Coaxial electrohydrodynamic atomization: Microparticles for drug delivery applications

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A B S T R A C T

As cancer takes its toll on human health and well-being, standard treatment techniques such as chemotherapy and radiotherapy often fall short of ideal solutions. In particular, adverse side effects due to excess dosage and collateral damage to healthy cells as well as poor patient compliance due to multiple administrations continue to pose challenges in cancer treatment. Thus, the development of appropriately engineered drug delivery systems (DDS) for effective, controlled and sustained delivery of drugs is of interest for patient treatment. Moreover, the physiopathological characteristics of tumors play an essential role in the success of cancer treatment. Here, we present an overview of the application of double-walled microparticles for local drug delivery with particular focus on the electrohydrodynamic atomization (EHDA) technique and its fabrication challenges. The review highlights the importance of a combination of experimental data and computational simulations for the design of an optimal delivery system.

1. Introduction

Over the last few decades, fabrication of polymeric microparticles with different geometries has gained numerous interesting applications in many industrial as well as biomedical areas. In the biomedical domain, the polymeric microparticulate structures can find applications in drug delivery as depots encapsulating anti-cancer agents or in tissue engineering as scaffolds used for the growth of cells with spatial configurations. In addition, these polymeric matrices can be loaded with multiple agents which may stimulate specific signaling pathways and instruct cellular responses in a biological micro-environment [1,2].

The rising demand for polymeric microparticles with superior functionalities and complicated release profiles has led to the development of many processes for the fabrication of composite microparticles with well-defined configurations and morphologies [3]. Generally, the composite microparticles consist of a heterogeneous distribution of different polymers together with encapsulated agents integrated inside a polymeric shell layer. Based on the ultimate application, different hydrophobic and hydrophilic polymers can be utilized during the fabrication process. However, the number of polymers which can be employed is confined by the nature of the fabrication techniques and the compatibility between the inherent properties of the encapsulated agent and polymer matrix.

With increasing understanding about cancer cells and their proliferation pathways, the number of anti-cancer drugs that have appeared in the market has significantly increased. However, many of available and new drugs (i.e., biopharmaceutics classification system (BCS) class II components) often fail to show significant therapeutic efficacy due to their poor solubility in aqueous solutions. Therefore, one of the main objectives of utilizing drug delivery systems is to find solutions to (i) improve the solubility of these drugs, (ii) enhance their bioavailability, (iii) increase cell targeting functionalities, and (iv) reduce the number of downstream processes (e.g., handling and storage). However, the capability of conventional methods such as emulsion/solvent evaporation, spray drying and supercritical anti-solvent to synthesize microparticles with controlled morphology and complex micro-/nano-structures remains fairly uncertain. In fact, traditional particle preparation techniques face challenges in producing uniform-sized microparticles for drug delivery purposes. Moreover, long contact with organic solvents and a high level of shear stress on the solution dissolving the agents during fabrication process could accelerate denaturation of biomolecules (e.g., protein and DNA). For instance, in spray drying, the production of fine particles in large quantities and narrow size range distribution remains a challenging problem to be resolved.

Electrohydrodynamic atomization (EHDA), also called electro-spraying, has been widely employed for encapsulating therapeutic agents in biodegradable polymeric particles and microbubbles for controlled and sustained drug release applications [4–7]. EHDA produces
very fine droplets from a capillary liquid stream by using an electric field [8]. Depending on the properties of the liquid, the liquid flow rate and the applied electric potential, different modes of EHDA (i.e., dripping, cone-jet or multi-jets) can occur. The cone-jet mode is the most popular EHDA condition for the production of uniform-sized particles. For drug-loaded particles, narrowly dispersed particles are able to provide a precise controlled drug release with minimum batch-to-batch variations [9,10]. Henceforth, EHDA could be a potential improvement over the aforementioned techniques for generating particles in the micro-/nano-meter range with a narrow size distribution by posing less destructive effects on pharmaceutical agents [11–13].

This review aims to summarize the recent progress of the EHDA technique for the fabrication of composite microparticles via coaxial electrospraying, which has been employed for the encapsulation of therapeutic agents in biodegradable polymeric particles for controlled and sustained release. The important parameters affecting EHDA process for the reproducible tailoring of particle morphology, size distribution, encapsulation efficiency and in vitro drug release characteristics will be discussed. Finally, the major constraints and the proposed solutions for fabrication of reduced size and functionalized multilayered microparticles will be presented.

2. Coaxial electrospraying for core-shell microparticle production

2.1. Coaxial electrospraying: basic concept

The concepts of monoaxial and coaxial electrospraying processes are similar, regardless of differences in the experimental setup. For monoaxial electrospraying, a polymer solution is injected into a capillary nozzle and subjected to a strong external electric field, created between the nozzle and a grounded collector by a high electric potential generator. Given that the liquid is electrically conductive, it will result in the formation of a fine polymer jet. The jet eventually breaks up into charged droplets that fly towards the grounded collector. Some setups make use of a closed chamber with continuous air or nitrogen flow that reduces the evaporation rate of solvent and allows the formation of particles with smooth surface morphology [14,15]. If the liquid is highly viscous or solidifies at the onset of jetting, fibers can be formed.

