European Journal of Pharmaceutics and Biopharmaceutics xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

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

Research paper

Towards the bioequivalence of pressurised metered dose inhalers 1: Design and characterisation of aerodynamically equivalent beclomethasone dipropionate inhalers with and without glycerol as a non-volatile excipient

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Aerosol Performance
pMDI
Beclomethasone dipropionate
Bioequivalence
Non-volatile excipients
Glycerol

ABSTRACT

A series of semi-empirical equations were utilised to design two solution based pressurised metered dose inhaler (pMDI) formulations, with equivalent aerosol performance but different physicochemical properties. Both inhaler formulations contained the drug, beclomethasone dipropionate (BDP), a volatile mixture of ethanol co-solvent and propellant (hydrofluoroalkane-HFA). However, one formulation was designed such that the emitted aerosol particles contained BDP and glycerol, a common inhalation particle modifying excipient, in a 1:1 mass ratio. By modifying the formulation parameters, including actuator orifice, HFA and metering volumes, it was possible to produce two formulations (glycerol-free and glycerol-containing) which had identical mass median aerodynamic diameters (2.4 μm ± 0.1 and 2.5 μm ± 0.2), fine particle dose (⩽5 μm; 66 μg ± 6 and 68 μg ± 2) and fine particle fractions (28% ± 2% and 30% ± 1%), respectively. These observations demonstrate that it is possible to engineer formulations that generate aerosol particles with very different compositions to have similar emitted dose and *in vitro* deposition profiles, thus making them equivalent in terms of aerosol performance. Analysis of the physicochemical properties of each formulation identified significant differences in terms of morphology, thermal properties and drug dissolution of emitted particles. The particles produced from both formulations were amorphous; however, the formulation containing glycerol generated particles with a porous structure, while the glycerol-free formulation generated particles with a primarily spherical morphology. Furthermore, the glycerol-containing particles had a significantly lower dissolution rate (7.8% ± 2.1%, over 180 min) compared to the glycerol-free particles (58.0% ± 2.9%, over 60 min) when measured using a Franz diffusion cell. It is hypothesised that the presence of glycerol in the emitted aerosol particles altered solubility and drug transport, which may have implications for BDP pharmacokinetics after deposition in the respiratory tract.

1. Introduction

Pressurised metered dose inhalers (pMDIs) contain a drug suspended or solubilised in a liquid propellant, with/without stabilising excipients. For solution-based pMDIs, a co-solvent (typically ethanol) is often required, to enhance the solubility in the propellant of the incorporated drug, thus ensuring a therapeutic dose is emitted when the metering valve is actuated. In order for the drug to penetrate the respiratory tract, it is generally agreed that aerosol particles require an aerodynamic diameter ⩽6 μm to avoid impaction in the upper respiratory tract [1]. Furthermore, it is evident that regional deposition throughout the lung will be dependent on the particle size distribution, with smaller particles (ca. <1 μm) being deposited in the alveoli and larger particles (ca. 2–5 μm) in the tracheo-bronchial regions [1]. Since lung physiology varies with respect to region, it stands to reason that the clinical

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http://dx.doi.org/10.1016/j.ejpb.2013.02.014

effectiveness of a particular product may be dependent on particle size.

Solution-based pMDIs generally produce particulate aerosol clouds with a smaller median aerodynamic diameter than suspension-based systems. This is mainly due to the final particle size being governed by the solution properties, rather than the size and physical stability of a suspended material as would be the case in suspension-based systems. During the reformulation of CFC to HFA-based pMDIs, the smaller aerodynamic diameter aerosols produced by the HFA-based systems required full clinical trials, since the active pharmaceutical ingredient (API) had higher peripheral lung deposition than the original CFC formulations [2]. To overcome these issues, non-volatile agents such as glycerol were incorporated into the solution to increase the median aerodynamic diameter of the aerosol to enable product matching in terms of aerosol cloud particle size distribution [3,4].

During the past decade, a series of fundamental mechanistic studies on solution-based pMDIs have been undertaken. These include investigating factors such as vapour pressure [5–7], actuator and orifice design [8,9], co-solvent [10] and non-volatile excipients [3,11] as well as studies of plume geometry [12] and aerosol droplet formation [13]. From these studies, theoretical models have been developed to describe the relationship between the physical properties of the propellant solution, the geometry of the actuator device and the ultimate aerosol size distribution. By utilising this knowledge, it should be possible to engineer a formulation that produces a well-defined aerosol cloud particle size distribution.

