International Journal of Clinical Medical Research

In-vitro aerodynamic particle size distribution of Symbicort® Turbuhaler® at 28.3 L/min and 60 L/min inhalation flows

Mohammed Almeziny[1], Brian Clark[2], Henry Chrystyn[3]

Correspondence:
Mohammed Almeziny
Consultant Clinical Pharmacist, Prince Sultan Military Medical City (PSMMC), Riyadh, KSA
Email: meziny@hotmail.com

1 Consultant Clinical Pharmacist, Prince Sultan Military Medical City (PSMMC), Riyadh, KSA

2 Institute of Pharmaceutical Innovation, School of Pharmacy, University of Bradford, UK

3 Inhalation Consultancy Ltd, Leeds, UK

Volume number 3
Issue number 3
Pages 45-51

10.61466/ijcmr3030001

Received: 01.03.2025
Accepted: 16.04.2025
Published: 18.04.2025
0nline: 01.06.2025

Abstract

Background

The study investigates the in-vitro aerodynamic particle size distribution of Symbicort® Turbuhaler®, a dry powder inhaler containing budesonide and formoterol, at different inhalation flows.

Methods

The primary objective was to assess the effect of inhalation flow on drug delivery by analyzing the fine particle dose (FPD) and mass median aerodynamic diameter (MMAD) using an Andersen Cascade Impactor at 28.3 L/min and 60 L/min inhalation flows.

Results

The results reveal a statistically significant impact of inhalation flow on drug deposition ($p<0.05$). A higher inhalation flow (60 L/min) led to an increase in FPD, a decrease in MMAD, and a higher fine particle fraction (FPF), indicating improved lung deposition. Additionally, throat deposition decreased with increasing flows, suggesting better de-aggregation and dispersion of drug particles. Despite these changes, the ratio of budesonide (R and S epimers) to formoterol remained constant, ensuring consistent pharmacological efficacy.

Conclusions

The findings highlight the importance of flow considerations in dry powder inhaler performance and suggest that higher inspiratory flows may enhance drug delivery efficiency. This study supports the need for variable flow testing in pharmacopoeial standards to optimize inhaler design and ensure effective drug administration for patients with asthma and chronic obstructive pulmonary disease.

Keyword: in-vitro; aerodynamic particle size distribution; Symbicort; Turbuhaler; inhalation flows

Introduction

Symbicort® Turbuhaler® is an inhaled drug, made up of a combination of budesonide and formoterol [1] which shows synergistic effects in terms of reduction of asthma and chronic obstructive pulmonary disease (COPD) exacerbations [2]. Combining the anti-inflammatory corticosteroid budesonide and the rapid and long-lasting bronchodilator formoterol in the same device is aimed to provide a simple, convenient and effective treatment [3].

A major issue in the formulation is that budesonide is provided as a mixture of two epimers, 22R and 22S. The budesonide epimer R is known to be 2 to 3 times more potent than the budesonide epimer S [4].

The inhalation flow produced by the patient when using dry powder inhalers (DPIs) is critical in drug delivery since no propellant is not in the DPI like the pressurised metered dose inhalers (pMDIs). [5] So patient should inhale as fast and deep as possible to deliver the inhaled dose. However, COPD, elderly patients and children

cannot produce this fast inhalation flow that reaches 60 L/min. Hence, the influence of inhalation flow on drug delivery by DPIs has been established [6-8]. Most of the guidelines does not recommend DPI for COPD and children. Additionally, the rate flow of each component may be different with different inhalation flow and therefore the pharmacological ratio may vary in delivery to the patient. As a result, it is essential to keep the combination ratio constant. The aim of the study is to quantify the impact of inhalation flow (28.3 vs. 60 L/min) on aerodynamic particle distribution of budesonide/formoterol from Symbicort® Turbuhaler®. And to determine the in-vitro performance of formoterol and the two epimers of budesonide and to assess flow-dependent changes in R/S epimer ratio under 28.3 L/min and 60 L/min flows from a Turbuhaler® by determining the fine particle dose (FPD) and the mass median aerodynamic diameter (MMAD) of Symbicort turbuhaler.

