

EFFECT OF COATING MATERIAL ON THE AERODYNAMIC PARTICLE SIZE DISTRIBUTION (PSD) OF OXIS TURBOHALER[®] USING MIXING INLET WITH AN ANDERSEN CASCADE IMPACTOR (ACI)

Mohammad Yousuf Khan^{1, 2*}, Maria Qureshi³, Taha Nazir^{2, 4}, Nisar-ur-Rahman⁵, M Khan⁶

1. Division of Pharmacy & Pharmaceutical Science, School of Applied Sciences, University of Huddersfield, Huddersfield, HD1 3DH, UK
2. Faculty of Pharmacy, University of Sargodha, Sargodha 40100 Pakistan
3. Department of Special Education, University of The Punjab, Lahore, Pakistan
4. Intellectual Consortium of Drug Discovery & Technology Development, Saskatoon SK Canada
5. Faculty of Pharmacy & Alternative Medicines, Islamia University of Bahawalpur, Pakistan
6. School of Pharmacy, University of Alberta, Alberta, Edmonton, Canada

ABSTRACT

The aim of the present study was to explore the potential effect of the coating material on the aerodynamic particle size distribution (APSD) of formoterol from Oxis Turbohaler[®] using mixing inlet with Andersen Cascade Impactor (ACI) operated at flow rate of 60 Lmin⁻¹. As the aerodynamic properties of the emitted dose from a dry powder inhaler (DPI) are usually flows dependent but have not been calibrated for low flow rates at yet. We have used novel methodology to measure these at even low flow of 28.3 Lmin⁻¹. The Andersen Cascade Impactor (ACI) designed for 60 Lmin⁻¹ was adapted to include a mixing inlet (MIXINLET) which allows inhalation flows through the DPI from 5 to 60 Lmin⁻¹. The mean (SD) Mass Median Aerodynamic Diameter (MMAD) for no coating, silicone, 100% and 50% glycerin, 100% and 50% propylene glycol was 2.17 ± (0.06), 1.40 ± (1.23), 2.00 ± (0.42), 2.10 ± (0.10), 3.20 ± (0.00) and 3.17 ± (0.06) µm respectively. The geometric standard deviation (GSD) values for no coating, silicone, 100% and 50% glycerin, 100% and 50% PEG were 1.70, 0.90, 2.30, 2.53, 1.80 and 1.83 respectively. The mean ± (SD) fine particle dose (FPD) for no coating, silicone, 100% and 50% glycerin, 100% and 50% PPG was 32.31 ± (8.19), 21.69 ± (18.83), 21.13 ± (0.06), 3.86 ± (0.10) and 2.55 ± (0.05) respectively. The one way ANOVA with the application of Bonferroni's correction was used to compare the aerodynamic droplet characteristics of the formoterol. The results indicate a significant difference between aerodynamic PSD when different coating materials were used. The MMAD was highest for PPG making it a suitable coating agent compared to other coating materials.

Keywords: Coating material, Particle size distribution, ACI, Turbohaler, Formoterol.

*Corresponding author: Mohammad Yousuf Khan, Division of Pharmacy & Pharmaceutical Science, School of Applied Sciences, University of Huddersfield, Huddersfield, HD1 3DH, UK E-mail: y.khan@hud.ac.uk

INTRODUCTION

In-vitro characterization of device-related parameters such as total emitted dose (TED), fine particle dose (FPD), fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), is necessary while assessing the potential clinical output of the dry powder inhalers (DPIs) or making comparison with other DPIs as they are indicative of potential clinical performance. The aerodynamic characterisation of the dose emitted from DPIs is, primarily, based on the degree of the de-aggregation of the metered dose inside the inhaler during inhalation manoeuvre. The de-aggregation of the metered dose inside the inhaler occurs, predominantly, by the turbulent energy and thus, turbulent energy is produced by the interaction of the inhalation flow and the inhaler's internal resistance [1]. Flow dependent dose emission has been reported to be a property of all passive DPIs with some more prone to this phenomenon than others [2, 3 and 4]. It has been reported that a failure to inhale deeply and forcibly from the start of the inhalation manoeuvre results in insufficient de-aggregation of the drug particles from carrier molecules and less deposition of drug particles into the lungs leading to no clinical efficacy [5]. Pharmacopoeia methodologies for the in-vitro dose emission characteristics from the DPIs usually use inhalation flow corresponding to a pressure drop of 4 kPa across the inhaler using inhalation volume of 4L [6, 7 and 8]. Studies have reported that many patients are not able to achieve this high inhalation flow particularly required to achieve a pressure drop of 4 kPa [9, 10 and 11]. Inhalation flows are generally reduced during an acute exacerbation [12, 13] thus the emitted dose will be reduced at a time when the patient requires extra relief from medication.



Fig.1. The mixing inlet (Copley Scientific, UK; reproduced with permission).

