Controlled Drug Release for Tissue Engineering

Material, Mechanisms and Classification

Haniyeh Rafipour

حانیه رفیع پور

دانشجوی دکترای پزشکی، دانشگاه علوم پزشکی دانشگاه تهران

Abstract:

The term of tissue engineering is generally considered as a combination of material science and processing with molecular technology, in order to regenerate tissue to design or repair skin, cartilage or bone and some other organs. In the last decades, tissue engineering is widely considered as the new approach for solving the drawbacks of organ transplantation and treating some traumas and many advantages are achieved. Applying drug delivery in addition to tissue engineering may ultimately lead to controlled release of signaling molecules to guide developmental process in tissue differentiation. Therefore controlled released tissue engineered devices provide more suitable properties for medical applications.

Contents:

1. Introduction

Accidents, diseases, traumas can cause tissue degeneration and destruction, so it is necessary to provide suitable treatments. Transplanting organs and tissues has dominance over the other methods, but this method causes significant problems and side effects and has some limitations. Therefore, most of these difficulties can be solved by a new field which is the integration of material science and medical science and regarded as tissue engineering (TE). The base structure of TE is a three dimensional scaffold which is loaded with active molecules and cells. [11]

Initially TE scaffolds have just provided some mechanical and structural support that is not adequate any more. These kinds of scaffolds are now replaced with smart scaffolds which control some parameters that can affect the implant. Choosing proper materials and fabrication techniques can answer our demands. [52]

Some considerations are important for selecting the suitable materials and fabrication methods for tissue engineering are:

1. Biocompatibility: It is the ability of material and scaffold to apply without harmful immune response or inflammatory reaction. Cells must move through the scaffold, adhere and perform a normal function.
2. Biodegradability: Scaffold implant should be replaced by tissue's body. After degradation the products should not be toxic. The scaffold's regeneration and degradation rate should be matched.
3. Mechanical Properties: Mechanical properties must be appropriate for the anatomical site on which the scaffold is to be implanted. This is more challenging for fabrication orthopedic (bone and cartilage) and cardiovascular scaffolds. Tensile strength, surviving under in vivo condition, etc are the examples of mechanical properties.
4. Porosity: Porous structures allow scaffolds to interact with cells and the pore size determines the kinetic release of bioactive molecules.
5. Binding Affinity: the strength of binding between matrix and bioactive molecules
6. Loading capacity: how much drug can be loaded in scaffold
7. Process ability

Ideal scaffolds should demonstrate these properties along with controlled degradation for releasing factors and medicines. [1]

Developments in drug delivery systems and devices in recent years and mixing it with tissue engineering lead to create controlled release devices which can be triggered and release the desired amount of medicine or factor at desired time at desired location. For instance enzymatically triggered systems work just with introducing the special enzyme or chemicals. However, some limitation are not solved. [20]

In this review, we will first introduce materials that are commonly used in tissue engineering, then we are mentioned at some fabrication techniques which provide suitable scaffolds with high loading capacity and porosity. At the end some drug release systems and bioactive molecules are introduced.

2. Tissue engineering scaffolds' material for matrix

Choosing functional materials for scaffold synthesis are always challenging. The materials abilities can influence directly on scaffolds. On the other hand, fabrication methods are completely dependent on substance molecular structure. In medical application, selecting materials are based on material molecular structure, solubility, surface energy, ability for water uptake, surface erosion. [53]

In this review, materials divided into three main groups: ceramics, synthetic polymer, natural polymer which their properties are mentioned. [2]

2.1. Natural-based polymer

Natural-derived materials obtained from vertebrates and invertebrates animal, microorganisms and vegetal structure; Bioactive properties, better interaction with cell and biological recognition are the advantages of these material. Protein-based (collagen, gelatin, fibrin, albumin and elastin), carbohydrate-based (chitosan, starch, alginate, hyaluronic acid, chondroitin sulfate, dextran and agar), polynucleotide-based (DNA and RNA) organic materials are the three main class of natural polymer. [2, 3]

Table 1.natural-based polymer

Material	Properties	Encapsulated/ seeded cell	Tissue	References
1. Protein-based				
1.1. Collagen	High mechanical strength, good biocompatibility, low antigenicity, ability of crosslinking, water uptake ability, biodegradability	Chondrocyte, mesenchymal cell, epithelium fibroblast, smooth muscle cell, osteoblast, preadipocyte	Bone, cartilage, skin, intervertebral disc, tooth, cardiovascular, adipose, renal glomerular	[3,33,61]
1.2. Gelatin	Biodegradability, biocompatibility, derived from collagen, low antigenicity, electrical, physical and homeostatic property, high cytocompatibility, biosafety, ability of crosslinking	Preadipocyte, Chondrocyte, mesenchymal cell, osteoblast	Bone, cartilage, skin, adipose	[3, 46, 61]
1.3. Fibrin	Immunocompatibility, fibrin glue (hemostatic and chemotactic ability), rapidly invaded	Keratinocyte, urothelial cell, tracheal epithelial cell, murine embryonic cell, mesenchymal cell,	Bone, vessel, skin, spinal cord, cartilage, intervertebral disc	[3]
1.4. Albumin	High compatibility, easy process ability,	Osteocyte	bone	[46]
1.5. Elastin	Bioactive property, elasticity, Biodegradability, biocompatibility, low poly-dispersity	Chondrocyte, fibroblast, adipose cell	Vascular-smooth muscle cell, cartilage, adipose	[3]

