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REVIEW

Drug delivery systems for tissue engineering: exploring novel strategies for enhanced regeneration

Julia Lemos de Oliveira · Maria Eduarda Xavier da Silva · Dachamir Hotza · Claudia Sayer · Ana Paula Serafini Immich

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Abstract This study investigates recent advancements in drug delivery systems (DDS) for tissue engineering, emphasizing their role in the targeted and sustained release of therapeutic agents to promote tissue regeneration. It explores innovative approaches, including nanotechnology, 3D printing, and immunomodulation, which enhance the effectiveness of tissue engineering therapies. This review provides a brief overview of the fundamentals of controlled drug delivery, comparing controlled release and slow release. It also introduces drug delivery vehicles, drug release mechanisms, release kinetics, and recent applications in the field of regenerative medicine. It highlights the benefits of nanotechnology, such as increased drug loading capacity and stability, and identifies 3D-printed scaffolds as a promising method for sustained drug release. Additionally, the growing interest in using DDS for immunomodulation to improve tissue regeneration is discussed. The rapidly evolving field of DDS in tissue engineering presents new opportunities for developing more effective therapeutic strategies. This study contributes to the understanding of these innovations and their potential applications.

Keywords Drug delivery systems · Drug release · Therapies · Scaffolds · Tissue regeneration

Introduction

The last few decades have seen the emergence of regenerative medicine, which aims to create functional tissues to repair or replace the function of tissues or organs that have lost their function due to age, illness, injuries, or birth defects. Regenerative medicine also presupposes the growth of tissues and organs in the laboratory and their safe implantation in the body [1].

Achieving the goals of regenerative medicine ultimately requires contributions from many areas, including tissue engineering, cell therapy (using, for example, stem cells), and molecular therapy (therapeutic cloning, gene, and drug delivery) [2–4]. Among these areas, tissue engineering has received considerable attention, presenting itself as a fundamental tool in regenerative medicine strategies [4, 5].

Tissue engineering is one of the most prominent examples of interdisciplinary fields, where scientists

Julia Lemos de Oliveira and Maria Eduarda Xavier da Silva equally contributed to this review article.

J. L. de Oliveira · D. Hotza · C. Sayer · A. P. S. Immich (✉)
Department of Chemical Engineering and Food Engineering, Federal University of Santa Catarina, Florianópolis, SC 88040-900, Brazil
e-mail: ana.immich@ufsc.br

M. E. X. da Silva · D. Hotza
Department of Mechanical Engineering, Federal University of Santa Catarina, Florianópolis, SC 88040-900, Brazil

with different backgrounds work together to boost the quality of life by addressing critical health issues. Tissue engineering is a technique that uses the combining of cells, scaffolds, or biologically active molecules into functional damaged tissues. It is a subfield of regenerative medicine. The objective of tissue engineering is to assemble functional constructs that restore, maintain, or improve damaged tissues or whole organs. Patients have received laboratory-grown tissues and organs made out of their cells, thus eliminating the risk of rejection [6]

The process of fabricating 3D artificial tissues and organs involves several critical steps. First, cell sourcing is performed, which includes the isolation and/or expansion of cells that will provide functionality to the artificial tissues and organs. Next, biomaterial synthesis occurs, where biomaterials are designed to mimic the properties of the mammalian extracellular matrix, providing essential structural support. This is followed by genetic manipulation, where the genetic properties of cells are modified to enhance their function and reduce apoptosis and other adverse effects. In the scaffold cellularization step, cells are combined with scaffolds. Embedded sensors are then incorporated to monitor tissue development and maturation. Bioreactors are subsequently used to deliver controlled physiological stimulation, guiding the development and maturation of the artificial tissues and organs. Vascularization is another crucial step, required to support the metabolic activity of the 3D structures. Finally, the process concludes with in vivo assessment, where the functional performance of the artificial tissues is tested in a living organism [7, 8].

Besides the rapid advancements in various aspects of TE, the field of drug delivery has also made significant progress in biomedical applications. These developments aim to overcome challenges associated with the efficient and controlled delivery of therapeutics [7].

Drug delivery is an emerging application in tissue engineering with significant potential to improve therapeutic outcomes. It involves delivering drugs to specific targets in the body, increasing their effectiveness by delivering medicines precisely where they are needed [9]. Drug delivery systems (DDS) transport active compounds and release them into target tissue. In the drug delivery domain, there is a specific focus on targeted drug delivery, using various approaches to ensure specific delivery and release of drugs at the intended target site [10, 11].

Targeted drug delivery employs strategies to increase delivery specificity, such as ligand-receptor interactions, active targeting using antibodies or peptides, or passive targeting through the enhanced permeability and retention (EPR) effect on tumors [12, 13]. These approaches improve drug accumulation at the target site, reduce systemic side effects, and increase therapeutic efficacy [14]. For example, Wang et al. (2017) designed a hydrophilic dendritic copolymer as a platinum-based drug nanocarrier targeting ovarian cancer, composed of poly(amidoamine)-b-poly(aspartic acid)-b-poly(ethylene glycol) conjugated to cRGD peptide and anthocyanin 5 (Cy5) fluorescent dye [15].

Conventional drug delivery systems may lack specific targeting mechanisms, relying on factors like drug properties and natural distribution processes. While effective, targeted drug delivery systems offer a more accurate and efficient way to deliver medications, especially for localized treatment needs [12].

Small molecule drugs lack tissue and organ specificity, suffer from rapid in vivo body clearance, and are often accompanied by many side effects, especially chemotherapeutic agents, which are generally highly toxic. In recent decades, drug delivery systems (DDS) have been used as one of the most promising strategies to solve this problem [16]. DDS can be described as platforms that carry active compounds and release them into the target tissue to increase the safety and efficacy of the drug [10]. However, traditional DDS may not achieve targeted therapeutic levels and personalized medical treatment [17]. Developing a speedy and highly targeted DDS poses a significant challenge in modern medicine. Overcoming this challenge can revolutionize medical treatments, leading to improved therapeutic outcomes [18].

The primary objective of DDS is to maintain drugs at optimal therapeutic levels in the body throughout treatment. This is achieved by protecting the drug and regulating its concentration within the therapeutic range to reduce the administered dose, the frequency of drug intake, and, consequently, the associated adverse effects. This controlled approach allows for the modification of the drug's kinetic and dynamic properties, leading to more effective and safer treatment outcomes [19].

By using a carrier system, the safety and effectiveness of therapeutic, diagnostic, or prophylactic agents can be enhanced [18]. This is achieved by allowing control over the amount of drug released and increasing the bioavailability of the drug [20]. The protective nature of the carrier system prevents or reduces the rapid degradation of drug molecules, ensuring their stability and potency [21, 22].

Transporters in DDS have multiple functions, including extending the drug's half-life, improving specificity, transporting suitable drug molecules, and preserving the payload until it reaches the intended target site. These functions enable the precise delivery of drugs to specific tissues and cells, minimizing effects on non-target tissues and reducing side effects [16]. Moreover, DDS enhances patient comfort through reduced doses and improves the pharmacokinetics of the drugs. These systems encompass the absorption, distribution, biotransformation, and excretion processes of drugs after administration [22]. Designing controlled DDS involves considering several key factors, including the properties of the drug, the structure of the drug carrier, and the mechanism of drug release [23].

Numerous carriers such as gels, liposomes, cyclodextrins, polymeric carriers, and other materials have been developed for controlled release DDS [24]. Among carriers, many biocompatible and biodegradable polymeric nanofibers and nanoparticles [25] have been reported for drug delivery applications due to their high surface area to volume ratio, highly porous structure, high loading capacity, and controllable release [26–28].

This article aims to summarize recent advancements in DDS within the context of tissue engineering and their potential for developing more effective therapeutic strategies. These systems allow for controlled drug release in response to specific environmental triggers and DDS can be designed to release the drug when exposed to specific conditions, such as changes in pH, temperature, or the presence of certain molecules. This innovative approach provides greater precision and control in drug release, leading to improved therapeutic outcomes.

Additionally, this review article will further explore the use of various materials and processing techniques in the production of DDS scaffolds capable of sustained drug release upon implantation. By shedding light on these innovative perspectives, this study offers valuable insights into the evolving landscape of DDS for tissue engineering. It fosters the advancement of therapeutic approaches that enhance drug bioavailability, mitigate adverse effects, and improve patient well-being within the realm of regenerative medicine and personalized healthcare.

Drug delivery fundamentals

Delivery vehicles

Advanced tissue engineering systems often combine one or more of these three integral components: biomaterial matrices, living cells, and bioactive drugs. Researchers increasingly recognize the need for more spatiotemporal control over the release of drugs that directly or indirectly affect cellular signaling or tissue regeneration. Specifically, there is a growing desire to mimic the inherent complexity of natural tissue by delivering multiple drugs simultaneously, sequentially, or in multiphasic patterns. Researchers hypothesize that having fine control over the delivery of multiple stimuli over time will enhance the speed, quantity, and quality of tissue regeneration [29].

The drug release process to the specific target is a fundamental role of drug delivery, applied to tissue engineering, which is not dependent only on the drug administration route. The delivery systems and vehicles for these drugs are also of great importance in the active compound delivery step.