The Andersen Cascade Impactor (ACI) is considered as a method of choice to determine the quality of the dose emitted from inhalers. The ACI has primarily been designed to operate at an inhalation flow of 28.3 Lmin^{-1} with recent modifications to allow determinations at 60 and 90 Lmin^{-1} . As DPIs have a different resistance depending on their design [1] then the inhalation flows required to achieve the compendial recommended pressure difference of 4kPa will vary. When using non-standard flows the ACI, the cut-off diameters of the stages have to be recalculated [14, 6, 7 and 8]. Identification of the dose emission of properties of the emitted dose at low flows will be more clinically relevant than identifying these properties using optimal conditions as recommended by the pharmacopoeias. Patients will receive no therapeutic dose even though they have performed the best inhalation manoeuvre when de-aggregation at low flow is not sufficient to deposit drug particles into lungs.

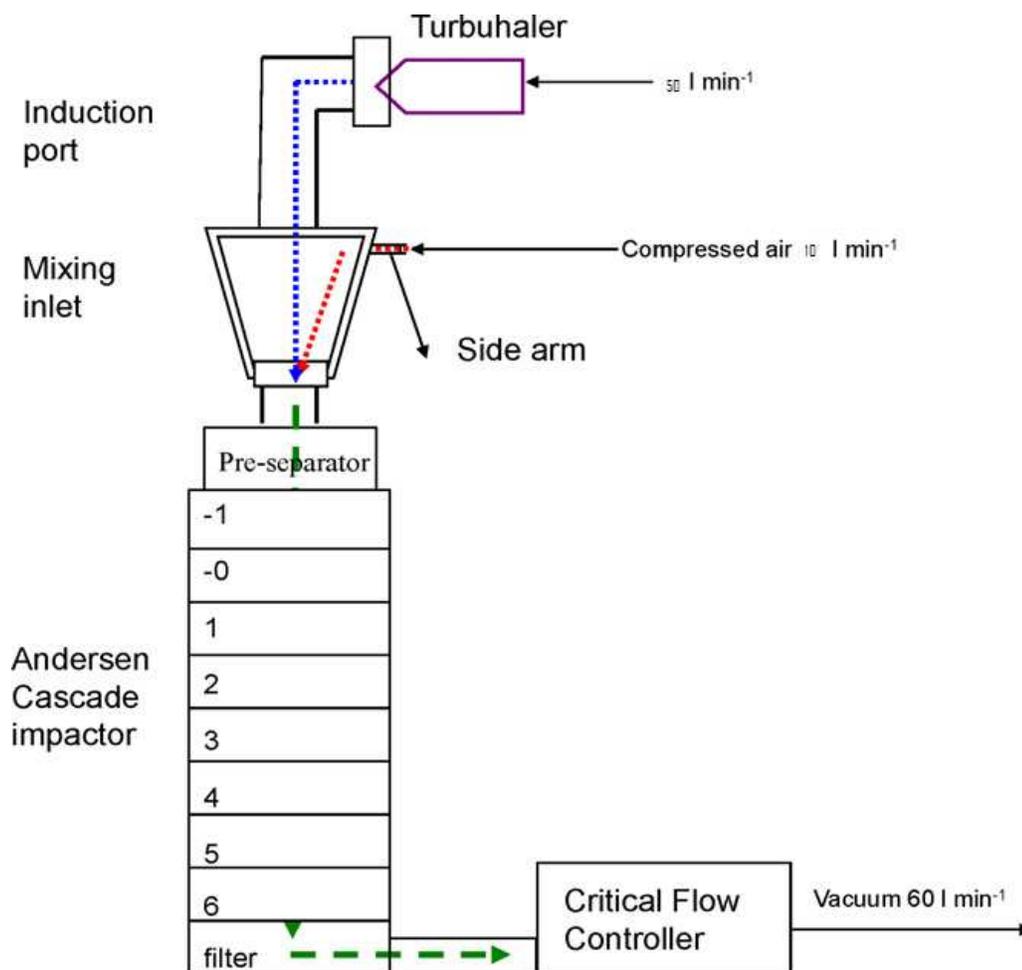


Fig.2. Schematic design of the Andersen Cascade Impactor methodology using mixing inlet.

In order to measure the particle size distribution from a DPI at low inhalation flow, we have adapted the ACI methodology using mixing inlet. Fig.1 shows the mixing inlet. The central tube is surrounded by a sheath into which the supplementary air is introduced and has the same internal dimension as the induction port. The thickness of the central tube usually tapers towards the bottom such that it ends as a knife sharp edge. This together with the internal

shallow angles ensures minimal turbulence when the two flows meet. We have adapted the ACI designed to be operated at 60 Lmin⁻¹ with supplementary air supplied through side arm of the mixing inlet. The difference between these is the inhalation flow is the inhalation flow usually drawn through the DPI. We have explored the total drug output and particle size distribution of formoterol fumarate from an Oxis Turbohaler (Astra Zeneca, UK) using the coated plates with silicone, 100% and 50% glycerine, 100% and 50% propylene glycol and no coating.