2. Carbohydrate-based				
2.1. Chitosan	Biologically renewability, Biodegradability, biocompatibility, low antigenicity, permeability, biofunctional, bioadhesive, high chemical versatility, high wound healing potential, haemostatic property	Leukocyte, macrophage, fibroblast, osteoblast, ligament cell, chondrocyte	Cartilage, bone, vessel, nerve, skin	[3]
2.2. Starch	Cytocompatibility, biocompatibility, bioadhesive, mechanical property*	Bone marrow cell, endothelial cell, osteoblast	Bone, vessel	[3,46]
2.3. Alginate	Mucoadhesive, water uptake ability, porosity, pH dependent behavior	Bone marrow cell, chondrocyte, fibroblast	Cartilage, bone, vessel, nerve, liver, pancreas	[3,46]
2.4. Hyaluronic acid	Viscoelastic property, bacteriostatic, free radical scavenger	Chondrocyte, mesenchymal, preadipocyte	Cartilage, bone, vessel, spinal cord, skin, adipose	[3,46]
2.5. Chondroitin sulfate				
Binding to protease inhibitor, bioadhesive,	Chondrocyte, myoblast, mesenchymal, fibroblast	Bone, cartilage, heart valve, kidney	[3]	

*mechanical properties is affected by water

2.2. Synthetic polymer

Synthetic polymers are one of the options that can be utilized for scaffold synthesis. Porosity, degradation rate, non-toxicity and suitable mechanical properties make them a suitable material for manufacturing controlled release scaffolds. In addition, these polymers have cheaper price, but comparable quality to natural-based polymers.

Aliphatic polyesters, poly(ortho esters), polyanhydrides, Poly(alkyl cyanoacrylates), poly(urethane), Poly(amino acids) are widely used in designing application.[22]

Table 2.synthetic polymer

Material	Properties	Tissue/disease and biomedical application	References
1.Aliphatic polyester		Bone, soft tissue(cartilage),nerve	[45,46]

1.1. Poly(glycolic acid)(PGA)	Highly crystalline, high melting temperature(>200), high tensile strength, low solubility in organic solvent, high degradation rate		
1.2. Poly(lactic acid) (PLA)	Semi-crystalline, high melting temperature(>170), low degradation rate, good processability, mechanical property		
1.3. Poly(caprolactone)(PCL)	Semi-crystalline, low melting temperature(55-60), cheap, high solubility in organic solvent, blend forming ability, low degradation rate		
1.4. Poly(hydroxyalkanoate) (PHA)	Biocompatible, biodegradable, thermoplastic		
2. Poly(ortho ester) (POE)	Biodegradable, hydrophobic, surface erodible	Ophthalmic disease	[1,46]
2.1. I	Autocatalytic effect,		
2.2. II	Highly hydrophobic, acid treatment for degradation		
2.3. III	Wide range of physical property		
2.4. IV	Appreciable degradation		
3. Polyanhydride	surface erodible, high biocompatible, hydrolytically unstable, poor mechanical property	Brain, chemotrophic agent	[45,46]
3.1. Poly(sebacic anhydride)(PSA)	Highly crystalline, high degradation rate		
3.2. Aromatic poly anhydride			

4. Poly(alkyl cyanoacrylates)	Tissue adhesive, embolization agent, high degradation rate ranging (hours to days), haemostatic property	Cancer agent element, skin	[46]
5. Poly(amino acids) (PAA)	High crystalline, low degradation rate, mechanical property	Orthopedic implant, bone	[45,46]
5.1. Tyrosine-derived polycarbonates	Perfect compatibility, slow degradation rate		
5.2. tyrosine-derived poly(imino carbonate)	High mechanical strength, high degradability, low processing temperature, processability		
6. Poly(urethane)	Mechanical property, biocompatibility, cell adhesive	Bladder muscle, vascular endothelium, cartilage	[45]

2.3. Ceramic

Currently, bioactive ceramics are widely used as orthopedic and dental implants. In addition, coating some joint replacement with bioactive ceramics reduce the immune and inflammatory responses. crystalline and amorphous structures are commonly utilized in medical application. Good mechanical properties and bioactivity make them , one of the best choice for biomedical purpose.

