International Journal of Pharmaceutics 492 (2015) 258–263

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Investigation on the aerosol performance of dry powder inhalation hypromellose capsules with different lubricant levels

I.Y. Saleem[a,*], F. Diez[b], B.E. Jones[b], N. Kayali[c], L. Polo[c]

[a] School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, Byrom Street, Liverpool L3 3AF, UK
[b] Qualicaps Europe, S.A.U., Calle de la Granja 49, 28 108, Alcobendas, Madrid, Spain
[c] Mass Spectrometry Centre, Faculty of Chemistry, Complutense University of Madrid, Madrid, Spain

ARTICLE INFO

Article history:
Received 21 May 2015
Received in revised form 9 July 2015
Accepted 11 July 2015
Available online 18 July 2015

Keywords:
Hypromellose (HPMC) capsules
Dry powder inhalation
Lubricant
Inhaler
Atomic force microscopy (AFM)

ABSTRACT

HPMC capsules are made by a dipping process and a surface lubricant for the mould pins is an essential processing aid for removing dried capsules shells. For the purpose of this study, the level was determined by quantifying methyloleate (MO) a component found in the lubricant but not in the hypromellose capsules. Here we investigated the influence of the lubricant, low (10.81 μg/capsule = 60 mg/kg MO), medium (15.97 μg/capsule = 90 mg/kg MO) and high (23.23 μg/capsule = 127 mg/kg MO) content on powder (binary mixture of salbutamol: lactose, 1:50 w/w) aerosolization properties was investigated. Results indicated significantly lower emitted dose from capsules with 60 mg/kg MO. Furthermore, the 90 and 127 mg/kg MO level of lubricant capsules produced almost double the Fine Particle Dose & Fine Particle Fraction compared with the low level of lubricant. The data indicates that lubricant level within capsules has an influence on deposition profiles and amount of drug remaining in capsule and inhaler device after actuation. It is suggested lubricant levels greater than 60 mg/kg MO per capsule are required to minimise powder retention within capsules and maximise deposition profiles. AFM (atomic force microscopy) data suggest that internal surface roughness may be related with this phenomena.

1. Introduction

Delivery of therapeutic agents *via* the pulmonary route has gained increasing applications for lung diseases such as asthma and COPD. Pulmonary delivery has many advantages including delivery of medication directly to site of action, bypassing first pass metabolism in the liver (Geller, 2009; Labiris and Dolovich, 2003), it is non-invasive and can achieve therapeutic outcome at lower doses than administration *via* the oral route (Smith and Parry-Billings, 2003).

Dry powder inhaler (DPI) are able to deliver low and high doses within the range of 5–500 μg, do not require co-ordination between actuation and inspiration as with pMDI (Kaialy et al., 2012). They have been developed since the 1960's for a range of conditions such as asthma and COPD using short and long acting beta agonists, anti-cholinergic agents and corticosteroids drugs in order to facilitate drug administration to the lungs *via* the inhalation route (Atkins, 2005). Today there are currently more than twenty commercially available DPI, both active and passive (Chan et al., 2014). New active DPI incorporate additional mechanisms within the device to aid the fluidization of the powder from the device and reduce the reliance on the patient's inspiratory force. These mechanisms include vibration mesh which oscillates upon the patient's inhalation, others include release of the powder formulation only when the patient has achieved the correct inspiratory force (Chan et al., 2014). Passive DPI have unit doses of drug in either blister packs or capsules, which contain the drug and a carrier, *e.g.* lactose, and drug deposition relies on the patient's inspiratory force to de-aggregate the drug from the carrier (Chan et al., 2014; Kaialy et al., 2012; Zhou and Morton, 2012).

The powder mass in the capsules allows flexibility for the administration of low and high dose drugs within the range of 5 to 500 μg. Examples of capsule based devices include the single unit HandiHaler® (Boehringer-Ingelheim) (Islam and Gladki, 2008), TOBI® Podhaler™ (tobramycin) and Colobreathe® Turbospin® for delivery of large doses (Claus et al., 2014), Breezhaler® (Novartis), (Young et al., 2014) and novel multiple pre-metered unit-dose Flowcaps® (Hovione) that contains up to 20 capsules (Friebel and Steckel, 2010). These devices are simple to use, cost-effective and can administer low and high doses. In addition, the capsule based devices improve patient compliance, as they can provide feedback to the patient in the form of a rattling sound, indicating correct

* Corresponding author. Fax: +44 0 151 231 2170
E-mail address: i.saleem@ljmu.ac.uk (I.Y. Saleem).

http://dx.doi.org/10.1016/j.ijpharm.2015.07.034

inhalation flow rate was achieved and passed through the device to deliver the correct dose (Behara et al., 2014; Smith et al., 2010). Moreover, the patient can visually check the capsule to determine if the dose has been administered (Smith et al., 2010).

Hypromellose (HPMC) is used to make inhalation grade capsules (Quali-V®-I) for use in DPI, as it is unaffected by moisture content changes (Jones, 2008). Hence, it does not become brittle as it loses moisture, a common phenomenon with gelatin capsules as patients do not store them as directed resulting in broken capsules and poor performance in their DPI (Nagata, 2002; Ogura et al., 1998; Renswouw et al., 2010). In addition, it has also been shown that HPMC capsules are less influenced by tribo-electrification which is common with gelatin capsules (Nakate et al., 2005). Inhalation grade HPMC capsules are made from different grades of raw material chosen for their puncturing properties (Torrisi et al., 2013) and as a result have a slightly higher moisture content; 4.5–6.5% compared to 4.0–6.0% in oral pharmaceutical grade capsules. The HPMC Capsules are manufactured by dipping stainless steel mould pins at room temperature into a warm solution of hypromellose containing carrageenan as a network former and potassium chloride as a network promoter (Jones, 2004). The change in temperature causes the HPMC solution to gel and form a film on the surface of the mould pins. The films are dried by passing groups of pins through a series of drying kilns in which large volumes of air at controlled temperature and humidity is blown over them. As the films dry they shrink on to the pins. To remove them without damage it is essential for the mould pins to be coated with a surface lubricant to act as a release aid. Capsules cannot be manufactured without this lubricant (Jones, 2008). However, a search of the literature only shows one study investigating the influence of the amount of mould lubricant on the internal surfaces of capsules in relation to the aerosolization properties of powders from a capsule based DPI (Saim and Horhota, 2002). Furthermore, this study relates to gelatin capsules and not HPMC.

