The Impact of Flow rate on Inhaler Dose Delivery from a Dry Powder Inhaler using a Two Stage Impinger

Huner K. Omer
Department of Pharmaceutics, College of Pharmacy, Hawler Medical University, Erbil, Kurdistan Region, Iraq.

ARTICLE INFO

Article History:
Received: 08/01/2018
Accepted: 09/07/2018
Published: 04/09/2018

Keywords:
Transferosomes
Two stage impinger
Dry powder inhaler
Respiratory flow rates
Carbohydrate carriers.

*Corresponding Author:
hkomer@pha.hmu.edu.iq

ABSTRACT

The purpose of this study is to investigate the effect of various flow rates and morphology of spray-dried transferosomes depending on the amount of drug delivered in “respirable” fractions from a monodose dry powder inhaler (DPI). A two-stage impinger (TSI) was used to investigate the deposition of salbutamol sulphate (SS) as a model drug incorporated within four different carrier-based transferosomes (sorbitol, inulin, trehalose and maltodextrin). The amount of drug was collected from each stage of the TSI, as well as the device and capsule at three different flow rates: 30, 60 and 90 L/min, and subsequently quantified by high performance liquid chromatography (HPLC). Results from this study showed that the 30L/min flow rate was not as effective as 60L/min or 90L/min at delivering drug to the lower stage of the TSI. However, 90L/min flow rate had a higher drug deposition in the lower impinger when compared to 60L/min. Sorbitol was found to be the least effective carrier at delivering drug to the lower chamber of the TSI, followed by maltodextrin, whereas trehalose and inulin were more spherical and smaller in size and were found to be the most effective carrier systems in the spray-dried formulations. In conclusion, trehalose and inulin-based transferosomes were the most effective delivery system for depositing the drug into the lower part of two stage impinger.

1. INTRODUCTION

The respiratory system can be exploited as a route for non-invasive and patient-friendly drug delivery (Shakshuki and Agu, 2017). Pulmonary drug delivery has gained much importance in recent decades due to the ability of targeting the drug directly to the lung tissues both for local and systemic effects (d’Angelo et al., 2015; Newman, 2017; Kaur, 2017).

Air flow rate is a patient variable which is considered to be important because it can affect the amount of drug delivered from the device to the peripheral airways (Buttini et al., 2015). Inter-individual variation occurs between healthy people, and further variation in air flow rate occurs in people with compromised lung function (Muralidharan et al., 2015; Chen et al., 2016). Two of the very common diseases of the lung are asthma and chronic obstruction...
pulmonary disease (COPD). Both of these are inflammatory; asthma is characterised by narrowing of the airways and COPD by the destruction of the alveolar walls (Nakawah et al., 2013). There are many drugs used in these conditions, for example, salbutamol sulphate which is a selective β2-adrenergic receptor agonist which relieves asthma by dilating the bronchioles. These drugs are administered by inhalation using metered dose inhalers, dry powder inhalers or nebulisers (Elhissi et al., 2007). Dry powder inhalers are a breath controlled drug delivery systems in which the patient’s own flow rate is required to achieve sufficient release of the drug from DPI devices and subsequent diffusion of the drug into the lungs, thus the inspiratory flow rate of the patient has a significant influence on delivery of drugs prepared as DPI formulations (Yokoyama et al., 2007). Pulmonary drug delivery is advantageous as local targeting allows minute drug dosing because drug metabolism in the lung is lower than the gastrointestinal tract and the liver with less systemic side effects (Paranjpe and Müller-Goymann, 2014). However, there are also disadvantages of pulmonary delivery; the duration of action of the inhaled drug is often short-lived because of the mucociliary clearance and metabolism by the enzymes and this necessitate frequent dosing (Shah et al., 2012).

There are three main mechanisms of particle deposition in the airway, inertial impaction, sedimentation and Brownian diffusion. Inertial impaction occurs in the upper airway which is caused by the velocity and the mass of the particle. Sedimentation occurs in the peripheral airway and Brownian diffusion is relevant to particles < 1 μm (Heyder, 2004; Tsuda et al., 2013).

In this study, the drug was incorporated within transferosomal dispersions containing high carbohydrate concentrations, followed by spray drying to yield flowable transferosomal powders. Sorbitol, inulin, trehalose or maltodextrin was used as the stabilizing carriers in the process of spray drying. The delivery performance and characteristics of the delivered formulations were studied and the influence of type of carrier and flow rate through the two stages impinger was evaluated.

