DEVELOPMENT OF INHALED THERAPEUTIC POLYMERS

FOR THE TREATMENT OF RESPIRATORY INFECTIONS

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Background: Respiratory diseases and infections are a considerable global public health concern. They rank third and fourth among the leading causes of death worldwide (WHO), with lower respiratory infections as the leading communicable cause of death resulting in 2.6 million deaths in 2019.1 Treatment of bacterial respiratory infections is becoming increasingly problematic given the rise in multi-drug resistant bacteria.

Nitric oxide (NO) is a promising antimicrobial and an alternative to antibiotics. NO has been shown to effectively kill a broad range of bacteria, viruses and fungi due to its ability to disrupt the cellular functions of such microorganisms. Given its multimechanistic mode of action, there is little tendency for bacteria to develop resistance mechanisms.2 However, as NO is a gas, delivery to the site of an infection is challenging. The aim of this project is to develop polymeric drug delivery vehicles that will encapsulate nitric oxide donors for inhaled drug delivery applications.

Methods: These particular polymers were chosen due to their advantageous traits, including low toxicity and readily available starting monomers. Both the linear and hyperbranched configurations of two cationic polymers, each characterised by distinctly different degradable backbones, were synthesised in anhydrous solvents to ensure a high yield and purity of the reaction. The reactions were systematically optimised to produce polymers of high molecular weights (10-30 kDa). Two different hyperbranching monomers were chosen to investigate the effects of structural changes to the molecular weight and properties of the polymers.

Following synthesis these polymers were modified and nitrosylated with an in house synthesised NO-donor to form stable NO-donating compounds. This chemical modification changes the properties of the novel polymer and gives the capacity to store high payloads of nitric oxide.

Results: Characterisation of the in house synthesised polymers was carried out using, 1H, 13C, 13C DEPT, COSY, HSQC, HMC nuclear magnetic resonance spectroscopy (NMR), FTIR and gel permeation chromatography (GPC). NO release was directly measured in PBS under varying conditions (light/ dark, EDTA, pH) by chemiluminescence.

Hyperbranched polymers with high molecular weights are capable of storing and therefore releasing a higher quantity of NO. This makes them promising candidates for antimicrobial treatment and various medical applications including inhaled therapeutics.

Conclusions: We have synthesised high molecular weight linear and hyperbranched polymeric drug delivery carriers that have then be used to covalently bond NO donor molecules with a sustained release of NO. Ongoing and future work includes aerosolisation tests, antimicrobial efficacy testing and cell cytocompatibility analysis.