Methods

The Andersen cascade impactor (ACI) is an eight-stage cascade system intended for measuring the particle size distribution produced by pMDIs and DPIs. In order to test the effect of flow on particles size distribution, The ACI can be operated at different flows. However, it is essential to consider a modification in cut-points for each stage since the flow has an effect on the cut-points at each stage. As an example the USP indicates that at 60 L/min, stages 0 and 7 are removed and replaced with two different stages, -0 and -1.

A GAST 1023 Pump, 0-100L/min (GAST, Brook Hampton, Doncaster, UK),Electronic digital flow meter Model DFM (Copley Scientific Ltd. Nottingham UK), Andersen MKII cascade impactor (Copley Scientific Ltd.), Critical Flow Controller Model TPK. (Copley Scientific Ltd.), and Copley Inhaler Testing Data Analysis Software (CITDAS) (Copley Scientific Ltd) were used for the study. In addition analytes and general chemicals e.g. Budesonide (Sigma, Gillingham UK), Formoterol (Cipla Ltd, Kurkumbh, India), Releasil Silicone spray (Dow Corning Ltd, Barry Glamorgan, UK.), Glass microfibre filter grade GF/A 81mm (Whatman international Ltd, Kent, uk), Glass microfibre filter grade GF/A 47mm (Whatman International Ltd), Glass fiber filter type A/E 25 mm (Pall Corporation, Michigan, USA), and a Symbicort 400/12 Turbohaler® containing budesonide 400 µg and formoterol fumarate 12 µg /metered inhalation, were obtained from (AstraZeneca UK Ltd Luton, UK)

The study was performed 5 times for each inhalation flow using The amount of drug deposited in each stage was measured using the HPLC method of analysis [9]. All the aerodynamic calculation were conducted using the Copley software (CITDAS version 2). The one-way ANOVA with the Bonferroni effect test was used to compare the aerodynamic particle size characterization of the different flow using SPSS V15.0 (SPSS Inc., Chicago, USA).

Result

There were statistically significant differences ($p<0.05$) for formoterol, budesonide R and budesonide S between 28.3L/min and 60 L/min in total emitted dose (Tables 1-3). The aerodynamic particles size distribution of formoterol, budesonide R, and budesonide S from the Symbicort® Turbuhaler® device are shown in Tables 1-3 and Figures 1-5. The comparison of aerodynamic particles size characterization results from the Symbicort® Turbuhaler® device showed that the FPD significantly increases ($p<0.001$) as the inhalation flow increased. Also, there was a statistical significant difference between flow 28.3 L/min and 60 L/min in the MMAD ($p<0.05$). Where it decreases with increasing the flow. On the other hand, the effect of inhalation flow on fine particle fraction (FPF) was statistically significant $p < 0.001$ and the high flow increases the FPF. Figures 1-5 showed that the combination ratio was constant at all inhalation flows in term of FPD, MMAD and throat deposition for formoterol, budesonide R, and budesonide S. Furthermore, the standard deviation of fine particles distribution reduced as the inhalation flow was increased which indicates an improvement in dosage form uniformity. Besides, as the inhalation flow increased, there was a decrease in the amount of formoterol, budesonide R, and budesonide S deposited in the throat induction port and the pre-separator. Figure 5 clearly showed the decrease in the amounts deposited in the throat as the inhalation flow increases from 28.3 to 60 L/min.