Spray drying is a process which provides control over particle size and morphology; reduce powder density (Yang et al., 2015; Omer et al., 2018). Moreover, agglomerated particles generated via spray drying may have high flowability (Augsburger and Hoag, 2008). These characteristics using spray dried powders can promote the ability of inhaled particles to reach the lower respiratory airways, bearing in mind that particles should have a size less than 5μm to be regarded “respirable” or in “fine particle fraction” (Rojanarat et al., 2012). Other factors that may influence the respirability of powdered formulations include the specific features and design of inhaler device (Ibrahim et al., 2015; Berkenfeld et al., 2015).

It is important to remember that even healthy individuals have different inhalation profiles, leading to different deposition patterns in the respiratory tract. Diseases such as asthma and COPD are additional contributors to different patterns of deposition following drug inhalation. In a study of inhalation flow measured through a variety of DPI devices, it was found that patients with COPD generate an air flow rate between 32 and 98 L/min and patients with asthma generate an air flow rate of 45 to 110 L/min (Chrystyn and Price, 2009). When patients are given inhalation therapy for their condition, they are all given the same dose regardless of their inspiratory flow rate. It was reported that 28 of 233 patients who inhaled corticosteroids for asthma could not
achieve the optimal flow rate of 60 L/min, of whom 5 were treated for exacerbation of symptoms (Barnes et al., 1998). Thus, it is very important to clarify the relationship between inspiratory flow rate and amount of drug delivered into the lungs when using a DPI. Hence the aim of this study was to investigate the impact of flow rate on the respirable dose, and the effect of higher flow rates on oropharyngeal impaction and also to compare the effect of different carriers (sorbitol, inulin, trehalose and maltodextrin) based transferosomes.

2. MATERIALS AND METHODS

2.1. Materials

Sorbitol, trehalose, and methanol (HPLC grade 99.9%) were purchased from Sigma-Aldrich, UK. Water (HPLC grade) and absolute ethanol were purchased from Fisher scientific, UK. Inulin and maltodextrin were purchased from VWR, UK. Salbutamol sulphate (99%), sodium 1-hexane sulfonates monohydrate (99%) and glacial acetic acid (99%) was all supplied by Alfa-Aesar, UK. Soya phosphatidylcholine (SPC, Lipoid S-100) was a gift from Lipoid, Switzerland.

2.2. Methods

2.2.1 Preparation of spray-dried transfersomes

The transfersomes were formulated by thin film hydration method (Ghanbarzadeh and Arami, 2013; Ali et al., 2015; Hassanpour Aghdam et al., 2016). Briefly, desired amounts of SPC (100 mg), Salbutamol sulphate (5 mg) and span 80 (15 mg) were dissolved in 20 ml of ethanol. The container tightly closed, protected from light and maintained at room temperature make sure of formation of complete and homogeneous solution. The mixture was transformed to a round-bottomed flask for solvent removal using a rotary evaporator (Heidolph, Germany) at reduced pressure at 40 ºC for two hours to remove traces of solvent. The dried film was hydrated with deionised water including the carbohydrate carriers (sorbitol, inulin, trehalose or maltodextrin) in 1:5 w/w lipids to carrier ratio. Transfersomes were spray-dried using the Buchi mini spray dryer B-290 (Buchi, Switzerland). The inlet temperature was set up at 130ºC and atomizer pressure was 800 KPa, the feed rate was adjusted to 13%, and the outlet temperature was 76 ± 1ºC. The transfersome powder was transferred from the collecting chamber into a desiccator until used.

2.2.2 Scanning electron microscopy (SEM)

Surface morphology of the transfersome particles was examined by SEM. A sample was sprinkled onto an aluminum stub and coated with gold by a sputtering technique using a JFC-1200 Fine Coater (JEOL, Tokyo, Japan) for 120 s. The particles were observed under SEM (Quanta-200, FEI) at 20 kV.

2.2.3 HPLC analysis

A buffer comprising sodium hexane sulfonate (5mM) in water was mixed with methanol (75:25 v/v) to prepare the mobile phase to which glacial acetic acid was added to constitute 1% of the total volume. The HPLC instrument (Agilent 1200 with UV detector; Hewlett-Packard Co., USA) was set up with a symmetry C18 column (150 mm_4.6 mm, 5 m; Waters Ltd, UK) and samples were analysed at 276 nm. The mobile phase flow rate was adjusted to 1mL/min at 40 oC, and the volume of automatically injected sample set to 20 µL
(Elhissi et al., 2006). A calibration curve of ascending drug concentrations was constructed.