Table 3.ceramic

Material	Properties	Tissue/disease and biomedical application	References
1. Hydroxyapatite(HA)	Stable in in vivo, spongy structure, physical strength, biocompatible, biodegradable	Bone	[1,34,35,36]
2. Tri-calcium phosphate(TCP)	Biocompatible , osteoconductive	Bone	[7]
3. Biphasic calcium phosphate(BCP)	Bioadhesive, controllable degradation rate	Bone	[8,12]

3. Scaffolds manufacturing methods

Diverse technique have been mentioned in chemical engineering articles for designing and fabrication of scaffolds. However, some specific approaches have been utilized for manufacturing each types of scaffold, such as porous, microsphere-based, hydrogel, etc. scaffold fabrication technique in tissue engineering [39,53,57]:

- Porous scaffold fabrication/drug delivery [45]
  - Solvent casting/particulate leaching
  - Supercritical fluid processing (supercritical CO2)
- Electrospinning fabrication

- Microsphere-based scaffold fabrication
  - Solvent-evaporation
  - Particle aggregation
- Hydrogel fabrication [23]
  - Cryogelation
  - Gas foaming
  - Microemulsion
  - Freeze-drying
  - Microfluidics
- Ceramic scaffold fabrication [16]
  - Emulsion templating
  - Ca-phosphate sintering

3.1. Solvent casting/particulate leaching

Mixture of solid biodegradable polymer and salt particles was placed into the mold after that solvent was poured into the mold to fill voids of the polymer/salt particles (under negative pressure); it allowed the polymer to being dissolved and merged. Addition of Non-solvent to salt/polymer composite made the composite solidify. Large amount of liquid (water) was introduced into mold for washing the inside salt particles. [29]

Advantages:

Quick and fast technique

Affecting parameters:

Particle size

3.2. Supercritical fluid processing (supercritical CO2)

Supercritical fluid is any material at temperature and pressure beyond the critical pressure and temperature. CO2 is a suitable fluid for many different application as a consequence of its property, for instance, non-toxicity, non-flammability and its critical parameter is easily accessible. Two main technique use scCO2: RESS and PGSS. [5]

1. RESS (rapid expansion of scCO2): particles was solubilized in scCo2 fluid, then the solution expansion occurred through capillary nozzle (diameter>150) into precipitation chamber. Solution decompress rapidly to provide supersaturating, nucleation and particle formation.

Advantages:

Large particle is produced

Affecting parameters:

1) Temperature
2) pressure
3) nozzle geometry

2. PGSS (particle from gas saturated solution): scCO2 addition decreases polymers

critical temperature, it enables the material to liquefy at ambient temperature. On the other hand, reduction in viscosity in the presence of scCO2 allows the drug particles to be homogeneously integrated with solution by stirring device.

Advantages:

1) Solvent absence at any stage
2) Rapidity
3) Mild processing condition (150 bar, <40)

3.3. Electrospinning

This technique is commonly used for fabrication nanoscale or microscale fiber.

A capillary tube filled with solution and is put under high voltage. An electrical equipment produce mutual charge repulsion which is induced in solution. It is against the surface tension of the solution. Increasing the intensity of electrical field causes dominance of charge repulsion on solution surface tension to jet forming. Final fiber is formed by solvent evaporation. [27,57]

Advantages:

1) Quick
2) simple

Affecting parameters:

1) viscosity
2) conductivity
3) surface tension
4) operational condition (hydrostatic pressure, electrical field, collector and tip distance)

3.4. Solvent-evaporation

In this process, polymer is dissolved in immiscible solvent (water) and drug is diffused and dissolved in the solution. for forming the discrete droplets, the solution is emulsified by adding it to an aqueous continuous phase. Microsphere formation occurs when the organic solvent diffuses into aqueous phase and then evaporates at the interface of water and air. After evaporation harden microspheres are formed and they can be obtained with proper filtration. [48]

Advantages:

1) prevention of protein degradation
2) regulation of microsphere morphology

Affecting parameters:

1) drug solubility and loading
2) internal morphology
3) solvent type
4) diffusion rate
5) temperature
6) viscosity

3.5. Particle aggregation

This method is based on crosslink ability of polyelectrolytes with counterion to hydrogel beads forming (gelisphere forming). The main steps [40,50]:

1. Microsphere gelation using ionotropic gelation methods:
Drug-loaded polymeric solution drops into aqueous polyvalent cation solution. Three dimensional network is formed by cation diffusion into drug-loaded polymeric solution. The particles are collected and rinsed until neutral pH then, placed into mold and coat with gelatin.
2. Sphere characterization by SEM

Advantages:
1) Non-toxic
2) cheap

Affecting parameters:
1) concentration of polymer and crosslinking electrolyte
2) temperature
3) pH
4) drug concentration

3.6. Cryogelation

Semi-frozen condition (-12°C to -18°C) causes ice crystal growth to perform as a porogen. Shape and size of the pores which are formed after defrosting, depend on the shape and size of the ice crystal. [22,46]
Advantages:
Cryogel advantages:
1) High mechanical stability
2) Immobilization of cells at mild condition

