INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

SCAFFOLDS FOR PHARMACEUTICAL USE: A REVIEW

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ARTICLE INFO

Article history
Received 19/03/2017
Available online
12/04/2017

Keywords
Alginates,
Proteins,
Collagens,
Gelatine,
Fibrins And Albumins.

ABSTRACT

Scaffolds are 3 dimensional structures that are used as implants or injects which are used to deliver drugs, cells, genes into body. A scaffold provides a suitable substrate for cell attachment, cell proliferation, cell migration and differential function. Scaffold matrices are highly efficient in drug delivery especially targeted drug delivery. The fabrication of scaffolds is done by using the biomaterials like alginates, proteins, collagens, gelatine, fibrins and albumins. Some synthetic materials like polyvinyl alcohol and polyglycolide are also used. Their application of late has extended to delivery of drugs and genetic materials, including plasmid DNA, at a controlled rate over a long period of time. In addition, the incorporation of drugs (i.e., inflammatory inhibitors and/or antibiotics) into scaffolds may be used to prevent infection after surgery and other disease for longer duration. The present review gives a detailed account of the need for the development of scaffolds along with the materials used and techniques adopted for the manufacture of scaffolds for prolonged rug delivery.

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*Please cite this article in press as **A. Susmitha** et al. Scaffolds for Pharmaceutical Use: A Review. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTRODUCTION

A scaffold is a 3D structure used that serves as a support for isolated cells to grow. They are implants or injects which are used to deliver drugs, cells, genes into body. There are the following types of scaffolds available for drug delivery.

1. A typical three dimensional porous matrix
2. A nanofibrous matrix
3. A thermo sensitive solgel transition hydro gel
4. A porous microsphere

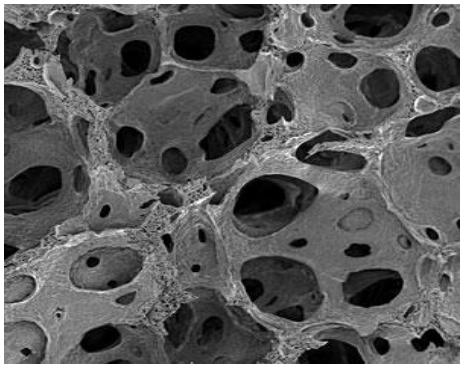

Fig: A typical three dimensional porous matrix.

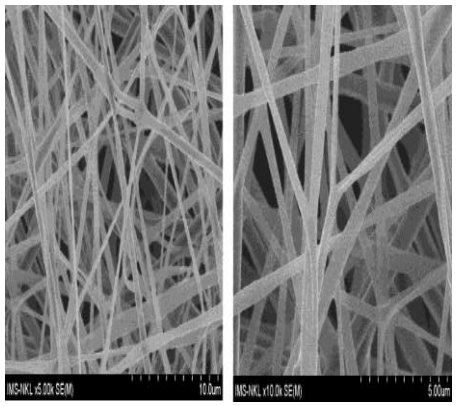

Fig: A nanofibrous matrix.

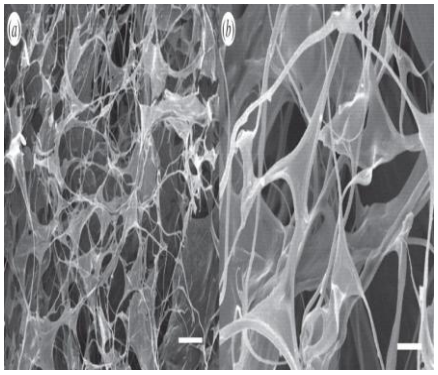

Fig: A thermo sensitive solgel transition hydro gel.

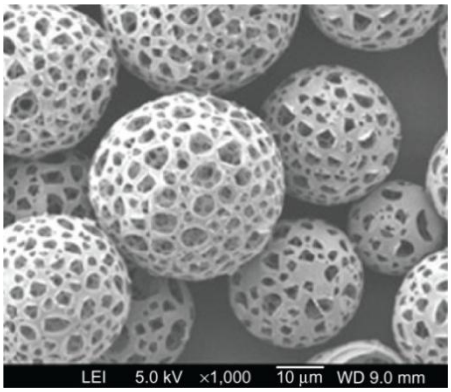

Fig: A porous microsphere.

A scaffold provides a suitable substrate for cell attachment, cell proliferation, cell migration and differential function. Scaffold matrices are highly efficient in drug delivery especially targeted drug delivery. The fabrication of scaffolds is done by using the biomaterials like alginates, proteins, collagens, gelatine, fibrins and albumins. Some synthetic materials like polyvinyl alcohol and polyglycolide are also used. Bio ceramics like hydroxyapatites and tricalcium phosphates are used. The fabrication of scaffold include particulate leaching, freeze drying, superficial fluid technology, thermally induced phase separation, rapid prototyping, powder compaction, sol-gel and melt moulding. These techniques allow the preparation of porous structures with regular porosity. Scaffold are used successfully in various fields of tissue engineering such as bone formation, periodontal regeneration, repair of nasal and auricular malformations, cartilage development, as artificial corneas, as heart valves, in tendon repair ,in ligament replacement, and in tumours. They also are used in joint pain inflammation, diabetes, heart disease, osteochondrogenesis, and wound dressings. Their application of late has extended to delivery of drugs and genetic materials, including plasmid DNA, at a controlled rate over a long period of time. In addition, the incorporation of drugs (i.e., inflammatory inhibitors and/or antibiotics) into scaffolds may be used to prevent infection after surgery and other disease for longer duration.