In tissue engineering, various drug delivery vehicles are utilized to enhance the regeneration and healing processes. These vehicles include polymers, nanoparticles, hydrogels, scaffolds, nanofibers, microspheres and microcapsules, liposomes, and biomacromolecules. These vehicles are designed to optimize the delivery and release of therapeutic agents, ensuring effective and sustained tissue regeneration and repair.

Biomaterials used in the process of tissue regeneration can modify the pharmacokinetics of drugs, resulting in prolonged action duration or delayed absorption. This occurs because the presence of biomaterials in the tissue can alter the way drugs are processed, metabolized, and distributed within the body. Polymers (or other biomaterials) scaffolds play an important role in the drug delivery system, as they will define the physicochemical properties and

drug release profile in the specific tissue target [30] [31–33].

Nanotechnology plays a significant role in the development of drug delivery systems. Nanoparticles are extensively studied and utilized in this field. However, various factors need to be considered when designing such systems. These include the properties of the biomaterial used in the process of regeneration (e.g., biocompatibility, hydrophobicity, rheological and mechanical properties, and chemical characteristics), the administration route (oral, topical, ocular, parenteral, etc.), and the tissue barriers that the system must overcome (e.g., epithelial, mucosal, and endothelial barriers). Nanoparticles have the advantage of easily traversing these barriers due to their small size, offering benefits over conventional administration systems [31, 33].

Hydrogels offer efficient, customizable drug delivery vehicles for various diseases, including cancer and diabetes, with their versatility and diverse applications extending beyond targeted drug delivery [34]. Hydrogels can provide spatial and temporal control over drug release, offering therapeutic benefits due to their tunable physical properties, controllable degradability, and ability to protect labile drugs from degradation [35]. Smart hydrogels, which respond to environmental stimuli, offer less severe side effects, sustained drug delivery, and enhanced convenience and efficiency in cancer treatment [36]. Hydrogels can effectively deliver poorly water-soluble drugs, offering potential therapeutic applications in cancer treatment [37]. Alginate-based hydrogels show potential as drug delivery vehicles for cancer treatment, wound dressing, and bioink in 3D bioprinting [38]. Hydrogels offer versatile drug delivery platforms, with recent advances in "smart"; hydrogels, 3D printing, and microneedles, and polymer-free systems for peptides, small molecules, and colloids [39]. Challenges in hydrogel drug delivery include burst release at administration, limited ability to encapsulate certain drugs, and poor tunability of geometry and shape for controlled drug release [40]

Polymer scaffolds are used as drug delivery vehicles in fields like regenerative medicine and cancer therapy, offering controlled spatiotemporal releases of active compounds [41]. Scaffolds provide a suitable substrate for cell attachment, proliferation, differentiated function, and migration, allowing for high loading and efficiency drug delivery to specific sites [42]. Electrospun polymeric micro-/nanofibrous scaffolds are used as drug delivery platforms for controlled and sustained release of therapeutic agents in situ [43]. Electrospun scaffolds offer site-specificity, lower overall medicinal dosages, and high porosity for precise controlled drug release, making them viable drug delivery vehicles for various biomedical applications [44]

Liposomes are also used as drug delivery vehicles in medicine, adjuvants in vaccination, signal enhancers/carriers in medical diagnostics, and solubilizers in cosmetics [45]. Liposomes are beneficial for stabilizing therapeutic compounds, improving biodistribution to target sites, and minimizing systemic toxicity [46]. Liposomes offer excellent entrapment capacity, biocompatibility, and safety, making them potential drug carriers for oral delivery [47]. Liposomes offer advantages in drug delivery by reducing systemic toxicity and offering biocompatibility and modular properties [48]

Biomacromolecules can also be used as drug carriers in a drug delivery system. The advantage of using these molecules, compared to other vehicles, refers mainly to the ability to perform different functions, since they are present in a natural environment and can provide a reduction in the immune system attack. Proteins, such as albumin and transferrin, are key macromolecules of interest in drug delivery, serving as carriers for drugs and essential nutrients. However, research and application efforts in drug delivery and tissue engineering also focus on polysaccharides and lipoproteins [49, 50]. It is noted that the efficient delivery of drugs to a specific target is not limited to small molecules only. This is due to its tertiary structure, which provides an increase in contact with specific sites, giving these macromolecules greater potency and reduced toxicity. Nevertheless, proteins face certain limitations in terms of their stability. They are prone to degradation in both storage environments and in vivo settings. Factors such as exposure to proteases, fluctuations in temperature, and pH changes within the body can lead to alterations in protein structure and function [51, 52].

Furthermore, certain polymers, particularly natural ones known as polysaccharides, are commonly employed in scaffolds with drug delivery systems. One notable example of a polysaccharide is chitosan, which finds extensive applications across various fields of knowledge. Its adhesive properties,

particularly on mucous membranes, allow for effective attachment, while its ability to penetrate even small intercellular spaces is advantageous. It holds immense potential in wound healing, drug and bioactive molecule administration, and tissue engineering. Moreover, synthetic polymers like poly(ethylene glycol) (PEG) [53] and poly(vinyl alcohol) (PVA) [34] are also valuable in drug delivery systems. These polymers exhibit good biocompatibility and suitable degradability, further expanding their applications in the field [54–58].

Efficient drug delivery to a specific location requires consideration of four crucial parameters. Firstly, the carrier vehicle should remain in the system for an appropriate duration. Secondly, measures should be taken to inhibit or minimize immune system attacks on the drug delivery system. Thirdly, the system must be capable of reaching the target site effectively. Finally, drug delivery at the desired location should be executed efficiently [59].

Targeting the drug in these systems can be achieved through two approaches: passive or active targeting. Passive targeting involves designing a system that includes the drug and carrier to prevent their elimination from the body, particularly through immune system phagocytosis. This allows the drug to be absorbed and eventually reach the intended target site. On the other hand, active targeting involves incorporating specific markers, such as antibodies or receptors, into the entire drug delivery system. These markers facilitate interactions between the drug delivery system and the target cells or tissues, aiding in precise drug delivery to the desired location [60, 61].

Mechanisms of drug release

Each drug delivery system exhibits distinct physical, chemical, and morphological characteristics that determine its release mechanism for drugs or other bioactive molecules. Additionally, the polarity of the encapsulated drug in the scaffold has an impact on its release behavior. Consequently, drug delivery systems can be classified into two categories: matrix systems and reservoir systems (Fig. 1) [62–64].

Matrix systems involve the drug being dispersed or embedded within a solid matrix, such as a polymer matrix. The drug is released as it diffuses through the matrix, with the release rate influenced by factors like matrix composition and structure. In matrix systems, the release of drugs can occur through several mechanisms, including polymer swelling, active diffusion, and matrix erosion, which can be influenced by the

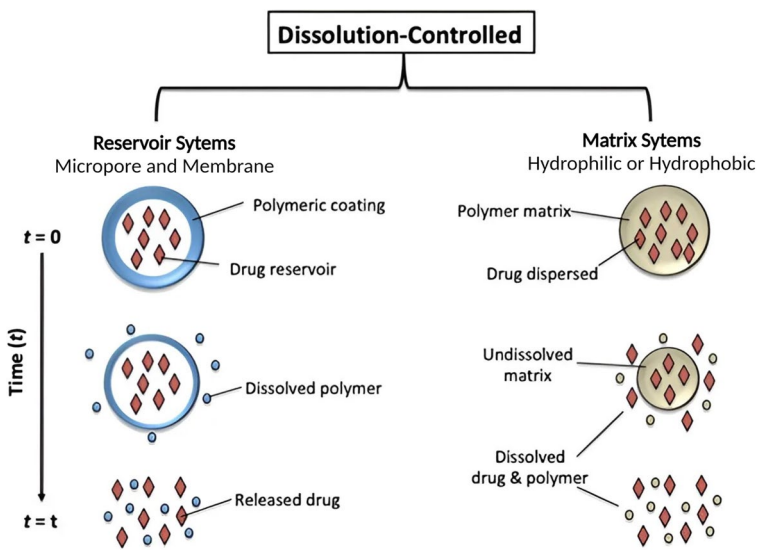

Fig. 1 Classification of drug delivery systems into two categories: reservoir systems and matrix systems. Reservoir systems: micropore reservoir, small pores allow controlled drug release through a membrane; membrane reservoir, drug release is regulated by a semipermeable membrane. Matrix systems: hydrophobic matrix, drug dispersed in insoluble matrix, releasing slowly through dissolution; hydrophilic matrix, drug dispersed in soluble matrix, controlling release by swelling in body fluids. Source: Authors, 2024

hydrophilic or hydrophobic nature of the matrix. In hydrophobic matrices, water-insoluble polymers are used, and when exposed to gastrointestinal fluid, the fluid penetrates the matrix, dissolving the drug within the system. As a result, channels are formed within the matrix structure, allowing for gradual drug release through diffusion. In hydrophilic matrices, the release process involves swelling, drug diffusion, and matrix erosion. When exposed to fluid in the gastrointestinal tract, the polymer absorbs water, causing it to swell and form a gelled layer. The drug within this hydrated layer then dissolves and diffuses or is released when the gelled layer undergoes erosion. The erosion process exposes the polymer to the fluid again, leading to a repeat of the swelling and gelation process, enabling further drug release. The choice between hydrophobic and hydrophilic matrices depends on the desired release profile and the properties of the drug and polymer used in the system [63–65].

