Direct Photolithographic Patterning of Electrospun Films for Defined Nanofibrillar Microarchitectures

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In this letter, a method of generating spatially defined electrospun microarchitectures by direct photolithographic patterning of electrospun films is described. A photoinitiator, benzoin methyl ether, is incorporated into a solid thermoplastic electrospun polyurethane matrix selectively photo-cross-linked by standard photolithographic methods. Subsequent development in an organic solvent yields spatially defined electrospun microstructures on a single substrate. Utilizing a multilayer approach, the method allows for the assembly of complex hierarchical electrospun structures on single substrates using methods analogous to the conventional microfabrication of solid-state devices.

Introduction

Electrospinning, a technology for continuous fabrication of microscale- or nanoscale-diameter fibers, has attracted extensive research interest and has been proposed for a number of applications exploiting the unique properties of micro- and nanostructured materials (e.g., microfluidic cell incubators or immunoassays, tissue engineering applications, photovoltaic devices, photonic devices, catalyst supports, and composite reinforcements). In many of the suggested applications, it is desirable to achieve spatially ordered microstructures of electrospun fibers in order to obtain functional devices or structures, for instance, within lab-on-a-chip applications where localized electrospun nanostructures act as physical biomimetic structures for cell culture in in-vivo-emulated microenvironments. However, because of the inherent nature of the electrospinning process, the formation of microscopic patterns of electrospun fibers poses a challenge. In general, electrospun fibers are randomly deposited on large 2D macroscopic collector surfaces, resulting in macroscopic layouts of electrospun fibers, confining fiber deposition to well-defined patterns with controlled pitch and high selectivity remains a challenge with these methods. However, scanning tip electrospinning and the closely related process of near-field electrospinning have shown significant potential in achieving high spatial resolution through direct localized writing of electrospun fibers. With near-field electrospinning, Chang and co-workers have demonstrated the predictable deposition of electrospun patterns with 50 μm pitch. In contrast to these serial direct writing methods, Shi et al. introduced a method of parallel pattern formation based on the transfer of electrospun fibers by microcontact printing and subsequent patterning by standard photolithography and reactive ion etching of exposed fiber areas, resulting in well-defined electrospun microarchitectures. In addition to macro- and microscopic configurations, alterations of electrospun fibers on the nanoscale are an alternative or complementary route to acquiring or enhancing functionality.

As an example, di Benedetto et al. demonstrated emission enhancement in electrospun conjugated polymer nanofibers after...
physically patterning single fibers by nanoinprint lithography.\textsuperscript{7} Clearly, the combination of defined electrospun microstructures and nanoscale alterations on the single-fiber level presents intriguing opportunities and challenges.

In this letter, we report a method of direct photolithographic patterning of electrospun fibers, where the benefits of high-throughput, low-cost, conventional electrospinning are combined with the high spatial resolution capabilities, repeatability and quick parallel processing of photolithography. The process is summarized in Figure 1. First, electrospun fibers are deposited on a substrate by conventional electrospinning. The polymeric material utilized is premixed with a photoinitiator capable of initiating covalent cross-linking between the polymeric chains upon UV irradiation, thus significantly reducing the solubility in organic solvents. Hence, as illustrated in Figure 1, selective exposure in a standard photolithographic procedure provides the capability to define discrete microscopic patterns where a photo-chemical reaction renders the fibrous material insoluble. Finally, through development in an organic solvent the defined pattern emerges on the substrate as the soluble regions are removed. In brief, the deposited layer of electrospun fibers have a function analogous to that of a negative photoresist where exposed regions become insoluble in the developer. Thus, as in conventional microfabrication, it is possible to define complex multilayer structures consisting of electrospun fibers (e.g., structures integrating fiber meshes with different angular alignments) by multiple deposition, exposure, and development in defined sequences.

### Experimental Section

A biocompatible\textsuperscript{3} aromatic polyether-based thermoplastic polyurethane (TPU) (Desmopan 9370A, Bayer MaterialScience AG) was dissolved in a mixture of tetrahydrofuran (THF) and N,N-dimethylformamide (DMF). To sensitize the solution to ultraviolet light, a photoinitiator, benzoin methyl ether (BME) with strong absorption in the deep ultraviolet (DUV) wavelengths, was added in specific amounts to the solution. After homogenization, the solution was transferred to a syringe fitted with a stainless steel cannula. Two separate electrospinning setups were utilized for electrospinning. For the random deposition of fibers, a standard commercial device equipped with a slowly rotating grounded conveyor belt collector was utilized (KATO TECH, Japan). For aligned fiber deposition, a custom setup consisting of a syringe pump, a high-voltage power supply, and a rotating grounded cylindrical collector was used. The cylindrical collector had a diameter of 60 mm and a rotational speed of approximately 2500 rpm. Aligned and randomly oriented fibers were prepared using identical parameters. Twenty-six KV was applied to a 27 gauge stainless steel cannula fitted with a circular electrode to provide confined deposition. The feed rate was 0.5 mL h\textsuperscript{-1}. The distance to the collector was approximately 25 cm. All experiments used 18 x 18 mm\textsuperscript{2} glass substrates of 150 μm thickness directly mounted on the conveyor belt collector or, alternatively, the cylindrical collector.

