Structural Deformation Studies of Scaffolds and Method for Non-Invasively Monitoring Tissue Growth

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Statement of Purpose: Several shapes and configurations of bioreactors have been explored to regenerate tissues in-vitro in combination with scaffolds made of materials with wide variety of mechanical properties [1-3]. Numerous computational fluid dynamics (CFD)-based studies have also been performed to model the fluid flow within bioreactors assuming porous scaffold as a rigid structure i.e., largely ignoring the mechanical properties of scaffold. Moreover, effectively monitoring tissue regeneration has been hampered by the lack validated parameters that could be assessed non-invasively. The objectives of this study were i) to understand the effect of fluid flow on structural deformation with varying mechanical properties and ii) to develop a relationship between pressure drop and flow rate, considering the mechanical properties and the porous architecture, that can be used to monitor tissue regeneration non-invasively.

Methods: Two different scaffold preparations: i) salt leaching and freeze drying using polycaprolactone (PCL) and chitosan-gelatin respectively. Tensile tests were performed at physiological conditions to evaluate the elastic modulus and using a custom setup, the Poisson's ratio was determined. Scanning electron microscope (SEM) micrographs were assessed to determine the pore characteristics from which permeability was calculated using Kozeny-Carman relationship for respective pore shapes (**Figure 1a**). These values were used in CFD simulations performed by coupling fluid flow modeled using Brinkman equation and structural deformation using structural mechanics and moving mesh with the dimensions of the experimental set-up. The simulation was extended to various permeability values and broad range of elastic moduli and Poisson's ratio. Permeability value upto 10^{-14} m^2 (typically reported for soft tissue), elastic modulus in the range 0.01 MPa to 10 MPa and Poisson's ratio in the range of 0.1 to 0.49 were simulated. A flow-through bioreactor was constructed in-house which was connected to a flow-loop using a system previously reported [1, 2]. Pressure drop across the scaffolds was determined at various flow rates.

Results: PCL scaffolds had Poisson's ratio of 0.3 (±0.1) while chitosan-gelatin was 1(±0.1). The elastic modulus of Freeze dried chitosan gelatin was 2 (±0.5) kPa, while salt leached PCL scaffolds had an elastic modulus of 7000 (±1000) kPa. Analysis of scaffold SEM showed freeze dried scaffold to have cylindrical pore of average diameter of 0.055± 0.010 mm with 318 pores/mm^2. The salt leached scaffold had rectangular pores with an average pore length and width of 0.053±0.0102 mm and 0.027±0.049 mm respectively and pore density of 128 pores/mm^2. Simulation results showed higher deformation at the beginning and around the periphery of the scaffold (**Figure 1b**). Experimental pressure drop agreed with the simulation results for both scaffolds (**Figure 1c**). Simulations with different permeability values showed a significant increase in pressure drop at lower permeabilities, especially at higher flowrates. Moreover, simulating a combinations of elastic modulus and permeability showed that at lower permeabilities, significant deviation in the pressure drop is expected which is proportional to the elastic modulus of the material (**Figure 1d**). Effect of Poisson's ratio was less significant compared to Elastic modulus. Based on the flowrate, the increase in experimental pressure drop across the scaffold can be associated to change in permeability. This permeability change can be used to predict the amount of tissue regenerated.

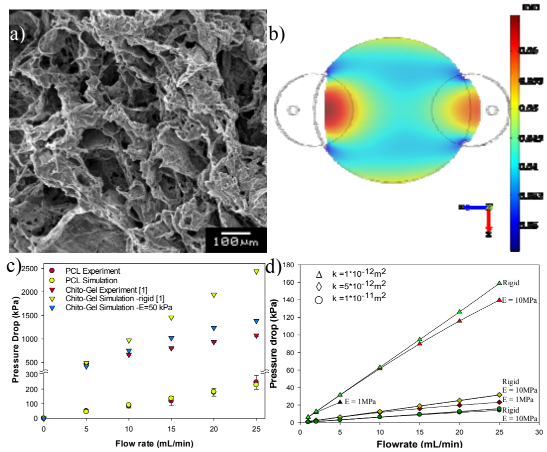

Figure 1. a)SEM of Salt-leached PCL scaffold, b)Structural deformation of chitosan-gelatin scaffold at 20ml /min. c)Pressure drop validation for chitosan-gelatin scaffold. d). Pressure drop – flowrate relationship based on scaffold permeability and elastic modulus

Conclusions: Estimating permeability of scaffolds using pore shape and diameter in Kozeny-Carman relationship is useful in determining pressure drop. Deformation of scaffolds due to fluid flow results in decreased pressure drop across the scaffold. This decrease is affected by the permeability of the scaffold and the elastic modulus at a known flow rate. In summary, monitoring the pressure drop across the porous scaffold of known initial permeability at a known flow rate and elastic modulus is a useful approach to assess the regenerative process in bioreactors for both soft and hard tissues.

References: [1] Lawrence BJ, Devarapalli M, Madihally SV. Flow Dynamics in Bioreactors Containing Tissue Engineering Scaffolds. Biotechnology/Bioengineering. 102(3): 935-947, 2009. [2] Devarapalli M, Lawrence BJ, Madihally SV. Modeling Nutrient Consumptions in Large Flow-Through Bioreactors for Tissue Engineering. Biotechnology/ Bioengineering. 103(5):1003-1015, 2009. [3] Podichetty JT, Madihally SV. Dynamics of Diffusivity and Pressure Drop in Flow-Through and Parallel-Flow Bioreactors During Tissue Regeneration. Biotechnology Progress.

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