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Electrosprayed nanoparticles for drug delivery and pharmaceutical applications

Radhakrishnan Sridhar[1,2] and Seeram Ramakrishna[1,2,3]

[1]Center for Nanofibers and Nanotechnology; National University of Singapore; Singapore, Singapore; [2]Department of Mechanical Engineering; National University of Singapore; Singapore, Singapore; [3]NUS Nanoscience & Nanotechnology Initiative; Singapore, Singapore

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Nanotechnology based Pharma has emerged significantly and has influenced the Pharma industry up to a considerable extent. Nanoparticles technology holds a good share of the nanotech Pharma and is significant in comparison with the other domains. Electrospraying technology answers the potential needs of nanoparticle production such as scalability, reproducibility, effective encapsulation etc. Many drugs have been electrosprayed with and without polymer carriers. Drug release characteristics are improved with the incorporation of biodegradable polymer carriers which sustain the release of encapsulated drug. Electrospraying is acknowledged as an important technique for the preparation of nanoparticles with respect to pharmaceutical applications. Herein we attempted to consolidate the reports pertaining to electrospraying and their corresponding therapeutic application area.

Introduction

Nanotechnology in healthcare. Nanotechnology not only in academic research but has emerged as a wonderful tool in product perspective in all the industry sectors. Nanotechnology mediated drug delivery research has attracted Pharma, biotech and healthcare industries during the recent decades.[1] The projected timelines "from invention to market" (**Fig. 1**) was shortened from 30 y to ten or 15 y regarding the nanoparticulate drug formulations. And the research has gained momentum to see more FDA approvals in near future. But the expected commercial tissue engineering scaffolds or artificial organs or nano robots is getting delayed. Therapeutic benefits of nano-formulated drugs, drug eluting stents, drug coatings and devices involve improved efficacy, targeted drug delivery, reduced active drug ingredient and reduced drug side effects. Nanopharma technologists attempt for the nanoformulation that delivers the drug selectively, effectively and in a sustained manner at the site of requirement. Nanopharma drug delivery entered the healthcare industry as a result of many generic blockbuster drug patent expiry, excess cost of drug discovery and development and nanotechnology mediated drug formulation. The nanotherapeutics can enhance the efficacy and sustained release of drugs and also add to the commercial value of the healthcare products. The polymer carrier carters the drug to target, reduces the metabolic drug degradation, accounts for sustained release, increases the activity of the active pharmaceutical ingredient and reduces the side effects of the drug. The total market for nanotechnology-enabled drug delivery[2] was estimated to be $26 billion by 2012 and further projected to the sky rocket $220 billion by 2015 with an average annual increase of 37%. The current trend in Nanomedicine[3] drug formulations (**Fig. 2**) works with the nanoformulation of existing generic drug and hence reducing the cost of drug development into many folds. The main aim of the nano-formulations is to fine-tune the normal metabolic profile of proven established drug molecules by significantly improving the drug efficacy, sustained release and reduced side effects. Abraxane® is a marketed product[4] of Abraxis and is a similar nanoformulation that has brought in up to 70% increase of Paclitaxel delivery against solvent based Paclitaxel delivery for breast cancer and non-small-cell lung cancer. Abraxis Bio Sciences has invented this first-in-class nanoformulation with blockbuster Paclitaxel (Taxol) drug from Bristol-Meyers-Squibb Company. Nanotechnology based drug delivery systems include nanoemulsions, lipid or polymeric nanoparticles, liposomes and nanofibers. Polymeric nanoparticular drug delivery systems have the advantages of cheaper cost, scalability, targeted delivery, biodegradability, biocompatibility, sustainability in release of encapsulated drug and improved efficacy. The biopolymers of carbohydrate origin such as Chitosan, Alginate and proteinous origin such as albumin, gelatin and silk proteins have added advantage over the synthetic polymers when there can be a compromise for long lasting stability. At the same time there are many synthetic polymers that are biocompatible and comparatively less biodegradable in comparison with natural polymers, which include polylactides (PLA), polyglycolides (PGA), poly(lactide-co-glycolides) (PLGA), polyorthoesters and polyanhydrides. These nanoparticulate drug delivery systems modify the normal pharmacokinetic profile of encapsulated therapeutic drug and help in targeted and sustained release of drug. Thus they overcome the barrier of systemic delivery which is the only way of administration for a wide range of active pharmaceutical ingredients. Nanotechnology based drug delivery systems can be classified under three major categories which can be further subdivided as tabulated (**Table 1**). Of these

*Correspondence to: Radhakrishnan Sridhar; Email: seeram@nus.edu.sg; Seeram Ramakrishna; Email: mperadha@nus.edu.sg
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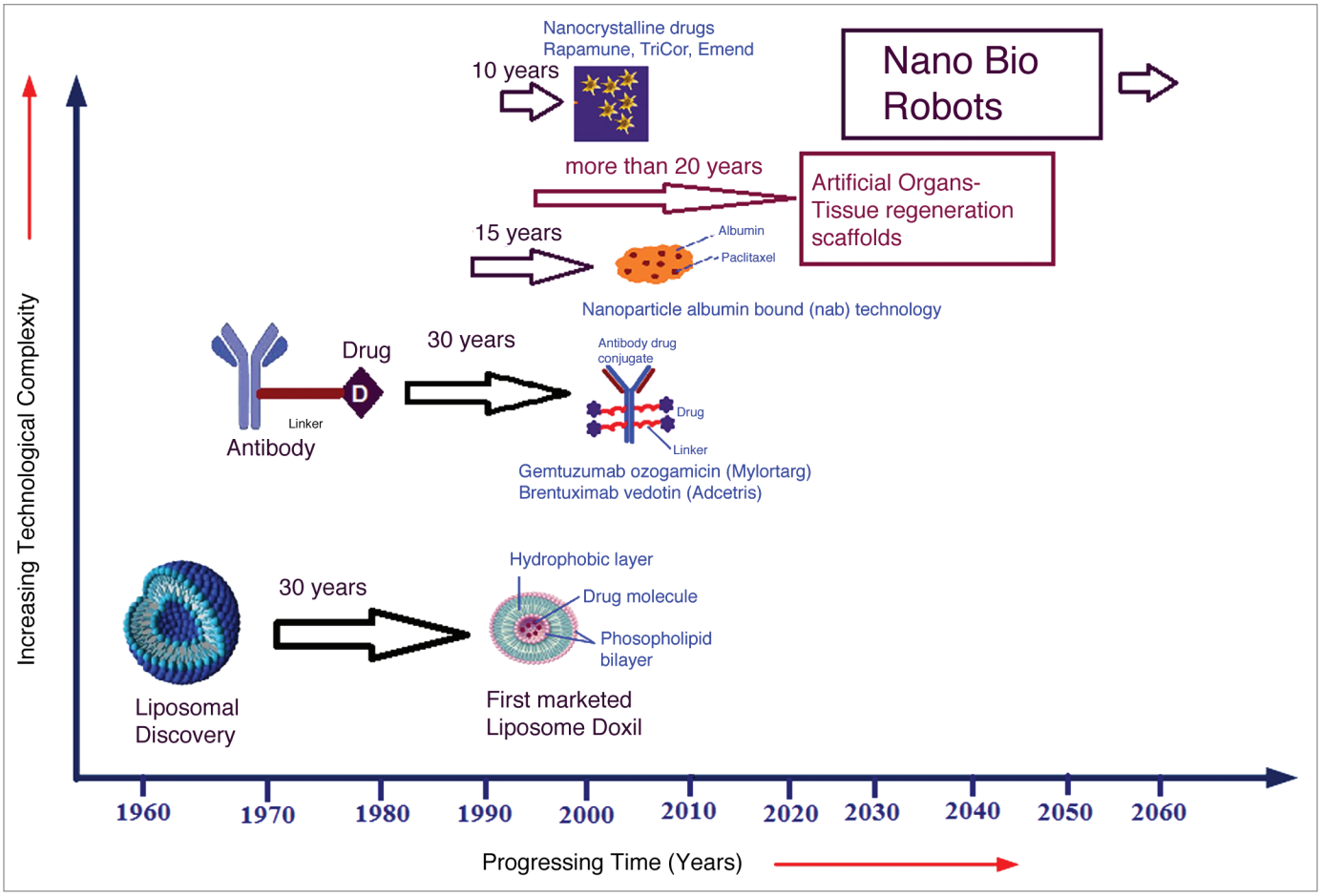