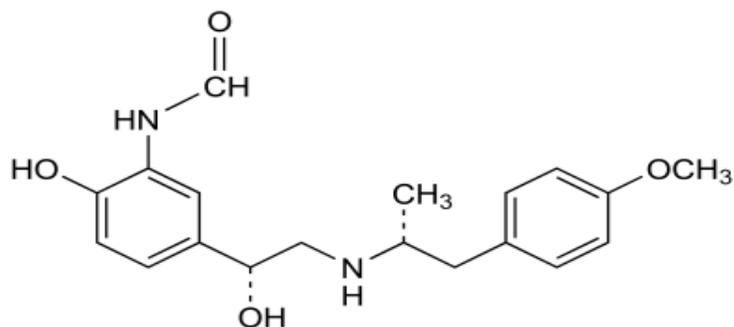


Fig.3. Chemical Structure of Formoterol

Formoterol, β_2 agonist, occurs as a racemic mixture, which arformoterol the *R*, *R*-enantiomer, is the active form. It has been suggested that stereo selective metabolism and excretion may account for the individual variation in duration of effect seen with formoterol, although the exact mechanism remains unclear. It is potentially used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Inhaled formoterol is rapidly absorbed. It is largely metabolized by glucuronidation and *O*-demethylation, with about 10% being excreted in the urine as unchanged drug. The mean terminal elimination half-life after inhalation is estimated to be 10 hours.

MATERIALS AND METHOD

1. Andersen Cascade Impactor with the mixing inlet valve

The ACI designed to be used at 60 Lmin⁻¹ was used so the stages 0 and 7 of the CI were replaced by -1 and -0 (Copley Scientific, UK). The collection plates were sprayed with silicone lubricant (Pro-Power Silicone Lubricant, Premier Farnell plc, UK), 100% and 50% glycerine, 100% and 50% propylene glycol and with no coating. The 100% coating was left to dry for 1 hour prior to analysis, whereas the 50% coating was left to dry for 30 min. The ACI stages were assembled with coated plates and a GF/A filter (Whatman plc, UK) was placed in the final stage of the ACI. The preseparator was filled with 10 ml of 60% methanol (in water). Pharmacopoeias [6, 7 and 8] recommend the use of pre-separator for dry powder inhalers (DPIs) to capture the large particle usually $\square 10 \mu\text{m}$ [15]. The mixing inlet (Copley Scientific, UK) was fixed between the induction port and the pre-separator as shown in Fig.2. The figure illustrates how a flow of 40 Lmin⁻¹ was drawn through the Turbohaler with the ACI operated at 60 and 10 Lmin⁻¹ of supplementary air provided into the mixing inlet through its side arm. The ACI was connected to a Critical Flow Control Model TK2000 (Copley Scientific UK) to ensure sonic flow and provide the required inhalation flow and volume. The vacuum flow was provided by HCP5 High Capacity Vacuum Pump (Copley Scientific, UK).

2. Measurement of pressure drop (ΔP) across the DPI

The standard pharmacopoeia method was modified using an adaptation of methodology [1] to measure the pressure drop across the inhaler at flow rate of 60 L min^{-1} . The adaptation method is described in Fig.3. The standard mouth piece adapter was replaced by a specially made adapter to allow an outlet to be connected to the MKS Baraton Type 223B pressure transducer (MKS Instruments, GmbH). So the Turbuhaler was encased in a specially made chamber which was connected to the transducer. Leak test was carried out to ensure airtight sealing of the ACI. The inhaler chamber was also connected to the MKS Type 1500 Mass-Flow Meter (MKS Instruments, GmbH) in order to measure the mass flow through the inhaler. The flow rate through the ACI was usually set at 60 L min^{-1} . Thus the pressure drop (ΔP) across the inhaler determined was 4 kPa .

