DESIGN OF MINIATURIZED ELECTRO SPRAY INSTRUMENT FOR GENE AND DRUG THERAPEUTIC TREATMENT OF IPF

Fiave P.A 1, Boehringer S. 2, Gazdhar A. 3, Geiser Th. 3, D. Hradetzky 2

1 Department of Biomedical Engineering and Department of Clinical Research, University of Bern, Switzerland
2 School of Life Sciences, Institute for Medical and Analytical Technologies, University of Applied Sciences and Arts Northwestern Switzerland
3 Department of Pulmonary Medicine and University Hospital Bern, Department of Clinical Research, University of Bern, Switzerland
prosper.agbesi@students.unibe.ch

Abstract: Electric field accelerated plasmid droplets to permeate tissues has been demonstrated on cell culture and ex-vivo lung tissue of rats using enhanced green fluorescence protein reporter gene for transfection. This opens a window of opportunity to design an electrospray instrument usable within the working channel of bronchoscope to noninvasively treat idiopathic pulmonary fibrosis (IPF). We elaborate a concept and realized a device usable in the working channel of a flexible bronchoscope taking into account restrictions within typical bronchoscopy procedure.

Keywords: Gene delivery methods, Electrospray, Idiopathic pulmonary fibrosis, bronchoscopy

Introduction

Electric field accelerated plasmid droplets have been used to permeate cell culture and ex-vivo lung tissue of rat using enhanced green fluorescence protein reporter gene for transfection [1]. This presents great clinical potential to treat idiopathic pulmonary fibrosis (IPF) using electric fields accelerated fluidic gene or drug droplets. IPF is a devastating disease affecting the distal lung and currently has no reliable treatment. Gene therapy has been demonstrated as a viable option for the treatment of IPF using hepatocyte growth factor (HGF) for cell repair and regeneration to reduce fibrosis [2]. Gene delivery requires that the powerful cell membrane protecting the cells has to be conquered effectively to deliver substances avoiding side effects [1]. Genes can be delivered by viral and non-viral means. Viral methods have adverse implications and are not applicable in clinical situations. Some non-viral methods include: electroporation, biolistics (gene guns), microinjection and using femtosecond lasers. Our focus is on new device for non-viral gene transfer to the distal lung tissue by the use of an electrospray process [2].

Electrospraying or electrohydrodynamic atomization (EHDA) is the process where an electrified liquid is dispersed to fine droplets owing to an electrostatic force working on the charged surface of a liquid [3]. These droplets can be accelerated towards a grounded counter electrode. The physical properties of the liquid that govern the atomization process include: surface tension, the viscosity and the density, electrical conductivity and relative permittivity. Other factors include the capillary diameter, potential and liquid volume flow rate [4].

Design and Fabrication

We anticipate a device which delivers electrosprayed fluidic genes or drug droplets to the interior of lung tissues overcoming the cell membrane by impact of the sprayed droplets on the tissue surfaces. Our aim is to design a device usable within bronchoscopy procedure, requiring a single access port to the lung. Therefore a flexible tubular instrument providing high voltage and fluidic drugs to be delivered, fitting within the working channel of the bronchoscope, has to be designed. One crucial point within miniaturization refers to the integration of required high voltage (electric field distribution) for electrospray processes within the device. Finite Element Methods (FEM) using COMSOL Multiphysics® was employed to verify the electrical compatibility for our miniaturized device. Materials selection for the design of the device was done so as to conform to regulatory standards regarding medical devices.

![Figure 1: Sketch of the miniaturized flexible device](source: https://doi.org/10.7892/boris.45668)

The device (Figure 1) consists of a tubular inner electrode (i.Ø177.8µm.o.Ø236 µm), acting as electrical and fluidic interconnect, a second counter electrode (cup electrode Ø 2000µm) including the electrical interconnect (spiral electrode, wire Ø 200µm). For electrospray process between the two electrodes an acceleration cavity (Ø 1400 µm, 4-8 mm length) is required. In order to achieve a flexible device usable within the flexible bronchoscope, all this parts including insulation has to be integrated in a...
flexible way. For insulation we are investigating on Teflon, silicone, polyurethane and polyethylene.

To evaluate the electrical fields within the device, FEM was used to solve Maxwell’s equations:

\[ E = -\nabla V \]  
\[ \nabla^2 V = 0 \]  
\[ D = \varepsilon_0 \varepsilon_r E \]

where \( E \) denotes the electric field, \( V \) the potential, \( D \) the electric displacement field, \( \varepsilon_0 \) the permittivity of air or free space \((8.854 \times 10^{-12} \text{F/m})\) and \( \varepsilon_r \) is the relative permittivity of the material.

A terminal potential was applied to the inner tube electrode, while the spiral electrode and the cup electrode were connected to ground. The Solidworks® model of the device was imported to the COMSOL environment. The entire device was placed in an air environment, and a mesh using free tetrahedral elements was applied shown in Figure 2.

For each insulation material we performed electrostatic stationary studies for the 3D model, applying an electric potential of 5 kV at the inner tube, representing a common configuration. Particular we were focusing whether the calculated field would exceed the material field strength, leading to an electrical break down.

A longitudinal section of the electric potential distribution and electric field distribution calculated through the device with silicone is as shown in Figure 3.

While using silicone \((E_b = 19 \text{kV/mm})\) the calculated fields is close to the dielectric strength or even exceeds, polyurethane \((E_b = 39.4 \text{kV/mm})\) offers electrical fields below the dielectric strength. Therefore silicone offers inadequate insulation while polyurethane, as well as PTFE \(E_b = 55 \text{kV/mm}\) or polyethylene \(E_b = 45 \text{kV/mm}\) show a sufficient electrical insulation and do not exceed the dielectric strengths. However, using PTFE as insulation material will result in a quite rigid device. Therefore polyurethane or polyethylene seems to be more suitable for a flexible miniaturized device.

To fabricate a first device we established a sacrificial tubing process shown in Figure 4:

First the cup electrode was electrically and mechanically connected to the spiral electrodes. The inner tube electrode was placed within a PMMA tube (offering two accessible ports for introduction of insulation material and air removal) acting as sacrificial mould. Using two plugs, one of them containing a mandrel to create the acceleration cavity at the distal tip of the device, were used to apply external forces on the inner tube to assure a concentric positioning. All electrodes were assembled within the PMMA mould and pourable insulation material was introduced. To speed up the curing process hot air and an oven was used. After adequate curing time, the sacrificial PMMA tube was raptured to obtain the final device.

Conclusions
We proposed and proofed the feasibility of realizing a flexible miniaturized electrospray system usable within the working channel of the bronchoscope to deliver fluidic drugs or genes for the treatment of IPF. Furthermore we created a prototype of this device taking into account critical concerns during perceived service situations.

References