Reservoir systems (Fig. 2), on the other hand, consist of a central reservoir or compartment that contains the drug. The drug is released from the reservoir through various mechanisms, such as diffusion, osmosis, or erosion of the reservoir walls. In these systems, the drug is typically coated by a polymeric membrane, which acts as a barrier. The drug is released through diffusion, either directly through the membrane or via micropores present in the membrane, if applicable. The choice of the polymer for the membrane is crucial, as it must have adequate diffusivity to allow the drug to pass through. Another approach for drug release in reservoir systems involves using alternating layers of drug and water-soluble polymer. As the polymeric layer dissolves, the drug is gradually released. The release rate depends on factors such as the thickness of the polymeric film and the specific type of polymer used in the system. These reservoir systems offer a controlled release of the drug, allowing for precise modulation of the release rate based on the design of the polymeric membrane or the thickness of the alternating layers [62, 63, 65].

Scaffolds for tissue engineering can provide different drug release profiles, which can be defined by applying mathematical models. Some mathematical models that can be applied consist of zero-order, first-order, Higuchi, and Hixson-Crowell models. Zero-order kinetics defines the active release process as a constant release from a system; i.e., its plasmatic levels remain the same throughout the release; in contrast, first-order kinetics defines it as a velocity-dependent release of the active concentration. Therefore, the greater the concentration of the drug in the scaffold, the faster its release [66].

The Higuchi model defines drug release based on drug diffusion and can be applied to modified release forms. When the release kinetics follows the Hixson-Crowell model, it is suggested that the release rate of the action is dependent on the dissolution rate of the drug particles (Fig. 3) and not on the diffusion that can occur from the matrix [66].

The choice of the active substance delivery method in a scaffold should take into consideration several factors, including the intended application (target tissue), the route of administration or application, and the scaffold material itself [41]. The release of the drug is dependent on the degradation or breakdown of the scaffold over time, considering the healing time for tissue regeneration. However, caution must be exercised when employing this technique to ensure that the efficiency and biological activity of the drug are not compromised during the binding process with the scaffold. It is crucial to optimize the conjugation

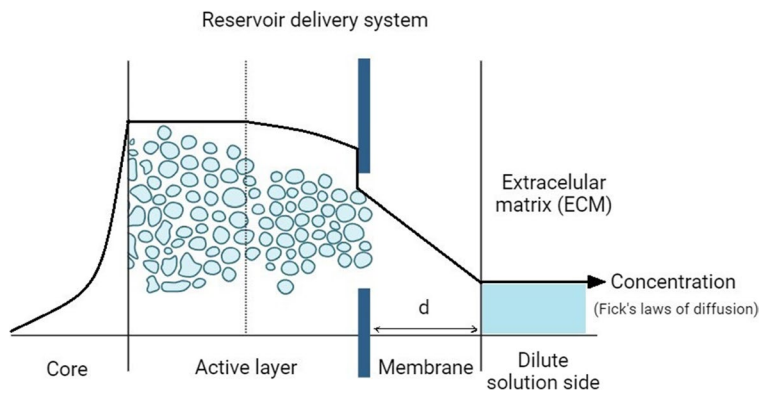

Fig. 2 Mechanism of drug release in reservoir systems. Source: Authors, 2023

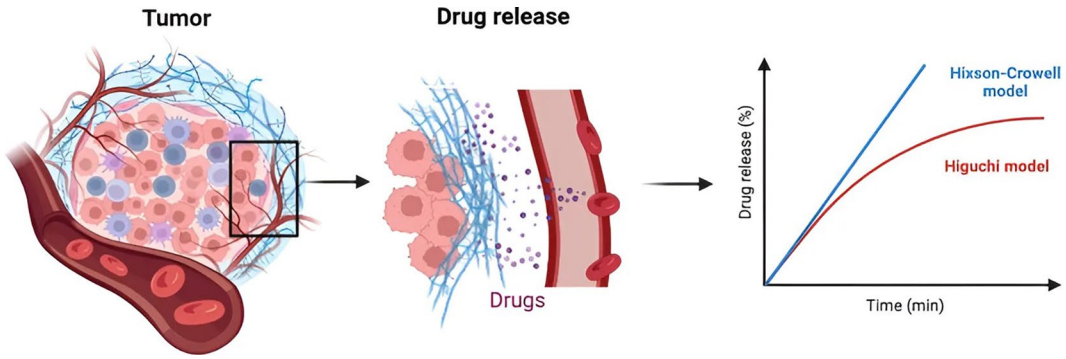

Fig. 3 Drug release based on drug diffusion by Higuchi and drug dissolution by Hixson-Crowell model. Source: created by the authors with Biorender®, 2023

method to maintain the integrity and functionality of the drug inside the scaffold. Moreover, degradation processes induced by covalent bonds can occur, leading to the formation of byproducts that may interfere with the binding of the drug to the target tissue site. These byproducts could potentially impede the drug's effectiveness or cause unintended toxicity in individuals [7, 67].

An interesting aspect to note is the development of thermosensitive scaffolds that can be generated from micelles. These scaffolds enable drug encapsulation, allowing for precise control over the release duration. The release can be triggered by various stimuli, such as changes in pH, magnetism, light, temperature, or even ultrasound. These stimuli facilitate improved targeting of the drug's activity and offer greater control over the dosage [52, 68, 69].

Controlled release vs. slow release

In tissue engineering, the controlled release of drugs from a scaffold can accelerate the local regenerative process and circumvent the concerns over the potential undesired systemic effects of a drug in the body. Drugs must meet a minimum threshold to be effective, but due to their short half-lives in vivo, it is challenging to achieve a relevant dose at the site of injury for an extended period without causing unwanted side effects of over-exposure of cells and tissue that could occur when drugs are delivered systemically [70]. Controlled release of drugs from tissue engineering scaffolds can help establish localized, clinically relevant drug concentrations for extended periods of time. The challenges in the field of controlled release lie in the ability to finely tune the release of the drug without negatively affecting the mechanical or structural properties of the scaffold and without damaging or quickly eluting the drug itself [70].

The development of pharmaceutical forms focuses on achieving rapid release of the active component, whether it is a drug or another bioactive molecule. The goal is to administer the necessary dose for preventing or treating a specific medical condition or disease. In conventional therapy (Fig. 4), a soluble diluent is commonly used to favor the dissolution of the pharmaceutical form, the solid pharmaceutical form, considering that liquid pharmaceutical forms do not go through the dissolution and disintegration step [57, 71]. In this type of delivery system, the active component must remain in a range that corresponds between the ineffective level and the toxic level.

The absorption of a drug consists of the stage in which the active principle reaches the bloodstream, where it will present a maximum peak of dissolution and then begin to decline. The need for a new administration of the drug is a result of the decline in the plasmatic level of the drug so that it does not reach the ineffective level. However, the administration of high concentrations of the drug can cause the peak to exceed the therapeutic window and thus lead to toxicity to patients, or even to a failed therapy since it can induce therapeutic noncompliance by the patient [72] [73].

The modification of the release of active compounds is aimed at reducing the amount of drug administered. In this regard, it is not possible to produce a common pill with high doses of the drug, since this would result in plasma levels that would

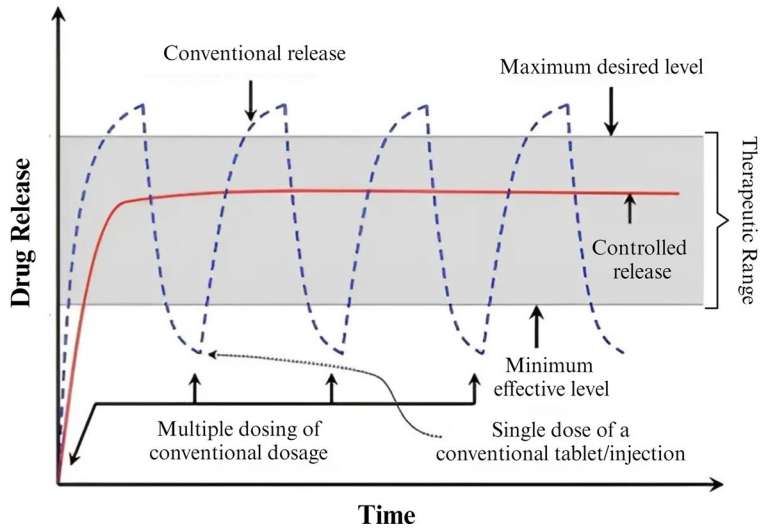

Fig. 4 The representation of drug release shows the difference between conventional release (with various dosages) and controlled release (modified) within a therapeutic range. Source: Authors, 2023

reach the toxic level. These modified release systems have several advantages, such as greater control over the release of the active compound, reduced drug administration, and even directing the active compound to specific targets. Nevertheless, it is important to acknowledge that these pharmaceutical forms also come with certain drawbacks. For example, they may not be suitable for drugs with a short half-life or those poorly absorbed by the gastrointestinal tract. Additionally, in cases of drug intoxication, it may not be possible to quickly halt the treatment, and there is a potential risk of drug accumulation in the body [73].

