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Performance of novel high throughput multi electrospray systems for forming of polymeric micro/nanoparticles

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ABSTRACT

In order to maintain a stable cone-jet mode in electrospray low flow rates are used while most applications require a high throughput. We compare two different designs of the multiple electrospray system in order to increase the output for large scale production applications. In this study, the solution was fed through four separate needles that were attached to either a circular or a rectangular metallic plate that were connected to a high voltage DC power supply. The behaviour of the electrospray jets as well as the deposition of particles were investigated. It was shown that the throughput of particles was increased while particles with narrow size distribution were produced from all four uniform electrospray jets.

1. Introduction

Particles generated via electrospraying have many applications in several technological and scientific processes [1,2]. Following the pioneering work by Zeleny [3], needles or tips are being used as an important part of the electrospray experimental setups for production of particles. In order to produce particles of micrometre and submicrometre dimension via electrospray, very low flow rates and high values of the electrical conductivity of the liquid sample are often required [4]. This causes severe limitations to the use of a single electrospray emitter in industrial applications [5]. A solution to this problem is to increase the number of emitters.

Multiplexed electrospray setups have been primarily investigated by several researches in order to increase the throughput for the purpose of large scale production [6]. Various configurations for electrospray deposition have been proposed [7,8], while the nozzle-substrate system was mostly used in both experimental and numerical studies [9]. Multiple-electrospraying using microchannels was also investigated owing to the development of microfabrication techniques [10]. The limitations of these designs are however multiple. The advantages of using separate needles that are fed through parallel tubing compared to nozzles or channels are mostly that they are easier and cheaper to manufacture [11]. This technology enables cheap mass production in many industrial scale applications. Multiplexing involves the presence of a reservoir from which each emitter is fed. One of the issues related to multi nozzle electrospraying is the equal distribution of liquid in all nozzles [12].

In multi needle systems, increasing the quantity of needles lead to having a high number of stable cone-jet mode electrosprays per unit area. This causes the space charge to increase significantly due to the cloud of charged droplets [8]. As a result, shielding of the electric field occurs near the surface of some conical menisci which can lose their conical shape. Depending on the geometry of the multi spray system, this phenomena usually affects the needles located in the central region of the atomizer [13]. One of the most difficult issues associated with the multi-needle system is that the adjacent jets repel each other and as a result the electric field on the tip of each needle at different positions is not uniform [14]. This causes instability and in some cases dripping or non-working needles during the electrospraying process occur. In order to have uniform particle size, it is important to ensure that all the emitters or needles operate in a steady cone-jet mode [15]. One of the primary goals of particle synthesis, is the ability to produce monodisperse particles at flow rates sufficient for various applications. Regardless of the application, from drug delivery [16], to the synthesis of nanoparticles for other non-biomedical applications [17], superconductors [18], quantum dots [19] and thin films, it is crucial that the processing method can be tailored to suit the criteria. For instance, in controlled drug release application, the size and composition of

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particles has a dramatic impact on the release profile of the drug [16]. The processes involved in drug release from biodegradable polymeric matrices are complex and not only the size of the particles but also other factors such as drug solubility and its diffusion coefficient in the polymer matrix can contribute to the process. The difference in the surface/volume ratio of the polymeric microspheres with different size due to differences in the rates of solvent extraction between smaller and larger emulsion droplets during preparation have an impact on the drug loading of these particles [20].

One of the key issues of commercializing the multi electrospraying technology is to design a setup that reduces the interference between the neighboring needles and disruption of the stable cone jet at each needle. In addition, a suitable design should control the spraying jets travelling towards the collector simultaneously, ensuring homogeneous deposition of particles. Recently, there has been an intense amount of interest in the design and investigation of multi needle systems for production of particles and fibres. Xie et al. [21] studied the effect of electric field on the multi needle electrospinning technique. They proposed spinnerets with two kinds of needle array, linear three-needle and triangular three-needle. They produced finer and more uniform nanofibers using an auxiliary plate. Zhang et al. [22] proposed multi pore electrospraying for high throughput production of biodegradable microparticles using a flute-like multi-pore emitter device. Almeria and co workers [1] produced PLGA particles using a multiplex electrospray system. They used multiplexed arrays consisting of multiple electrospray nozzles operating in parallel to encapsulate amphiphilic agents such as doxorubicin, Rhodamine B and Rhodamine B octadecyl ester perchlorate.

The present study focuses on the design of a multi needle system that can provide electrospray in the cone-jet mode. The aim is to propose a device that can produce monodisperse droplets/particles over a wide size range, from a few hundred nanometers to tens of micrometers. The ultimate purpose of the new multi-spray design is to overcome the main drawback of nanoparticle fabrication: low throughput. Experiments were performed to demonstrate the robust multi-needle electrospraying designs, as well as a comparison study on the particle size, production rate and spray/deposition pattern from each geometry with respect to the single electrospraying setup.

2. Materials and methods

2.1. Materials

PLGA (copolymer 50:50, Resomer RG503H, molecular weight of 33,000 Da, inherent viscosity 0.41 dl g^{-1}) was purchased from Boehringer Ingelheim (Ingelheim, Germany). Dimethylacetamide (DMAc) was obtained from Sigma Aldrich (Poole, UK). PLGA solutions (2 wt%) were prepared by dissolving the polymer in DMAc or Acetone and mechanically stirring for 400 s.

2.2. Characterization of solutions

The viscosity, surface tension, density and electrical conductivity of all the prepared solutions were measured. Density was measured using a standard density bottle DIN ISO 3507- Gay-Lussac. Viscosity measurements were conducted using a U-tube viscometer (size E, VWR, UK). Prior to measurements the viscometer was calibrated and checked with ethanol to remove any residue. A Kruss tensiometer (Model DSA100, Kruss GmbH, Hamburg, Germany) was used to measure the surface tension using the Wilhelmy's plate method. Electrical conductivity of each solution prepared was estimated using a conductivity probe (Jenway 3540 pH/conductivity meter). All the measurements, presented in Table 1, were conducted at the ambient temperature (21 °C) and relative humidity of 40–50% after calibrating the equipment with distilled water.

Table 1
Physical characteristics of the solutions used to prepare particles.

	Viscosity (mPa s)	Surface tension (mN/m)	Electrical conductivity (mS/m)
2 wt% PLGA-Acetone	1.02	25	0.36
2 wt% PLGA-DMAc	1.62	27	0.37
Acetone	0.36	23	0.02
DMAc	0.98	25	0.14

2.3. Experimental setup

Fig. 1 shows the experimental setups for the four-nozzle electrospray deposition process with the nozzle-substrate configuration used in this work. Two different configurations were considered. The first geometry consisted of nozzles that were arranged in a linear array and were mounted on a rectangular plate. The second nozzle array geometry composed of four electrospraying nozzles with capillary spacing set at 5 mm between centers of adjacent capillaries that were mounted on a circular plate. The needle distribution is shown in Fig. 1a and b for the circular and rectangular plate configurations, respectively. The four needle positions are labeled as 1, 2, 3 and 4. The nozzles were stainless steel capillaries (Bignell Surgical, USA) with outer and inner diameters of 0.8 and 0.5 mm, respectively. The liquid was fed through 4 separate chemically resistant Tygon tubing that were attached to two double pumps. The solutions were infused via two double syringe pumps (PHD 4400, Harvard Apparatus Limited, Edenbridge, UK) at constant flow rates of 2 to 20 μl/min. A positive voltage of up to 20 kV was applied to the nozzles with a positive-polarity high-voltage DC power supply. A high precision voltage generator (Glassman Europe Ltd., Bramley, UK) supplied the required electric field to the solution. The particles were collected at a working distance of 20 mm below the device exit directly onto glass slides placed on stainless steel substrates. The shapes of the liquid menisci at the capillary outlets were observed with a Photron SA1.1 high speed camera with 5400 fps at full megapixel resolution (Photron, UK).