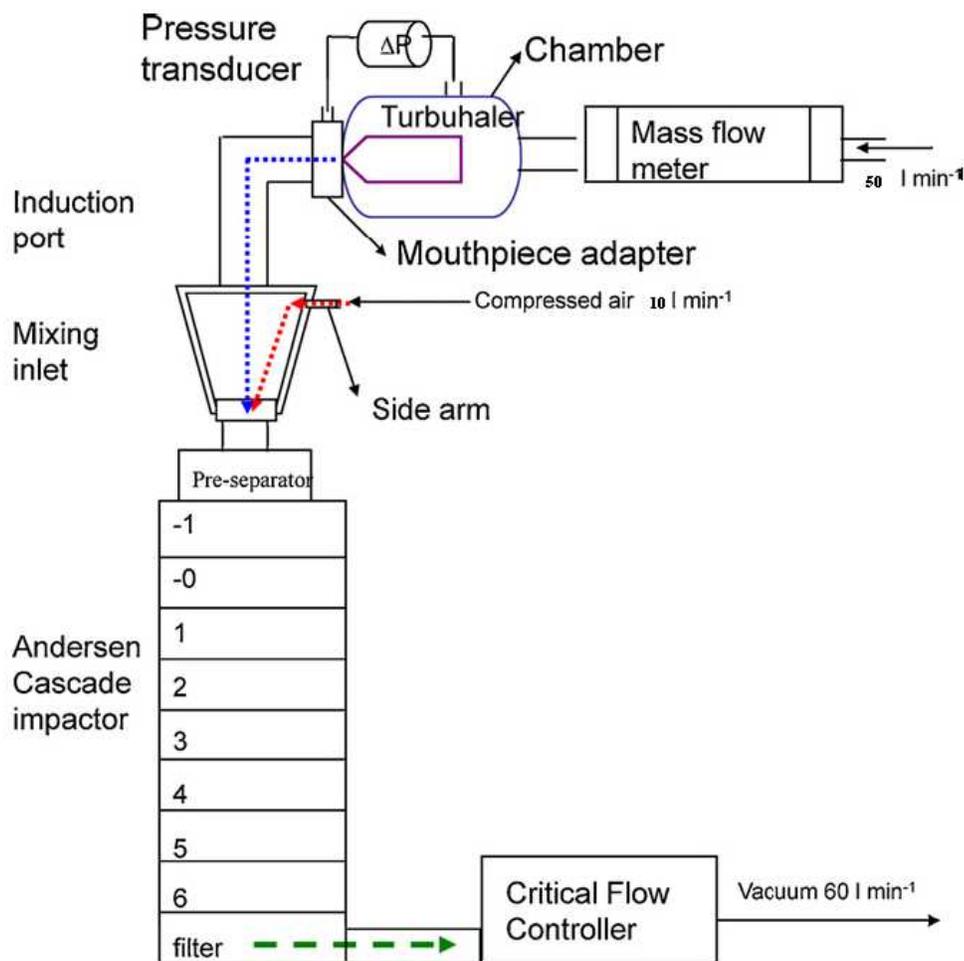


Fig.4. Schematic design of the Andersen Cascade Impactor methodology with mixing inlet to measure the pressure drop across the DPI.

3. Determination of the aerodynamic characteristics of the emitted dose from DPI

The aerodynamic characteristics of formoterol fumarate from an Oxis Turbohaler (nominal labelled dose of 12 µg formoterol fumarate dose and nominal emitted dose of 9 µg; Astra Zeneca, UK) were determined using inhalation flow of 60 L min⁻¹ with an inhalation volume of 4 L. For each determination 10 consecutive doses were actuated into the ACI and each dose was loaded according to the manufacturer's recommended patient instructions. To overcome the variability of the dose emission from the Turbohaler, 10 separate doses were used [16]. The mean of the 10 doses, hence, limit any influence from erratic dose emission. Three separate determinations were made for each coating.

Quantification of formoterol

All the plates and stages of the ACI, the induction port and pre-separator, after each determination, were washed with 60 % methanol (in water). The amount of formoterol fumarate from these washings was analysed using high performance liquid chromatography (HPLC). The mobile phase used was acetonitrile : 5 mM disodium hydrogen orthophosphate buffer (70:30 v/v) adjusted to pH 3 with orthophosphoric acid. The mobile phase was filtered through a membrane filter (47 mm diameter, pore size 0.25 µm) and sonicated under vacuum for 10 min prior to use. The chromatographic studies were carried out at 25°C on a C18 Sphericlone[®] (250 mm × 4.6 mm × 5 µm) column (Phenomenex, UK). The mobile phase was delivered at a flow of 1.0 ml min⁻¹ using the injection volume of 100 µL. UV detection was set out at 214 nm. The calibration curves were quite linear ($r^2 = 0.9987$) for formoterol concentrations ranging from 10 to 100 µg ml⁻¹ (n=5). The method showed an accuracy of 99% and intra- and inter-day precision CV of □ 1.9% and □ 1.2%. The limit of detection (LOD) and lower limit of quantification (LLOQ) of formoterol were found to be 2.5 and 10.1 µg ml⁻¹ respectively.

4. Data analysis

The Copley Inhaler Testing Data Analysis Software (CITDAS version 2.0) was used to determine the dose emission characteristics. The total emitted dose (TED) was the amounts deposited in the induction port (USP Throat), the mixing inlet, the pre-separator and all the stages of the ACI. For each determination the software confirmed that the spread of each aerodynamic particle size distribution was unimodal and also log normal such that the parameters can be easily calculated. TED has also been expressed as a percentage of the nominal (labelled) dose. The amount of drug deposited in the induction port, mixing inlet and pre-separator was calculated as emitted dose pre-impactor (EDPI).

A plot of the logarithm of the percentage less than stated size on a probability scale against the logarithm of the effective cut-off diameter of the stages was made according to that recommended in the Pharmacopoeias. The fine particle dose (FPD) was the amount calculated from the cumulative percentage drug mass associated with the particles □ 5µm. The fine particle fraction (FPF) was FPD divided by nominal (labelled) dose and expressed in %. The mass median aerodynamic diameter (MMAD) was the size corresponding to the 50th percentile of the cumulative mass-weighted distribution. MMAD values were calculated by interpolating the data points closest to 50th mass percentile. As the bulk of the aerosol was present in this region of the distribution, then the estimates of the FPD and MMAD are as precise as possible for this method. The geometric standard deviation (GSD) was determined as the square root of the ratio of 84.1 to 15.9 mass percentiles of the aerodynamic particle size distribution [17].

