PLGA-Porous Silicon composite microspheres: optimization insights of a double controlled release platform for tissue engineering applications

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Statement of Purpose: Creating an artificial environment allowing cells proliferation and differentiation is crucial to induce tissue regeneration and healing. Growth factors (GFs) release is a promising strategy to trigger specific cell behaviors and regenerate target tissues. The ability to control the release kinetics of GFs during tissue healing became greatly attractive in the last decades. Poly(lactide-co-glycolide) (PLGA), a food and drug administration (FDA) approved polymer, has been extensively used in the fabrication of delivery systems due to its biodegradability and biocompatibility [1]. Moreover it is possible to tune material properties to tailor the degradation rate of the polymer by adjusting the lactic acid and glycolic acid ratio and its molecular weight [2]. Nanoporous silicon microparticles (pSi), due to their biodegradable and biocompatible constitution, have been extensively used in tissue engineering and drug delivery. pSi particles' size, shape, porosity and pore size can be finely tailored during manufacturing. In this study, a wide set of PLGA-pSi composite microspheres loaded with fluorescein isothiocyanate labeled bovine serum albumin (FITC-BSA), with different PLGA coatings and pSi sizes has been evaluated. Each platform has been tested as a double controlled release system to obtain a zero order release and ensure a constant and sustained release rate of the proteins up to three weeks.

Methods: PLGA have been dissolved in dichloromethane (DCM) to form 10 w/v PLGA/DCM solution. pSi with with an average diameter of 1, 3 and 7µm, were loaded with FITC-BSA, and subsequently encapsulated in PLGA microspheres. Per each type of pSi, three PLGA coatings were attempted, using the copolymer ratios 50:50, 75:25 and 85:15. The encapsulation was performed following modified solid-oil-water (S/O/W) emulsion method [3]. The release of FITC-BSA from PLGA-pSi was performed in physiological-like conditions (PBS, 37ºC, under mild agitation). Samples were collected at defined time points, up to 1 month. The amount of released FITC-BSA was quantified by fluorescence using a spectrophotometer at 493/518 nm.

Results: To change pSi particles' surface charge from negative to positive and enhance their loading efficiency, particles surface has been modified with (3-aminopropyl) triethoxysilane (APTES). Zeta potential analysis showed a surface charge of 6.44 mV after APTES modification, instead of the initial value of -30.39 mV. BSA, in fact, had a negative charge and the electrostatic interaction between APTES amine groups and acidic moieties of BSA intensified the ability of FITC-BSA to be loaded into the pores of pSi particles. The ideal platform, which allowed us to obtain a zero order release, presented, as a core, pSi with an average diameter of 1 µm and 51% of porosity and a 20% PLGA (85:15) coating. As we can see in figure 1, the release profile of BSA-FITC from PLGA-pSi formulated with both the (50:50) or (75:25) copolymers displayed an initial marked burst release. Optical microscopy demonstrated that median number of 3 (±0.2307) pSi has been encapsulated in the PLGA microsphere. The improvement of PLGA-pSi fabrication and pSi dispersion through the microspheres was crucial to ensure a more homogenous release of payload.

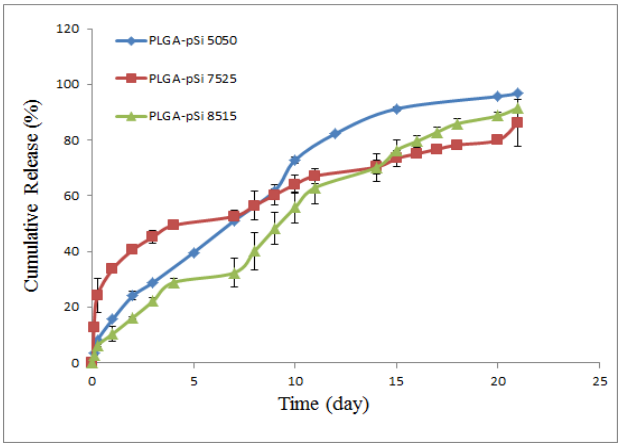

Figure 1A. Release profile of BSA-FITC from different micro-composite formulations over three weeks.

Conclusions: The flexible manufacturing of each component of the microspheres resulted in a customizable platform, where each component is fully unable, and contributes to the release kinetic of the payload. The optimized system prolonged the delivery of the payload over a longer period of time and avoided the initial burst release of proteins.

References: [1] S. Minardi. *Small*, 2014, 3813-3813
[2] Jain RA. *Biomaterials*. 2000; 21:2475–2490
[3] D. Fan. *Adv. Funct. Mater.*, 2012, *2*, 282-293