In the paper, the literature is presented according to the classes of nanoparticles: ceramic nanoparticles (hydroxyapatite, calcium phosphates, bioactive glass, zirconia, alumina), etc. The materials are particularly important in bone tissue engineering because of their ability to replicate the mineral bone, to increase the osteoconductivity and to increase the stiffness of the scaffold. The paper points out, however, that many ceramics are brittle, or too inert to use alone, and therefore are incorporated into composite scaffolds.

Table:2.1
MAJOR CLASSES OF NANOPARTICLES USED IN SCAFFOLDS

NP class	Typical examples & main roles

Ceramic/bio ceramic	**Nanohydroxyapatite, TCP, Calcium phosphate: Enhance osteoconductivity, Stiffness, and bone-like mineral phase.**
Metal/metal oxide	**Au, Ag, Cu, Zn, FeO^4, ZnO: add conductivity, antibacterial activity, imaging, magnetic guidance.**
Carbon-based	**Graphene/GO, CNTs, nanodiamonds, carbon dots: improve mechanics, conductivity, cell signalling, especially in bone, neural, cardiac scaffolds.**
Polymeric/organic nanoparticle	**PLGA, Lipid NPs, Protein NPs: Controlled release of growth factors, genes, drugs within scaffold.**

2.2 CERAMIC NANOPARTICLES

Bioceramics are many different man-made ceramic materials that are designed for use in Process of repair and replacement of damaged or diseased body tissues. They are used in numer[13]s ways. different forms in clinical use, for example in the form of bulk components (e.g., for reconstruction of the middle ear ossicles or in load-bearing joint prostheses), powders and granules (bone defect filling) and coatings for metallic implan[13]in the form of injectable .Porous scaffold structures and bone cements are examples of systems. Based on their biological response, bioceramics can be classified i[17] three categories: nearly inert, bioactive, or resorbable ceramics. The bioceramics could be divided into three groups, based on their: biological response: nearly inert (e.g., alumin[38]nd zirconia) bioactive (e.g., bioactive glass)There are two types of resorbable ceramics used: β- and α-tricalcium phosphate (TCP).

Because of their mechanical strength and stability, applications such as dental implants, acetabular cups in hip replacements and nearly inert ceramics (femoral heads) are widely used. They are, however, n[34] normally used for making scaffolds because they generally have bioinert properties, which results in the formation of the thin fibrous capsule at the implant interface. This does not stimulate a strong foreign body response but will not allow direct adhesion of the implant to surrounding tissue.One of the key criteria that are considered when selecting a bioceramic for its use in scaffolds should be its ability to create a stable tissue-bonding. In this respect, the bioactive and bioresorbable ceramics would be more suitable. The advantage of the bioresorbable ceramics, in particular, is that they slowly absorb into new tissue, and eventually fade away when the task of a temporary structural framework is finished.

In order to understand how bioceramics can be used in orthopedic applications, they can be divided into four categories and their properties will be explained.

Bioceramics are a heterogeneous group of materials, which can be [7]ssified by their composition, functional properties, and their clinical indications. Generally, they are classified into three categories based on their biological tissue interaction: bioresorbable, bioactive, & bioinert. The bioinert ceramics used are high strength and stability materials and low biological reaction, like alumina and zirconia. Bioactive ceramics, however, like hydroxyapatite, certain calcium phosphates and bioactive glasses, will be

able to form direct bonds with bone or soft tissues, and can stimulate tissue regeneration and enhance osteointegration. Bioinert ceramics used are materials with high mechanical strength and stability and low biological reaction such as alumina and zirconia. Bioactive ceramics, on the other hand, such as hydroxyapatite, some calcium phosphates, and bioactive glasses, can develop direct bonds with bone or soft tissues, and can promote

tissue regeneration and improve osteointegration.

Bioresorbable ceramics are ceramics that break down in a controlled way in the body such as Tricalcium Phosphate and certain glass ceramic, composition. The degradation process helps to replace the tissue with new growth over time, so that surgical removal is not required after healing.

Fig 1: Illustrates the different types of bioceramics

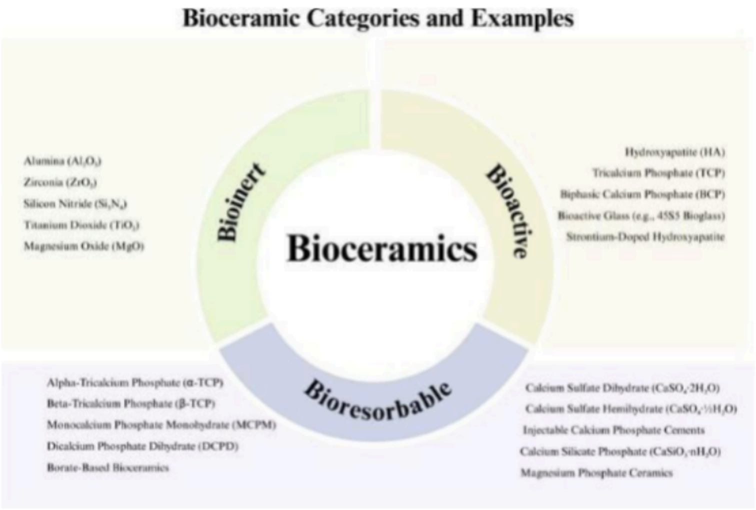


Table:2.2 Types of Bioceramics, and their properties

Bioceramic Materials	Characteristics	Benefits	Limitations	Products
Alumina	Alumina is a ceramic substance that is inert. high mechanical properties and good chemical stability. Among those characteristics are resistance and environmental friendliness.	Stability, non-cytotoxic; biocompatible and has very good wearing properties.	Poor mechanical properties and little rigidity.	ceramics made of inert alumina and nanoporous alumina.

	include higher raw Materials, low Price, wide Use, high mechanical Strength, pressure.& resistance,high-temperature resistance, and environmental friendliness.			
Zirconia	Like inkjet 3D printing, a liquid binder is used to bind Combine the powder together into a ball, then support layer is printed layer by layer, finally, the powder printing stand is melted directly. mechanical strength, high strength ,high toughness, high hardness, minimal good chemical corrosion and wear resistance, very low thermal conductivity, good insulation, and self- lubrication Bioactive glass.	Fracture The resistance and flexural strength properties.	Micro-cracks or inducing a phase Treatment by grinding or sand blasting the teeth (transformation n), chemical aging and wear.	Yttria-stabilized Polycrystalline zirconia (Y-TZP), zirconia vs silica-based ceramics.
Glass Ceramics.	Glass- ceramics are mainly composed. of ~70 vol % of interlocked rod-such as lithium disilicate crystals with high compressive strength. High mechanical properties,	It is strong enough and chemically stable, has excellent aesthetic and transparency and has low thermal conductivity and	The formation process is complicated and high cost.	Strontium doping (TiO2) containing glass-ceramics are called glass-ceramic. Material.

	adjustable thermal. expansion, chemical corrosion resistance, and wide application. Principal	adequate strength. Besides biocompatibility, corrosion resistance, resistance, and chemical durability. Very good		
Calcium phosphates.	Similar in the most common synthetic bone substitutes are composition to bone minerals.	biocompatibility, Bioactivity, bone conductivity and absorbability.	Very low Toughness: none, Strength: compression, Degradation: slow.	Beta-tricalcium. Bioinks based on phosphates. (β-TCP), 3D printed calcium phosphate cement. (CPC).

