ADVANCEMENTS IN SCAFFOLD-BASED DRUG DELIVERY SYSTEMS: A COMPREHENSIVE OVERVIEW AND RECENT DEVELOPMENTS

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ABSTRACT

In the field of tissue engineering, there is a growing focus on developing strategies for the reconstruction of dysfunctional tissue models through the transplantation of cells using stable scaffolds and biomolecules. Recently, significant attention has been focused on the expansion of dynamically responsive platforms that mimic the extracellular environment, leading to the integration of tissues and organs. The successful regeneration or restoration of tissues relies on the presence of a scaffold that serves as a temporary framework for cell proliferation and extracellular matrix formation. Various methods, including solvent abstraction, freeze drying/abstraction/gelation, particle compression, and phase reversal, can be employed to fabricate scaffolds. In the context of drug delivery systems utilizing polymeric scaffolds, careful consideration of optimal parameters such as drug loading capacity is crucial. Biodegradable polymers and bioceramics are commonly utilized to fabricate scaffolds. This review provides an overview of the significance of scaffolds, the materials employed, and the fabrication techniques utilized in the expansion of scaffolds for sustained drug delivery and tissue engineering applications.

Keywords: Engineering, Delivery, Implant, Novel, Regeneration, Scaffold

INTRODUCTION

Tissue engineering (TE) is the use of a blend of biomaterials, cells, and bioactive substances to replace or speed up the healing of injured or diseased tissue [1]. To restore or heal human tissues that have been harmed by ailment/injuries, thousands of clinical procedures are carried out every day. The injured tissue is traded by using donor graft tissues (autografts, allografts, or xenografts), but the main issues with this are a lack of donors or donation sites, disease transmission, graft rejection, pain and morbidity at the donor site, the amount of donor tissue that can be collected safely, and the probability of adverse immune reactions [2].

There are objectives for the regeneration of injured tissue by creating biological substitutions that restore, sustain, or enhance tissue function as opposed to substituting spoiled tissue with transplants, TE, or regenerative medicine [3, 4]. In the last two decades, TE and regenerative medicine have sparked scientific study and advance in this field [5]. Because they offer a temporal and space environment for cell enlargement and tissue growth, biodegradable (BDL) polymer scaffolds (SFDs) for TE have attracted a lot of interest [6, 7]. Scaffolding (SFDG) is the core component used to offer cells, medications, and genes to the body.

SFD, or "Scaffold for Drug Delivery," encompasses two main categories: drug-delivery SFDs and cell-delivery SFDs. Within the realm of cell/drug delivery, various types of polymeric SFDs have been developed. For instance, a typical 3D porous matrix (MTX) with a highly porous structure allows for rapid tissue growth and facilitates high cell seeding rates. Another option is an electro-spun or shuffled nanofiber (NFB) MTX, which provides a more physiologically accurate representation of the cellular environment. Additionally, a sol-gel transition hydrogel (HGL) that exhibits thermo sensitivity can be utilized as an SFD. Finally, a porous MSP (Microsphere) is another type of SFD that can be employed for drug or cell delivery. These diverse SFDs offer a range of options for researchers and practitioners seeking effective strategies for drug and cell delivery applications [8-10].

These have been used in TE for the prospect of usage as a cell transport carrier or supporting MTX, and they are already commonly used as sustained protein-discharge formulations [11]. The implantable forms of these polymeric SFDs are a conventional 3D porous/nanofibrous MTX, while the injectable forms are thermo-sensitive sol-gel transition HGL and porous microspheres (MSP).

This biological trinity supports TE tactics, which need the correct interplay of 3 components [12]:

The SFD is a vital component in tissue formation. It binds cells together, provides structural support, and guides their growth and development. Through its three-dimensional structure, the SFDG mimics the natural extracellular MTX, allowing cells to organize and form tissue-like structures. It also acts as a reservoir for biological signaling molecules, such as growth factors, which instructs cells to adopt specific tissue phenotypes and regulate their growth. The SFDG, along with cells and signaling molecules, creates an environment conducive to TE, facilitating the formation of functional and well-organized tissues.

Requirements for SFD for tissue engineering

An effective SFD for cell delivery requires specific qualities. It should possess the mechanical strength to protect cells from stresses while allowing biomechanical cues. The desired volume, shape, and strength are important, along with a highly porous structure that enables rapid tissue growth and high cell seeding densities. The SFD must be biocompatible, avoiding strong immunological or inflammatory responses. Additionally, it should support bio adsorption and provide physical structures that promote cell adhesion, interaction, and motility. These features are essential for a successful SFD in TE, facilitating cell integration and tissue formation [13, 14].

Requirements for SFD for drug delivery

A successful Scaffold for Drug Delivery (SFD) should possess key features for optimal drug delivery. It should enable uniform medication distribution, ensuring consistent drug release throughout its structure. The SFD should also have the capability to deliver the drug at a predetermined rate, allowing for controlled and sustained release. Additionally, the drug should remain stable within the SFD, retaining its therapeutic properties due to a low drug-binding affinity. Long-term stability, including biological activity, chemical structure, and physical parameters, is essential for reliable and effective drug delivery over an extended period. These characteristics collectively contribute to an efficient SFD for drug delivery applications [15, 16].

The design and production of SFDs that metal of the aforementioned criteria and have the capability of regulating the discharge kinetics of drugs or growth factors throughout therapy or tissue regeneration (TR) present a substantial challenge.

Properties of SFD matrices in cell/drug delivery

The utilisation of SFDs is crucial in TE. Cells are either implanted into the porous structure of the substrate or move there from nearby tissue, and the substrate's job is to control the expansion of those cells. Since the great majority of mammalian cell types are autonomous, they will perish in the absence of an adhesive substrate. To distribute cells with high and efficient loads to precise areas, SFDG dies can be employed. As a result, the SFD has to offer an appropriate substrate for cell adhesion, explosion, differentiation, and migration [17, 18] to allow the transport of nutrients and substances, waste, and signalling factors. Cell survival processes are biological processes. The substrate material should cause little to no immunological and/or inflammatory responses *in vivo* and should biodegrade at a controlled rate that is close to the natural rate of TR. Tissue-engineered SFDs must communicate the chemical and physical signals required to guarantee appropriate tissue progress since they are designed to be constructed by cells. To advance tissue repair and TR, proteins and growth factors can be delivered with or without cells using synthetic polymeric substrates. The key specifications for a perfect tissue-engineered SFD namely biometric [19-21], biodegradability [22], good mechanical assets [23], macro/microstructure with a high surface area-to-volume ratio appropriate for cell/drug binding [24], interface conformance [25], porosity [26], nature [27], processability into the proper shape as needed with [28, 29], discharge kinetics [30], binding affinity [31], and stability [32].

