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Comparative In-Vitro Aerodynamic Characterization of Marketed Dry Powder Inhalers Using the Aerolizer Type of Device

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COMPARATIVE IN-VITRO AERODYNAMIC CHARACTERIZATION OF MARKETED DRY POWDER INHALERS USING THE AEROLIZER TYPE OF DEVICE

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ABSTRACT

Formoterol fumarate (FF) and Budesonide combination in a dry powder inhaler dosage form is very commonly prescribed for the treatment of asthma, bronchospasm, chronic bronchitis, emphysema, and chronic obstructive pulmonary disease (COPD). The aerodynamic characteristics and delivered dose of different marketed products are generated during the patient's inhalation and reach the lungs, and give the necessary therapeutic action. To develop a dry powder inhalation product with the consistent delivery of aerodynamic characteristics until the product's shelf life is a challenge for many pharmaceutical companies. The in vitro evaluation is determined by using various techniques, such as Next Generation Impactor (NGI), Glass Twin impinger (GTI), and uniformity of delivered dose (UODD). This study fully compared aerodynamic properties in NGI, GTI, and UODD performance of different marketed products with the Aerolizer type of device. Hence, this technique is preferred by many pharmaceutical companies for the routine quality control testing for dry powder inhaler characterization. It is statutory in a multitude of Pharmacopoeias and adopted by the majority of regulatory bodies across the globe. The main purpose of this study was to evaluate statistically the in vitro evaluation generated using the latest NGI, GTI, and UODD operated at fixed flow rates of 60 L/min. Four marketed products, Foracort 200, Budetrol 200, Combihale FB, and Budamate 200, were chosen for the study and compared with the Aerolizer type of device. The aerodynamic character and delivered dose uniformity. We found a statistically significant difference in the above marketed products available on the Indian market.

Keywords: Next Generation Impactor, Deposition Of Emitted Dose, Uniformity Of Delivered Dose, Aerodynamic Particle Size Distribution, Aerolizer type of device

INTRODUCTION

The inhalation therapy for the management of asthma and chronic obstructive pulmonary disease (COPD) has existed for several years. Compared with oral or parenteral dosage forms, the drug is directly delivered to the lung region in inhalation formulations. Because of this, the undesired systemic impact of the drugs is reduced with a faster onset of action. Therefore, the class of bronchodilator and corticosteroid formulations used for lung disorders such as asthma and COPD is dry powder inhalation formulations[1-2]. In DPIs, various factors can potentially impinge on the aerodynamic

effectiveness of the administered drugs. Other factors such as polymorphism of drug substance, crystal habit of drug substance, drug/carrier ratio, particle size distribution of the drug and the carrier, storage condition, pack resistivity against temperature & humidity would affect the regional deposition of the drug in lungs, and hence on the effectiveness of the drug[3] .The moisture is very effective on a very crucial factor, which is the aerosolization of the drug powder, which is inhaled by the patient. This in turn affects the change of fine particle mass, partly due to the lower standards found in these areas. The particle size distribution of inhalation products, as determined in vitro, includes the aerodynamic particle size distribution (APSD) using different cascade impactors. This technique involves classifying the inhaled dose into several particles based on the aerodynamic diameter of the particles in question. As described before, the particle size range of 1-5µm is inhaled and deposited in the lung region. The fraction is called the Fine Particle Fraction (FPF)[4]. In the assessment of fine particles and characteristics, the BP permits the use of four different apparatuses for aerodynamic considerations. These include the twin glass impinger, multi-stage liquid impinger, Anderson cascade Impactor (ACI), and next generation Impactor (NGI). Impactors have collection trays in which particles settle after impacting on a dry impaction plate or cup. Impingers, in contrast, have a liquid collection surface[5]. Applying these apparatuses to the standard of the BP, it is possible to make a correlation with the mass of the therapeutically active pharmaceutical ingredient (API) and the particle aerodynamic size. This can be used to signify areas in which deposition takes place within the respiratory tract[6]. The twin glass impinger is employed in research in academia because it is simple, easy to operate, and assemble. The device has the ability to separate the delivered dose into respirable and non- respirable fractions in a two-stage separation. The upper part of this structure looks like the oropharynx and throat, and the lower part like the deep lungs[7]. The next generation Impactor is a new product developed to be used in the pharma industry for evaluating the performance of inhalers[8-9]. This is expected in the NGI since it is an alternative to the ACI and is less labour- consuming. The NGI has eight nozzle pieces representing seven consecutive size fractionation pieces, and a micro orifice collector (MOC) where exceedingly small particles are captured; the latter has a filter in other Impactors. The cutoff stages from one to seven at a flow rate of 60 L/ min are 8.06 microns, 4.46, 2.82, 1.66, 0.94, 0.55, and 0.34 microns, respectively[10]. For inhaler testing, the NGI is connected to an induction port, plus a pre-separator. The immediate purpose of the induction port is to mimic in terms of size the