2.3 Metal/Metal oxide

Generally, the metal-based nanoparticles are divided into three types: Metallic NPs, metal oxide NPs, and magnetic NPs. Specifically, metallic NPs possess unique characteristics, such as high antimicrobial activity, catalytic characteristics, improvement in mechanical property and electrical conductivity and thus are very attractive for use in tissue engineering applications in cosmetic
and medical applications. Au nanoparticle is widely used due to its good Biocompatibility
and low cost of synthesis and applied to the diagnosis and therapy of cancer, biosensor and . Drug delivery system. Synthesis of . gold NPs of around 20 nm diameter has been reported by Zhang et al. to show
strong anti-angiogenic properties by blocking multiple growth factors that bind to heparin and preventing the growth of ovarian and pancreatic tumors.
Likewise, silver nanoparticles are widely used in the biosensing, food processing, dental industry.tissue engineering, etc., and Dr. Likely designed an innovative hybrid coating comprised of silver nanoparticles and assessed its antibacterial capabilities. The in vitro and in vivo results revealed that the PDT effect of the silver nanoparticles along with the physical effect, has proven to be effective in killing the bacteria without causing any side effect.
Moreover, the physicochemical properties of other metal-based nanoparticles have been thoroughly
studied for a range of applications such as drug delivery, vaccine delivery, modulation of immune system
and others. Metal oxide nanoparticles (NPs) have been used extensively in a types of applications
including contrast imaging, delivery of a drug, biosensing and catalysis. The versatility is achieved
because the structural properties, size, and surface chemistry can be easily changed to meet the desired
functional properties. In a case study, Hashimoto et al. demonstrated the bioactivity of composite materials
made of titanium dioxide (TiO_2) nanoparticles, which turned them as biologically active as natural bone,
and also increased mechanical properties.
Properties such as bending strength, Young's modulus. The advantages imparted by the TiO_2 nanoparticles
position them as a popular advanced biomaterial for used in bone tissue engineering in implant, related
applications. Magnetic nanomaterials have strong magnetic properties which are strongly dependent on
magnetic fields. They are extensively developed for targeted drug delivery, controlled drug release, bio
enhancement of tissue regeneration, and prevention of implant-associated infections.

Magnetic nanoparticles with superparamagnetic (SPM) properties are commonly magnetite (Fe_3O_4), spinel ferrites (AFe2O4) or maghemite (γ-Fe2O3).[35]These materials are magnetic, and possess the advantageous characteristics of nanoscale materials, such as their small size and huge surface area. and capacity to interact. This allows them to be controlled and targeted with external magnetic devices, absorb electromagnetic energy and produce heat under alternating magnetic fields. These properties render them ideal for targeted transportation of chemotherapeutic agents, such as doxorubicin and docetaxel. Research applied the heat produced by such magnetic nanoparticles to cancer treatment, and they were able to inhibit or kill tumor cells by co-encapsulating. γ-Fe_2O_3 and the anti-cancer drug doxorubicin hydrochloride in a Altered version of the same technique.

Gold NPs

Gold nanoparticles (AuNPs) have gained significant interest for their application in [11]various biomedical fields such as drug delivery, targeted therapy, biosensing, tissue engineering (TE) and in particular, bone tissue engineering (BTE). This is because their favourable properties— low toxicity, antibacterial activity, and excellent biocompatibility—are mostly attributed to the chemically stable and inert gold-core, which is the main component of their structure. But there are some concerns about their interactions on the cellular level.It has been demonstrated that various AuNP size, concentration, surface, and cell type characteristics affect the cytotoxicity. These effects can happen at any dose and are dose dependant. involve damaging the membranes, intracellular component leakage, and [5]production of ROS That can cause derangements of cellular redox balance.
In the field of bone (TE) Tissue Engineering, AuNPs was shown to induce osteogenesis of stem cells via several signaling pathways. The addition of AuNPs to a hybrid system of hydrogels has been an effective approach to promote bone regeneration in vitro and in vivo, which has provided promising results. Gold nanorods (AuNRs) has been less widely exploited, however, because of their potential toxicity resulting from the synthesis- related surfactants, and their tendency to aggregate.
However, such challenges can be overcome by surface modification techniques, like using Natural polymer for stabilization to enhance the drug delivery potential.

Even more importantly, Bone mesenchymal. stromal cells are important in tissue regeneration and growing evidence indicates the importance of microRNAs (miRs) as epigenetic regulators that control gene expression after transcription. AuNPs of ultra-small size have been evaluated as an effective microRNA delivery system, which provide protection and targeted delivery of microRNA molecules and facilitate and promote osteogenesis and support bone tissue regeneration.

Silver (Ag) NPs

Silver nanoparticles (AgNPs) hold promises for orthopedic and tissue engineering applications, there are also certain challenges, including ensuring antimicrobial activity without toxicity to ensure effective bone healing and implant function.

Silver in the form of metal and as ions in ionic compounds is well known to make biomaterials more antibacterial. It works by entering into bacterial cells, disrupting DNA replication processes, and causing death of the cells. Ag-based scaffolds have been found to have several advantages including high antimicrobial activity, good cytocompatibility, and promoting osteogenesis and cellular growth. Their clinical use is limited by a small therapeutic window, however, with high concentrations, cytotoxicity can occur.

For instance, Research reported that Ag and Sr were incorporated into hydroxyapatite/chitosan scaffolds, which not only had anti-bacterial activity but also had [7] osteoinductive properties. Due to their potent antimicrobial activity, AgNPs have been utilized in bone tissue engineering, antimicrobial dressings, as drug transport systems, as coatings for medical devices, and [4] other applications. The behavior of cells in the interaction with AgNPs has been examined in the case, of human mesenchymal stem cell . which has an osteoblast differentiation inducing ability. They are, however, highly concentration and time dependent and it is important to optimize so that they will have the greatest [25] biological activity while at the same time causing minimum cytotoxicity.
In recent years a number of studies have been conducted on the development of nanocomposite scaffolds containing AgNPs to improve their antibacterial properties without compromising cell viability and to facilitate applications in bone tissue engineering. Moreover, the studies conducted in research (2015) have shown that silver doped materials have potent antimicrobial properties, which helps to decrease implant-associated infections and enhance the results of bone regeneration.

Iron NPs

For tissue engineering, iron-based nanoparticles (NPs) have become promising scaffolds for fabrication because they can improve the mechanical properties and provide porous structures for infiltration of cells and tissue integration into the scaffolds. created a three-dimensional scaffold made of a polycaprolactone (PCL) matrix with reinforcement of Iron-doped hydroxyapatite (FeHAp[21]) nanocrystals that facilitated the attachment and proliferation. of (BMSCs), especially when subjected to a static
magnetic field.

While these benefits are present, issues with the use of metallic materials (i.e. iron) are associated with the release of metal ions, that could contaminate the local tissue and may necessitate the removal of the implant. However, iron has an important physiological function in tissue formation and regeneration, and can be applied in designing scaffolds. Furthermore, cell death induced by nanoparticles has been recognized as a key morphological parameter and strategies that modify the surface of nanoparticles to increase their biocompatibility are required in order to make nanoparticles more accessible for medical applications. Limitations like fast degradation and possible cytotoxic effects have led to the development of alloying approaches to overcome these. For example, iron and tungsten. alloys have been developed to maintain biodegradability while reducing the rate of deterioration. and little toxicity. Researchers created porous double-layered scaffolds made of Fe/FeW and discovered that reducing the rate of corrosion enhanced cell survival, indicating that these materials would be suitable for tissue engineering applications, because of their controlled degradation behavior and enhanced biocompatibility.

Iron Oxide Nanoparticles (IONPs) in Tissue Engineering

The use of inorganic nanoparticles, especially iron oxide nanoparticles (IONPs), to the development of porous scaffolds in (TE) has been extensively investigated. The nanoparticles can be used to prepare stable emulsions that can resist harsh polymerization conditions and precisely control the scaffold porosity and pore architecture. Apart from their stabilizing properties, IONPs possess many beneficial biological properties such as antibacterial and pro-angiogenic properties.

A promising method for the synthesis of the scaffolds is that the oil phase monomers are encapsulated with surface modified IONPs (e.g. oleic acid-functionalized IONPs (OA- Known as Pickering emulsion polymerization, IONPs are formed by a phase interface. Thus, scaffolds with very high porosity and structural stability can be produced by use of this technique. The properties of the constructs generated may be tailored through careful choice of monomers by mechanical and biological properties. Glycidyl methacrylate (GMA), for example, has been extensively used in tissue engineering because of its beneficial effects on crosslinking and mechanical properties. It has been discovered that the introduction of GMA into the system can lead to the formation of a more methacrylated scaffold system, leading to higher compressive strengths of the scaffold system. Likewise, trimethylolpropane triacrylate (TMPTA), a multifunctional acrylate monomer, helps to create strong polymer networks, thereby enhancing the strength of the scaffold structure. The GMA and TMPTA co-fabricated scaffolds, when using IONP-stabilized Pickering emulsions, demonstrate better mechanical properties and favorable biological properties.

