World Academy of Science, Engineering and Technology
International Journal of Aerospace and Mechanical Engineering
Vol:12, No:06, 2018

Surface Acoustic Waves Nebulisation of Liposomes Manufactured in situ for Pulmonary Drug Delivery

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Abstract : Pulmonary diseases, such as asthma, are generally treated by the inhalation of aerosols that has the advantage of reducing the off-target (e.g., toxicity) effects associated with systemic delivery in blood. Effective respiratory drug delivery requires a droplet size distribution between 1 and 5 μm. Inhalation of aerosols with wide droplet size distribution, out of this range, results in deposition of drug in not-targeted area of the respiratory tract, introducing undesired side effects on the patient. In order to solely deliver the drug in the lower branches of the lungs and release it in a targeted manner, a control mechanism to produce the aerosolized droplets is required. To regulate the drug release and to facilitate the uptake from cells, drugs are often encapsulated into protective liposomes. However, a multistep process is required for their formation, often performed at the formulation step, therefore limiting the range of available drugs or their shelf life. Using surface acoustic waves (SAWs), a pulmonary drug delivery platform was produced, which enabled the formation of defined size aerosols and the formation of liposomes in situ. SAWs are mechanical waves, propagating along the surface of a piezoelectric substrate. They were generated using an interdigital transducer on lithium niobate with an excitation frequency of 9.6 MHz at a power of 1W. Disposable silicon superstrates were etched using photolithography and dry etch processes to create an array of cylindrical through-holes with different diameters and pitches. Superstrates were coupled with the SAW substrate through water-based gel. As the SAW propagates on the superstrate, it enables nebulisation of a lipid solution deposited onto it. The cylindrical cavities restricted the formation of large drops in the aerosol, while at the same time unilamellar liposomes were created. SAW formed liposomes showed a higher monodispersity compared to the control sample, as well as displayed, a faster production rate. To test the aerosol's size, dynamic light scattering and laser diffraction methods were used, both showing the size control of the aerosolised particles. The use of silicon superstate with cavity size of 100-200 μm, produced an aerosol with a mean droplet size within the optimum range for pulmonary drug delivery, containing the liposomes in which the medicine could be loaded. Additionally, analysis of liposomes with Cryo-TEM showed formation of vesicles with narrow size distribution between 80-100 nm and optimal morphology in order to be used for drug delivery. Encapsulation of nucleic acids in liposomes through the developed SAW platform was also investigated. In vitro delivery of siRNA and DNA Luciferase were achieved using A549 cell line, lung carcinoma from human. In conclusion, SAW pulmonary drug delivery platform was engineered, in order to combine multiple time consuming steps (formation of liposomes, drug loading, nebulisation) into a unique platform with the aim of specifically delivering the medicament in a targeted area, reducing the drug's side effects.

Keywords : acoustics, drug delivery, liposomes, surface acoustic waves
Conference Title : ICAA 2018 : International Conference on Acoustics and Applications
Conference Location : Copenhagen, Denmark
Conference Dates : June 11-12, 2018