Samples of particles were collected on microscopic glass slides at 21 °C and 40–50% relative humidity. These were analyzed mainly under an optical microscope (Nikon Eclipse ME 600) fitted with a camera (Micropublisher 3.3 RTV, 3.3 megapixel CCD Color-Bayer Mosaic, Real Time Viewing camera, Media Cybernetics, Marlow, UK). The collected particles were also imaged using scanning electron microscopy. Both optical and SEM micrographs were analyzed using Image J to determine the average diameter and relative standard deviation of the population of particles (200 particles were measured from each sample).

3. Results and discussion

3.1. Particle size and size distribution

For the initial experiments, 2 wt% PLGA dissolved in acetone was used. All four needles were fed via two double pumps at three different constant flow rates of 5, 10 and 20 μl/min. Once the droplets were formed at the tip of all needles, the electric field was increased to 18–27 kV until a stable cone jet was formed at the tip of all four needles. Both geometries with circular and rectangular plate were used. From the experimental observations, the system requires a few seconds to settle in a stable spraying mode where all four needles are functioning with flow in single cone jet mode. This time is measured and investigated further in the following sections. It was also noted that the rectangular configuration required slightly higher voltages to produce particles at each given flow rate (Table SI 1 of supplementary Information). Particles were collected on microscope glass slides from

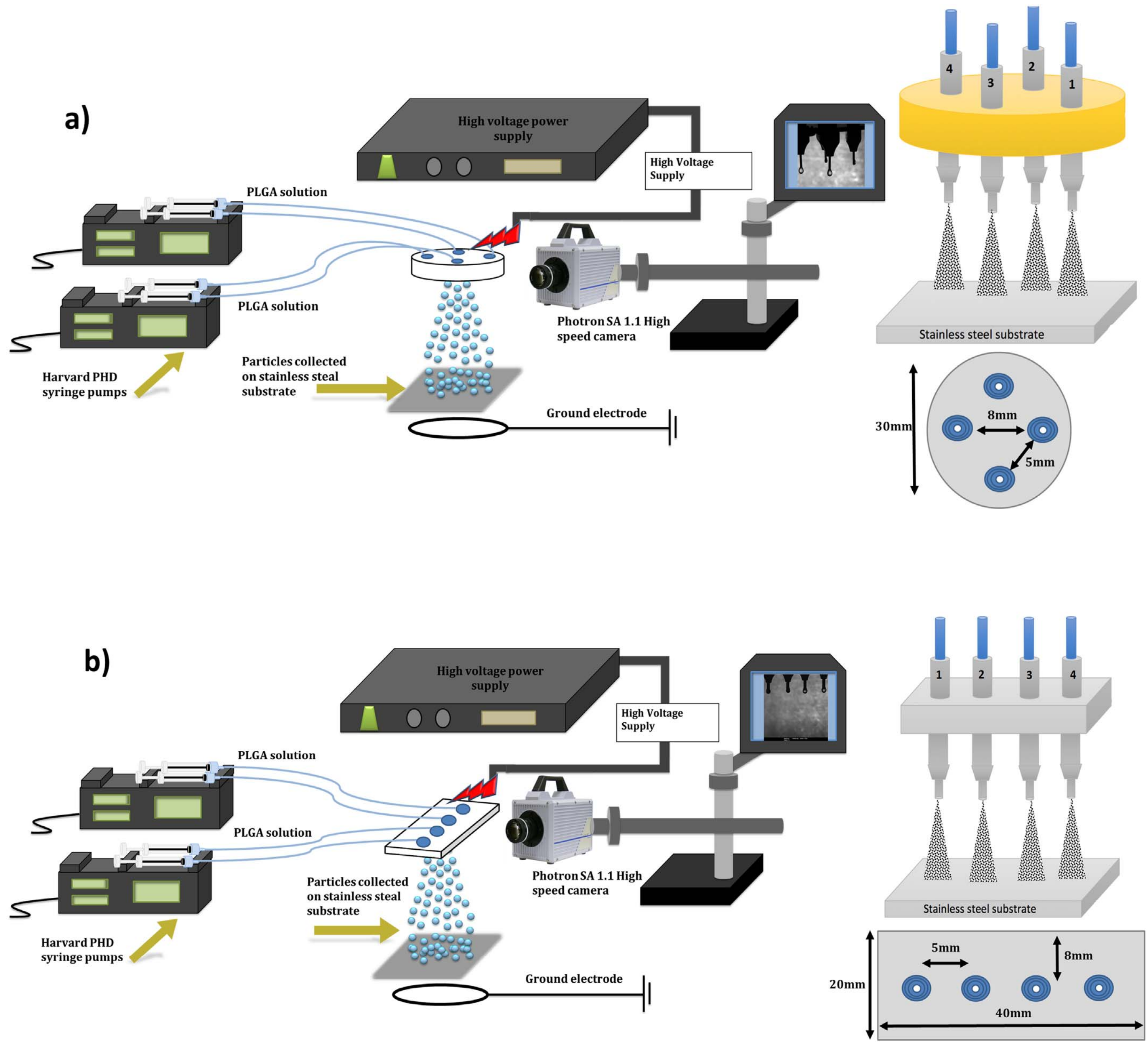

Fig. 1. Schematic diagrams of the four nozzle experimental setup with a) circular and b) rectangular plate configurations.

all four deposition areas on the collector substrate corresponding to each electrospray nozzle (labeled as 1, 2, 3 and 4) and the size and size distribution of particles were measured. The SEM analysis (Fig. 2a, b) confirmed all of the particles were nearly monodisperse in size (that is more evident in the circular configuration setup) and solid with a smooth outer surface.

Further experiments were conducted using both the circular and rectangular plate configurations, with 2 wt% PLGA dissolved in DMAc solution, in order to confirm successful production of particles with narrow size distribution through all four needles. The properties of the solution differs from the earlier mentioned PLGA solution used (Table 1). The rationale behind this set of experiments was to evaluate whether both systems were adaptable with solutions of various characteristics. As shown in Table 1, the solution containing DMAc, has a higher conductivity. At the same time, DMAc has a higher dielectric constant than acetone, and hence the solution containing this solvent requires higher voltages to be charged and achieve the stable cone jet mode [23]. It is therefore suggested that the flow rate should be reduced to minimize the voltage required to electrify the solution. In addition to this effect, producing particles at smaller scales require the solution to be fed at very small flow rates [24]. In this case, the flow rate was set at a constant rate of 5 μl/min, while the voltage was increased to 19 kV. Optical microscope images and size distribution graphs shown in Fig. 3a and b, for the circular and rectangular configuration, respectively, demonstrate that all four needles produced particles with 650 nm average diameter while the size distribution was still narrow (SD = 0.11 ± 0.02 μm).