Over centuries, the field of regenerative skin tissue engineering has had several advancements to facilitate faster wound healing and thereby restoration of skin. Skin tissue regeneration is mainly based on the use of suitable scaffold matrices. There are several scaffold types, such as porous, fibrous, microsphere, hydrogel, composite and acellular, etc., with discrete advantages and disadvantages. These scaffolds are either made up of highly biocompatible natural biomaterials, such as collagen, chitosan, etc., or synthetic materials, such as polycaprolactone (PCL), and poly-ethylene-glycol (PEG), etc. Composite scaffolds, which are a combination of natural or synthetic biomaterials, are highly biocompatible with improved tensile strength for effective skin tissue regeneration. Appropriate knowledge of the properties, advantages and disadvantages of various biomaterials and scaffolds will accelerate the production of suitable scaffolds for skin tissue regeneration applications. At the same time, emphasis on some of the leading challenges in the field of skin tissue engineering, such as cell interaction with scaffolds, faster cellular proliferation/differentiation, and vascularisation of engineered tissues, is inevitable. In this review, we discuss various types of scaffolding approaches and biomaterials used in the field of skin tissue engineering and more importantly their future prospects in skin tissue regeneration efforts. The main objective of the present review is to give detailed account of the need for the manufacture of scaffolds, their development of along with the materials used and techniques adopted for the manufacture of scaffolds for prolonged rug delivery.

Requirements for an ideal scaffold:

The design of the scaffold determines the functionality of the construct to a high extent. Although the final requirements depend on the specific purpose of the scaffold, several general characteristics and requirements need to be considered for all designs. The scaffold should be/have: -

Biocompatible; the scaffold should provoke an appropriate biological response in a specific application and prevent any adverse response of the surrounding tissue

- Biodegradable; the scaffold materials should degrade in tandem with tissue regeneration and remodeling of the extracellular matrix (ECM) into smaller non-toxic substances without interfering with the function of the surrounding tissue
- Promote cell attachment, spreading and proliferation; vital for the regulation of cell growth and differentiation
- Suitable mechanical strength; its strength should be comparable to in vivo tissue at the site of implantation as evidently, a scaffold requires more flexibility or rigidity depending on the application in e.g. cardiovascular versus bone prostheses
- Good transport properties; to ensure sufficient nutrient transport towards the cells and removal of waste products the scaffold should be highly porous with good pore connectivity, however, it should maintain sufficient mechanical strength implying optimization of porosity
- Easy to connect to the vascularisation system of the host; to ensure good nutrient supply throughout the scaffold post-implantation, the scaffold should be connected to the natural nutrient supplying system
- Suitable surface characteristics; apart from optimal physiochemical properties, research suggests that the introduction of e.g. surface topography into the scaffold improves tissue organization leading to increased tissue function

MATERIALS

Common biomaterials

Due to the variation in mechanical properties required in 'soft' versus 'hard' TE applications, the constructs for these two sub-categories generally use different classes of biomaterials. For soft TE applications, e.g. skeletal muscle or cardiovascular substitutes, generally a wide variety of polymers are applied. On the other hand, hard tissue replacements, e.g. bone substitutes, are generally based on more rigid polymers, ceramics and metals. Frequently used biomaterials originate from a wide range of natural as well as synthetic sources. Table 1 lists polymers extensively applied in scaffold fabrication for 'soft' TE applications. Apart from single polymers, scaffolds are also commonly fabricated from co-polymers of two or more polymers (not listed) to improve the overall characteristics; co-polymers generally have an average of the mechanical properties of the incorporated single polymers.

Table 1: Materials frequently applied in soft TE applications.

Origin	Polymer (family)
Natural	Collagen
	Fibrin
	Gelatin
	Poly(hydroxybutyrate)
	Polysaccharides
	most common are hyaluronic acid, chitosan, starch and alginates
Synthetic	Poly(esters)
	most common are poly (α-hydroxy acids): poly(lactic acid) (PLA) and poly(glycolic acid) (PGA)
	Poly(ε-caprolactones)
	Poly(propylene fumarates)
	Poly(anhydrides)
	Poly(anhydrides)

Scaffold fabrication for hard TE applications employs a wider variety of classes of materials; including polymers, ceramics, composites and metals. Table 2 presents materials extensively used in hard TE, besides the polymers already listed in Table 1. Often, polymers alone might not have sufficient mechanical strength, which can be improved by adding reinforcements resulting in composites. Herewith, combining two or more classes of materials improves the mechanical properties, similar to the principle behind co-polymer.

Table-2: Materials frequently applied in hard TE applications.