Types of SFDs

For clinical applications, a wide range of biomaterials are available. 3D SFDs must be developed, made, and used to regenerate tissue in a way comparable to the anatomical structure and function of the tissue or its original agency for the unused or repair to repair and regenerate lost or impaired tissues and organs. This article describes many SFD types, such as porosity SFDs, MSP-SFDs, HGL-SFDs, fibrous SFDs, bio-ceramic polymer composite SFDs, and cell-free SFDs (fig. 1) [33-35].
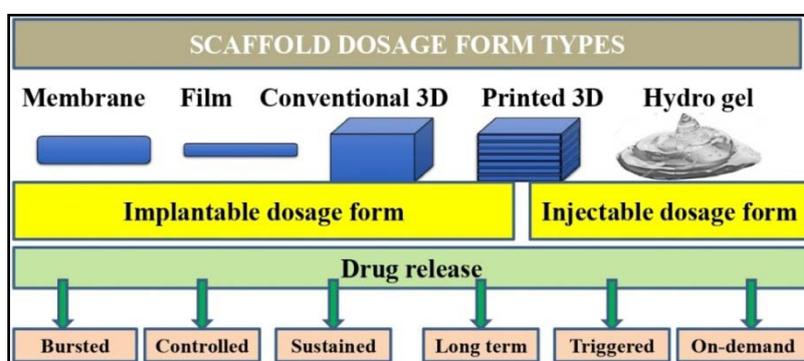

Fig.1: Types of Scaffolds and their pattern of Drug release

Porous SFD

The greater the porosity TE can benefit from a 3D polymeric porous SFD with a consistent network of interconnecting pores. Sponges and porous media have been employed in TE applications such as host tissue increase, bone regeneration, and visceral vasculature. Their porous network mimics an extracellular matrix (ECM) design, which allows cells to efficiently interact with their surroundings. Even though foams and sponges are structurally more robust than truss systems, their application is still restricted due to the open space throughout the SFDG [36]. The polymeric foam SFDG method offers various potential benefits for proliferative or adherent cell lines, including [37].

Scaffold for Tissue Engineering (SFD) plays a vital role in TE and regenerative medicine. It provides a surface for cell attachment, facilitating their growth and development. The porous and permeable structure of the SFD enhances nutrient delivery to the tissue. It also helps regulate clump size, preventing the formation of necrotic cores. By controlling bubble formation, the SFD's pore structures can be tailored to specific requirements. Additionally, for applications such as artificial blood vessels or peripheral nerves, structural advancements and improved pore connections are essential. Overall, SFDs offer critical support for TE, promoting cell integration and the formation of functional tissue structures.

A precise 3D form was required, which necessitated the advance of complicated extrusion technology and tactics of glueing foam layers to the appropriate shape. Cells and tissues have different optimal pore sizes. Porous SFDs with particular pore size, porosity, surface area to volume ratio, and crystallinity may be created. The pores in the controlled porous discharge device are broad enough to facilitate drug diffusion. As porous SFDG materials, BDL synthetic polymers such as Polylactic acid, polyglycolic acid, polylactic glycolic acid and polycaprolactone etc. are employed. Solvent casting and particle filtering have been developed to offer better control of porosity and pore diameter than conventional production processes. The most recent advancement in the subject is a cutting-edge approach for electrospinning porous SFDs made of nano-and microscopic BDL fibres.

HGLs SFD

HGLs have become more indispensable in the ground-breaking subject of TE, where they are utilized as media to drive the creation of new tissue, over the last decade. The creation and deployment of BDL-HGLs have meaningfully enhanced the potential influence of HGL materials in the biomedical industry, allowing for promising breakthroughs in controlled delivery and applications [38].

HGLs are made up of natural macromolecules that have the potential for biological, cell-controlled breakdown, and intrinsic cell-cell interactions. They can vary in mass and have a narrow and limited range of mechanical features. Synthetic polymers, on the other hand, may be made with precisely regulated musters and functions. HGLs are BCL because they are architecturally comparable to the macromolecular components of the body.

Gels develop when the network is covalently cross-linked. HGLs are formed from synthetic or natural polymers that are joined together with covalent or non-covalent linkages. TE HGLs must fulfil several design requirements to operate correctly and stimulate the expansion of new tissue. These criteria include both traditional physical metrics (such as attenuation and mechanical qualities) and biological activity parameters (e. g., cell adhesion). To maximise TEG, it is widely understood that the pace of disintegration of the tissue SFD must match the rate of various cellular activities [39].

As a result, the degrading behaviour of all BDL HGLs must be properly considered, predictable, and controllable via the HGL's chemistry. BCL HGLs are being employed in cartilage wound healing,

bone construction, wound dressings, and as drug delivery carriers. HGLs containing growth factors can directly assist cell progress and differentiation in freshly created tissues. In general, HGLs promote cell motility, angiogenesis, high water content, and efficient nutrient transport.

HGL-SFDs have been intensively researched for application in connective tissue auxiliary engineering, owing to their biochemical similarities to connective tissues highly hydrated GAG components. Natural [Collagen, gelatin, fibrin, alginate, and chitosan (CSN)], derived (PLA) and synthetic (polyethene glycol and PVA) polymers [40].

Fibrous scaffolds

The creation of NFBs has increased the requirement for tiny SFDs that can mimic the gathering of natural human tissues. There are currently 3 ways to make NFBs: electrospinning, self-assembly, and phase parting. The most focus has been placed on electrospinning, which also looks to hold the most promise for TE uses. Research into the likelihood of using shuffle and phase-separated NFBs as SFDs for TE [41, 42] has garnered little notice. Due to their high surface charge ratio and microporous building, NFBs are ideal for TE uses because they encourage cell adhesion, growth, migration, and differentiation. NFBs are employed as SFDs for designing musculoskeletal tissue, such as bone, cartilage, skeletal ligaments and muscles, skin, blood vessels, and nerve TE, and as medication delivery and protein and DNA control vehicles. In medical applications, natural and synthetic polymers such as collagen, gelatin, CSN, fibroin silk, poly lactic acid, polyurethane, polycaprolactone, poly lactic glycolic acid etc. like fibre SFDs are being investigated. Mixing is a common method for functionalizing NFBs. However, most polymer NFBs lack particular functional groups and must be functionally considered before they can be used. Physical mixing and coating are the most popular and straightforward tactics for altering NFBs. Surface graft polymerization has also been employed in the accessory of ligand molecules and adhesion proteins to surfaces [41].

Microsphere scaffolds

The expansion of TE SFDs built on MSP has attracted a lot of attention lately. MSP setups offer stiffness for interface TE and are regionally and temporally adjustable. In addition to other advanced TEs uses like gene therapy and the use of antibiotics to heal diseased bones, MSP rigs are widely used as medication distribution systems [42]. The impact of nanotechnology on SFD design and the potential for creating growth factor continuous-discharge formulations using MSPs. MSPs are commonly used in drug packing as a polymeric building to help drugs discharge progressively over time. High-molecular-weight polymers can be used to produce MSP for a prolonged drug discharge profile due to their dense construction, whereas low-molecular-weight polymers are used to make porous MSP for fast drug release. For consumers of restricted substances, injectable MSP has also been developed [43]. One advantage of using MSP as building blocks is the simplicity of production, control over the shape and physicochemical properties, and control over the timing of the encapsulated material release. Thermal sintering, solvent vapour behaviour, solvent/non-solvent sintering, and solvent-free sintering processes were all used to create MSP-based SFDs.