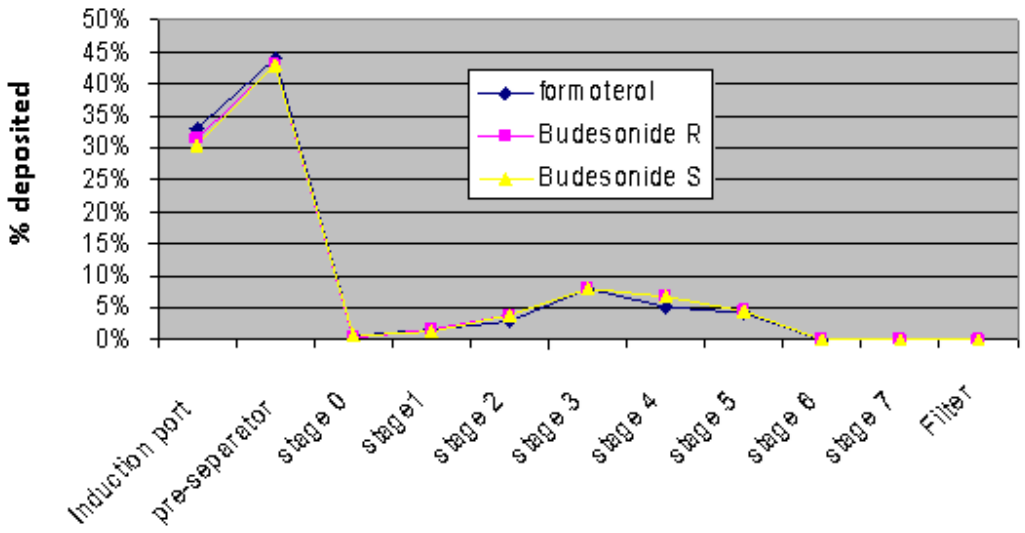

Figure 1 A comparison of percentage of formoterol, budesonide R and budesonide S deposited on each stage of ACI, at 28.3 L/min from Symbicort® Turbuhaler® device.

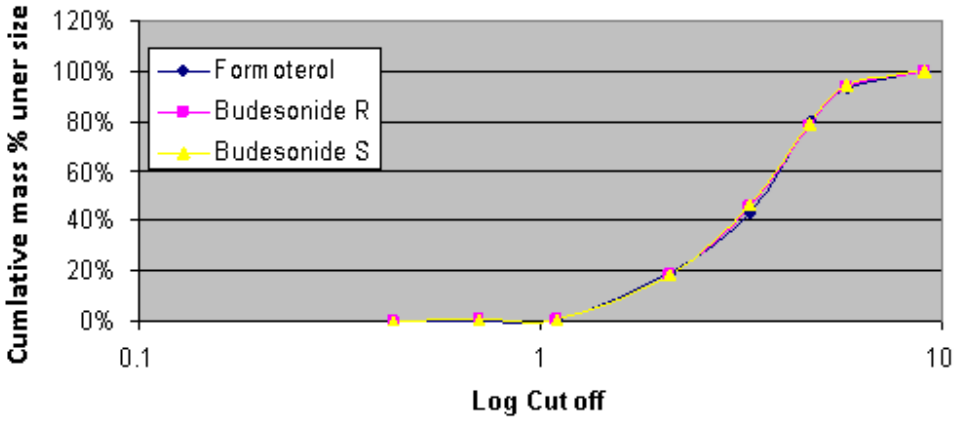

Figure 2 A comparison of cumulative mass percentages under size for formoterol, budesonide R and budesonide S deposited on each stage of the ACI at 28.3 L/min from Symbicort® Turbuhaler® device

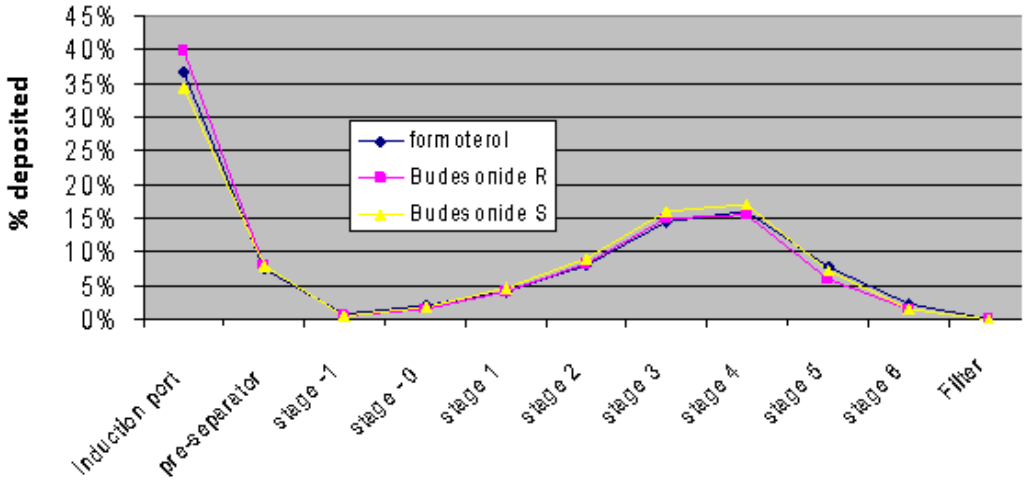

Figure 3 A comparison of the percentage of formoterol, budesonide R and budesonide S using five doses, deposited on each stage of the ACI at 60 L/min from Symbicort® Turbuhaler® device