Affecting parameters:
1) Crosslinking type and degree
2) temperature
3) freezing rate
4) gel composition

3.7. Gas foaming

Polymer is saturated with CO2 gas by exposing polymer to CO2 in high pressure. Gas pressure reduction creates thermodynamic instability in polymers. Therefore, unstable dissolved CO2 is formed so separation between polymer and phase occurred. CO2 molecule clustering minimizes free energy and it causes pore nucleation. This pores grow when the surrounding polymers' dissolved CO2 is diffused into the pore nuclei. [32]
Advantages:
1) Fabrication high porous polymer
2) Absence of organic solvent

Affecting parameters:
1) Temperature
2) Pressure reduction rate

3.8. Microemulsion

Aqueous and oil elements are mixed together with a specific rate in the presence of surfactant. Surfactant adsorbing causes reduction in surface tension and microemulsion form. [47,56]

Advantages:
1) Rapid polymerization rate
2) Making polymer with high molecular weight

Affecting parameters:
1) Monomer concentration
2) Temperature
3) Emulsifier concentration

3.9. Freeze-drying

This method has three major step: 1) freezing 2) sublimation (primary drying process) 3) secondary drying process

Freezing: freezing the solution at low temperature (-70°C to -80°C)

Sublimation: the frozen solution placed in a chamber and the pressure is lowered through a specific vacuum. During this step, organic solution and ice are removed

Secondary drying process: most of the remaining unfrozen water is removed by desorption [30,57]

Advantages:
Absence of organic solvent

Affecting parameters:
1) pressure
2) crystal size
3) self-temperature
4) chamber pressure

3.10. Microfluidics

Fluids at microscale demonstrate different Fluid mechanic properties, this matter can be used for manipulating droplets with immiscible fluid. [42]

Microfluidic devices with accurate geometry and design are required for manipulating the droplets. Two types of microfluidic device are mentioned in this review: 1) glass capillary 2) PDMS

1. Glass capillary: a square glass capillary carefully surrounds a cylindrical glass capillary for forming the water-in-oil or oil-in-water single emulsion droplets. Flowing direction of the fluid inside the cylindrical and square capillary can be the same or different. When both fluid rates decrease, monodisperse droplets are shaped at the capillary tip.

2. PDMS: sandwich method and solid-object printing are the fabrication methods for producing the PDMS device to form the microchannel. This microchannel is made for separation and the flowing direction of the fluids are the same.

Advantages:
1) Well-controllable
2) Engineered divers type of microsphere

Affecting parameters:
1) Fluid properties
2) Channel geometry
3) Flow condition

4. Controlled release mechanisms

Using a controlled-release system in medical applications would solve previous systems limitations. Preventing drug and protein from degeneration, increasing the releasing efficiency, controlling the rate, time and location of releasing are some of these system properties. Controlled-release drug delivery system are classified [25]:

- Rate-pre programmed drug delivery
- Activation-modulated drug delivery
- Feedback-regulated drug delivery
- Site-targeting drug delivery

4.1. Rate-pre programmed drug delivery

Preprograming delivery at the specific rate has occurred in this system. Diffusion rates of molecules are controlled by barriers which are surrounding the media or located in it.

4.1.1. Polymer membrane permeation-controlled drug delivery

A rate-controllable polymeric membrane covered the drug reservoir which can be a drug solid particle. This membrane can be non-porous or semi-porous. [18,25]

4.1.2. Polymer matrix diffusion-controlled drug delivery

This system is based on the release rate of drugs from the reservoir through the water insoluble membrane and it depends on diffusion ability of the drug through the membrane. Two type of diffusion device are mentioned here [20,25,52]:

1. Reservoir type:

This type is based on exchanging the inner membrane drug with particle surrounding fluid.

2. Monolithic (matrix) type:

In this system, release is controlled by drug diffusion through matrix material.

4.1.3. Polymer (membrane/matrix) hybrid drug delivery

This system is a combination of the last two systems, the solid drug diffuse in a polymer matrix which is encapsulated in a membrane. [25]

4.1.4. Microreservoir Partition-Controlled Drug Delivery

In this system, drug reservoir is a suspension (drug solid particle and aqueous solution of

water-miscible), but overly, it is similar to last methods. [25]

4.2. Activation-modulated drug delivery

Physical and chemical interaction cause activation in these systems.

