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Design and fabrication of a non-clogging scaffold composed of semi-permeable membrane

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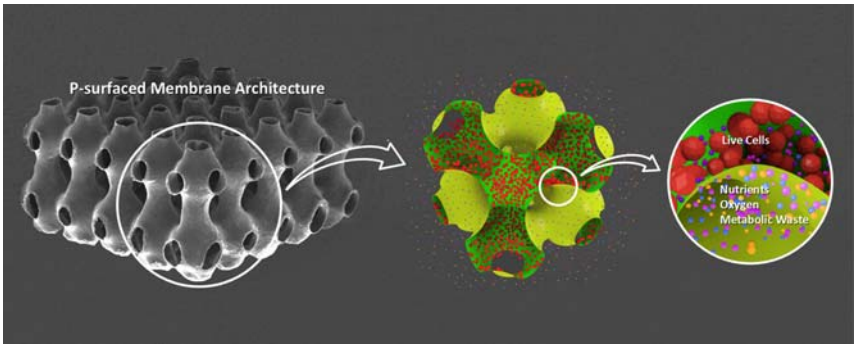
HIGHLIGHTS

- A 3D polymer membrane architecture was proposed as a novel concept of bio scaffold.
- It had two sub-volumes that were intertwined but separated by a semi-permeable membrane.
- One sub-volume was used for cell culture, while the other served as a perfusion channel.
- Mass transfer was implemented through the interfacial semi-permeable membrane.
- Despite very high porosity, its strength & modulus was appropriate for bones or cartilages.

GRAPHICAL ABSTRACT



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ABSTRACT

In this study, a novel concept of polymer scaffold was proposed based on 3D porous membrane architecture. It had two distinct sub-volumes intertwined with each other but separated by a single continuous smooth semi-permeable membrane. One sub-volume was used for cell culture, while the other served as a perfusion channel. Mass transfer was implemented through the interfacial porous membrane. Consequently, this scaffold was expected to be completely free from clogging problem due to growing tissue. The sample scaffolds of poly L-lactic acid (PLLA) was fabricated based on 3D UV photo-lithography and porogen leaching technique, which provided a P-surface-like architecture composed of porous membrane having smooth and fine texture with considerably high porosity. Despite high overall porosity of approximately 97%, these scaffolds had strengths and Young's moduli appropriate for regeneration of bones or cartilages. Wettability and permeability of polydopamine-coated PLLA porous membrane were sufficiently high.

1. Introduction

Tissue engineering is a multidisciplinary field that regenerates biological alternatives for damaged tissues and organs using a combination of cells, scaffolds, and bio-signals [1]. As an essential part of tissue engineering, the scaffold (i.e., artificial extracellular matrix) plays a crucial role in cell growth, proliferation, and new tissue regeneration in three dimensions. A variety of bioactive degradable scaffolds have been fabricated by various techniques such as particulate leaching, gas forming, freeze-drying and rapid prototyping in the past decades [2].

However, mass transfer limitation remains a serious challenge in the field of tissue engineering. In in-vitro engineering of living tissues, non-homogeneous growth of cells inevitably occurs in conventional porous solid scaffolds due to limitation in continuous delivery of nutrients and oxygen as well as limitation in removing metabolic waste products

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[3]. Because the mass transfer is limited by growing cells, active cells that migrate into the deeper part of a porous structure can become necrotic. Almost no cells can survive far from the outer surface of more than 500 μm [3,4]. In conventional 3D structures such as salt-leached scaffolds, cells commonly congregate only at the outermost region.

Recently, porous materials with triply periodic minimal surface (TPMS) configuration have attracted attention as scaffolds for tissue engineering applications, because TPMS has zero (or "a constant" in a wider sense) mean curvature over the entire surface while being periodic in three directions [5]. TPMS partitions space into two disjointed but intertwined sub-volumes that are simultaneously continuous. To date, a scaffold in TPMS configuration comprises one solid sub-volume and another sub-volume of air (void), while the interface has TPMS configuration [6–11]. Because TPMS possesses desirable characteristics such as smooth surface, high surface area, excellent permeability, and sufficient mechanical strength and stiffness, a scaffold with TPMS is regarded as ideal for cell adhesion, migration, and vitalization in tissue engineering. The excellent permeability of such scaffold allows superior diffusion, facilitating the inflow of nutrients and disposal of metabolic waste, which can partly relieve clogging issues due to cell growth in perfusion channels (i.e., the void sub-volume). This type of scaffold has gained popularity because it can be precisely fabricated by means of CAD modeling and additive engineering [12,13].

Nevertheless, previous TPMS scaffolds are not free from clogging issues, because an identical place (i.e., the void sub-volume) is shared for dual functions of cell culture and perfusion. Consequently, penetration of cell culture is inevitably limited. In addition, the solid sub-volume is likely to be too dense as a scaffold for most applications in tissue engineering except for bone regeneration. The large portion of such solid sub-volume may be a burden for in-vivo degradation. Thus, higher porosity (i.e., lower relative density) is desirable.