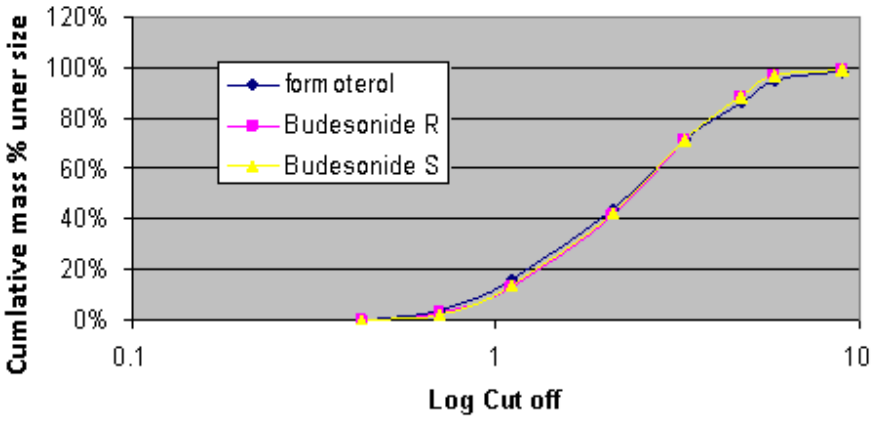

Figure 4 A comparison of cumulative mass percentages under size for formoterol, budesonide R and budesonide S deposited on each stage of the ACI at 60 L/min from Symbicort® Turbuhaler® device

Table 1 Aerodynamic characterization of formoterol (n=5) at two different flows from Symbicort® Turbuhaler® device

	ACI 28.3		ACI 60	
	AVG	STDEV	AVI	STDEV
Induction port [%]	33.48	5.86	34.33	4.68
Pre-separator [%]	44.63	12.71	6.88	3.05
TDPS [µg]	10.71	2.37	12.41	1.12
FPD [µg]	2.13	1	6.55	1.5
FPF [%]	19.16	5.6	52.48	8.32
MMAD [µm]	3.62	0.14	2.3	0.62
GSD	1.43	0.03	1.93	0.23

FPF= Fine Particle Fraction [%], TDPS= Total Dose Per Shot [ug] , FPD= Fine Particle Dose [ug], GSD= Geometric Standard Deviation, MMAD = Mass Median Aerodynamic Diameter, STDEV= Standard Deviation, AVG= AVERAGE, ACI 28.3 L/min = Andersen Cascade Impactor at flow 28.3L/min, ACI 60 L/min = Andersen Cascade Impactor at flow 60 L/min

Table 2 Aerodynamic characterization of budesonide R (n=5) at two different flows from Symbicort® Turbuhaler® device

	ACI 28.3		ACI 60	
	AVG	STDEV	AVG	STDEV
Induction port [%]	33.54	7.09	34.92	5.58
Pre-separator [%]	45.90	12.27	6.92	2.95
TDPS [µg]	334.62	56.78	405.19	68.84
FPD [µg]	70.48	31.72	204.27	46.08
FPF [%]	20.77	8.03	50.15	3.79
MMAD [µm]	3.48	0.16	2.35	0.56
GSD	1.44	0.08	1.83	0.26

Table 3 Aerodynamic characterization of budesonide S (n=5) at two different flows from Symbicort® Turbuhaler® device

	ACI 28.3		ACI 60	
	AVG	STDEV	AVG	STDEV
Induction port [%]	36.77	12.00	32.06	2.81
Pre-separator [%]	52.23	20.25	7.55	3.73
TDPS [µg]	305.48	63.47	394.85	43.03
FPD [µg]	112.40	32.19	219.13	34.87
FPF [%]	36.79	10.68	55.34	3.90
MMAD [um]	3.46	0.22	2.31	0.63
GSD	1.55	0.14	1.86	0.30