To achieve the enhanced integrated bone and cartilage interface obligatory for this application, a particle aggregation technology is presented to create a two-layer SFD for osteocyte TE. Polylactic acid microsphere scaffolds are in the trabecular bone range, implying that porous MSP matrices have the potential to be employed as SFDs for creating load-bearing bone tissues. The sintered microsphere seems to be a promising SFD for bone remodelling. Sintered MSP can create inter-pore bonding and the proper 3D pore dimensions. In both gel MSP and cemented MSP, cyclic permeable rallies were made by randomly encapsulating PLAGA MSP. Additionally, complex MSPs are used to create ceramic polymer composites for use in bone use. Microsphere scaffolds made from CSN were created [44].

Polymer-bioceramic composite scaffolds

The creation of composite materials for TE is intriguing because their features can be couturier to the physiological requirements of

the recipient tissue by changing the volume proportion, shape, and reinforcement step tactic. Ceramics used in the manufacture of implants can be categorised as non-absorbable (relatively dormant), bioactive or surface responding (semi-inert), or BDL or re-absorbable (non-inert). Inert bioceramics include materials like carbon, zirconia, silicon nitride, alumina, and zirconia. Pottery made of coralline, plaster of Paris, concentrated poly amino hippuric acid (PAHs), and TCP, as well as those made of aluminium and calcium phosphate, may reabsorb compounds. Concentrated PAHs and some glass pottery are semi-typical (bioactive). Ceramics are renowned for their high tensile strength, superb interoperability, and resilience to corrosion. Brittleness, poor tensile strength, difficulty in manufacturing, limited physical dependability, lack of robustness, and high density are all downsides of ceramics [45]. Ceramics utilized for these reasons are thus designated as bioceramics [45]. Polymers are often soft and lack strength and rigidity, but inorganic materials like ceramics and glass are considered to be too hard and brittle.

Composites with better physical assets are produced when polymers and inorganic phases are combined because of the enhanced stiffness and strength that inorganic materials have by nature. Second, the disintegration behaviour of bioabsorbable polymers can be changed by the addition of bioactive phases to the substrate.

Maintaining strength and surface stability throughout degradation and auxiliary by natural host tissue, as well as an adaptation from resorption rate to body TR rate developed for rigid tissue implants and tissue-engineered SFDs due to their excellent study in calcified tissue due to biologic, bioactivity, and bioavailability, were complications during the expansion of bioceramic polymer composite SFDs [46].

The highly porous polymer/ceramic hybrid substrate appears to be a promising substrate for bone TE because of its better physical and osteogenic assets. SFDs made of poly lactic acid composites have good hard tissue biologic, draining, and bioactivity. Composite media facilitate seeding, cell growth, and uniform tissue creation. Bioceramics, the primary inorganic module of native bone, are used frequently as SFDG materials for bone healing. Examples of these materials include calcium phosphate (CP), hydroxyapatite (HAP), and tricalcium phosphate (TCP) with polylactic acid, collagen, gelatin, and CSN [47].

Acellular SFD

Creating a fake MTX or physically and chemically mining cellular apparatuses from the tissue to produce collagen-rich substrates are two ways to create a tissue MTX. These substrates slowly degrade during injection and are typically replenished by ECM proteins released by ingesting cells. Any demyelination therapy's main goal is to abolish all cellular matter while keeping the remaining ECM's makeup, mechanical stability, and bioactivity intact. Physiological backdrop SFDs that are similar to those found in real blood arteries were produced using molecular biological SFDs. In genital tissues like the urethra and bladder, the tissue MTX has been shown to promote cell expansion and renewal without resulting in immunogenic rejection. The progress of urethral tissue in rodents used the ureteral cell substrate as an SFD. The cellular bladder foundation in rodents serves as a scaffold for the growth of the host bladder wall constituents. Because the association of the proteins (such as collagen and elastin) in the cell MTX is well preserved and routinely ordered, the mechanical features of the cell MTX are not suggestively different from the mechanical features of the natural bladder substrate. To create the substrate, the bladder tissue's entire cellular makeup is mechanically and chemically eliminated [48].

Effective tissue architecture requires careful SFD choosing. Biological structures have been replicated in several kinds of synthetic BDL polymer SFDs to rally them, but cell-free SFDs have the following advantages over other varieties of SFDs:

Cellular SFD for TE possesses key characteristics for effective TR. It retains the correct anatomical association even after decomposition, preserving tissue structure. The SFD maintains the native ECM architecture and incorporates cell adhesion ligands, promoting cell

attachment and interaction. By excluding cellular modules through meiosis, immune responses are reduced. Additionally, the degradation process promotes biomechanical qualities comparable to natural tissues, ensuring the long-term functionality of tissue grafts. These attributes make Cellular SFDs valuable tools in TE, enabling the regeneration of functional tissues with native-like properties.

Animal models for TE have successfully used extracellular matrices of different kinds, and products like depolarized cardiac valves, small intestine submucosa, and bladders have been discovered. It now has the legal right to treat patients who are humans. The fact that this SFD is made up of ECM proteins, which are broadly distributed throughout the body, is advantageous. The macromolecular coating can expand the mechanical stability and protein substrate compatibility of tissue-derived cell-free SFDs. A bio/macromolecular composite material served as a starting point for TE [49]. These hybrids may take the form of intricate gatherings like heart valves built from depolarized pig aortic valves and covered with a BDL polymer.

Fabrication tactics

Cells and tissues are agreed in a 3D architecture within the human body. To build these tissues and organs, SFDs must be built using various technologies that allow cell distribution and direct their expansion in space-time. The primary tactic for producing SFDG is described below.

Solvent-casting and particulate leaching tactics

The two methods that are most frequently utilized to create tissue-engineered frameworks are solvent casting and granulation. In this method, soluble salt particles (such as NaCl and sodium citrate) are mixed in an aqueous solution with BDL polymers. The slurry is then shaped into the appropriate form using a mould. To create a permeable arrangement, the salt particles must first be desiccated or lyophilized to remove the solute. This method has the advantages of being easy to use and allowing for adequate control of pore size and porosity based on the salt-to-polymer ratio and the added salt's molecular size. Create BDL polymer platforms using this method to construct exoskeletons.