![Fig. 1.](image_url)
For coaxial electrospraying, a nozzle with two needles of different gauge sizes are arranged coaxially to dispense two different solutions simultaneously (Fig. 1a). Depending on the solvents used, the two solutions can either mix or phase-separate at the needle tip. By replacing the core solution with a gas stream, one can employ EHDA for microbubble production where a polymeric shell forms a barrier around a gas core (a comprehensive review will be presented in Section 5.3). Fig. 1b and c illustrates the formation of composite microparticles and the corresponding intraparticle drug distribution with the drug loaded in the core phase of the particle, respectively.

The geometrical features and the various types of the jet encountered as functions of the operating parameters have been classified previously by Jaworek and Krupa [16]. Various parameters, including liquid parameters (e.g., density, viscosity, conductivity and surface tension) and process parameters (e.g., electric field strength and flow rate) will determine the electrohydrodynamic mode [17]. At low voltages, there is only partial or intermittent jet formation resulting in a dripping mode. Within a stable voltage range, a sustained and continuous jet can be formed and a stable Taylor cone-jet mode is observed. At higher voltages, a multi-jet mode may be observed. In these modes, the jet usually breaks up into particles a few millimeters below the nozzle under the influence of large voltages. The conical shape observed (Fig. 1d) is the result of the balance between electrostatic forces imposed by the external electric field and surface tension [18].

The greatest advantage of coaxial electrospraying is its versatility in the polymer type, drug type (small molecules and macromolecules) and size of particles that it can produce [19–22]. As compared to monoxial electrospraying, the coaxial electrospraying technique could offer better drug stability, more complete drug encapsulation and superior control over the drug release kinetics (Table 1).

2.2. Computational fluid dynamic (CFD) simulation for preparation of core-shell microparticles

The cone-jet formation in EHDA determines the condition of jet break up and droplet production. It is essential to understand the formation of the Taylor cone-jet to acquire an insight into the physics of EHDA. There have been a few computational fluid dynamics (CFD)-based numerical simulations used to study the electrospraying process.

One of the pioneering works is the numerical cone-shape model proposed by Hartman et al. [23] who solved coupled Navier–Stokes equation with electric tangential and normal stresses to track the evolution of the liquid–gas interface. Hartman's model is capable of simulating the shape of liquid cone-jet as well as figuring out the electric and velocity fields inside/outside the cone. The results fitted well with experimental values and scaling laws. He also demonstrated that the liquid flow in the space only affects the overall electric field locally. However, the one-dimensional momentum conservation equation in the model is unable to capture the radial motion of the fluid flow inside the Taylor cone.

Lastow and Balachandran [24] developed a 2D axisymmetric model to investigate parameters influencing the cone-jet formation process. Lim et al. [25] proposed an estimation of the interfacial charge density through a trial-and-error approach that gave the best fit of the Taylor cone-jet from the CFD simulation to the experimental data. The model incorporates all the surface stresses including the electric stresses and surface tension in the momentum equations. In this approach, the model can be used to investigate the microscopic physics of droplet charging in mechanically-driven droplet-based ion sources.

Recently, a model assisted by CFD simulation on coaxial EHDA was developed and presented in our previous work [27] to predict the preparation of core-shell structured microparticles. By extending the previous approach of the numerical simulation on monoxial EHDA, Xu et al. [27] employed the volume of liquid (VOF) technique to track the fluid interface evolution. The CFD simulation was performed near the nozzle tip to examine the detailed atomization profiles of the droplets. The effects of nozzle electric potentials on the structure of core-shell droplets and droplet size distribution obtained from coaxial EHDA process were investigated. To better design the microparticle structure, facilitate the scale-up to industry and further understand the fabrication process, the previous work [27] was extended to different nozzle tip configurations (Fig. 1(e)). The simulated results corresponding to different nozzle tip configurations are shown in Fig. 1(f). One can observe that the nozzle configurations have an obvious effect on the cone-jet mode and the droplet formation. Each configuration has its unique advantage. For instance, with the cone-shaped tip (configurations (iv) and (v) in Fig. 1(e)), the produced droplet size is much smaller than that with