oropharynx of an adult human being, while the pre-separators used to capture carrier-bound API particles, which are much larger than the carrier-free API particles[11]. The particle size that is most suitable to be deposited in deep lungs ranges between 2 and 6 μm. Carriers are used to enhance the powder flow, which improves the dosing accuracy of the drugs[12-13]. For the present study, we have selected Budesonide and Formoterol, molecules very commonly prescribed for chronic obstructive pulmonary disease (COPD). All four products are widely available in the market from different pharmaceutical companies as a conventional single-dose dry powder inhaler (DPI) for the treatment of asthma.[14-15]. Aerosols generated by dry powder inhalers (DPIs) are among the most promising forms to deliver therapeutic agents by inhalation to the lungs[16]. DPI powders often consist of micronized drug particles and larger, coarse carriers. Over the last decades, extensive research has been performed to study the influence of formulation design on the aerosolization of DPIs[17].However, the effects of device design on DPI aerosolization is much less studied. Performance of DPI depends on many variables, including formulation design, device selection, environment, and patients' inhalation[18]. The characteristics of the inhaler device are very important in determining the properties of the aerosol particles from DPI formulations. The influence of air turbulence on in vitro DPI performance of carrier-based albuterol sulfate powders was evaluated by our experimental set-up, where a powder deagglomeration rig was used[19].



Fig:1 Next Generation Impactor

DRUG PROFILE:

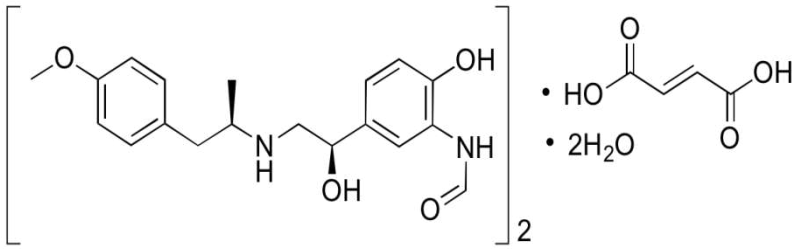


Fig.2.Chemical structure of Formoterol Fumarate

Formoterol Fumarate is a β2-agonist used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. The variability in the duration of formoterol's effect among individuals may be due to differences in its stereo selective metabolism and excretion, although the exact mechanism is not fully understood. After inhalation, Formoterol is rapidly absorbed and primarily metabolized through glucuronidation and O-demethylation, with about 10% excreted unchanged in the urine. Its mean terminal elimination half-life is approximately 10 hours.

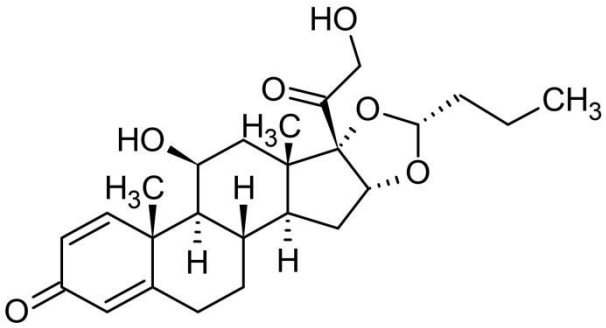


Fig.3.Chemical structure of budesonide

Budesonide is a corticosteroid used to manage inflammation in asthma and chronic obstructive pulmonary disease (COPD). It works by reducing airway inflammation, which alleviates symptoms such as wheezing, coughing, and shortness of breath. Budesonide is typically administered via inhalers for respiratory conditions, though it is also available in other forms, including nasal sprays and oral capsules for different inflammatory conditions. It is used regularly to control symptoms and prevent flare-ups, but does not provide immediate relief for acute asthma attacks. Common side effects include oral thrush, hoarseness, and coughing, which can often be minimized by rinsing the mouth after use.