In order to verify the consistency of particle production with narrow size distribution from all the four needles, particles were collected and the mean diameter was measured for each needle labeled as 1, 2, 3 and 4. Fig. 4 comprises of graphs showing mean particle diameter for each corresponding needle at three different flow rates of 5, 10 and 20 μl/min for the solution containing acetone at 5 μl/min for the solution containing DMAc. It is shown that for both geometries, particles were similar in size for all four needles when the flow rate was 5 μl/min. The standard deviation was approximately the same for all four needles in both cases (0.11, and 0.21 μm for the circular and rectangular plate, respectively). The graphs prove good monodispersity and suggest that

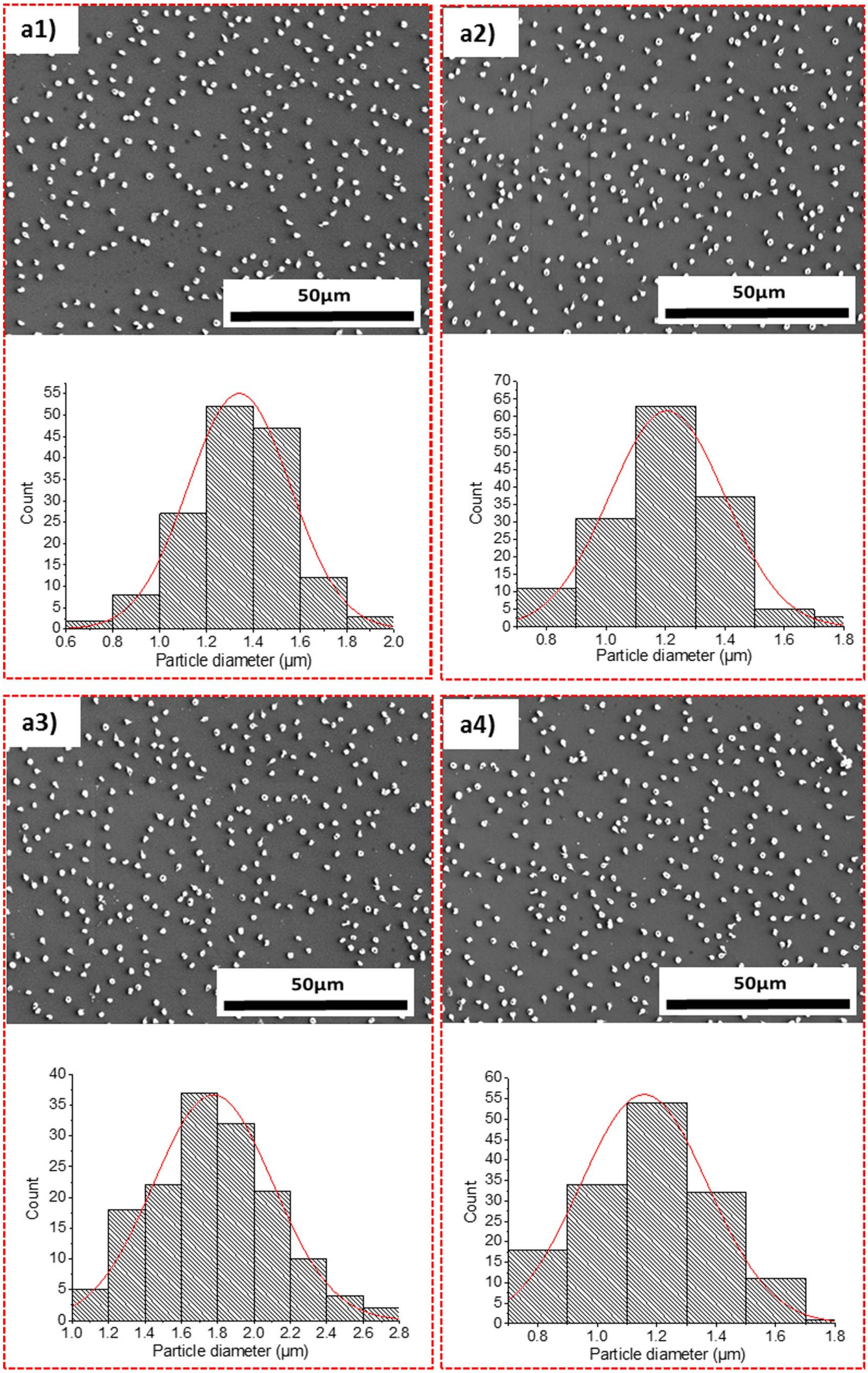

Fig. 2. a): SEM images and size distribution graphs of PLGA particles (acetone as solvent) collected at four deposition areas on the substrate from electrospray jets of all four nozzles from the circular plate configuration. b): SEM images and size distribution graphs of PLGA particles (acetone as solvent) collected at four deposition areas on the substrate from electrospray jets of all four nozzles from the rectangular plate configuration.