4.2.1. Osmotic pressure activated drug delivery

Coating drug particles with semi permeable polymers is a suitable method for controlled release. Particles exposed to aqueous fluid after releasing from the capsule. Particles uptake water based on the osmotic pressure and the drug is dissolved, it leads to a gradient, so more water is uptake. The coating is expanded and the wall stress is increased. Finally the coating ruptures and drug release. [44]

4.2.2. Hydrodynamic pressure activated drug delivery

Hydrodynamic pressure provides a source of energy for the delivery system. This system can be produced by loading liquid drugs into impermeable and collapsible capsules as a reservoir. One absorbent layer, one hydrophobic swellable layer laminate the reservoir and all the parts are coated with rigid, shape-retaining cover. In the digestive tract, absorbent layers imbibe fluid and generate hydrodynamic pressure. Thus, the drug reservoir collapsed and released the molecules. [6,18,44]

4.2.3. Vapor pressure activated drug delivery

The devices of this system are designed with two compartment: infusion compartment and pumping compartment which are physically separated. a vaporizable fluid is one of the sectors of the pumping compartment which generates vapor pressure with vaporizing at body temperature. Under pressure the partition moves upward and drives the drug solution to be delivered in the infusion compartment. [25]

4.2.4. Mechanical force activated drug delivery

Mechanical force can be categorized into three classes: 1) compressive 2) tensile 3) shear forces. Compressive and tensile force activated delivery systems are related to the stretchable material or hybridized into flexible components and the drug is released by deformation or breakage in chemical bonds.

Shear force activated systems are suitable for cardiovascular systems. Deformation and disaggregation are two mechanisms for releasing drugs in this system. [41]

4.2.5. magnetic activated drug delivery

Magnetic activated delivery systems have a high efficiency to deliver drugs to specific locations of the body. This transportation method is based on drug encapsulation into the sphere or conjugation on the surface of the nano/microsphere. Accumulation occurred after microsphere injection and it can lead to increased efficiency of local drug transportation. One magnetic field also can help and facilitate this process. Very high drug concentrations are provided near the target place without any toxicity. [38]

4.2.6. sponophoresis activated drug delivery

Though this process microbubbles interact with cells under ultrasound. Microbubbles are gas-filled particles which are encapsulated by shells. The oscillation occurs by microbubbles when they are induced by ultrasound at the close microbubble resonance frequency. These oscillations increase cellular uptake and permeability by forming transient pores in the cell membrane. Therefore it provides a targeted drug delivery at a specific location. [55,59,60]

4.2.7. iontophoresis activated drug delivery

Iontophoresis is based on the mild electrical current and includes two predominant mechanisms: electromigration and electroosmosis. Electromigration refers to repulsion

of ions by cathodes or anodes and the Ionic flux is generated through electrode reaction. Electroosmotic is the motion of water by electrical current. Electroosmotic can be applied for neutral molecules. [37,58]

4.2.8. hydration activated drug delivery

Hydration devices consist of swellable hydrophobic polymer which the drug is homogeneously dispersed into and the release is activated by polymer hydration-induced swelling. [25]

4.3. Feedback-regulated drug delivery

In these groups feedback mechanisms activate drug releasing. They might be triggered by biochemical substances in the body.

4.3.1. Bioerosion-Regulated Drug Delivery System

It is also called biodegradation systems. The drug is dispersed into the polymer and one stimulus can degenerate the polymer and allows the remaining particle drug to dissolve in water to disperse into the water. [9]

4.3.2. Bioresponsive Drug Delivery Systems

In this system, a reservoir is surrounded and encapsulated by a responsive polymeric membrane which is triggered by pH, light, temperature, enzyme, biomolecule, etc. Biomolecule-responsive drug delivery is one of the typical delivery systems. Biomolecules can either react with matrix or cleave some chemical bond. [14]

4.3.3. Self-Regulating Drug Delivery Systems

In contrast with other feedback regulated delivery systems whose activation depends on the outer activator, this system is stimulated by membrane permeability to biomedical agents. As an example, Peppas et al, found the association between release behavior and surrounding fluid pH. This study indicates that in acidic conditions diffusion coefficient reduces duo to strong ion-ion interaction in hydrogel. In the other hand, in basic and neutral media, hydrogen swelling is occurred and the result is drug diffusion.[4]

4.4. Site-targeting drug delivery

Site-targeting or targeted delivery system is based on delivering a certain amount of an agent to a specific area within the body for a prolonged period of time. These system devices are being prepared by considering target cell properties and receptor-ligand association. Two main approaches for this system include: active targeting and passive targeting.

Passive targeting is directly associated with circulation, whereas active targeting enhances the passive targeting effect to make it more specific to the target site. [25]

Material	Advantages	Affecting parameters	System types
1. Rate-programmed			
1.1. Polymer membrane permeation-controlled	Low risk of accidentally burst and release	Partition coefficient, membrane thickness, drug diffusivity	Progestasert IUD, Ocusert, Transderm-Nitro, Norplant subdermal implant
1.2. Polymer matrix diffusion-controlled			