Photolithographic patterning was carried out in a standard mask aligner (Karl Süss, KS MJ83) connected to a DUV light source of 248 nm wavelength. The mask aligner was operated in vacuum contact mode. The exposure dose was optimized to 450 mJ cm\textsuperscript{-2} (1.5 mW cm\textsuperscript{-2} at 5 min of exposure time). Development was carried out for 30–90 s through immersion in THF with gentle agitation. The development process was halted by immersion of the substrate in deionized water, followed by gentle rinsing.

Samples were characterized by standard SEM inspection (Supra 60 VP, Carl Zeiss). Prior to inspection, samples were sputter coated with 20 nm of gold to reduce charging effects. The fiber diameter and orientation were measured using the image analysis software ImageJ. The analysis of angular data was performed with the MATLAB toolbox CircStat.\textsuperscript{19}

### Results and Discussion

Figure 2 displays typical results of photolithographic patterning of substrates covered with approximately 860 nm mean diameter (standard deviation 290 nm), randomly oriented polyurethane fibers. Figure 2a,b displays fabricated arrays of discrete circular pads of 50 μm diameter at 100 μm pitch. Similarly, Figure 2c,d demonstrates 40 μm pitch arrays of circular 20-μm-diameter pads. By studying Figure 2d, it is clear that the pad diameter is approaching the fundamental dimensions of the electrospun film itself (i.e., pore size and fiber diameter), limiting the possibility to define smaller structures. To investigate the ability to scale complex geometries, grid patterns of circular pads connected by lines were fabricated. Clearly, as seen in Figure 2e,f, the geometries scale well from line widths of 100 μm down to approximately 10 μm, at which the effects of the microstructure of the electrospun film itself become pronounced. Figure 2g,h demonstrates the fabrication of 100-μm-wide lines at 200 μm pitch, confirming the possibility to produce well-defined edges in close proximity to each other. Additionally, to examine the definition of corner structures, serpentine patterns containing both inner and outer corners were defined. In Figure 2k, displaying a 100-μm-wide pattern, it is clear that distinct inner and outer corners without defects were achieved. Finally, a combination of sharply defined cornering in combination with thin lines (approximately 30 μm) is exhibited in Figure 2l. In all experiments, exposed areas exhibited good adhesion to the substrates with exposed patterns maintaining spatial integrity during development.

The photolithographic process demonstrated is dependent on a photoinitiated covalent cross-linking process occurring in the TPU through the introduction of the photoinitiator benzoin methyl...
ether and subsequent DUV irradiation, significantly reducing the solubility of the material in organic solvents in exposed areas. Benzoin methyl ether, a Norrish type 1 photoinitiator, undergoes photofragmentation through $\alpha$-cleavage when irradiated with UV light, resulting in free-radical formation.\textsuperscript{20} The expected reaction mechanism of the cross-linking process is macroradical formation through hydrogen abstraction from the methylene groups situated between the phenyl rings of the diphenyl methane disiocyanate of the polyurethane polymer chains, followed by cross-linking through macroradical combination.\textsuperscript{21,22} Consequently, a covalently cross-linked network is superposed on the ‘virtual’ cross-link of the TPU\textsuperscript{23} (i.e., the strongly aggregated rigid blocks of the segmented polyurethane chains), removing the solubility and thermoplastic properties of regions exposed to UV light. It is well known that thermoplastic aromatic polyurethane can undergo covalent cross-linking as part of the photodegradative processes induced by exposure to UV light, reducing the polymers’ solubility in organic solvents.\textsuperscript{22,23} To assess whether pronounced photodegradative processes inducing cross-linking were present during the experiments, substrates with fibers composed of pure TPU, excluding the photoinitiator, were subjected to radiation. Despite significant radiation doses of up to 900 mJ cm\textsuperscript{-2}, no difference in solubility between exposed and unexposed regions could be observed, confirming the effect of the photoinitiator.

