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Control of shape and size of poly (lactic acid) microspheres based on surfactant and polymer concentration

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ABSTRACT

Biodegradable, poly (lactic acid) (PLA) microspheres have been synthesized via solvent evaporation method using ultrasonic homogenizer as emulsifier. The effect of added surfactant, PVA [poly (vinyl alcohol)], and PLA concentration on the shape and size of the resultant PLA microspheres has been studied. The prime objective of this work was to identify an optimal PVA/PLA concentration to prepare PLA microsphere with a size distribution of 1–2 micrometers as in many literature it has been reported as ideal range of size for non-endocytosis-mediated cellular drug delivery. In this pursuit it was found that an optimal concentration of 2.5% w/v of PVA into water and 2.5% w/v PLA into DCM [Dichloromethane] is suitable to create PLA microspheres with a size distribution of 1–2 micrometers. The PLA microspheres were characterized by FESEM to assess their shape and size. FT-IR analysis (Supplementary data) was used to assess the functional groups present in the PLA microspheres, whilst zeta-potential measurements (Supplementary data) provided insight into the likely dispersion properties of the microspheres in aqueous media.

1. Introduction

Cellular-level drug delivery techniques offers efficient and safe drug disposition in the affected tissues and thus provide a more suitable way to cure disease by selective drug delivery approaches [1]. Recently, polymer microsphere-based intercellular delivery, termed beadfection, has been shown to be a facile and highly promising cellular-level drug delivery platform [2]. The reason why microspheres form such an attractive delivery mechanism is principally because nano-sized drug delivery vehicles and labeling agents are known to induce size dependent toxicity [3] in part due to their high surface area to volume ratio. On the other hand a number of recent reports have shown that cells are capable of engulfing larger particles by a non-endocytosis mediated mechanism in a process termed as beadfection [4,5]. This discovery makes it possible to use micron-sized particles to deliver drugs and/or bio-imaging agents into cells. These reports suggest that microspheres with the size range of 1–2 micrometers are optimally sized for non-endocytosis-mediated, cellular level drug delivery [6].

There are many techniques that have been developed to convert polymers into uniform polymeric microspheres. Out of those techniques the solvent evaporation method is arguably the most simple to employ and is also readily scalable. This method is based on efficient emulsification of two different phases using a homogenizer. Among various homogenizing techniques [7,8], use of ultrasonic homogenizer is preferable as it is relatively simple and significantly reduces the time of microsphere synthesis. Despite this, to date there are no significance efforts have been seen on the size and shape modulation of the microspheres generated using this technique.

Herein we report a systematic study that evaluates the effect of polymer: surfactant ratio on the shape and size of the resultant polymer microspheres. Such a study is vital as uniformity in size and shape of the microspheres is critical for applications like cellular level drug delivery assay such as beadfection, where relative amounts of delivered drug are clearly essential. This article describes the synthesis of poly (lactic acid) microspheres, produced using a variety of reaction conditions, the identification of the optimal reaction conditions to generate microspheres and characterization of the morphology of the resultant microspheres in aqueous media. Specifically FESEM analysis was used to assess particle size and shape, FT-IR spectroscopy (Fig. S1) provided insight into microsphere chemical functionality whilst zeta potential

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measurements (Table S1) gave an insight into solvent accessible surface charge and thus likely aqueous compatibility of the microspheres, key for cell-based applications.

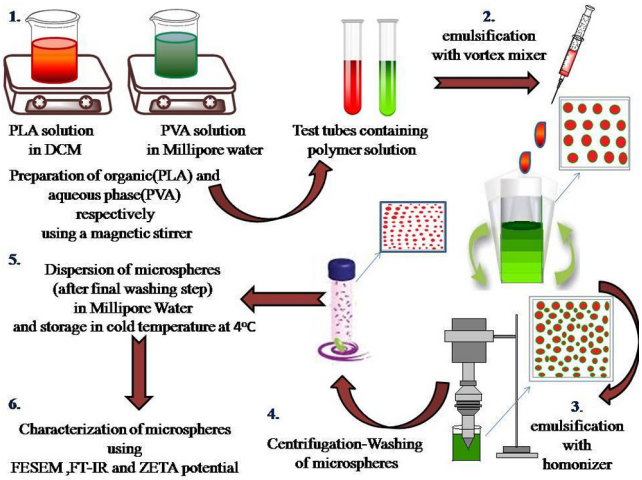

Fig. 1. Schematic representation of fabrication process of PLA microspheres.

Table 1
PLA and PVA relative concentration chart.