Notably, OA-IONPs are added to the scaffolds, adding a multifunctionality. The nanocomposites have been demonstrated to have no adverse effects on the viability of a variety of cell types (fibroblasts and osteogenic cells) and to promote cell adhesion and proliferation. In addition, they show remarkable antimicrobial properties, such as against Staphylococcus aureus, which is mainly achieved by production of reactive oxygen species. In addition, these scaffolds stimulate angiogenesis, as seen in experimental models with greater blood vessel formation and branching.

In conclusion, IONP-reinforced scaffolds are a promising approach in tissue engineering, providing a material with structural properties that can be tuned and with bio-functions that are improved to enable effective tissue regeneration.

Copper NPs

It is a critical trace element for humans, with its important role in the body for a variety of biochemical and physiological processes such as enzymatic function, tissue metabolism and neural function. It has unique characteristics, including catalytic activity and antibacterial and antifungal properties, as well as its role in the synthesis of collagen and the formation of new blood vessels, that make it of great value in the area of tissue engineering. Cu is believed to play a part in mesenchymal cell development, partly through the activity of the Cu-dependent enzyme, lysyl oxidase, these involved in the formation of structural proteins, including collagen, elastin and keratin, as well as in controlling mineral deposition in tissues. Copper deficiency has been linked to poor tissue formation, deterioration of the mechanical integrity, and dysfunction of cells, underscoring its role in the regenerative process. The rising popularity of (CuNPs) is a result of their high physicochemical properties which enable them to work effectively at minimal concentrations and Antimicrobial activity .In the field of (TE)Tissue Engineering, CuNPs have been shown to help crucial tissue-repair mechanisms, like adhesion, proliferation, and formation of the extracellular matrix, which are essential for tissue development and repair, although they are limited by the potential cytotoxicity and inflammatory responses, depending on. the particle size, concentration, solubility, and biodistribution. In response, surface modification and coating techniques with biocompatible materials have been investigated to increase the stability, decrease the oxidation and increase the biocompatibility in general. The recent development of CuNP-incorporated nanocomposites for scaffolds is one of the recent advancements. For instance, CuNP-based composites made of polymers have exhibited sustained ion release, improved angiogenic activity, better cellular response, and outstanding antibacterial activity, showing great potential as tissue regeneration materials. In a similar fashion, hybrid scaffolds containing Cu-based alloy nanoparticles have shown improved physicochemical characteristics, controlled degradation, improved antimicrobial properties and improved cell supporting properties.

Zirconium NPs

Zirconium (Zr) is a naturally occurring element that exists in the biological tissues in trace amounts and is well known for its excellent biocompatibility and bioactivity. It has been demonstrated to stimulate cellular responses including proliferation and differentiation, in part by activation of cellular signalling pathways including BMP/SMAD. Zirconium is a highly promising material for a number of biomedical applications because of its mechanical properties, corrosion resistance, magnetic property, and low cytotoxicity.

The development of composite scaffold systems with the addition of zirconium nanoparticles (ZrNPs) has been a major interest recently to promote improved functional performance. For instance, Research developed a biodegradable nanocomposite scaffold composed of ZrNPs and chitosan, hydroxyapatite , and wollastonite by the drying-freeze technique. The scaffold exhibited better mechanical strength and biocompatibility, showing its potential for use in tissue engineering.

Additionally, the dentistry and medical fields have made extensive use of zirconium-based materials. implants field, due to their good chemical stability and excellent tissue compatibility. They also have the ability to facilitate apatite layer formation, which further enhances their tissue bonding properties, making them useful for regenerative applications in the field of zirconium-containing coatings or composites.

Aluminium NPs

Aluminium and its derivatives, especially when oxidized to aluminum oxide (Al2O3), have been recently considered as promising materials for tissue engineering because of their interesting mechanical and biological properties. These materials are used in regenerative applications because of their ability to increase the mechanical strength, improve cell adhesion, proliferation and increase structural stability of scaffolds. Moreover, ceramics based on aluminium are more resistant to fracture and have longer durability than scaffold systems. Tissue integration is further improved and implant failure is minimised over a very long period of time by the use of these types of materials with porous ceramic coatings.

Aluminum oxide and its ionic compounds have also been demonstrated to increase cellular function (e.g. proliferation) and the activity of multinucleated cells without being highly. cytotoxic to cells or having poor biodegradability in composite material like Ca2Al2SiO7.

Surface morphology and nanoscale features affect the biological response to aluminium-based nanostructures. The nanopores of the —Chen et al. 2017 demonstrated that— are capable of trapping and isolating a single molecule.

anodized aluminium surfaces can control the behavior of cells, such as spreading, gene expression and release of regenerative factors. Reduced Inflammatory response and reduced levels of reactive oxygen species (ROS) were associated with larger nanopores (100-200nm), while markers of mineralization were increased with smaller nanopores (~50nm), but smaller nanopores might have an impact on cell viability.

Comparative studies have also focussed on the size dependent bio-effects of the aluminium based nanomaterials. It was reported that the antioxidant activity of nanoscale Al_2O_3 was more than that of microscale Al_2O_3 by Karunakaran et al. (2014) meaning that there is increased interaction with cells on a smaller scale. In addition, biomimetic modifications, such as the coating of alumina ceramics with calcium phosphate that can change the porosity of scaffolds and lead to enhanced biological performance, highlight the significance of surface engineering of scaffolds.

Aluminium nanoparticles-based hybrid material systems are also investigated. Research concluded that feasibility of the cells in composite systems increased as the number of reinforcing nanomaterials, like carbon nanotubes, was decreased. Furthermore, Yu et al. (2020) found that composite scaffolds reinforced with Al_2O_3 promoted the generation of inter-linked macroporous networks, which play a crucial role in cell adhesion and tissue development. The higher the percentage of aluminium oxide, the lower the degradation rate, which will result in more stable environment for the tissue regeneration to continue.

Nickel NPs

Nickel (Ni), a transition metal which is present in the human system in trace amounts, has low toxicity at physiological concentrations but is dose dependent. Nickel-based materials and alloys have been brought to the interest of tissue engineering brcause of their multifunctional properties. these material are strong, elastic, have a relatively low Young's modulus and show shape memory properties, allowing for the development of scaffolds that have controlled porosity, geometry, and surface properties for tissue regeneration.

Alloys that contain nickel have been thoroughly studied for the purpose of scaffold manufacturing, especially the TiNi systems. To date, were able to prepare a porous TiNi scaffold by applying a self-propagating high-temperature synthesis technique. This scaffold was able to promote differentiation of mesenchymal stem cells

(MSCs) and is also important for vascularization and nutrient transport within the scaffold for effective tissue regeneration.

Furthermore, nano biological effects of Ni doped nanomaterials have been found worthy. The cell viability of Ni doped nHAp was found to be good with no significant toxicity. The gene expression analysis revealed the upregulation of differentiation markers that are essential in tissue differentiation processes through the signaling pathways associated with cell development, indicating a possible regulatory role of nickel ions in tissue differentiation processes. Nickel is also used in composite scaffold system to improve the structural and functional properties. Research developed a composite Scaffold made of several different components, including nickel foam, graphene oxide, poly pyrrole, and hydroxyapatite. The scaffolds were found to be suitable for cell growth; they were able to stimulate cell adhesion and proliferation. These systems can not only include Ni as a structural component, but can also use Ni as a topological guide to create the morphology of the scaffold, surface properties, and interactions with cells in general. To conclude, nickel and its compounds are important in the development of more complex scaffold systems, as they enhance the mechanical properties, offer flexibility in design, and are bioactive, thus making them useful in tissue engineering strategies.

Magnetic NPs

In the field of tissue engineering, magnetic nanoparticles (NPs) are multiple function materials which can be used to improve the properties of tissue scaffolds, to deliver stem cell therapy, and to enhance the treatment of tissues with advanced technologies such as tumor treatment. Among these, nanoparticles and derivatives of them based on Iron (Fe_3O_4 and Magnetite) are most important. The two forms of magnetite γ-Fe_2O_3 and maghemite γ-Fe_2O_3 have been much studied due to their superparamagnetic characteristics. and their capacity to. react to magnetic fields from the outside. These materials are also catalytic and have been used in different composite systems for biomedical uses such as targeted therapies and drug delivery.