To elaborate the presented fabrication process further, a methodology for the definition of hierarchical electrospun microstructures through multiple deposition and exposure was devised. An illustration of the methodology is given in Figure 3a. By depositing an electrospun film with a specific morphology (e.g., aligned in a particular direction) followed by exposure and development, additional layers (e.g., with fiber alignment perpendicular to the preceding layer) can be deposited and subsequently patterned with corresponding masks, forming complex multi-layer structures. An example of this type of structure is given in Figure 3b–d. Figure 3b displays layer 1 composed of aligned fibers of approximately 570 nm mean diameter and a standard deviation of 170 nm (the reduced fiber diameter compared to that of randomly oriented fibers produced under identical parameters emanates from the stretching effect imposed on fibers during deposition on the collector rotating at high speed), patterned as 50-μm-wide lines (100 μm pitch). After the processing of layer 1 was finished, layer 2, consisting of identical fibers aligned perpendicularly to the first layer, was deposited. The result after exposure and development is visible in Figure 3c,d. The secondary layer has been patterned as lines perpendicular to the lines of layer 1, (i.e., a duplicate structure at 90° rotation). Figure 3e gives the normalized fiber angle histograms ($n = 100$ per layer) of the respective layers and a plot of the circular normal distribution of each set of data (mean value of 5 and 85° and circular standard deviations of 12 and 15°, respectively). Evidently, the fibers of the two layers are approximately perpendicularly aligned with respect to each other.

The possibility to assemble intricate microstructures consisting of several different fiber morphologies and organizations on a single substrate is illustrated in Figure 3f. As demonstrated by methods analogous to regular microfabrication, where a number of patterning sequences of corresponding layers lead to the formation of a device, it is possible to create microstructures consisting of multiple defined areas with electrospun films having diversified properties (e.g., different diameter fibers (Figure 3f: $d_1$, $d_2$, and $d_3$) deposited with specific alignment angles (Figure 3f: $\alpha_1$ and $\alpha_2$)). The presented methodology, allowing the introduction of electrospun structures into microsystems, opens up a number of new or improved applications profiting from heterogeneous integration of electrospun fibers, in particular, within the field of

(21) Bayer, O.; Mülle, E. Angew. Chem. 1960, 72, 934–939.
biomedical engineering. As an example, Yang et al. demonstrated improved performance of microfluidic immunoassays by exploiting the large specific surface areas of electrospun films for protein absorption. Comparable microsystem devices of high dimensional accuracy can be achieved with the technology introduced in this letter. Furthermore, the proposed technique may find successful integration in applications merging microfabrication and cell culture technology (e.g., cell-based biosensors and microscale cell culture analogues allowing for fundamental studies of cell biology, such as cell differentiation, proliferation, and migration). A fundamental aspect of these systems is cellular micropatterning, commonly achieved by lithographic lift-off or microcontact printing of, for instance, cell-adhesion proteins or functional self-assembled monolayers on 2D substrates, immobilizing cells in defined culture patterns. Microscale patterning of electrospun films can act as a complementary method, utilizing the well-documented ability of 3D electrospun fibrillar structures to mimic the extracellular matrix of in vivo tissue, providing patterned cell immobilization under in-vivo-like conditions. This opens up for large-scale, single-substrate, parallel in-vitro experiments on the effect of (extracellular-matrix-emulated) physical cues on cell development. As an example, studies of neural progenitor cell migration along defined tracks of aligned fibers are of significant interest in potential neuronal replacement therapy. Furthermore, in combination with related methods (e.g., high-resolution patterning of individual fibers on the nanoscale by nanoimprint lithography), the proposed technology may find further areas of application.

The described methodology, which is based on selectively photo-cross-linking an electrospun solid polymer matrix, is not believed to be limited to the particular chemistry outlined in this letter. Indeed, several electrospun polymer types (e.g., polystyrene and polyacrylonitrile) are also well studied in terms of photo-cross-linking through the addition of photoinitiators or the incorporation of photoactive functional groups on the polymer.

Conclusions

We have devised a method of photolithographically micro-patterning electrospun polyurethane fibrous films over large areas.

surfaces. The method allows for the assembly of complex microstructures on single substrates via a multilayer approach involving multiple photolithographic exposures, which is analogous to conventional photolithography in the microfabrication of solid-state devices. Indeed, we believe that this technique can be used in a variety of applications where it is beneficial to integrate micropatterned electrospun structures into microfabricated devices, in particular, within biomedical engineering applications.

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