Sustained release formulations are developed to release the active principle at a predetermined rate, duration, and location, maintaining the plasmatic levels of the active substance within the therapeutic window. Slow-release products (also called delayed release) present a delay in the release of the drug, usually due to an enteric coating, allowing its passage through the stomach, releasing only in the gastrointestinal tract [64, 74]

Yao et al. [75] developed silicate nanoparticles for controlled protein delivery for bone regeneration. Morphogenetic proteins were encapsulated and incorporated into the scaffold and the release of these proteins was evaluated in vitro. The release profiles showed that there was a rapid release at the beginning of the process, which was kept in a sustained way for 28 days. Chen et al. [76] also evaluated the controlled release rate for bone regeneration with the help of hydroxyapatite, due to its good biocompatibility and osteoconductivity. In this study, the authors developed a combination of hydroxyapatite nanoparticles within a biopolymer matrix. The delivery rate of albumin was evaluated at different pH values. The release rate was higher at pH 7.4 than when compared to pH 4.5.

In tissue engineering, the release patterns of drugs in soft and hard tissues differ significantly due to the distinct physiological and structural characteristics of these tissues. The primary difference between drug release in soft and hard tissues lies in the rate and duration of drug delivery. The high vascularization of soft tissues leads to quick drug absorption into the bloodstream and equally rapid clearance, necessitating frequent dosing to maintain therapeutic levels [77]. To address these limitations, modified release systems such as sustained, prolonged, or controlled release are employed. These systems are designed to release the drug gradually over time, maintaining a steady therapeutic level in the plasma. For instance, sustained release formulations allow for a slow, consistent release of the drug, which helps in reducing the frequency of administration and improving patient compliance [29, 78]

In contrast, hard tissues, including bones and teeth, require controlled and localized release systems that can provide sustained therapeutic levels over longer periods, accommodating their denser structure and slower diffusion rates. Due to the lower vascularization, systemic delivery methods are less effective, necessitating localized delivery approaches.

Controlled release systems for hard tissues often utilize scaffolds and nanoparticles to deliver drugs directly to the site of action. These systems can provide an initial burst release to achieve therapeutic levels quickly, followed by a sustained release to maintain these levels over extended periods [29, 78–81].

The goal in soft tissue drug delivery is often systemic, aiming to maintain steady plasma levels, whereas in hard tissue delivery, the focus is more on localized, long-term release to support processes like bone regeneration [82].

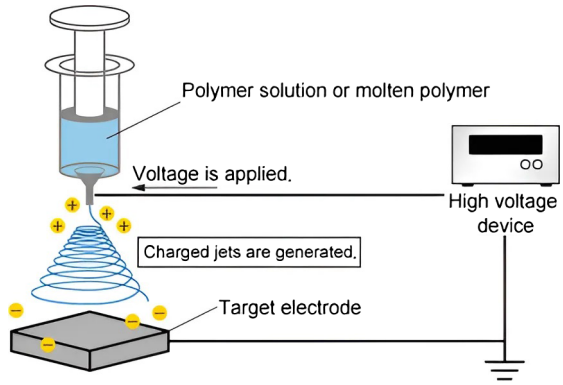

Fig. 5 Mechanism of action of electrospinning in solution. Source: Authors, 2023

Design of drug delivery

Several methodologies can be used in the production of scaffolds to deliver drugs to a given target tissue, the choice being made mainly by the nature of the drug and the polymer to be used in the technique (Table 1).

Electrospinning (Fig. 5) is mostly used in the production of scaffolds for targeted drug delivery and provides fibers with sizes that can vary from nanometers to submicron sizes. Electrospinning in solution, as the name suggests, uses a solvent to solubilize the chosen polymer, while electrospinning by fusion applies a system that supplies heat so that the polymer is in a liquid state. This technique involves the layer-by-layer construction of structures using biopolymers or other suitable materials.

Additive manufacturing, commonly known as 3D printing (Fig. 6), is a widely used technique with significant applications in the field of medicine, particularly in tissue engineering. One of the methods used in 3D printing for producing scaffolds for drug delivery is stereolithography (SL). SL involves the solidification of a photosensitive polymer by applying ultraviolet (UV) light to a resin. This UV light causes the resin to solidify in specific areas as defined by the software used in the printing process [88]. Alternatively, fusion and deposition modeling (FDM) involves the fabrication of scaffolds from a computer-generated surface or solid model. In FDM, a filament is fed into a liquefier, where the polymer is melted at

Table 1 Types of drug delivery techniques

Technique	Description	Ref
Electrospinning	Produces nanometer to submicron-sized fibers for targeted drug delivery scaffolds. Uses solvent to dissolve polymer (solution) or heat to liquefy it (fusion). Enables layer-by-layer construction with biopolymers or other materials	[83]
Additive manufacturing (3D printing)	Used in tissue engineering, especially for drug delivery scaffolds. Methods include stereolithography (SL) and fusion and deposition modeling (FDM). Allows precise control over the scaffold's 3D structure	[84]
Nanoparticle preparation	Various methods were used. Solvent evaporation involves volatile solvent-polymer solution emulsification in water and then solvent evaporation. Polymerization involves monomer polymerization in aqueous medium. Drug encapsulation occurs through dissolution or adsorption by nanoparticles	[85]
Spontaneous emulsification	Combines oil, surfactant, water, and additives to rapidly reduce interfacial tension, dispersing the oil phase in the aqueous phase. Surfactants stabilize droplets, creating a stable microemulsion system	[86]
Ionic gelation	Based on electrostatic interaction between amino groups of chitosan molecule (positive charge) and crosslinking agents like sodium tripolyphosphate (negative charge). Produces natural polymer nanoparticles forming nanoscale coacervates	[87]

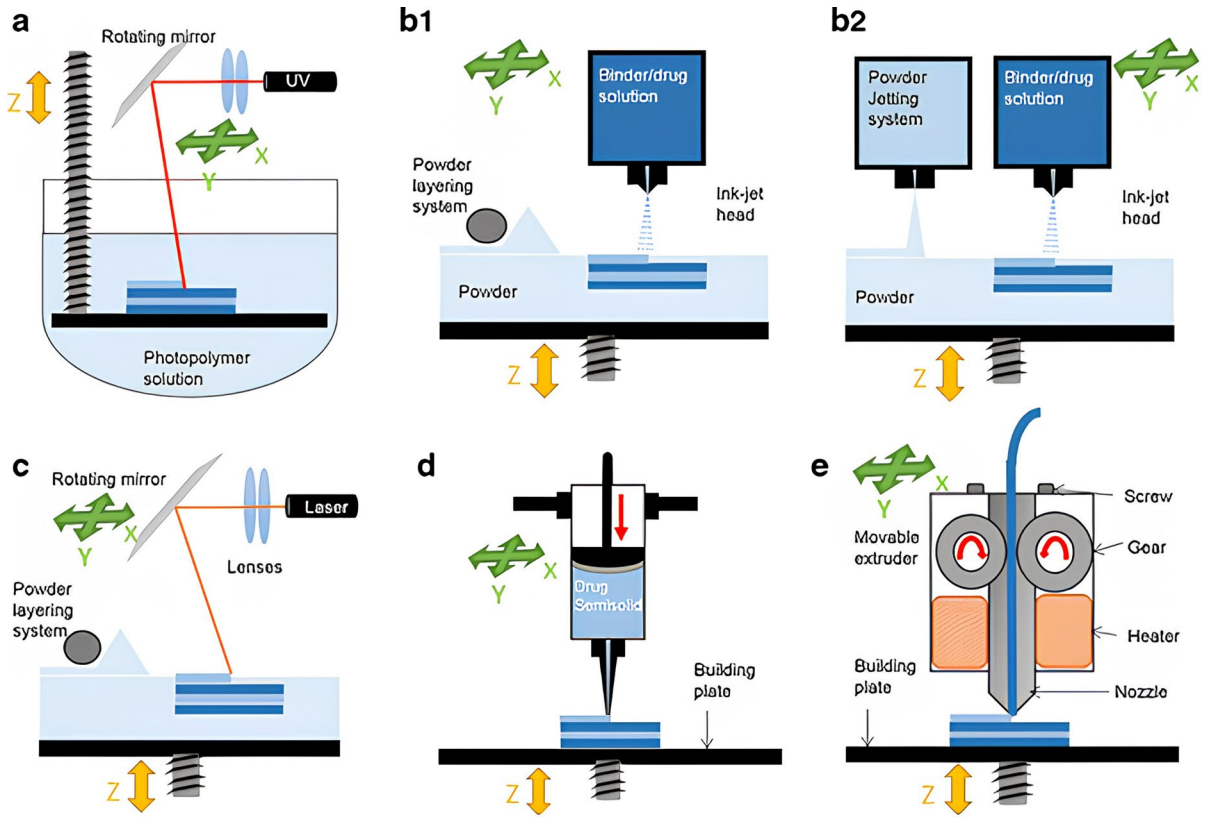

Fig. 6 Mechanism of various 3D printing technologies: (a) stereolithographic (SLA), (b1, b2) powder bed and powder jetting, (c) selective laser sintering (SLS), (d) semi-solid extrusion (EXT), and (e) fused deposition modeling (FDM). Source: [89]

a controlled temperature. The semi-molten polymer is then extruded layer by layer onto a platform, gradually building up the 3D structure of the scaffold [88].