5. Statistical analysis

Descriptive statistics are presented for the endpoints and for a comparison between these endpoints, their mean difference were thus calculated. The latter were usually obtained from a one way ANOVA that compared the six different coating conditions (No coating, silicone, 100 and 50% glycerine, 100 and 50% propylene glycol) with respect to FPF%, MMAD, TED, FPD and GSD using SPSS V 19.0 (SPSS Inc., Chicago, IL) using the Bonferroni correction test. From this difference the mean difference (95% confidence interval) were obtained for each coating compared to No Coating. The table 2 shows the mean difference (95% confidence interval) for No Coating compared to other coating materials.

RESULTS

1. Aerodynamic characterisation of the emitted dose

Table 1 summarises the aerodynamic characteristics of the emitted dose from formoterol Turbohaler. The fig.5 shows the log aerodynamic size distribution of dose emitted from Oxis Turbohaler when the collection plates were coated with silicone, 100% and 50% glycerine, 100% and 50% propylene glycol and no coating. The data in the Table 1 summaries the effect of coating material on the dose emission properties of the formoterol emitted from Turbohaler. This table shows that how aerodynamic properties of the product are significantly changed when the different coating materials are applied on the collection plates of the ACI. The 100% propylene glycol coating ensures the increased deposition of the drug particles on the collection plates and reduced rebound back of the fine particles. The table 2 explains the mean difference (95% confidence interval) for No Coating compared to other coating materials when the stages were coated with different coating materials. The data in the table 2 also shows the probability difference revealing the comparison among the different aerodynamic characteristics of the formoterol turbohaler. The data reveals that the coating of collection plates with 100% propylene glycol increases the fine particle dose (FPD) thus leading to increase the fine particle fraction (FPF) of the drug particles having a diameter equal to or less than 5 μm . The mass median aerodynamic diameter (MMAD) is 3.2 micron ensuring the greater deposition of drug into the alveoli [15] resulting in enhanced therapeutic effects. Fig.6 shows the TED and FPD comparison of formoterol with respect to different coating materials. The TED for no coating, silicone, 100% glycerine, 50% glycerine, 100% propylene glycol, 50% propylene glycol and the graph shows the TED was very low when the collection plates were coated with 50% glycerine. The TED was 5.93 μg when uncoated plates were used. Pharmacopoeias specially recommend the use of coating when dry powder inhalers (DPIs) are characterised [6, 7 and 8]. The potential effect of coating is to possibly prevent the rebound back phenomenon of the fine drug particles when they impact with some velocity on the surface of the collection plates. Similarly the fig.7 shows the comparison between the fine particle fraction (FPF %) and the TED (% nominal dose). While the MMAD comparison is shown in fig.6. The smaller MMAD of formoterol is due to the increased fraction of fine particles [5] describing that the drug particles are striking on the surface of the collection plates with great inertia thus resulting into increased fine particle fraction.

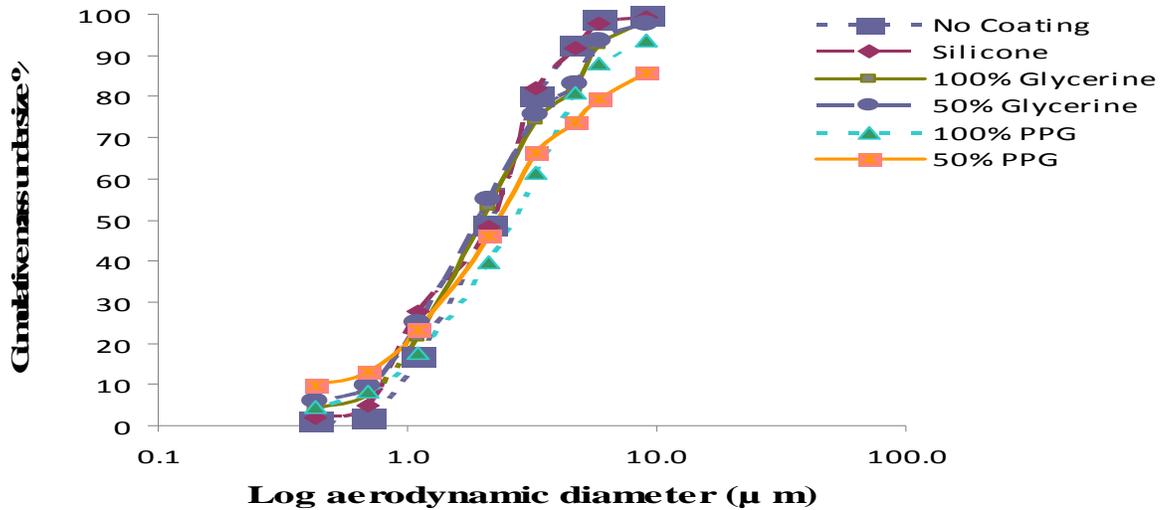


Fig.5. A comparison of the log aerodynamic particle size distribution of the dose emitted from a Formoterol Turbohaler.