<table>
<thead>
<tr>
<th>Core material(s)</th>
<th>Shell material(s)</th>
<th>Preparation method</th>
<th>Size</th>
<th>Drug(s)</th>
<th>Application(s)</th>
</tr>
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<tbody>
<tr>
<td>1 Poly(vinylpyrrolidone)</td>
<td>Poly(vinylpyrrolidone)</td>
<td>Coaxial electrospraying</td>
<td>1.74 ± 0.58 μm</td>
<td>Acyclovir/sucralse, and sodium dodecyl sulfate</td>
<td>Drug delivery [29]</td>
</tr>
<tr>
<td>2 PLLA</td>
<td>PLGA</td>
<td>Coaxial electrohydrodynamic atomization</td>
<td>15–20 μm</td>
<td>Paclitaxel/suramin</td>
<td>Drug delivery [30]</td>
</tr>
<tr>
<td>3 PEG</td>
<td>PLA</td>
<td>Coaxial electrohydrodynamic spray drying</td>
<td>1.47–3.33 μm</td>
<td>Lysozyme</td>
<td>Protein delivery [31]</td>
</tr>
<tr>
<td>4 Olive oil</td>
<td>Dual-layer porous titania (TiO2) + Poly(vinylpyrrolidone)</td>
<td>Coaxial electrospray of immiscible liquids</td>
<td>1.0–3.0 μm</td>
<td>Paclitaxel, magnetite (Fe3O4), carbon (graphene) quantum dots Bovine serum albumin (BSA) and lysozyme Vanillin (VAN), ethylmalto tetramethylsilane (EMA), and maltol (MA)</td>
<td>Multifunctional core-shell capsules: drug delivery [32]</td>
</tr>
<tr>
<td>5 PEG: 40% (w/v) aqueous solution Stearic acid</td>
<td>Ethylcellulose</td>
<td>Coaxial electrospray</td>
<td>7.9–10.4 μm</td>
<td>Bovine serum albumin (BSA) and lysozyme</td>
<td>Protein delivery [33]</td>
</tr>
<tr>
<td>6 Bovine serum albumin (BSA)</td>
<td>Poly(ε-caprolactone)-polylactic acid ethylene phosphate block copolymer</td>
<td>Single jet electrospray (pre-mixed protein and polymer)</td>
<td>2–8 μm</td>
<td>Drug delivery [34]</td>
<td></td>
</tr>
<tr>
<td>7 PDLLA</td>
<td>PLGA</td>
<td>Coaxial electrohydrodynamic atomization</td>
<td>28.1–31.5 μm</td>
<td>Doxorubicin</td>
<td>Drug delivery [27]</td>
</tr>
<tr>
<td>8 PLGA</td>
<td>PLA</td>
<td>Precision particle fabrication</td>
<td>66.1–74.9 μm</td>
<td>Doxorubicin</td>
<td>Drug delivery [36]</td>
</tr>
<tr>
<td>9 PLGA</td>
<td>Bovine serum albumin (BSA)</td>
<td>Precision particle fabrication</td>
<td>75.1–84.5 μm</td>
<td>Bovine serum albumin (BSA)</td>
<td>Protein delivery [37,38]</td>
</tr>
<tr>
<td>10 PLGA</td>
<td>Alginate</td>
<td>Capillary microfluidic devices</td>
<td>20–80 μm</td>
<td>Rifampicin</td>
<td>Drug Delivery [39]</td>
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uniform lengths of inner and outer needles (configuration (i)). Based on the previous work reported in Xie et al. [28], increasing the flow rate could increase the droplet size, which means that a larger flow rate can be applied to form the same size of droplets as compared with the normal nozzle (configuration (i)). Therefore, one can gain insights into the ways to optimize the process and improve the productivity.

2.3. Thermodynamic predictions for successful preparation of core-shell microparticles

Rather than attempting to adjust operating conditions in EHDA, the thermodynamic behavior of two polymer solutions (interfacial tension in particular) should be taken into account for the successful fabrication of desired core-shell structured microparticles. In general, the tendency of a polymer phase to spread on a liquid or solid substrate for the forma-

\[ \lambda_{ij} = \gamma_{ij} - \gamma_{i} - \gamma_{j} \]  

where \( \gamma_{i}, \gamma_{j} \) and \( \gamma_{ij} \) are the surface tensions of polymer phases \( i \) and \( j \), and the interfacial surface tension between the two phases, respectively. Based on Harkin’s equation, the spreading of phase \( i \) on phase \( j \) will occur when the spreading coefficient is positive \( (\lambda_{ij} > 0) \) (Fig. 2a). However, the negative spreading coefficient results in two other possible configurations, as shown in Fig. 2b and c [42].

To perform the calculation of spreading coefficient in Eq. (1), the interfacial tension can be approximated by employing the surface tension values into dispersive and polar terms, and substituting them in Eq. (4) [41,42]:

\[ \gamma_{ij} = \left( \sqrt{\gamma_i} - \sqrt{\gamma_j} \right)^2 \]  

\[ \gamma_{ij} = \gamma_{i} + \gamma_{j} - 4 \left( \frac{\gamma_{i}^d \gamma_{j}^d}{\gamma_{i}^d + \gamma_{j}^d} + \frac{\gamma_{i}^p \gamma_{j}^p}{\gamma_{i}^p + \gamma_{j}^p} \right) \]  

where \( \gamma^d \) and \( \gamma^p \) are the dispersive and polar contributions, respectively.

These equations, of course, give an approximation for the interfacial surface tension at equilibrium condition; however, the equilibrium condition is not easy to achieve in EHDA. In fact, polymeric droplets could solidify quickly particularly when volatile solvents are used (e.g., dichloromethane). Therefore, there could be discrepancies between model predictions and experimental results.

