Received: 7 August 2013 Revised: 12 December 2013 Accepted article published: 15 January 2014 Published online in Wiley Online Library: 10 February 2014

(wileyonlinelibrary.com) DOI 10.1002/jctb.4300

Polymeric hollow fiber membranes for bioartificial organs and tissue engineering applications

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Abstract

Polymeric hollow fiber (HF) membranes are commercially available, i.e. microfiltration and ultrafiltration cartridges or reverse osmosis and gas separation modules, to be applied for separation purposes in industry, for instance to recover valuable raw materials or products, or for the treatment of end-of-pipe wastes to avoid environmental impacts, to regenerate or treat waters for reuse and for the separation of key components or clarification in food and beverage industries. They have also shown important benefits as hemodialyzers, hemodiafiltration or plasma purification devices in patients with liver or kidney damage. The good mass transport properties characterizing the polymeric HFs have opened new research areas of application in the biomedical field, such as the tissue engineering (TE) and the construction of bioartificial organs (BAO). In TE, the HFs act as scaffolds or supports and/or allow high permeance of nutrients and waste removal for cell proliferation and differentiation. In BAO, HFs are used for the fabrication of bio-hybrid constructs that replace the damaged organs of the patient or can be used as *in vitro* models for therapeutic studies. This review presents the state-of-the-art concerning preparation and application of HFs for TE and BAO and discusses the challenges and future perspectives of the HFs in both fields.

Keywords: Membranes; Tissue Engineering; Biodegradable; Filtration

INTRODUCTION

Hollow fibers (HFs) are tubular membranes with diameters ranging from 50 to 3000 μm.[1] Their geometry confers upon a series of benefits such as compactness, excellent mass transfer properties[2] and resistance to high external hydrostatic pressures. The first applications of HFs in medicine were in blood purification devices (e.g. hemodialysis and hemodiafiltration)[2] and they are nowadays a keystone in daily medical practices. Moreover, in the 1970s, HFs were also proposed as catheters for local drug delivery[3] that later derived into injectable drug reservoirs easily removed by minor surgery should complications occurred during treatment.[4] Knazek *et al.*[5] first reported the employment of HF modules for tissue culture supports in a perfusion system. After this, HFs found a potential niche for tissue engineering (TE) applications.

TE is a multidisciplinary field that involves materials science, engineering and biology principles.[6] Its main objective is the regeneration of damaged tissues or organs whose structural function can hardly be restored by conventional treatments and require substitution or transplanting. Engineered tissues are usually constructed using supporting structures or scaffolds favoring cell attachment, proliferation and differentiation. The application of HF scaffolds in TE is schematically illustrated in Fig. 1. Briefly, the HFs are seeded with cells isolated from the patient (autologous cells), which overcomes the problem of rejection of the transplanted engineered tissue. Cell proliferation and differentiation is carried out under *in vitro* dynamic conditions in a bioreactor where the nutrients supply is enhanced. Finally, the tissue engineered construct is transplanted in the patient and eventually the HF scaffolds degrade and are replaced by the patient's cells. Besides the development of TE constructs where HF from biodegradable materials are used, HFs prepared using non-degradable materials are employed for perfusion bioreactors for cell expansion as well as extracorporeal bioartificial organs (BAO). In the latter, HFs are used for the fabrication of bio-hybrid constructs that replace the damaged organs of the patient or can be used as *in vitro* models for therapeutic studies. This work presents a review of the state-of-the-art and brief reflection on the advances of the employment of polymeric HFs for TE and BAO.

POLYMERIC MATERIALS

In general, the scaffolds for TE can be produced using either inorganic or organic materials or a combination of both. Glass, ceramic, titanium and other inorganic materials have traditionally been employed for tissue engineering[7–9] (e.g. in bone regeneration) alone or doped in polymeric HFs such as for instance hydroxyapatite (HA).[10] Our review focuses only on the application

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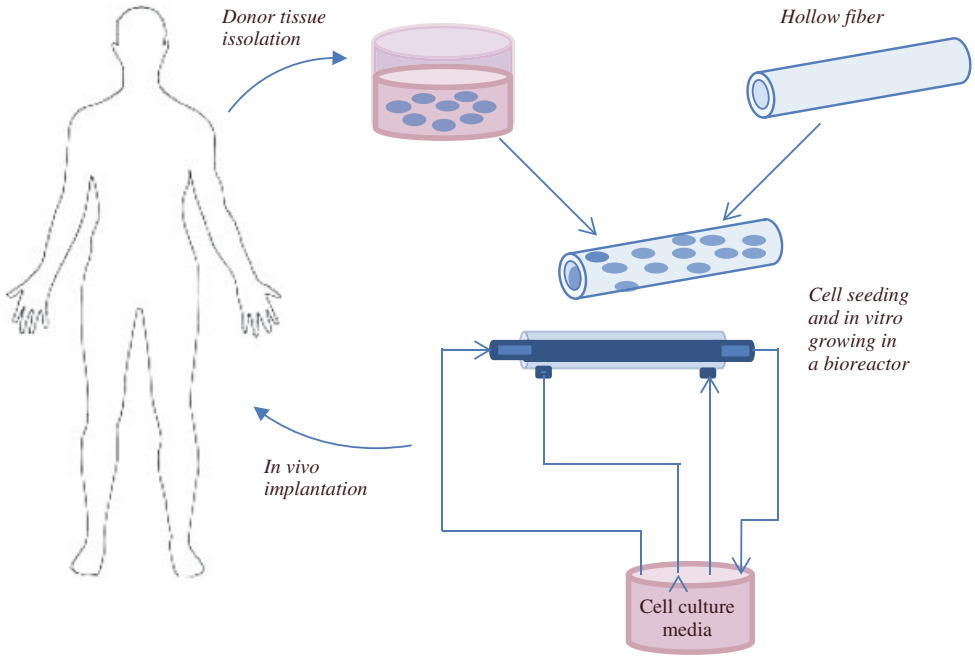