EXPERIMENTAL WORK

Reagents and Materials

All four brands were collected from the Indian market: Pharmaceutical respiratory

grade Formoterol Fumarate, budesonide, and working standard. HPLC grade methanol and acetonitrile (Rankem), Milli-Q water, Sodium Dihydrogen Orthophosphate Monohydrate, Decane Sulphonic acid sodium salt, Orthophosphoric acid, Acetonitrile,0.45 m nylon syringe, and filter paper were used in this study.

Device



Fig.4: Aerolizer type of device

Instrumentation

Copley Scientific, UK provided the NGI, GTI, UODD, high-capacity pump, and critical flow controller used in the in vitro aerodynamic characterization of several brands. A Shimadzu P series HPLC with a quaternary gradient module, degasser, auto-sampler, thermostatically controlled column compartment, and UV detector was used to analyse the characterization. Lab solution software and a C18 Kromosil column (150 mm * 4.6 mm, 5 µm) were used for separation and quantitation.

Chromatographic Condition

To prepare the buffer, weigh 1.38 g of sodium dihydrogen orthophosphate monohydrate and 1.22 g of sodium salt of decane sulphonic acid in 1000 ml of water. Then, use orthophosphoric acid to get the pH down to 3.0. Pass through a 0.45 µ nylon filter. **Setting up the Mobile Phase:** 350 ml of acetonitrile and 650 ml of a buffer solution are combined. Give it a good shake and sonicate for 20 minutes.