The use of magnetic NPs in scaffold systems has been shown to improve cellular responses including cell proliferation and differentiation, which can lead to improved tissue regeneration. Kim et al., 2014 have demonstrated that magnetic nanoparticles can be introduced into a polycaprolactone (PCL) scaffold to improve the scaffolds' mechanical properties, mineralization potential and hydrophilicity, all of which are desirable for regenerative applications. In fact, magnetic nanoparticles are also crucial in the field of regenerative medicine, being used for cell labeling and tracking in vivo, especially using mesenchymal stem cells (MSCs). They can be surface functionalized in order to enhance their functional properties by preventing aggregation, dispersing in the scaffold matrices and enhancing the overall biocompatibility. Magnetic nanoparticles, apart from the application involving regeneration, have been identified to be of tremendous importance in therapeutic applications such as the hyperthermia treatment of cancers. It has been proposed that these nanoparticles selectively target tumor cells, are heated by an alternating magnetic field and then selectively destroy the tumor cells without harming other cells. adjacent healthy tissues. Besides, their inclusion in biomaterials such as bioactive glasses and polymer scaffolds extends their applications, but it remains difficult to achieve optimal magnetic property and thermal efficiency in these materials. In addition, composite scaffolds made of magnetic nanoparticles with other biomaterials, such as hydroxyapatite (HAp) and chitosan, have been found to be more bioactive and to induce more favorable cellular reactions and thus, are suitable for tissue regeneration applications.

Titanium oxide

Tissue engineering has been a field of great interest to the use of titanium dioxide (TiO_2) nanoparticles to modulate tissue cell-cell communication and tissue regeneration. TiO_2 NPs have been demonstrated to induce the secretion of both immature and mature osteoblast derived exosomes (Exo) with unique proteomic signatures.

Based on the functional analyses, these exosomes can be shown to have regulatory properties over the separation of human mesenchymal stem. , pointing toward a role of TiO_2 in cell–cell communication in the context of cellular regeneration in the microenvironment. An important development of nanotubes of TiO_2 is the ability to create precise control of surface morphology by electrochemical anodization methods. The tunability at the nanoscale enables the design of surfaces that can be optimized for the integration of biomaterials with the environment: cells are directly attached to the surface, and fibrous tissue deposition is decreased.

The ability of mimicking key features of the Extracellular matrix (ECM), supporting cell adhesion, proliferation and growth, is thought to be responsible for many of the properties of TiO_2 nanotubes. They possess a very high surface area that can lead to more proteins being adsorbed on its surface which, in turn, would mean better cellular adhesion and spreading. These materials with nano-scale architecture and topography have been shown to significantly influence cellular responses – activation of tissue forming cells.

Beyond that, it is possible to find a combination of appropriate biomolecules that, combined with TiO_2 nanostructures, can induce cell differentiation, highlighting the synergism between material characteristics and biochemical stimuli. The interaction is important in the context of stem cells because under the right conditions, the mesenchymal stem cells (MSCs) can differentiate into specialized cells that can repair and regenerate tissues. Besides being a structural component, TiO_2 nanotubes can also be used as an effective carrier of therapeutic agents. Their structure is tubular and they can be filled with the drugs, growth stages, etc., Medications or antimicrobial products that can be administered in a controlled manner to help heal tissues and to avoid infection.

CERIUM OXIDE

The unique redox properties of cerium oxide nanoparticles or nanoceria are because of them Ability to change the state between Ce^{3+} and Ce^{4+} which is beneficial for scavenging ROS\RNS and reducing oxidative stress.

This antioxidant activity helps in the modulation of pathways like Nrf2 and the reduction of inflammatory mediators such as iNOS which helps in protecting the cellular components and supports tissue repair.

CeO_2 NPs exhibit minimal toxicity and increase cell proliferation and survival. When functionalized with stabilizing agents like PEG or citrate/EDTA, the biocompatibility of CeO_2 NPs is further improved. They have been reported to enhance cell viability, extracellular matrix production, and mechanical properties, promoting tissue regeneration in different tissues when incorporated into scaffolds.

CeO_2 NPs have also shown to have neuroprotective properties, evidenced by their ability to decrease oxidative stress and enhance neuronal survival, such as through the mediation of BDNF and TrkB, as well as having the potential to decrease ROS in neuroinflammatory conditions and promote functional outcome. For ophthalmic use, these nanoparticles have shown to preserve the retina and prevent abnormal vascularization, and can be modified to achieve better delivery to the target tissue.

In addition, CeO_2 NPs promote the healing of tissues by their antioxidant, anti-inflammatory, antibacterial and pro-angiogenic properties when embedded in biomaterials like hydrogels and nanofibrous scaffolds. Their safety profile will however vary dependent on size, surface chemistry and dose, and so the long-term toxicity and biodistribution should be investigated further. New methods involve delivery in 3D-printed scaffolds for controlled and personalized therapy uses in regenerative medicine.

Yttrium oxide Nanoparticles

The use of yttrium oxide(Y2O3) nanoparticles in polymeric scaffolds for tissue engineering applications has been investigated for the purpose of improving their properties, such as cell adhesion, proliferation, and vascularization. They possess potent anti-oxidative and free radical scavenging activity which helps to lower oxidative stress and trigger angiogenic responses, encouraging tissue regeneration.

The possible enhancement of cellular activity by promoting the release of factors involved in cell proliferation and neovascularization when added to polycaprolactone (PCL) scaffolds makes Y_2O_3 nanoparticles a promising candidate for application in (TE).

Regenerative and wound. This kind of nanoparticle integration is highly suited to healing applications, and electro spun based PCL scaffolds with a natural ECM architecture with large surface area, variable pore size, and strong oxygen permeability greatly help it.

The mechanical properties of scaffolds are also impacted by the addition of Y2O3 nanoparticles. with the best concentrations emphasizing strength without adversely affecting biocompatibility. Scaffolds with suitable amounts of Y_2O_3 have shown to be biocompatible with blood, cytocompatibility and to improve cell adhesion. In addition, they have been demonstrate to be Angiogenic in vitro and in vivo models, such as chick chorioallantoic membrane (CAM) and rat studies, which suggests their ability to induce vascularized tissue regeneration.

Zinc Oxide Nanoparticle:

The properties of nanoparticles such as zinc oxide (ZnO) make them a focus of interest in tissue engineering: they have inherent antibacterial properties and are believed to promote tissue regeneration. ZnO has less toxicity than other metal ions, and shows antimicrobial activity. It has been discovered that incorporating roughly 5% ZnO into the polymeric scaffolds can result in up to 99% antibacterial efficiency against Escherichia coli.

The nanoparticles have been successfully incorporated into the biopolymer composites like chitosan and fucoidan based scaffolds to enhance their biomimetic and physicochemical characteristics. The nanocomposite scaffolds have interconnected porous structures, high mechanical stability, high swelling ability, and controllable degradation, which are good for tissue regeneration. In summary, scaffolds made of ZnO are appropriate for cell growth and can protect against microbial infection.

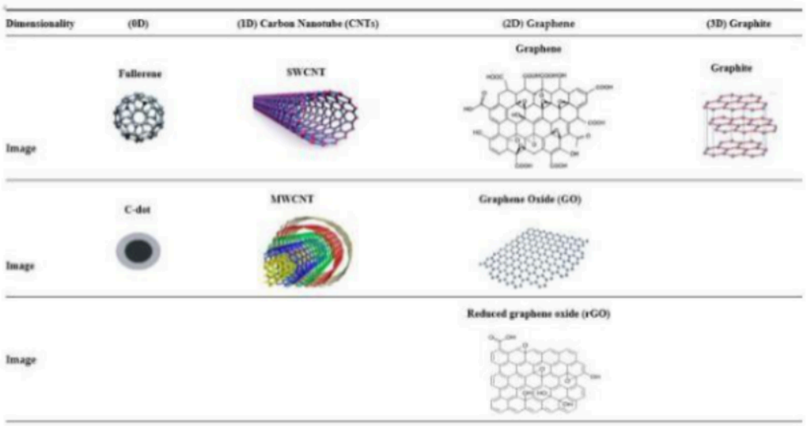
UiO-66-NH 2 Nanoparticles

Scaffolds serve as a structural platform that facilitates tissue repair, regeneration and function restoration. New developments have been directed towards the synthesis of scaffolds with multifunctional properties and antimicrobial properties. Forexample, one composite scaffold was created from pectin and gelatin, which was embedded with metal–organic framework nanoparticles (UiO-66-NH_2) containing the antibiotic drug amoxicillin.Thesystem was created to emulate the native tissue environment with adequate mechanical properties and infection control. The use of nanoparticles led to an improvement in the scaffold's performance,interms of mechanical strength (optimized of ~3% nanoparticles) and porosity that allows the transport of nutrients and infiltration of cells. The experimental studies proved the antibacterial efficacyagainstEscherichia coli and Staphylococcus aureus and good cytocompatibility. The scaffold promotedtheviability,adhesion and migration of fibroblasts suggesting its potential to facilitate wound healing and tissue regeneration.