Sample No.	PLA conc. (w /v%)	PVA conc. (w /v%)
1	1.0	1.0
2	2.5	2.5
3	1.5	0.5
4	1.5	1.0

2. Experimental section

2.1. Materials

Poly (lactic acid) (PLA) (MW 150, 000) was purchased from Sigma Aldrich, Poly (vinyl alcohol) (PVA) (MW160, 000) and Dichloromethane (DCM) (MW 84.93) were purchased from Himedia Laboratories Pvt. Ltd., Mumbai, India. Millipore water was taken from laboratory Elix water purification system.

2.2. Microsphere Preparation using emulsion solvent evaporation technique

The principle behind this method is the emulsification of a polymeric solution in a continuous phase. Accordingly, two phases are required in this fabrication procedure (Fig. 1). Firstly, an organic phase was prepared by dissolving various concentrations of PLA in DCM (10 mL) and stirred for about one hour. The second aqueous phase was prepared by dissolving different concentrations of PVA in water (20 mL); dissolution was achieved by stirring the mixture at 90 °C for 2 h using a magnetic stirrer [9,10].

An emulsion was then formed in a two-step process. In the first step, an aliquot of the PLA-containing solution (1 mL) was added slowly to an aliquot of the PVA-containing solution (2 mL). The PVA-containing solution was mixed continuously at room temperature using a vortex mixer during the addition of the PLA-containing solution. Due to high speed vortex mixing an emulsion started to form, the vortex mixing (SPINIX vortex mixer) was continued for a further 10 min. Subsequently, to reduce the size of the PLA particles, the emulsion was immediately transferred to an ultrasonic homogenizing unit (SONICS vibra cell-20% amplitude with 3 s pulses).After which the emulsion was stirred at room

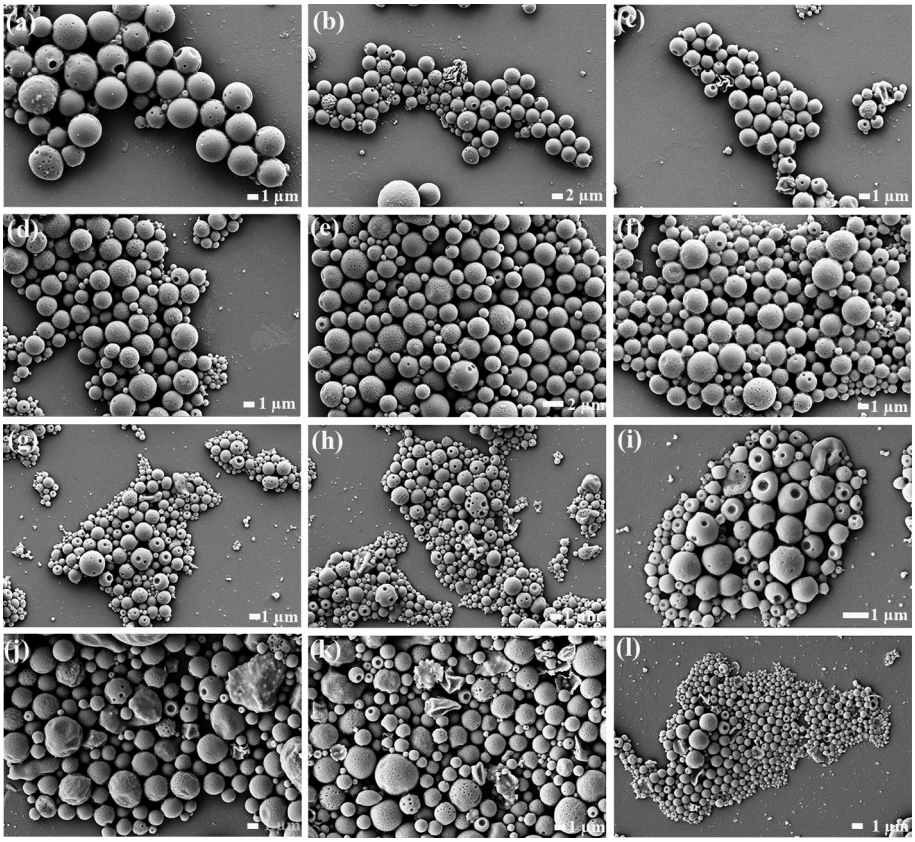

Fig. 2. FESEM micrographs of PLA microspheres prepared from PLA/PVA solutions with various concentrations. PLA: PVA concentration (w/v%:w/v%); (a–c) 1.0:1.0, (d–f) 2.5:2.5, (g–i) 1.5:0.5 and (j–l) 1.5:1.0.