Table1. The mean (S.D.) aerodynamic characteristics of dose emitted from a formoterol Turbohaler (6 µg nominal dose per shot) using different coating materials (n=10)

Stages	No coating	Silicone	100%glycerine	50%glycerine	100%PPG	50%PPG
UIP	1.56 (0.4)	1.58 (0.7)	0.94 (0.3)	0.47 (0.1)	1.70 (0.1)	0.19 (0.0)
Pre-separator	0.27 (0.14)	0.49 (0.3)	0.32 (0.1)	0.17 (0.0)	0.20 (0.0)	0.22 (0.1)
-1	0.01 (0.0)	0.02 (0.3)	0.06 (0.0)	0.04(0.0)	0.55(0.0)	0.6 (0.0)
0	0.04 (0.0)	0.05 (0.1)	0.16 (0.1)	0.07 (0.1)	0.51 (0.1)	0.26 (0.1)
1	0.26 (0.1)	0.17 (0.1)	0.32 (0.20)	0.18 (0.1)	0.49 (0.1)	0.24 (0.1)
2	0.5 (0.2)	0.29 (0.1)	0.23 (0.1)	0.13 (0.0)	0.62 (0.1)	0.31 (0.1)
3	1.3 (0.3)	1.0 (0.1)	0.63 (0.1)	0.35 (0.0)	1.70 (0.1)	0.85 (0.0)
4	1.3 (0.3)	0.60 (0.2)	0.95 (0.1)	0.52 (0.1)	1.90 (0.2)	0.95 (0.1)
5	0.62 (0.2)	0.68 (0.3)	0.42 (0.2)	0.26 (0.1)	0.84 (0.0)	0.42 (0.1)
6	0.04 (0.1)	0.09 (0.1)	0.10 (0.0)	0.07 (0.0)	0.31 (0.0)	0.15 (0.1)
Filter	0.04 (0.1)	0.05 (0.1)	0.12 (0.0)	0.10 (0.0)	0.40 (0.0)	0.4 (0.1)
TED (µg)	5.93 (1.6)	4.83 (2.1)	4.21 (0.4)	2.36 (0.1)	9.22 (0.6)	4.59 (0.9)
TED (% Nominal dose)	48.5 (12.0)	40.2 (12.5)	35.1 (4.1)	19.7 (10.2)	76.9 (19.2)	38.3 (22.1)
FPD □ 5 µm (µg)	3.8 (1.0)	2.6 (1.0)	2.5 (0.1)	1.6 (0.2)	6.3 (2.1)	3.3 (1.6)
FPD □ 5 µm (% Nominal dose)	32.3 (8.1)	21.7 (12.1)	21.13 (0.1)	26.7 (2.5)	2.55 (0.4)	55.3 (9.5)
%FPF	66.0 (0.9)	36.2 (1.5)	60.6 (7.3)	67.8 (7.8)	68.3 (0.2)	71.7 (10.6)
MMAD (µm)	2.2 (0.1)	1.4 (1.3)	2.0 (0.1)	2.1 (0.1)	3.2 (0.0)	3.2 (0.3)
GSD (no units)	1.9 (0.1)	0.9 (0.2)	2.3 (0.1)	2.5 (0.2)	1.0 (0.1)	1.3 (0.2)

Table2. Aerodynamic characteristics comparison of Formoterol using No coating as a comparator with other coating materials using mean difference (95% confidence interval; p=0.05)

Coating Comparison	FPF (%)	MMAD (μm)	(TED) (μg)	FPD (μg)	GSD
Silicone vs No coating	29.7 (4.6, 54.8)	-4.3 (-1.0, 1.5)	1.1 (-2.7, 4.9)	1.3 (-0.8, 3.4)	-129.9 (-256.6, -3.3)
Glycerine 50% vs No coating	16.0 (-9.2, 41.0)	0.03 (-5.8, 5.8)	5.0 (1.2, 8.8)	3.4 (1.3, 5.5)	-0.9 (-111.8, 110.1)
Glycerine 100% vs No coating	8.7 (-19.9, 37.3)	-8.5 (-7.4, 5.7)	2.0 (-2.3, 6.4)	1.5 (-0.9, 3.9)	-13.9 (-140.5, 112.7)
PPG 50% vs No coating	27.1 (2.0, 52.2)	-1.0 (-5.8, 5.8)	5.1 (1.3, 9.0)	3.6 (1.5, 5.7)	-0.2 (-111.1, 110.8)
PPG 100% vs No coating	26.4 (1.3, 51.5)	-1.1 (-5.8, 5.8)	5.2 (1.3, 9.0)	3.6 (1.5, 5.7)	-0.2 (-111.1, 110.1)