Thick 3D scenes are challenging to construct because solvent particles are tough to remove from the polymer arrangement. Most permeable materials are separated by spraying dispersion, and the thickness of the granulation is restricted to 0.5 to 2 mm. The granulation and homogeneous expansion of the tissues are further hampered by the constriction between their pore networks [50]. Small fragments of the poly lactic glycolic acid/salt composite material are broken down into thinner patterns by pressure, which subsequently decomposes the salt to deliver the platform prerequisite for bone tissue design studies in the biological reactor (fig. 2). Cell growth and mineralization were always constrained outside the frame, which scientists attribute only to the enhanced transport situations [51].
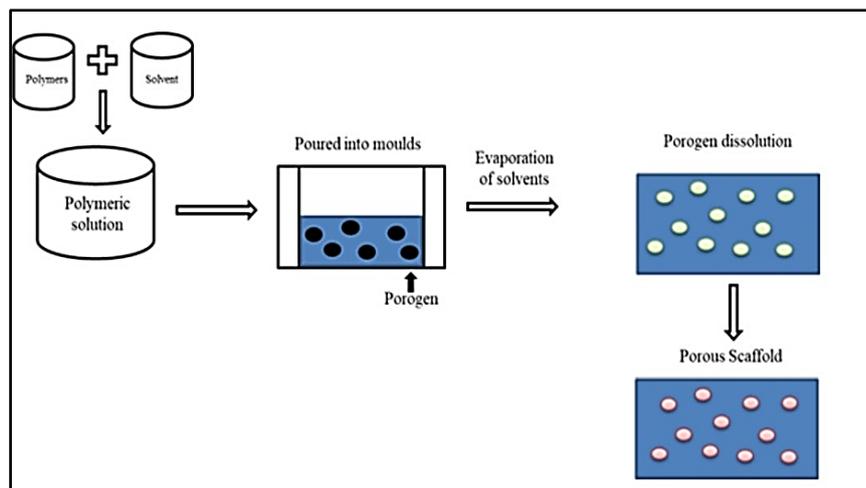

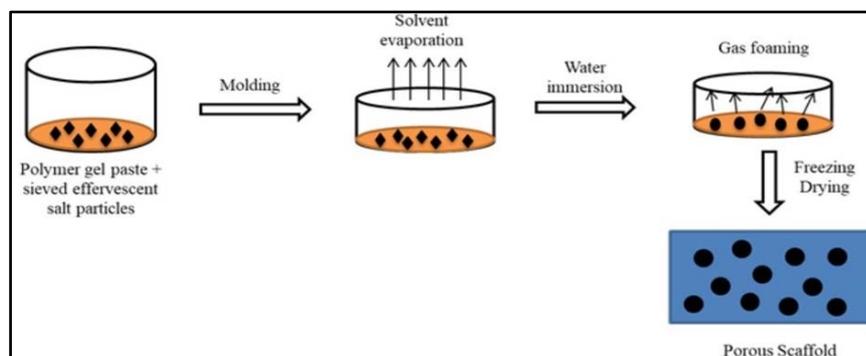
Fig. 2: Depiction of solvent casting [51]

Fig. 3: Depiction of the gas-foaming process [52, 53]

Gas-foaming process

Without using organic solvents, the gas-foaming tactic may be utilized to foam polymers with remarkable penetrability. Carbon

dioxide (CO_2) is frequently employed in this technology as a particular agent for the improvement of polymer foams. High CO_2 weights are supplied in strong polymeric rings to enable CO_2 saturation in the polymer. Therefore, the quick discharge of CO_2

from the polymer framework, brought on by nucleation and gas progress in the material, is what causes the thermodynamic instability [52]. By using this tactic, polymer sponges up to 93 n in porosity and 100 m in pore size may be created (fig. 3).

Electrospinning

Electrostatic energy is used in the electro-spinning process for rebar planning to produce polymeric fibres from the nano to the microscale. A strong electric field between two anodes with opposing charges regulates this process. The polymer planning is on one end, while the header is on the other. In most cases, a drop of arrangement is framed by injecting a polymer organisation. Following that, an electric field is generated, which is expected to deliver energy, causing the resulting particles to work against the organisation's surface deformation. After the NFBs have been recorded in the collection, a polymer plane is shot, generating the fibres as the dispersion starts to evaporate as a result of the plane's layout. Electrospinning employs more than 200 polymers, comprising gelatin, collagen, CSN, and silk threads[53]. The electro-spinning tactic is related to how the NFB is agreed upon in the field of tissue synthesis. When employing polymers, the practice is very adaptable, non-invasive, and doesn't need the use of clotting science or high temperatures for the fibre process. Fundamentally, in this way, a charged polymer array or fusing plane is created using high voltage and frames the polymer fibres by curing or cementing. This method may produce a skeleton with a noteworthy accessory part that is personalised to cell expansion and subsequent tissue linking, which is one of its main advantages. It can create ultra-fine fibres with meticulous pore geometry, a high aspect ratio, and a rare introduction. These appearances, which directly disturb cell binding, cell expression, and the delivery of more oxygen to the cell, are better for cell growth than those found *in vitro* and *in vivo*. This creates an environment in space where new tissues may develop and function physiologically. The foundation of mining energy innovation is cell seeding. The production of concordant biofilm or cryo spinning which enables the construction of space in the electrode array of the necessary size, overcomes this (fig. 4).
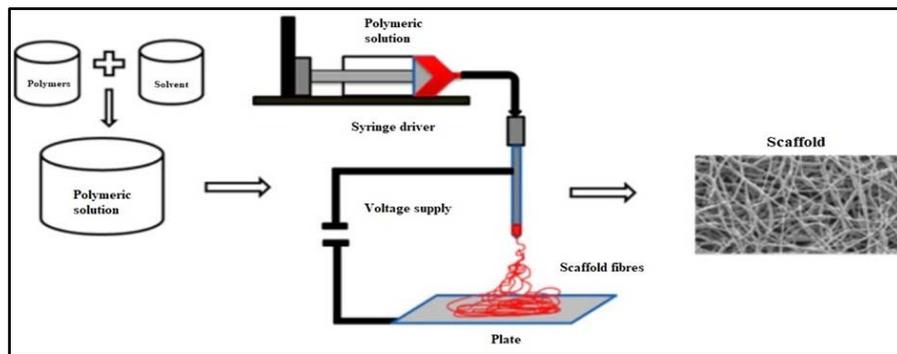

Fig. 4: Depiction of the electrospinning process [53, 54]

Porogen leaching

One of the best-known methods for placing substrates with regulated porosity is the leaching of the porogen. The porogen dispersion in liquid particles or powdered materials through a method of dissolution, crosslinking, or other reactive liquid that may be bonded is the only basis of the particle filtration approach. In a genuine framing method, these poisons serve as stand-ins for pores and pore-to-pore interactions. Using this technology, a deep permeable frame with porosity up to 93% and a pore breadth of up to 500μ can be installed. The main objectives of this process are to identify larger pore areas and join holes. The primary benefits of this method are its simplicity, versatility, and ease of control over pore size and shape. Pore size is regulated by sifting Porogen molecules to a certain size, and pore form is regulated by specifying a shape for particular Porogen specialists [54, 55].