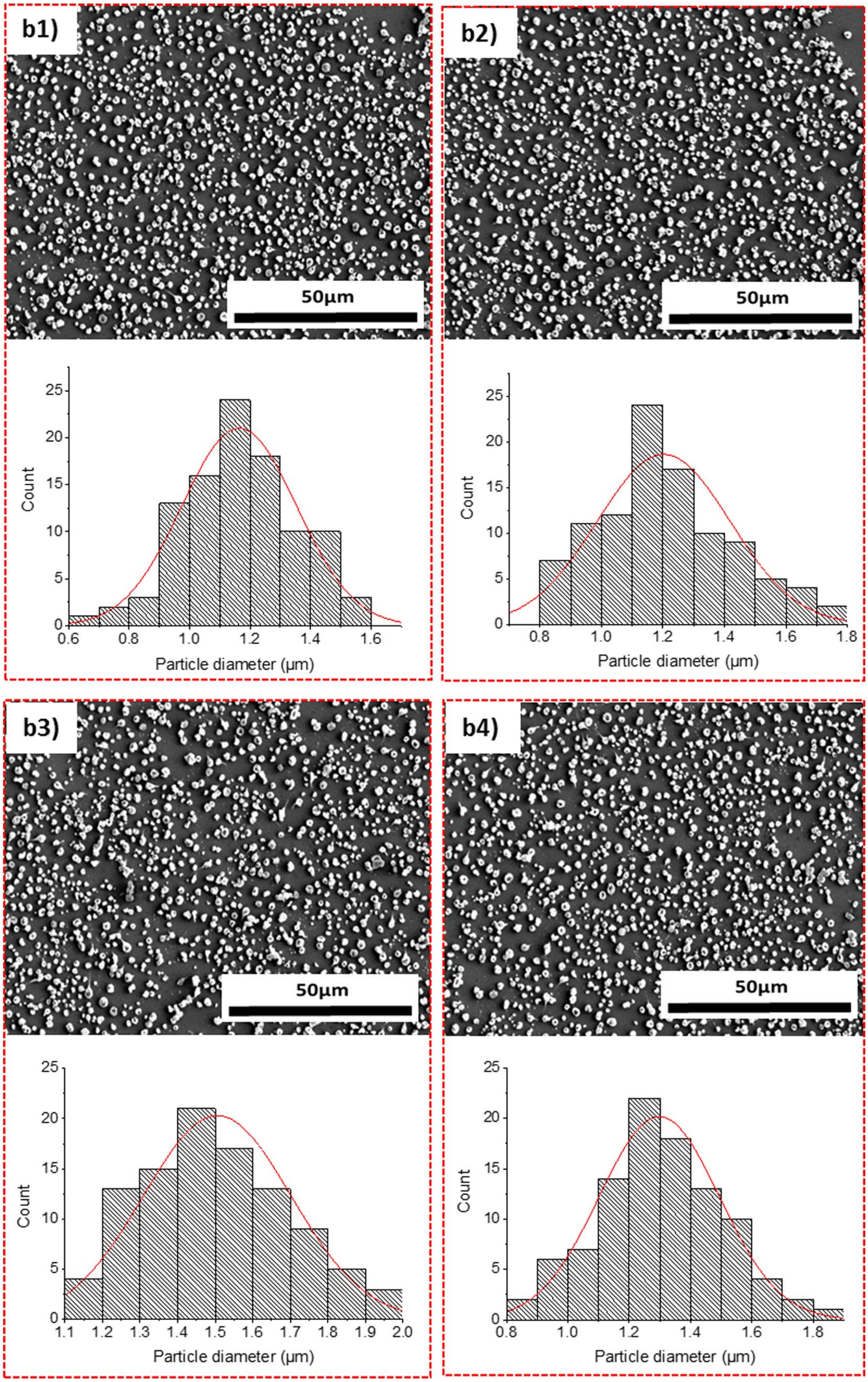

Fig. 2. (*continued*)

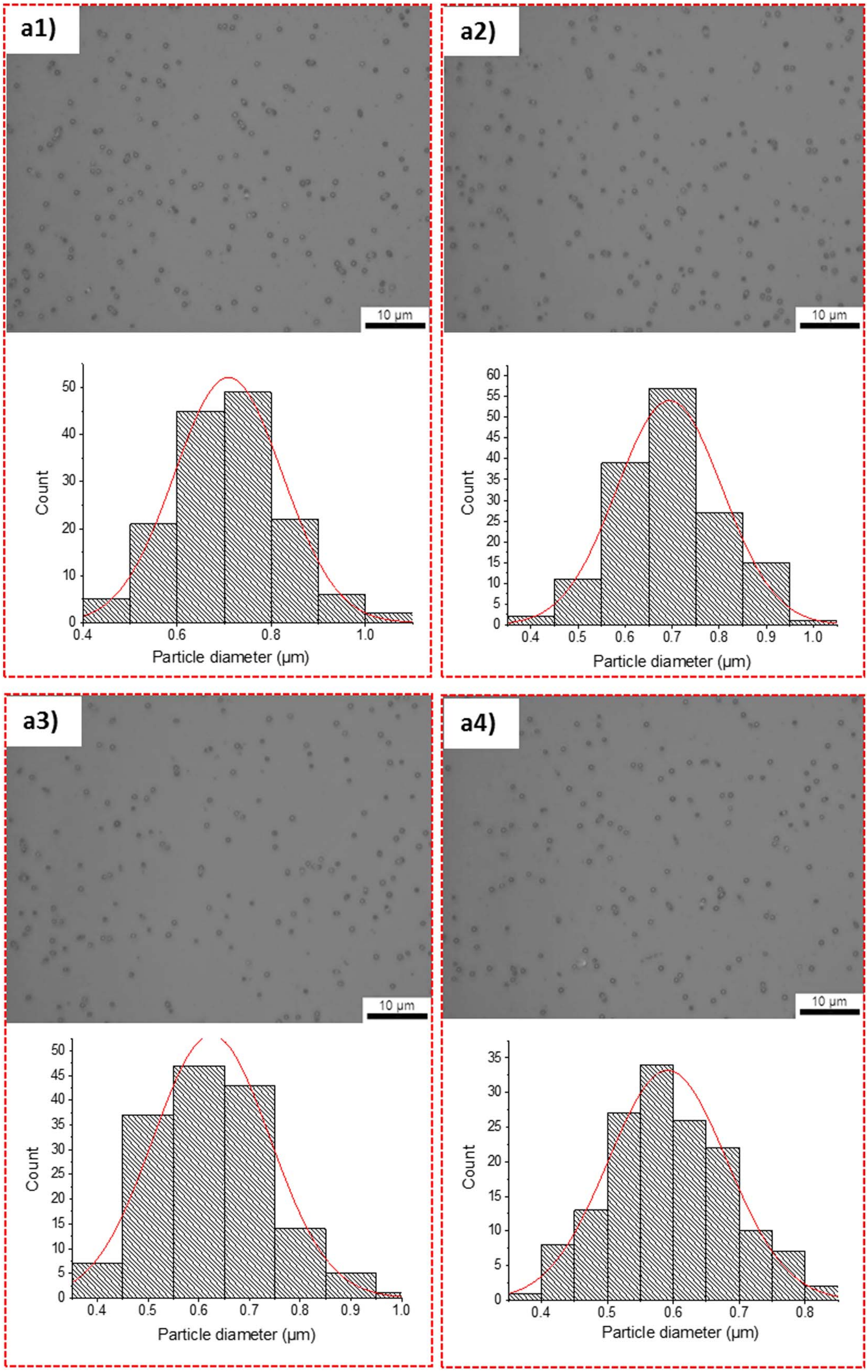

Fig. 3. a): Optical microscope images of PLGA particles (DMAc as solvent) collected at four deposition areas on the substrate from electrospray jets of all four nozzles from the circular plate configuration. b): Optical microscope images of PLGA particles (DMAc as solvent) collected at four deposition areas on the substrate from electrospray jets of all four nozzles from the rectangular plate configuration.

