MICROFLUIDIC DEVELOPMENT OF MICROPARTICLES TO ENHANCE CELL ENGRAFTMENT

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Background: Intrahepatic engraftment of islets or hepatocytes can eliminate the need for pancreas or liver transplantation. But, poor revascularisation and inflammatory reactions results in approximately 60-70% of cells failing to engraft. The delivery of immunomodulatory molecules such cytokine inhibitors, and growth factors including cytokines, has been shown to increase cell engraftment. However, delivering and maintaining these molecules locally at therapeutic doses remains a significant challenge. We propose a new paradigm of PLGA-based microparticles fabricated using microfluidic droplet methods as a replicable, automated, and scalable process to produce highly monodispersed microparticles that can provide a tuneable and controlled release. The inclusion of galactose will enable binding to hepatocytes in the liver to ensure localised delivery of immunomodulatory molecules.

Methods: Poly(D,L-Lactide-co-Glycolide) (PLGA) 50:50, Mw 61kDa, and galactosylated PLGA (Gal-PLGA), synthesised using D-(+)-Galactose Mw 180Da chemically attached to PLGA, microparticles were fabricated using a 100µm flow focusing hydrophilic microfluidic chip. PLGA and Gal-PLGA were dissolved in Dichloromethane (DCM) Mw 85Da, to form the dispersed phase. A surfactant solution of Poly(vinyl alcohol-co-vinyl acetate) (PVA) 88% hydrolysed, Mw 25kDa, at different concentrations with or without Tween 20, molecular weight 1227g/mol sourced from Acros Organics, USA, in deionised water made the continuous phase. A syringe pump was used to push both the dispersed and continuous phases through the chip at a rate of 0.15ml/hr and 4ml/hr respectively. At the junction where the dispersed and continuous phase met, droplets pinched off and were collected in deionised water. Microparticles were imaged using scanning electron microscopy and the size distribution of particles was quantified using Fiji (ImageJ), an image analysing software.

Results: 10% PLGA with 2% PVA in water was used with microfluidics to produce microparticles with low polydispersity. Varying the concentration of PVA directly influenced the average particle size and played a role in maintaining the stability of the microfluidic system. 2% and 1% PVA enabled a stable microfluidic system, however, low system stability was observed when 0.5% PVA was used which resulted in higher polydispersity index (PDI) and coefficient of variance (CoV) values for these microparticles. Lastly, 7% Gal-PLGA was used with 2% PVA which successfully produced microparticles. However, notable pores were observed therefore the concentration of PVA was decreased to 1% PVA which reduced the extent of porosity, but pores were still visible. The addition of Tween 20 to the 1% PVA in the continuous phase, resulted in no visible pores on the surface of the Gal-PLGA microparticles.

Conclusions: Microfluidics has the potential to produce monodispersed microparticles. To achieve this, optimisations of materials, surfactants, and operations are needed. Gal-PLGA can also be used as a material to form microparticles. However, it is also evident that further material characterisation and analysis is needed to ensure porosity has been eliminated.