The fact that this tactic may easily generate thin sheets or films up to 3 mm thick and that it is very challenging to define frames with accurate holes between the supports is one of its major limitations (fig. 5).
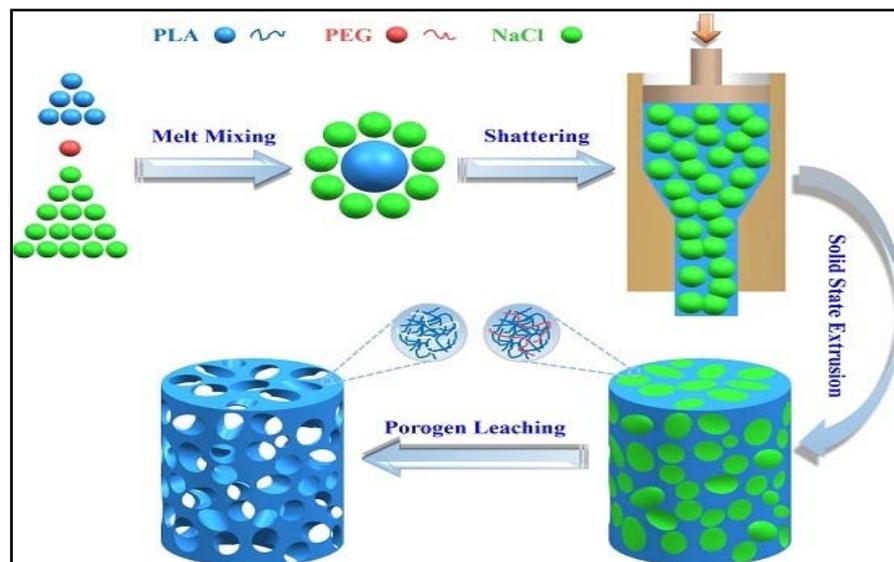

Fig. 5: Depiction of porogen leaching process [55]

Fibre bonding

The producer of polyglycolic acid SFDs was the one who initially invented the fiber bonding tactic. They benefited from the fact that this polymer is readily available as a staple and consequently as a lengthy thread. For instance, Poly lactic acid was applied to the Polyglycolic acid fibres and removed after the polyglycolic acid was immersed in a solution, chilled, and dried. SFDs were made by attaching a collagen MTX to the polyglycolic acid polymers using collagen fibres as thread. Fibre bonding tactics have two primary advantages: a high surface area to volume ratio that makes them ideal for TE uses and a high porosity that delivers more surface area for cell accessories and enough space for MEC renewal [56]. The limitations include low mechanical integrity, lingering organic solvents, a lack of basic stability, the capacity to only produce tiny films, and the fact that not all materials are right for all applications. It is challenging to manage the membranes' porosity and shape in both measures (fig. 6).
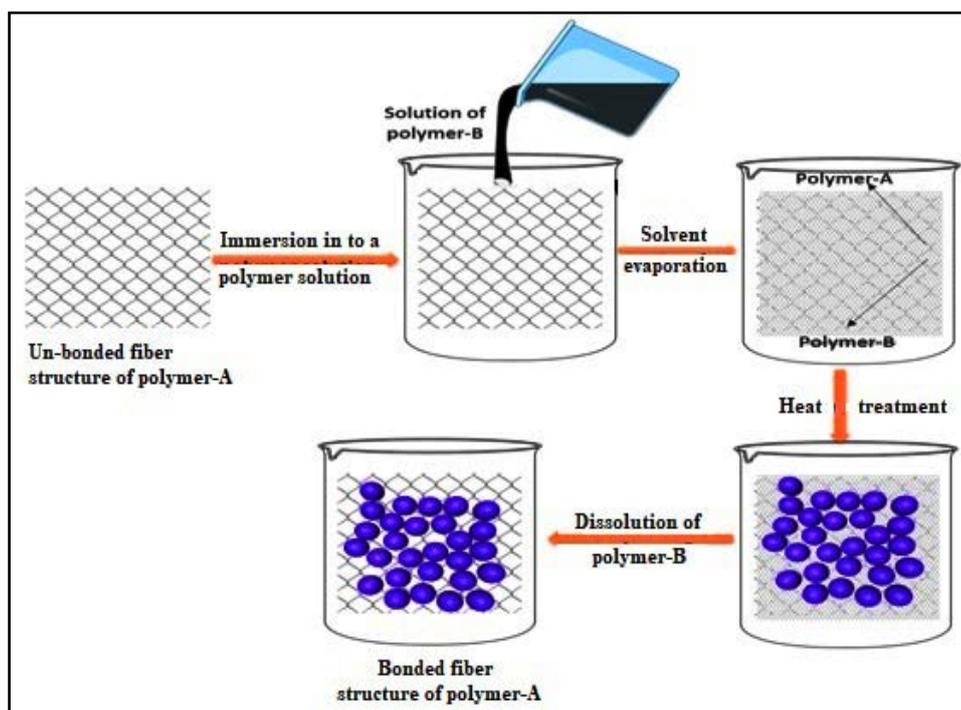

Fig. 6: Depiction of the fibre bonding process [56]

Fibre mesh

The wire mesh method creates SFDG by weaving or entangling minuscule threads in a 3D model with a variety of pore diameters. A non-woven fabric made of a separate polymer is covered with a polymer solution, which is then poured on top of the fabric and evaporated. Polyglycolic acid was the first degradable polymer and BCL to be spun and utilised as a synthetic bandage. Due to the large surface area and rapid diffusion of nutrients that are good for cell viability and growth, this tactic has a high cell binding capacity. One of the main shortcomings of this tactic is the absence of mechanical stability. Heat-induced drying of the polylactic acid fibres can be used to solve this issue and enhance the edifice's crystallinity and orientation [57].

Self-assembly

The random organisation of a molecule into an ordered building essential for a particular purpose inside a given system is known as self-assembly. When organic or synthetic molecules shuffle from microscopic strands, NFBs are created. Amphiphilic peptide sequencing is a popular tactic for constructing 3D NFB assemblies for TE. The weak non-covalent interactions between the hydrophobic and hydrophilic domains of these peptides in an aqueous solution result in notably fast HGL recovery and anaerobic interactions with water when the molecules collide. Diblock polymers can shuffle to form synthesised polymer NFBs instead of peptides (AxBy). When the two blocks are incompatible and separate in large quantities, the volume growth of A and B can be measured to create a nanometric-diameter cylindrical domain B embedded in MTX A. NFBs may also shuffle from polymer dendrimers. Triblockdiand peptide ampholytes (PA) have an assembly like that of a rod [58]. As a result, a novel method for regulating pH and modifying the peptide head group of APs to shuffle APs into NFBs has been devised.

Rapid prototyping (RP)

Another name for the RP is "solid-free prototyping." This approach to producing SFDG is more complex. It is a computer-controlled manufacturing tactic. The stacked manufacturing method allows for the rapid production of 3D objects. In RP engineering, an SFD model is frequently created using computer-aided design (CAD) tools and then depicted as a series of cross-sections. The RP machine will position layers of material under each cross-section, beginning at the bottom and working their way up one layer at a time, to construct the SFDG. In a normal example, a patient's bone defect can be made as a 3D CAD computer model [59].