2.2.4 In vitro powder aerosolisation

Powder aerosolisation performance and particle deposition profile were determined in vitro using a TSI (figure 1) (Copley Scientific Limited, Nottingham, UK; British Pharmacopoeia, 2000) with the Miat Monodose inhaler device (Miat S.p.A., Milan, Italy) as the aerosol dispersion device. The flow rate was adjusted to 30, 60 or 90 L/min using the critical flow controller (TPK 2000) and a flow meter (DFM 2000) (Copley Scientific Limited, Nottingham, UK). Spray dried formulation (25 mg) was weighed and transferred into size 3 HPMC (Hydroxypropyl methylcellulose) capsules (Qualicaps Europe, Madrid, Spain), which were individually installed in the inhaler device. The inhaler was attached to the “mouth” of the TSI following its assembly using deionised water as collection medium (7 and 30 ml in upper and lower stages respectively). Each capsule was actuated from the inhaler over 5 s for each measurement. The amount of powder deposited in the different stages of the impinger was determined using HPLC (section 2.2.3).

3. Statistical analysis

All experiments were performed in triplicates and values were expressed as mean ± standard deviations. Statistical significance was assessed using one way analysis of variance (ANOVA) and student t-tests, as appropriate. Values with P < 0.05 indicate that the difference is statistically significant.

4. RESULTS AND DISCUSSION

The morphologies of spray-dried transferosome particles were primarily dependent on the type of carrier and the differences in morphologies were clearly evident (figure 2). SEM shows that inulin and trehalose-based transferosomes (figure 2b,c) were small spherical particles with low tendency for aggregation. While, sorbitol-based transferosomes (figure 2a) showed particles of various size with irregular shape particles and greater tendency for aggregation compared to inulin and trehalose based transferosomes. Furthermore, the discrete particles were smaller, spherical and smooth when maltodextrin was used as carrier, the spray-dried particles formed massive agglomerates, owing to the hygroscopic nature of maltodextrin as reported by previous studies (Loret et al., 2004; Sansone et al., 2011; Akhilesh et al., 2012).

Figure (1): Schematic representation of a two stage impinger (Hallworth et al., 1987)
Figure (2): SEM images of spray-dried transfersomes, (a) Sorbitol-based transfersomes (b) Inulin-based transfersomes (c) Trehalose-based transfersomes (d) Maltodextrin-based transfersomes.

Figure 3, 4 and 5 shows the effect of flow rate on the amount of drug delivered to both upper and lower compartments of the TSI, as well as that left within the device and capsule. The results demonstrated that with increased flow rate, there were fewer drugs left in the device and capsule and more drugs delivered to the lower chamber of the TSI. These results agree with Borgström et al., 1994 and Cheng, 2014, they studied that inspiratory flow rate has an important effect on the drug deposition at various stages of impinger. When looking at each individual transfersome formulation and the percentage of drug delivered to the lower chamber of TSI. At 30 L/min maltodextrin and sorbitol-based transfersomes (figure 3) had the greatest percentage of drug deposition when compared to inulin and trehalose-based transfersomes. This difference could be attributed to the surface morphology of different transfersomes (Figure 1). Sorbitol-based transfersomes (figure 3) were shown to have the least amount of drug left in the device (p=0.0002) and capsule (p<0.0001), therefore
more of the drug was delivered to the TSI. The transferosomes which show the highest percentage of drug left in the capsule and device were inulin-based transferosomes (45.21±12.64%) and trehalose-based transferosomes (62.9±11.26), which may not be as beneficial to the patient in practice as they could result in a sub-therapeutic dose being delivered (Jones et al., 2014).

Results at 30 L/min showed that maltodextrin-based transferosomes were the most effective transferosome formulation to use for inhalation delivery of salbutamol sulphate because this formulation achieved the highest drug delivery to the lower chamber of the TSI (p<0.0001). The reason for this could be that the low flow rate resulted in a reduced velocity of the spray, with no enough force to overcome the cohesive forces between the sticky particles of inulin and trehalose-based transferosomes (Cheng, 2014). Therefore, most of the particles remained in the device and capsule and even after delivery deposited in the upper chamber of the TSI because the agglomerated particles were not small enough to reach the lower chamber of the TSI. Inhaled particles must have a diameter of 1.0–6.0 µm (Timsina et al., 1994; Saini et al., 2007), under 7 µm (Newman et al., 1994) or 0.5–8.0 µm (Davies et al., 1976) to be defined as ‘respirable particles’ and to be deposited on the bronchi or alveoli. Particles larger than ‘respirable sizes’ are generally deposited within the upper respiratory tract by inertial impaction and then expelled from the respiratory system (Martins et al., 2015). Maltodextrin-based transferosome particles were irregular in shape, as shown by SEM (figure 2c), and seemed less sticky on handling compared to inulin and trehalose-based transferosomes. They may not require the generated spray velocity to be as high as with the other formulations in order to overcome the cohesive forces between particles and deliver the drug to the lower chamber of the TSI.