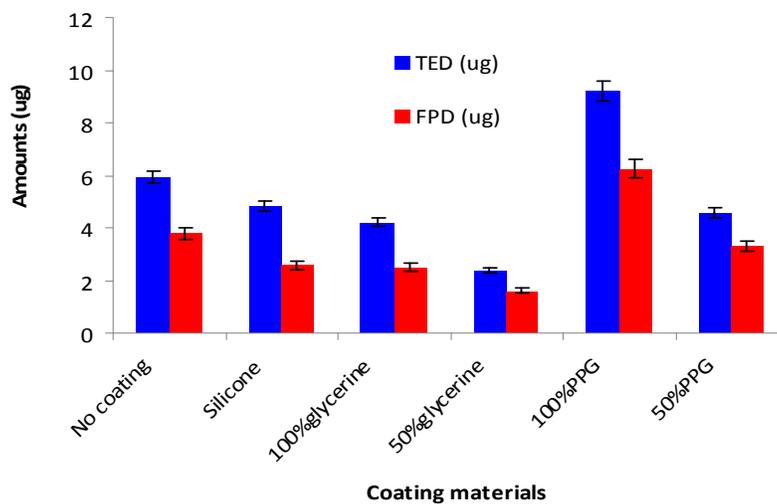


Fig.6 TED and FPD comparison using different coating materials

The smaller is the MMAD and greater the FPD and FPF, the greater will be the lung deposition and more likely the therapeutic effect. The above figure represents the total emitted dose (% nominal dose) that was impacted into the Andersen Cascade Impactor (ACI) at flow rate of 50 Lmin^{-1} drawn through the DPI and 10 Lmin^{-1} was supplied through mixing inlet. The FPF was 68.4% with TED of $9.22 \mu\text{g}$ for 50% propylene glycol coating. The MMAD ($1.4 \mu\text{m}$) for silicone coating is too small to allow the drug deposition deep into the lungs. The 100% propylene glycol coating thus producing the fine particles having a MMAD

of 3.2 μm more suitable to allow the drug deposition onto the target site (alveoli) because of the abundance presence of β_2 receptors in that region.

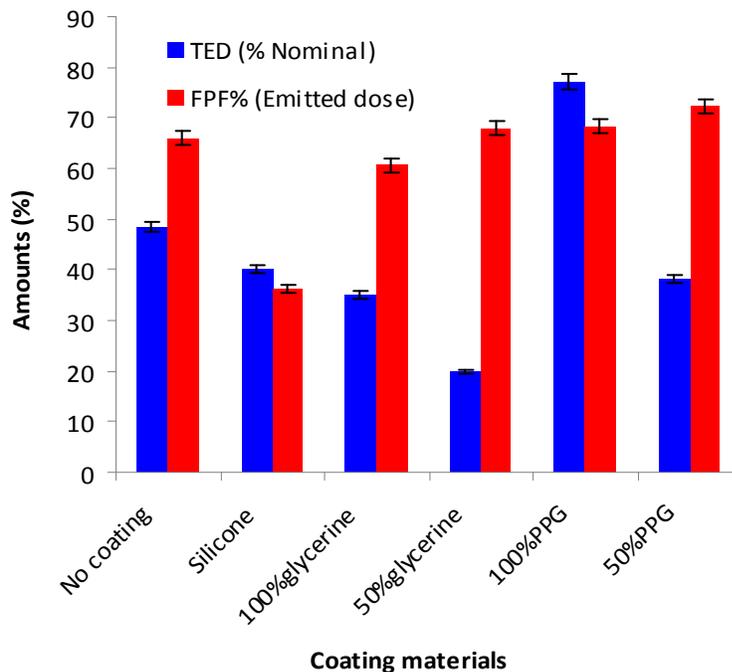


Fig.7. TED (% nominal) and FPF (% emitted dose) comparison using different coating materials.

DISCUSSION

By choosing a suitable coating agent which would be compatible with analytical methods, provides advantages such as prevention of bouncing back of fine particles, reducing wall loss and represents a true measurement of particle size distribution of particles. Studies have shown that glycerine and silicone have an equal effect to eradicate bouncing of the particles when using the ACI [18] while, others have recommended propylene glycol as a coating agent [19]. In this study four different types of coating agent were examined (silicone, glycerine, propylene glycol and no coating agent) when using the ACI. Each method was carried out ten times and in each run ten separated doses of formoterol from the Oxis Turbuhaler® were used. The results showed that the mean (S.D.) total emitted dose (TED) and fine particle fraction (FPF%) of formoterol emitted from Oxis Turbuhaler using propylene glycol 100% and 50% was 9.22 (0.6) and 4.59 (0.9) and that of FPF was 68.3 % (0.2) and 71.7 % (10.6) respectively. A decrease in the TED and FPF% was observed when silicone was used as the coating agent where the mean (S.D.) TED 4.83 (2.1) 36.2% (1.5) respectively. When the ACI was used without using a coating agent, the percentage of TED (μg) and FPF% was found to be higher than silicone. The reduction in the percentage of TED and FPF with silicone could be due to a difficulty in the extraction of the drug from the non polar coating agent (Silicone). Although formoterol is readily water soluble and binds to silicone, the recovery is decreased. Alternatively, non-polar solvents such as cyclohexane being a non-toxic solvent could be used to achieve high recovery. But this solvent would affect the C18 columns as well as the sensitivity of the HPLC system. The TED of glycerine 100% and 50% was 4.21(0.4) and 2.36 (0.1) and the FPF was that of 60.6% (7.3) and 67.8%

(7.8) respectively which was found to be significantly less than propylene glycol 100% and 50%.