Class of material	Type
Crystalline ceramics	Hydroxyapatite
	Tricalcium phosphate
	Calcium metaphosphate
Amorphous glass	Silica
	Bio-glass
Composites	Hydroxyapatite / poly(ε-caprolactone), chitosan, and/or collagen
	Titanium/calcium phosphate, polyvinyl alcohol, and/or boron
	Poly(lactic acid)/ tricalcium phosphate, silica, and/or ceramic
Metals	Stainless steel
	Alumina
	Titanium

Poly (lactic acid) (PLA):

PLA belongs to the polyester family, as is the case for the vast majority of biodegradable polymers. PLA exists in different isomeric forms, namely semi-crystalline D (-) (PDLA), semi-crystalline L (+) (PLLA) and amorphous racemic D, L (PDLLA). PLA degrades by bulk hydrolysis and leads to the production of lactic acid. In case of PLLA, degradation results in L (+) lactic acid, a substance that exists in the human body under natural circumstances as well, therefore PLLA is generally preferred over PDLA. The body transports the produced L (+) lactic acid to the liver, converts it into pyruvic acid and upon entering the tricarboxylic acid cycle, secreting it as water and carbon dioxide. Despite the FDA-approval of PLLA and the large number of clinical applications, a number of literature studies report inflammatory responses. During degradation, the produced lactic acid can lower the pH in the environment adjacent to the polymer. This local acidity can aversively affect cellular function and induce inflammatory response. Additionally, highly crystalline parts might stay behind which can cause an inflammatory response of the surrounding tissue. However, it was also noted that in case of relatively small material volume, no adverse biological responses occur. In addition, other literature reports that PLA does not leave significant amounts of accumulating degradation products behind in the body.

The degradation of PLLA in vitro occurs in the order of years, whereas in vivo degradation takes approximately 8-10 months; degradation of PDLLA is in the order of months. The degradation rate of PLA scaffolds highly depends on amongst others molecular weight and polydispersity of the polymer, process parameters and scaffold design. PLLA exhibit superior mechanical strength compared to PDLLA due to its semi-crystalline nature (10- 40 % crystallinity) and higher Tg of around 65 °C versus around 54 °C for PDLLA. Therefore, mostly PLLA is selected over PDLLA as scaffold material, as is also the case for the vast majority of the work.

Poly (ε-caprolactone)

Another polymer selected of the polyester family is poly (ε-caprolactone (PCL), a semi-crystalline rubbery polymer with a very low Tg of around -60 °C. Generally PCL degrades by bulk hydrolysis like PLA, although also enzymatic degradation can occur under certain conditions. Degradation is significantly slower compared to PLA due to limited fluid inflow as result of the close packed macromolecules; in vivo degradation time extents to over 2 years. Therewith, PCL is mainly suitable for long-term implants.

Poly (tri-methylene carbonate)

Poly (tri-methylene carbonate) (PTMC) is another rubbery material with high elasticity which can be attractive in certain soft TE applications. Amorphous PTMC exhibits a Tg of around -15 °C. High molecular weight PTMC yields relatively good mechanical properties. PTMC hardly degrades in aqueous solutions, whereas it degrades in the order of weeks via enzymatic degradation in vivo. Degradation of PTMC does not lead to local decrease of pH in the surrounding tissue of the scaffold, as in the case of e.g. PLA.

Poly (ethylene oxide)/poly (butylene terephtalate)

This copolymer consists of hydrophilic poly (ethylene oxide) (PEO) and hydrophobic poly (butylene terephtalate) (PBT) segments. Variation in the composition of the PEOT/PBT copolymers allows tailoring of the mechanical, biological and physicochemical properties of the material. Herewith allows PEOT/PBT application in a range of TE constructs, of both soft as well as hard TE origin. PEOT/PBT is well studied as bone filler material, due to the bone-bonding character of the copolymer (especially with a high PEO content). Degradation occurs upon hydrolysis and oxidation and is in the order of months, depending on its composition.

Poly (dimethyl siloxane)

(PDMS) is extensively used in microfluidics and a “lab on a chip” application as it is easy processable, cheap and transparent offering the opportunity of easy imaging. In the past 10–15 years, there has been an increased interest in the use of microfluidics in TE. The lab on a chip approach allows scientists to control the accuracy of tests, perform high throughput screening of biomaterials regarding cell response or biological reactions in general. As these fields more and more expand to biomedical applications, often PDMS is selected within specific studies related to these disciplines. Beneficial is the high gas permeability of PDMS which can be exploited for O2 supply and CO2 removal during cell culture. However, thin PDMS sheets have relatively poor mechanical strength and often needs to be coated with e.g. fibronectin to allow good cell attachment.

FABRICATION METHODS

A great variety of well-known fabrication techniques are used in scaffold design. This section briefly describes frequently applied techniques, with in the end special attention to polymer casting and phase separation as these are the main fabrication methods used in this thesis.

Emulsion freeze-drying

In emulsion freeze-drying, homogenization of a polymer–solvent system and water leads to formation of an emulsion. An emulsion exists of two phases, a continuous phase and a dispersed phase within; here, the continuous phase consists of the polymer-rich phase, whereas water is the dispersed phase. The emulsion is cooled down quickly to freeze the solvent and water, resulting in solidification of the polymer directly from the liquid state and the creation of a porous polymer structure. Subsequently, the frozen solvent and water are removed by freeze-drying. Emulsion freeze-drying is attractive for creation of relatively thick scaffolds with large pores. Additionally, incorporation of proteins is enabled during the fabrication of the scaffold. The obtained morphology is mainly non-percolated (solid-wall like pores), which is the major drawback of freeze- drying as this often limits cell in-growth and nutrient transport through the scaffold.