Figure 1. Projected timelines for Nanopharma "from research to market."

various drug delivery technologies some of which are marketed and a few in clinical trials (**Table 2**),[5] our main interest is the nanoparticulate drug delivery which in general falls in to the following categories based on their synthesis method.[6-8]

Lipid-Based Delivery Systems

Submicron lipid-drug nanocapsules constitute oily lipid core encapsulated by a solid or semisolid shell. These DDSs have the dual character of colloidal stability of solid particle suspensions in biological fluids and the solubilizing properties of liquids.[9,10] Because of the solubilizable matrix, it can incorporate the active pharmaceutical ingredient from metabolism[11] and ensure sustained release of the drug component.[12]

Micelles (Polymer Nanoparticles) in Drug Delivery

The nanoparticle polymeric micelles have the merits of solubilizing hydrophobic drug molecules, smaller particle size formation, in vivo thermodynamic stability, sustained release of various drugs and sustaining the drug against the reticulo-endothelial system.[13] These polymeric micelles can deliver the lipophilic drug in oral route. Target specific drug delivery through drug encapsulated polymeric micelles followed ultrasound mediated increased intracellular drug uptake in tumor cells was reported by Gao etal as a new technology.[14]

Polymer-Based Nanoparticulate Drug-Delivery Systems

A variety of non-lipid nanoparticulate systems are available as ideal carriers of drug encapsulation and sustained release, out of which hydrogels, dendrimers, chitosan based saccharide nanoparticles, protein based gelatin or albumin nanoparticles and lactide based biodegradable polymer nanoparticles are very common. In this review we focus only on the polymer nanoparticle drug carriers synthesized by electrospraying method and their worthiness as drug delivery systems. Various synthetic methods are available for the synthesis of the polymer nanoparticles mainly classified in to top-down and bottom up processes (**Table 3**). The electrosprayed nanoparticle synthesis falls under the top-down category where the larger particle is broken down into a smaller nanoparticle with the application of potential charge difference.

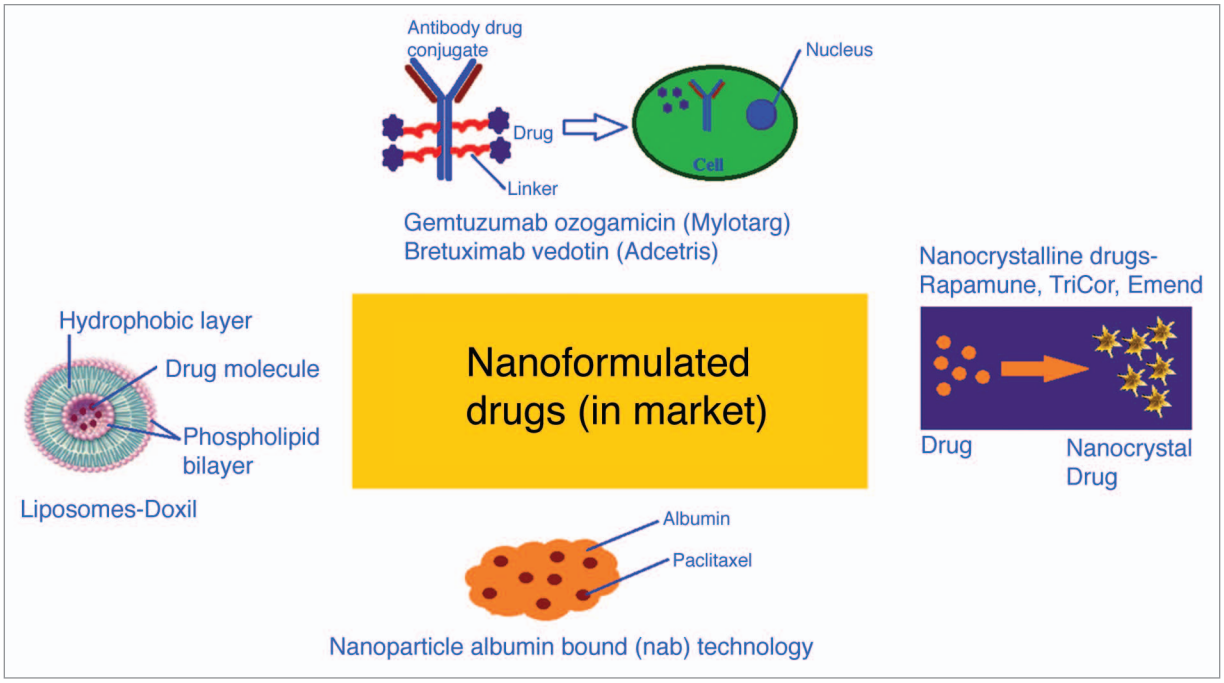

Figure 2. Existing nanomedicines in clinical usage.