		Temperature, viscosity, matrix free volume	Nitro-Dur, Compudose
1.2.1. Reservoir type	Variable release rate		
1.2.2. Monolithic rate	Easier to produce, deliver molecule with high MW		
1.3. Polymer (membrane/matrix) hybrid	Both polymer matrix diffusion and polymer membrane permeation	Diffusivity, permeability, membrane thickness	Norplant
1.4. Microreservoir Partition-Controlled		Drug concentration rate, thickness, drug diffusivity in lipid layer	Nitrodisc, Syncro-Mate-C implant, Transdermal contraceptive device
2. Activation-modulated			
2.1. Osmotic pressure activated	easy to formulate, simple, prolonged therapeutic e□ect, inexpensive	water permeability, effective surface area, thickness of housing,	Alzet osmotic pump, Acutrim tablet,
2.2. Hydrodynamic pressure activated	Some medical benefit (mitigate food-effect, increase patient compliance and tolerance	proportion in the membrane, tablet surface area, osmotic agent proportion, drug layer polymer grade	
2.3. Vapor pressure activated			
	Fluid delivery in very small volumes, fluid deliver at programmed rate	differential vapor pressure, viscosity, delivery cannula size	Infusaid system
2.4. Mechanical force activated	Providing predictable control, patient controlled delivery	Temperature, vessel diameter, velocity	
2.5. magnetic activated	Bio adaptability, non-toxicity, reducing the concentration of free drug over circulation,	Particle size, surface characteristic, field strength, and blood flow rate	
2.6. sonophoresis activated	Safe, non-invasive, widely available, inexpensive,	Frequency, Intensity, Pressure, Pulse length,	
2.7. iontophoresis activated	High controllable delivery rate, bioavailable	Drug concentration, pH, current	LidoSite, Zecuity, Ionsys
2.8. hydration activated	High drug release rate for hydrophobic and hydrophilic component	Orifice size, drug loading	Syncro-Male-B implant, Valrelease
3.	Feedback-regulated		
3.1. Bioerosion-Regulated		Thickness of the membrane, membrane Diffusion coefficient, pH	

3.2. Bioresponsive	Carry high dosage, non-toxic, stimuli-responsive	pH, temperature, light, enzyme, biomolecule	
3.3. Self-Regulating	Intelligent delivery system	pH, stimulant molecule concentration, membrane permeability	
4. Site-targeting drug delivery	High specificity and efficiency	Depends on the delivery type	

5. Bioactive molecules

In fact, bioactive molecules are important to consider for their significant role in all kinds of treatment. Choosing a suitable delivery approach is completely dependent on molecules which are wanted to be released. So, the materials and synthesis mechanisms are selected based on the types of the molecules.

In tissue engineering, bioactive proteins are more interested in delivery including: growth factors and adhesive factors as the main factors. [19]

1) Growth factors:

Growth factors contribute a significant role in tissue engineering. These molecules are ligands for cell receptors and cause turning on signal transduction within the cell. The most important examples include:

a. morphogenetic proteins (BMPs)
b. transforming growth factor (TGF)-β
c. vascular endothelial growth factors (VEGFs)
d. platelet-derived growth factors (PDGFs)
e. fibroblast growth factors (FGFs)
f. neurotrophins
g. insulin like growth factors

2) Adhesive factors:

Another important candidate for drug delivery in the field of tissue engineering are adhesive factors. These molecules are bound to the ECM (ExtraCellular Matrix) and transmit the pressure stress between cytoskeleton and ECM. As an illustration for adhesive factors:

a. Fibronectin
b. vitronectin
c. laminin
d. peptide mimics of these proteins

6. conclusion

For the last several decades, there has been a significant number of studies which have focused on the methods and materials for designing controlled-release devices. In this review the four main components for designing devices are mentioned: materials, active molecules, synthetic methods and drug delivery systems. Natural, synthetic and ceramic materials are manipulated to produce the devices which are coupled with various delivery systems. On the other hand, active molecules are bound to the scaffolds based on their chemical properties. The combination of all these techniques provide devices that release

controlled amounts of drug at specific times in specific locations.

Additional future works on the computational and modeling methods would help to make more specific, efficient and cheaper scaffolds for implantation aims.

Uncategorized References

1. Polymeric Scaffolds in Tissue Engineering Application: A Review: International Journal of Polymer Science. 2011. 2011.

2. Guarino, V., F. Causa, and L. Ambrosio, Bioactive scaffolds for bone and ligament tissue. Expert Review of Medical Devices, 2007. 4(3): p. 405-418.

3. Malafaya, P.B., G.A. Silva, and R.L. Reis, Natural–origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. Advanced Drug Delivery Reviews, 2007. 59(4): p. 207-233.

4. Intelligent Materials for Controlled Release, Copyright, Advisory Board, Foreword, in Intelligent Materials for Controlled Release. 1999, American Chemical Society. p. i-vii.

5. Davies, O.R., et al., Applications of supercritical CO2 in the fabrication of polymer systems for drug delivery and tissue engineering. Advanced Drug Delivery Reviews, 2008. 60(3): p. 373-387.