Figure 1. Graphical representation of tissue engineering using hollow fibers as scaffolds.

of polymeric materials for TE. Concerning inorganic materials and composites the reader should refer to other reviews.[7,8,11–13]

Table 1 presents an overview[14–88] of some of the most important polymeric materials used to produce HFs, fabrication methods and potential applications in TE and BAO. The polymers are classified based on their origin (natural or synthetic) and on their degradation properties (degradable or non-degradable). Natural materials such as collagen, elastin, fibronectin, laminin or the polysaccharide chitin and its derivative chitosan,[87] present in the extracellular matrix (ECM) of the tissues from animal or vegetal sources, have classically been used for artificial scaffolds. These materials promote the biological cue for cell growth and differentiation. Most natural polymers are enzymatically degradable.[90] A main limitation of the protein-animal-origin materials is their high risk of infectious disease transmission and immune response. Besides, another concern is the high cost of all these natural materials.

Synthetic biodegradable polymers and related copolymers have been used extensively for scaffolds for TE. Polyesters attracted major interest, mainly those approved by the US Food and Drug Administration (FDA) as suture materials,[91] e.g. poly(ϵ-caprolactone (PCL), polylactic acid (PLA), polylactic-co-glycolic acid (PLGA). Among these three polyesters, PCL is the most economical material and highly elastic but has a very low tensile strength. On the contrary, PLA and PLGA are stiff and have good tensile strength that can be complementary to those mechanical properties of PCL. PCL also has a very long degradation rate (1–2 years) that can help improve the properties of shorter degradation rate polymers, such as PLA and PLGA, or other natural polymers, such as collagen. Another important characteristic of these materials to consider in the selection is the formation of acidic degradation products (i.e. lactic acid, and glycolic acid in the case of PLA and PLGA) that might cause immune responses. This is usually not the case for PCL whose hydrolytic degradation does not produce acidic products. The characteristics of different polyesters and other polymers have been presented in detail previously.[90]

In perfusion bioreactors for cell expansion or BAO, non-degradable synthetic polymers are used (Table 1). Those more frequently employed are polyethersulfone (PES), polyetheretherketone (PEEK-WC) and polysulfone (PS), and occasionally polyacrylonitrile (PAN). These materials, mainly PES and PS, have traditionally been employed in the production of HF membranes for different applications and commercial and economical HF modules are available. Other non-degradable materials employed less often for BAO are poly(vinylidene difluoride) (PVDF),[92] polycarbonate (PC)[93] or for cellular therapies using patented HF materials like Polyflux consisting of a blend of polyarylethersulfone, polyvinylpyrrolidone and polyamide.[94]

All these materials could be processed to HF alone or in blends. Polymer blending is a simpler technique than copolymerization to overcome certain limitations of single materials, i.e. poor mechanical properties, inadequate degradation rate, or to tailor specific properties such as hydrophobicity/hydrophilicity. One of the polymers with high potential for blending is PCL which can form miscible blends with a wide range of polymers. For instance, collagen has been blended with more elastic polymeric materials (e.g. with PCL[14]) to reduce the intrinsic stiffness of this natural material and to give slower degradation rates and thus, better mechanical resistance of the polymeric scaffold for longer periods of time. Due to their hydrophilicity, polyvinyl alcohol (PVA) and polyethylene glycol (PEG) have been employed in blends to increase the permeability of the HFs.[31,38] However, the polymer blends are limited only to those cases where the polymers involved are miscible, either spontaneously or using the assistance of a compatibilizer. To overcome the limitations of finding compatible polymers with adequate characteristics a simple strategy is the employment of layers of the polymers. For instance, some natural materials have been utilized as coatings or additional layers to enhance biological cues or mechanical properties.[15–25] For deeper insight to the characteristics of polymeric materials for TE, the reader is referred to more specific reviews on this topic.[90,95–101]

Table 1. Literature review of polymeric materials, fabrication methods and applications of HFs in TE.