Electrosprayed Nanoparticulate Drug Delivery Systems

Electrospray technique (**Fig. 3**) is one of the most efficient techniques for the preparation of Nano particles/Nanospheres. The experimental set up has a syringe pump with polymer solution connected to the high voltage power supply that constitutes the functional electrode. A metal foil collector placed opposite functions as the ground electrode. The flow rate and the applied voltage were optimized depend on the type of the solution used for electrospraying. The liquid emerging from the nozzle into the electric field forms tailor cone because of the surface tension.[15] By increasing the electric field the Taylor cone breaks into highly charged droplets, selecting the suitable conditions leads those droplets close to micro or nano size level. Solid particles can be produced by solvent evaporation. Needle gauge diameter, applied voltage, flow rate and working distance differ for the respective drug delivery systems. The principle of electrospraying is to apply a high voltage to a polymeric solution to force the polymer to come out from the syringe in the form of nanoparticles. Electrospraying has emerged as a similar technique as the electrospinning which uses the analogous technology for the production of nanostructures. The nanoparticles can be useful for numerous biological, medicinal or pharmaceutical applications because of its zero dimensional nature, whereas the nanofibers can be only useful for their two dimensional applications. Even then the research work done on electrosprayed nanoparticles quantified in terms of journal publications is quite less in comparison with that of the electrospun nanofibers. The advantages of the electrospraying include increased scalable synthesis, reproducibility

Table 1. Nanotechnology based drug delivery systems classification

Delivery Method/Routes of administration	Therapeutics	Technology
Oral administration	Cancer therapy	Nanoparticulate encapsulation
Transdermal delivery	Vaccines	Dendrimer-based targeted therapeutics technology
Injectable delivery	Antibody	Liposomes nanotechnology
Topical delivery	DNA-based therapy	Nanotube technologies
Nasal/pulmonary delivery		Nanoparticles coating technology
Implantable delivery		Silica-chitosan nanocomposite
		Nanosome technology
		Nanosuspension technology
		Nanocrystal technology
		Nanoshell technology
		Polymer therapeutics

Table 2. Nanotechnology products approved for market/in clinical trials

Nanocrystalline drug products	Technology of /Licensed to (Year of approval)	Indication
Rapamune (Sirolimus), oral	Elan/Wyeth (2000)	Immunosuppressant
Emend (Aprepitant), oral	Elan/Merck (2003)	Antiemetic
Tricor (Fenofibrate), oral	Elan/Abbott (2004)	Treatment of high cholesterol and high triglycerides
Invega Sustena (Paliperidone Palmitate), IV	Elan/Johnson and Johnson (2009)	Treatment of schizophrenia
Liposomal drug products		
Ambisome (Amphotericin B), IV	Gilead (1990)	Severe fungal infections
Abelcet (Amphotericin B), IV	Cephalon (1995)	Severe fungal infections
Depacyt (Cytarabine), Epidural	Napp (2002)	Neoplastic meningitis and lymphomatous meningitis
DepoDur (Morphine sulfate), Spinal	Flynn Pharma Limited (2004)	Pain Management
Polymeric micelles		
NK-911 (Doxorubicin), IV	Nippon Kayaku Co (Phase II)	Cancer targeting
NK-6004 (Cisplatin), IV	Nanocarrier Co (Phase II)	Cancer targeting
SP-1049C (Doxorubicin), IV	Anti-multidrug resistance (Phase II)	Supratek Pharma Inc.

and high encapsulation efficiency. This method is not only convenient for the synthesis of synthetic polymer nanoparticles but also for natural polymer nanoparticles either protein or carbohydrate and was found to produce stable nanoparticles without any loss of their bioactivity of either the drug or encapsulating biomolecules. These nanoparticles have broad spectrum applicability from soft tissue to hard tissue regeneration. When the PLGA nanoparticles are used for soft tissue applications, coatings of calcium phosphate nanoparticles find application on titanium implants[16] and for developing bioceramics scaffolds of zirconia.[17] Electrospray nebulizers were used for producing micro particles of size range 2–5 microns and the particles serve the purpose of inhaling medicines through lungs. These "breathable size range particles" are designed to deliver the medicine in to the lower airways without loss of drug activity of the encapsulated medicine.[18-23] Electrosprayed nanoparticles can encapsulate drugs and can be specific drug carriers because of their active surface absorption, binding or complexation with drug.[24] In the other hand the nano particle size plays an important role in the therapeutic treatment, the particle size is one of the factors to decide the drug carrier velocity, specificity towards binding or adhesion and reactivity.[25] Thus the electrosprayed nanoparticle technology opens a new domain for drug delivery applications and therapeutic use (**Table 4**).

Advantages of electrospraying technique:

(1) Can produce lowest and uniform particle size as possible. (2) Easy to control the operation parameters. (3) Fast preparation and one step technique. (4) This involves simple ideology. (5) This technique can be able to extend for bulk production.[26]

Disadvantages of electrospraying technique:

This technique may induce some macromolecule degradation due to the stress involved in the operation parameters (ex: thermal stress in drying, shear stress in the nozzle).[27,28]

Cancer Drug Delivery

Gulfam et al.,[29] electrosprayed nanoparticles of natural gliadin polymer for controlled release of cyclophosphamide anticancer drug. Cyclophosphamide is a cyclic phosphamide ester of mechlorethamine used to treat retinoblastoma, neuroblastoma, lung cancer and breast cancer by cross-linking with DNA and prevent cell division. Over 72.02 ± 5.6% of drug loading was achieved with the 7% gliadin based nanoparticles. At 7% gliadin, the particles were homogeneous and had an average size 218.66 ± 5.1 nm and have a narrow distribution. The particle size of gliadin or gliadin-gelatin composite nanoparticles were found increase with increase in gelatin concentration as observed by dynamic light scattering and X-ray diffractometry experiments. The drug loading of 64.23 ± 8.9% with the particle size of 398 ± 4.2 nm and 52.77 ± 12.6% with the particle size of 450.10 ± 9.7 nm were obtained with the 7% gliadin/4% gelatin and 7% gliadin/8% gelatin respectively. Also the gliadin-gelatin composite nanoparticles released cyclophosphamide rapidly whereas gradual release was noted with gliadin nanoparticles for 48 h. By culturing breast cancer cells with cyclophosphamide-loaded 7% gliadin nanoparticles for 24 h, downregulation of Bcl-2 protein was observed with western blot analysis which confirmed the apoptotic effect of the nanoparticle formulation. Even though the preparation of gliadin and gliadin-gelatin composite nanoparticles carried the same active drug component, gliadin based nanoparticle had the advantage over gliadin-gelatin composite nanoparticle because of its smaller size and slow drug release. Electrosprayed chitosan nano/micro particles were attempted for drug delivery with chitosan as a natural biodegradable and biocompatible polymer.[30] Kim etal.,[31] observed 3D chitosan nanofibrous networks by freeze-drying the electrosprayed chitosan nanoparticles. Doxorubicin (DOX) is the well-known anticancer drug has its own side effects such as cytotoxicity to normal tissues, induction of multidrug resistance and acute cardio toxicity. In order to reduce these effects and to improve the therapeutic efficiency

Table 3. Comparison of nanoparticle synthesis methods

Type	Method	Mechanism	Merits	Demerits	Application Domain
Bottom–Up Synthesis	Gas (Vapor) phase fabrication-Pyrolysis	Precursor vaporization, nucleation, growth	Simple, low cost, continuous operation, high yield	More chances of polymer, drug or biomaterial degradation	Calcium phosphate microspheres and Au nanoparticles for drug delivery
	Liquid Phase Fabrication- Sol-Gel or solvothermal synthesis	Precursor solution (involves catalyst), nucleation, growth	Simple, low cost, continuous operation, high yield	Needs removal of catalyst components, May involve excess solvent usage for scale ups	Highly explored technology for drug delivery and biomedical applications
Top-Down Synthesis	Lithography, Etching, Milling or Machining	Breaking down of large piece of material	Offers reliability and device complexity	Higher energy spent and more waste produced	Electronic device Industry
	Electrospraying	Driven by difference in electric potential and surface viscosity	Increased drug encapsulation efficiency, simplicity, low cost, continuous operation, high yield.	Chances of shear or thermal stress in some biomaterial nanoparticle synthesis	Has good prospects in drug delivery and pharma based industry