2.4 carbon-based nanoparticle

Because of their intriguing physicochemical characteristics, like their large surface area, higher biocompatibility, and power to interact with cells, interest in using carbon-based nanoparticles in tissue engineering has grown. It has been showed that graphene, carbon nanotubes, and fullerenes promote cell attachment, proliferation, and differentiation and can be used in regenerative applications.

The same nanoparticles can also be used as good delivery agents for bioactive molecules and growth factors, and therapeutic molecules can be delivered using these. They have a structural and functional property that makes them supportive frameworks which support tissue formation. In conclusion, carbon-based nanoparticles are a encouraging class of materials for the advancement of tissue engineering strategies and enhancing the regenerative outcome.



Dimensionality	(0D)	(1D) Carbon Nanotube (CNTs)	(2D) Graphene	(3D) Graphite
Image	Fullerene	SWCNT	Graphene	Graphite
Image	C-dot	MWCNT	Graphene Oxide (GO)	
Image			Reduced graphene oxide (rGO)	

FIG.2

1 Zero-Dimensional Carbon-Based Nanomaterials in Tissue Engineering

1 Carbon Dots (C-Dots)

Thecarbon dots arenanosized particles(<10 nm) that show highstability and intrinsic fluorescence, and can be used in therapeutic and diagnostic applications. They have been found to have a strong proclivity for regeneration of tissue and they are known to localize in growing and repair tissues. Their targeted localization is also confirmed in vivo and they could be used for site-specific delivery systems.

The fluorescent and targeting ability of C-dots make them potential theranostic agents. They may also act as imaging agents for early detection and therapeutic agents as transporter, to treat targeted and minimize systemic side effects.

2. Fullerene (C_{60}) in Tissue Engineering

The carbon nanomaterial called fullerene, a unique cage-like carbon compound (C_{60}), has been of interest for tissue engineering because of its stability and unique physicochemical properties. The structure is highly symmetrical, and is able to interact with biological systems, particularly well-suited for regenerative applications. One of the possible applications of fullerenes is their high antioxidant properties. They are involved in the defense of Reactive Oxygen Species (ROS) that may cause oxidative stress and have a negative effect on tissue regeneration. Fullerene derivatives, e.g., $C_{60}(OH)_{30}$ and $C_{60}(OH)_{16}$AMBP have been found to .be affinity towards mineralized tissues and to have the ability to influence the mineralization processes, being able to control tissue remodeling.

Also, fullerenes' free radical scavenging effect protects the cells from oxidative stress, which results in better healing process. Their antioxidant activity is especially significant in situations that involve oxidative stress, thereby damaging tissue integrity. Cell adhesion, proliferation and alignment have also been demonstrated as an effect of fullerene nanostructures. C_{60} Nano whiskers can be used to guide the development of cells, for example. Improve the cell response thereby rendering them as potential materials for use as scaffold in regenerative systems. Though these are promising characteristics, further research needed to optimize the bio compatibility & functionalization for fullerene-based material and to gain greater insights into long-term biological impact of these materials.

Nanodiamonds (NDs) in Tissue Engineering.

The properties described above make nanodiamonds interesting for tissue engineering applications, because they are highly biocompatible, have a large surface area, are chemically stable and have high mechanical properties that enable application in the construction of advanced scaffold systems for supporting tissue regeneration. The three- dimensional porous structures that are reminiscent of cells' natural extracellular matrix are easily functionalized, potentially increasing their interaction with mammalian tissues and enabling the dtransportation of therapeutic agents to target tissues. Further, NDs possess antioxidant properties that may help reduce oxidative stress, by neutralizing free radicals that cause damage to cells, and by assisting in repairing them.

This is particularly beneficial in cases where there is oxidative stress that interferes with the re-growth. It is also reported that the application of ND scaffolds enhances the cell response (adhesion, growth, and/or other cell responses) and thus promotes tissue formation. These benefits are present, but long-term biological consequences and optimum use of them in clinical practice needs to be ascertained by further studies. These carbon-based nanoparticles are very interesting for tissue engineering because of very interesting physicochemical properties like high surface area, good biocompatibility, and strong interaction with cells. These nanoparticles can also be used as efficient vehicle to transport bioactive molecules like growth factors and other therapeutic agents. They can be used as supportive structures which promote tissue formation due to their structural and functional characteristics. In conclusion, carbon-based nanoparticles hold great promise for the area of tissue engineering and enhancing regeneration processes.

2.One-Dimensional Carbon-Based Nanomaterials for TE

Carbon Nanotubes (CNTs)

CNTs appear as very promising material in recent years because of their ability to enhance -bone regeneration. Depending on the number of cylinders present CNTs can be either single walled CNTs (SWCNTs) or multi-walled CNTs (MWCNTs). CNTs have good mechanical properties, high surface area and are important to improve the osteoconductive properties of composites. CNTs have been demonstrated to stimulate the attachment, growth and ,differentiation of osteoblasts, which play vital roles in the process of bone tissue formation when attached to scaffolds. The CNTs and cells interaction is due mainly to the properties of the surface of CNTs that can be modified to interact favorably with the bone
.cells to establish an environment that is conducive to bone repair

Mechanical properties of the CNTs are similar to that of the natural bone, the support and stability of which can be provided by the CNTs. Moreover, their chemical
The composition is suitable for the growth factors to be absorbed and retained by the scaffolds efficiently which improves the osteogenic property. All of these characteristics contribute to the creation of scaffolds that are greatly helpful to bone regeneration.

Moreover, studies have revealed that when properly functionalized CNTs have low toxicity and long-term side effects, thereby indicating their use in Regenerative Medicine

3 Two-Dimensional Carbon-Based Nanomaterials for TE

In tissue engineering, the exceptional mechanical properties and biological function of graphene-based NPs, such as graphene oxide , have attracted a lot of interest.
Graphene is a 2D material that has high tensile strength and flexibility, whilst GO has oxygen functional groups (hydroxyl, carboxyl, epoxy) that make it more dispersible and interact with biomolecules.

GO and GO composites have been demonstrated to be biocompatible and promote cell adhesion, proliferation and differentiation. Research has demonstrated that GO incorporated scaffolds, including chitosan–GO systems, are able to promote the cellular responses and to create a favorable environment for growth and differentiation of stem cells. Moreover, GO has intrinsic bioactivity, as the viability of the cultured MSCs on GO surfaces does not require external stimuli to undergo differentiation.

Another advantage of GO incorporation is the improvement of mechanical properties of scaffolds like tensile strength and elasticity, which are necessary to preserve the integrity of the scaffolds in physiological conditions. In addition, the graphene-based materials also induce osteoconductive and osteoinductive responses, which stimulates tissue formation. For instance, the high surface area and microenvironment of 3D graphene scaffold have been demonstrated to preserve stem cell viability, stimulate their differentiation.

GO can also be blended with other biomaterials like hydroxyapatite, which further enhances the mechanical and biological properties, promoting cell proliferation and general regenerative results. In vivo experiments have also shown that graphene-based nanoparticles could promote tissue formation and mineralization when combined with stem cells, suggesting that they have potential practical applications for tissue regeneration.