Non-volatile agents can be included in a formulation to increase the size of the inhaled particles. Interestingly, however, little work has been undertaken to investigate the physicochemical properties of particles produced from solution pMDIs, and how the incorporation of excipients, such as glycerol, into these particles may alter drug uptake in the lung after deposition. A recent study by Grainger et al. [14] investigated the physicochemical properties, dissolution, and absorptive transepithelial flux *in vitro* of two solution-based pMDIs: Qvar® and Sanasthmax®. While both pMDIs contained ethanol, Sanasthmax also contained glycerol. Grainger et al. reported that the Sanasthmax particles were larger, less porous and possessed a greater degree of amorphicity. Importantly, they demonstrated that Sanasthmax particles had both a slower dissolution rate and slower absorptive flux following deposition on a respiratory epithelial cell drug absorption model. While these reported observations were interesting, it was difficult to isolate the reason for the differences in uptake, since there were multiple variables in the particle characteristics (i.e. uptake could be influenced by size, difference in porosity or the presence of glycerol). This programme of research was undertaken to develop glycerol-free and glycerol-containing solution-based pMDI formulations that generate identical aerodynamic size distributions and enable the influence of the non-volatile excipient on the physicochemical properties of the maturated particles to be studied and in the absence of conflicting variables related to particle size, be linked to biopharmaceutical outcomes in the lungs. This paper describes the theoretical process and limitations of creating such a system, investigates the robustness of the pMDIs and studies the physical and chemical properties of the particles and aerosol performance characteristics.

1.1. Theoretical pMDI design considerations

It has been shown that aerosol particle size can be modulated by propellant choice and pertinent selection of non-volatile excipient addition, while the respirable dose can be controlled by judicious selection of volatile excipient addition, actuator orifice diameter and metering volume [3,15,16]. The mass median aerodynamic diameter (MMAD) of an aerosol cloud generated from an ethanol-based solution HFA-134a formulation, containing non-volatile components can be predicted from the following equation:

$$\mathrm{MMAD}_{134} = 2.31\mathrm{n}^{1/3} \quad (1)$$

where n is the total non-volatile formulation content (% w/w) [17]. Similarly, the MMAD of an aerosol cloud generated from an ethanol-based solution HFA-227 formulation can be predicted from the following equation [15,16]:

$$\mathrm{MMAD}_{227} = 3.26n^{1/3} \quad (2)$$

It is important to note that the non-volatile component includes not only the performance modifying excipient but also the drug. In addition to the propellant properties, the ability to produce a respirable dose is dependent upon other aspects of the pMDI's formulation (such as ethanol content), valve and actuator characteristics [8,17,18]. Eq. (3) provides a semi-empirical relationship between respirable ex-valve fine particle fraction reported for ethanol-based HFA 134a solution pMDIs [17] with an actuator orifice diameter (a [mm]), metered dose volume (v [μl]) and HFA 134a content (C [% w/w]).

$$\mathrm{FPF} = 2.1 \times 10^{-5} \times a^{-1.5} \times v^{-0.25} \times C^3 \quad (3)$$

This theoretical approach provides the ability to pre-determine particle size characteristics based on initial formulation properties. Thus, by varying HFA, ethanol concentration and actuator orifice, it becomes possible to prepare two formulations that produce a final particle mass that contains either drug alone or drug and glycerol at a ratio of 1:1 and possesses similar aerodynamic aerosol properties. Current approved approaches to assess bioequivalency of oral inhaled products include the following: unit dose sampling, cascade impaction, spray pattern and plume geometry [19]. pMDI containing these formulations were prepared and evaluated in terms of stability, aerosol performance and physicochemical properties of the aerosol particles.

2. Materials and methods

2.1. Materials

Actuators (630 series with either 0.30 mm or 0.33 mm atomisation orifices) and pMDI valves (with either 50 μl or 63 μl fill chambers) were provided by Bespak Ltd. (Norfolk, UK). pMDI canisters (C128) were provided by Presspart Ltd. (Lancashire, UK). The drug, beclomethasone dipropionate, was supplied by Teva Pharmaceuticals (Harlow, UK). Ethanol (⩾99.5%) was supplied by Sigma Aldrich (Gillingham, UK). Glycerol (⩾99%) was provided by Sigma Aldrich (Gillingham, UK). HFA134a (1,1,1,2-tetrafluoroethane) and HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) were supplied by Mexichem Fluor (Runcorn, UK). Water was purified by reverse osmosis (MilliQ, Millipore, Watford, UK), and all other solvents were of analytical grade Sigma Aldrich (Gillingham, UK). All experiments were conducted in air-conditioned laboratories at 21 ± 3 °C and 40–60% RH.

2.2. Quantification of BDP

Beclomethasone dipropionate samples collected from dose uniformity and cascade impactor studies were quantified using a Waters Acquity UPLC with SQD system (Waters Ltd., Elstree, UK). Briefly, BDP was detected using mass spectrometry (SQD) using 2 mM ammonium formate solution (0.1% formic acid) in methanol and water mobile phases. A solution of 85/15% v/v methanol/water was used as the solution for collection of samples. Acquity UPLC BEH C18 1.7 μm, 2.1 × 50 mm column (Waters, Elstree, UK) was

Please cite this article in press as: D.A. Lewis et al., Towards the bioequivalence of pressurised metered dose inhalers 1: Design and characterisation of aerodynamically equivalent beclomethasone dipropionate inhalers with and without glycerol as a non-volatile excipient, Eur. J. Pharm. Biopharm. (2013), http://dx.doi.org/10.1016/j.ejpb.2013.02.014