3D printing techniques associated with nanotechnology allowed a breakthrough in tissue engineering research, producing scaffolds from both natural and synthetic materials, such as collagen, alginate, and chitosan, which are natural polymers, and poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(lactic acid-co-glycolic acid) (PLGA) which are synthetic polymers [41, 90]. The techniques for preparing nanostructured systems for drug delivery are varied, such as solvent evaporation, where a polymeric solution is prepared from the selection of volatile solvents, such as dichloromethane, chloroform, or acetate ethyl. The polymer and drug solution are emulsified in an aqueous solution, undergoing subsequent solvent evaporation, forming a stable emulsion that can have its particles reduced to the nanometer scale by the application of high-pressure homogenization or ultrasound [91]. Nanoparticles can be produced by the polymerization method, where monomers are polymerized in aqueous solution. Drug encapsulation can occur through its dissolution in the polymerization medium or adsorb by nanoparticles at the end of the polymerization process [92, 93].

Spontaneous emulsification is a straightforward approach for generating nanoemulsions. This technique entails combining essential ingredients such as oil, surfactant, water, and additives under specific conditions. By rapidly reducing the interfacial tension, the oil phase swiftly disperses within the aqueous phase. Surfactants are employed to stabilize the droplets, resulting in a kinetically stable nanoemulsion system [94]. Nanoparticles of natural polymers can be produced from a technique called ionic gelation, which is based on the electrostatic interaction between the amino groups of the chitosan molecule (positive charge) with a crosslinking agent that has a negative charge, most commonly used sodium

tripolyphosphate, forming nanoscale coacervates [94].

Drug delivery applied to regenerative medicine

Interaction with scaffolds

Cells are usually connected to the extracellular matrix (ECM) composed mainly of bioactive agents, structural proteins, adhesive proteins, and proteoglycan-protein polysaccharide complexes [95]. Tissue engineering provides porous biodegradable scaffolds with growth factors and bioactive agents that mimic the nature of ECM and help in the regeneration/development of various tissues [96]

When it comes to manufacturing methods and drug release profiles, various approaches can be used, including membranes, films, conventional 3D printing, and 3D printing of implants and hydrogel of injectables (Fig. 7). These methods offer different advantages and can be tailored to achieve specific drug release profiles [41].

Biodegradable and biocompatible scaffolds are essential in tissue regeneration, serving as temporary support structures that facilitate cellular growth by using the available nutrients. These scaffolds are also utilized for the delivery of cells, drugs, and genes into the body [41, 97].

In situ tissue regeneration is a promising approach for repairing damaged tissues and organs by utilizing biocompatible scaffolds that support the body's natural regenerative processes. These scaffolds serve as a temporary framework to guide and facilitate the growth of new tissue. Various scaffold types have been developed for different tissue regeneration needs; some common scaffold types are described in Fig. 8.

Those scaffolds are used for medication/drug administration as part of tissue construction, as this structure is highly permeable to allow tissue growth [98]. It provides a suitable substrate for cell attachment, cell proliferation, differentiated function, and cell migration. Scaffold arrays can be used to achieve drug delivery with high payload and efficiency to specific sites [42].

It is highly desirable to trigger and/or regulate the delivery of biological agents (e.g., drugs and cells) with external signals because dynamic control over delivery could potentially improve the safety and efficiency of new therapies [99]. In the field of drug delivery, active biomaterials that respond to external stimuli such as temperature, pH, enzymes, and various physical fields have been extensively explored for controlled delivery [68]. On the other hand, porous scaffolds currently used in tissue engineering and cell therapy are mostly passive as they deliver biological agents primarily through mechanisms involving molecular diffusion, material degradation, and cell migration, which do not allow for dynamic external regulations [100].

The limit loading for release kinetics is characterized as the maximum measure of medication that can be added to the scaffold [16]. Medication must

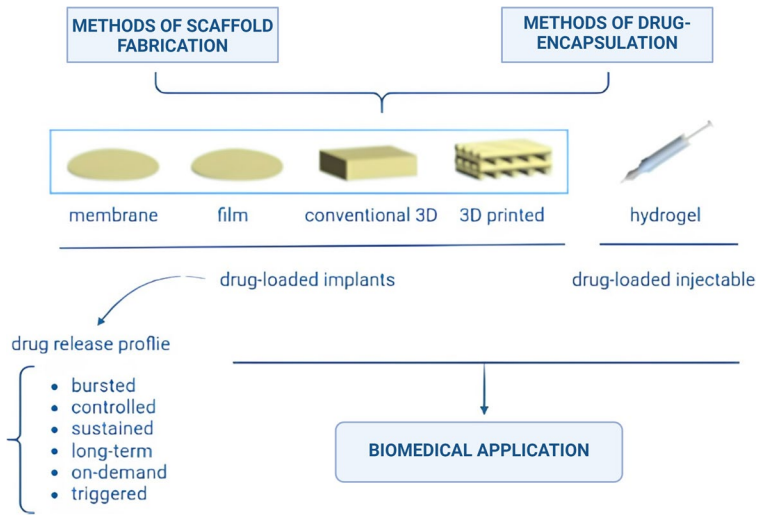

Fig. 7 Methods of scaffold fabrication and drug encapsulation. Source: Authors, 2023

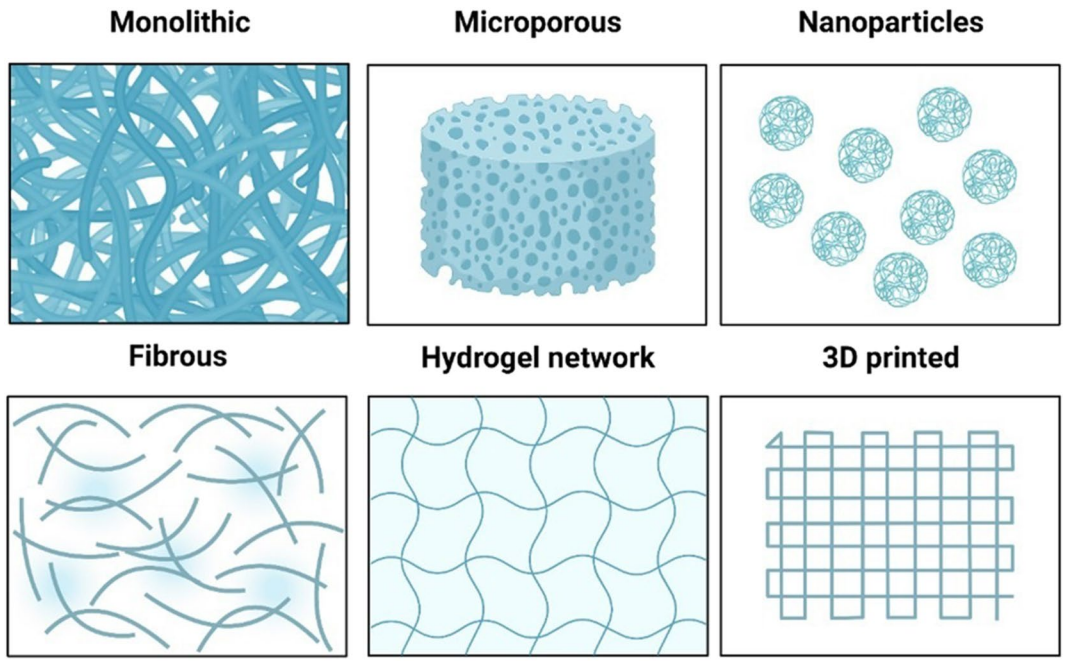

Fig. 8 Scaffold types for in situ tissue regeneration. Monolithic: single, continuous material providing uniform support for cell growth and tissue development. Microporous: scaffolds with small, interconnected pores that enhance cell infiltration, nutrient diffusion, and waste removal. Nanoparticles: composed of nanoparticles for targeted drug delivery and controlled release of therapeutic agents. Fibrous: consists of fibrous materials mimicking the extracellular matrix, providing a high surface area for cell attachment and proliferation. Hydrogel Network: water-swollen, crosslinked polymer networks that create a hydrated environment similar to natural tissues. 3D printed: customizable scaffolds fabricated using additive manufacturing techniques, allowing precise design and complex structures for specific applications. Source: Created by the authors with Biorender®, 2023

be dispersed evenly across the structure or in discrete regions and must maintain a strategic distance from an underlying disruptive impact. The discharge of drugs from the structure must be controlled to allow proper medication measurements to reach the cells over a given period.

The biomaterials used to manufacture the scaffold can be natural polymers, such as alginate, proteins, collagen, gelatin, fibrin, and albumin, or synthetic polymers, such as polyvinyl alcohol and polyglycolide [101]. Bioceramics such as tricalcium phosphates and hydroxyapatites have increased enthusiasm as drug carriers due to their conductivity and biocompatibility [102].