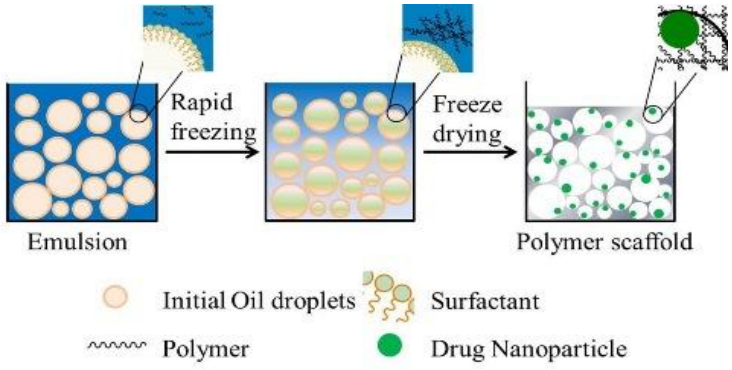

Fig: emulsion freeze drying of scaffolds.

Foaming

In general, foaming uses a soluble inert gas, e.g. CO2 or N2, in the supercritical region as blowing agent to create porosity in polymers via pressure quenching. Variation of the process conditions enables tuning of the scaffold properties. Instead of using a single polymer, this method is also applicable for composites of polymer and (bio) ceramic to employ in hard TE constructs. Beneficial is the lack of solvent, eliminating the risk of remaining residues, and the low processing temperatures preventing degradation of the polymer during processing. The scaffolds often have a closed surface (skin) and mainly non-percolated pores which can be a serious drawback of the method as these characteristics limit nutrient transport through the scaffold. Nonetheless, it is possible to obtain open porous morphologies in particular cases; however, the pore size is often too small for TE applications. Through additional post-processing steps, interconnected pores can be introduced by, for example, plasma treatment or pulsed ultrasound to break the walls of the non-percolated pores.

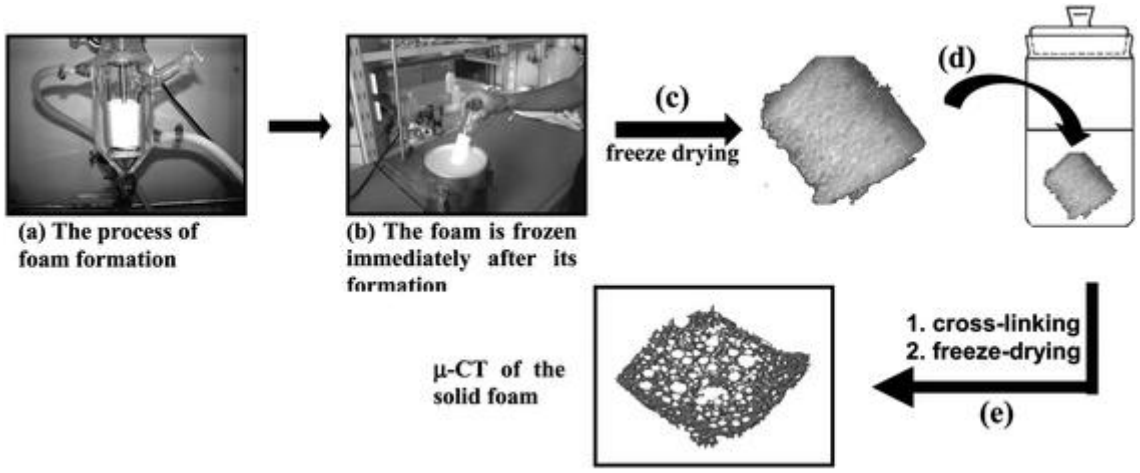

Fig: foaming.

Particle leaching

Particle (or particulate, salt, porogen) leaching combines with various different techniques such as solvent casting, compression-molding or foaming. Particle leaching incorporates particles, e.g. salt, sugar or specifically prepared spheres, dissolved in a polymer sample and subsequently washed out after processing the polymer sample into the final form creating (additional) porosity in the scaffold. The biggest advantage of particle leaching is the creation of scaffolds with big pores, well-controlled high interconnected porosity and pore morphology. However, the method is not applicable for all materials such as soluble protein scaffolds and additionally, it may be a time-consuming post-processing method with the risks of remaining residues after processing.

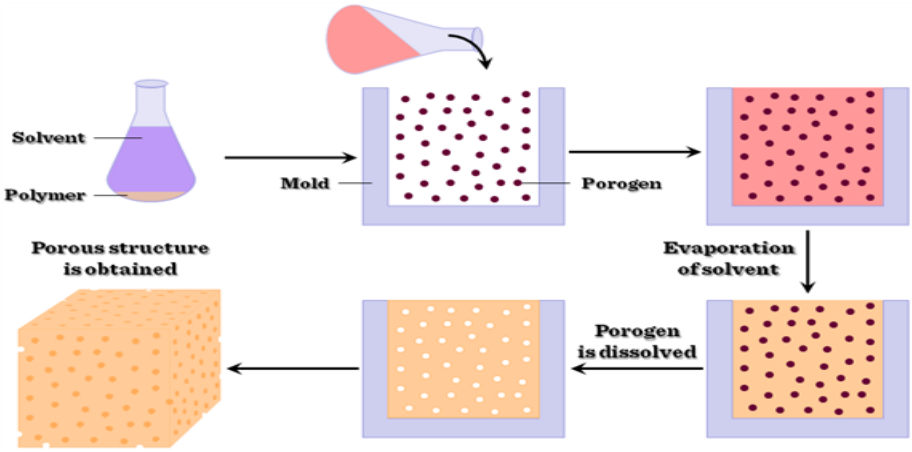

Fig: particle leaching of scaffolds.