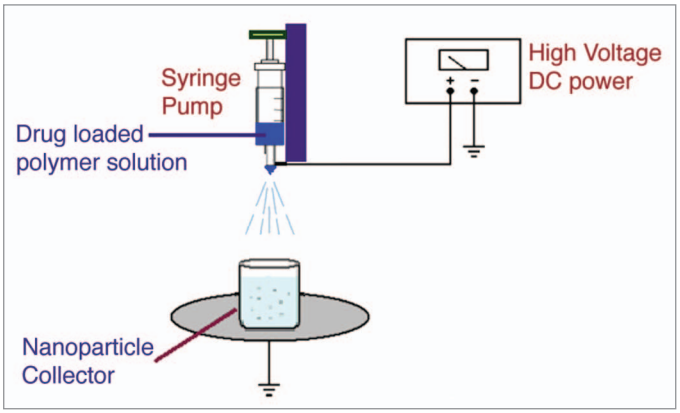

Figure 3. Illustration for electro spraying technique.

of DOX, DOX-loaded chitosan stabilized with Tripolyphosphate nanoparticles tried for its feasibility using an optimized electrospray ionization technique. Doxorubicin loaded chitosan nanoparticles were electrosprayed with Tripolyphosphate stabilization[32] and achieved high encapsulation efficiency (EE) up to 67.9%. The controlled release of the drug from the biopolymer nanoparticle was up to 70% over the period of 72 h. The variation of the parameters such as applied voltage, working distance, needle gauze and flow rate were manipulated so as to obtain nanoparticles of the drug loaded chitosan-Tripolyphosphate nanoparticle system. Titanium dioxide (TiO_2) nanoparticles loaded with Paclitaxel (TiO_2 electrosprayed core-shell microspheres for Paclitaxel delivery) was electrosprayed as core shell nanoparticles by Jing et al. The particle size was observed in 600 nm to 6 μm with the Titania protecting the initial burst release of the drug. The drug release was triggered with ultrasonic stimulation of the nanoformulation. Yun Wu et al.[33] produced oligodeoxynucleotide (ODN) encapsulated lipoplex nanoparticles by coaxial electrodynamic spraying for intravenous injection and for pulmonary delivery. Lipoplex had its own advantage that it has phospholipids bilayers that can encapsulate and carry drug or gene within the hydrophobic bilayers or in the hydrophilic core. ODN is a potential therapeutic agent against viral infection, cardiovascular inflammation, other pulmonary diseases and cancer. G3139 type ODN/lipoplex nanoparticles were successfully generated by coaxial electrospray technique. Lipoplex nano particles of size 190 ± 39 nm showed Zeta potential of +4.5 ± 0.4 mV were produced. The G3139 encapsulation efficiency up to 90 ± 6% was achieved with the above conditions. Transferrin was well conjugated with the lipoplex nanoparticles formed and provided the ability for the leukemia cellular uptake. G3139 in both non targeted and Tf-targeted lipoplex nanoparticles was efficiently delivered to K562 cells by 34 ± 6% and downregulated the bcl-2 protein expression by 57 ± 3%.

Cardiac Applications of Nanoparticular Formulations

Injectable nanoparticles have been widely studied for cardiomyoplasty both by means of acellular and cellular approach. In general the injectable nanoparticulate materials form a hydrogel or occupies the intrices of the infarcted myocardium, renders temporary mechanical support, assist in cardiomyocyte regeneration and thereby cardiac restoration. Electrosprayed PLGA porous beads were cellularized with human amniotic fluid stem cells (hAFSCs) and tested as injectables.[34] The microporous, cellularised microparticles improved regional contractile capacity together with neovascularization and myocardial regeneration. Li et al.[35] attempted hydrogen peroxide releasing electrosprayed core-shell microparticle together with cardiosphere-derived cells (CDCs) and thermosensitive hydrogel, from hydroxyethyl methacrylate-oligo hydroxybutyrate (HEMA-oHB) as cardiac regeneration. The oxygen releasing scaffold improved survival and assisted in cardiac differentiation of CDCs. Further the combination hydrogel system matched the stiffness of a cardiac tissue, supported cardiomyocytes formation and sustained the release of oxygen up to two weeks.

Table 4. Therapeutic area and conditions for the synthesis of electrosprayed drug loaded micro/nanoparticles

No	Polymer carrier	Drug encapsulated	Particle size (nm)	Therapeutic area	Condition
1	Polycapolactone[36]	Budesonide	116.1 ± 19	Asthma	0.5 to 6% PCL, 120 μg/ml of drug, 0.001% (v/v) surfactant flow rate 1ml/h, Applied voltage 5–15 kV.
2	PLGA[37]	Celecoxib	1 to 4 μm	Anti-inflammatory	Total concentration at 5% PLGA+ drug, Flow rate 1.2 ml/h, Applied voltage 11–13 kV.
3	-	Carbamazepine[38]	320 to 1000	Anticonvulsant	Up to 3 wt % solution, Flow rate up to 1.2 ml/h, Applied voltage 20 kV
4	Lactose[39]	Bovine Serum albumin (BSA)	700	Formulations as dry powder inhalers	2% BSA with respect to solvent ethanol/ acetic acid (96/4), Flow rate up to 0.3 ml/h, Applied voltage 5 kV
5	Stearic acid and Ethyl cellulose[41]	Tamoxifen	922 ± 52 nm	Lipid nanoparticles (for Breast cancer treatment)	Polymer carrier/drug ratio was 10/1. Flow rate up to 0.6 ml/h, Applied voltage 30 kV.
6	Polyvinylpyrrolidone (PVP) and Tristearin (GTS)[42]	Naproxen	720 ± 700 nm	Self-assembled solid lipid nanoparticles. (anti-inflammatory)	PVP/GTS/Naproxen ratio was 20/5/1. Flow rate up to 1 ml/h, Applied voltage 6–12 kV.