Polymer classification	Polymer type	Fabrication methods	Applications
Natural	Collagen	Electrospinning[14–18]	Nerve regeneration[14] Blood vessel regeneration[15–18]
	Alginate	Solvent spinning + gellation[19,20]	General scaffolds for vascularized systems [19,20]
	Chitosan	Knitting+ dip coating+ thermally induced phase separation (TIPS)[21,22]	General scaffolds[21,22]
	Cellulose (and derivatives like cellulose acetate)	Commercial membranes[23–25]	Blood vessel regeneration[23] Bioreactor[24,25]
Synthetic degradable	Poly lactic acid (PLA)	Melt spinning[26,27] Dip coating and diffusion induced phase separation (DIPS) or TIPS[28–30] Electrospinning[16,31] Wet phase inversion spinning[32,33]	Blood vessel regeneration[16,26,28] Nerve regeneration[27,31] Vascularized systems[29,30,32,33]
	Poly lactic-co-glycolic acid (PLGA)	Wet phase inversion spinning[10,34–40] Electrospinning[15,16,41–43] Mold casting and salt leaching[42,44]	Nerve regeneration[34,36,41–43] Bone regeneration[10,35,37,39] Blood vessel regeneration[15,16,40,44] Adipose tissue regeneration[39] General TE applications[38]
	Poly (ϵ-caprolactone) (PCL)	Electrospinning[16,17,41,43,45–50] Wet phase inversion spinning[40,51–53]	Nerve regeneration[41,43,51] Blood vessel regeneration[16,17,40,45–48,52,53] Bone regeneration[50] General tubular tissues[49,51]
	Poly(lactide-co-ϵ-caprolactone) (PLCL)	Melt spinning[54] Electrospinning[16,54]	Blood vessel regeneration[16,54]
	Poly(ethylene glycol) (PEG)	Electrospinning[31]	Nerve regeneration[31]
	Poly(hyroxybutyrate-co-hydroxyvalerate) (PHBHV)	Electrospinning[42] Wet phase inversion spinning[51]	Nerve regeneration[42] General scaffolds[51]
	Biodegradable polyurethanes (bPU)	Wet phase inversion spinning[55] Mold casting and TIPS[56] Electrospinning[56]	Nerve regeneration[55] Blood vessel regeneration[56]
	Poly(trimethylene carbonate) (PTMC)	Dip-coating and salt leaching[57,58] Compression molding and salt leaching[59]	Blood vessel regeneration[57,58] Nerve regeneration[59]
Synthetic non-degradable	Polyethersulfone (PES)	Melt spinning[60,61] Commercial (not specified)[62–69]	Blood vessel regeneration[60,61] Nerve regeneration[62,64] Bioreactor[66,67] Bioartificial liver (BAL)[62,63,65] Bioartificial kidney (BAK)[68,69]
	Polypropylene (PP)	Commercial (not specified)[67,70–72]	Bioreactors for vascularized tissues[67] e.g. bone[70] or low vascularized as cartilage[71,72]
	Polyurethane (PU)	Wet phase inversion spinning[73] Electrospinning[18]	Nerve regeneration[73] Blood vessel regeneration[18]
	polyetheretherketone (PEEK-WC)	Wet phase inversion spinning[65,74–77]	Bioreactor[74–76] Nerve regeneration[77] BAL[65]
	Polyacrylonitrile (PAN)	Wet phase inversion spinning[77–81]	Nerve regeneration[77,78] Bioartificial pancreas (BAP)[79] Bioartifical kidney (BAK)[80,81]
	Polysulfone (PS)	Commercial (not specified)[62,82–85] Wet phase inversion spinning[80]	BAK[80,82,83] BAL[62,84,85]
	Polyethylene coated with ethylene vinyl alcohol (PE-EVAL)	Commercial (not specified)[86–88]	BAL[86-88]

POLYMER PROCESSING

HFs are fabricated by means of extrusion or spinning techniques. Wet phase inversion spinning is widely applied while melt spinning is less utilized due to the high temperatures required and limited control of the porous structure. Other fabrication methods include electrospinning or dip coating (Table 1) although those could be more appropriately defined as techniques for the fabrication of tubular structures. In electrospinning a polymer solution droplet is electrically ejected from a nozzle and is stretched into a nanofiber that is collected at the other extreme of the electrical field that in the case of producing tubular structures is a cylindrical mandrel of adequate dimensions. Dip-coating is more a technique employed to procure additional polymeric layers on tubular scaffolds made of different materials and processing techniques. Dip-coating involves immersion of the tubular scaffold in a polymeric solution creating an external or internal layer. The solvent is then allowed

to evaporate. This process can be repeated to achieve a specified layer thickness. Electrospinning has been very popular because it arranges the polymer into a micro- or nano-fibrous structure similar to the architecture of natural ECM.[18] It can be used for the preparation of scaffolds with good mechanical properties and high porosities, but their production at industrial scale and their commercialization is difficult.

As mentioned earlier, wet phase inversion spinning is the most popular technique to fabricate HFs for TE and BAO (see a typical HF spinning set up in Fig. 2). This technique was developed in the 1960s and represented a major event in membrane technology.[2] Briefly, this processing technique involves the extrusion of a polymer solution (dope solution, 10–40%w/w of polymer, depending on the polymer molecular weight) from a coaxial nozzle (spinneret). A coagulating medium (bore solution) is pumped through the internal tube of the spinneret while the polymer solution is forced from the outer concentric nozzle. The HF leaving the spinneret is further precipitated during its immersion in the coagulation bath where the HF becomes mechanically stable. The HF properties can be tailored by adjusting different working variables[33,35,52,53] e.g. the air gap, dope and/or coagulation bath solution composition, bore and/or dope solutions flow rate, etc. Figure 3 shows some examples of the different morphologies and porosities that can be achieved. The porous morphology and pore size can be tuned, for instance, to allow cell infiltration and colonization of the HF.[53] A gradient in pore size can be created (asymmetric membranes) within a few micrometers of HF thickness from large macropores of several microns down to dense layers, to restrict at will the cell migration from lumen to shell sides. This is very useful for co-culturing different cell lineages.[40] One of the most important characteristic of the HF membranes for TE and BAO is the tailoring of the mass transport properties by tuning the fabrication conditions.[33] The importance of this is discussed in more detail in the next section concerning the applications of HFs.