Interaction with cells

Currently, only a few targeted DDS can achieve high targeting efficiency after intravenous injection, although several surface markers and targeting approaches have been developed. In this way, cell-mediated drug delivery targeting systems have received considerable attention for their greater therapeutic specificity and effectiveness in treating the disease [16]

This emerging field includes the encapsulation of drugs within cells or adhered to the surface and subsequent transport throughout the body. Another approach involves the genetic engineering of cells to secrete therapeutic molecules in a controlled manner [103]. Next-generation systems integrate synthetic biology knowledge to generate therapeutic gene networks for highly advanced sensory and output devices. These developments are very exciting for the drug delivery field and could radically change the way biological medicines are administered to patients with chronic diseases [104].

Pharmaceutical success lies in the ability to target drugs to specific sites of tissue injury, tumors,

or infections with minimal toxicity. Immunocytes, encompassing mononuclear phagocytes (dendritic cells, monocytes, macrophages), neutrophils, and lymphocytes, exhibit remarkable mobility, enabling them to traverse impermeable barriers and release therapeutic agents at sites of infection or tissue damage. Consequently, immune cells can be harnessed as Trojan horses for drug delivery, offering a promising strategy to precisely deliver medications to desired locations while minimizing off-target effects [105].

The use of cells as delivery vehicles presents a valuable approach that enables targeted drug transport, extended circulation times, and reduced toxicity to cells and tissues. These innovative systems for drug transport and targeted delivery represent a novel disease-fighting strategy that is being applied across a wide range of human disorders [106]. The design of nanocarriers for cell-mediated drug delivery may differ from those used for conventional drug delivery systems; however, involving different defense mechanisms in drug delivery may open new perspectives for active drug delivery [107].

Drug delivery through the skin is an attractive alternative route to conventional drug delivery systems such as oral and parenteral. It offers many advantages over other routes of administration because it is a non-invasive drug delivery system that maintains the drug level within the therapeutic window for prolonged periods, prevents drug degradation in the gastrointestinal tract, eliminates the first-pass effect, offers easy application, and improves patient compliance and acceptability of drug therapy [16, 108].

Cell-mediated drug delivery for treating cancer (Fig. 9) is an emerging field that harnesses the unique properties of cells to target and deliver therapeutic agents specifically to tumor sites. This approach involves engineering cells to carry and release anticancer drugs directly to the tumor, enhancing drug efficacy while minimizing systemic toxicity [109].

The advantages of cell-mediated drug delivery for cancer treatment include targeted delivery, prolonged drug release, reduced systemic toxicity, and the potential to overcome biological barriers that limit drug access to tumors [16]. However, there are challenges associated with this approach, such as the immune response to the administered cells, cell viability and retention at the target site, and the engineering and scalability of the cell delivery systems [110].

In a study by Khiev et al.'s group, they assessed that nanomedicine offers considerable opportunities to improve pharmacology and reduce toxicity for tumor therapy. However, the application of nanomedicine has met with little success in clinical trials due to multiple physiological barriers to drug administration [111]. The application of circulating cells in conjunction with nano-drug delivery systems offers significant potential for enhancing the physical delivery of drugs and augmenting their therapeutic effects. Circulating cells possess excellent biocompatibility, low immunogenicity, extended circulation times, and strong binding specificity, which enable them to effectively overcome various biological barriers [27].

Extracellular matrix

The extracellular matrix (ECM) is a complex network of proteins, glycosaminoglycan, and other molecules that provides structural support and regulates cellular functions in tissues and organs. ECM components interact with cells through specific signaling

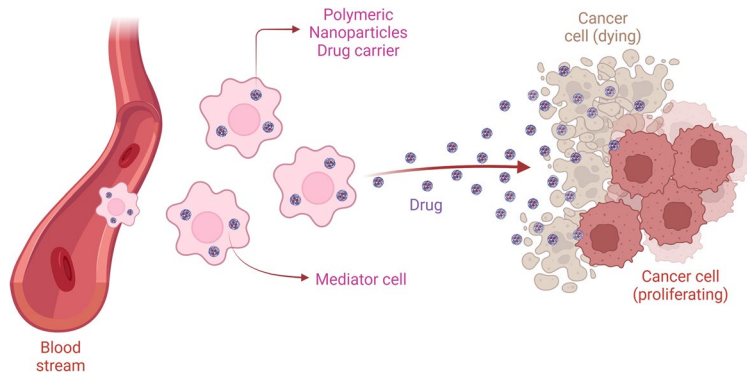

Fig. 9 Mediation of drug delivery by cells for treating cancer. Source: created by the authors with Biorender®, 2023

pathways, and aberrations in these interactions can lead to various diseases and disorders [112, 113].

In drug delivery, the ECM presents a significant challenge as it can limit the penetration and distribution of therapeutic agents to the targeted cells and tissues. However, recent research has shown that targeting the ECM and its biological signals can enhance drug delivery efficacy and improve therapeutic outcomes [114].

One approach is to use ECM-targeting ligands, such as peptides and antibodies that can bind to specific ECM components and facilitate drug delivery. For example, integrins are a family of cell surface receptors that bind to ECM proteins, and targeting integrin with ligands has been shown to enhance drug delivery to cancer cells and improve treatment efficacy [115].

Another strategy is to use ECM-degrading enzymes, such as matrix metalloproteinases (MMPs) that can cleave specific ECM proteins and promote drug penetration. For example, liposomes loaded with MMPs have been shown to enhance drug delivery to tumor cells by degrading the ECM and increasing liposome penetration [116].

Additionally, the use of biomimetic materials that can mimic the structure and function of the ECM has gained significant attention in recent years. These materials can provide a supportive environment for cells and promote tissue regeneration while also serving as drug delivery vehicles [117]. For example, hydrogels made from ECM proteins and glycosaminoglycans have been developed as drug delivery vehicles for various applications, including wound healing and tissue engineering [118].

Research in this area is ongoing, and new approaches are continually being developed to overcome ECM barriers and enhance drug delivery efficacy. Some recent works in this field include a study by Han et al. [119] that created a novel peptide-based drug delivery system that targets fibronectin, an ECM protein, and enhances drug accumulation in tumor tissues. Another strategy used by Li et al. [120] developed a hydrogel-based drug delivery system using a biomimetic peptide that can mimic the structure and function of collagen, an ECM protein, and promote bone regeneration.

A study by Dalmizrak et al. [121] developed a drug delivery system using exosomes derived from mesenchymal stem cells that can target and penetrate the ECM and deliver therapeutic agents to cancer cells. The research group of Machado et al. [122] studied a nanomedicine platform that targets the ECM and promotes drug penetration using an aptamer that binds to hyaluronic acid, a major ECM component.

Another approach used by Zhang et al. [123] created a liposomal drug delivery system coated with a recombinant ECM protein, fibronectin, that enhances drug accumulation in tumor tissues. And finally, a study guided by Soprano et al. [124] developed a biomimetic nanocarrier made from a self-assembling peptide that can target the ECM and deliver therapeutic agents to cancer cells.

In conclusion, the ECM and its biological signals play a crucial role in regulating cellular functions and can significantly impact drug delivery efficacy. Targeting the ECM and developing innovative drug delivery strategies that can overcome ECM barriers are essential for improving therapeutic outcomes. These studies demonstrate the potential of ECM-targeting strategies for improving drug delivery efficacy in various applications, including cancer therapy and tissue regeneration. The use of ligands, enzymes, and biomimetic materials, along with novel drug delivery systems such as exosomes, shows promise for improving therapeutic outcomes and overcoming the limitations presented by the ECM. The development of novel materials and technologies that can mimic or interact with the ECM will likely continue to be a major area of focus in drug delivery research.

However, further research is needed to fully understand the complex interactions between the ECM and drug delivery systems and to optimize these approaches for clinical use. As new technologies and insights emerge, the field will likely continue to evolve rapidly, leading to more effective and targeted drug delivery strategies.

Applications

Soft tissues

Epithelial tissue

Skin is the largest organ in the human body, accounting for about 15% of body weight in adults. Epithelial tissue has a very complex multilayer structure, mainly composed of three layers: epidermis, dermis,

and subcutaneous hypodermis, which serves as a protective layer against external physical, chemical, and mechanical agents and pathogenic microorganisms [125]. Within the scope of drug delivery systems, many of them act directly on the skin, such as patches, injectable devices, and subcutaneous implants. In recent years, research has focused on treating, closing, and healing wounds and burn treatment, intending to prevent the inflammatory process [126].

Porsio et al. demonstrated that nanoparticles coated with PEG (to make them mucoinert) and TAT peptide (to enhance cell permeation) enhanced both penetrations through artificial cystic fibrosis mucus and across lung epithelial cells [127]. A system developed by Tan et al. uses PEG-coated 170-nm silica nanoparticles that were loaded with cell-penetrating peptide (CPP), penetratin, along with therapeutic peptide. These particles not only penetrated mucus, but also showed improved cellular uptake, exocytosis, and transcellular permeation across mucosal epithelium compared to particles that were able to either penetrate the mucus barrier or contain CPPs [128].

Komori et al. demonstrated that the lymph node can serve as a transplantation site of different tissues and this will reduce the chances of rejection. For instance, hepatocytes and thymocytes transplanted into mouse jejunal lymph nodes induced survival in mice with lethal metabolic disease and restored a functional immune system in athymic mice. While these data suggest that tolerance was induced in these cells, there is no mention of how the transplantation into the lymph node actually altered the immune response [129].