The lubricant is a mixture of food and pharmaceutical grade materials registered with regulatory authorities and the composition is proprietary for each capsule manufacturer. Hence for quantitative analysis it is necessary to choose a component of the lubricant which is not found in the HPMC capsules. In this study we chose methyloleate (MO) as a marker for lubricant content consisting of free fatty acids together with their esters. A number of sample preparation methods have been proposed in the literature to convert free fatty acids into their esters, such as silylation (Woo and Kim, 1999) or reaction with alkyl chloroformates (Gimeno-Adelantado et al., 2001) as well as for transesterification of the triglycerides (Mason and Waller, 1964).

The aim of this study was to investigate the aerosolization properties of dry powder formulations composed of inhalation grade lactose and micronized salbutamol, filled in to size 3HPMC inhalation grade capsules manufactured with 3 different lubricant levels *via* an 8-pin inhaler device. Size 3HPMC capsules was chosen because this is the size used in the pharmaceutical industry for development of capsule-based DPI. For example the last significant developments in inhalation capsule-based devices, Ultibro and Seebri Breezhaler, incorporate their respective dry powder formulation into a size 3 capsule. This size capsule (0.8 mg/mL) has a powder fill weight of 225 mg. Furthermore, to the best of our knowledge, the capsule inner surface lubricant content has not been determined by GCMS or its distribution in HPMC capsules by AFM. Hence, we describe a new technique with results obtained using these methods in this study.

2. Material and methods

2.1. Materials

8-pin monodose inhaler was provided by Plastiape S.p.a Italy. Hypromellose (HPMC) inhalation grade capsules, size 3 (Quali-V®-I) for this inhaler, manufactured using three different lubricant levels (satisfactory physical quality capsules were made at each level); low (10.81 μg/20 mg of blended powder within capsule = 60 mg/kg MO), medium (15.97 μg/20 mg of blended powder within capsule = 90 mg/kg MO) and high (23.23 μg/20 mg of blended powder within capsule = 127 mg/kg MO) were obtained from Qualicaps® Europe, S.A.U, Spain. Inhalation grade lactose (Respitose) was supplied by DFE Pharma, The Netherlands. Micronized salbutamol was obtained from Lusochimica, Spain. Methanol and 1-heptane sulphonic acid sodium salt were purchased from Sigma, UK. Methyloleate analytical standard, hexane and chloroform were from Sigma–Aldrich (St. Louis USA). 1,2,3 Trichlorobenzene was purchased from Fluka and was used as internal standard. Trimethylsulfonium hydroxide solution, (TMSH), 0.25 M in methanol was used for GC derivatization.

2.2. Determination of methyl oleate (MO) in capsules by gas chromatography mass spectrometry

Gas chromatography mass spectrometry, GCMS, is the technique most suitable for its qualitative and quantitative determination after derivatization and extraction into an organic solvent (Driscoll et al., 2009; Sutherland, 2007; Zhanga et al., 2014). Capsules inner lubricant content was evaluated by determining MO which was taken as a marker of the lubricant content using GCMS. Eleven HPMC capsules were weighted in a glass vial and 5 mL of Hexane: chloroform, 60:40 (v:v) extraction solvent containing 10 mg/L of the internal standard was added. The vial was sonicated for 1 h in an ultrasonic bath; then 100 μL of the extract was transferred into a 2 mL vial for derivatization using 50 μL of TMSH. The MO was identified by MS (Mass spectrometry) and was quantified using an internal calibration method with six points in the 0.5–20 mg/kg concentration range. 1 μL of the derivatized MO was injected in split less mode in the GCMS instrument.

2.3. Preparation of inhalation grade lactose & powder mix

Inhalation grade lactose and powder mix were prepared according to previously published method (Saleem et al., 2008) with slight modifications. Inhalation grade lactose was fractionated by sieving with a sieve stack (250, 125, 90, 63, and 45 μm) using vibration amplitude of 40 for 10 min and collected on a 90 μm sieve to be used in all subsequent studies. Micronized salbutamol sulphate and lactose were mixed in a ratio of 1:50 (w/w) *via* geometric dilution to obtain a 2% binary blend. The formulations were blended with a Turbula® orbital mixer (Glen Mills, Clifton, New Jersey) for 30 min at 46 rpm. The blend uniformity was determined by randomly selecting five 20 mg samples, and formulations were considered uniform when the coefficient of variation (% CV) was ≤6%. Samples were analyzed using high-performance liquid chromatography (HPLC) method below (Section 2.4). Once blend uniformity was achieved 20 ± 1 mg of blended powder was manually loaded into HPMC capsules (size 3) with different lubricant levels (low, medium and high) and stored in a humidity chamber (Sanyo Atmos Chamber) at 22 °C and 40% RH for 2 weeks (Nine HPMC capsules were filled for each lubricant level at weeks 1 and 2).