CORE/SHELL MICROSPHERES VIA COAXIAL ELECTROHYDRODYNAMIC ATOMIZATION FOR SUSTAINED RELEASE OF DRUGS

Chi-Hwa Wang, Hemin Nie

Department of Chemical and Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576

Introduction

Tissue engineering and cancer therapy are two different examples of the application of drug delivery systems. Each application is essentially a multistage process that is regulated by a serial of growth factors or inhibition factors. Here, each factor requires different time scales and concentration profiles due to the nature of the repair/inhibition process. This suggests that the sequential or coupled release of multiple factors with different temporal profiles will become essential and critical for a successful tissue regeneration or tumor inhibition strategy [1-3]. [3]However, in modern design, most delivery systems only accounts for a single factor, limiting the overall efficacy of the therapy [4-5].

Experimental

The coaxial needle (Popper and Sons, Lake Success, NY, USA) is made of 316L stainless steel. The outer capillary has an outer diameter of 0.72mm and an inner diameter of 0.50mm. The core capillary has an outer diameter of 0.40mm and an inner diameter of 0.20mm (Figure 1). Two syringe pumps (KD Scientific, Holliston, MA, USA) deliver the polymer solutions at a specific rate into the inner and outer capillary of the coaxial needle. A voltage generator (Glassman High Voltage Inc., High Bridge, NJ, USA) supplies a high voltage to the nozzle by means of a crocodile clip. In order to stabilize the electric field around the nozzle, another high voltage is applied to the ring (5 cm in diameter) surrounding the nozzle. By increasing the nozzle voltage (V_{nozzle}) and ring voltage (V_{ring}), the emerging droplets were gradually accelerated by the potential difference until a stable Taylor cone jet can be visually observed. In order to avoid the agglomeration of microspheres, a petri dish filled with anhydrous ethanol was utilized to collect the microspheres, substituting the aluminium foil normally used.

The objective is to fabricate, by coaxial EHDA, microspheres of distinct core/shell structures. In order to ensure that the drug in the core is not released prematurely, the core must be of slower degrading material than the shell. Hence PLLA was chosen for the core and PLGA for the shell in this study. Ideally, paclitaxel and suramin are encapsulated in PLLA core and PLGA shell respectively or the reverse in radial distribution, with suramin inside the core and paclitaxel in the shell. Therefore, the release of dual-drugs can be predicted and tailored.

Results and Discussion

Morphology and diameters of microspheres fabricated from different core/shell flow rate ratios were investigated. It was found that the values 1.2 ml/h /1.5 ml/h and 1.6 ml/h /2.0 ml/h (Q_{core}/Q_{shell}) are advantageous over 2.0 ml/h /2.5 ml/h and 2.4 ml/h /3.0 ml/h on producing smooth and uniform microspheres (data not shown). For the effects of flow rates on diameters, the increase of either inner or outer flow rate increases microsphere diameter non-linearly (data not shown). Considering all the observations on morphology and size distribution, it is concluded that a Q_{core} ranged between 1.0-2.0 ml/h and a constant Q_{shell} of 2.0 ml/h may maintain stable cone-jet structure in the process of atomization and consequently result in uniform and smooth microspheres with varied core sizes.

The existence of the core/shell structure within the microspheres fabricated from the core/shell flow rate ratio of 1.5 ml/h / 2.0 ml/h was confirmed by confocal microscope (Figure 2b-2d). Distinct cores and shells are observed in another two formulations with different Q_{core}/Q_{shell} ratios (1.2 ml/h / 2.0 ml/h and 1.8

ml/h / 2.0 ml/h) as well (data not shown). The confocal images confirm that Coaxial EHDA can produce core/shell structured microspheres with distinct and tailorable distributions of cores and shells.

The co-axial electrohydrodynamic atomization method utilized in the current study elucidates the single step operation of encapsulating drugs with different hydrophilic properties inside a core/shell polymeric carrier, which supersedes other methods requiring two or more steps to achieve the encapsulated product [6]. Especially, hydrophilic drug can be encapsulated in the core, while hydrophobic drug is located in the shell. By altering drug solutions between the inner and outer needles, different drug distributions are obtained in the core/shell microspheres, allowing different temporal release profiles of each drug. Depending on the time frame of tumor treatment, a particular group will be more advantageous than the others. The different drug release rates and release patterns from the core/shell microspheres developed in this study are attributed to the distinct core/shell structures of microspheres and the difference of two drugs in hydrophilic properties.

Conclusions

In summary, this work presents a modified method, namely coaxial electrohydrodynamic atomization, in the preparation of microspheres with distinct core/shell. This allows the encapsulation of two drugs with different characteristics in hydrophilic properties in one single step. Variation of ratios between outer flow and inner flow produces polymer microspheres with different core/shell ratios, and consequently results in variable release rates of drugs.

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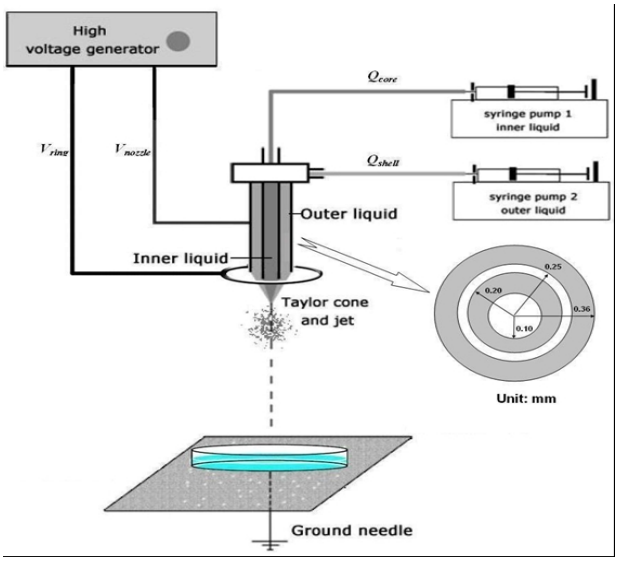

Figure 1: Schematic diagrams depicting the set-up of coaxial electrohydrodynamic atomization (CEHDA). V_{nozzle} and V_{ring} are 6.5 KV and 3.5 KV respectively in a typical fabrication.