European Journal of Pharmaceutics and Biopharmaceutics xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Can 'extrafine' dry powder aerosols improve lung deposition? ☆

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ARTICLE INFO

Article history:
Received 27 March 2015
Revised 7 July 2015
Accepted in revised form 11 July 2015
Available online xxxx

Keywords:
Dry powder inhaler
Extrafine aerosol
ICS
Lung deposition
Small airway targeting
Submicron particles

ABSTRACT

There is increasing interest in the use of so-called 'extrafine' aerosols to target the small airways in the management of asthma and COPD. Using previously presented deposition data, we assessed whether submicron (<1 μm) particles can improve central and deep lung deposition. Our data show instead that particles in the range 1–3 μm are much more relevant in this respect. Based on this finding the Symbicort Turbuhaler, Seretide Diskus, Rolenium Elpenhaler and Foster (Fostair) NEXThaler ICS/LABA combination DPIs were tested *in vitro* as a function of the pressure drop (2, 4 and 6 kPa) across the inhaler. Obtained fine particle fractions (FPFs) <5 μm (as percent of label claim) were divided into subfractions <1. 1–3 and 3–5 μm. Differences of up to a factor of 4 were found between the best (Turbuhaler) and worst performing DPI (Elpenhaler), particularly for the FPF in the size range 1–3 μm. The NEXThaler, described as delivering 'extrafine' particles, did not appear to be superior in this size range. The marked differences in amount and size distribution of the aerosols between the devices in this study must cause significant differences in the total lung dose and drug distribution over the airways.

1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are characterized by airflow obstruction and chronic inflammation of the respiratory airways. In the last few years, management of these diseases has improved considerably, as a result of the introduction of new drugs, drug combinations, drug administration devices and management strategies. Inhaled corticosteroids (ICSs) are the cornerstone of asthma and, to a lesser degree, COPD therapy because of their long-term efficacy and safety [1] but optimal effects may be expected when an ICS is administered in combination with a long acting beta$_2$-agonist (LABA) [2]. This has resulted in an increasing number of ICS/LABA inhalers becoming available. There is also a growing awareness of the importance of small airways in asthma and COPD [3,4] and the existence of a wide range of clinical phenotypes related to small airway involvement [5]. Small airways are those less than 2 mm in diameter, comprising the ducts between generation 8 and the alveoli. It has been postulated that finer aerosols than those delivered by most currently available inhalers may be needed to target these small airways more effectively and by that, to achieve a better drug distribution over the whole bronchial tree [6]. The origin of this idea may have been the findings in the literature when chlorofluorocarbon (CFC)-based pressurized metered dose inhalers (pMDIs) containing beclometasone dipropionate (BDP) were replaced by hydrofluoroalkane (HFA)-based pMDIs, as a response to environmental concerns about the ozone layer in the 1990s [7]. It was shown that with the HFA pMDI only half the BDP dose is needed compared with CFC pMDI for effective treatment of moderate asthma [8,9]. The effect was attributed to the much finer aerosol from the HFA pMDI of which the particles had a mass median aerodynamic diameter (MMAD) of 1.1 μm versus 3.5–4 μm for the CFC pMDI. More devices delivering finer aerosols have since become available, most of them being HFA solution pMDIs [10–12]. The only ICS/LABA combination delivered so far as a fine aerosol from a pMDI and now from a dry powder inhaler (DPI) is the BDP–formoterol combination in Foster (Fostair), from Chiesi Pharmaceuticals [6]. The reported benefit of so-called 'extrafine' aerosols from HFA pMDIs has resulted in the expectation that the same improvement can be obtained with the dry small particle aerosol from this new Foster (Fostair) NEXThaler DPI compared to other DPIs with the same drug combination [6]. Several comparative studies with these new devices have recently been reviewed and it was concluded that treating the peripheral airways with smaller drug particle aerosols achieves comparable, and in some studies superior, efficacy compared with larger particles [13,14]. A reduction in the daily ICS dose was also reported, in addition to greater asthma control and quality of life in some of the real-life studies.

☆ Foster/Fostair® NEXThaler®, Symbicort® Turbuhaler®, Seretide® Diskus®, and Rolenium® Elpenhaler® are registered trademarks of the manufacturer.

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http://dx.doi.org/10.1016/j.ejpb.2015.07.016
0939-6411/

However, many questions remain to be answered before these improvements can be attributed to improved peripheral and total lung deposition from finer aerosols compared to deposition of conventional medications with larger particle size. It all starts with the size definition for 'extrafines'. Different terms have been used to describe finer aerosols, such as ultrafine [10], extrafine [6] and, more recently, small particle aerosols [13,14]. In this introduction, only the term extrafines will be used until the presentation of the term 'submicron particles'. Originally, extrafine aerosols from newly developed HFA BDP formulations were characterized as having an average diameter of 1.1 μm and a respirable fraction of approximately 60% [15]. For the Foster NEXThaler, extrafine particles are described as having a MMAD of 1.4–1.5 μm [16], while the definition for extrafine aerosols in the scientific literature has recently been widened to particles with a diameter (D) < 2 μm [13,14]. These different definitions partly overlap each other and do not bring clarity about which aerosols are to be considered as extrafine. Polydisperse aerosols from nearly all MDIs and DPIs may contain substantial mass fractions of particles with D < 2 μm. In contrast, devices producing the so-called extrafine aerosols may also deliver significant mass fractions of particles with D > 2 μm. Therefore, aerosols from all currently available MDIs and DPIs comprise both extrafine and non-extrafine particles according to the most recent definition (D < 2 μm). The difference is in the relative amounts of each of these fractions within the aerosols. Hence, for polydisperse aerosols the term extrafine has to be defined not only in terms of size, but also in the quantified mass fraction of these extrafines in the aerosol. For this reason, the rather imprecise terms extrafines and small particle aerosols will be used no further in this manuscript as an aerosol characterization term. Instead, a distinction will be made between submicron (<1 μm) and micron range (>1 μm) particles of which the micron range particles are divided into size fractions 1–3 μm and 3–5 μm to provide more detailed information about the structure of the fine particle fraction. The limit of 1 μm has been chosen because submicron particles (D < 1 μm) in the particle concentration of therapeutic aerosols have a significantly lower probability of total lung and alveolar deposition than micron range particles [17–19].