Optimized chromatographic Condition

Flow rate	2 ml/min
Wavelength	UV 220nm
Oven temperature	25℃

Injection volume	200 µl
Run Time	18min
Diluent	Mobile Phase

RESULTS

Diluent

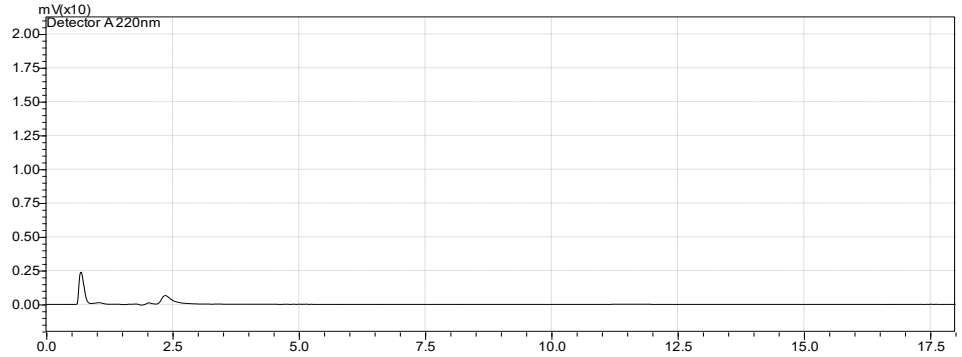


Fig:5 Typical chromatogram of Diluent

Standard

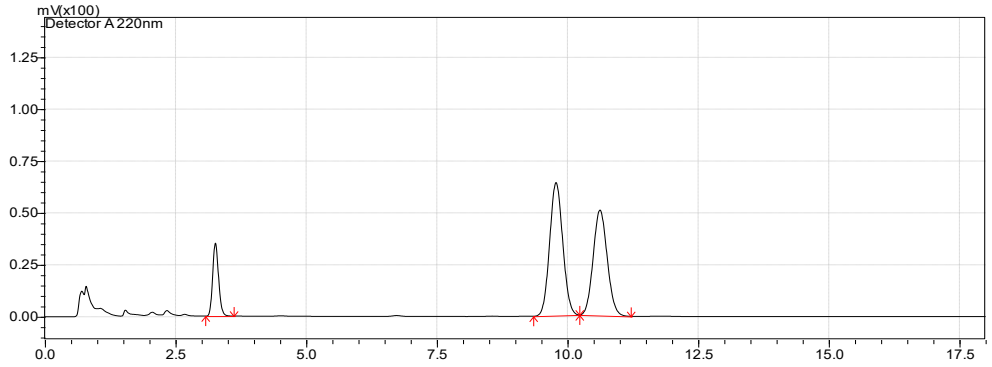


Fig:6 Typical chromatogram of Standard solution

Drugs	RT	Area	NTP	TF	Resolution
Formoterol fumarate	3.234	260,960	2,518	1.193	--
Budesonide Epimer B	9.790	1,863,025	6,561	1.066	17.688
Budesonide Epimer A	10.638	1,498,880	6,842	1.085	1.699

Sample

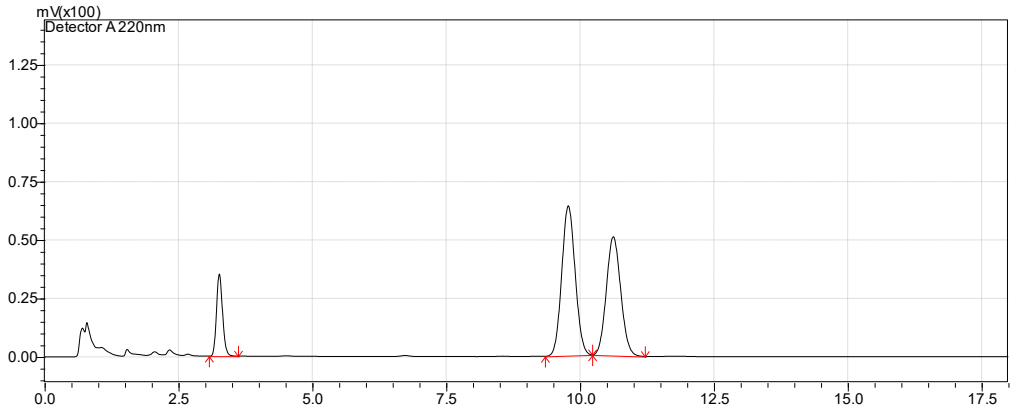


Fig:7 Typical chromatogram of Sample

Drugs	RT	Area	NTP	TF
Formoterol Fumarate	3.232	61,177	2,509	1.212
Budesonide Epimer B	9.765	185,925	6,598	1.059
Budesonide Epimer A	10.605	155,027	6,906	1.077

NGI Study:

Before using the NGI instrument, make sure it is clean. The flow rate was maintained at 60 L/min in accordance with the corresponding device resistance. Ten capsules are used in each product after the capsule is loaded using an aerolizer-style device and punctured. Following the test, each NGI stage, mouthpiece adapter, induction port, and inhaler device were properly cleaned with diluent and charged separately for HPLC testing.