Reduced Graphene Oxide (rGO) in Tissue Engineering

Reduced graphene oxide (rGO) is observed as a potentially useful nanomaterial for tissue engineering because of its potential to improve the performance of scaffolds and to facilitate cell activities. Abbreviated elastic modulus and fracture resistance are enhanced by its incorporation in scaffold systems resulting in more suitable composite material properties for structural applications.

In addition to other materials, such as hydroxyapatite (HAp) and β-tricalcium phosphate (β-TCP), rGO composites exhibit enhanced strengths and stabilities that are beneficial compared to the conventional scaffolds. In addition to mechanical improvement, rGO was also found to be cell adhesive material and a promoter of cell proliferation, based on its high surface area and favourable surface characteristics which favour protein adsorption and improve the hydrophilicity of the scaffold.

Furthermore, scaffolds created with rGO can induce stem cell differentiation, and can be used to create an (ECM) like environment that can provide biochemical cues for tissue formation. For instance, nanofibrous scaffolds with rGO integration have been shown to encourage the proliferation and separation of mesenchymal stem cells , which has significant, implications for their regenerative applications.

But there are potential problems such as stress to the cells, distribution in the body and immune reactions that must be taken care of. The surface has been functionalized using biocompatible molecules, which have demonstrated to improve the stability of rGO and reduce the possible negative effects.Overa 19 he use of rGO based materials has a high potential for development of advanced scaffolds; however, the long-term safety and efficacy of these materials must be demonstrated in additional in vivo studies.

3-D Carbon Based Nanomaterials for TE

Well-known three dimensional (3D) carbon-based materials such as graphite and diamond have different crystal structures and properties. Their use in scaffolds has been restricted, however, because they do not have any intrinsic porosity, which is crucial for tissue engineering applications for differentiation, cell adhesion, and differentiation.

To Overcome this limitation porous 3D carbon structures have been prepared, e.g. carbonization of polyacrylonitrile (PAN). The resulting carbonized PAN (cPAN) scaffolds have interconnected pores of 75-100 μm in size and have a graphitic structure which is similar to that of a carbon nanotube. These features enable improved cellular interactions and nutrient transport.

Comparative studies have shown that cPAN scaffolds are also superior to conventional materials such as glass and CNT-based scaffolds in terms of cell viability, proliferation and differentiation. Increased alkaline phosphatase activity, expression of osteogenic markers, and calcium deposition in MSCs has been confirmed as enhanced biological performance.

The enhanced functionality of cPAN scaffolds is believed to be due to their protein adsorption present in the (ECM), such as fibronectin, which also provide the cells with signals and promote tissue formation.

Table: 2.4

	Carbon Nanomaterials	Composition	Applications in Tissue Engineering
1	Carbon Nanodiamonds	Hydrazide-Functionalizrd carbon nanotubes pericardial matrix derived hydrogel	Improved cardiac tissue engineering
2	Fullerene whisker scaffolds	Cellular development into muscle cells is regulated by a well aligned 1D scaffold	encouragement of myoblast development into myotubes
3	NDs(Nano diamonds)	Nanodiamond functionalized with octadecyl amine and poly (lactic acid).	used in regenerative medicine as parts of surgical instruments and bone scaffolds
4	(CDs)Carbon dots	Nanofibrous mats	CD-based composite Hydrogel generated from the pericardial matrix.
5	Carbon Nanofibres	Electroactive CNF/gelatin nanofibrous cardiac patches	Improved cellular adhesion and proliferation; increased gene expression & angiogenesis
6	(GN)Graphene Nanosheets	Biomimetic gelatin and bioactive glass scaffolds	Excellent biocompatibility and engineered stiffness.

2.5 Polymeric nanoparticle

The versatility of polymer-based nanoparticles in tissue engineering, ranging from their ability to produce scaffolds to delivering drugs and promoting regeneration, makes them an essential tool in the field. The polymers applied in this field can be broadly divided into synthetic polymers, natural polymers and composite systems.

Synthetic Polymers

These polymersarewidely used for scaffold design because their controllable degradation and tunable mechanical properties. They can be engineered with a high degree of control of their physicochemical properties for specific biomedical applications. However, they are generally not bioactive by themselves and frequently need to be modified by surface chemistry or the addition of bioactive molecules to improve cell–material interactions.

Polylactic Acid (PLA)

It is a biodegradable synthetic polymer made from renewable resources, like carbohydrates,. Hydrolyzes to lactic acid, which is processed in the body. The use of PLA-based scaffolds is common because of their biocompatibility, appropriate mechanical properties and degradation rates. These characteristics are customizable, by adjusting the molecular weight. crystallinity and L: D isomer ratio. Incorporation of bioactive agents, however, can be needed to enhance biological performance, and because PLA is not inherently cell adhesive, it can be subject to surface modification to achieve this.

Polyglycolic acid (PGA)

A more popular synthetic polymer, PGA degrades more quickly than PLA, making it more suitable for applications requiring quicker scaffold resorption. It does, however, have a short degradation time, which may affect mechanical properties before tissue has been restored, and prevents it from being used in load-bearing situations. For this reason, PGA is commonly co-polymerized with PLA to create (PLGA), it is a copolymer that has tunable degradation properties and enhanced mechanical capabilities. PGA, similar to other synthetic polymers, is hydrophobic in nature and generally needs to be modified to improve cell adhesion.

Polycaprolactone (PCL)

Polycaprolactone (PCL)is a polymer that degrades much slower than PLA and PGA and is semicrystalline. It has very good mechanical strength, flexibility and can be used in load carrying applications. PCL can be extruded into a number of different architectures, such as electro spun nanofibrous scaffolds, It can be used to[19]mic the (ECM). It is, however, hydrophobic and not bioactive enough and needs to be functionalized with bioactive molecules or agents to enhance the cellular response and tissue formation.

[28]

(PLGA) Poly(lactic-co-glycolic acid)

The PLGA is a mixture of PLA and PGA, and the. ratio of the two acids is used to control the rate of degradation. It is widely used because of its tunable mechanical properties, bio degradability and bio compatibility. It can, however, break down to create acidic products that can cause local changes in pH and impact on surrounding tissues. To overcome this limitation, PLGA is often modified with bioactive molecules or combined with other materials to neutralize the acidic environment.

Poly (vinyl alcohol) (PVA)

PolyvinylAlcohol (PVA)isan artificial polymer with good mechanical strength, flexibility and stability that is biocompatible. It can be fully dissolved in water and will not need to be treated with organic solvents, thus making it easier to use and safer. Good chemical and thermal stability are also one of the reasons why PVA is used.

PVA, however, does not contain any biological recognition sites, which restricts its bioactivity and cell interaction capabilities. This drawback is overcome by incorporating natural polymers like gelatin which can enhance cellular response without compromising the mechanical properties.

Natural polymers

Naturalpolymers are derived from biological sources and extensively used in tissue engineering for their natural biocompatibility and their structure and function that resemble that of the native extracellular matrix (ECM). These properties facilitate desirable cell–material interactions and tissue regeneration.

Natural polymers, however, are less known to possess good mechanical strength and their degradation properties are less predictable than those of their synthetic counterparts, and this may restrict their use in load-bearing systems.

Collagen

Itisthemost abundant structural protein in the body .and an important constituen[10]f bone and connective tissues which are useful for scaffolds fabrication. It offers an environment that is biomimetic for cell adhesion, migration, proliferation and differentiation. Furthermore, collagen is immunogenic, but not highly, and has natural osteoinductive properties which encourage the differentiation. of the (MSC) into cells that form tissue.

Although there are these benefits, collagen is not very strong and breaks down easily, making it unsuitable for use in load-bearing systems. These limitations are overcome by crosslinking or by mixing it with synthetic polymers or ceramics to improve its stability and mechanical properties. Newly published research also shows that collagen can combine with chitosan to create injectable "hydrogels" with potential for regenerative applications.

[6]

Chitosan

It is a natural polysaccharide [10] that is derived from chitin, which is found in the shells of crustaceans. Because of their biocompatibility, biodegradability and inherent antimicrobial [9] properties it is widely used in tissue engineeri[10]applications.

The chitosan-based scaffolds favor cell adhesion and proliferation and can also be functionalized for growth factors or nanoparticles to increase the regenerative potential. However, its mechanical properties and degradation rate are relatively low and is dependent on the deacetylation degree, which restricts its use in load bearing system. In order to resolve these restrictions, chitosan is frequently blended with synthetic polymers or ceramic substances to enhance the structural stability and performance.