APPLICATIONS OF HOLLOW FIBERS FOR TISSUE ENGINEERING

Hollow fibers as scaffolds

HF membranes have been widely used as scaffolds for cell proliferation and differentiation of tissues that require a tubular shape, e.g. intestine, urethra, blood vessels or nerves.[49] Moreover, tubular scaffolds have been used for the regeneration of tissues like cartilage, showing that this 3D structure can help preserve the phenotype of the chondrocyte cells rather than their differentiation into fibroblasts and can favor the production of ECM macromolecules.[72] The most popular applications of HFs as scaffolds have been the regeneration of small-caliber blood vessels and nerves (Table 1). There, as previously mentioned, degradable materials, either natural or synthetic, that can be resorbed and eliminated through metabolic pathways are preferred.

Synthetic large-diameter vascular grafts are already commercialized, while small-caliber vascular grafts (<6 mm) fail to successfully regenerate these tissues *in vivo* due to the occurrence of thrombus and intimal hyperplasia.[102] Autologous arterial and venous grafts have resulted in very successful prostheses for small-caliber revascularization;[45] however their availability is very limited. Therefore, synthetic polymeric HFs have been widely investigated for small-diameter blood vessel regeneration.

For this two important issues are widely discussed in the literature: (i) the thrombogenicity and (ii) the mechanical properties. Some polymeric HFs may be prone to the occurrence of thrombus when blood is perfused through the lumen as has been reported with the use of hemodialyzers (there, an anticoagulant is injected in the blood stream to avoid this problem). Solutions proposed to avoid thrombus formation are: (i) to conjugate heparin within the polymeric matrix;[48] (ii) endothelialization of the lumen;[15,28,46,103] and (iii) encapsulation of the endothelial cells in the HF.[19,20] Actually, a monolayer of endothelial cells in the lumen of the HF would procure a thrombo-resistant surface that isolates the polymeric material from the blood media and improves the patency of the scaffold.

The development of HF scaffolds mechanically compliant with the natural blood vessels is a major problem still under investigation. Natural materials such as collagen have insufficient mechanical properties.[104,105] Thus, much work has focused on developing HFs based on highly elastic materials such as PCL,[52,53] polytrymethylene carbonate (PTMC),[57,58] blends of natural and synthetic polymers[15–18,23,26,46] or of different synthetic polymeric materials[30,40,49] that could improve scaffolds compliance.

HF or tubular membranes are also used for cell guidance for example in spinal cord injury and neural regeneration. Although previously believed that the adult mammalian brain and spinal cord could not regenerate after injury, recent studies have shown neurogenesis in different regions of the central nervous system (CNS).[106] When the loss of nervous tissue is substantial (i.e. 10–15 mm gap) and spontaneous or adequate nerve regeneration is compromised, the gap between damaged nerve stumps is usually bridged by substrates that guide axonal outgrowth.[36] Similarly to blood vessel regeneration, the clinical application of autologous grafts for nerve regeneration present acute problems such as function loss at the donor sites, formation of potential painful neuromas, structural differences between donor and recipient grafts preventing successful regeneration, and shortage of graft material for extensive repair.[38] Therefore, interest in artificial grafts or nerve guide conduits such as HFs has increased since the 1990s.[55] In Table 1 the reader can find some work that reported polymeric tubular and HFs as nerve guide. Certain modifications to the tubular scaffolds morphology, like fabricating axially aligned grooves or patterns in the lumen side, enhanced the alignment and growth rate of the regenerated axons in comparison with those with smooth inner surface.[73] Tubular scaffolds with axially aligned electrospun fibers were very often used.[18,31] Yucel *et al.*[42] combined the micropatterned structure of the HF and filled the lumen with an aligned electrospun mat to maximize the effect of topographic cues. Other work[55] extruded solid fibers and the phase inversion created big pores in the lumen forming cavities that simulated uniaxially aligned hollows. *In vivo* implants on rat models of electrospun tubular scaffolds made of PCL/PLGA blends as nerve conduits already proved to have high potential for axonal and spinal cord regeneration.[41,43]

Hollow fibers in perfusion bioreactors

The number of cells required to engineer tissues *in vitro* is in the order of 10^{10} for each application.[38] The traditional static 2D culture flasks limit the rate of expansion of the cells and it is very time consuming. Dynamic culture bioreactors accelerate the process to obtain the required number of cells. Different bioreactor configurations exist, such as stirred flasks, rotating wall and perfusion bioreactors, and their advantages and disadvantages have been compared recently.[107,108] The most usual perfusion bioreactor configurations are depicted in Fig. 4(A). HF membrane bioreactors have a large surface area/volume ratio that