6. Malaterre, V., et al., Approach to design push–pull osmotic pumps. International Journal of Pharmaceutics, 2009. 376(1): p. 56-62.

7. Hu, J., et al., Beta-tricalcium phosphate particles as a controlled release carrier of osteogenic proteins for bone tissue engineering. Journal of Biomedical Materials Research Part A, 2012. 100A(7): p. 1680-1686.

8. Ladrón de Guevara-Fernández, S., et al., Bioactive glass-polymer materials for controlled release of ibuprofen. Biomaterials, 2003. 24(22): p. 4037-4043.

9. Wood, D.A., Biodegradable drug delivery systems. International Journal of Pharmaceutics, 1980. 7(1): p. 1-18.

10. Tabata, Y., Biomaterial technology for tissue engineering applications. Journal of the Royal Society, Interface, 2009. 6 Suppl 3(Suppl 3): p. S311-S324.

11. O'Brien, F.J., Biomaterials & scaffolds for tissue engineering. Materials Today, 2011. 14(3): p. 88-95.

12. Lee, E.J., F.K. Kasper, and A.G. Mikos, Biomaterials for tissue engineering. Annals of biomedical engineering, 2014. 42(2): p. 323-337.

13. Langer, R., Biomaterials in Drug Delivery and Tissue Engineering: One Laboratory's Experience. Accounts of Chemical Research, 2000. 33(2): p. 94-101.

14. You, J.-O., et al., Bioresponsive matrices in drug delivery. Journal of biological engineering, 2010. 4: p. 15-15.

15. Yoshikawa, H. and A. Myoui, Bone tissue engineering with porous hydroxyapatite ceramics. Journal of Artificial Organs, 2005. 8(3): p. 131-136.

16. Porter, J.R., T.T. Ruckh, and K.C. Popat, Bone tissue engineering: A review in bone biomimetics and drug delivery strategies. Biotechnology Progress, 2009. 25(6): p. 1539-1560.

17. Paul, W. and C.P. Sharma, Ceramic Drug Delivery: A Perspective. Journal of Biomaterials Applications, 2003. 17(4): p. 253-264.

18. Tojo, K., et al., Characterization of a membrane permeation system for controlled drug delivery studies. AIChE Journal, 1985. 31(5): p. 741-746.

19. Tiwari, R., CONTROLLED RELEASE DRUG FORMULATION IN PHARMACEUTICALS: A STUDY ON THEIR APPLICATION AND PROPERTIES. Vol. 5. 2016. 1740-1720.

20. Madhusudhan Reddy, A., et al., Controlled release matrix drug delivery system – a review. Vol. 5. 2017. 2017-384.
21. Plieva, F.M., et al., Cryogel applications in microbiology. Trends in Microbiology, 2008. 16(11): p. 543-551.
22. M. A. Henderson, T., et al., Cryogels for Biomedical Applications. Vol. 1. 2013. 2682-2695.
23. Li, J. and D.J. Mooney, Designing hydrogels for controlled drug delivery. Nature Reviews Materials, 2016. 1: p. 16071.
24. Langer, R. and D.A. Tirrell, Designing materials for biology and medicine. Nature, 2004. 428: p. 487.
25. Chien, Y.W., Drug Delivery : Controlled Release. Encyclopedia of Pharmaceutical Technology 2010.
26. Bhardwaj, N. and S.C. Kundu, Electrospinning: A fascinating fiber fabrication technique. Biotechnology Advances, 2010. 28(3): p. 325-347.
27. Teo, W.-E., W. He, and S. Ramakrishna, Electrospun scaffold tailored for tissue-specific extracellular matrices. Biotechnology Journal, 2006. 1(9): p. 918-929.
28. Wang, X., et al., Emulsion-templated fully three-dimensional interconnected porous titania ceramics with excellent humidity sensing properties. Sensors and Actuators B: Chemical, 2016. 237: p. 894-898.
29. Liao, C.-J., et al., Fabrication of porous biodegradable polymer scaffolds using a solvent merging/particulate leaching method. Journal of Biomedical Materials Research, 2002. 59(4): p. 676-681.
30. Autissier, A., et al., Fabrication of porous polysaccharide-based scaffolds using a combined freeze-drying/cross-linking process. Acta Biomaterialia, 2010. 6(9): p. 3640-3648.
31. Siepmann, J., R. Siegel, and M.J. Rathbone, Fundamentals and applications of controlled release drug delivery. 2012. 1-594.
32. Huang, Y.-C. and D. Mooney, Gas Foaming to Fabricate Polymer Scaffolds in Tissue Engineering. 2005. p. 155-167.
33. El-Sherbiny, I.M. and M.H. Yacoub, Hydrogel scaffolds for tissue engineering: Progress and challenges. Global cardiology science & practice, 2013. 2013(3): p. 316-342.
34. Xu, H.H.K., et al., Injectable and macroporous calcium phosphate cement scaffold. Biomaterials, 2006. 27(24): p. 4279-4287.
35. Hertz, A. and I.J. Bruce, Inorganic materials for bone repair or replacement applications. Nanomedicine, 2007. 2(6): p. 899-918.
36. Yoshikawa, H., et al., Interconnected porous hydroxyapatite ceramics for bone tissue engineering. Journal of The Royal Society Interface, 2009. 6(suppl_3): p. S341-S348.
37. Kalia, Y.N., et al., Iontophoretic drug delivery. Advanced Drug Delivery Reviews, 2004. 56(5): p. 619-658.
38. Jangde, R., Magnetically modulated Drug Delivery Systems: An Overview. Vol. 4. 2011.
39. Czernuszka, J.T., Making tissue engineering scaffolds work. Review: the application of solid freeform fabrication technology to the production of tissue engineering scaffolds. . European cells & materials
2003. 5: p. 29-39; discussion 39-40