The model can then be broken down into slices or layers by the computer. RP methods with unified deposition modelling (FDM), selective laser sintering, 3D printing, or embossing are used to build 3D things layer by layer. Another advantage of this method, which is now better at producing the proper attribute frames due to RP dates, is the creation of highly reproducible planned apparatuses and component variations. RP has an advantage over other production methods because it can control the MTX design (size, form, alignment, branching, geometry, and orientation) that gives a simulation edifice. Biological, with a wide variety of patterns and materials. It has the skill to control the mechanical assets, biochemical effects, and rates of SFD degradation.

Sol-gel tactic

When inorganic metal salts or organometallic compounds are liquefied in a solvent, a sequence of hydrolysis and polymerization

processes results in the expansion of a colloidal suspension, which is how SFDs are made. The wet gel that results from pouring the soda into the mould is then further dried and heated to produce thick porcelain or glass goods. Due to its excellent chemical homogeneity, low dispensation temperature, and capacity to regulate particle size and shape, the Sol-gel technology has lately grown in popularity [60].

Materials made from sol-gel are good substrates for many different organic and inorganic chemicals. The capacity of doped sol-gel materials to maintain the physical and chemical assets of the doping material is one of their key qualities. The advantages of sol-gel technology may be leveraged to create laser materials, biological sensors, and delayed delivery. The drawbacks include expensive raw material costs, substantial shrinkage after dispensation, hydroxyl and carbon residues, and health risks from prolonged exposure to organic solutions.

Melt moulding method

To create SFDs, hazardous materials (such as sodium chloride and sugar crystals) are melted with polymers or ceramics; once the mixture has cooled, porosity is created by dissolving the porogen in water. Last but not least, the foam truss is often freeze-dried. The compression moulding tenet was introduced in 1995. Teflon moulds are used with gelatin and PLGA-MSP of a certain diameter. The mould is heated at PLGA's glass transition temperature while the mixture is being compressed. The PLGA particles bind with one another as a result of this process. The SFD is cleaned by soaking the gelatin in water once the mould has been removed, and it is then dried. The positive aspect of this technology is the capability to independently adjust porosity and pore size, as well as the macroscopically noteworthy form, alignment, and geometry of pores, all of which are critical for nutrition and waste metabolism. "From one gap to another." The requirement for a high temperature

for the unformed polymers and the remaining porogen is a limitation [61].

Membrane lamination

Another SFF-like method used to create anatomically accurate SFDs made of cyclically BDL polymer foam is membrane lamination. Lamination is produced during production by solvent casting, washing the beads, and layering peptides and proteins. After being soaked in a solvent, appropriately shaped films were layered in temporal assemblies with a continuous pore edifice and morphology. The final 3D SFD's bulk features are comparable to those of the individual membranes. Since computer-aided modelling may be utilized to create the model with the essential implant form, this technology creates porous 3D polymeric foams with a specific anatomical shape. The lamination of the foam sheets results in reduced inter-pore bonding, which is a drawback of this technology. Another drawback is that only one thin film may be utilized in the process, which lengthens the process [62].

Freeze-drying

Porous SFDs are made using the freeze-drying process. The sublimation theory serves as the foundation for this tactic. To create a solution with the necessary concentration, the polymer must first be softened in a solvent. A high-porosity, high-crosslinking substrate was created by glacial the solution and lyophilizing it under a high vacuum to remove the solvent. These methods are used on a variety of polymers, counting blended silk proteins made of PGA, PLLA, PLGA, and PLGA/PPF. The pH and freezing rate both affect pore size; a rapid glacial speed results in smaller pores. To create a consistent 3D pore building, skilful solidification in one direction was achieved. This method's primary aspect is that neither high heat nor a separate washing phase is necessary (fig. 7). The smaller pore size and lengthy dispensation time are this tactic's limitations [63].
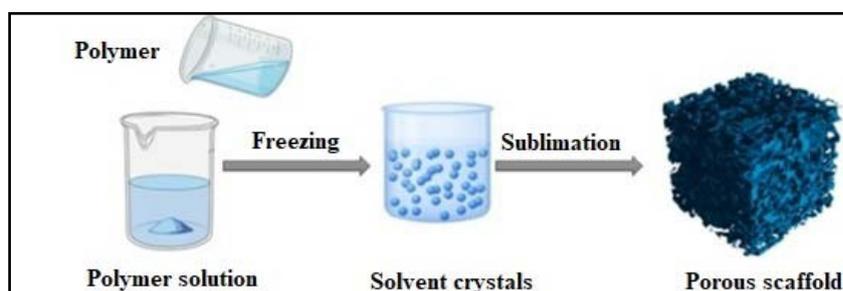

Fig. 7: Depiction of the freeze-drying process [63]

Freeze extraction and freeze gelation tactic

To produce a 3%-by-weight polymer solution, PLGA and PLLA were liquefied in dioxane. A beaker containing the polymer solution was frozen at 20 °C. The frozen solution is subsequently processed to extract the solvent using cryogenic parting. Below is a description of the glacial measures. The frozen polymer solution is submerged in a previously cooled 20 °C ethanol aqueous solution. It should be mentioned that during the creation of the PLLA, the ethanol concentration was 80% by weight, and for the PLGA, it was 30% by weight. The solvent (dioxane) is removed and swapped with an aqueous solution of ethanol, a solvent-free agent for PLLA and PLGA due to the miscibility between the two[64]. After removal, the aqueous ethanol solution that was present in the polymer MTX was jettisoned by drying at room temperature. After the drying process, the PLLA and PLGA mesh may then be produced. The goal of thickening parting tactics is to disregard the solvent through solvent-free removal. Upon removing the solvent, the solvent without solvent fills the original area occupied by the solvent, and the solvent without solvent is then positioned around the polymer. In this situation, the polymer won't dissolve even at room temperature. As a result, drying at ambient temperature may be used to remove air, creating a vacuum that turns into a void on the SFD. It should be stressed that the extraction is carried out at a temperature below the freezing point (FP) of the polymer solution

to ensure that the polymer won't suffer further deterioration during the process. The solvent-free solution must have a lower FP than the polymer solution to remain liquid throughout the drawing out. The solvent-free solution used in this research was an aqueous solution of ethanol, and this solution's makeup can distress its FP. When removing dioxane from the frozen solutions of PLLA and PLGA, the uncooled reservoir (aqueous ethanol solution), with the proper composition, is in a liquid state. It is difficult to excerpt the solvent (an aqueous solution of acetic acid) from CSN without any solvent.

Supercritical assisted phase inversion method

A high-pressure phase inverter, a specially designed tool for this purpose, was used for phase reversal studies (pressure converter; controller; TICT temperature controller; FM thermometer; pressure regulator). Each experiment involved placing a stainless steel stopper with a diameter of 2 cm inside a high-pressure receptacle along with a tiny amount of the polymer solution. The beaker was heated using an electric thin-band burner (OGDEN), which is associated with a temperature controller that maintains the temperature at 1 °C (TC). A high-pressure piston pump is used to feed carbon dioxide into the receptacle up until working pressure is reached (P200A Thar Technologies). The pressure inside the receptacle is measured using a pressure sensor (P). The machine was shut down for 45 min to enable phase parting. To guarantee

that the SFD dried completely, the system was flushed for a further 45 min while using a very low flow rate of carbon dioxide (5 g/min) measured with a flowmeter [61].

