

Surface Acoustic Wave Nebulisation for Targeted Inhalation Drug Delivery to Central and Peripheral Airways

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Summary

This work presents surface acoustic waves (SAW) as a technology for controlled aerosolisation of formulations with a wide range of physical properties, including viscous solutions and those with low surface tension that are often challenging to deliver. The acoustic waves were coupled into microstructured arrays of cavities with sizes in the range of 100s of micrometers to nebulise liquids. The aerosols generated by the nebuliser engine were characterised using an Anderson Cascade Impactor. The mass median aerodynamic diameter (MMAD) was consistently $<2\mu\text{m}$ for model drug systems, ranging from 1% sodium chloride to 50% ethanol, whilst it was ca. $1.3\mu\text{m}$ for antibiotic drug formulations of Tobramycin and Amikacin. These results demonstrate significant reduction in the size of the droplets in the aerosol compared to previous technologies. This suggests a route for targeted delivery of inhalable antibiotic drugs to the central and peripheral airways, potentially avoiding side effects associated with intravenous or oral application, as well as reducing drug waste and the risk of development of drug resistant bacteria often linked to other modes of delivery.

Key Message

Surface Acoustic Waves coupled into an array of microstructured cavities can aerosolise a wide range of formulations with a high respiratory fraction, enabling targeted delivery of inhalable antibiotic to the peripheral airways.

Introduction

Pulmonary drug delivery remains a challenge for many drug formulations, due to the many mechanical and physicochemical barriers that make up the lung tissue. With its complex network of airways, the lung evolved into an effective aerosol and particle “filter” making access to the conducting airways and alveoli difficult. Deposition of drugs into the main bronchus requires droplets smaller than $5\mu\text{m}$ whereas deep lung deposition in the alveolar epithelium requires aerosols with particle sizes of less than $3\mu\text{m}$ [1, 2]. Pulmonary bacterial infections in these lung tissues requires targeted antimicrobial delivery. However, more commonly used oral and intravenous delivery are often associated with side effects, especially during long term use [3]. They also require higher amounts of the compounds and increase the risk of the development of antibiotic resistance.

Targeted pulmonary drug delivery has the potential to overcome these challenges, by increasing the antimicrobial compound concentration locally at the site of infection, thus reducing drug amounts used and circulating systemically, limiting side effects. In particular, nebulisers could enable topical drug deposition in the deep lung tissue. However, current nebulisers often have limitations around the physical properties of the formulations they are able to deliver efficiently (e.g. low surface tension $<40\text{mN/m}$), due to difficulties in producing large drug laden aerosol populations with the required particle sizes of $3\mu\text{m}$ or lower. They also tend to retain large amounts of drugs in the device, causing drug waste [4].

In this work we demonstrate that surface acoustic wave (SAW) technology can be engineered to produce a large fraction of aerosol particles of less than $3\mu\text{m}$ during the nebulisation of antibiotic drugs and liquids with challenging physical properties. Our technology couples the SAW into a microstructured chip to confine the liquid formulation within cavities, consequently providing the ability to control the capillary waves on the surface of the liquid, generating aerosols with fine droplets.

Experimental methods

A 13.6 MHz Interdigitated transducer (IDT), fabricated using a metal lift-off process on 128° Y-cut lithium niobate piezoelectric substrate, was used for this study. The microstructured chip was produced by a

dry etch process to form an array of cavities of 600 μm diameter. It was placed on top of the IDT and the liquids dispensed to the nebuliser via a syringe pump. Formulations models were prepared using sodium chloride and ethanol (Sigma Aldrich) as well as generic drug formulations of Amikacin (50 mg/ml, Vianex) and Tobramycin (40 mg/ml, Flynn Pharma Ltd).

