Viscosity Reduction of Model Cystic Fibrosis Fluids by DNA Condensing Agents

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Cystic Fibrosis is a hereditary disease that infects over 30,000 children and adults in the United States alone. It is caused by the malfunctioning of a chloride ion channel which leads to a thick, sticky mucus and decreased mucociliary clearance. Specifically, patients suffer chronic lung infections from Staphylococcus aureus and Pseudomonas aeruginosa. Leukocytes accumulate to fight infection in purulent sputum and are lysed releasing DNA. DNA, a large linear polyanionic biopolymer, in purulent lung secretions partially accounts for the high viscosity of the sputum. Severe lung disease is the primary cause of death in cystic fibrosis patients. Median survival age has greatly improved with modern treatments from 6 months to more than 37 years. However, this is still short when compared to the mean life expectancy of most Americans. Treatment of cystic fibrosis patients aims at maintaining healthy lung function by clearing the airways. Antibiotics are used to treat infection, while rhDNase and airway clearance techniques provide a synergistic treatment to enhance clearance of viscous purulent lung fluid. It is likely that compaction of DNA might also reduce the viscosity of DNA laden purulent sputum. Other biological processes that require DNA compaction through a condensation reaction are gene regulation, cell division, and production of sperm. Biologically derived polycations, such as protamine, spermine and poly-L-lysine, can electrostatically bind the negatively charged phosphate DNA backbone resulting in electrostatic repulsion between nucleotides. The result is both inter- and intra-molecular collapse which could result in a significant decrease in overall viscosity and, hopefully, easier sputum clearance. To examine this structural effect, model cystic fibrosis sputum was prepared from calf-thymus DNA and high purity water at two concentrations and their viscosities were measured at 25 °C, 37.78 °C, and 50 °C because the temperature dependence of viscosity is as important and insightful as the viscosity itself, particularly in complex fluids. The measured decrease of viscosity from 25 °C to 37.78 °C and its subsequent increase from 37.78 °C to 50 °C is a strong indication of structural change in the solutions. The model mucus with the higher DNA concentration was then mixed with three concentrations of protamine, spermine, and poly-L-lysine, respectively, and their viscosity was also measured at 25 °C, 37.78 °C, and 50 °C. Because of the complex rheological and wetting behavior of the sample liquids two different techniques were employed for the viscosity measurements in the Newtonian limit. The densities of the solutions were also measured. This work applies thermophysical property metrology in a biomedical context, which is an emerging field with great challenges and promises.