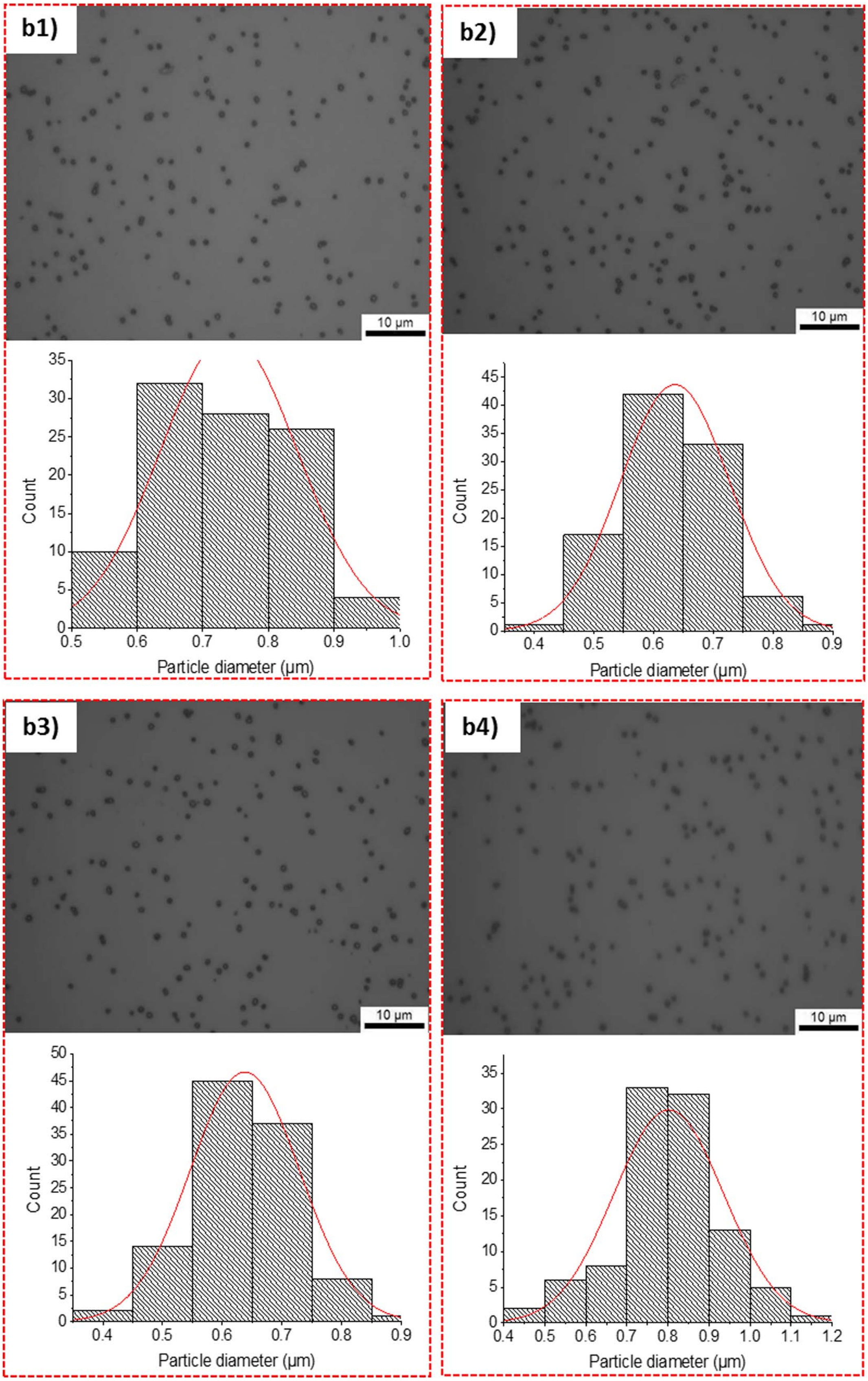

Fig. 3. (*continued*)

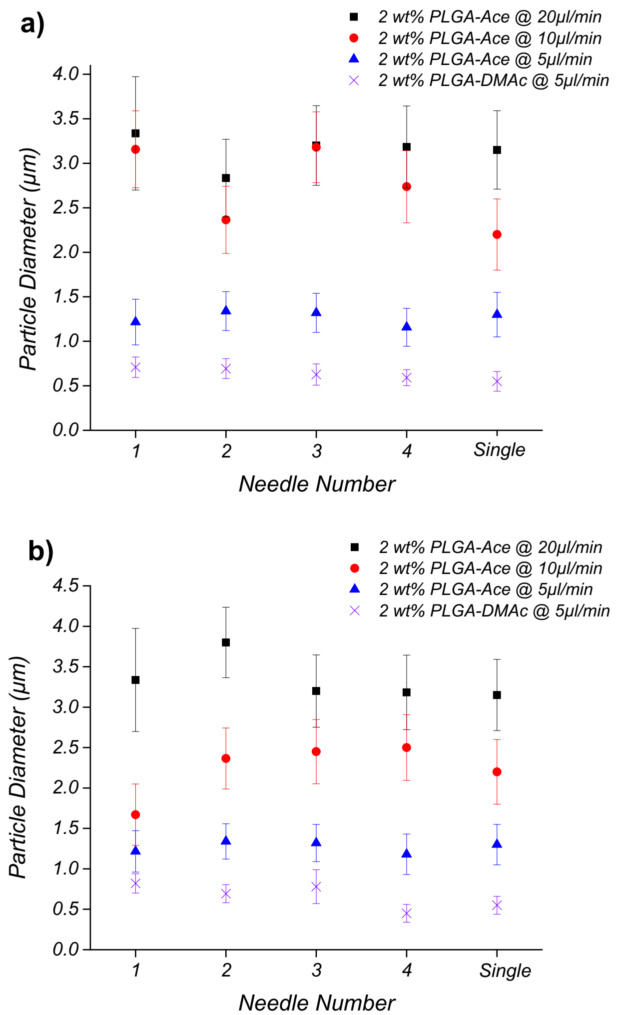

Fig. 4. Mean particle diameter in individual cone-jet electrosprays needles in the multiplexed mode for a) circular and b) rectangular configurations, the single needle values are also indicated in each case.

all four needles operated in stable cone-jet mode. However, at higher flow rates (10 and 20 μl/min), the particle mean diameter and standard deviation varied at different needle positions. Overall, the circular plate configuration produced more uniform particles at any given flow rate. This could be attributed to the non-uniformity of electrospray jets due to the squeezing of the envelope cones of the inner jets, when the nozzles are arranged in a row, as predicted and experimented in previous research [25].

Single needle electrospraying setup was also used in the experiments and particles produced were measured to obtain their size and size distribution. Particles were produced with the identical conditions as both multi needle electrospraying configurations and the size of particles is presented in Fig. 4. It was shown that for each given solution flow rate, particles produced with the single needle electrospray system had similar size to the ones produced with multi needle electrospraying systems. In conventional single needle electrospraying, particle size is manipulated by varying flow rate, applied voltage and deposition distance. Similarly, in multi needle electrospraying systems, the adjustment of these parameters can lead to variation in size of particles based on the desired application [22].

3.2. Spray characteristics

In electrospraying, it is well established that under given operating conditions, for instance where the flow rate is controlled, the shape of the meniscus is affected by the applied voltage. It is therefore suggested that the surface area of the meniscus changes as well as the rate of the evaporation of the liquid from the meniscus [26]. While increasing the high voltage, the electrospray exhibits a sequence of regimes. By increasing the applied voltage from an initial absolute value until the liquid meniscus takes the cone jet shape, the liquid meniscus passes a few spray modes [27].