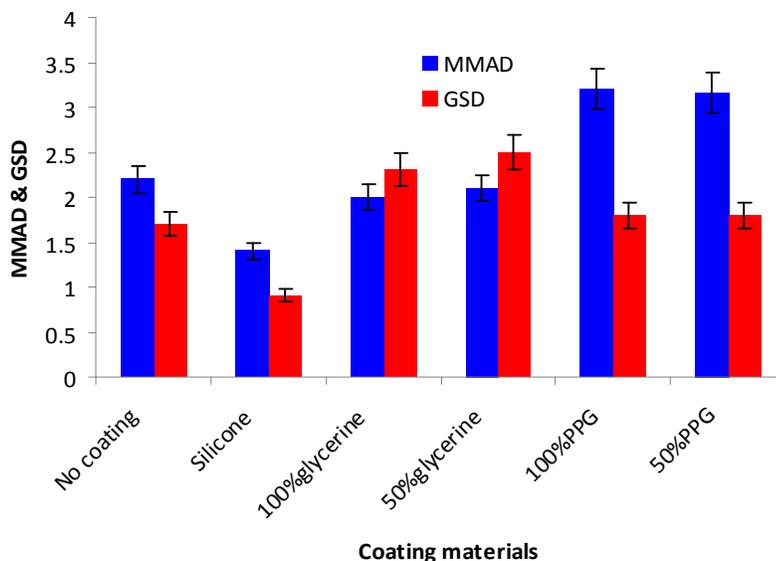


Fig.8. MMAD and GSD comparison using different coating materials.

Unlike silicone or no coating agent, 100% and 50% glycerine, propylene glycol gave more consistent MMAD values. Propylene glycol therefore is a suitable coating agent for the measurement of the particle size distribution of formoterol through the ACI stages. Reduced particle bouncing and wall loss would also be achieved by using propylene glycol and this could be perceived as a good advantage. All types of impactors have been shown to exhibit considerable wall losses, especially in the top few stages [20, 21]. The wall loss and particle bouncing depends on the nature of the impaction surface, the type of coating agent, the type of particles, particle loading on the impaction surface, the sampling conditions and the designs of impaction substrate [22, 23]. The results highlight that wall loss was minimal. The minimization of the effect of particle bouncing and wall loss from the impaction surfaces is a critical factor to obtain reliable particle size distributions. Studies have shown that the coating agents can reduce the particle bouncing and wall loss, leading to improved collection efficiency when using the Andersen Cascade Impactor [24]. Other advantages of choosing propylene glycol as the coating agent is its lack of UV absorbance thus no interfering peaks would be noticed with the formoterol peaks. In conclusion, optimizing the efficiency of the ACI is important in the evaluation of the particle size distributions of the drug particles emitted from inhaler. This study has revealed that propylene glycol is a suitable coating agent.

Studies have revealed that for particles to stick to impaction surfaces, high-viscosity grease coatings have been used. As particles accumulate on the surfaces, the efficiency of grease coatings decreases rapidly with particle loading [25]. Particle build-up on impaction surfaces may also affect the flow stream such that smaller particles get collected prematurely, resulting in a larger MMAD [26].

Table 2 shows the mean difference (95% confidence interval) for flow rate at 60 L/min that compares the coating agents with a non-coating agent with FPF, MMAD, emitted dose and GSD and was determined by analysis of variance. Significant differences were observed for the FPF% with coatings of PEG and silicone ($P < 0.05$) which suggested a better particle size distribution (PSD) at various stages of the ACI. There were no significant differences seen between coatings of glycerine with no coating.

Table 1 also represents the geometric standard deviation (GSD) measure of the variability of the particle diameters within the aerosol. An aerosol with a GSD of < 1.2 is described as monodisperse (uniform diameter distribution); an aerosol with a GSD > 1.2 is described as polydisperse (heterogeneous particle distribution). The Oxis Turbohaler had a smaller measured particle diameter distribution (GSD) for 100% propylene glycol (1.8) compared with other coating agents indicating particles generated from the turbohaler were more of a uniform size.

CONCLUSION

The aerodynamic particle size distribution characteristics of formoterol Turbohaler were enhanced using the 100% propylene glycol considered as a suitable coating material for In-vitro characterization of Formoterol Turbohaler using Andersen Cascade Impactor (ACI). The reduction in the percentage of TED and FPF with silicone could be due to a difficulty in the extraction of the drug from the non-polar coating agent (Silicone). Although formoterol is readily water soluble and binds to silicone, so the recovery is decreased. While there was no significant result was observed in PSD of formoterol employing silicone and 100 and 50% glycerine.

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