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Delivery of theophylline as dry powder for inhalation

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ABSTRACT

Theophylline (TP) is a very well established orally or intravenously delivered antiasthma drug with many beneficial effects. This study aims to improve asthma treatment by creating a dry powder inhalable (DPI) formulation of TP to be delivered directly to the lung, avoiding the side effects associated with conventional oral delivery. The DPI TP formulation was investigated for its physico-chemical characteristics using scanning electron microscopy, laser diffraction, thermal analysis and dynamic vapour sorption. Furthermore, aerosol performance was assessed using the Multi Stage Liquid Impinger (MSLI). In addition, a Calu-3 cell transport assay was conducted *in vitro* using a modified ACI to study the impact of the DPI formulation on lung epithelial cells. Results showed DPI TP to be physico-chemically stable and of an aerodynamic size suitable for lung delivery. The aerosolisation performance analysis showed the TP DPI formulation to have a fine particle fraction of 29.70 ± 2.59% ($P < 0.05$) for the TP formulation containing 1.0% (w/w) sodium stearate, the most efficient for aerosolisation. Regarding the deposition of TP DPI on Calu-3 cells using the modified ACI, results demonstrated that 56.14 ± 7.62% of the total TP deposited (13.07 ± 1.69 μg) was transported across the Calu-3 monolayer over 180 min following deposition, while 37.05 ± 12.62% of the deposited TP was retained in the cells. This could be due to the presence of sodium stearate in the current formulation that increased its lipophilicity. A DPI formulation of TP was developed that was shown to be suitable for inhalation.

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1. Introduction

Theophylline (TP) is a well established orally or intravenously delivered antiasthma drug [1–5]. The main drawbacks of this active pharmaceutical ingredient (API) are related to its narrow therapeutic index and several side effects, i.e. nausea, headache, dizziness and vomiting [2,6]. Increasing evidence shows that it has significant anti-inflammatory effects in chronic obstructive pulmonary disease at lower plasma concentrations [3]. Already in the early 90s authors have demonstrated that delivery of sub-bronchodilator doses of TP (serum concentration of about 8 μg/ml) significantly attenuated late asthmatic response, which is inflammatory in nature [7,8]. The steady-state peak serum TP concentration is a function of the dose, dosing interval, and rate of TP absorption and clearance in the individual patient. Because of marked individual differences in the rate of TP clearance, the dose required to achieve a peak serum theophylline concentration in the 10–20 mcg/ml range varies fourfold among patients (e.g., 400–1600 mg/kg/d in adults <60 y old and 10–36 mg/kg/d in children) [9,10]. The dose of TP must then be individualised on the basis of peak serum concentration measurements in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.

With the aim to reduce these side effects and exploit the anti-inflammatory benefits of this old drug, there is the potential to reformulate this API for lung delivery as a dry powder inhaler (DPI). This should open up benefits that would not be possible using the historical routes of delivery. The authors have already presented re-purposing TP as pressurised metered dose (pMDI) solution [11] with good *in vitro* aerosolisation and cell results, but the disadvantage of this delivery platform is that doses are limited to a few micrograms.

Dry powder inhalers have many benefits over other lung drug delivery platforms, such as pMDIs or nebulisers. They can **deliver** high doses, have longer stability due to their solid state, absence of cold chain storage during transport, high patient compliance, shorter delivery times, lack of propellants and absence of the need of patient coordination when the API is delivered [12–14].

It is a common strategy to include lubricants or surfactants in an inhalable formulation to improve aerosol performance [15], reduce powder adhesion to inhaler device [16] and capsules or blisters [17,18]. Common lubricants or surfactants usually include trileucine, leucine and cyclodextrin [15]. Furthermore, lipophilic components, such as cholesterol and phospholipid [19], have also been utilised to achieve the above-mentioned purposes.

Sodium stearate is the sodium salt of stearic acid with a hydrophobic chain of 18 carbons. Due to its lipophilic nature, it has been used as a lipophilic adjunct in the formulation of inhalable aerosols to promote microparticle aerosolisation and also formulation resistance to environmental humidity [19]. For example, a previous study has demonstrated that the addition of a small amount of sodium stearate (1%, w/w) significantly improves the aerosol performance of tobramycin spray-dried powders [19].

A review of the literature suggests only few have engineered TP as a DPI for lung delivery. In 1994, Raeburn and Woodman [20] showed that TP could be delivered intra-tracheally to **guinea pigs** via DPI, and investigated bronchospasm, inflammation and airway microvascular leakage. In 2011, Salem et al. [21] presented nanoparticles of TP for DPI delivery with a view to enhance the dissolution rate since TP is relatively insoluble in water. More recently, in 2013, Alhalaweh et al. [22] manufactured of a series of TP co-crystals, with and without excipients or other APIs, using spray drying as a particle engineering approach. Their findings produced SD-TP particles. Both the 2011 and 2013 manuscripts were focused more on the use of particle engineering (controlled agglomeration [21] or spray drying of co-crystals [22]) for inhalation pharmaceutical applications and not on the actual re-formulation and aerosol characterisation of TP as a DPI, as studied here. Specifically, the aim of this manuscript is to present a TP formulation and to study its optimisation, physico-chemical properties and interaction with lung epithelia using a Calu-3 epithelial cell model.

2. Materials and methods

Anhydrous theophylline (TP) and sodium stearate were supplied by MP Biomedicals, Australia. Water was purified by reverse osmosis (MilliQ, Millipore, France). All solvents used were of analytical grade and were supplied by Chemsupply (Victoria, Australia). All sterile culture plastic ware was supplied by Sarstedt (Adelaide, Australia).

2.1. *Particle production*

Solutions of TP for spray drying were prepared by mixing equal volumes of individually prepared TP aqueous solution (30 °C) and alcoholic solutions of sodium stearate at various concentrations (30 °C). The total solid content was maintained at 20 mg/ml and the ratio of sodium stearate to TP was varied. Sodium stearate weight fractions of 0%, 0.5%, 1.0% and 1.5% w/w, respectively, based on TP mass were used for spray drying [19]. Solutions were spray dried using a Büchi B-290 spray dryer (Büchi Mini Spray Dryer B-191, Flawil, Switzerland) under the following conditions: inlet temperature 100 °C, measured outlet temperature 48 °C, solution feed rate 40 ml/min, aspirator rate 100% and atomising airflow 700 l/h.

2.2. *Scanning electron microscopy*

The morphology of the spray dried TP microparticles containing various weight fractions of sodium stearate was studied using a scanning electron microscope (JEOL-6000, Tokyo, Japan) at 5 kV. TP raw material and spray-dried samples were deposited onto double-sided adhesive carbon tape, mounted to aluminium stubs and sputter-coated with gold at a coating thickness of 15 nm prior to imaging.

2.3. *Thermal analysis of TP*

The thermal response of TP raw material and spray dried formulations were analysed using differential scanning calorimetry (DSC, model 823e, Mettler Toledo International Inc.,