In order for a successfully designed multi spray system to function well, one should ensure that all the needles operate simultaneously for a wide range of flow rates, producing uniform droplet size from all of the emitters. Due to the monotonic dependence of droplet size on the flow rate, maintaining the uniformity of droplets from all needles requires consistency from all needles [28]. Optimizing the flow rates and electric field, in order to have identical conditions for all needles, poses challenges in the design and fabrication of a simple and robust multi spray system. Several researchers suggest that the applied voltage and consequently, the electric field strength can significantly affect the shape of the cone jet [26]. In the next two sections, the behaviour and shape of the electrified jet are investigated and explained for each geometry.

3.2.1. Multi jets with circular plate configuration

In order to investigate the behaviour of electrospray jets, the shape of the liquid menisci at the tip of each capillary outlet was observed with the high speed camera. In these sets of experiments, 2 wt% PLGA dissolved in DMAc solution was used and was fed at 5 μl/min. Prior to measurements, the electric field was gradually increased to 19 kV, at which point all the needles were functioning in the stable cone jet mode. Fig. 5a) shows all four needles with liquid droplets before the application of the electric field. The liquid menisci at the tip of all four needles acquired the stable cone jet shape after the immediate application of electric field to 19 kV as shown in Fig. 5b). Flow from the tip of each needle was then studied individually to investigate the time frame required for the stabilization of the cone jet at the tip of each capillary. Fig. 5c) demonstrates the time scale needed (2.75 s) for the cone jet to stabilize upon the application of electric field for one of the needles shown. This time is different for each needle, and it was measured independently for each capillary tip as shown in supplementary information video and Tables (SI 1 and SI 2).

Time evolution of the electrospray jet from a droplet at the tip of the needle to a single cone jet at 24 kV is shown in Fig. 6. The first stage of the process involves the breakup of the initial liquid droplet. When the applied voltage was increased from an initial absolute value, the liquid meniscus surface area was decreased and the diameter of the neck of the liquid meniscus reduced until the first droplet was detached from the needle tip. This is clearly shown in Fig. 6a), with the first liquid droplet breaks at 510 ms and increasing the volume of the second droplet. The volume of the second droplet increased until 750 ms after the application of the electric field and the liquid meniscus then changed to a conical shape. During this time frame, dripping at the liquid meniscus occurred. As demonstrated in Fig. 6b), the conical liquid meniscus produced a spray of droplets until 850 ms after the application of electric field when the jet was elongated downstream and broken up from the main droplet. This process was repeated many times with a pulsating jet while the diameter of the neck became smaller and the frequency of the pulsation was increased closer to the stable cone jet mode at 1771 ms after applying the voltage (Fig. 6c). After this time, the jet remained stable at the final stage of the period measured. The phenomena are also illustrated in supplementary video (SI 2).

3.2.2. Multi jets with rectangular plate configuration

For these sets of experiments, the same solution containing 2 wt% PLGA in DMAc was infused at 5 μl/min. The applied voltage was increased to 21 kV until all four needles produced a stable cone jet. This configuration also exhibited the same effect as the circular plate, with a time difference between needles until they all stabilized. Fig. 7

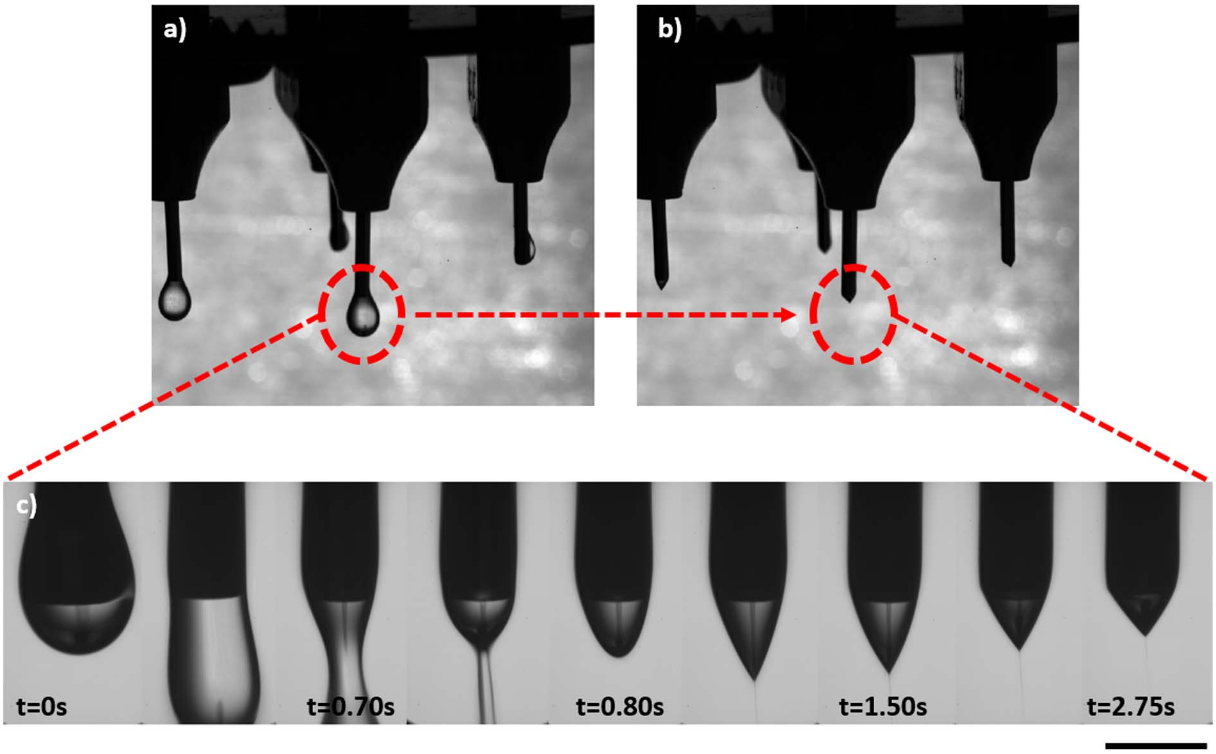

Fig. 5. High speed camera images of multi needle electrospray setup with the circular plate configuration at a) 0 kV, b) 19 kV and c) evolution of electrospraying jet for 2 wt% PLGA-DMAc solution at 5 μl/min (scale bar 1 mm).