At flow rate 60 L/min (figure 4), there was a noticeable decrease in the amount of drug left in the device (p=0.23) and capsule (p=0.0007) for all four transferosome formulations, compared to flow rate 30L/min. Therefore, there was an increase in the amount of drug delivered to the lower chambers of the TSI (p<0.0001). Borgström et al., 1994 have studied the lung deposition of budesonide and terbutaline sulphate at different inspiratory flow rates. They found that decreasing the inspiratory flow rate resulted in reducing the amount of drugs deposition in the lungs. When looking at different transferosome formulations (figure 4), sorbitol-based transferosomes were the least effective transferosomes to deliver drug to the lower chamber of the TSI, as drug delivery was 14.2±1.8% (p<0.0001). This was
low compared to inulin and trehalose-based transferosomes, which had more than a two-fold increase in the percentage of drug delivered to the lower chamber of the TSI (44.95±1.95 and 45.51±2.84%, respectively) (p<0.0001). Maltodextrin-based transferosomes achieved a higher drug delivery to the lower chamber of the TSI (31.53±0.25%) compared to sorbitol formulation (p<0.0001). They were less effective, however, compared to inulin and trehalose-based transferosomes (p<0.0001). The reason for this could be due to the velocity of the spray generated at 60L/min, which was sufficient to overcome the cohesive forces between small (<5 µm), spherical particles of inulin and trehalose-based transferosomes. These formulations have good flow properties at flow rate 60 L/min and can be delivered into the lower chamber of TSI. While sorbitol and maltodextrin-based transferosomes were not sticky as inulin and trehalose-based transferosomes but their particles seemed bigger once agglomerated, which meant that most of the particles were delivered from the device but did not reach the lower chamber of the TSI, and mostly deposited in the upper compartment of the TSI instead. Figure 4 shows that 60 L/min was the flow rate least likely to deliver drug to the upper chamber of the TSI, particularly with inulin and trehalose-based transferosomes, when compared to flow rate 30 and 90 L/min, which can be desirable. Maltodextrin-based transferosomes were shown to be less effective than inulin and trehalose formulations (p<0.0001) but more effective than sorbitol-based transferosomes (p=0.0043). The reason for this could be that at 30 L/min there was not enough velocity to force the drug particles to the lower chamber of the TSI.

![Figure (4): The percentage of drug deposition with four different carriers (Sorbitol, inulin, trehalose and maltodextrin) at flow rate of 60L/min.](image)

At flow rate 90 L/min (figure 5), inulin and trehalose-based transferosomes clearly showed a higher percentage deposition of drug in the lower chamber of the TSI (57±2.89% and 55.42±4.31%, respectively) when compared to sorbitol and maltodextrin-based transferosomes (21.22±0.64 and 38.69±4.80, respectively) (p<0.0001). At flow rate 90 L/min, there was a significant decrease in the amount of drug left in the device (p<0.0044) and capsule (p<0.0001) when compared to flow rate 30 and 60 L/min for all formulations. Therefore, there was an increase in the amount of drug delivered to the lower chambers of the TSI, compared to flow rate 30 and 60 L/min (p<0.0001). This is probably because the high flow rate has helped with disaggregating the particles or overcome the cohesive forces between particles, resulting in allowed the maximum amount of drug to be delivered from the device (Prime et al., 1997).
L/min the velocity was too high, leading to inertial impaction on the oropharynx, therefore a reduced velocity is preferred to prevent the deposition of particles on the oropharynx by inertial impaction (Chrystyn, 2003; Tsuda et al., 2013).

Figure 5: The percentage of drug deposition with four different carriers (Sorbitol, inulin, trehalose and maltodextrin) at flow rate of 90L/min.

5. CONCLUSIONS

This study investigated that 90L/min was the best flow rate compared to 30 and 60L/min at delivering drug to the lower chamber of the TSI. Flow rate 60L/min had an only slightly lower amount of drug in the lower chamber of the TSI, particularly with inulin and trehalose-based transferosomes. Results indicate that sorbitol formulations were the least effective transferosomes followed by maltodextrin, as they failed to deliver an adequate dose of drug to the lower chamber of the TSI, at flow rate 60 and 90L/min. These two formulations delivered a higher amount of SS to the lower chamber of the TSI at flow rate 30L/min, compared to inulin and trehalose-based formulations. This study proved that the inspiratory flow rates and the type of carbohydrate carrier have a significant role on the amount of drug delivering to the different positions of two-stage impinger.

6. ACKNOWLEDGMENTS

I would like to thank the university of central Lancashire, school of pharmacy for providing laboratory facilities and MIAT (Milano, Italy) for the gift of monodose dry powder inhaler.

REFERENCES