Powder compression

Trusses are created by compressing polymers or ceramics with the use of balls, punches, or dies. The compression ratio of the bullet, punch, or die is altered to get the essential porosity in the powder consolidation. Sintering is an alternative to uniaxial or isostatic pressing in this tactic [65].

Heat-induced phase separation

Schugens originally used Thermally Induced Phase Separation (TIPS) on Poly (lactic acid), (PLA) rigs, and several other researchers followed suit to create composite rigs. It includes the advancement of solid-liquid or liquid-liquid phase parting. The polymer must first be liquefied in a liquid, and the resulting fluid must then be cooled to a specific temperature. Quenching causes phase parting into a polymer-rich phase and a polymer-poor phase. In particular, TIPS induces phase parting by using heat energy as a latent solvent. The separated solutions must next be lyophilized to eliminate the solvent [66].

SFD drug delivery with BDL polymers

The BDL polymer is used when the majority of the material is put where it is mandatory and is used for temporary barriers, organisational reading, tissue adhesives, and tissue adhesion in addition to DDS. Each of these uses requires data with physical, chemical, biological, and biological features to create effective medications. In contrast to typical bone healing, polymers used in bone regeneration must be BDL, BCL, and non-normally driven. There are 3 primary types of BDL polymers [natural (collagen), synthetic (poly(hydroxy acids) or their combination] [67, 68].

Natural polymers for drug delivery

Excellent biometric compliance and both features may be found in natural polymers. They can also create chemical changes and hydroelectric gel when employed in low amounts. These polymers are quickly rejected by the recipient's cells when utilized as a graft. Additionally, the SFDG's assembly and porosity may be altered during construction because of the polymer's fibrous properties. Collagen [69], CSN [70], Hyaluronic acid [71], alginate [72] and fibrin [73].

Synthetic polymers for drug delivery

Synthetic polymers are used as transporters of peptides, medicines, genes, proteins, and other substances in TE and drug delivery. Synthetic polymers are Inert and break down into harmless byproducts. Poly (lactic acid), poly (lactic, glycolic acid), poly (caprolactone), and polyethene glycol are the manufactured polymers most frequently used in TE is polyethene glycol. Recent research on SFD tactics in drug delivery is as per table 1.

Table 1: Past successful attempts made on SFD tactic in drug delivery

Drug	Polymer	Targeted tissue	Reference
Aceclofenac	CSN	TR	[74]
Allicin	CSN and polyvinyl alcohol (PVA)	Diabetic wounds	[75]
Calcium phosphate	Sodium alginate (SA)	TR	[76]
Dexamethasone	PLGA	Bone regeneration	[77]
Dexketoprofen and trometamol	CSN and PVA	24h drug discharge in chronic and non-healing wounds	[78]
Erythropoietin	Polylactic acid and polyethene glycol	Endothelial cells	[79]
Fluconazole	Nanocellulose and gellan gum	Vagina	[80]
Fluconazole	HPMC, PAA	Vaginal formulation, Freeze-dried SFDs	[81]
Furosemide	HPMC	Buccal, epithelial cells	[82]
Gentamycin	CSN	Bones	[83]
Glutaraldehyde	CSN	Bone tissue	[84]
Graphene oxide	CSN	Cartilage tissue	[85]
Hyaluronic acid	Poloxamer-407 and Polysorbate-80	Non-viral gene delivery	[86]
Ibuprofen	PVA	TR	[87]
Ketoprofen	Polycaprolactone (PCL)	Bone regeneration	[88]
Lornoxicam	Polylactic acid	Periapical lesions	[89]
Naproxen and Ibuprofen	Ethyl cellulose and PVA	Nano sponges and precise discharge of drugs	[90]
Naproxen sodium	PLLA and polycaprolactone	TR	[91]
Norfloxacin	CSN	Foot ulcers, pressure sores	[92]
Prednisolone	Hyaluronic Acid	Osteoarthritis	[93]
Quercetin and voglibose	PVA and PEG	Regulated discharge	[94]
Raloxifene HCl	Cellulose	Bone regeneration	[95]
Simvastatin	Soyabean lecithin and CSN	Diabetic wounds	[96]
Squalene-Loaded Topical Agar	Agar	burnt skin tissue defects	[97]
Telmisartan	Polycaprolactoone/gelatin	Vascular	[98]
Tetracycline HCl	CSN and hydroxyapatite	Measured discharge	[99]
Thiazolidine-4-one	CSN	TR	[100]
Tricalcium phosphate	Calcium carbonate, Alginate	Growth factor. releasing bone impact	[101]
Xanthane	CSN	Anti-diabetic	[102]

Evaluation

Drug excipient compatibility studies

The most widely adopted dosage form for SFD is micro/nanoformulation (NMFS). The compatibility of the drug and the excipients were tested by DSC, power XRD and Fourier transform infrared (FTIR) spectroscopy tactics.

In vitro biomineralization assessment

In a synthetic bodily fluid (SBF) for 14 d at 37±0.5 °C, the bioactivity of the NMFS was assessed in terms of apatite development on the NMFS surface. Following incubation times, the samples were cleaned, disinfected, and desiccated for 24 h at 60 °C in an oven. The study of morphological alterations was done using scanning electron microscopy (SEM), FTIR, and X-ray diffraction (XRD) [103, 104].

In vitro degradation and porosity measurement

NMFS's *in vitro* breakdown was examined using simulated body fluid (SBF) at pH 7.4 without any enzymes. Following a 28-day immersion in 20 ml of SBF solution, the NMFS was removed, carefully rinsed in distilled water, dehydrated at 60 °C, and measured. Utilizing the following method, the NMFS's weight loss (rate of deterioration) was calculated (eq.1) [36].

$$\text{weight loss the SFD}(\%) = \frac{(W_i - W_f)}{W_i} \times 100 \text{--- (1)}$$

Where Wi is the initial dry weight of the NMFS and Wf is the final dry weight of the NMFS after immersion.

According to the prior procedure, the solvent auxiliary tactic with absolute ethanol was used to govern the porosity of the drug-loaded NMFS. After 48 h of immersion in ethanol, the NMFS was fully saturated, and weight readings were taken. The weight of the air-dried NMFS was used to calculate the permeability of the NMFS using the following algebraic formula (e. q.2) [105]:

$$Porosity(\%) = \frac{(M2-M1)}{\rho V} X100---(2)$$

Where M_1 is the mass of the NMFS weighed before immersion, M_2 is the saturated wet weight after immersion in absolute ethanol, ρ is the density of ethanol, and V is the volume of the NMFS.

