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Review

Micro/nano replication and 3D assembling techniques for scaffold fabrication

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ABSTRACT

The development of tissue engineering field entails the creation of micro/nanoscale features for cellular alignment and biocompatibility improvement. As replication techniques, hot embossing and soft lithography can be used to produce micro/nanoscale features on biodegradable membranes. Subsequently the generation of 3D scaffolds can be done by means of assembling techniques.
Using the described techniques, high resolution of features, as small as 5 nm, can be achieved. Nevertheless membrane assembling must be fully studied to avoid feature fluctuations and even collapse of the scaffold.
The present review focuses on the state-of-the-art in the replication techniques used to create micro/nanoscale features on biodegradable polymers and assembling approaches to construct scaffolds with the aim of exploring existing advances and limitations of the reported methods.

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Contents

1. Introduction

Organ failure and tissue loss are the major problems in human health care [1]. To circumvent these problems, surgical strategies, such as, organ transplantation, tissue transfer and prosthesis replacement are the most commonly used approaches [1,2]. Nevertheless, several disadvantages are associated with these therapies, namely, shortage of organ donors, disease transmission and biocompatibility issues [3].

In the past few years, tissue engineering emerged in the field of orthopedic surgery and biomedical engineering as a discipline able to offer promising alternatives to actual therapies [4,5]. This new field of research was defined by Langer and Vacanti as "an interdisciplinary field that applies the principles of engineering and of life science towards the development of biological substitutes that restore, maintain or improve tissue or organ function" [6].

Earlier, different approaches to create scaffolds, such as, compression molding followed by porogen leaching [7,8], gas foaming [9–11], fiber-bonding [12–14], freeze-drying [15,16], and solvent casting [17] have

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been studied. Nevertheless, these methods are limited by their random micro-geometries, low-resolution features, random distribution of pores, residual particles and solvents in the polymer matrix and limited oxygen/nutrient supply [18]. Afterwards, machine-based processes, such as, micro injection molding [19] and rapid prototyping including fused deposition modeling (FDM) [20,21], stereolithography (SLA) [22] and 3D printing [23,24], were also used to produce biocompatible organized structures but the limited resolution is still a drawback.

In the recent years, micro/nanofabrication technologies have emerged as versatile and powerful approaches for micro/nanoscale feature creation and can be broadly separated into direct methods and replication methods. As the name implies, the first method creates patterns directly on the substrate (e.g. photolithography) and the second one replicates features using several times the same master mold (that is usually produced by direct methods). Despite of direct methods being able to create patterns with good resolutions, they are usually more expensive methods than replication techniques [25].

Replication methods are emerging tools for tissue engineering applications since they can tailor biochemical cues and surface patterns capable of controlling cell adhesion or orientation producing precisely arranged co-culture systems [26–32] with lower associated costs. These technologies offer the possibility of building large-area stamps (from 4 to 100 cm^2, [33,34]) with features at length scales from <5 nm to >1 cm creating feature scales smaller than those of cells [35,36]. A variety of different approaches has been successfully applied to produce different types of features on polymeric surfaces in the micrometer and submicrometer range [37–39] such as fibrillar ECM alignment [40,41], round features [42] and submicroscale textures and microgrooves [43]. Furthermore, the osteogenic differentiation of mesenchymal stem cells [44,45] and vascularization [46] were also reported to be promoted by micro/nanostructured substrates.

This review will focus on the state-of-the art of replication methods and 3D assembling methodologies providing also a discussion of the advances and limitations of each technology and a perspective of the future trends regarding micro/nanofabrication techniques.