40. Fideles, T., et al., Mechanical and Morphological Characterization of Chitosan Scaffolds Produced by Particle Aggregation Method. Vol. 04. 2017. 1-12.
41. Zhang, Y., et al., Mechanical Force-Triggered Drug Delivery. Chemical Reviews,

2016. 116(19): p. 12536-12563.
42. Li, W., et al., Microfluidic fabrication of microparticles for biomedical applications. Chemical Society Reviews, 2018. 47(15): p. 5646-5683.
43. Li, P.S., et al., A novel albumin-based tissue scaffold for autogenic tissue engineering applications. Sci Rep, 2014. 4: p. 5600.
44. A Keraliya, R., et al., Osmotic Drug Delivery System as a Part of Modified Release Dosage Form. Vol. 2012. 2012. 528079.
45. Sokolsky-Papkov, M., et al., Polymer carriers for drug delivery in tissue engineering. Advanced Drug Delivery Reviews, 2007. 59(4): p. 187-206.
46. Nair, L.S. and C.T. Laurencin, Polymers as Biomaterials for Tissue Engineering and Controlled Drug Delivery, in Tissue Engineering I, K. Lee and D. Kaplan, Editors. 2006, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 47-90.
47. Ghayempour, S. and S.M. Mortazavi, Preparation and investigation of sodium alginate nanocapsules by different microemulsification devices. Journal of Applied Polymer Science, 2015. 132(17).
48. O'Donnell, P.B. and J.W. McGinity, Preparation of microspheres by the solvent evaporation technique. Advanced Drug Delivery Reviews, 1997. 28(1): p. 25-42.
49. Kost, J. and R. Langer, Responsive polymeric delivery systems. Advanced Drug Delivery Reviews, 2001. 46(1): p. 125-148.
50. Patil, P., D. Chavanke, and M. A. Wagh, A review on ionotropic gelation method: Novel approach for controlled gastroretentive gelispheres. Vol. 4. 2012. 27-32.
51. Holland, T.A. and A.G. Mikos, Review: Biodegradable Polymeric Scaffolds. Improvements in Bone Tissue Engineering Through Controlled Drug Delivery, in Tissue Engineering I, K. Lee and D. Kaplan, Editors. 2006, Springer Berlin Heidelberg: Berlin, Heidelberg. p. 161-185.
52. Garg, T., et al., Scaffold: A Novel Carrier for Cell and Drug Delivery. Vol. 29. 2012. 1-63.
53. Ma, P.X., Scaffolds for tissue fabrication. Materials Today, 2004. 7(5): p. 30-40.
54. Champion, E., Sintering of calcium phosphate bioceramics. Acta Biomaterialia, 2013. 9(4): p. 5855-5875.
55. Delalande, A., et al., Sonoporation: Mechanistic insights and ongoing challenges for gene transfer. Gene, 2013. 525(2): p. 191-199.
56. Zhao, Y., H. Li, and P. Liu, Study on microemulsion polymerization of N-butyl maleimide. Journal of Applied Polymer Science, 2000. 77(4): p. 805-809.
57. Lu, T., Y. Li, and T. Chen, Techniques for fabrication and construction of three-dimensional scaffolds for tissue engineering. International journal of nanomedicine, 2013. 8: p. 337-350.
58. Ita, K., Transdermal iontophoretic drug delivery: advances and challenges. Journal of Drug Targeting, 2016. 24(5): p. 386-391.
59. Pitt, W.G., G.A. Husseini, and B.J. Staples, Ultrasonic drug delivery--a general review. Expert opinion on drug delivery, 2004. 1(1): p. 37-56.
60. Mullick Chowdhury, S., T. Lee, and J.K. Willmann, Ultrasound-guided drug delivery in cancer. Ultrasonography (Seoul, Korea), 2017. 36(3): p. 171-184.
61. Biondi, M., et al., Controlled drug delivery in tissue engineering. Advanced Drug Delivery Reviews, 2008. 60(2): p. 229-242.