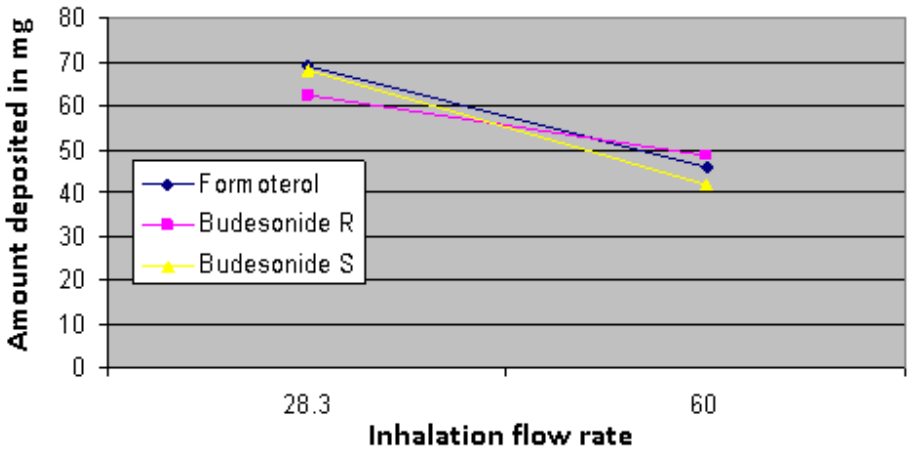

Figure 5 Amount in µg of formoterol, budesonide R, and budesonide S (n=5) deposited on pre-separator stage + induction port (throat deposition) of the ACI at 28.3L/min and 60 L/min from Symbicort® Turbuhaler® device.

Discussion

The influence of flow on drug delivery via the Turbuhaler® has been investigated in this study. The results showed that a direct relationship exists between inhalation flow through the Turbuhaler® and the deposition on the stages. The literatures suggested similar data were reported for terbutaline sulphate in an in-vivo study [7]. Equally in-vitro results suggested that a high inhalation flow through the Turbuhaler® eases de-aggregation of drug particles, it reduces particle impaction in the oropharynx, and therefore enhances lung deposition [6]. Other studies on DPIs when operated at 28.3 L/min revealed lower value for lung deposition. For instance the value for Spinhaler® was 12%, [10]and for Rotahaler® and Diskhaler® were close to 10% [11-13].

Tarsin et al. [14]demonstrated that adult patients with severe asthma achieved a high inspiratory flow through the Turbuhaler®. Furthermore, it has been reported that the most preferred inhalation rate for Turbhaler was 60 L/min [15]. In addition, Engel et al. [16] measured the flow through the Turbuhaler device for a variety of patients with different severities of asthma. They found that the mean peak inspiratory flow was 59 L/min with a range from 25 to 93 L/min.

The results of the MMAD and FPF showed a decrease in value as the flow was increased. The Symicort® formulation consists of formoterol, budesonide and lactose monohydrate as carrier [1]. The carrier plays an important role for the fine particle size dispersion. It has been recognized earlier that separation of drugs and carrier particles occurs easer when the carrier crystals are smaller [17]. Engel and co-workers [17] examined a mixture of small drug crystals and large carrier particles, and they found that drug particles larger than 5 µm are separated at flows of 60 L/min while particles in the size range 5–7 µm needed a higher inhalation flow to be separated. As a consequence, the efficiency of the penetration and deposition within the airways is dependent upon both the inhalation flow and the aerodynamic size distribution of the inhaled aerosol. At a specific flow, the higher pressure drop devices such

as Turbuhaler® produced a higher FPF compared with the lower pressure drop devices that used capsule reservoirs. The high specific resistance devices would be expected to generate higher turbulence, and thus the high turbulence will generate a higher FPF [18]. For a patient reaching high inhalation flows it will be more likely that lung deposition will be increased and hypothetically more doses would be deposited in the central zone of the lungs.