2. Replication technologies for tissue engineering applications

Replication technologies, which allow the development of biofunctionalized surfaces with micro/nano patterned cues on both synthetic and natural based polymers become increasingly important to medical diagnostics, biochemical analysis, cell-based assays, sample preparation [47] and tissue engineering applications [48,49]. The use of these novel technologies, by achieving high resolution features at the nanoscale, improves the formation of new blood capillaries since cells attach to topographical cues avoiding the simple addition of cells to scaffold without any type of biochemical or physical cues that often leads to random and inadequate results [48,50]. Furthermore, synthetic and natural based biodegradable polymers can be cast onto micro/nanofabricated molds to produce structures with small feature resolution [51–54]. Table 1 lists some of these replication technologies envisaging their application on the tissue engineering field.

Included on replication techniques, hot embossing (also known as nanoimprint lithography) and soft lithography (micro-casting) have been used to achieve patterns with dimensions as small as 5 nm [36,55–58].

The master mold used for these replication techniques are usually produced using a hard or a soft material, being mold rigidity, the major difference between hot embossing and soft lithography. The following sub-chapters extensively describe the characteristics of each method.

2.1. Soft lithography

Soft lithography, developed in 1997 by George Whitesides and coworkers, emerged as an alternative procedure to photolithographic techniques for micro/nanofabrication [59]. This method is included in replication methods and is characterized by using a patterned elastomer (usually made from PDMS) as a stamp or mold, to generate microstructures and a pre-polymer for posterior thermal or photo curable process [60].

Several elastomeric materials are used in the preparation of molds for soft lithography such as, poly(methylmethacrylate) (PMMA) [61], perfluoropolyether (SIFEL) [62] and polydimethilsiloxane (PDMS) [63]. Nevertheless, PDMS is the most widely used due to its transparency to visible wavelengths [64,65] and to its elastomeric characteristics providing also a low interfacial free energy on the surface and releasing easily from the substrate [66,67]. The schematic fabrication process of the elastomeric mold is shown in Fig. 1A. In this process, a master mold is usually made on a silicon wafer by photolithography. Afterwards, the PDMS pre-polymer is cast in the rigid master mold for further thermal curing and finally peeled off.

As the fabrication of PDMS mold is based on replication process, multiple PDMS molds (or stamps) can be produced and each elastomeric stamp can be used for at least 50 times [60,68], depending on the replication technique conditions, mold material and feature patterns. This characteristic improves the productivity of the process with low associated costs. Nevertheless, the main disadvantage of using PDMS mold is the damage of the pattern height with consequent lower resolution of features [69] and even distortion/deformation of microstructures [70]. Soft lithographic techniques can be divided into: i) microcontact printing, ii) micromolding in capillaries, iii) microtransfer molding, iv) replica molding and v) solvent-assisted micromolding [56,59,71]. Up to now, only some of these techniques are being used for tissue engineering applications and are described as follows.

2.1.1. Replica molding

The process of replica molding (REM) (Fig. 1B) consists of using a soft mold and a photo or thermally curable pre-polymer. The pre-polymer is cast into the PDMS mold and solvents are photo or thermally removed to produce the micro/nano patterns on polymer substrate. With REM method it is possible to pattern features as small as the capillaries using different types of substrates. However, this technique uses solvents for polymer conformation into the mold.

Table 1
Replication techniques used in tissue engineering.

	Method	Resolution	Main characteristics	References
Soft lithography	Microcontact printing (μCP)	35 nm	Pattern substrates for cell culture to control the attachment of cells. Formation of self-assembled monolayers on an elastomeric mold to stamp the desired pattern and to create films.	[112–114]
	Replica molding (REM)	30 nm	Uses PDMS mold to cast a pre polymer. After, the polymer is cured and detached from the mold. Ability to mold against nonplanar, rigid and soft topographic surfaces.	[51,72–74]
	Micromolding in capillaries (MIMIC)	1 μm	Based on capillary force to fill the channels between the mold and the support. Uses a low viscosity polymer precursor and after, the PDMS mold is removed remaining only the molded polymer.	[82,83,86,115]
Hot embossing		5–10 nm	Produces high-aspect-ratio structures. Utilizes temperature above Tg and vacuum conditions to prevent trapping of air in microstructures.	[36,98,116–119]

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