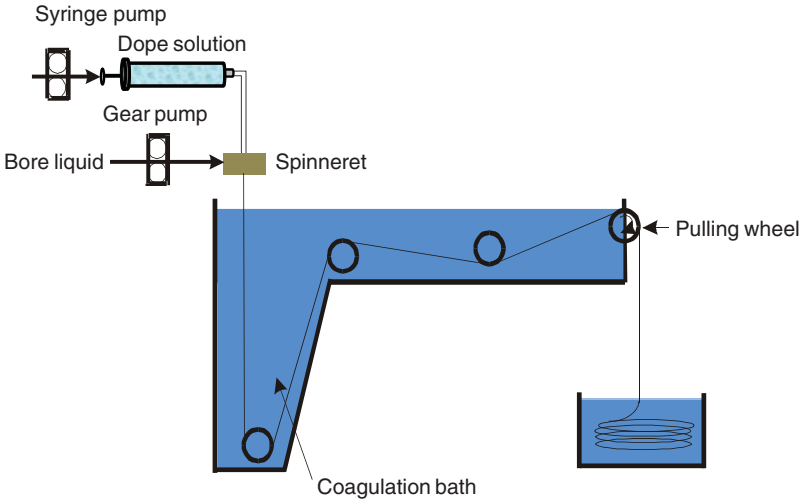

Figure 2. Typical diagram of a set up to fabricate HFs by phase inversion spinning (adapted from Ref. (40) with permission of Elsevier).

allows high cell expansion densities (number of cells/volume of media).[109] Moreover, it has been demonstrated that HF perfusion bioreactors using pulsatile flow conditions maintain 3D high cell density cultures and stimulate mammalian cells proliferation.[66] Several examples of the application of HF bioreactors for TE are summarized in Table 1 including studies of the expansion of human lymphocytes used for cell therapy in the treatment of malignant diseases (e.g. metastatic melanoma or renal cancer) or viral infections (e.g. cytomegalovirus and Epstein-Barr virus).[74–76]

Besides high density cell expansion, the employment of perfusion HF bioreactors has evolved towards new challenges. Thin two-dimensional tissue constructs possessing low organized blood capillaries are already commercialized.[23] However, the development of complex 3D and intensively vascularized engineered tissues is very challenging due to limitations in nutrients supply to the tissue. HF-based bioreactors can simulate capillary-systems[5] providing adequate substrate for cell proliferation, appropriate nutrients supply and waste removal,[110] while the cultured cells are protected from major mechanical and shear stress.[25] Some work has utilized this system to regenerate cartilage tissues[71,72] or highly vascularized tissues.[24,27]

A major limitation of HF perfusion bioreactors made of non-degradable HFs is that once the *in vitro* cultured cells have proliferated and even differentiated on 3D bulk tissues, they cannot be recovered maintaining their tridimensional structure to be implanted *in vivo*. A solution proposed was the use of highly permeable HF membranes (usually of non-degradable materials) inserted into an artificial scaffolding matrix that supports cell attachment and proliferation. In this system, the HFs simply act as a means for nutrients supply.[67,111] An example of this configuration, namely dual perfusion HF bioreactor, used by Bettahalli *et al.*[67] is represented in Fig. 4. This system gave good results for mouse pre-myoblast C2C12 cells proliferation inside the 3D scaffold in comparison with normal perfusion cell culture. Instead of a polymeric 3D scaffold, other work utilized alginate-gels[94] or collagen-gels[25] to immobilize the cells on the shell side of a HF bioreactor, e.g. a commercial dialyzer.[94] For example, De Napoli *et al.*[70] utilized Matrigel® to re-suspend the cells which was polymerized after cell seeding to create the 3D scaffold.

Biodegradable HFs can also be used to develop *in vitro* 3D tissue architectures on HF perfusion bioreactors.[33,35] In this case, the cell seeded HF structures could be later implanted *in vivo*. For instance, Ellis and Chaudhuri[35] found that using PLGA HFs in a bioreactor allowed 1 cm bone constructs (a highly vascularized organ). It is deemed that larger 3D tissue constructs could be successfully obtained *in vitro* by this approach that could be later implanted *in vivo*. Additionally, HFs may be organized in complex 3D architectures imitating the intricate and branched structure of blood capillaries. These complex 3D structures could be created by using techniques such as rapid prototyping,[112] self-assembling,[113] arranging them randomly on layers,[27,32] or knitting.[114] Tailoring the capillary porosity as well as cell culture in such systems is still challenging.[114]

Bioartificial organs

The shortage of available organs for transplantation stresses the importance of laboratory-made organs to replace or substitute those damaged in patients or looking for therapy strategies that boost the natural healing process.[115] The blood purification devices currently available cannot support the metabolic functions of the patients with severe organ damage. Therefore, the logical evolution dictated the necessity of including specific cells that could comply with the production of the missing metabolic compounds, that is, constructing bio-hybrid systems. HF membrane bioreactors have been largely utilized in bioartificial organ assist devices[35] (see concept in Fig. 5(A)). Some examples such as bioartificial liver (BAL),[62,63,65,84–87] bioartificial pancreas (BAP)[79] and bioartificial kidney (BAK)[80–83] are collected in Table 1. Extensive reviews on BAL,[116–122] BAK[123,124] and general bio-hybrid organs for patient therapy[115] have been published, and thus, the reader is referred to those works. Here, we discuss certain aspects related to the HF membranes.

