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Preparation of theophylline inhalable microcomposite particles by wet milling and spray drying: The influence of mannitol as a co-milling agent

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ABSTRACT

Inhalable theophylline particles with various amounts of mannitol were prepared by combining wet milling in isopropanol followed by spray drying. The effect of mannitol as a co-milling agent on the micromeritic properties, solid state and aerosol performance of the engineered particles was investigated. Crystal morphology modelling and geometric lattice matching calculations were employed to gain insight into the intermolecular interactions that may influence the mechanical properties of theophylline and mannitol. The addition of mannitol facilitated the size reduction of the needle-like crystals of theophylline and also their assembly in microcomposites by forming a porous structure of mannitol nanocrystals wherein theophylline particles are embedded. The microcomposites were found to be in the same crystalline state as the starting material(s) ensuring their long-term physical stability upon storage. Incorporation of mannitol resulted in microcomposite particles with smaller size, more spherical shape and increased porosity. The aerosol performance of the microcomposites was markedly enhanced compared to the spray-dried suspension of theophylline wet milled without mannitol. Overall, wet co-milling with mannitol in an organic solvent followed by spray drying may be used as a formulation approach for producing respirable particles of water-soluble drugs or drugs that are prone to crystal transformation in an aqueous environment (i.e. formation of hydrates).

1. Introduction

The classical formulation approach for drug delivery to the lungs using dry powder inhalers (DPIs) is micronising the active pharmaceutical ingredient (API) and then mixing with a suitable coarse carrier (e.g. lactose, mannitol). Micronisation (e.g. by ball or air-jet milling for particle size reduction) may generate amorphous domains on the drug particle surface. The amorphous state tends to revert back to a lower energy and more stable crystalline state upon storage, which may adversely influence the product performance as it affects critical particle properties such as the morphology, particle size distribution, dissolution and aerosolisation (Brodka-Pfeiffer et al., 2003; Chow et al., 2007). Therefore, preparation of nanosuspensions by a wet size reduction technique (e.g. wet milling, high pressure homogenisation, antisolvent precipitation) followed by solidification, using spray drying, has been suggested as a preparation platform for inhalable micron-sized composites of nanocrystals with enhanced dissolution and aerosolisation efficiency (Bosch et al., 1999; Malamatari et al., 2015; Pilcer et al., 2009; Yamasaki et al., 2011).

The majority of such reported applications (nanos-in-micros particle engineering approach) has focused on poorly water-soluble drugs and thus the size reduction step can take place in aqueous media where the drug is dispersed but not dissolved (Duret et al., 2012; Pomázi et al., 2013). However, some drugs used for the treatment of respiratory diseases are moderately or very water-soluble, such as salbutamol sulfate (albuterol sulfate) and terbutaline sulfate, or are prone to hydrate formation, e.g. nedocromil sodium. Therefore, water cannot be used as the wet milling medium, in the preparation of nanosuspensions for such drugs, nor as the solvent during the spray-drying step as for poorly water-soluble drugs. Instead, an appropriate organic solvent has to

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be selected, in which the drug exhibits a solubility lower than 10 mg ml^{-1} and ideally lower than 5 mg ml^{-1} (Hong and Oort, 2011), to eliminate the possibility of crystallinity changes (e.g. amorphisation) during milling and spray drying.

Theophylline has been chosen as the model compound in this study as it has a long history of use within respiratory medicine, and its solid-state properties have been extensively investigated. More specifically, anhydrous theophylline is a challenging molecule with respect to wet milling and spray drying due to the following physicochemical properties:

(i) It is moderately water-soluble (7.36 mg ml^{-1}, at 25°C, Yalkowsky and He, 2003).
(ii) Its needle-like crystal morphology can affect its fracture/breakage behaviour, as reported for other organic crystalline materials.
(iii) It is prone to process-induced solid-state transformations as it exists in four polymorphic forms (forms I–IV) along with a monohydrate form (Fucke et al., 2012). Form II is the stable polymorph at room temperature while the monohydrate is the stable form in water and at high relative humidity environment.

Theophylline is a widely available and inexpensive methylxanthine that has been used in the treatment of airways diseases such as asthma and chronic obstructive pulmonary disorder (COPD) for more than 90 years (Barnes, 2013).

The use of theophylline has been limited by its narrow therapeutic index (TI) and the marked inter-subject variability of its clearance. A therapeutic plasma concentration of 10–20 mg L^{-1} is required for theophylline to achieve bronchodilation comparable with β_2-agonists, while side effects (e.g. nausea, vomiting, heartburn, diarrhea) become an issue at concentrations above 20 mg L^{-1} (Barnes, 2013). Due to its narrow TI, it is administered as oral sustained-release preparations.