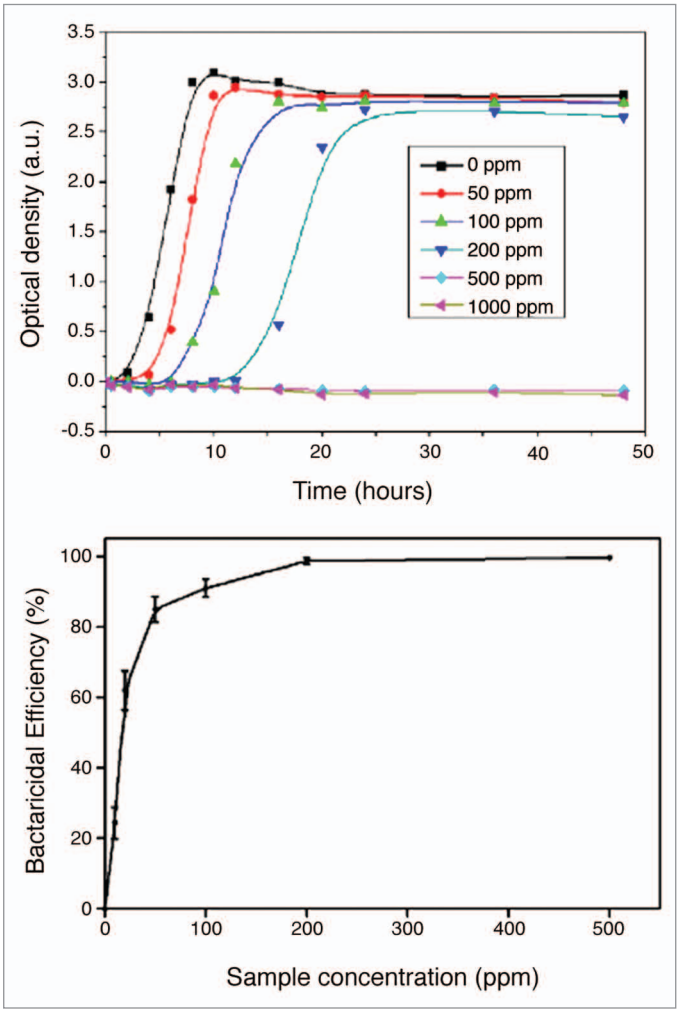

Figure 4. Antimicrobial efficacy and bactericidal efficiency as a measure of silver/silica nanoparticle sample concentration.

Nanoparticles as Antibacterial Agents

Hazeri et al. electrosprayed nanopowder of Sericin, an antibacterial agent used in food, cosmetics and drug delivery. Basically Sericin is a porteinous substrate available in Bombyx mori (silk worm). Electrospraying solution was prepared by dissolving the Sericin sponge in Dimethyl Sulfoxide and achieved 25 nm particle size which consists of small crystallites and high moisture absorbance.[36] Roine et al. discussed about the feasibility of preparing the mesoporous silicon (PSi) nanoparticles which can be used as a drug carrier in drug delivery system.[37]

Ag nanoparticles play an important role as antibacterial agent and this property of Ag^+ ion extends its use biomedicine. So far Ag nanoparticles used in cosmetics, pigments and antibacterial agents. Zhijun et al.[38] investigated the synthesis of Ag nano particles. In order to prevent coagulation or oxidation Ag nano particles, it has to be stored in stabilizer matrix so that it can act as an antibacterial agent without degradation for long time. SiO_2 is highly recommended by many users as a stabilizer because of its chemical stability and biocompatibility. These silica stabilized silver nanoparticles can be made by coating the synthesized Ag nanoparticles with a thin layer of SiO_2. These nano particles are quite stable with notable surface properties that of SiO_2. But the antibacterial efficiency of Ag nanoparticles toward microorganism gets reduced. The other method for the synthesis of silica stabilized Ag nano particles involves incorporation of Ag nanoparticles into the porous silica surface by coupling or chemical adsorption. In this case the Ag nanoparticles can be directly contact with microorganism and can establish its activity as an antibacterial agent. But the interaction between Ag nano particles and SiO_2 is weak or unstable and thereby it loses its antibacterial activity within the required period of time. The practical biomedical applications demand the long lasting antibacterial activity in order to avoid further infections after any treatment or implantations. In order to achieve the

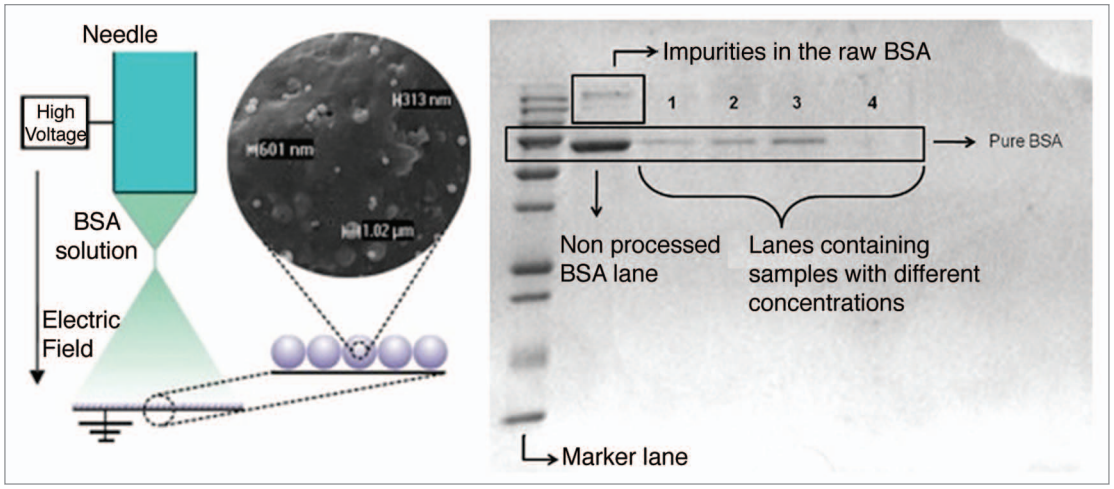

Figure 5. SEM image of the composite lactose plus BSA obtained by EHDA and SDS-PAGE of the BSA not processed and of 4 different samples of the composite lactose–BSA. Lanes 1, 2 and 4, lactose exposed to the jet for 1,200s. Lane 3, lactose exposed to the jet for 3,600s.

long lasting anti-infective property, Zhijun et al. attempted the new efficient Ag NPs-SiO_2 microspheres by electrospraying. In this method, the Ag nanoparticles were doped inside SiO_2 and were also embedded on the surface of the SiO_2. The resultant nanoparticles were proved to be very efficient and more stable. The silica precursor was made by adding 4.5 mL HNO_3 in to 30 ml of tetra ethoxysilane in 30 ml of ethanol solvent and finally hydrolyzing the mixture at 80°C for almost 3 h. In parallel, Ag solution was prepared by dissolving required amount of $AgNO_3$ in 2:1 ethanol/acetonitrile and was added to silica precursor. The resultant solution was electrosprayed, dried at room temperature for 24 h, annealed at 400°C and reduced with 5% H_2, 95% N_2. The bactericidal efficiency was calculated with the *E. coli* count and was shown that maximum bactericidal efficiency was achieved at 500 ppm. Further it was also shown (**Fig. 4**) that the Ag-NPs-SiO_2 microspheres were biocompatible with a cytotoxicity study using human Bone marrow derived mesenchymal stem cell (BMSC) as a model cell. The shelf life was investigated for Ag-NPs-SiO_2 microspheres and was shown to be very good antibacterial efficiency even after two months of storage.