Electrospinning

Electrospinning (ESP) is based upon charging of a polymer solution and subsequent ejection through a capillary tip or needle. The jet coming from the needle draws towards a collector due to an electric field ranging from 10 to 30 kV. Evaporation of the solvent from the jet after leaving the needle results in fiber deposition on the collector. To obtain continuous fibers, the method requires using solutions containing relatively high polymer concentrations of usually around 10-15 wt%. Rotating the collector creates a non-woven mesh with a preferential orientation of the fiber. The diameter of the fibers is within the range of nanometers to microns. Varying the process parameters, e.g. strength of the electric field, distance between needle–collector, polymer concentration, allows tuning of the fiber diameter. A major advantage of electro spinning is the high flexibility and fiber resolution of the obtained scaffold. Additionally, alignment of the electrospun fibers is enabled to induce cell and tissue alignment. A drawback of electro spinning is the risk of breaking fibers during fabrication, which might lead to inferior quality of the scaffold.

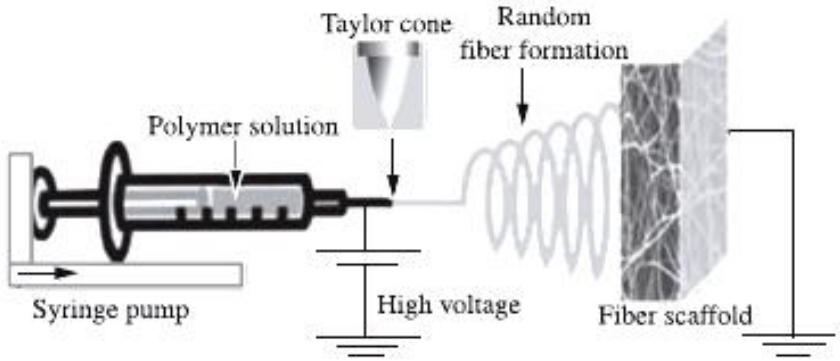

Figure 1. Electrospinning setup.

Fig: electron spinning.

Sintering

Sintering refers heat-treatment of a powder to make the particles adhere to each other. Application of scaffolds fabricated by sintering is mainly in hard TE constructs. Traditionally, sintering uses ceramic powders; however, this method is also applicable for other materials such as metals, glasses and certain polymers as well as composites. In the latter, the heat-treatment pyrolizes the polymer and the ceramic particles adhere taking over the porous design of the polymer sheet. The possibility of creating controlled and graded porosity is the main advantage of sintering. Detrimental is the possible risk of low interconnectivity of the pores and the brittleness of the fabricated scaffold in case of using certain materials.

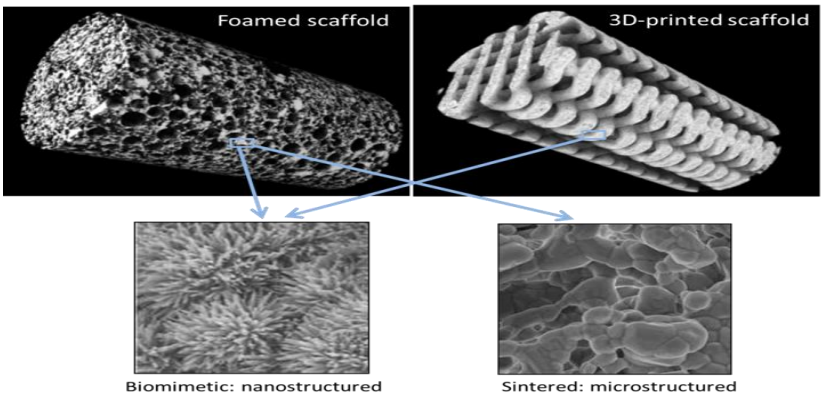

Fig: sintering.

Polymer casting and phase separation

Several fabrication methods based on polymer casting, with or without subsequent phase separation, are frequently applied to produce TE scaffolds. Methods often used for phase separation are e.g. liquid induced phase separation (LIPS, immersion precipitation) and thermally induced phase separation (TIPS). Without phase separation, polymer solidification is generally achieved by solvent evaporation. These methods allow processing of pure polymers as well as composites of polymer–(bio) ceramic for application in hard TE. In this thesis, generally polymer casting is performed on a micro patterned mold. In this case, due to the solidification of the polymer on the mold, the inverse micro pattern is imprinted in the polymer sheet. When combined with LIPS, this technique is called phase separation micro-molding (PSμM). The advantage of PSμM is the combination of micro patterning with porosity both in one fabrication step. Variation of the mold design enables variation in the obtained micro pattern whereas tuning of the process parameters allows tailoring of the sheet porosity. The advantage of polymer casting is the possibility to create a wide range of porosities, pore sizes and morphologies. The major drawback of these techniques, however, is the use of organic solvents, which may leave residues after processing and therefore possibly harm the cells. Therefore, effectively washing the scaffolds prior to their contact with cells is essential.

