THE UNIVERSITY OF ARIZONA
COLLEGE OF ENGINEERING
Biomedical Engineering

BME IS PROUD TO ANNOUNCE THE DOCTORAL DEFENSE OF

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BME PhD Candidate

"Application of Microfluidic Bilayer Devices for Permeability and Pharmacokinetic Analysis"

Abstract: Drug development has become bottlenecked over the past several decades by rapidly increasing costs in both time and money to bring new therapies to market. Organ-on-a-chip systems can be utilized to potentially reduce those costs drastically and streamline the process allowing for the supply of more advanced therapies at a more affordable price for patients. These systems typically consist of two stacked microchannels with a porous membrane sandwiched between them. The membrane is used as an anchor for the culture of two cell types, communicating through its pores, to mimic complex human tissues. In this work, such microfluidic bilayer devices were used to study molecular transport under various conditions. While flowing downstream with constant media flow rates, without cell barriers, molecules also diffuse across the membrane due to concentration gradients. With cell barriers, molecules can cross the cell layer either via the paracellular and transcellular transport routes. As a result, a steady molecular concentration distribution develops in the microfluidic device, which can be manipulated by several control variables. Concentration distributions were experimentally measured and numerically computed in devices without cells characterizing the effects of flow rate, membrane porosity, molecular size, and microchannel dimensions. The steady-state molecular concentration in the microchannel, with initially pure media flow, is approximately inversely proportional to the flow rate and increases almost exponentially with increasing porosity; the effect of other variables is relatively minor.

The concentration measurements were then used to estimate compound permeability and extract pharmacokinetic parameters from concentration-time plots with and without cells. The molecular flux through the porous membrane in microfluidic bilayer devices, without cells, is inversely proportional to the molecular size due to decreasing diffusivity with increasing size. In general, transcellular of all tested compounds was negligible, while the paracellular transport was found to be molecular size dependent. Consequently, the permeability of large molecules such as HMW dextran, in the presence of cell barriers, is practically zero. The permeability of the smaller LMW dextran was not affected as much due to the flow induced shear stress known to enhance transport through leaky tight junctions. Finally, bio-aerosols were generated and driven through the microfluidic bilayer devices, with air-liquid interface, to obtain concentration-time plots. The established curves were used to extract standard pharmacokinetic parameters: area under the curve, maximum concentration, and time to maximum concentration. Heavy agitation of compounds such as insulin, associated with aerosol generation, could result in fibril formation effectively increasing its molecular size; consequently, the concentration-time curve and extracted parameters are not reliable. Therefore, while microfluidic bilayer devices provide an attractive alternative to obtain pharmacokinetic parameters, it is paramount to include stabilizing agents in aerosolized compound formulations to construct reliable concentration-time plots.

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