Nano Particles in Inflammatory Drug Delivery

Midhun et al.[39] synthesized Budesonide loaded polycaprolactone nanobeads by using electrospray technique. Budesonide is a glucocorticoid steroid used for treatment of asthma, non-infectious rhinitis or allergies, nasal polyposis and inflammatory bowel disease. Polycaprolactone as a biodegradable polyester was used as a drug carrier and 116.1 ± 19 nm size particles were synthesized from optimal operating conditions of 1.5 wt% polymer concentration, 0.001% (v/v) surfactant concentration, flow rate 1 ml/h, tip-target distance 10 cm and with the applied DC voltage ~8 kV. The drug encapsulation efficiency was found to be 75 ± 2.4% and the drug release profile observed at pH 7.4 and 5.6 in vitro showed the sustainable result at 37°C. The analytical methods dynamic laser light Scattering (DLS) used for particle size conformation, laser Doppler anemometry for stability

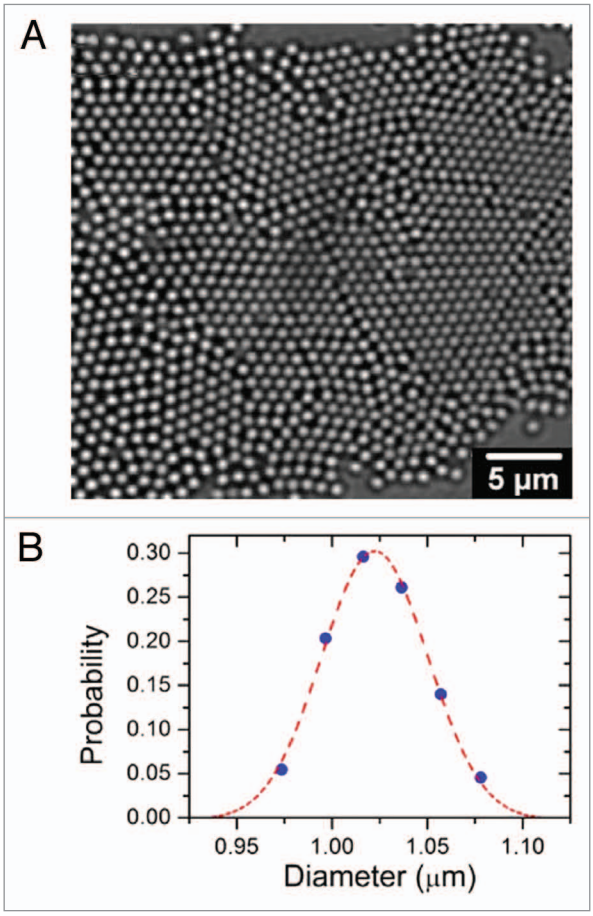

Figure 6. Monodisperse wax emulsions produced with a collection solution of 80 wt% ethanol, 20 wt% water, 0.005 wt% of Tergitol 15-S-9 and 20 mM SDS. The flow rate is 4 ml/h and the voltage is 2.8 kV. (**A**) Micrograph of the hexagonal lattices of emulsion droplets confirms size uniformity. (**B**) Droplet size distribution measured by dynamic light scattering. The diameter of the droplets is 1.02 ± 0.03 µm, and the polydispersity is 2.7 ± 0.1%.

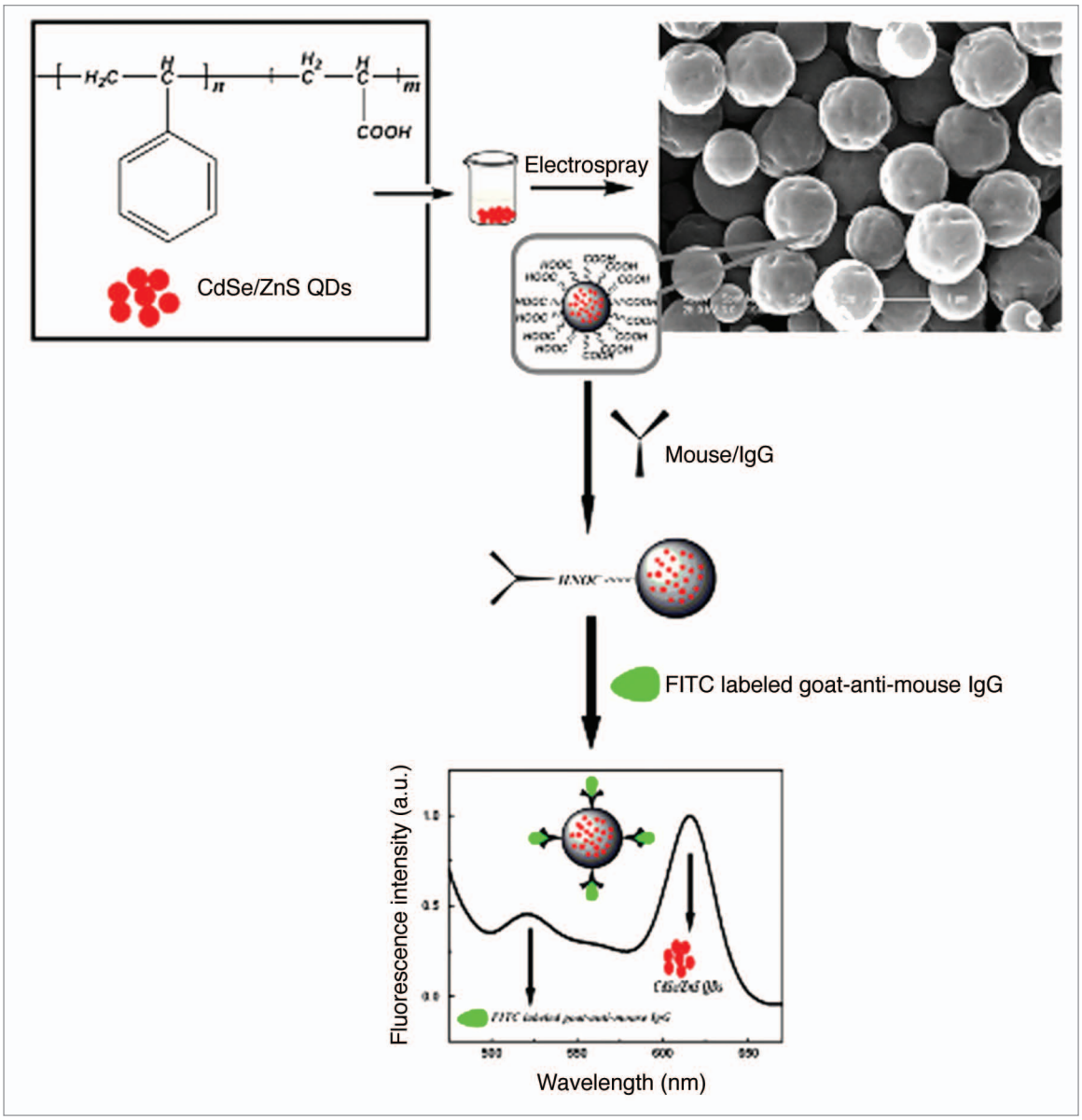

Figure 7. Quantum dot encoded microspheres synthesized by electrospraying.

of colloidal suspension and SEM for surface morphology. The drug entrapment in the PCL matrix was confirmed using Fourier Transform Infrared spectrometry (FT-IR). Celecoxib, a sulfo non-steroidal drug for inflammatory disease nano beads were prepared with PLGA by electro hydrodynamic spraying. The particle size can be produced in the range of 1 to 4 μm by this method.[40]

Nanoparticles in Neurology

Mao Wang et al.[41] produced nano crystals with anticonvulsant drug called carbamazepine. It is a poor water soluble drug and continually used for pharmaceutical manufacturing process. They developed the electrosprayed carbamazepine crystals of 320 nm particle size. The crystallization was accelerated by annealing at 90°C for 5 min and the resultant T50 of the formed carbamazepine = 3 ± 3 mins. This shows that its solubility increased by 26.4%. It is confirmed by XRD and surface morphology by SEM.