The requirements of scaffolds for tissue engineering are complex and specific to the structure and function of the tissue of interest. The scaffold fabrication technique therefore needs to be developed appropriately to manufacture the scaffold with the desired characteristics such as the degradation rate, porosity, pore size, shape, distribution, and mechanical properties. Factors such as pore size, shape, and tortuosity can all affect tissue in- growth but are thought to be difficult to control precisely using these processing techniques. New design and manufacture methodologies are required, and rapid prototyping tools are believed to be a good alternative.

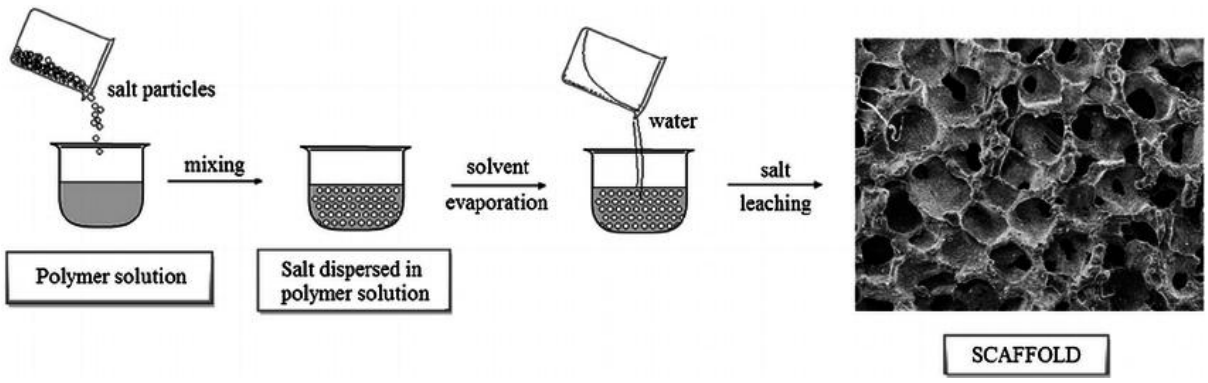

Fig: polymer casting and phase separation.

DESIGN STRATEGIES FOR CELL AND DRUG DELIVERY SYSTEMS

Although prefabricated scaffolds are most widely used for tissue regeneration as well as drug delivery purposes, different forms of polymeric scaffolds for cell/drug delivery are also available. These forms can be classified as (1) a typical 3D porous matrix, (2) a nano fibrous matrix, (3) a thermo sensitive sol-gel transition hydrogel, and (4) a porous microsphere. Of these, the typical 3D porous matrix and nanofibrous matrix are the implantable forms and the thermo sensitive sol-gel transition hydrogel and the porous microsphere are the injectable forms. Injectable scaffold materials formed in situ have received much attention recently because they can be administered using a syringe needle and thus avoid surgery. To mimic the topological and micro structural characteristics of the ECM, a biomaterial must have a high degree of porosity, a high surface: volume ratio, a high degree of pore interconnection, appropriate pore size, and geometry control. These properties can be well controlled in an injectable scaffold. Some of the drug/cell delivery systems and their design strategies are given in the following sections.

Hydrogel-Based Systems

Hydrogel matrices are physically or chemically cross-linked, water-soluble polymers, which swell to form a gel like substance on exposure to water. Hydrogels are appealing for biological applications because of their high water content and biocompatibility. Hydrogels can be made from naturally occurring polymers such as collagen, chitosan, and gelatine or synthetic polymers such as poly (ethylene glycolide) and poly vinyl alcohol. Growth factors are released from hydrogels through diffusion of the growth factor through the highly hydrophilic scaffold, mechanical stimulation, or hydrolytic degradation of the scaffold or upon swelling in response to an environmental stimulus. For example, gelatin and dextran can be fabricated as an interpenetrating polymer hydrogel for drug delivery and can exhibit an intelligent property of degradation in response to dual stimuli. Release behavior can be regulated by controlling the chemical and physical properties of the gels from a few days to several months. Above critical concentrations, these hydrogels show a sol state at room temperature, but change into a gel state at body temperature; hydrogels can be administered in a minimally invasive manner and therefore they are used in tissue engineering strategies as a potential cell and protein delivery vehicle. Additional advantages of hydrogels are that they may protect drugs, peptides, and especially proteins against the potentially harsh environment in the vicinity of the release site; they enable enhanced residence times, sustained delivery, and/or targeted drug delivery; and they have significant potential in wound healing applications, though pore size and degradation properties must be optimized. For example, injectable poly (N-isopropylacrylamide) physical hydrogels encapsulating cells have been prepared for cartilage and nerve regeneration. Pluronic/heparin composite hydrogels delivering growth factor also have been studied to induce angiogenesis. Photo crosslinked poly (ethylene glycol) (PEG)–based hydrogels have been utilized for delivery of chondrocytes and osteoblasts. Bone morphogenic protein introduced into the hydrogel material (temperature-sensitive chitosan-polyol salt combination) has been effective in promoting de novo bone and cartilage formation in vivo. Poly (lactic acid–glycolic acid) (PLGA) grafted with PEG and PEG grafted with PLGA hydrogels capable of sustained insulin delivery and cartilage repair were synthesized. Pluronic copolymers at a higher concentration (more than 20% [w/v]) have been used to encapsulate chondrocytes and produce engineered cartilage.