Amounts of budesonide and formoterol emitted from the same dose were similar. The inter-inhaler variability for the combination product is similar to that previously shown in a study [8]. Nevertheless, Zanen and co-workers [19] demonstrated that the high availability of salbutamol mass due to increasing the flow was not expressed as a stronger bronchodilator. Also, they concluded that the impactor is able to detect minor differences but these are too small to make clinical differences.

At a 60 L/min flow the particles deposition in the throat (the pre-separator and the induction port) has reduced compared to a flow of 28.3L/min. An explanation for this change can be linked to the change in inhalation flow that would de-aggregate particles more easy. Since the high flow enhances particle de-aggregation and reduces the MMAD as result less large particles available to deposit in the pre-separator [6]. Zanen and co-workers [20] conducted a study to determine the optimal particle size for a bronchodilator and their results demonstrated that the 3 μm has an optimum clinical effect. The study also showed that particles having a diameter greater than 5 μm have a tendency to either deposit in the throat or the mouth and therefore, they show significantly lower clinical effect.

The results of our study agreed with the common recommendation that DPI with high resistance like Turbuhaler are not recommended for elderly, children and COPD patients since they would not be cable of generating high inhalation flow. [21] Some study suggested that for such a patient, he should inhale twice form the same dose resulting in similar drug delivery to fast inhalation flow [22, 23]. So we suggest more studies to be performed to find out a way for elderly, children and COPD patients to use DPI since DPI is considered one of the most important inhalation devices that is used to treat obstructive lung diseases.

Conclusion:

From the data obtained it can be expected that at a lower flow the drug particles might be deposited on the oropharyngeal. In addition the low FPD indicated that lung deposition would be low. Since, most of the DPIs such as the Turbuhaler®, devices depend on the patient's inspiratory flow to emit and de-aggregate the drug, device design should minimize patient factors as much as possible such as inhalation flow effects, environmental effects, and complexity in operation. This will ensure that the patient receive a safe and efficacious dose. The design of different DPI results in different resistances. A higher air velocity is more likely to induce turbulent air than a low velocity. The higher the turbulence generated by the device, the greater the FPF that is likely to be obtained. It is a principle in the formulation of a dry powder that the device should give a high FPF of drug whilst the carrier such as lactose, in the formulation should remain only in the upper airways. The flow-dependent particle deposition results emphasize the need for the Pharmacopoeias to use a variety of inhalation flows for in-vitro tests rather than one that is determined according to the resistance of the dry powder inhaler.

References:

.1 Product_Information, *, budesonide formoterol fumarate inhalation powder*, A.A.S. Sweden, Editor 2008.

.2 Pauwels, R.A., Lofdahl, C.G., Postma, D.S., et al., *Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group.* N Engl J Med, 1997. **337**(20): p. 1405-11.

.3 Brunton, L.L., Lazo, J.S., and Parker, K.L., *Goodman and Gilman's the pharmacological basis of therapeutics*. 11th ed. 2006, New York ; London: McGraw-Hill. 2021p.

.4 Ryrfeldt, A., Andersson, P., Edsbacker, S., et al., *Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid.* Eur J Respir Dis Suppl, 1982. **122**: p. 86-95.

.5 Boshra, M.S., G., A.A., Randa, S.E., et al., *Total emitted dose of salbutamol sulphate at different inhalation flows and inhalation volumes through different types of dry powder inhalers.* Experimental Lung Research, 2018. **44**(4-5): p. 211-216.

.6 Jaegfeldt, H., Andersson, J.A.R., Trofast, E., et al. *Particle size distribution from different modifications of Turbuhaler®*. in *A new concept in inhalation therapy. Amsterdam*. 1987. Amsterdam Medicom.

.7 Newman, S.P., Moren, F., Trofast, E., et al., *Terbutaline sulphate Turbuhaler: effect of inhaled flow rate on drug deposition and efficacy.* International Journal of Pharmaceutics, 1991. **74**(2-3): p. 209-213.

.8 Tarsin, W., Assi, K.H., and Chrystyn, H., *In-Vitro Intra-and Inter-Inhaler Flow Rate-Dependent Dosage Emission from a Combination of Budesonide and Eformoterol in a Dry Powder Inhaler.* Journal of Aerosol Medicine, 2004. **17**(1): p. 25-32.

