Advances in Drug Delivery to the Lung: a Controlled Release Perspective

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ABSTRACT SUMMARY

Drug delivery to the lung is an obvious route for the treatment of local respiratory diseases (e.g. asthma and chronic obstructive pulmonary disease), infection (e.g. tuberculosis and pneumonia) and as a systemic portal at the alveolar level.

However, the actual delivery of therapeutics to the lung is a significant challenge, since the particles must have an aerodynamic diameter < 5 µm to reach the conducting airways and <1 µm to reach the alveoli. Aerosol particles are inherently difficult to generate due to the high energies required for their preparation and high interfacial interactions.

To complicate matters, over the past decade, there has been increasing interest in generating aerosols that not only penetrate the lung but also have controlled release properties. For example, in asthma you may wish to increase the permeability rate of a poorly soluble steroid or, in the case of infection, you may wish to prolong the residency time of an antibiotic at the lung surface where the infection occurs. This presentation highlights some of the advances in the field the Respiratory technology group at the Woolcock Institute are making from a particulate engineering and in vitro testing perspective.

ENGINEERING CONTROLLED RELEASE INHALATION PARTICLES

There are a number engineering approaches for controlled release inhalation microparticles. Methods include polymer-mediated release, solid lipid particles and encapsulation in liposomes. A couple of examples are outlined below along with a discussion on the methods for evaluating release at the epithelia:

(1) Polymer and lipid mediate release

Previous work by the group has studied the applicability of co-spray drying polymers, such as poly-vinyl alcohol (PVA) with small molecule anti-asthmatic drugs, proteins and antibiotics [1-5].

Salama et al., prepared a number of formulations containing sodium cromoglycate (DSCG) and PVA and showed that by controlling the surface chemistry and moisture sorption properties of the particles it became possible to control both the aerosol performance and drug release [2-3].

Importantly, in this study each of these particulate systems were studied using a series of ‘dissolution’ methodologies. These included: the (a) Pharmacopeia Apparatus 2 (b) flow through cell and (3) Franz cell. It was found that the Franz cell was the most powerful method for identifying differences in release of DSCG between formulations that contained between 0-90% w/w PVA [3]. It was suggested that the Franz cell best represented the epithelia of the lung, which is essentially a ‘wetted surface’, rather than a conventional liquid sink. Furthermore, it was shown that with DSCG (and later a model protein, BSA), increasing the PVA concentration in the particle increased the diffusion dissolution rate into the surrounding media (Figure 2A) [1,3]. Using this approach, the authors went on to study the release of PVA/DSCG microparticles in an in vivo ovine model and showed that after inhalation, they could maintain significant blood plasma levels for at least 6 days post treatment (Figure 2B)[4].

Interestingly, using this approach and a different molecule (ciprofloxacin), the authors found they could enhance drug transport via amorphous stabilization at the lung-air interface [5]. In this later study, Ong et al., utilized an in vitro air-interface cell model that mimics the lung epithelia and allows for the direct deposition of aerosols and the measurement of drug transport across the epithelia.

Recently, this technique was used to evaluate the release of the flavonoid quercetin, encapsulated inside a solid lipid matrix, which
was shown to have a prolonged, zero order release across the epithelia [6].

**Figure 1(A)** release of DSCG from PVA microparticles using the Franz cell and 1(B) ovine blood plasma in an ovine model.

(2) The use of liposome technology

An alternative approach to lipid emulsification and co-spray drying is using self-assembled based systems, such as liposomes. Recently the team has investigated the potential for using ciprofloxacin-loaded liposomes for prolonging the residency time of antibiotics in treating local lung infections [7,8]. It was found that liposomal particles could be successfully nebulized as an aerosol and that the release of drug was reduced when compared to ciprofloxacin alone [7]. Specifically, the group studied a range of methods for evaluating release, including dialysis, air interface cell model and ex vivo perfused lung (Figure 2) and compared the data to in vivo animal models [8]. It was found that correlations existed between the methodologies, suggesting that a robust model for predicting controlled release in the lung may be possible in the future.

**CONCLUSIONS**

The development of controlled release pulmonary formulations for lung delivery offers many possibilities in the treatment of a variety of diseases. However, a lot is yet to be done in the area to develop robust in vitro tools to accelerate formulation development.

**REFERENCES**