Alginate

Apolysaccharide that is naturally sourced from brown seaweed, alginate is widely used in biomedical applications for its biocompatibility, biodegradability and gel forming properties.

Alginate is often used in tissue engineering for scaffold and hydrogel applications, frequently in combination with bioactive molecules like bone morphogenetic proteins (BMPs) or hydroxyapatite (HA) to promote tissue regeneration.

But it suffers from low mechanical properties and uncontrolled degradation characteristics, which restricts its use in load-bearing devices. To overcome this disadvantages alginate is often modified with synthetic polymers or reinforced with nanoparticles to enhance its mechanical and biological properties.

2.6 Composite scaffolds

Composite scaffoldsare made of synthetic and natural polymers to balance mechanical strength and biological properties. The purpose of these systems is to provide structural support for load-bearing applications, as well as to mimic a natural environment to enable cell adhesion, proliferation and differentiation. They can also be further modified with bioactive molecules or nanoparticles, increasing their regenerative potential.

A commonly used formulation is polycaprolactone (PCL) and hydroxyapatite (HA) that enhances the bioactivity and mineralization, respectively. Likewise, composites like PLGA–collagen and PLGA–chitosan display similar mechanical properties. and degradation rates, while retaining properties of the extracellular matrix. The hybrid systems take advantage of both the strength and tunability of synthetic polymers, as well as the bioactivity and cell-recognition properties of natural polymers, and hence, provide better scaffold properties. Several recent studies have shown that the use of composites: PCL–collagen and PLGA–chitosan promotes tissue regeneration in vitro and in vivo. Furthermore, alginate–PCL has been found that composites are appropriate for load-bearing applications. s as they enhance the elastic properties and support the formation of vascularized tissues.

Even with these developments, there are certain trade-offs with each material system. For example, PLA is strong but inflexible, while PCL is durable but has low bioactivity. In the same way, fabrication processes like freeze drying give high porosity but not a much precise control over structure as compared to advanced fabrication processes like 3D printing. The fact that different scaffold designs can be used for different clinical needs underlines the need to design scaffolds according to clinical needs rather than using a single scaffold or material.

CHAPTER 3

Applications of nanomaterials in (TE)Tissue Engineering

3.1 Nanomaterial Applications in Dental Tissue Engineering

In fact, in the early 21st century, nanomaterials have become more and more significant in the field of periodontal diseases, which are becoming more prevalent in society, and are found to be linked with systemic diseases like cardiovascular disease, diabetes and rheumatoid arthritis. The tissues of the periodontium possess very limited reparative potential; therefore, advanced therapeutic methods are required to restore tissue structure and function. Nanomaterials, in particular metal and polymer-based, have demonstrated great potential in this context.

The use of nanomaterials in dental applications is mainly focused on: (i) use as antibacterial agents for controlling oral infections, (ii) as nanofillers to improve the mechanical and biological properties of dental materials, (iii) in the coating on dental implants, and (iv) in oral care products.

(PLGA) has been extensively studied for use in periodontal regeneration because of its biocompatibility, tunable degradation, and mechanical properties. Guided tissue regeneration, infection control, drug delivery, cementum formation, and alveolar bone preservation are a few examples of uses of PLGA-based composites. For example, PLGA based bilayer scaffolds have been shown to improve the regeneration of cementum, the thickness of the trabeculae and bone formation compared to conventional membranes.

Nanomaterials are becoming more significant in dental tissue engineering since the onset of systemic diseases like cardiovascular disease, diabetes, and rheumatoid arthritis in relation to periodontal disease, which is also prevalent in the early 21st century. Periodontial tissues have limited capacity for self-repair, so that advanced therapeutic strategies are required to restore tissue structure and function. Nanomaterials, particularly those based on metals and polymers, have demonstrated great promise in this application.

The antibacterial qualities of metal-based NPs, like silver, gold , titanium dioxide , and zinc oxide (ZnO), are well known. Their effectiveness is dependent on physicochemical properties including size and shape; particles smaller than 10 nm and triangular shapes with increased bactericidal efficacy. Particularly in oxidative environments, bimetallic Ag/Au nanoparticles have shown potent antibacterial activity against important periodontal pathogens including Porphyromonas gingivalis.
Furthermore, systems based on gold nanostructures have been created for regulated antibiotic release, combining chemotherapeutic and photothermal effects to improve antibacterial efficacy in vitro and in vivo.

3.2 Nanomaterial Applications in Neural Tissue Engineering

The nervous system is classified into two sections: the central nervous system and the peripheral nervous system . These systems are relatively-regenerative and when injured or diseased, often cause a lifetime loss of function. With the increasing prevalence of neurodegenerative disorders, there is a growing need for effective therapeutic strategies. Traditional methods including surgical repair and nerve grafting are associated with immune rejection, multiple surgeries and suboptimal results.

An alternative approach is through neural tissue engineering using nanomaterials that either promote or inhibit the extracellular matrix (ECM) environment and influence cellular behavior to improve nerve regeneration. Polymer scaffolds, hydrogels, nanoparticles and nerve conduits are examples of commonly-used systems that typically need to be biocompatible, biodegradable, porous, strong, resistant to infection and conductive.

The natural polymers, collagen, gelatin, elastin, keratin and silk, have been extensively investigated. One of the most widely used components in the ECM, collagen is found in large quantities in the nerves and has been clinically approved for peripheral nerve repair with commercial products like NeuraGen® and Neuromaix® that have shown efficacy in repairing nerve defects. Collagen-based material called gelatin has benefits of low cost, biodegradability, and promoting cell adhesion and proliferation. It can be modified to improve its performance by electrospinning or polymer composite with polymers such as PCL or PLA, which can facilitate axonal growth and neural differentiation.

keratin, Elastin and silk are also protein- based materials that contribute to the regeneration of neurons. Elastin-based systems are elastic and give structural support, including keratin which is easily functionalized and forms an adhesive with cells. The silk fibroin has an Excellent Mechanical Properties, minimal immunogenicity, Biocompatibility. it is ideal for hydrogels, scaffolds, and nerve conduits to promote neuronal differentiation and regeneration. Because of their electrical conductivity and stimulation of neural activity, carbon-based nanomaterials, like graphene, carbon Nanotubes , and fullerene are critical. Graphene materials promote neuronal differentiation and proliferation, and CNTs due to their neurite-like structure promote the formation of neural networks and repair. These materials are especially useful in scaffolds which stimulate nerve regeneration by electrical activity.

Furthermore, many synthetic and natural polymers have been explored and shown to have great potential in neural repair by enhancing cell viability, neurite outgrowth and functional recovery, including chitosan, alginate, PLGA, PLA and PEG. In summary, the use of nanomaterials offers a versatile platform that can be adapted for types of applications in neural (TE) and overcome the drawbacks of traditional methods.

3.3 Nanomaterial Applications in Bone Tissue Engineering

The primary focus of Bone tissue engineering, is to address irreversible damage of the bone with the help of the advanced scaffold-based approaches, sometimes aided with nanomaterial-based implants. The different strategies currently being pursued involve the design of scaffolds, the physicomechanical modification of the scaffolds, and biological strategies, particularly the three-dimensional (3D) scaffolds that can promote natural bone regeneration. Biodegradable nanomaterials are commonly used because they are biocompatible, promote better mineralization, and do not need to be surgically removed after being implanted in vivo.

In bone tissue engineering, scaffolds are required to have mechanical properties and to support cell adhesion, proliferation and differentiation. The properties of porosity, biocompatibility and bioactivity are critical. While polymer scaffolds are mostly used, nanomaterials such as ceramics, metals, carbon-based materials or chitosan-based nanoparticles can help solve their mechanical problems. These nanomaterials can be further functionalized to enhance cell signaling and protein interactions, further enhancing the regenerative outcomes.