An Anderson Cascade impactor (ACI, Copley) was used for aerosol characterisation. The ACI was cooled at 5°C. The results are provided based on the recovered material from the collection plates of the ACI. In order to measure the concentration of formulation models, all of the stock solution were prepared with 1.1 mg/ml Allura Red solution. ACI plates were rinsed with DI water and the rinsates were analysed with a UV/Vis spectrophotometer at 504 nm to obtain aerosol concentration. The concentration of Tobramycin was measured using solution conductivity. A gravimetric analysis of ACI plates before and after nebulisation of Amikacin were performed to obtain aerosol distribution. The ACI plates were stored over-night in a drying cabinet to remove the water content prior to gravimetric analysis (both before and after the aerosols deposition).

Results

Figure 1 shows the recovered mass fraction from the different stages of the ACI, indicating a high fraction of droplets between 0.7 μm and 2 μm , for all of the solutions. The mass median diameter of the produced aerosols together with the residual of the active material on the SAW platform are presented in Table 1. The SAW nebuliser is capable of nebulising these solutions with a flow rate between 70 to 200 $\mu\text{l}/\text{min}$.

The nebulised solutions (Figure 1) include sodium chloride and sodium sulfate, as samples with salt, 10% PEG 400, as a more viscous solution, 2.5% sodium dodecyl-sulphate (SDS) with low surface tension and 50% ethanol as a solution with high viscosity and very low surface tension, beyond the limit of current nebulisers (<40 mN/m, Table 1). The Amikacin (50 mg/ml) and Tobramycin (40 mg/ml) solutions were nebulised with flow rates of 100 $\mu\text{l}/\text{min}$. Nebulisation of these antibiotic drug models resulted in aerosols with a MMAD of 1.3 μm and a peak of droplets are observed in range of 1 μm (Figure 1).

Figure 1 – Collected mass fraction in each ACI stage for 1% sodium chloride (Yellow), 1% Sodium sulfate (Grey), 10% PEG400 (Green), 50% ethanol (Blue), 2.5% SDS (Black), 50mg/ml Amikacin (purple horizontal pattern) and 40mg/ml Tobramycin (red cross pattern).