The thermodynamic approach can also be employed for the prediction of drug distribution in the core and/or shell compartments. Although there is insufficient data regarding drug distribution in core-shell polymeric microparticles fabricated via EHDA, the distribution theory may help to predict how a drug distributes predominantly to a particular polymer compartment [44]. Eq. (5) demonstrates the concentration of drug molecules \( S \) within two different polymer phases A and B [41]:

\[ \log \left( \frac{X_A}{X_B} \right) = \frac{V_s \left( \delta_b - \delta_a \right)^2 - \left( \delta_b - \delta_a \right)^2}{2.3 \ R \ T} \]  

where \( [X_A] \) and \( [X_B] \) are the mole fraction of the drug (solute) in phases A and B, respectively, \( \delta_b \) and \( \delta_a \) are the solubility parameters of the drug, and phases A and B, respectively, \( V_s \) is the drug molecular volume, \( R \) is the universal gas constant, and \( T \) is the absolute temperature. According to the above equation, the drug distribution depends on the solubility parameter differences of the phases, and a larger difference determines the tendency of the drug to remain in one phase versus the other. If the polymer can form completely separated core and shell phases, their solubility parameters can be approximated by Eq. (6) [44]:

\[ \delta_i = \alpha_i \delta_{\text{polymer},i} + (1 - \alpha_i) \delta_{\text{solvent},i} \]  

where \( \alpha_i \) is the volume fraction of polymer \( i \) in the \( i \)th solution, and \( \delta_{\text{polymer},i} \) and \( \delta_{\text{solvent},i} \) are the solubility parameters of the \( i \)th polymer and solvent. Since the experimental data is unavailable for all substances, one may calculate the solubility parameters using the group-contribution method [45].

3. Sustained and controlled release of agents from microparticulate structure

3.1. Delivery of small molecule drugs

Coaxial electrospraying has gained significant attention in the production of particles with distinct core-shell structure in view of the flexibility in polymer–drug composition and high encapsulation efficiency.

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These core-shell structured microparticles often exhibit a reduction in the initial burst release as compared to single-polymer microparticles and provide a sustained drug release that is tunable by adjusting the shell material or thickness [50,51]. The other degree of freedom is introduced by enabling the encapsulation of multiple drugs interchangeably in the core and shell compartments to achieve either in-series or in-parallel release patterns for triggering synergistic therapeutic effects [30,52].

Lee et al. [47] reported the production of PLGA-coated drug particles by coaxial electrospraying of drug and polymer solutions as core and shell phases, respectively. The particle size ranged from 165 nm to 1.2 μm with almost 100% encapsulation efficiency. The particles had two features: the drug release profile for particles less than 1 μm showed mainly water penetration and drug diffusion, and the core-shell structure could minimize the initial burst release of drug at the initial stage. In another study, the same group [48] presented the production of PLGA particles with multiple drug compounds incorporated in various layers from a coaxial tri-capillary electrospray system. They also compared the differences in release profiles of coaxial dual-capillary and tri-capillary electrosprayed microparticles. In particular, the tri-layered particles could release multiple drugs under the modulation of the chemical composition and thickness of the individual layers.

Nie et al. [30] demonstrated the flexibility of the coaxial electrospraying technique by encapsulating hydrophobic (paclitaxel) and hydrophilic (suramin) drugs in different compartments of microparticles consisting of a PLLA core surrounded by a PLGA shell layer. For the case of hydrophobic and hydrophilic drugs entrapped in the core and shell phases, respectively, the particles exhibited a sequential release of the two drugs over a period of 30 days. In contrast, for the case of the reverse entrapment, i.e., hydrophilic and hydrophobic drugs entrapped in the core and shell phases, respectively, the particles exhibited a parallel release of the two drugs over the same time period. The release profiles of the two drugs could be customized by adjusting the inner and outer flow rates of the coaxial electrospraying process.

### 3.2. Delivery of macromolecules

Macromolecules such as proteins, peptides and DNA are rapidly developing as potent agents for several therapeutic applications. By encapsulating protein drugs in biodegradable polymeric particles, they could provide sustained release and protect the non-released protein from degradation. For example, Nie et al. [30] demonstrated the flexibility of the coaxial electrospraying technique by encapsulating hydrophobic (paclitaxel) and hydrophilic (suramin) drugs in different compartments of microparticles consisting of a PLLA core surrounded by a PLGA shell layer. For the case of hydrophobic and hydrophilic drugs entrapped in the core and shell phases, respectively, the particles exhibited a sequential release of the two drugs over a period of 30 days. In contrast, for the case of the reverse entrapment, i.e., hydrophilic and hydrophobic drugs entrapped in the core and shell phases, respectively, the particles exhibited a parallel release of the two drugs over the same time period. The release profiles of the two drugs could be customized by adjusting the inner and outer flow rates of the coaxial electrospraying process.

