Creating PLGA microspheres with monodisperse size by droplet-based microfluidics

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Background: Glioblastoma (GBM) is a primary malignant brain tumor with unmet medical needs. The blood-brain-barrier (BBB) is a major obstacle to treating GB systemically and limits drug options. Local treatment could be employed to deliver drugs accurately to the target site and circumvent the BBB. Up to now, only Gliadel® has been approved by the Food and Drug Administration for the local treatment of GBM. However, the drug release from the Gliadel® wafer is too fast. Most of the payload is released within one week. PLGA is a biodegradable and biocompatible material. Many studies showed PLGA microspheres have long-term sustained drug release. However, the traditional emulsion evaporation method is difficult to control the size distribution. Droplet-based microfluidics could generate micron scale droplets with monodisperse size. The commercially available plastic microfluidics chips have the advantage of low cost and good quality control, so could potentially be used to prepare PLGA microspheres with better size distribution.

Methods: The PLGA material and a repurposed drug (vortioxetine) were dissolved in the acetonitrile as the disperse phase. 2% fluoro surfactant was dissolved in HFE-7500 oil as the continuous phase. Droplets containing PLGA and drug were generated using a microfluidic flow focusing device. The droplets were solidified by evaporating the acetonitrile, to yield dry microspheres after purification. The morphology of the microspheres was characterized by SEM. Particle size distribution was analyzed by ImageJ from bright field microscope images. FTIR spectra were scanned to analyze the encapsulation of the drug. Different ratios of vortioxetine to PLGA from 1:2 to 1:10 were used to prepare drug loaded PLGA microspheres and analyze drug loading efficiency by UPLC. Drug release studies were performed to evaluate the release pattern.

Results: An O/O (acetonitrile in HEF oil) emulsion was prepared by microfluidics. The purification method was optimized, and dry powder microspheres were produced. The size of the vortioxetine loaded PLGA microspheres (1:10 drug to polymer ratio) was 35.41 ± 1.05 μm. Three different batches of vortioxetine loaded PLGA microspheres were prepared which confirmed the reproducibility. SEM pictures showed the spherical structure of the microspheres. The peaks of vortioxetine in FTIR spectrum disappeared compared with the FTIR spectrum of vortioxetine loaded PLGA microspheres, which indicated the success of encapsulating the drug into the microspheres. The results of drug loading efficiency showed that around 90% of the drug were encapsulated in the 1:10 formulation, while it decreased to 60% for the 1:2 formulation. The drug release profiles showed that a small amount of drug was released slowly over the first 20 days. An increasing rate of release was observed between Day 20 and Day 30, which might be due to the degradation of the PLGA.

Conclusions: Microfluidic techniques could be a promising way of preparing PLGA microspheres with monodisperse size. A novel method was developed to generate O/O emulsion by droplet-based microfluidics. After the purification, dry powder PLGA microspheres could be obtained. The encapsulating efficiency of vortioxetine loaded microspheres reached around 90%. One month sustained drug release was achieved in the vortioxetine loaded PLGA microspheres.