The majority of work on BAO employed HF made of non-degradable materials like PES, PS, PAN and PE-EVAL [62,63,65,84–87] (Table 1). These materials have also been used extensively in commercial haemodialyzers, blood purification and/or plasma separation devices due to their good haemocompatibility.[90] These BAO were either intended for extracorporeal therapy (BAL[62,63,65,84–88] and BAK[80–83]) or for implantation in the patient (BAP).[79]

In BAO, the HF must act as a barrier that fulfils the mass transfer requirements of the metabolic compounds and achieves immunoisolation of the patient's organism. Hence, the pore

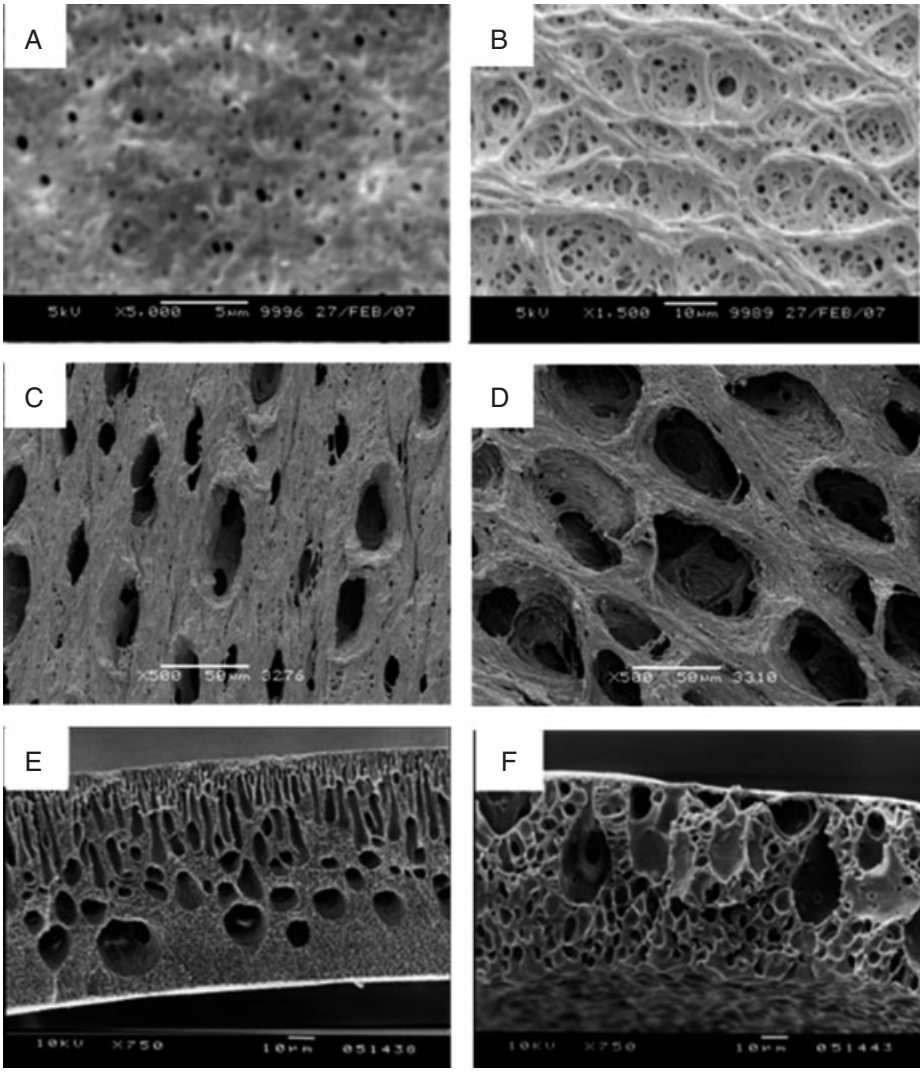

Figure 3. SEM images of HF membranes fabricated by liquid induced phase separation using various processing conditions. (A and B) external surface of poly L-lactic acid (PLLA) HF membranes spun with different air gaps (0 and 2 cm, respectively) (reprinted from Ref. [33] with permission of Elsevier), (C and D) external surface of a blended poly(lactic-co glycolic acid) (PLGA)/poly(ϵ-caprolactone) (PCL) HF using different coagulation baths (2-propanol and ethanol, respectively) (image D reprinted from Ref [40] with permission of Wiley); and (E and F) cross-section of PLGA HFs using different solvents in the dope solution (N-methylpyrrolidone and dioxane, respectively) (reprinted from Ref. [35] with permission of Elsevier).

size of the HF membrane should be small enough to isolate the embedded exogenous cells and antibody compounds but sufficiently high to allow appropriate mass transfer of nutrients to cells and removal of the metabolites generated by those cells. For example, comparison between an ultrafiltration (UF) HF module with molecular weight cut-off (MWCO) 100 kDa and a microfiltration (MF) HF module with a pore size of 0.1 µm, showed that the MF HF achieved better mass transfer of the metabolites (urea and most importantly albumin) and this stimulated the cell metabolic functions of the BAL.[85] Iwamuru *et al.*,[84] also observed higher albumin mass transport through 500 kDa and 0.2 µm pore sized HF membranes than 100 kDa MWCO HF membranes. The authors attributed the low transport of albumin (~67 kDa) through the 100 kDa MWCO membrane to fouling and therefore the immunoglobulin IgG (147 kDa), which should be retained by size exclusion, could not be selectively separated with this type of membrane.