Microsphere- and Micro particle-based Systems

Microspheres and micro particles have attracted attention as carrier matrices in both the biomedicine and bioengineering fields and could satisfy the need of delivering biomolecules such as growth factors, genes, and cells. Prior to injection, the porous structure (30 μm) would allow sufficient cell seeding in and out of the matrix. After injection in vivo, the porous matrix would permit infiltration of cells and in-growth of tissue from the host, facilitating the regeneration process. Microparticles also can be used as injectable scaffolds to support cell growth and proliferation directly and as vehicles of growth factor, and to enhance cell proliferation and expansion simultaneously. Microspherebased technology has an application for tissue engineering as well as gene therapy. Gene delivery has several potential advantages, such as the inherent stability of plasmid DNA, reduced fabrication costs, extended shelf-life, a more economical use, and application in skin repair. Application is pellets incorporated with basic fibroblast growth factor– loaded microspheres into alginate porous scaffolds to enhance vascularisation after implantation in the rat peritoneum. Chitosan scaffolds loaded with basic fibroblast growth factor contained in gelatin micro particles were effective in accelerating wound closure. of pressure ulcers. Biodegradable PLGA microspheres have been studied for delivery of chondrocytes for cartilage engineering. Nanofabricated particles could offer better delivery properties to direct cell fate and to regulate processes such an angiogenesis and cell migration.

Membrane-based Systems

Human skin is considered the gold standard for treatment of skin wounds. However, skin grafts are not always the perfect solution. They are limited in terms of the conditions needed for tissue.

MATRICES/SCAFFOLD FOR DRUG DELIVERY

Low molecular weight drugs that control proliferation or differentiation of cells can be incorporated into biodegradable scaffolds to induce cellular differentiation and tissue remodelling. For example, dexamethasone, a steroidal anti-inflammatory drug, was loaded into the bulk phase of PLGA scaffolds for sustained release. It was observed that sustained release of dexamethasone effectively induced differentiation of bone marrow stem cells to osteoblasts or chondrocytes.

COMMERCIAL STATUS OF SCAFFOLDS

The first bioengineered skin to receive Food and Drug Administration approval in 1998 was Apligraf (bilayered collagen gels seeded with human fibroblasts in the lower part and human keratinocytes in the upper layer; Organogenesis, Inc. Canton, MA), used as the "dermal" matrix of an artificial skin product. Revitix (a topical cosmetic product), VCTO1 (bilayered, bioengineered skin) or Forta-Derm antimicrobial (an antimicrobial wound dressing) are collagen-based products, also commercialized by Organogenesis, Inc. infuse, marketed by Medtronic Sofamor Danek (Memphis, TN) in the United States, is a collagen sponge that has been used as an osteoconductive carrier of bone morphogenetic protein for spinal fusion. Collagen sponges also have been used for the treatment of long bone fractures. Collagraft is a mixture of porous hydroxylapatite, tricalcium phosphate, and animal derived collagen I, commercialized by Angiotech Pharmaceuticals, Inc. (Vancouver, British Columbia, Canada), has been used clinically for the treatment of long bone fractures for more than a decade. Healos bone graft replacement, availability, graft rejections, and conformability with the surrounding tissue with respect to thickness and pigmentation. Current strategies for wound dressings have been aimed at the development of the bilayer-structured membrane, with incorporation of growth factors into these matrices for improved healing.

For example, gelatin hydrogel containing epidermal growth factor–loaded microspheres has an enhanced effect on re-epithelization, improving the healing of the wound area. Antibiotics should be incorporated into the membranes to prevent infections because sustaining a sufficient drug concentration at the site of infection is important for the treatment of an infected wound. For example, a bilayered membrane combines silver sulphadiazine and a laminin-modified collagen membrane, which was shown to facilitate the dermal wound healing process marketed by DePuy Orthopaedics, Inc. (Warsaw, IN), is an osteoconductive matrix constructed of cross-linked collagen fibers that are fully coated with hydroxylapatite and has been approved recently for clinical use as a bone graft substitute in spinal fusions. Biomend is a collagen membrane conventionally used in the regeneration of periodontal tissue and is a registered trademark of Integra Lifesciences Corp. (Plainsboro, NJ). Gelfoam is an absorbable gelatin surgical sponge used as a hemostatic device, commercialized now by Pfizer (New York, NY). Pfizer also has a commercially available Gelfilm, an absorbable gelatine film designed for use as an absorbable gelatin implant in neuro, thoracic, and ocular surgery. A commercially available porous, absorbable gelatine disk is Surgifoam, distributed in the United States by Ethicon Inc. (Cornelia, GA). CultiSpher-G is a gelatin-based product in which macro porous gelatine micro carrier beads are used as micro carrier cell cultures, marketed by Percell Biolytica AB (Åstorp, Sweden). CultiSpher- S is the same product with a different cross-linking procedure conferring a higher thermal and mechanical stability. Tisseel VH consists of a two-component fibrin biomatrix with highly concentrated human fibrinogen to produce fibrin gel from a blood sample, commercialized in the United States by Baxter (Deerfield, IL).