There is increasing evidence that theophylline at low doses (plasma concentrations <7 mg L^{-1}) exhibits immunomodulatory properties in the pathophysiology of both asthma and COPD (Barnes, 2013). Moreover, it has been reported that theophylline has the potential to enhance the anti-inflammatory effect of corticosteroids and to reverse steroid resistance that is common in COPD patients (Hirano et al., 2006; Tilley, 2011). These observations may lead to the re-evaluation of this old drug in the future, once clinical trials of low-dose theophylline therapy are completed (Barnes, 2008, 2003).

Theophylline applied intratracheally as a dry powder formulation to the airways of anaesthetised guinea pigs exhibited smooth muscle relaxant and anti-inflammatory properties at very low doses that would be predicted to have no systemic toxicity (Raeburn and Woodman, 1994). Thus, developing inhalable formulations for theophylline may offer advantages over oral administration for the treatment of inflammation in asthma and COPD, enhancing the local efficacy of the drug while minimising systemic side effects (Raeburn and Woodman, 1994; Zhu et al., 2015a).

There are few published studies on engineering inhalable theophylline particles. A low-dose pressurised metered-dose inhaler (pMDI) formulation of theophylline (Zhu et al., 2015a) and formulations for dry powder inhalers (polymeric composite particles, microspheres, cocrystals and nanosized rods agglomerates) have been produced and characterised (Alhalaweh et al., 2013; Kadota et al., 2015; Momeni and Mohammadi, 2009; Salem et al., 2011; Zhang et al., 2009; Zhu et al., 2015b). Blends of theophylline microparticles (63–90 μm) with inhalable budesonide and terbutaline particles (<5 μm) were proposed as a formulation approach for concurrent oral and pulmonary drug delivery with theophylline acting as a carrier (Salama et al., 2014).

Dry powder inhalers (DPIs) have many advantages (inherent stability of dry powders, administration of high doses, short delivery times, the absence of propellants and breath-actuation) compared to other inhalation devices, namely pMDIs and nebulisers (Atkins, 2005).

The aim of the present work is to produce inhalable dry powder formulations of theophylline, by coupling wet bead milling in an organic solvent with spray drying of the milled suspension. The effect of mannitol addition during the wet milling of theophylline on the micromeritic, solid state and aerosol performance of the produced spray-dried particles was investigated. The experimental data of this study were complemented with a computational study of the interactions between theophylline and mannitol (i.e. crystal morphology modelling and lattice matching calculations) in order to elucidate the role of mannitol as a co-milling agent.

2. Materials and methods

2.1. Materials

Theophylline (THEO), 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione (LKT Laboratories, USA), was used as the drug under investigation. D-mannitol (MAN, Pearlitol 160C®, Roquette Freres, France) was used as co-milling agent and matrix former of the microcomposites. Isopropanol (IPA, Thermo Scientific, UK) was used as the milling medium for the preparation of suspensions. Methanol and water both from Fisher Scientific UK, and trifluoroacetic acid (TFA, Sigma-Aldrich Co., USA) were used for the HPLC analysis. All the solvents used were of analytical grade.

2.2. Methods

2.2.1. Preparation of suspensions

Suspensions were prepared by wet bead milling using a laboratory planetary mill (Pulverisette 5, Fritsch Co., Germany). 1.0 g of solids (THEO and MAN) and 10 g of milling beads (0.5 mm diameter aluminum borosilicate glass grinding beads, Gerhardt Ltd., UK) were weighed into a glass vial of 14 ml capacity and suspended in 10 ml IPA, as the dispersing medium. The total

Table 1
Nominal composition and assayed theophylline content (% w/w) of microcomposite particles together with the calculated drug loading efficiency (%) (mean ± SD, n = 3).

Formulation	Content (% w/w)			Drug loading efficiency (%)
	Nominal		Assayed	
	THEO	Mannitol	THEO	
SD susp. THEO	100	–	n/a	n/a
SD susp. THEO:MAN 75:25	75	25	76.2 ± 0.1	101.6 ± 0.1
SD susp. THEO:MAN 50:50	50	50	53.3 ± 0.1	106.7 ± 0.1
SD susp. THEO:MAN 25:75	25	75	28.7 ± 0.2	114.1 ± 1.0
SD susp. MAN	–	100	n/a	n/a