Interconnected Biodegradable Polymers in Sub-Micron Precision

Rainer Fasching, WonHyoung Ryu, Fritz Prinz.
Rapid Prototyping Laboratory, Stanford University, Stanford, CA 94305 USA

Statement of Purpose:

Biodegradable polymer scaffolds for tissue engineering require highly interconnected and controlled geometry of microstructures in order to guide cell growth and to achieve sufficient supply of nutrients and oxygen [1,2]. Implantable controlled drug delivery devices are another example that require precisely micro structured polymer constructs in order to program the desired device release rates [3].

In response to these demands we have developed a micro structure technology particularly suited for biodegradable polymers. Hot embossing methods have been explored and developed for fabrication high aspect surface structures in sheets in precision down to the sub micron scale. For the first time, molding conditions could be established that allow for manufacturing massively interconnecting structures in polymer sheets in this study. These inter connected sheets with a controlled geometry in sub-microns can serve then as a building block for three-dimensional multi layered constructs.

Methods and Materials

50/50 poly (DL-lactide-co-glycolide) (50/50PLGA) was purchased from Absorbable Polymer Technologies, Inc. 85/15PLGA and poly (p-dioxanone) (PDO) were donated by Ethicon, Johnson & Johnson Company.

A Carver Auto C press (Carver, Inc. Indiana) was used for hot embossing. The hot embossing stack was comprised of a mold tool carrying the micro/nano features, a polymer film, and a soft back substrate. The molding tools were fabricated using combined reactive ion etching (RIE) silicon processes and surface modification to achieve simultaneously high aspect ratio micro/nano features with low surfaces roughness, positive wall tapering, and low surface energy.

The inherent viscosity of the polymers was measured before and after processing. A Cannon-Ubbelohde viscometer with a pore size of 50 was used to determine the viscosity .

Results and Discussion:

Poly (dimethylsiloxane) (PDMS) was used as a soft back substrate to shape interconnecting microstructures in 20µm thick biodegradable polymers. The molding tools have to satisfy certain geometric conditions that dependent on the film thickness and mold geometry. Fig.1 (a, b) shows the interconnecting micro-structure in 50/50 PLGA film. The micro openings have the dimension of 20µm at one side and 10µm at the other side which correspond to the shape of the mold tool used. This test structure were designed for capturing of hepatocytes cells Fig. 1 (b) [4]. Larger interconnecting micro-holes with 100µm diameter for e.g fluidic through connections were shaped in a high molecular weight 85/15PLGA polymer film, as shown in Fig.1 (c).

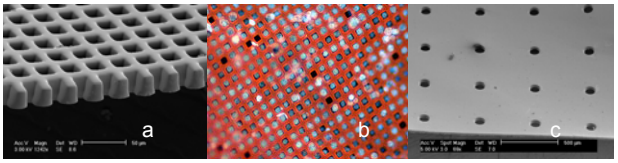

Fig. 1: Interconnecting microstructures: a.) 20µm/10µm cell sieving structure in a 25µm thick 50/50PLGA film unloaded and b.) loaded with hepatocytes cells; c.) 100µm fluidic through connection structure in 25µm thick 85/15PLGA film.

The viscosity measurements showed only a small decrease in the inherent viscosity after processing the polymers. The reduction of the inherent viscosity can be interpreted as the decrease of the molecular weight of the polymer chains. The degradation in PDO is more noticeable than in 85/15PLGA. This can be explained by the fact that PDO has been processed at a temperature closer to its melting temperature.

All results in this study are achieved using a 4 inch process. The active structured area of the polymers is typically 60mm*60mm and results in an overall film size of 75mm*75mm.

Conclusions:

In this study we investigated hot embossing technique to micro shape biodegradable polymers. Guidelines could be established for sub-micron controlled interconnecting micro-geometries for polymeric devices or constructs. The initial properties of the studied polymers, especially the biodegradable polymers here, are preserved throughout the process. This process not only represents a unique micro fabrication technology for basic research on tissue engineering, but also, by virtue of its relative simplicity and low cost, opens the door to the mass production of micro-fluidic devices, controlled drug delivery devices, tissue scaffolds, and other devices in relevant areas.

References:

[1] B. Kim and D. J. Mooney, “Development of biocompatible synthetic extracellular matrices for tissue engineering”, Trends in Biotechnology, vol. 16, pp. 224-230, May, 1998

[2] C. S. Chen, M. Mrksich, S. Huang, G. M. Whitesides, and D. E. Ingber, “Geometric Control of Cell Life and Death”, Science, vol. 276, iss. 30, pp.1425-1428, May, 1997

[3] A. C. R. Grayson, I. S. Choi, B. M. Tyler, P. P. Wang, H. Brem, M. J. Cima, and R. Langer, “Mulit-pulse drug delivery from a resorbable polymeric microchip device”, Nature Materials, vol. 2, pp. 767-772, Nov. 2003

[4] K. Hammerick, W-H. Ryu, R. Fasching, S-J. Bai, L. Smith, R. Greco, F. Prinz. Synthesis of Cell Structures, 73-103, in Nanoscale Technology in Biology. Greco et al. Ed. , CRC Press, Boca Raton, 2005, 73-102.