The CryoSeal fibrin sealant system, which enables the production of autologous fibrin sealant components from a single unit of a patient's blood plasma in approximately 60 min, is manufactured in the United States by Thermogenesis Corp. (Rancho Cordova, CA). The Vivostat system, which is an automated system for the onsite preparation and application of patient-derived fibrin sealant or platelet-rich fibrin, has been commercialized by Vivolution (Denmark). GeniaBeads CN are hydrogel beads made from chitosan and have been commercialized by geniaLab (Braunschweig, Germany). The HemCon bandage, which is a chitosan bandage applied with pressure to a severe external wound, in several minutes attracts blood cells (negatively charged surface) that merge with chitosan to form a blood clot; it has been commercialized by HemCon Medical Technologies Inc. (Portland, OR). Alginate-based products Nu-Derm, commercialized by Johnson & Johnson (New Brunswick, NJ); Curasorb by Kendall (Mansfield, MA); or AlgiSite by Smith & Nephew (Continental), have been marketed widely as wound dressings. Hyalgan and Hyalubrix, commercialized by Fidia (Turin, Italy), and Artz, commercialized by Seikagaku Corporation (Tokyo, Japan), have been used widely as lubrication and mechanical support for the joints in osteoarthritis. Bionect, commercialized by CSC Pharmaceutical, and Jossalind, commercialized by Hexal (Holzkirchen, Germany) have been used widely as viscoelastic gels for surgery and wound healing. Healon is commercialized by Advanced Medical Optics (Santa Ana, CA), Opegan R is commercialized by Seikagaku, Opelead is commercialized by Shiseido (Japan), and Orthovisc is commercialized by Anika Therapeutics (Bedford, MA); these have been used widely for implantation of artificial intraocular lens. EmbryoGlue is commercialized by Vitrolife, Inc. (Englewood, CO) and has been used widely for in vitro fertilization. Hyaff is a benzyl ester of hyaluronic acid that maintains the biological characteristics of the natural molecule from which it is derived and is commercialized by Fidia; it has been used widely as a biomaterial for biomedical applications.

The Integra dermal regeneration template, which is a bilayered membrane system for skin replacement that provides a scaffold for collagen and a glycosaminoglycan (chondroitin-6-sulfate) used for burn and reconstructive surgery; it is marketed by Integra in the United States. Viscoat is a solution of 4% chondroitin sulfate and 3% sodium hyaluronate that is used as a surgical aid in anterior segment procedures, including cataract extraction and intraocular lens implantation; it is commercialized by Alcon Laboratories (Hemel Hempstead, England). Gelrite, a novel ophthalmic vehicle, gels in the presence of mono- or divalent cations present in the lacrimal fluid. Natrosol 250HX, distributed by Hercules (Wilmington), and geniaBeads MC, marketed by geniaLab, are used in pharmaceutical formulations for various purposes: low-viscosity grades are used as tablet binders in immediate-release dosage forms, and medium- and high-viscosity grades are used in sustained-release matrix formulations. Commercially available poly-β-hydroxybutyrate homopolymer BIOPOLGO4 is commercialized by ICI Biological Products (Angiotech Pharmaceuticals, Inc. in Canada) in the form of compression-molded sheets 0.5 mm thick. Similarly, ICI commercialized BIOPOLP05, the copolymer poly (β-hydroxybutyrate-co-β-hydroxyvalerate) containing 24% hydroxyvalerate, used as polyhydroxybutyrates, which have been studied to some extent for tissue engineering applications, mainly for scaffold materials in combination with ceramic materials, as a vehicle for drug delivery, and as a material for cardiac tissue engineering.

CONCLUSIONS AND FUTURE STUDIES

Scaffolds have been well investigated with respect to the material requirement, properties, and technology for the production of scaffolds. The field of biomaterials has played a crucial role in the development of tissue-engineered products. In spite of this, few scaffolds are available commercially, particularly for cell/drug delivery. Most of the scaffolds studied are still in the investigation stage and are yet to be approved for clinical use. Looking into convenience and practicability, there is immense scope in developing injectable gel-sol scaffolds because they are easy to use, versatile, and involve the use of safe adjuvants; many of them are already listed in the Generally Recognized as Safe list or even have been approved by the Food and Drug Administration. New biodegradable polymers need to be developed to meet all requirements for surgically implantable scaffolds. New approaches targeting cell/drug delivery are the need of the hour, particularly for tissue regeneration, postsurgical management, cancer, and congenital malformations. Scaffolds provide adequate signals (e.g., through the use of adhesion peptides and growth factors) to the cells, induce and maintain them in their desired differentiation stage, and are necessary for their survival and growth. Thus, equal effort should be made in developing strategies of how to incorporate adhesion peptides and growth factors into the scaffolds to influence cell behavior and to establish the concentrations and distributions required for successful outcomes. At present, there is a vast amount of research being performed worldwide on all aspects of tissue engineering/regenerative medicine.

ACKNOWLEDGEMENTS

We acknowledge our management of Hindu college of Pharmacy and also very much thankful to Mr.V.Vasu Naik and Mr. A.Anka Rao for giving constant support and valuable guidance.

ABBRIVATIONS

PCL : Polycaprolactone
PEG : Poly-ethylene-glycol
ECM : Extracellular matrix
TE : Tissue engineering
PLA : Poly (lactic acid)
PGA : Poly (glycolic acid)
PTMC : Poly (tri-methylene carbonate)
PMO : Poly ethylene oxide
PBT : Poly (butylene terphtalate)
PDMS : Poly (dimethyl siloxane)
ESP : electro spinning
LIPS : Liquid induced phase separation
TIPS : Thermally induced phase separation
PSμM : Phase separation micro-moding
PLGA : Poly (lactic-acid-glycolic acid)

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