Protein Based Nanoparticles in Drug Delivery

Tavares et al.[42] successfully developed a protein based nano particle of size 700 nm by electrohydrodynamic atomization (EHDA). They used Bovine Serum albumin (BSA) as a model protein and lactose as a biological carrier (**Fig. 5**). This new approach opens a door for the production of new formulation for dry powders for drug delivery system. Christopher et al.[43] developed a ferritin

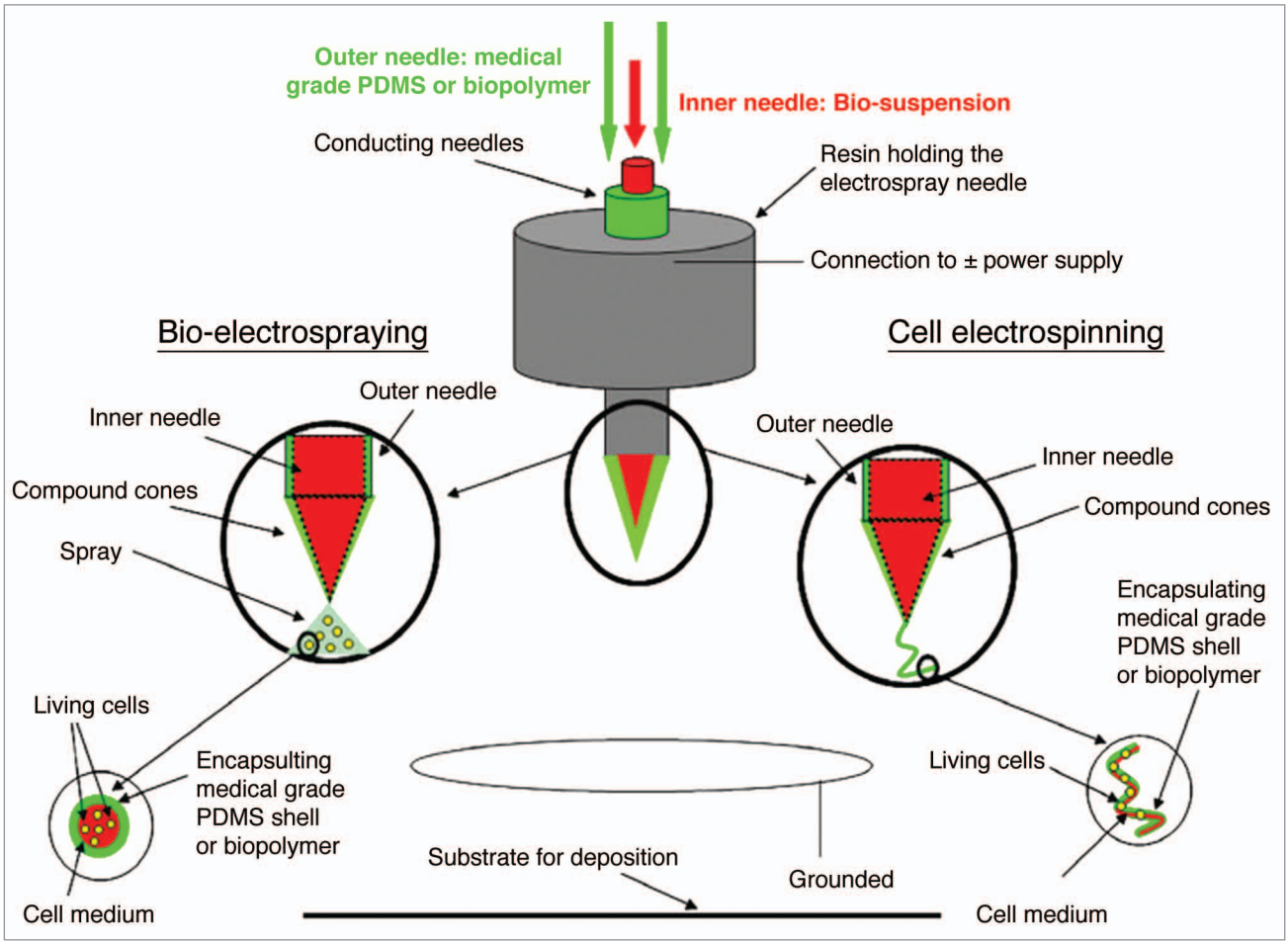

Figure 8. Schematic representation of a coaxial needle arrangement for controlled generation of either cell-bearing droplets or threads.

based nano particle. Ferritin is an intracellular protein molecule that stores the iron in a soluble and non-toxic form and releases it in a controlled fashion. The ferritin dissolved in 10 mM Ammonium acetate taken in the syringe and sprayed along with CO_2 gas flow 0.5l/min. The applied vvoltage was controlled at 2-3 kV and the ferritin-aerosol complexes were introduced into the furnace at the flow rate of 1.0l/min. The furnace temperature varied from 25°C to 800°C. The particle thus produced were sent to the radioactive source kr-85 to produce reduced and steady charged particles. The Scanning Mobility Particle spectra supports the size distribution and showed the result that the ferritin particle size is about 13.1 nm and apoferritin particle size is about 11.8 nm. Ferritin and apoferritin are clearly distinguishable and separated out with different degrees of compression.

Lipid-Based Nanoparticles in Drug Delivery

Biodegradable polymers can be used as drug carriers and they are very effective in terms or reducing the drug side effects. Lipids are the novel drug carriers and many researches have been done on lipid based drug delivery systems. It is evident that they can also be prepared as nanoparticles for effective and controlled drug release. Trotta et al.[44] tried a new method to prepare Lipid based nanoparticles by electrospraying. They prepared Tamoxifen-lipid nanoparticles. A known weight of drug was dissolved in Stearic acid and Ethyl cellulose mixture (4.5:0.5 w/w) and the solution was taken in a syringe. Then it was electrosprayed under high voltage and the nano particles were collected on the 150 mm distant aluminum tray kept as ground opposite to the syringe. The particle size of the nano particles formed was less than 1 μm with 76% drug encapsulation efficiency and the in vitro Tamoxifen drug release from lipid nanoparticles was observe by shaker experiment. The experiments showed 96% drug release from the encapsulated lipid nanoparticle in solution and followed slow kinetics through the through dialysis membrane. It was observed that there was an initial burst release of 30% and constant release up to 50% till 24 h through dialysis membrane. Deng et al.[45] developed a self-assembled lipid based nanoparticles for the drug Naproxen (NAP). NAP is a drug widely used for inflammatory bowel disease. By the electrospraying method they achieved 376 ± 20 nm particle size. The carrier chosen for the preparation of lipid based nanoparticle polyvinyl pyrrolidone K25, glyceryl tristearate (GTS) with NAP in the ratio of 20%:5%:1% at 50°C. The voltage applied was 6–12 kV, at the flow rate of 1 ml/h, the working distance kept at 25 cm and 50 degrees elevated-temperature was achieved by auxiliary apparatus. As a result of