![Fig. 3.](image-url)

(a) In vitro release profiles of paclitaxel and suramin for samples A and B. (b) BLI images of representative subcutaneous U87 MG-luc2 xenografted mice before treatment and 3 weeks after treatment. (c) Histological and immunostaining examinations of subcutaneous U87 glioma xenograft in mice after 21 days of treatment [52]. Reproduced with permission from Elsevier.
degradation, hence avoiding the need for repeated administration. While emulsion methods have been widely applied for protein drug encapsulation, the success is often limited and unsatisfactory due to protein instability and denaturation resulting from exposure to organic solvents and high shear stress [53]. To maintain the protein activity, the addition of stabilizers is required [54–56]. In multiple cases, the loaded protein drugs may be poorly encapsulated and are released with initial burst, or the loaded protein drugs are not released completely. These formulations face many challenges since the delivery of these protein drugs requires critical control of concentration and localization within the human body [57]. Besides, there are specific applications where pulsatile release of proteins is preferred as in the case of insulin delivery. This particular type of release is difficult to be achieved by biodegradable polymeric particles prepared by emulsion methods [53].

Monoaxial electrosprayed polymeric particles are promising to incorporate and release protein drugs in a sustained manner [4,58]. However, the distribution and release of protein drugs are not well controlled, and may suffer from significant decrease in bioactivity. Coaxial electrospraying could circumvent the technical limitations of monoaxial electrospraying by its core-shell design, allowing protein drugs to be released in a sustained manner [4,58].

![Fig. 4.](a) Double-walled microspheres: (A) Confocal micrograph of intraparticle drug distribution of coumarin 6 loaded in the shell phase, (B–E) Scanning electron micrographs for particles with (B) simvastatin (core) and BSA (shell), (C) BSA (core) and simvastatin (shell), (D) simvastatin (core) and PDGF (shell), and (E) PDGF (core) and simvastatin (shell). (b) Histological staining after 14 days of implantation: Microspheres with (A) BSA (core and shell), (B) simvastatin (core) and BSA (shell), (C) PDGF (shell), (D) PDGF (core) and simvastatin (shell), and (E) simvastatin (core) and PDGF (shell) [71].

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dissolved in aqueous solution for encapsulation. In recent studies, protein drugs loaded in biodegradable polymeric core-shell structured particles by coaxial electrospraying technique could provide high encapsulation efficiency, favorable release profile and retain their bioactivity [33,59].

Xie et al. [33] illustrated the encapsulation of bovine serum albumin (BSA) and lysozyme in PLGA microparticles by coaxial electrospraying of aqueous protein and organic polymer solutions as core and shell phases, respectively. The encapsulation efficiency could reach 80% while the release profiles showed biphasic release characteristics with a low initial burst, followed by a slow release over a period of more than 30 days. In addition, a comparison of the BSA before encapsulation and after release indicated no change in the secondary structure of the protein molecule. Furthermore, the bioactivity of the released lysozyme was close to 95%, which was significantly higher than those reported based on emulsion methods [60–63]. In another study, Zamani et al. [59] examined the influence of solution properties and processing parameters on the formation of core-shell structured BSA loaded PLGA microparticles and compared to those obtained by emulsion electrospraying. The encapsulation efficiency within the core-shell structured microparticles was significantly higher than that in the emulsion electrosprayed microparticles. Moreover, the release profiles exhibited a low initial burst followed by a slow release over a period of more than 40 days.

Due to the ability of the EHDA to produce nano-sized droplets, the technique has been used as an intriguing approach for plasmid DNA delivery. The comminution of plasmid DNA by the EHDA process resulted in no detectable DNA degradation and was deemed suitable for targeted lung delivery [64]. This approach has led to a series of works in the use of coaxial electrospraying for the production of polyplexes or lipoplexes for gene delivery and is an improvement over conventional bulk mixing [65–67]. In one study, Wu et al. [65] prepared oligodeoxynucleotide encapsulated nanoparticles by coaxial electrospraying of aqueous oligodeoxynucleotide and lipid mixture as core and shell phases, respectively. The optimization of process conditions resulted in lipoplex nanoparticles of about 190 nm and achieved close to 90% encapsulation efficiency. Both non-targeted and transferrin-targeted G3139 lipoplex nanoparticles were efficiently delivered to K562 cells and downregulated the bcl-2 protein expression by 34% and 57%, respectively. In another study, Wu et al. [66] applied the same technique in the preparation of polyethyleneimine-DNA polyplexes. It was observed that at nitrogen to phosphate (N/P) ratio of 6.7, the polyplexes obtained by coaxial electrospraying had delivery efficiencies up to 2.6 times higher than those produced by bulk mixing.