In BAL and BAK systems, the cells or islets were cultured in the intra- or extra-lumen compartment of the HF module either directly[63,65,80–85,87,88] or using a foam culture substratum.[86] The commercial haemodyalizers conventionally employed to hold the cells for BAK applications have the luminal surface optimized for haemocompatibility.[68] In order to favor attachment human primary renal proximal tubular cells (HPTC), two different alternatives were evaluated: (i) the modification of the lumen surface of a PES/PVP HF by a double coating of 3,4-dihydroxy-L-phenylalanine (DOPA) and collagen IV[68]; or (ii) proceed with the attachment of the HPTC cells in the external surface of different commercial HF haemodyalizers made of Polyarylethersulfone (PAES), PS or PES/PVP[69]. A fiber-in-fiber design was proposed by Fey-Lamprecht *et al.*[83] to develop a BAK where kidney epithelial cells were seeded between two concentric HFs (interfiber space) of different materials (PS and PAN or a PAN copolymer with N-vinylpyrollidinone). They observed that reducing the interfiber space helped the development of a functional cell monolayer (mainly on the PAN copolymer surface) with enhanced O_2 and nutrients transport in comparison with systems with cell multilayers. Preclinical experiments with rats, dogs and pigs,

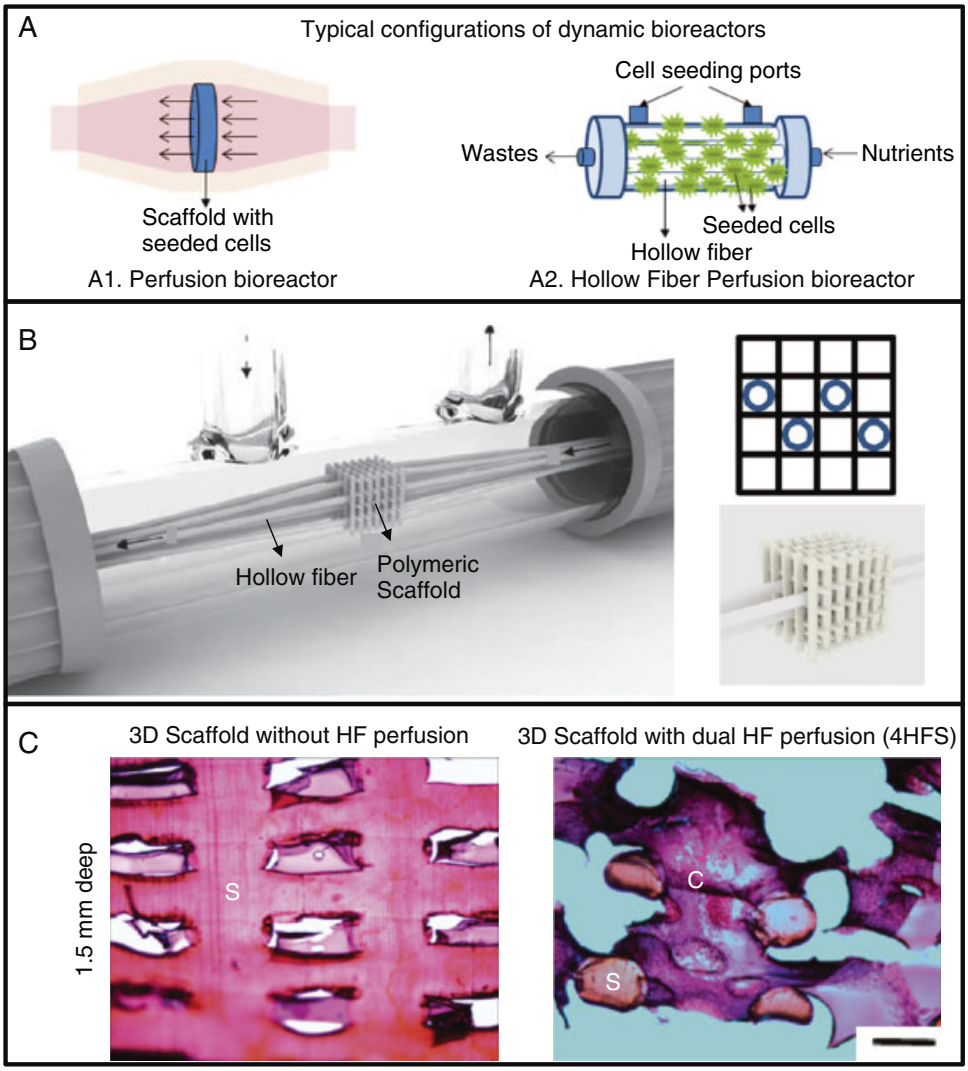

Figure 4. (A) Typical configurations of perfusion bioreactors; (B) diagram of a 3D scaffold-HF integrated module for dynamic dual perfusion cell culture system mounted within a glass bioreactor with side ports. (C) Comparison of light microscopic images of the cell proliferation of C2C12 cells at 1.5 mm in depth of the 3D scaffold after 7 days using traditional dynamic cell culture and dual perfusion bioreactor in (B) with 4 HFs inserted (scale bar 500 μm; S=scaffold polymer; C= cells). (Images B and C were adapted from Ref. [67], with permission of Elsevier). A remarkable higher cell density was observed in the internal part of the 3D scaffold when using the dual HF bioreactor in comparison with a traditional dynamic bioreactor.

showed that extracorporeal BAL therapy with commercial PE-EVAL HFs stimulated the regeneration of the damaged liver of these animals.[86,87]

The BAP concept developed by Delaunay *et al.*[79] consisted in the encapsulation of islets of Langerhans in the lumen of the PAN-based HFs that were later transplanted *in vivo*. This encapsulation assured their isolation from the patient and prevented the rejection of the device once transplanted. Thus, xenogeneic islets could be used without suppressing the immune system of the patient.