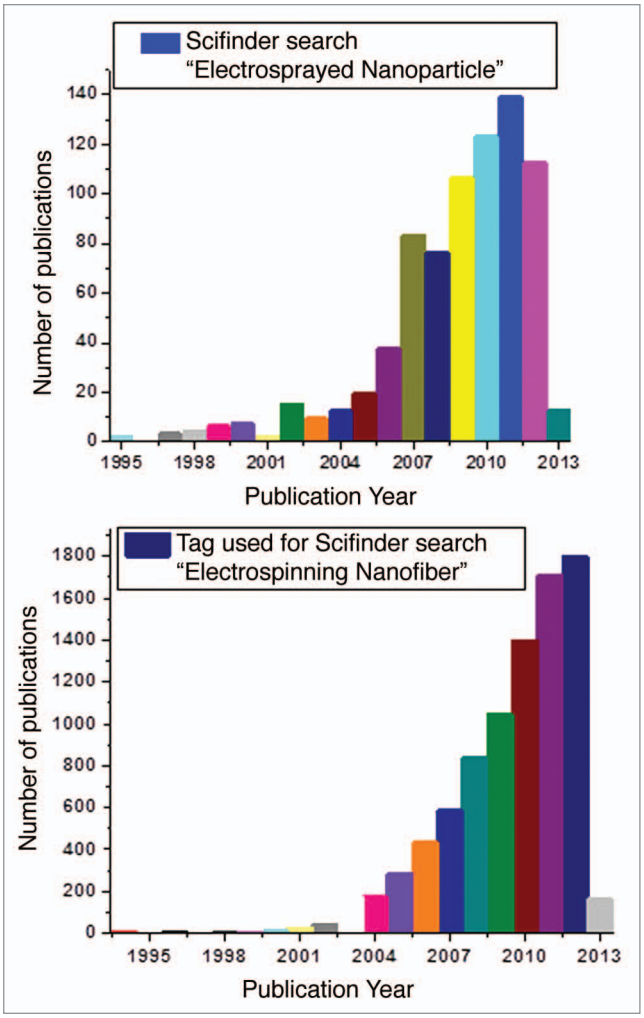

Figure 9. Comparison of publications of electrosprayed nanoparticles and electrospun nanofibers (based on Scifinder search).

electrospraying micro-particles were obtained and drug encapsulation efficiency was found to be 86.2%. The in vitro cumulative drug release was calculated as 85.6% after 24 h and was explained with the release mechanism which was via microparticle aggregation route. In the first step, the micro-particles absorb water, swell and finally collapse to liberate GTS and NAP molecules in to the buffer. In the second step there occurs strong interaction between the GTS and NAP molecules which results nanoparticle aggregates. This occurs when the PVP molecules dissolve completely, entirely collapse and thereby GTS and NAP self-assemble as nanoparticle and freed into the dissolution medium. This solid liquid nanoparticles (SLN) could find wide range of applications in cosmetics and drug delivery pharmaceutical fields.

Miscellaneous Electrosprayed Nanoparticles for Drug Delivery/Biomedical Applications

Andres et al.[46] formed α-eicosene wax nanoparticles of size range from 0.5–5 μm by electrospraying. The wax was preheated above its melting point, 26°C and introduced into the metallic syringe for electrospraying. The working distance is 7 cm with the applied voltage 2.6 to 2.9 kV and flow rate up to 3.0 ml/h. The particles thus formed washed with ethanol and dried. The Dynamic light scattering supports to analyze the particle size distribution (**Fig. 6**). The α-eicosene nanoparticles were produced owing to their prospective cosmetics preparations. Luis B et al.[47] tried to prepare TiO_2 agglomerates with ethanol by electrospraying method which is used to develop the nano structured film deposition. The film thus produced has précised nano structures and larger surface area when compared with the other printing methods. Lahann[48] developed an interesting compartmentalized nano particle by electrospray method. He tried electrospraying with different polymers using water and organic solvents. His idea of compartmentalization was a hint to achieve a targeted drug release from the drug delivery systems. Zhang et al.[49] fabricated the chitosan nanoparticles by one step electrospray deposition method. They obtained the smallest average particle size of 124 nm. Yiquan et al.[50] suggested an electrospraying technique that is flexible and effective method for generating stimuli-responsive drug particles. They fabricated the elastin-like polypeptide (ELPs) based nanoparticles of size 300–400 nm. Novel, quantum dots (QDs) encoded microspheres (**Fig.** 7) were electrosprayed for the detection of bio molecules by Lei sun et al.[51] They prepared polystyrene based microspheres with CdSe-ZnS QDs by electrospraying method. Polystyrene solution was prepared by dissolving in DMF at room temperature with vigorous stirring for 24 h. QD solution was prepared by dissolving 0.15 g in Chloroform. Then the two solutions were mixed, electrosprayed to yield microspheres and the particles were separated by ultrasound. The in vitro release of the quantum dots was examined by the incubation of the Hela cells with QD encoded microspheres at varying concentrations for 24 h and viability was measured with MTT assay.

Bio-Electrospraying

Bio-electrospraying is the technique which involves spraying of cells with the application of electrical potential difference. Jayasinghe et al., have electrosprayed human bood[52] (**Fig. 8**) and jurkat cells,[53] assessed for their viability by way of trypan blue staining. This methodology of bio-electrospraying provides a wide range of applications[54-57] spanning bio-analytics, diagnostics which has potential to form of synthetic or artificial tissues. Further it can be applied for repairing and replacing damaged/aging tissues, to the targeted and controlled delivery of personalised medicine through experimental and/or medical cells and/or genes.

Conclusions

This review dealt with the applications of electrosprayed nanoparticles mainly in the drug delivery and pharmaceutical domain where the technology is yet to reach its maximum utility. When both the nanofibers and nanoparticles have the accessibility by means of similar technique which involves the application of electrical potential difference, it was noted that the research in

the area of electrospun nanofibers has resulted in more number of publications when compared with the numbers from electrosprayed nanoparticles (**Fig. 9**). In terms of pharmaceutical applications, nanoparticles have wider applicability than the nanofibers. This implies that electrosprayed nanoparticles though have huge potential applications in various domains still remains unexplored as compared with the electrospun nanofibers. Though there may be issues with stability of biomolecules or thermal stress or shear stress, they can be overcome with suitable carrier molecules and appropriate electrospraying conditions which can set a breakthrough in Nanopharma industry.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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