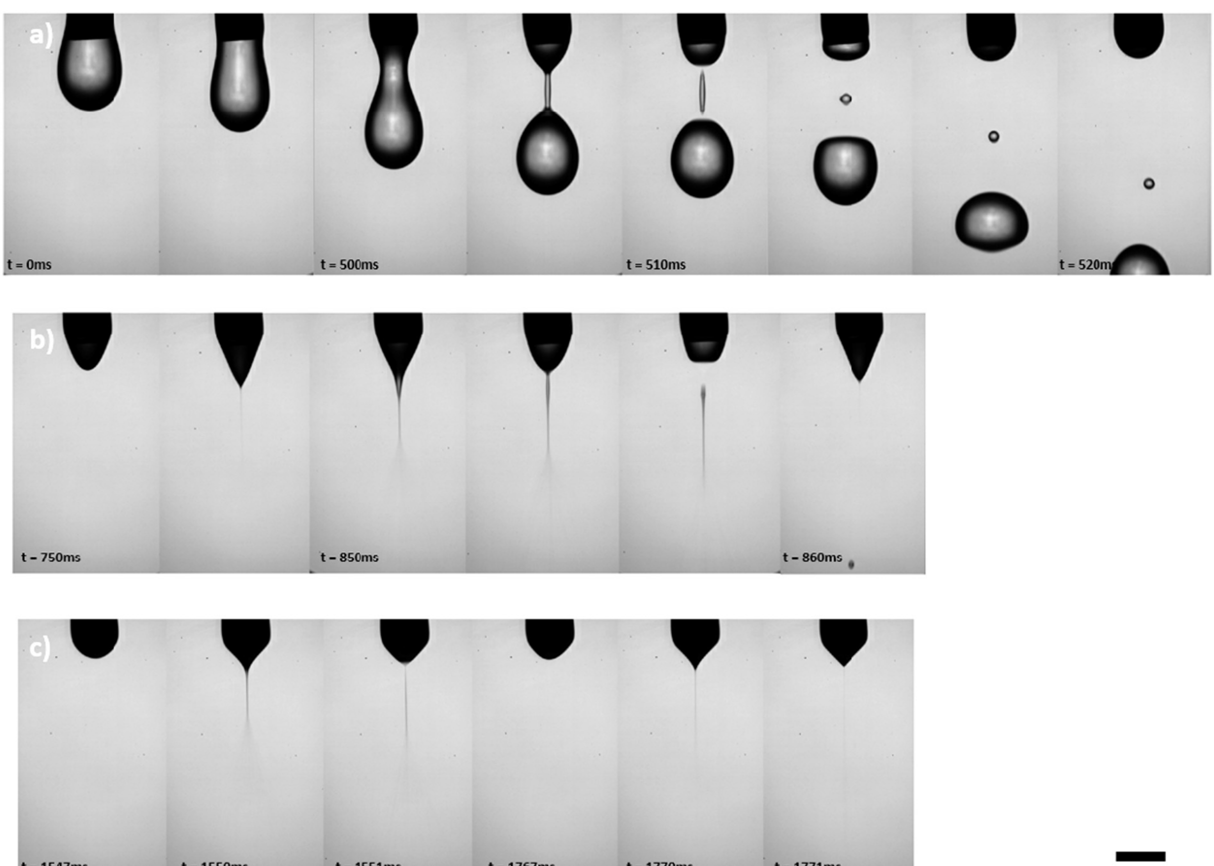

Fig. 6. High-speed video sequences of the liquid meniscus after application of 24 kV for 2 wt% PLGA-DMAc solution at 5 μl/min a) liquid meniscus dripping b) pulsating jet and c) stable cone jet (scale bar1.5 mm).

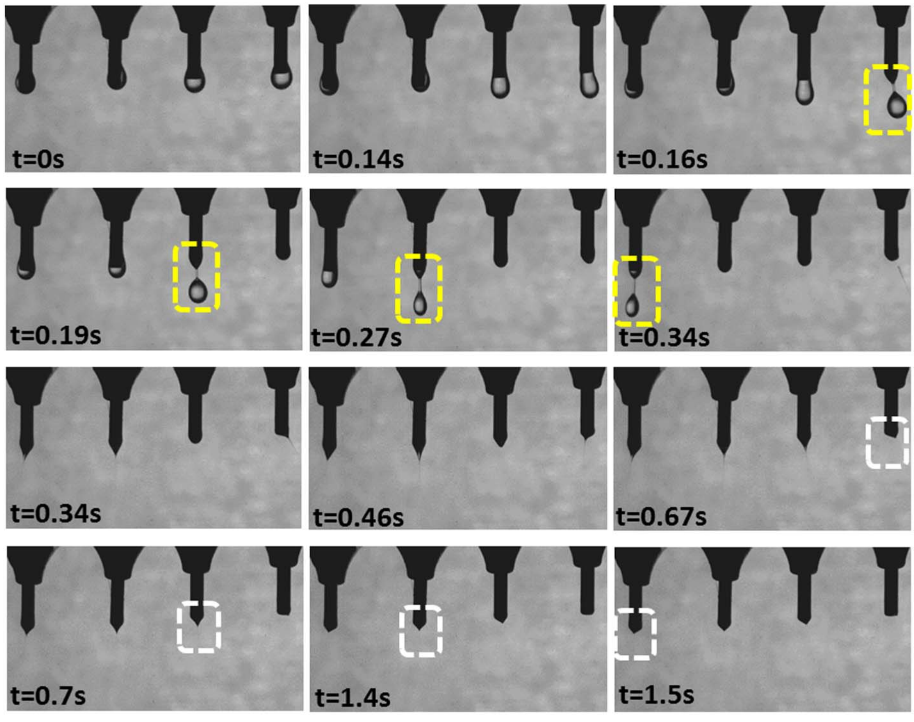

Fig. 7. High-speed video sequences of the liquid meniscus after application of 21 kV for 2 wt% PLGA-DMAc solution at 5 μl/min with the rectangular plate configuration (scale bar 10 mm).

demonstrates sequences of droplet breakup and jet formation for all four needles and they are further illustrated in supplementary information video (SI 3). As shown in Fig. 7, the needle that is positioned further from the electric field supply (4) reached a stable cone jet mode first at 0.67 s after the application of the electric field. This trend was followed until needle 1 that is attached closer to the electric field supply achieved a stable cone jet mode at 1.5 s. However, it was noted that while increasing the voltage to achieve a stable jet for all four needles, the needle that is placed further from the electric field source changed to multi jet mode. While all four needles were fed with the same flow rate (5 μl/min), it is difficult to match the electric field strength at the tip of each needle. As the needle distribution affects the electric field near the tips of the needles in multi-needle systems, the electric field strength at each tip of the needle is different from the others, and hence there is a range of electric field for each needle where a stable cone jet can be achieved [29].

Another effect that was observed with the high speed images was the difference in the angle of the cone shapes. Fig. 8 demonstrates the shape of the cone jet for all four needles. It can be observed that the needles positioned at the center of the linear array produced cone shape with 45 and 50° angles, which are closer to the ideal cone shape angle for electrospray jets [30]. However, the shape of cone jet deviates from this ideal scenario with 30 and 75° angles for needles 1 and 4, respectively. This suggests that all four needles are operating independently.

3.3. Characterization of deposition patterns

One of the advantages of using the circular/rectangular plate to attach the needles and connect them, is to concentrate the deposition area for the electrified jets from each needle, hence collecting the particles in a smaller deposition area [13]. Another function of the plate is to form a uniform electric field near the tips of each needle [31]. The deposited patterns by both four needle electrospray configurations were examined. The electrosprayed particles were collected for 3 h and the shape of the deposited particles on the substrate was studied. In these sets of experiments, 2 wt% PLGA in acetone was used. Fig. 9 shows images of the deposition area for both geometries while the solution was infused at 5, 10 and 20 μl/min. It is clear from the images that each needle deposited particles on a separate area and by increasing the solution flow rate, the circular regions of the deposited particles from each needle became distorted. This can be caused by the electrical repulsion from the adjacent electrospray jets. It was also observed that the area of each circle increased, which can be explained by the higher axial droplet velocity.

