Chemical Engineering Science 126 (2015) 244–256

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

On glucose diffusivity of tissue engineering membranes and scaffolds

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HIGHLIGHTS

- Glucose diffusivity in tissue engineering membranes and scaffolds are determined.
- The chosen materials are saturated with either water or cell culture medium (CCM).
- Insignificant difference in glucose diffusivity was found when the materials are in water or CCM.
- Pore size distribution, porosity and tortuosity of the materials are correlated to glucose diffusivity.
- Tortuosity and porosity relationship are found to be non-linear and non-monotonic in nature.

ARTICLE INFO

Article history:
Received 19 June 2014
Received in revised form
23 October 2014
Accepted 3 December 2014
Available online 22 December 2014

Keywords:
Membrane
Scaffold
Glucose
Diffusion coefficient
Tortuosity

ABSTRACT

There has been an increasing interest in the concept of growing artificial tissues in bioreactors which use numerous membranes and scaffolds to support the cellular processes such as cell growth and nutrient uptake. While these approaches are promising and may be considered to be successful in some circumstances, there is a general lack of quantitative information on the glucose (nutrient) diffusivity of these materials. In addressing this issue we have carried out a series of well-defined laboratory experiments to measure the glucose diffusion coefficient across a number of tissue engineering membranes and scaffolds saturated with water and cell culture medium (CCM). For this purpose, a diffusion cell was constructed and five different membranes and scaffolds with varying pore size and shapes were employed, which include cellulose nitrate membrane, polyvinylidene fluoride membrane, poly(L-lactide) scaffold, poly(caprolactone) scaffold and collagen scaffold. Pore size distribution, porosity and tortuosity of these materials were then determined and correlated to the glucose diffusivity values. As expected, we found that the diffusion coefficient increases with increasing pore size of the materials. These relationships are non-linear and may be non-monotonic in nature as they depend on a number of factors such as the basic building blocks of the materials which are non-periodic and heterogeneous in nature and vary within the same material, or from one material to another. We observed that glucose diffusivities in the materials saturated with CCM are significantly reduced at a given temperature which is contrary to what have been generally assumed in the previous studies on glucose transport processes. Therefore, a conclusion can be drawn that the presence of extra components and difference in fluid properties of CCM compared to water have a significant effect on the glucose diffusion coefficient in the tissue engineering membranes and scaffolds.

1. Introduction

The concept of growing cells outside the human body and their survival has been proven to work dated back almost a century ago when Wilhelm Roux, a German zoologist, had successfully cultured chick neural crest in warm saline water for over a period of few days (Hamburger, 1997). This is supported by Alexis Carrel, a Nobel Prize winner in 1912, whose work showed that not only it is possible to grow tissues including connective and heart tissues in vitro but also maintain their characteristics for over a long period of time (Carrel, 1912). Tissue engineering has emerged now to be a valuable tool as a solution to overcome health problems such as tissue damage, degeneration and failure.

Engineered bone (Kimelman-Bleich et al., 2011; Grayson et al., 2010), cartilage (Schulz et al., 2008), tendon (Abousleiman et al., 2009; Omae et al., 2012) and blood vessel tissues (L'Heureux et al., 2007) have been successfully cultured both in vitro and in vivo (Kimelman-Bleich et al., 2011; Omae et al., 2012; L'Heureux et al., 2007). But studies have shown that culturing functional tissues in vitro is more complex than in vivo due to the need for a controlled

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http://dx.doi.org/10.1016/j.ces.2014.12.029
0009-2509/

environment during cell cultivation (Li et al., 2014). Hence, a bioreactor system is essential. To date, there have been several types of bioreactors designed to culture and grow 3D tissues, such as spinner flasks (Page et al., 2013), rotating vessels (Nishi et al., 2013; Chao and Das, 2015), perfusion systems (Baptista et al., 2013), magnetic force bioreactors (Bock et al., 2010), compression or strain bioreactors (Abousleiman et al., 2009; Wartella and Wayne, 2009), combined bioreactors which may couple perfusion with compression (Liu et al., 2012) such as rotating compression bioreactors (Wu et al., 2013) and, another perfusion bioreactor, namely, hollow fibre membrane bioreactors (Ye et al., 2006; Abdullah et al., 2009; Napoli et al., 2011, 2014; Chapman et al., 2012). Even though these bioreactors give hopes to tissue engineering approaches, they may not be able to prolong the cell culture environments (Li et al., 2014). One of the reasons for this is limited nutrient diffusion through scaffolding matrix and membrane. To achieve the desired rate of mass transfer and allow the development of novel membranes and scaffold, a good understanding of the quantitative relationship between their properties and nutrient transport behaviour is essential (Leddy et al., 2004; Das, 2007; Chao and Das, 2015). A good understanding of the mass transfer behaviour in these materials is also necessary as these materials may be used to calibrate and develop biosensors, e.g., for monitoring glucose level (Boss et al., 2012; Wang et al., 2013).