The influence of other variables on lung deposition involved between the different devices used in comparative studies is also relevant. Lung distribution and deposition are not governed by particle size alone, but also by particle velocity and residence time in the lung [20]. The difference between the BDP CFC and BDP HFA formulations in the previously mentioned MDI studies [7–9] is not in the particle size alone, but more particularly in the velocity with which the aerosol is released from the mouthpiece. The lower velocity of the HFA aerosol plume leads to a considerable reduction in impact force against objects in the flow direction of the plume and thus, a reduction in oropharyngeal deposition [21]. For BDP from the HFA device (MMAD ≈ 1.1 μm) developed in the late 1990s, throat deposition was found to be much lower (30%) compared with the CFC device (94%; MMAD ≈ 3.5–4 μm) [7]. Consequently, a much higher dose fraction remained available for total lung deposition, the difference being (100–30)/(100–94) ≈ 11.5-fold. Due to these different factors, the expectation that a DPI delivering a finer aerosol (MMAD ≈ 1.5 μm for the fine particle fraction) at the same flow rate as competitor devices with only slightly coarser aerosols (MMAD ≈ 2.5–3 μm) can provide a more effective deep lung deposition may be false.

Inhalers used in various comparative studies to investigate the benefit of finer aerosols generally differ in more than particle size and velocity alone [13,14]. There may also be differences in delivered (fine particle) dose as percent of the label claim and many new inhaler types (both MDIs and DPIs) produce not only finer aerosols, but also higher fine particle doses [6,11]. In some recently reviewed studies [13,14] different types of inhalers (DPIs and MDIs) were compared with each other, and also different drugs in different strengths were involved and inhaled with different inhalation manoeuvres. In addition, many clinical studies were conducted without even recording the inspiratory flow manoeuvres and the duration of the breath hold pauses. Differences in resistance to air flow through an inhaler can lead to marked differences in flow rate at the same inspiratory effort [22]. With this variable as a major determinant for drug distribution and deposition in the respiratory tract, considerable differences in clinical effect may be expected, even if the aerosols from these devices are exactly the same *in vitro*. Several patient factors may also be involved, such as incorrect inhaler use [23], poor motivation or adherence to the therapy or to the study (for out-of-clinic studies), and severity of the disease, particularly when this affects pulmonary function and lung ventilation. As a consequence of this plurality of variables, it is virtually impossible to conclude which of them is most responsible for an improved clinical effect. Hence, clinical studies may be poor predictors for inhaler performance regarding aerosol generation and delivery. Therefore, a different approach seems necessary to investigate whether submicron particles can really contribute to improved therapeutic effects. The effects of inhaler and patient variables, including the inhalation manoeuvre, on aerosol generation, lung penetration, lung deposition and distribution and ultimately the clinical effect have to be considered separately, as well as in their interactions with each other. Judging an inhaler upon its potential to achieve a good clinical effect has to start with measuring the aerosol properties as a function of the flow rate and the emission pattern of the inhaler.

This manuscript has three aims: the first is to discuss whether submicron particles are likely to contribute to improved total and deep lung deposition. A second and equally important aim is to investigate which range of aerodynamic particle diameters is most favorable for total and deep lung deposition at the range of flow rates to be expected through a medium to high resistance DPI at moderate inspiratory effort (approx. 30–60 L/min). The third aim is to evaluate the delivered fine particle doses of four marketed ICS/LABA combination DPIs in relation to the outcome of both previous aims.

For the assessment, data from a previous deposition study in stable asthmatics were used and extrapolated towards particles in the submicron range and basic aerosol physics were used to check the validity of the extrapolations. Additionally, four DPIs, all delivering an ICS/LABA combination, were tested at three different pressure drops to measure their delivered fine particle doses (FPDs) and the structures of these FPDs as a function of the flow rate. FPFs < 1 μm were computed to obtain more detailed information about the presence and amount of submicron particles in the aerosol. Detailed information about differences in total delivered fine particle masses (FPFs < 5 μm) and the structures of the aerosols (FPFs < 1; 1–3 and 3–5 μm), as well as the flow rate at which the aerosols are delivered to the respiratory tract, is needed to decide whether differences in clinical effect are likely the result of any (or a combination) of these variables, or that of the involvement of yet unknown or overlooked parameters and mechanisms.

2. Materials and methods

2.1. Extrapolation of previously published deposition data

Usmani and co-workers measured lung deposition of radiolabelled monodisperse salbutamol particles (1.5, 3.0 and 6.0 μm) in patients with stable asthma at two different flow rates [24]. They discriminated between oropharyngeal, central plus

Please cite this article in press as: A.H. de Boer et al., Can 'extrafine' dry powder aerosols improve lung deposition?, Eur. J. Pharm. Biopharm. (2015), http://dx.doi.org/10.1016/j.ejpb.2015.07.016