A more recent approach is to use a cell-laden hydrogel reinforced with microfibers [14] or synthetic biomaterial [15–18]. Namely, the reinforced hydrogel is printed into a 3D lattice architecture and the interconnected interior pores function as perfusion channels. Because the cells are cultured in the hydrogel-based substance, while the pores are used for perfusion channels, this approach looks quite effective to solve the clogging issue, mentioned above. However, this approach may not be appropriate for regenerations of hard organs such as bone or cartilage.

Another effective approach to address the pervasive issue is to functionalize the scaffold by integrating perfusion channels that act as an artificial vascular system, enhancing mass transfer for cell growth [19]. Modified scaffolds designed with perfusion channels and fabricated by rapid prototyping [6] or lattice scaffolds combined with hollow fiber membranes [20] have significantly contributed to uniform distribution of cells. We regard the latter as the more effective way. Namely, the hollow fiber membranes act as perfusion channels of an artificial vascular system, while the lattice structure provides 3D spaces where the cells grow and proliferate and new tissues are regenerated. Mass transfer between cells and the perfusion channel, i.e., the inflow of oxygen and nutrients and disposal of metabolic waste, was implemented through the semi-permeable membranes of the hollow fibers.

Han et al. [21] have introduced a new type of 3D membrane architecture, named Shellular that is composed of a single continuous smooth membrane. In the authors' research group, it has been validated that a uniformly smooth surface results in high strength and stiffness; thereby TPMS is a good choice as the membrane architecture of Shellular [22–24]. Because TPMS has a smooth surface with a constant mean curvature, a Shellular in a TPMS configuration does not have stress concentration due to its geometrical irregularity, and it is likely to support external load by coplanar stresses, without causing bending stress. The thin membrane architecture of Shellular in TPMS configuration may serve as a stretching-dominated structure, as observed in trussed cellular materials, generally referred to as micro-architectured materials [25]. Also, as a 3D membrane architecture which supports internal pressure, Femmer et al. [26] showed effectiveness of TPMS configurations. In addition, it is expected that the thin continuous membrane in TPMS might play a role as transfer interface between two void sub-volumes as well as mechanical load support.

This study introduced a radical design of 3D membrane architecture as a novel functionalized tissue engineering scaffold. The conceptual model of this scaffold is shown in the upper of Fig. 1. Actually, this design is a combination of the above-mentioned two types of scaffolds: the scaffold in TPMS configuration with one solid sub-volume and the scaffold integrated with perfusion channels. This was composed of a semi-permeable polymer membrane in a form of TPMS Shellular with two non-intersecting void sub-volumes, as illustrated in the lower of Fig. 1. One sub-volume was used for cell culture, while the other served as a perfusion channel. Mass transfer between cells and the perfusion channel was implemented through interfacial semipermeable membrane. Namely, this intriguing scaffold was integrated with a vascular system (i.e., mass transfer channel); thereby it continuously provided nutrients and oxygen supply to proliferating cells as well as removal of waste through the thin semi-permeable membrane. Despite its ultra-lightness, this 3D membrane scaffold is expected to have sufficient strength needed for most organs, as mentioned above. Therefore, this scaffold plays dual roles as hollow fiber membranes and the lattice structure of Bettahalli's scaffold, mentioned above [20]. Each sub-volume of this scaffold in a TPMS Shellular has biomorphic geometry, which is ideal for facilitating cellular attachment and realizing uniform cell culture [7]. After the scaffold accomplishes its role of cell support and pseudo-vascularization, the 3D membrane architecture can be degraded and absorbed without causing any harm due to the small amount of solid material (i.e., the membrane). As a result of a preliminary study of such scaffold, this study described the fabrication process of the 3D membrane architecture developed for this purpose. Also, its mechanical properties, microstructure, wettability, and permeability were evaluated.

2. Materials and methods

2.1. Design of 3D membrane architecture

Among various TPMSs, *P*-surface was chosen as the 3D membrane architecture. *P*-Surface located in a cube of the unit cell size, D [7] is given by

$$\left(\cos\left(\frac{2\pi x}{D}\right)+\cos\left(\frac{2\pi y}{D}\right)+\cos\left(\frac{2\pi z}{D}\right)\right)+k_1=0, \tag{1}$$

where $x, y, z \in [-\frac{D}{2}, \frac{D}{2}]$, and k_1 is a level set value that decides the volume fraction, f, which is defined as ratio of the inner sub-volume to overall volume [7]. Calculation using a CAD program yielded relation between k_1 and f, and relation between surface area, A, and f as follows;

$$f = 0.29k_1 + 0.5 \quad \text{and} \tag{2}$$

$$\frac{A}{D^2} = -13.054(f-0.5)^4 - 4.555(f-0.5)^2 + 2.34, \quad \text{respectively.} \tag{3}$$

Eq. (3) reveals that surface area is the largest at $f = 0.5$. Because the 3D membrane architecture in this study was fabricated based on the technique, described in Han, et al. [21], geometry was elongated by a factor of k_2 in z-direction. Hence, the surface is given as follows:

$$\left(\cos\left(\frac{2\pi x}{D}\right)+\cos\left(\frac{2\pi y}{D}\right)+\cos\left(\frac{2\pi z}{k_2 D}\right)\right)+k_1=0 \tag{4}$$

Nevertheless, the surface area is still the largest at $f = 0.5$.

The authors chose the cell size of $D = 1$ mm, which may be appropriate for a scaffold for chondrocyte cells [27].