Cartilaginous tissue

Cartilage is present between bone surfaces, a highly specialized region of connective tissue characterized by its unique mechanical properties that offer resistance to wear under high load. Its frictionless surface facilitates the smooth gliding of bone movements. Cartilage is avascular, aneural, and lymphatic. Cartilage regeneration or reparability is poor due to avascularity, sparse and highly differentiated cell population, and slow matrix turnover. In this way, once worn out, it is very difficult to recover the cartilaginous tissue. The cartilage response to injury depends on the severity of the injury, and damage can range from fibrillation to the development of a serious injury [125]. Studies aiming at the localized delivery of drugs are in evidence for disease treatment, including osteoarthritis [130, 131].

Yang et al. developed a 3D bioprinted scaffold containing the aptamer HM69 and TGF-β3. The aptamer was immobilized with a decellularized cartilage extracellular matrix (DCECM) after the carboxyl groups were activated by MES, EDC, and NHS, while TGF-β3 was directly encapsulated into a DCECM/gel methacryloyl (GelMA) bioink [132]. The sustained release testing showed the sequential release of aptamer and TGF-β3. Zhu et al. developed a stem cell-homing peptide SKPPGTSS-functionalized hydrogel to deliver agomir-29b-5p. Agomir-29b-5p attracts to the functional motif sequence SKPPGTSS because of the positively charged lysine. In vitro, agomirs in functionalized hydrogel were released relatively slowly to approximately 70% in 40 days. These results suggest that the combination of encapsulation and immobilization is an effective method to achieve sequential release of multiple drugs [133].

Joshi et al. developed a liposome-based delivery system that was fabricated through microfluidics technology. The hydrophilic agent was loaded in the aqueous phase and entrapped within the lipid bilayer, while the lipophilic agent was loaded with insolvent lipids [134].

Gugoo et al. showed that TGF-β1 and IGF-1 led to greater hyaline cartilage formation with well-organized cellular arrangement in vivo compared to that induced by IGF-1 delivery alone [135].

Qiao et al. developed a trilayered 3D printed scaffold with a spatially varying fiber configuration and biologics for layer-specific tissue induction and applied it to induce osteochondral regeneration [136].

Wang et al. investigated hMSC osteogenic and chondrogenic differentiation induced with BMP-2 and IGF-1 and different carrier systems. In this study, hMSC osteogenic differentiation was most robust in a rhBMP-2/rhIGF-I silk microsphere gel system, but very little differentiation was evident in the corresponding PLGA microsphere gel system. In addition to GFs themselves, different carrier matrices that exhibit distinct GF loading and release properties are also important in determining hMSC differentiation [137].

Hard tissues

Bone tissue

Regenerative medicine applied to bone tissue consists of recovering and/or repairing bones and teeth that have suffered damage. Hard tissues are composed of an organic matrix and an inorganic matrix (Fig. 10), which influences the regeneration process and requires mechanical properties related to the hardness of the material [125]. Research in this area is related to fracture repair [138, 139] and dental surgeries [140].

One approach of bone tissue engineering is to create a bioactive scaffold that provides a local release of osteogenic factors to influence the healing bone. Delivery vehicles such as degradable polymeric scaffolds are therefore an obvious source of investigation, where drugs or bone-influencing proteins can be either covalently bound within the polymer and released as it degrades, or "trapped" between polymer chains giving an initial release of osteogenic factors on implantation. Encapsulated drugs that are released on degradation of a scaffold that forms a physical barrier to diffusion are also utilized [141].

Cho et al. have used a canine mandibular distraction animal model to test the efficacy of chitosan microspheres that slowly release encapsulated human growth hormones. Chitosan spheres loaded with growth hormone (incorporated during their manufacture) were suspended in hyaluronic acid and injected into the implant site. The growth hormone-loaded microspheres appeared to be effective in early bone consolidation in distraction osteogenesis [142, 143].

Witso et al. have impregnated cortical bone allografts with a variety of antibiotics for 1, 10, and 100 h and analyzed their elution rate in vitro (into PBS) over a 7-day period. An increase in the time of impregnation increased the amount of antibiotics released by the allografts. Rat in vivo experiments with the same implants showed effective eradication of *Staphylococcus aureus* [144].

Benghuzzi et al. have utilized a tricalcium phosphate lysine scaffold to locally deliver tobramycin—the effect of which reduced the incidence of infection at a femoral osteotomy by 50% [145]. Galjour et al. have also tested this same drug (delivered locally by incorporating it into a demineralized bone matrix) in a rat femur animal model. No infections were seen in either group, and the inclusion of antibiotics did not have an adverse effect on bone healing [146].

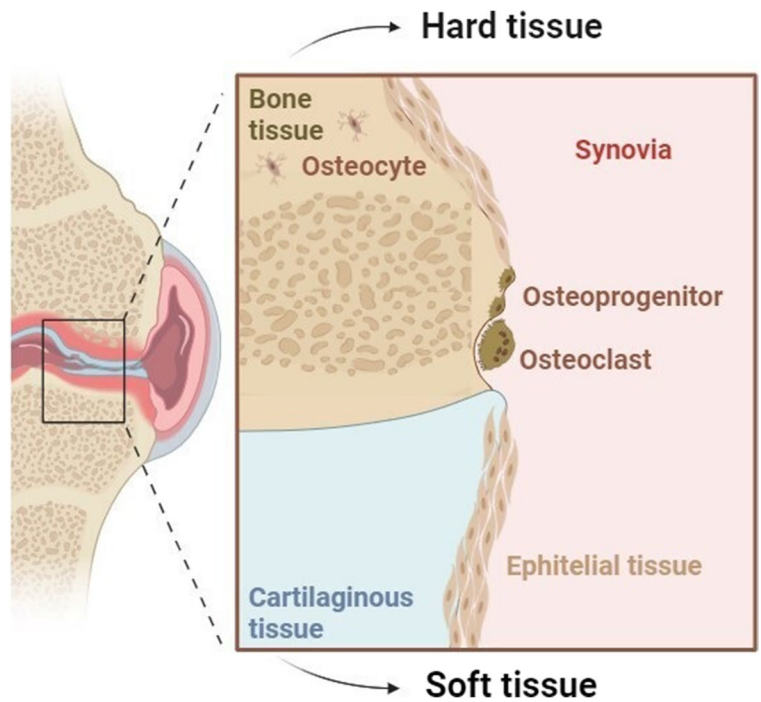

Fig. 10 General scheme differentiating soft from hard tissues. Source: created by the authors with Biorender®, 2023

Hengst et al. have also demonstrated the potential of bisphosphonate delivery to bone sites. They have created a bisphosphonate derivative—cholesterol-trisoxyethylene-bisphosphonic acid as a targeting moiety for liposomes. They have shown that this system binds well to hydroxyapatite and thus could be utilized as a targeting device for drug delivery to bone [147].

Dentin

Dentin is composed of hydroxyapatite, tricalcium phosphate, octacalcium phosphate, amorphous calcium phosphate, and dicalcium phosphate dehydrate, such as bone tissue. Demineralized dentin matrix (DDM) supports osteogenic and dentinogenic differentiation of bone mesenchymal stem cells. Bioactive molecules present in the dentin matrix support dentin formation naturally, especially for trauma and infection which may support the survival, apoptosis, and differentiation of human dental pulp stem cells [125].

Galler et al. showed the development of a customized self-assembling peptide hydrogel designed specifically for dental pulp tissue engineering. The advantage of this innovative system is the possibility of incorporating signaling molecules and the RGD amino acid sequence for cell adhesion to the structure of the scaffold. Additionally, the incorporation strategy involving adsorption of growth factors in porous microspheres with posterior encapsulation with alginate has been investigated [146].

Cordeiro et al. subcutaneously implanted stem cells from human exfoliated deciduous teeth seeded into a poly-L-lactic acid scaffold in human tooth slices in mice and showed the feasibility of engineering well-vascularized pulplike tissue [148].

Richardson et al. reported the earliest dual-release system comprising a PDGF-encapsulated PLGA microsphere and VEGF-incorporated PLGA scaffold composite for angiogenesis. The dual release of PDGF and VEGF showed enhanced blood vessel density and maturation in comparison with static administration of VEGF or PDGF alone. In another study, subcutaneous implantation of basic fibroblast growth factor–, TGF-b1–, and VEGF-incorporated self-assembling peptide hydrogel within dentin cylinders in mice resulted in the formation of a vascularized soft tissue similar to dental pulp [149].

Cancer treatment

Numerous innovative drug delivery methods are revolutionizing cancer treatment. A diverse array of nanoscale compounds, including synthetic polymers, proteins, lipids, and organic and inorganic particles, are being utilized to create advanced cancer therapeutics. Encapsulating drugs within carriers provides several advantages over direct administration, including protection from degradation in the bloodstream, improved solubility and stability, targeted delivery to specific sites, reduced toxic side effects, and enhanced pharmacokinetic and pharmacodynamic properties [12, 150]. Drug delivery systems provide an alternative to chemotherapy, offering localized release that enhances medication efficiency, reduces tumor resistance to treatment, and minimizes adverse reactions in patients [151]. This approach is particularly promising as it allows for a more targeted and effective delivery of therapeutic agents to cancer cells, while sparing healthy tissues from unnecessary exposure to cytotoxic drugs [152].