One of the important components of most tissue engineering bioreactors is the scaffold/membrane matrix which acts as a support for cells to grow into new tissues before being implanted into the host tissue. Some of the general characteristics of the support materials are that they must be porous for ease of nutrient diffusion and waste product removal (Florczyk et al., 2013; Guan et al., 2013; Deans et al., 2012), biocompatible (Stamatialis et al., 2008), the material must possess comparable mechanical properties to that of in vivo tissues (Karageorgiou and Kaplan, 2005; Karande et al., 2004), allow cell seeding, and others. Some examples of these support materials for tissue engineering purposes are summarised in Table 1.

Tissue growth and survival are undoubtedly complex, involving an immense variety of processes from intracellular transduction pathways to tissue-level mechanics (O'Dea et al., 2013). Cell differentiation, survival and proliferation of tissue-engineered constructs are highly dependent on the availability of nutrients. Therefore, the diffusion as well as the distribution and availability of the relevant solutes, e.g., nutrients, must be fully grasped as they are important for tissue formation, growth and survival (Liu et al., 2013). Glucose and oxygen are critical molecules in these regards as shown in both experimental and modelling studies (e.g., Mauck et al., 2003; Ye et al., 2006). In contrast to oxygen which has been extensively studied over the years (Malda et al., 2004a, 2004b; Kellner et al., 2002; Guaccio et al., 2008; Ellis et al., 2001), there is limited knowledge available on the diffusion coefficients of other nutrients or metabolites especially glucose and lactic acid in porous membrane and scaffold within cell culture media (CCM) (Liu et al., 2013). Most diffusion coefficient data are for cases where these materials are saturated with water at ambient conditions. However, the cell/tissue culture experiments are typically conducted at 37–38 °C and the materials are imbibed with cell culture medium (CCM).

The diffusivities of glucose in aqueous solutions were measured some sixty years ago (Longsworth, 1952). More extensive measurements of glucose diffusion coefficients in different fluid and porous media have been studied as well, such as water (Dionne et al., 1996), poly-ether-sulphone and poly-sulphone (Curcio et al., 2005), polyvinyl alcohol (Phanthong and Somasundrum, 2003), calcium alginate (Chai et al., 2004), collagen gel (Shaw and Schy, 1981), agarose gel (Weng et al., 2005) and haemodialysis films and hollow fibres for blood purification processes (Klein et al., 1977). However, there is little or no published information that discuss specifically the glucose diffusivity across membranes or scaffolds that are used for cell/tissue engineering. Lactic acid is beyond the scope of this study and will not be covered here.

Table 1
Some examples of commonly used support porous materials and their characteristics.

Material	Fabrication technique	Pore size (μm)	Porosity (%)	Reference
Poly(lactic-co-glycolic acid) (PLGA) scaffold	Fiber knitting	NA	NA	Ouyang et al. (2003) and Sequeira et al. (2012)
Poly(caprolactone) (PCL) scaffold	Salt leaching and thermal induced phase separation	NA	93.6 ± 0.6	Zhang et al. (2013)
Hydroxyapatite (HA) scaffold	Imaging techniques and stereo lithography	250	40	Chu et al. (2002) and Kim et al. (2007)
Poly(L-lactide)/β-tricalcium phosphate (PLLA/β-TCP) scaffold	Solvent self-proliferating/model compressing/particulate leaching	100–250	57	Xiong et al. (2002) and Kang et al. (2009)
Collagen-glycosaminoglycan (GAG) scaffold	Lyophilisation technique	96	99.5	O'Brien et al. (2005) and Keogh et al. (2010)
Poly(lactic-co-glycolic acid) (PLGA) membrane	Dry/wet- and wet-spinning	0.2–1.0	NA	Ellis and Chaudhuri (2006)
Poly(lactic-co-glycolic acid) (PLGA)/polyvinyl alcohol (PVA) membrane	Wet-spinning	0.54 ± 0.11 (PLGA) 0.67 ± 0.15 μm (1.25% PVA–PLGA) 0.89 ± 0.16 μm (2.5% PVA–PLGA) 1.1 ± 0.1 μm (5% PVA–PLGA)	46	Meneghello et al. (2009)
		0.67 ± 0.15 (1.25% PVA–PLGA)	67	
		0.89 ± 0.16 μm (2.5% PVA–PLGA)	76	
		1.1 ± 0.1 μm (5% PVA–PLGA)	77	
Poly (lactide-co-glycolide) (P_{DL}LGA) membrane	Wet-spinning phase-inversion	0.16 ± 0.006	NA	Morgan et al. (2007)
Nanoporous polyethylene membrane	Stereolithography using a biocompatible medical-grade resin (proform)	0.01649	28.9 ± 4.93	Boss et al. (2012) and Boss et al. (2011)
Polypropylene microporous membrane	Melt-extrusion/cold-stretch	0.10	45–50	Yu et al. (2008)
Titania nanotubular membrane	NA	0.125	60–70	Paulose et al. (2008)