4. Practical applications of core-shell microparticles

4.1. Case study I: core-shell microparticles for chemotherapy application

Cao et al. [68] proposed core-shell structured PVP/PLGA and PCL/PLGA nanoparticles loaded with anti-angiogenesis combretastatin A4 (CA4) and chemotherapeutic doxorubicin (DOX) in core and shell phases, respectively, via coaxial electrospraying and applied them for drug release in combined chemotherapy. Both CA4 (hydrophobic) and DOX (hydrophilic) drugs could be effectively loaded in the core-shell structured nanoparticles with encapsulation efficiencies at of least 90%, and the particles exhibited sequential drug release profiles in vitro. Overall, the melanoma cells (B16–F10) and human umbilical vein endothelial cells (HUECs) were sequentially targeted and killed by CA4 and DOX from the two different nanoparticle formulations. In another study, Nie et al. [52] prepared paclitaxel and suramin loaded core-shell structured microparticles by coaxial electrospraying for the treatment of brain tumors (Fig. 3a). The efficacy of the dual drug loaded microparticles was evaluated in vivo based on a subcutaneous U87 MG-luc2 xenograft model in nude mice (Fig. 3b). While the mice in the blank, placebo and single drug loaded groups showed a marked increase in BLI signal intensity, the dual drug loaded groups showed a decrease after a 3-week treatment, suggesting the effective inhibition of the tumor. Histological examination of subcutaneous U87 MG xenograft in dual drug group after 21 days post-surgery showed much fewer tumor cells as compared to the blank, placebo and single drug loaded groups (Fig. 3c). Moreover, Ki-67 staining of the same dual drug group also exhibited a lower degree of tumor proliferation in comparison to controls and single drug loaded groups (Fig. 3c). These studies suggest that the drug release rates of multiple chemotherapeutic agents could be customized and adjusted according to the treatment necessity of the patient and types of tumors.

4.2. Case study II: core-shell microparticles for dentoalveolar regeneration application

Dentoalveolar regeneration still remains a challenge facing dentistry as it requires a proper integration among several cascades of events such as appropriate signals, cells, blood supply and scaffold [69]. The administration of bioactive molecules (i.e., exogenous growth factors) such as bone morphogenetic protein (BMP), platelet-derived growth factor (PDGF) and simvastatin to dentoalveolar site could exhibit a significant improvement in dentoalveolar regeneration. However, considerable variations in the clinical outcomes were attributed to the failure to precisely control the release of therapeutics to the target site over a prolonged period of time and indicated an urgent need for reliable delivery systems with specific features. Moreover, the regeneration process can be divided into two sequential steps of proliferation and differentiation. Hence, the drug system should be able to release multiple therapeutics in a sequential manner according to their biological effects. Based on the desired application, polymeric core-shell microparticles could show the highest potential for dentoalveolar regeneration.

Recently, Chang and coworkers [70–72] employed double-walled PDLA-PLGA microspheres for the delivery of PDGF and simvastatin (differentiation factor) for dentoalveolar regeneration in rats. They fabricated different formulations of microparticles via coaxial electrospraying, and characterized them in terms of intraparticle drug distribution and particle morphology (Fig. 4a). The uniform-sized (~20 μm) polymeric microparticles showed significantly high encapsulation efficiency of about 92.2% and 71.3% for PDGF (core) and simvastatin (shell), respectively. The in vitro release tests showed considerable variations according to the different locations of PDGF and simvastatin within the microparticles. They also evaluated microparticle biocompatibility by inserting them subcutaneously in Sprague–Dawley rats for 10 and 14 days. The immunohistochemistry tests exhibited minimum inflammatory cell infiltration in all groups after 10 days. In addition, their results showed that minor infiltration appeared after 14 days, particularly in simvastatin–in-core and BSA-in-shell group. However, inflammation was relieved in the animals inserted with a combination of PDGF and simvastatin microspheres (Fig. 4b). In another study, the application of microspheres in animal experiments indicated a limited osteogenesis in the control group, while the sequential release of PDGF and simvastatin could accelerate the regeneration of alveolar bone [72]. A similar study was conducted to investigate the effect of PDGF and simvastatin delivery patterns on the bone apposition after thermal injuries which happened during dental implantation. The results demonstrated that the sequential release of PDGF and simvastatin from core-shell structured microparticles could facilitate bone regeneration after bone thermal destruction (Fig. 5) [73].

5. Challenges for the fabrication of core-shell microparticles

The technological advantages of EHDA in the fabrication of double-walled particles include controlled-size, core-shell structure and a wide range of available materials and drugs for encapsulation. However, there are challenges faced by the fabrication of multi-layered particles which are discussed in the following sections.
5.1. Fabrication of fine particles

Size control and structure design of microparticles and nanoparticles could overcome problems associated with initial burst release, drug loading and drug instability. The EHDA technique allows the control of droplet size directly from the source of production, resulting in particles with diameters ranging from nanometer to micrometer scales [11,74]. In addition, monodispersed particles have great economical and technological advantages over polydispersed ones. While it is difficult to achieve monodispersity of particles by typical emulsion methods, EHDA is a promising technique in producing nearly monodispersed particles.

To create smaller size down to the nano-meter scale, three main parameters need to be critically adjusted and optimized: (i) polymer solution concentration, (ii) polymer solution flow rate and (iii) electric field. The sizes of particles have been reported to decrease with lower polymer solution concentration and slower polymer solution flow rate under higher voltage [15,47]. However, the suitable ranges of these parameters are often narrow and restricted based on the material selected. The fabrication of polymeric nanoparticles is generally more difficult than metallic or inorganic nanoparticles due to different conductivity, viscosity and surface tension of material solution. The difficulty increases with increasing complexity of the structure of particles, such as double-walled microparticles, obtained from coaxial electrospraying.