Chitosan is a biodegradable and biocompatible polymer which has been used extensively in bone regeneration. The mechanical property and porosity of composite scaffolds made by mixing chitosan with nanocrystalline calcium phosphate (nCP) or hydroxyapatite (nHAp) have been improved, which allows stem cells to proliferate and differentiate toward osteogenic differentiation via BMP/Smad pathway. As the main inorganic constituent of bone, hydroxyapatite nanoparticles are especially effective in its ability to mimic the native bone structure and to promote cell adhesion and mineralization. Significant contribution of bioactive glass–ceramic nanoparticles is making stem cell proliferation and differentiation, which are often combined with polymers like PCL, PLGA, collagen, and alginate. These composites have an impact on osteogenesis and the process of angiogenesis, which leads to the regeneration of all tissues.

The carbon-based nanomaterials such as carbon dots, fullerenes, carbon nanotubes, graphene, and graphite exhibit high surface area, mechanical strength and tunable functionalities. Enhanced hydrophilicity and cellular interactions by graphene oxide (GO). With composite systems (e.g. polyethyleneimine/GO scaffolds), the proliferation of stem cells, the formation of focal adhesion and the differentiation of cells toward osteogenic lineage have been enhanced, while mineralization has been enhanced.

Other nanotechnology particles, including metal and metal oxide nanoparticles, including silver, gold and titanium dioxide, are also heavily studied. Silver nanoparticles are biocompatible and have the ability to positively modulate cellular activity without side effects. The osteogenic differentiation is induced in a size-dependent fashion by the gold nanoparticles and the scaffolds outperform with the addition of titanium dioxide nanoparticles, which also contribute to the osteogenesis. In the overall context, nanomaterials have several multifunctional properties that can be applied to bone tissue engineering, including mechanical enhancement, bioactivity and controlled regeneration, which makes them one of the main components in the development of new and more powerful regeneration therapies.

3.4 Nanomaterial Applicatons in Skin Tissue Engineering

The healing of wounds are complicated process consisting of inflammation, heamostasis proliferation and remodeling. There are two categories of skin wounds: acute (fast healing) and chronic (delayed healing, which may be linked to diseases such as diabetes). The importance of angiogenesis is its ability to provide oxygen and nutrients to the tissues, and when it fails, it causes chronic wounds.

Conventional therapies like cell-based therapies and autologous transplants have drawbacks like lack of donor sites, cost and inconsistent results. Thus, Nanomaterials use in skin tissue engineering has been introduced to improve the healing efficiency and biosafety. The ideal biomaterial should be protective, have adhesive properties, be pro-vascularization, and have mechanical support.

Chitosan is generally used because of its biocompatibility, biodegradability and antibacterial property. It is found to interact with bacterial membranes, resulting in cell damage, and promotes the adhesion of fibroblasts. The mechanical strength and efficiency in wound healing also enhance with chitosan-based composites.

Nanocellulose has been called out for its properties of absorbing exudates, managing moisture balance, and accelerated healing with decreased inflammation. Promotes tissue repair and new blood vessel development over conventional dressings. Poly (ethylene glycol), poly (vinyl alcohol), gelatin and alginate are other polymers used to enhance the performance of wound healing when combined with nanocellulose-based composites.

Further, nanomaterials are employed to deliver genes and for angiogenesis enhancement.

3.5 Nanomaterial Applications in Skin Tissue Engineering

The goal of (TE) Tissue engineering is to use cells, biomaterials, and bioactive chemicals to synthesize, repair, or replace tissues. However, poor cell survival following transplantation and the limited effectiveness of growth factor-based strategies continue to be significant barriers. Drug delivery systems are crucial for directing tissue regeneration without endangering nearby tissues due to their increase effectiveness and safety. However, biological barriers lower the bioavailability as well as effectiveness of medication administration in vivo.

Through loading or conjugating substances like enzymes, vaccines, peptides, and antibodies, biomaterials improve medication delivery. Delivery methods have been improved by nanomaterial-based systems, like dendrimers, polymeric nanospheres, liposomes, micelles, and inorganic nanoparticles (silicon, gold, and iron oxide). Many methods allow for regulated, stimuli-responsive medication release that is triggered by temperature, pH, enzymes, or other variables.Because of their stability and excellent distribution, polymer micelles—which are created by self-assembly—are useful drug carriers. Pharmacokinetics are enhanced by a low critical micelle concentration. Enhanced tumor targeting, penetration, and controlled drug release are all demonstrated by advanced micelle systems, which improve therapeutic efficacy with few adverse effects.

High branching, enhanced solubility, and decreased toxicity are some benefits of dendrimers. Drug loading capacity is increased by their structure, which enables drug attachment through covalent or non-covalent interactions. More functional groups are accessible for drug delivery in higher dendrimer generations. Tumor targeting, penetration, and anticancer efficacy have all improved using modified dendrimer–drug conjugates.

All things considered, metal-based, carbon-based, and polymeric nanomaterials have great potential for effective medication delivery and disease treatment in tissue engineering.

CHAPTER 4

4.1Challenges and future perspectives

Although nanoparticles have shown great promise for tissue engineering (TE)applications including improving the biological, mechanical and electrical properties of tissues, they also present certain challenges for their general clinical application.

An important concern is to develop and standardize the use of assessment tools to assess the toxicity, carcinogenicity and treat organicity of nanoparticles. Their response of these effects is extremely dose- and time-dependent. Nanoparticle are in use at levels below accepted threshold concentrations that are deemed safe, but the persistence of these in the body poses concern of bioaccumulation. In the long-term, the nanoparticle may come together in quantities that cause "cytotoxic" effects, facilitate cancer formation, and negatively affect reproductive health and development of fetuses.

Further, although there are many products on the market that already contain nanoparticles, there are important gaps in scientific knowledge and methodologies regarding specific hazards of nanoparticles. There are no internationally recognized standards for an-specific risk assessment, such as well-defined data needs and testing approaches. This non-standardization complicates the safety assessment, increases its time and expense. Currently, the safety of nanoparticle-containing products is the primary responsibility of the manufacturers, who must self-regulate and conduct their own safety assessments. Now, however, the regulatory structures are still not optimally suited for nanotechnology.
For instance, current requirements for chemical notification, classification and safety data sheets do not make reference to nanomaterials. Thus, there is a great need to create comprehensive regulatory policies and precautionary measures, especially with applications where long-term exposure and bioaccumulation are a possibility. These challenges must be tackled to produce safe and effective clinical tissue engineering applications that incorporate nanomaterials.

Conclusion

Nanoparticles have great biocompatibility and well-established surface modification strategies and are highly effective in many biomedical applications. They have demonstrated to increase the electrical coupling between the decellularized cells and increase the cell proliferation rate in different types of tissues. Moreover, their ability to inhibit the growth of bacteria has been extensively studied, and they have been shown to possess promising antibacterial properties. They can be used to control bacterial infections during reconstructive bone surgery and other procedures and be included in bio composite scaffolds.

In addition, nanoparticles have been shown to activate cell mechanotransduction—such mechanotransduction is involved in many body functions. This stimulation can be delivered by controlled nanoparticles that are remote from the cell, providing a novel means of cell behavior modification. A key development mentioned is the delivery of genes with nanoparticles, including one technique called magnetofection. In the present method, plasmid DNA is mixed with cationic lipids and magnetic interaction is utilized, to greatly improve the transfection efficiency.

Nanoparticles are also closely related to other applications in gene delivery such as cell patterning. Three major approaches have been tried for this: cationic magnetite liposomes or magnetite liposomes to which peptides containing RGD motifs have been attached as phospholipids, and amino silane nanoparticles that have been functionalized with the magnetic force and polyethylene glycol (PEG-Mags). These strategies allow spatial control of the cell structure, a crucial characteristic for tissue engineering .
The literature's list of applications demonstrates the enormous potential of nanoparticles in tissue engineering. especially with regard to the development of biosensors.

Extremely sensitive optical, electrical, and electrochemical biosensors have been developed using the nanoparticles for the accurate and precise detection of molecules, proteins and DNA. These biosensors could make a significant contribution to the field of medical diagnostics and therapeutic monitoring with further optimization.

Despite all these promising advances, there is a need to do more in vivo experiments to validate the promising results observed in vitro. The results in the laboratory need to be explored thoroughly before they are introduced into clinical use to assure that they are safe and effective. In the future, smart nanoparticles have the potential to communicate with stem cells, bring them to desired locations in the body, and control tissue formation in situ, thus furthering the field of tissue engineering.

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