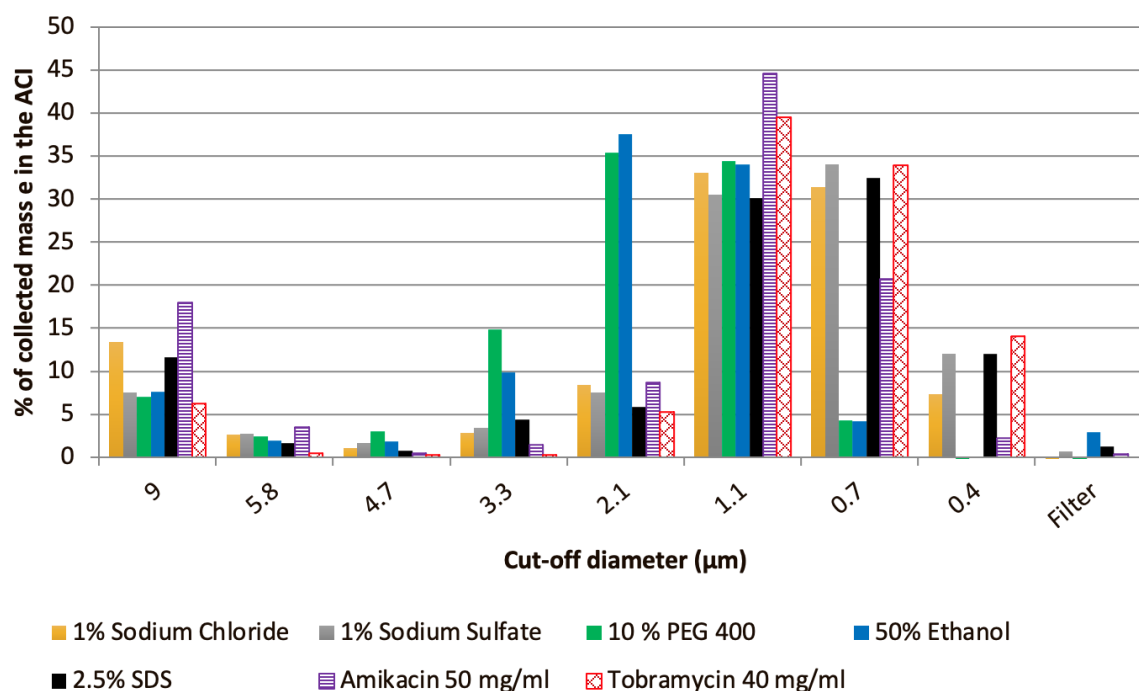


Table 1 –Performance of SAW nebuliser according to the Mass Median Aerodynamic Diameter (MMAD) of aerosol; residual concentration of the active material on the SAW platform; and the nebulisation flow rate for each solution. Also, viscosity, surface tension of each solution is provided, indicating the range of solutions that can be nebulised with the SAW platform.

Solution	1% Sodium Sulfate	1% Sodium Chloride	50%(v/v) Ethanol	10% PEG400	2.5% SDS	Amikacin 50mg/ml	Tobramycin 40mg/ml
MMAD (μm)	1.4	1.4	1.9	2.3	1.3	1.3	1.1
Residual on the platform (%)	9.4	6.1	4.5	11.2	7.7	5.8	16.5
Flow rate ($\mu\text{l}/\text{min}$)	200	200	170	100	200	100	70
Viscosity (cP)	1.0	1.0	2.0	1.56	1.3	N/A	N/A
Surface tension (mN/m)	72	72	27	55.7	31	N/A	N/A

Discussion

Nebulisation of formulations with different properties can be a challenging task, especially for liquids with very low surface tension and/or high viscosity. In this study, we present the data from different liquids models with various properties, including 50% ethanol that has a very low surface tension while having a relatively high viscosity (Table 1). We have shown that our SAW technology can produce aerosol with very small droplet sizes and MMAD of $2\mu\text{m}$, for example as an approach to reduce the surface tension in the alveolar region, decreasing sputum formation and enhancing drug uptake.

We demonstrated for the first time the nebulisation of commercially available antibiotic drug solution using surface acoustic waves in combination with a silicon microstructure technology. Our initial results showed that those drug formulations, can be adopted to produce aerosol with MMADs below $3\mu\text{m}$ and high fine particle fractions below $2\mu\text{m}$. While those numbers are encouraging, further studies on lung models, with specific focus on drug distribution in the tissue and whether it is suited for therapeutic purposes will be required to progress the development of the technology towards clinical use. The absorption of the drug (e.g. into macrophages) and the general lifetime of the drug before clearance will also require careful investigation. Moreover, patients with lung disease present changes in their lung structure in the form of narrowed or obstructed airways, which impact airflow and ultimately the drug deposition process, requiring smaller droplet size for efficient drug delivery. Further questions remain regarding treatment time which ideally should be short to avoid disruption of daily life as well as around the activity of the drug administered but novel drug carrier compounds may improve release and activity profiles to reduce treatment intervals and drug dose.

Conclusion

Topical delivery of antibiotics to deep lung tissue via inhalation has the potential to become an important therapeutic tool for the treatment of lung diseases caused by microbials. The challenge is to deliver the drug in a targeted manner with high drug concentration at the site of infection without stressing the patient's body through side effects as observed by traditional administration of repeated high doses antibiotic but also with reduced chances of antibiotic resistance through over- or misuse. New nebuliser technologies based on surface acoustic wave excitation present an opportunity to overcome the lungs innate particle filtering effect by producing fine aerosol particle fractions that are able to penetrate the conducting airways and alveoli more efficiently. Our SAW based technology enables nebulisation of

common antibiotics to produce particle sizes with MMADs of less than 3µm while maintaining a high fine particle fraction. For the same flow-rate, our technology will enable an increase in the inhalable fraction of the aerosol, decreasing the nebulisation time.

References

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