Zamani et al. [59] investigated BSA-loaded core-shell PLGA particles with mean size of 3.0–5.5 μm obtained from coaxial electrospraying by tuning the solvent type, and the concentration and molecular weight of PLGA. For other types of polymeric matrices, Zhang et al. [49] prepared griseofulvin-loaded core-shell particles based on poly(methacrylic acid-co-methyl methacrylate) in a size of ~1 μm using coaxial electrospraying deposition technology. The nanosizing and amorphization enhanced in vitro dissolution of the poorly water-soluble drug for improved oral absorption. Duong et al. [75] generated acid-sensitive imidazoquinoline adjuvant resiquimod encapsulated microparticles based on acetlated dextran and tween for treating visceral leishmaniasis. The core-shell particles were approximately 2 μm in size with 85% encapsulation efficiency.

For fast-dissolving drug delivery system, Li et al. [76] fabricated quercetin-loaded polyvinylpyrrolidone (PVP) composite microparticles by coaxial electrospraying equipped with a PVC-coated concentric spinneret. The quercetin encapsulated in the core was found to release within 1 min. The permeation rates were about ten-fold faster than the raw drug. In a similar study, Liu et al. [29] developed PVP microparticles loaded with acyclovir in the core phase by using coaxial electrospraying with an epoxy-coated concentric spray head. The average diameters of the obtained core-shell particles were 1.36 and 1.74 μm. The loaded acyclovir was released within 1 min and had permeation rates nearly 8 times faster than the raw drug.

5.2. Fabrication of functionalized particles

For advanced drug delivery applications, a new generation of multifunctional micro-/nano-carriers loaded with therapeutic agent and functionalized with a targeting moiety needs to be proposed and developed [77,78]. However, the fabrication of core-shell particles by coaxial electrospraying process with functional design in both core and shell phases is a highly challenging task. While the therapeutic agent can be encapsulated in the core phase [79–81], the targeting moiety is often limited to the surface or the shell phase that may require post-modification of the fabricated particles [82].

Duong et al. [83] demonstrated a novel nanocomposite preparation method that put together electrospray, a top-down, continuous particle fabrication technology, and bottom-up micellar self-assembly to form a semicontinuous micelle synthesis technique, i.e., micellar electrospray. Since the resultant nanocomposites are water-soluble, the approach should be easily adaptable to any hydrophobic drug and could create a vast array of nanocomposites, including those with targeting moiety. Gun et al. [84] encapsulated iron oxide (Fe$_3$O$_4$) nanoparticles in PLGA

Fig. 5. (A) Micro-CT assessments of rat maxillae, (B) index of sequestrum, and (C) bone fraction under irrigated and non-irrigated conditions at day 14 [73]. Reproduced with permission from SAGE.
microparticles by coaxial electrospraying process. The study demonstrated a convenient preparation method for nanoparticles loaded microparticles, which show high potential as transverse relaxation contrast agents in clinical magnetic resonance imaging and magnetically guided drug delivery.

5.3. Fabrication of gas-filled microparticles

Gas-filled microparticles (microbubbles) are well known ultrasound contrast agents for medical ultrasound imaging due to their ability to scatter and reflect ultrasound waves. By incorporating drugs into their shell layers, microbubbles can be used as drug carriers that can be traced through the body using a low intensity ultrasound and then burst with a high intensity ultrasound power for the release of the drug at the target site. Coated microbubbles for targeted drug/gene delivery applications have become an active area of research [7,85–88]. Due to the limitations of sonication, agitation and microfluidic method [89,90], such as broad size distribution of microbubbles or blockage of microchannels, the coaxial EHDA technique is found to have great potential for the production of relatively monodispersed gas-filled microparticles for drug delivery applications.

Edirisinghe and coworkers [91] were the first research group that demonstrated coaxial EHDA capability for fabricating microbubbles (<10 μm) with a narrow size distribution. They used glycerol for the outer stream, while air was pumped through the inner needle simultaneously. Later, the coaxial EHDA process was employed for producing phospholipid-coated microbubbles of 6.6 μm with a high yield (10⁹ bubbles/min) [92]. The generated bubbles were very stable at ambient temperature. However, the mean bubble diameter reduced rapidly to ~1–2 μm after 20 min at human body temperature (37 °C). This is because higher temperature could enhance the diffusion of gas from core phase to bulk solution through the shell layer.

Mahalingam et al. [93] investigated the stability of BSA microbubbles fabricated by coaxial EHDA and found that increasing BSA solution flow...
rate would enhance the monodispersity of the microbubbles. Using water–glutaraldehyde, glycerol and glycerol–Tween 80 solutions as the collection media obviously improved the stability of BSA microbubbles as compared to pure BSA solution. They proposed that the elasticity of the shell material, intrabubble interaction and interfacial viscosity was the potential factor affecting microbubble stability. Besides, they reported the mechanical properties of the microbubbles, such as compression stiffness, measured by nanoinindentation. However, a fully established method to control the mechanical properties of microbubbles has not been reported.