3.4. Particle generation throughput

The low throughput of the single-nozzle electrospraying limits its use in producing polymeric particles and exploiting their applications in areas such as targeted drug delivery. For instance, it has been reported that the typical throughput in the generation of PLGA micro particles is

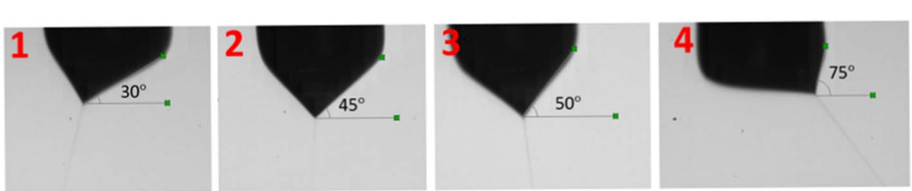

Fig. 8. High speed camera images showing cone jet angles for all four needles after application of 21 kV for 2 wt% PLGA-DMAc solution at 5 μl/min with the rectangular plate configuration.

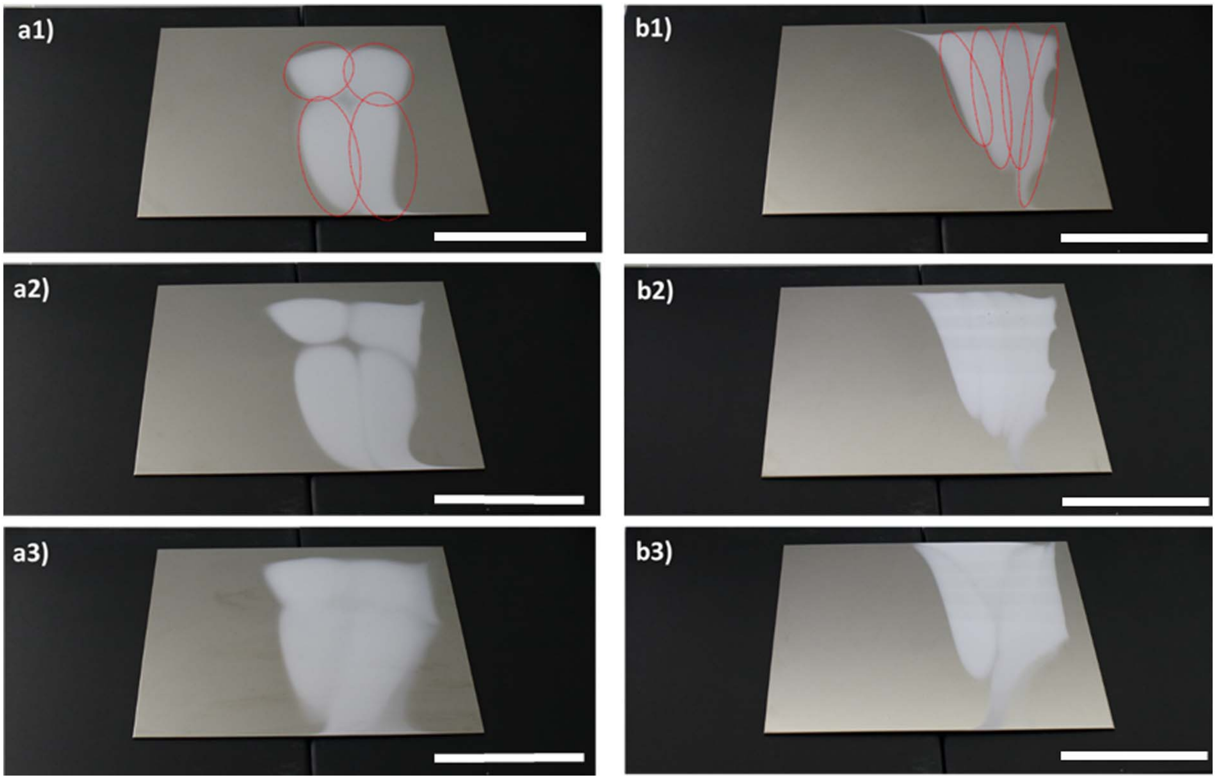

Fig. 9. Deposition pattern of particles collected on the substrate from all four needle electrospray jets when 2 wt% PLGA-acetone solution was used for a1) 5, a2) 10 and a3) 20 μl/min for the circular plate configuration, b1) 5, b2) 10 and b3) 20 μl/min for the rectangular plate configuration (scale bar 100 mm).

Table 2
Production yield of electrosprayed particles with 3 h of collection at different flow rates (ES indicates electrospray).

2 wt% PLGA in acetone	mg @ 20 μl/min	mg @ 10 μl/min	mg @ 5 μl/min
Single-ES	50	30	10
Multi-ES (circle)	180	120	50
Multi-ES (rectangle)	180	125	50

of the order of 0.01 g/h [28]. Depending on the solution properties, the flow rate of single needle electrospraying ranges from 0.2 to 1 ml/h; this is very low in commercial production of nano particles/fibres. In aerosol applications [2], the low flow rates present severe disadvantages where the initial droplets has to be small.

Generation of nanoparticles requires small droplets and due to the monotonic dependence of droplet size on the flow rate, it is necessary to minimize the mass flow rate [32]. In order to produce quantities of nanoparticles suitable for biological tests, pharmaceutical treatment or other high-value-added applications, multiplexing the spray source is crucial [2]. In order to test whether the multi needle configurations presented in this work can generate particles at higher throughputs than the single needle electrospray setup, a comparison study was performed. Particles were collected for 3 h at three different mass flow rates of 5, 10 and 20 μl/min with single needle electrospraying of 2 wt % PLGA in acetone solution. The same conditions were used for both multi needle configurations and all experiments were conducted in triplicates. The produced material was measured and presented in Table 2. It is evident that the amount of particles collected was more than four times higher than the single electrospraying at the lowest flow rate (5 μl/min) and this amount was consistently higher for both multispraying configurations at all flow rates used.

4. Conclusions

In this study, two multi needle geometries were designed and tested to check their robustness in manufacturing particles at higher production rates as well as being able to fine tune the size and uniformity of these materials. The electrospray jets from all four needles of both configurations were visualized and the sequence of meniscus dripping to stable cone jet was systematically examined. All four needles successfully formed a stable cone jet, suggesting the ability to control the uniformity of particles produced. The performance of multi needle electrospraying systems is critically dependent on the careful selection of needle configuration. In this study, it was demonstrated that the system with the circular plate configuration was easier to control with higher uniformity in particle size while it required lower voltages under the same operating conditions. The throughput of particle production was studied for a period of 3 h and compared with the single needle electrospray setup and it was shown that both geometries investigated here produced approximately similar amounts of particles at the same collection time.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.matdes.2017.04.029.

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Data supporting this paper are provided in the paper and as Supplementary Information accompanying this paper.

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