Bio-hybrid constructs have also been proposed as physiological models *in vitro* (e.g. liver, pancreas, skin, blood vessels) either to study diseases or to develop molecular therapeutics.[123] For instance, certain works studied the application of HF bioreactors to create *in vitro* neuronal models[64,77] and liver models.[63,65] It is worth mentioning a novel HF bioreactor configuration studied by De Bartolo *et al.*[65] (Fig. 5(B)), where two types of polymeric HFs (PES and PEEK-WC) with different MWCO and mass transport properties were cross-assembled. The design aimed at enhancing the selectivity of nutrients supply and waste removal in order to extend the functionality of hepatocytes in an *in vitro* liver model (Fig. 5(C)).

CONCLUSIONS AND FUTURE CHALLENGES

This review demonstrated the great potential of HFs for TE and BAO. Due to their geometry and size, HFs have been widely proposed in the literature to (i) repair small-caliber blood vessels and nerve gaps, (ii) for perfusion bioreactors mimicking vascularized systems and (iii) BAO in extracorporeal devices for therapy or organ models for treatment studies.

HFs can be fabricated using many different polymeric materials, although mainly polyesters approved by the FDA (i.e. PCL, PLGA, PLA) are preferred. The most relevant and simple fabrication technique to produce HFs is wet phase inversion spinning. The versatility of this method provides HFs a broad range of morphological, mechanical and permeable characteristics so they can be adapted to the requirements of the specific tissue to

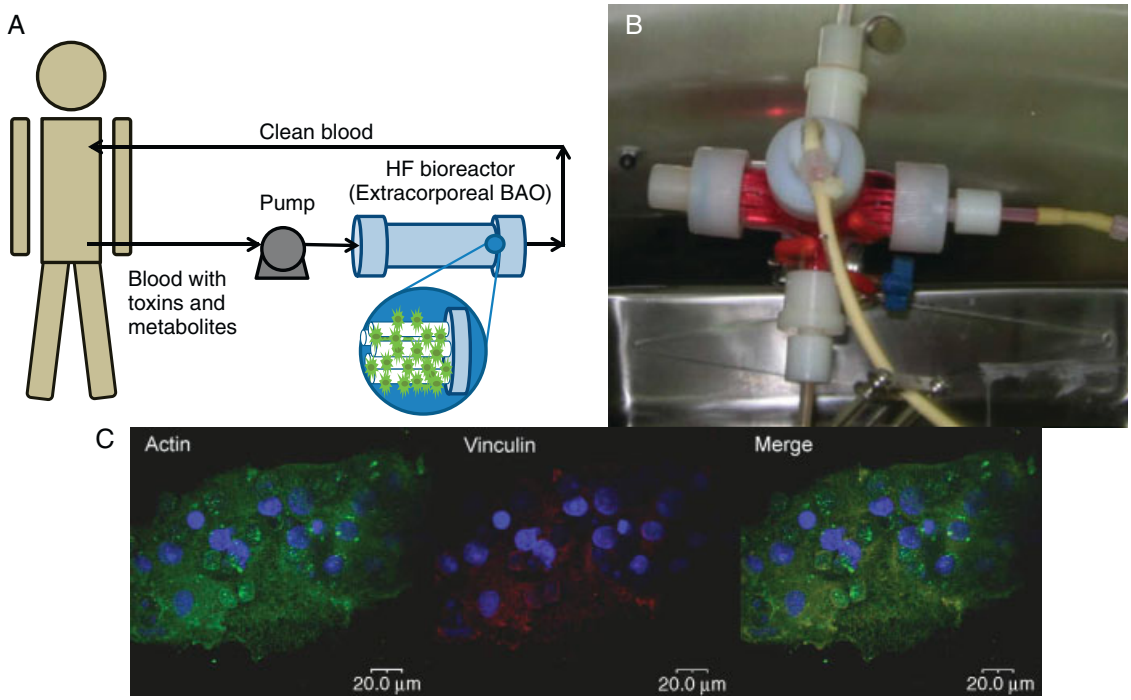

Figure 5. (A) Graphical representation of an extracorporeal bioartificial organ (BAO); (B) picture of the crossed HF bioreactor for BAL application; and (C) confocal laser scanning micrographs of the hepatocytes cultured on the crossed HF bioreactor after 18 days (hepatocytes were stained for actin (green), vinculin (red) and the nuclei detected by the counterstaining DAPI (blue)). (Images B and C adapted from Ref. [65], with permission of Elsevier.)

be regenerated and a surface morphology that promotes cell attachment and proliferation.

The development of new degradable and resorbable HFs with optimal pore size and morphological characteristics and optimal biocompatibility/cytocompatibility tailored to specific applications is an important future challenge.

ACKNOWLEDGEMENTS

A postdoctoral fellowship granted by the Spanish Ministry of Education (EX2009-1049) is gratefully acknowledged.

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