The utilization of various materials as drug carriers has shown efficacy in cancer treatment, offering specific advantages based on the material type. Carbon nanotubes functionalized with anti-P-glycoprotein antibodies and doxorubicin (CNT-doxorubicin) overcame multidrug resistance in human leukemia cells (K562) [153].

Layered double hydroxides (LDHs) efficiently co-delivered 5-fluorouracil and siRNAs, overcoming drug resistance and enhancing cancer treatment in different cell lines [154]. Intercalating raloxifene into LDH interlayer galleries increased therapeutic efficacy and reduced adverse effects in solid tumors [155]. Iron oxide nanoparticles coated with phospholipid-PEG (superparamagnetic) known as Nano Therm provide treatment via both chemotherapy and hyperthermia for solid cancers [156].

Mesoporous silica nanoparticles (MSN) modified with azobenzene for NIR-activated anticancer drug delivery enabled controlled drug release rates, varying intensity and/or time, suitable for solid tumors [157]. Another pH-sensitive MSN variant for doxorubicin delivery increased chemotherapeutic efficacy and overcame multidrug resistance in solid tumors [158].

Polymeric nanoparticles encapsulating CRLX101, a cyclodextrin-PEG conjugated

nanoparticle with covalently bound camptothecin, showed reduced side effects in lung and ovarian cancer [159]. PEG-PLGA nanoparticles of docetaxel (BIND-014) exhibited controlled biodistribution and targeted tumor accumulation with enhanced efficacy and reduced toxicity in various solid malignancies [160].

Liposomes encapsulating liposomal doxorubicin (Doxil) improved delivery to diseased sites and reduced systemic toxicity compared to free drugs, used in Kaposi's sarcoma, ovarian cancer, and multiple myeloma [161]. Liposomal cytarabine (Myocet) increased delivery to tumor sites and showed lower systemic toxicity, effective in intrathecal lymphomatous meningitis [162]. Liposomal daunorubicin (DaunoXome) also improved tumor delivery and reduced systemic toxicity, applied in Kaposi's sarcoma [163].

Polymeric micelles encapsulating paclitaxel (Genexol-PM) improved drug delivery and reduced systemic toxicity, used in breast, lung, and ovarian cancers [164]. The formulation of PEG-b-poly(α,β-aspartic acid) nanoparticles of paclitaxel (NK 105) exhibited higher antitumor efficacy and significantly lower neurotoxicity compared to free paclitaxel, applied in gastric and breast cancers [165].

Protein nanoparticles, such as paclitaxel-bound human albumin nanoparticles (Abraxane), improve solubility and delivery to tumors, effective in metastatic breast cancer [166]. Paclitaxel nanoparticles conjugated with folate and bound to bovine albumin increase solubility and cellular uptake, specifically targeting human prostate cancer cells (PC3) [167].

Carboxylated PAMAM dendrimers covalently conjugated with cisplatin improve loading efficiency and reduce cytotoxicity, showing significant antiproliferative activity against lung cancer cells (NCI-H460) [168]. Complexation of doxorubicin with cationic poly-L-lysine dendrimers significantly increases therapeutic efficacy in vitro and in vivo in solid tumors [169].

3D printing is another technology widely adopted in manufacturing medical devices and drug delivery systems, including cancer treatments. In cancer drug delivery, 3D printing can develop controlled release systems like hydrogel matrices and tissue engineering scaffolds, enabling the incorporation of multiple therapeutic agents into a single device for controlled and specific drug release, enhancing treatment efficacy, and reducing systemic side effects [170].

Drug resistance is a persistent challenge in medical treatment. Today, combination therapy is emerging as a more effective approach due to its broader target specificity and the synergistic enhancement of treatment efficacy, leading to improved clinical outcomes. This approach, which combines multiple drugs in a single delivery system, has been widely adopted in cancer research and therapy to combat multidrug resistance. Studies have shown that combination drug delivery can reduce therapeutic dosages and minimize adverse reactions, while maintaining or even enhancing efficacy and reducing drug resistance [171].

For instance, Zamora-Mera et al. conducted a study demonstrating the benefits of combination therapy in magnetic hyperthermia therapy. They crosslinked chitosan nanoparticles (CSNPs) with tripolyphosphate salts (TPP) through ionic interactions. Magnetic CSNPs were prepared by encapsulating them with three different concentrations of ferrofluid, along with a constant concentration of 5-fluorouracil (5-FU) [172]. The CSNPs showed dose-dependent cytotoxicity and were successfully up-taken in both cell lines. The study reported that the MH treatment in the A-172 cells produced a 67–75% cell viability whereas no cell viability was noticed in FHB. The study equally reported a 4-h regrowth of the population upon MH treatment with CSNPs loaded only with ferrofluid but a decreased amount of released 5-FU upon combination with the MH treatment and 5-FU demonstrating a positive result using a combination approach [172].

Researchers have been exploring various innovative approaches to enhance drug efficacy while minimizing adverse effects. De Lima et al. [173] developed mucoadhesives for bladder cancer treatment, aiming to increase drug residence time at the target site for sustained and localized release. Naeimi et al. [174] explored innovative strategies for colorectal cancer treatment to improve therapeutic outcomes and overcome challenges associated with conventional treatments. These studies reflect the growing interest in developing targeted and efficient drug delivery systems for cancer therapy.

Advances and future prospects

The field of smart drug delivery remains relatively unexplored, primarily due to the wide range of

stimuli that need to be assessed. These stimuli include pH, temperature, light, surface physical chemistry, proteins, extracellular matrix content, and more. Researchers have been investigating the role of internal and external biological stimuli as triggers for drug delivery devices. In recent studies, there has been an exploration of using this process to precisely direct drug delivery and treat cells exhibiting abnormal behavior, such as cancerous cells [175–177].

An additional area worth mentioning is the utilization of nanotechnology in drug delivery systems. Extensive research has been conducted on the design of drugs at the nanoscale, making it the most advanced technology in the field of nanoparticle and nanocapsule applications. Nanotechnology offers numerous potential advantages, including the ability to modify properties such as solubility, drug release profiles, diffusivity, bioavailability, and immunogenicity. One notable benefit of employing nanotechnology in these systems is the potential for localized and controlled release, while simultaneously reducing the risks of inflammatory reactions [91].

According to a study by Sahu et al. [178], nanometric DDS shows promise for the treatment of cancer and other chronic diseases. Additionally, nanostructured delivery systems involving silver and gold nanoparticles have been a subject of investigation, as highlighted in the research conducted by Yafout et al. [179]. Silver and gold nanoparticles are also the objects of study in nanostructured delivery systems, as observed in the studies by Yafout et al.

Another emerging area is the development of drug delivery systems using herbal substances, such as curcumin, eugenol, and propolis. These substances can be added to the device material or used as the drug to be released. Mendez-Pfeiffer et al. [180] investigated the use of propolis as a nanocarrier in DDS. Initial results were promising and should be followed by in vitro tests and clinical practice. Obeid et al. [181] performed a study on the use of curcumin as nanoparticles in similar systems. Research carried out by Paunovska et al. and Hou et al. [182, 183] investigated the use of drug delivery systems based on nanoparticles for mRNA delivery.

Furthermore, there is potential for developing modifications in the architecture, composition, or geometry of medical devices with drug release capabilities to enhance the release rate. Defining specific procedures for the use or insertion of these systems and obtaining patents for these inventions hold significant technological and commercial value, as evidenced by the considerable interest in existing patents in this field. Various companies have been actively involved in the development of medical devices with patented drug delivery mechanisms, reflecting the industry's recognition of their importance [184–188].

Concluding remarks

Drug delivery systems offer great potential for improving the diagnostic and therapeutic efficacy of drugs across various pathologies. By tailoring their specific properties, these systems hold promise for reducing tissue, cellular, genetic, and tumor damage through the administration of drugs with low toxicity, high specificity, biocompatibility, biodegradability, and controlled delivery to targeted tissues. Successful pharmaceutical products aim to achieve these objectives, enhancing therapeutic outcomes while minimizing adverse effects. Targeted drug administration has emerged as a significant approach to optimizing drug therapy by maximizing efficacy and reducing side effects for patients. In the design of a controlled drug delivery system, crucial considerations include the selection of the drug, the structure of the drug carrier, the choice of material for drug encapsulation, the appropriate dosage, the mechanism of drug release, and the delivery route. These factors collectively contribute to the development of effective and customized drug delivery systems.

Thus, drug delivery systems hold immense potential for clinical applications across a wide range of diseases. Depending on the desired therapeutic effect, various strategies and approaches can be employed. While there are limitations and challenges to be addressed in medication administration approaches, ongoing research and studies are essential to overcome these hurdles and establish them as standard practices. The emerging field of regenerative medicine, particularly in tissue engineering, is driving the exploration and development of advanced drug delivery systems. This pursuit promises to revolutionize the treatment of patients with chronic diseases and usher in a new era of targeted and effective drug delivery. As research continues to progress, we can anticipate significant advancements and positive impacts on patient care and outcomes.

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Declarations

Competing interests The authors declare no competing interests.

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