Entrapment efficacy

The drug-loaded NMFS were dispersed in a fluid that solubilizes the drug, soaked for an extended period, and then sonicated for 10 min to break up the complex. Following the appropriate dilution and analysis using UV spectroscopy or HPLC (e. q.3)[106, 107].

$$Entrapment\ efficiency = \frac{Actual\ drug\ content}{Theoritical drug\ content} X100--- (3)$$

Microscopy

To examine the morphology of the NMFS, the surface is examined by SEM and transmission electron microscopy (TEM) [108].

Particle size

Size and polydispersibility index (PDI) measure the particles by using a zeta sizer with a mass choice particle sizing software, dynamic light scattering can be used to calculate the particle size and PDI. A measure of breadth within the range of particle sizes is the PDI. While PDI is greater for samples with a wider particle size distribution, it is smaller for monodispersed samples [109].

Zeta potential

In particle-size devices, a second electrode can be used to detect zeta potential. Zeta potential can be used to define a particle's surface charge [110].

***In vitro* drug discharge studies**

The capsule filled with MSP/nanoformulation was allowed for dissolution at 37±0.5 °C, using a USP-I apparatus. The receptacles were turned at a 50 rpm pace. The dissolving medium was composed of 0.1N HCl for the first 2 h (900 ml) monitored by phosphate buffer pH 6.8 from 3-12h. A UV spectrometer/HPLC was used to measure the concentration of the drug at a specified wavelength after 5 ml aliquots were taken out at various periods and filtered through the Whatman filter paper [111-113].

***In vitro* drug discharge kinetics**

To regulate the drug discharge pattern and process, the drug discharge data from the dosage form was matched to kinetics models, with zero order, first order, Higuchi, Korsmeyer peppas and Hixson-Crowell [114-116].

Table 2: Marketed SFD Products and their research applications

Marketed sfd products	Recent research application
Apligraf	A synthetic skin product. The fibroblasts in the dermal substitute help produce ECM proteins, while the keratinocytes in the epidermal layer contribute to re-epithelialization and barrier function.
Bionect, and Jossalind	Viscoelastic gel for surgery and wound healing. This allows them to adhere to the wound surface, provide cushioning, and promote tissue healing.
Biomed	Used in the regeneration of periodontal tissue. Periodontal TR involves the restoration and regeneration of the supporting structures of the teeth, including the gums, periodontal ligament, and bone.
CryoSeal	From a single unit of a patient's blood plasma, the creation of autologous fibrin adhesive components. During this process, the cryoprecipitate, which is rich in fibrinogen and other clotting factors, separates from the plasma. The cryoprecipitate is then processed further to obtain a fibrin adhesive that can be used for medical purposes.
CultiSpher-G	Used as microcarrier cell culture. The surface of CultiSpher-G microcarriers is typically coated with a biocompatible material, such as collagen or gelatin that promotes cell adhesion.
EmbryoGlue	It contains high concentrations of hyaluronan, a substance naturally found in the female reproductive tract. Hyaluronan is thought to mimic the natural conditions of the uterus, providing a sticky and nurturing environment that supports embryo attachment and implantation. The medium also includes other components that help maintain embryo viability and support the implantation process.
Forta-Derm	Antimicrobial wound dressing. It contains antimicrobial agents, such as silver or other active ingredients, that have been shown to have broad-spectrum activity against a range of microorganisms commonly associated with wound infections.
Gelfoam	Hemostatic device. It quickly absorbs blood and other fluids, expanding in size and creating a physical barrier that helps to promote clot formation and seal off the bleeding vessels. Gelfoam also serves as a scaffold for platelets and clotting factors, supporting the natural clotting process.
Gelfilm	In neuro, thoracic, and ocular surgery. The film is applied to the dura mater, the protective covering of the brain and spinal cord, to help prevent cerebrospinal fluid leaks and provide support during the healing process. It can be particularly useful in cases where the dura has been damaged or repaired during surgery.
Hyaff	Biomaterial for biomedical applications. It has excellent biocompatibility, meaning it is well-tolerated by living tissues and does not elicit strong immune or inflammatory responses. This makes it suitable for various medical applications, including TE, drug delivery, and wound healing.
HemCon	Forming a blood clot. It consists of a dressing or bandage made from chitosan, a naturally occurring biopolymer derived from shrimp shells. Chitosan has unique hemostatic properties that help accelerate clotting and control bleeding.
Integra	Dermal regeneration. It provides a temporary framework that supports cell migration, proliferation, and the formation of new blood vessels. Over time, the dermal layer is gradually replaced by the patient's cells, resulting in the regeneration of functional dermal tissue.
Natrosol (hydroxyethyl cellulose), Genia Beads MC (microcrystalline cellulose)	It is used as a binder in tablet formulations to improve the tablet's strength and prevent it from crumbling or breaking apart.
Orthovisc, Opegan R, Opelead, and Healon	Intraocular lenses (IOLs) are artificial lenses that replace the natural lens of the eye after cataract removal or for vision correction purposes. They are permanent implants that help restore vision by focusing light onto the retina. IOLs come in different types, including monofocal, multifocal, and toric lenses, each with specific characteristics and applications.
Revitix	Topical cosmetic products used, including creams, serums, lotions, and gels, are designed to provide various skincare benefits such as moisturization, anti-aging effects, skin brightening, or targeting specific skin concerns.

CONCLUSION

In conclusion, tissue engineering is a rapidly evolving field with immense potential for regenerative medicine. The development of scaffold materials and fabrication techniques plays a crucial role in creating suitable environments for tissue regeneration. Polymeric scaffolds, such as PLLA, PLGA, and chitosan, have emerged as promising materials for bone tissue engineering due to their physical and mechanical properties. Incorporating drug delivery capabilities into these scaffolds has shown great promise in enhancing their functionality. Various techniques, including encapsulation, adsorption, and electrospinning, have been utilized to load the scaffolds with drugs. These drug-loaded scaffolds have demonstrated positive outcomes in terms of promoting osteointegration and controlled release of therapeutic agents. However, it is important to acknowledge that further research and optimization are needed, particularly in terms of *in vivo* studies and fine-tuning the release kinetics of growth factors. The development of suitable models and the optimization of drug delivery systems will be critical for future clinical and therapeutic applications.

Indeed, the field of composite bone tissue-engineered scaffolds with drug-delivery capabilities is advancing at a rapid pace. These advancements offer exciting possibilities for tissue regeneration and personalized medicine. The ability to combine scaffold materials with drug delivery systems opens up new avenues for targeted and controlled release of therapeutic agents, promoting enhanced tissue regeneration and healing. By tailoring the composition and properties of these scaffolds, researchers and clinicians can address specific clinical needs and optimize patient outcomes. As research and development continue to push the boundaries of this field, we are moving closer to realizing effective solutions for tissue regeneration and revolutionizing the practice of regenerative medicine. The potential impact on patient care and overall healthcare outcomes is significant, highlighting the importance of ongoing advancements in this promising area of research.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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