.9 Almeziny, M. and Clark, B., *High performance liquid chromatography assay method for simultaneous quantitation of formoterol and the two epimers of budesonide.* JOURNAL OF PHARMACY AND PHARMACOLOGY, 2007. **59**: p. 74.

.10 Auty, R.M., Brown, K., Neale, M.G., et al., *Respiratory tract deposition of sodium cromoglycate is highly dependent upon technique of inhalation using the Spinhaler.* Br J Dis Chest, 1987. **81**(4): p. 371-80.

.11 Vidgren ،M., Karkkainen, A., Karjalainen, P., et al., *Effect of powder inhaler design on drug deposition in the respiratory tract.* International Journal of Pharmaceutics, 1988. **42**(1-3): p. 211-216.

.12 Biddiscombe M, M.R., Melchor R, Short MD, Spiro SG, Taylor AJ., *The preparation and evaluation of pressurised metered-dose and dry-powder inhalers containing 99mTc-labelled salbutamol.* J Aer Med, 1991. **4**: p. (suppl 1): 9.

.13 Biddiscombe, M.F., Melchor, R., Mak, V.H.F., et al., *The lung deposition of salbutamol, directly labelled with technetium-99m, delivered by pressurised metered dose and dry powder inhalers.* International Journal of Pharmaceutics, 1993. **91**(2-3): p. 111-121.

.14 Tarsin, W.Y., Pearson, S.B., Assi, K.H., et al., *Emitted dose estimates from Seretide® Diskus® and Symbicort® Turbuhaler® following inhalation by severe asthmatics.* International Journal of Pharmaceutics, 2006. **316**(1-2): p. 131-137.

.15 Borgstrom, L., Derom, E., Stahl, E., et al., *The inhalation device influences lung deposition and bronchodilating effect of terbutaline.* American Journal of Respiratory and Critical Care Medicine, 1996. **153**(5): p. 1636-1640.

.16 Engel, T., Heinig, J.H., Malling, H.J., et al., *Clinical comparison of inhaled budesonide delivered either via pressurized metered dose inhaler or Turbuhaler.* Allergy, 1989. **44**(3): p. 220-5.

.17 Engel, T., Scharling, B., Skovsted, B., et al., *Effects, side effects and plasma concentrations of terbutaline in adult asthmatics after inhaling from a dry powder inhaler device at different inhalation flows and volumes.* British Journal of Clinical Pharmacology, 1992. **33**(4): p. 439.

.18 Engel, T., Heinig, J.H., Madsen, F., et al., *Peak inspiratory flow and inspiratory vital capacity of patients with asthma with and without a new dry-powder inhaler device (Turbuhaler®).* Eur. Respir. J, 1990. **3**: p. 1037-1041.

.19 Zanen, P., van Spiegel, P.I., van der Kolk, H., et al., *The effect of the inhalation flow on the performance of a dry powder inhalation system.* International Journal of Pharmaceutics, 1992. **81**(2-3): p. 199-203.

.20 Zanen, P., Go, L.T., and Lammers, J.W.J., *Optimal particle size for beta2 agonist and anticholinergic aerosols in patients with severe airflow obstruction.* Thorax, 1996. **51**(10): p. 977.

.21 Abdelrahim, M.E., H., A.K., and and Chrystyn, H., *Dose emission and aerodynamic characterization of the terbutaline sulphate dose emitted from a Turbuhaler at low inhalation flow.* Pharmaceutical Development and Technology, 2013. **18**(4): p. 944-949.

.22 Saeed, H., Salem, H.F., Rabea, H ،.et al., *Effect of Human Error, Inhalation Flow, and Inhalation Volume on Dose Delivery from Ellipta® Dry-Powder Inhaler.* Journal of Pharmaceutical Innovation, 2019. **14**(3): p. 239-244.

.23 Abdelrahim, M.E., *Emitted dose and lung deposition of inhaled terbutaline from Turbuhaler at different conditions.* Respiratory Medicine, 2010. **104**(5): p. 682-689.