

Fabrication and characterization of PLGA-loaded BCNU microcapsules produced via electrojetting for drug delivery to brain tumors

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Statement of Purpose: Despite significant progress in the development of new chemotherapeutic agents and drug delivery methods for brain tumors, malignant gliomas remains deadly with a median survival period of only about a year. The high dosage of chemotherapeutics required for penetration through the blood brain barrier not only kills cancer cells but also damages healthy tissues and causes adverse side effects. Thus, a major unmet challenge in the treatment of brain tumors is the development of effective local delivery methods. Drug-loaded poly(lactide-co-glycolide) (PLGA) microcapsules with high drug encapsulation efficiency and controlled shape and size are attractive candidates for effective and sustained local delivery of anticancer agents at the tumor sites. Here, we report the results of a systematic study of the size, shape, drug encapsulation efficiency, and drug release profiles of (PLGA) microcapsules-loaded with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) produced using electrojetting technique.

Methods: BCNU-loaded PLGA microcapsules (diameters of 1-10 μm) were directly electrojetted on the gold-coated plastic substrates. We precisely quantified shape and size of the microcapsules as a function of polymer concentration (1 to 10 wt. % PLGA) and flow rate (0.25 to 1 mLh^{-1}) of electrojetting process. Polydispersity of microcapsules were evaluated by calculation of coefficient variation (CV) of size. To evaluate the shape uniformity of BCNU-loaded microcapsules, we used scanning electron microscopy to measure the aspect ratio (AR) of these microcapsules as a function of PLGA concentration and flow rate. BCNU encapsulation efficiency and release profile (containing 0.63 mg of BCNU) in PBS solution was measured using UV spectrophotometer.

Results: We report production of BCNU-loaded PLGA microcapsules in the form of flattened microspheres, microspheres, and microfibers with significantly (1) higher drug encapsulation efficiency, (2) more tunable drug loading capacity, and (3) narrower size distribution than those generated using other encapsulation methods. The size and shape of PLGA microcapsule were precisely controlled by adjusting concentration of PLGA and electrojetting flow rate (Fig. 1 & Fig 2a-d). BCNU-loaded flattened microspheres, microspheres, and microfibers produced with a flow rate of 0.25 mLh^{-1} exhibit narrow polydispersity in size ($\text{CV} < 5\%$). The shapes of microspheres produced from 3, 4, and 5 wt% PLGA solutions were very well preserved (perfectly spherical), with better shape uniformity ($\text{AR} < 1.05$) than types 1 and 2 flattened microspheres produced from 1 and 2 wt% PLGA solutions ($1.05 < \text{AR} < 1.16$). The BCNU encapsulation efficiency was found to be $85 \pm 8\%$ for

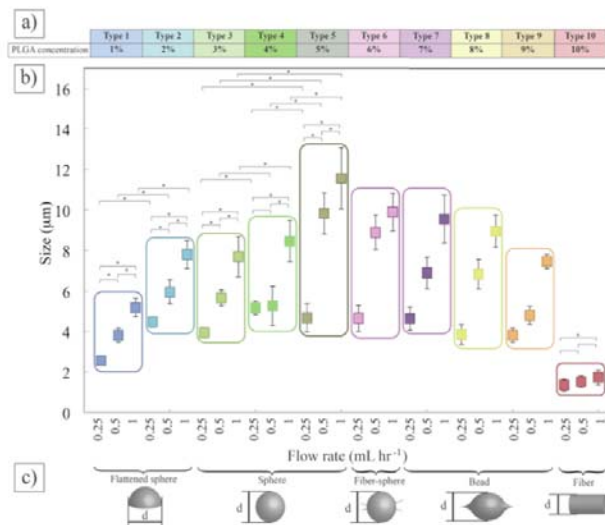


Figure 1. Effects of polymer concentration and flow rate on the size and shape of BCNU-loaded PLGA microcapsules.

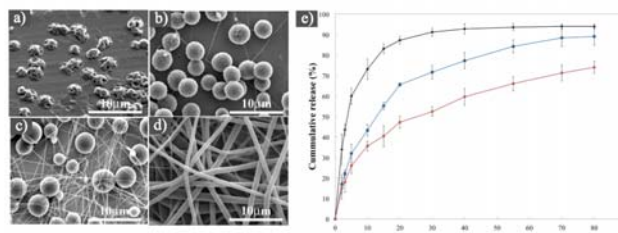


Figure 2. BCNU loaded : (a) flattened microspheres, (b) microspheres, (c) microspheres-nanofibers, (d) microfibers, (e) BCNU release profile

flattened microspheres, $89 \pm 4\%$ for microspheres, and $92 \pm 5\%$ for microfibers. Flattened microspheres exhibited a higher initial burst and release rate than microspheres and microfibers (Fig. 2e).

Conclusions: The use of an electrified liquid jet technique enabled us to produce tunable and monodisperse BCNU-encapsulated PLGA microstructures. The strategy described in the present work has three significant advantages: 1) it offers easy control over the shape and size of microcapsules, 2) it allows production of microcapsules with narrow size distribution and highly uniform morphology, and 3) it enables production of BCNU-loaded microcapsules with high drug encapsulation efficiency. We envision the extension of the strategy reported here to the production of monodisperse nano-capsules for drug delivery.

References:

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