Inhalable Magnetic Nanocomposite Microparticles (MnMs) Dry Powders for Targeted Pulmonary Delivery

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Statement of Purpose: Targeted pulmonary delivery facilitates direct, targeted application of bioactive materials to the lungs in a controlled manner. Certain medical conditions, such as asthma, implement targeted pulmonary delivery as a first line treatment, and there is a growing interest in inhalable lung cancer treatment modalities. This administration route boasts a variety of advantages with the most important being higher local concentrations and reduced systemic side effects of active species. Traditionally, inhaled therapies consist of small molecule drugs and excipients; however, targeted pulmonary delivery provides a platform for localizing novel nanoparticles to the lungs through direct, topical application. Iron oxide (Fe_3O_4) magnetic nanoparticles (MNPs) have generated considerable interest in biomedicine and contain the unique ability to generate heat in the presence of an alternating magnetic field. The heat generated from these particles can be used to trigger other therapies, increase transport of particles, and induce hyperthermia as a thermal treatment. Hence, the incorporation of MNPs into dry powder formulations yields the ability to remotely heat these particles after deposition into the lung providing enhanced control over actuating the onset of therapy. Here, we have formulated inhalable dry powders with composed of Fe_3O_4 MNPs and two common anti-cancer agents used in lung cancer therapy.

Methods: Cisplatin, erlotinib and MNPs were formulated into inhalable magnetic nanocomposite microparticle powders with advanced spray drying using a Büchi Mini Spray Dryer B290. D-mannitol was chosen as the excipient for these powders, and spray drying experiments were carried out in closed mode with an inlet temperature of 150°C. Feed mixtures were prepared at a dilute concentration of 0.1% wt/vol. The activity of the cisplatin and erlotinib released from these inhalable powders was studied by comparing their cytotoxicity profiles to their corresponding raw form of the drugs. Human lung bronchioalveolar (H358) cells were cultured and seeded into 96-well plates at 10,000 cells/cm^2. Cells were allowed to attach overnight and subsequently exposed to drugs for 24 hours before staining live cells with calcein AM. The mean fluorescence was quantified with a microplate reader, and the relative viability was calculated by normalizing to the mean fluorescence of the control. The heating capability of MnM powders was determined using a custom Taylor Winfield AMF source operating at a field strength of ~55 kA/m. Powders were dissolved at 10 mg/ml, placed in the AMF, and the temperature was measured with a Luxtron optical thermometer.

Results: Figure 1 shows the cytotoxicity profiles for raw and spray dried (SD) forms of cisplatin and erlotinib were very similar in H358 cells. These data indicate that both

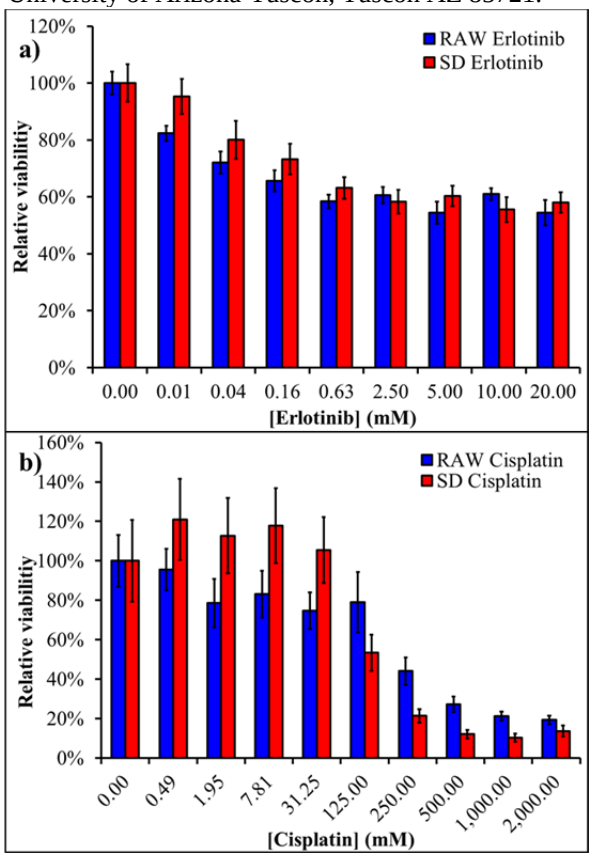

Figure 1: Cytotoxicity of raw and SD erlotinib (a) and cisplatin (b) on H358 cells

of these agents retain their activity and illustrate the potential of formulating anti-cancer agents into inhalable dry powders. The heating capability of dry powders was determined for MnM powders with MNP-loadings of 5 (MF5) and 20 (MF20) wt%. Results showed that MNPs released from powders retained their magnetic properties. The specific absorption ratio (SAR) of MNPs released from MF5 and MF20 were 251±53 and 316±51 W/g, respectively. Comparing these to the SAR value of MNPs before spray drying, 422±17 W/g, we can see that the MNPs heating capacity was moderately reduced; however, these SAR values are still very high and indicate that MNPs retain the ability to be remotely heated with AMF exposure.

Conclusions: Inhalable dry powder nanocomposites consisting of MNPs and ACAs were successfully synthesized with advanced spray drying. Cytotoxicity studies show that cisplatin and erlotinib retain their activity with human lung cell lines, and heating studies show that MNPs released from SD powders can be remotely heated. These results illustrate the potential of these materials for inhalable lung cancer treatment modalities