More recently, Parhizkar et al. [94] developed a preparation method for monodispersed microbubbles which combined a microfluidic set-up with EHDA process. The T-junction microfluidic device was modified by applying an external electrical field across the outlet channel. The modified microchannels could produce bubbles with diameters much smaller than that of the microchannel with a polydispersity index ~1%. The effects of applied voltage, solution viscosity and electrical conductivity were investigated. Fig. 6a shows the variation of microbubbling mode with the applied voltage. In particular, 12 kV was the critical voltage above which no significance size reduction was observed for the microbubbles. In one study, Zhou et al. [95] confirmed better thrombolytic activity of recombinant tissue plasminogen activator (tPA) with transcranial Doppler (TCD) ultrasound. One possible clinical application of microbubbles is to deliver thrombolytic agents to aid in the removal of clots by employing ultrasound to improve treatment outcome. In this way, tPA-loaded microbubbles together with ultrasound could provide a more controlled and targeted release of tPA into clot without the risk of bleeding. As proposed in Fig. 6b, clinical diagnostic ultrasound can be used to trace the blood flow, followed by the application of ultrasonic pulse to burst the microbubbles and trigger the release of tPA when blood clots are detected. The advantages in the use of tPA-loaded microbubbles via CEHDA will help reduce the risks of physical disability, speech impairment, memory loss and even death, all of which are serious repercussions of both stroke and brain hemorrhages in patients treated with systemic thrombolysis. Considerably reduced dose of tPA via local delivery would be expected to make thrombolytic agents safer and more efficacious. Although previous studies showed promising therapeutic applications of microbubbles, the lower stability, over-strong or over-weak mechanical properties and limitation of voltage effect on the size of the reported microbubbles confine the development of efficient drug delivery carrier via CEHDA.

![Tumor blood vessel](image)

Fig. 7. (a) The difference in pathological conditions between tumor and normal tissues: high interstitial fluid pressure and microvascular tortuosity. (b) Mechanism of drug transport, diffusion, metabolism and elimination: (1) drug diffusion from delivery device, (2) drug diffusion through the extracellular tortuosity, (3) convective drug transport due to interstitial fluid into the cell locations, (4) enzymatic metabolism in extracellular space, (5) diffusion through cell membrane enzymatic metabolism pathways, (6) diffusion across capillary blood vessel, and (7) transport of drug in the blood circulation [103–106].

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5.4. Multidrug loaded microparticles

Previous studies have reported multidrug loading in double-walled particles fabricated from coaxial electrospraying that could offer parallel or sequential drug releases. In general, the drug delivery characteristics are influenced by water penetration, polymer degradation and drug diffusion. Drugs loaded separately in each layer could potentially be tapped to alter and fine-tune drug release rates, achieving a desirable multi-drug release profiles with optimal release kinetics [96–98]. However, the maximum number of layers is often limited by the interfacial tension and phase separation of material solution in each layer. Obviously, this brings more opportunities and challenges for the EHDA technique.

6. Conclusions and perspectives

In conclusion, the EHDA technology has shown great potential in the drug delivery field. The EHDA technique is advantageous in many ways, including precise control on the particle size and distribution with high reproducibility, and flexibility in the types of drugs that can be encapsulated. By adjusting the process conditions and solution parameters, the encapsulation efficiency and drug release kinetics can be attained and optimized. As discussed in this review, coaxial electrospraying process could produce core-shell structured microparticles for controlled drug delivery. These particles may offer particular advantages as follow:

(i) Encapsulation of therapeutic agents in the core phase engulfed by a polymeric shell can reduce high initial burst release.
(ii) Improvement of drug stability can be attained by using aqueous solution as the core phase.
(iii) Drug release rates can be customized by selecting appropriate materials or controlling the thickness of shell layer.
(iv) Drugs can be delivered in tandem or in parallel by encapsulating them into core or shell phases based on their physicochemical properties to enhance therapeutic efficacy via synergistic effects.

Over the years, mathematical modeling and simulation have played a major role in the optimization of industrial and biomedical processes. In the domain of drug delivery, having a clear understanding of the whole process, i.e., from fabrication of a controlled release system to degradation of a carrier and release of drug at physiological condition within the target tissue, may help scientists to design an optimal delivery system for a desired therapeutic outcome [99–101]. After simulating the fabrication process, the results can be employed for the precise design of customized double-walled microparticles with specified core diameter and shell thickness, and optimization of the process according to prescribed release profiles [27,28]. To properly address the drug transport resistance at the tissue/organ level, one can employ mathematical models for local delivery of chemotherapeutic drug within the target tissue with consideration of particular resistances as shown in Fig. 7 [102].

Overall, computational simulation may provide a platform to design and optimize a treatment procedure through coupling the drug transport mechanisms with the drug delivery device fabrication technique simultaneously, while the in vitro cellular tests and in vivo animal experiments provide the essential data to optimize micro-/nano-particles for the greatest therapeutic efficacy. Having control over the release is a tremendous advantage because the release rate can be tuned to meet the requirements of a very specific application such as chemotherapy. This can also be combined with other forms of therapies such as radiotherapy and anti-angiogenesis therapy by designing the best scheduling and release profiles. In this way, the ideal personalized medicine design is realized through the integration of in vitro and in vivo studies, and simulation/optimization tool as an integrated package (Fig. 8).

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