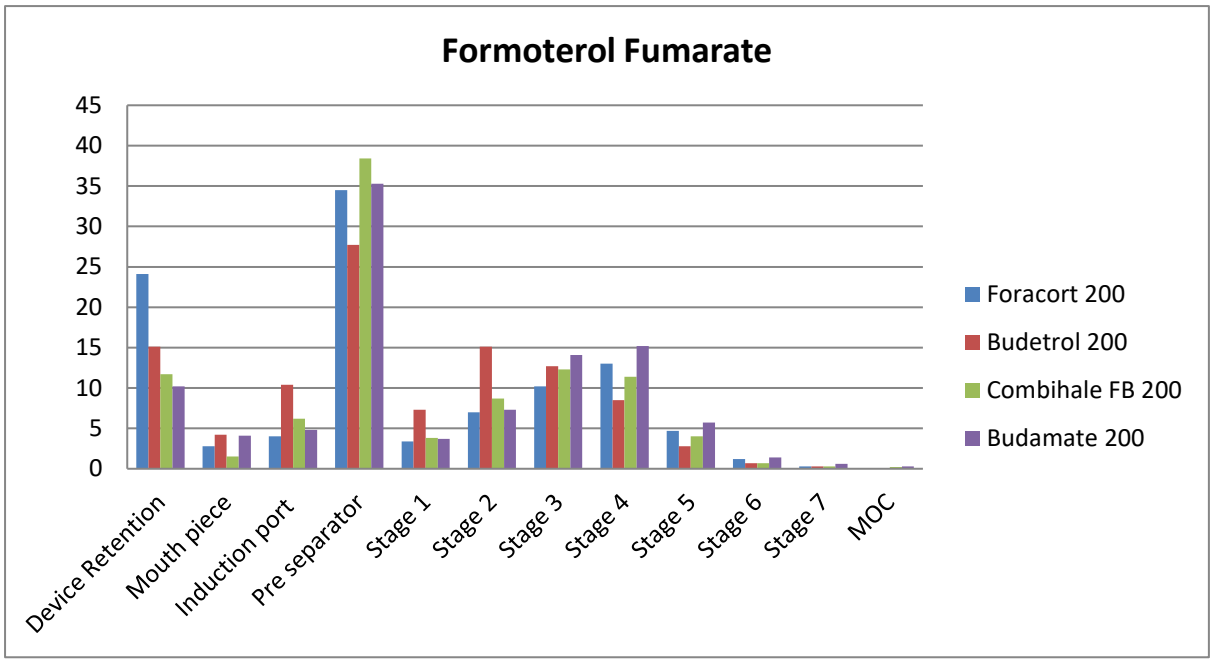
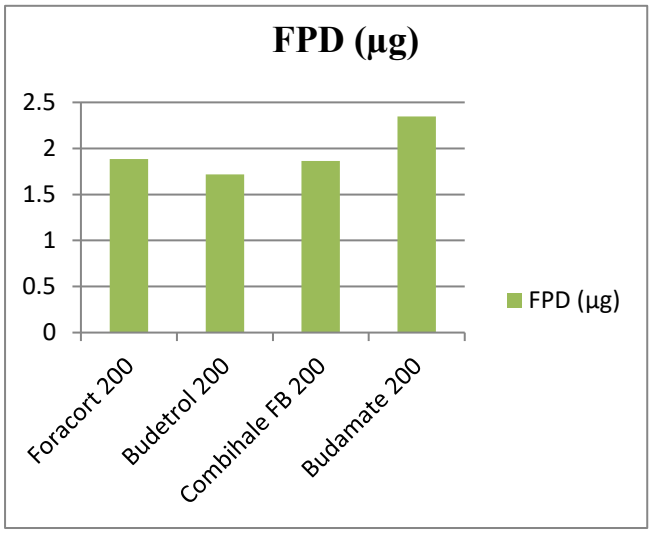
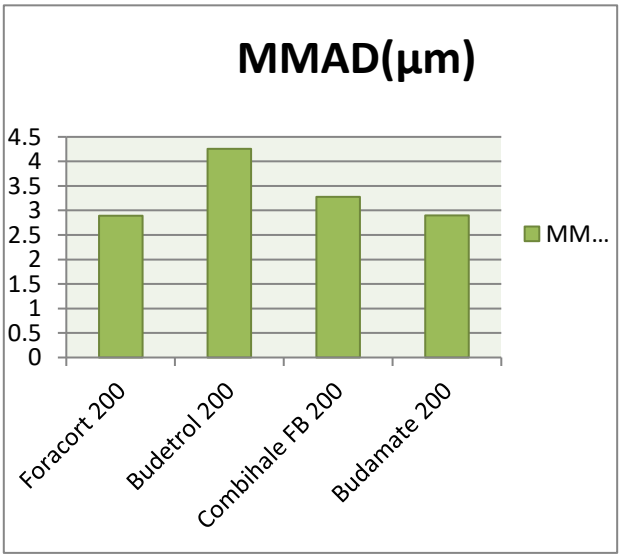


Fig:8 overall deposition of Formoterol Fumarate in various stages

Parameter	Formoterol Fumarate			
	Foracort 200	Budetrol 200	Combihale FB 200	Budamate 200
FPF (%)	38.63262	31.81883	35.43967	42.29091
MMAD(µm)	2.891	4.255	3.276	2.901
FPD (µg)	1.88515	1.71813	1.86262	2.34858
GSD	1.748	1.961	1.804	1.789





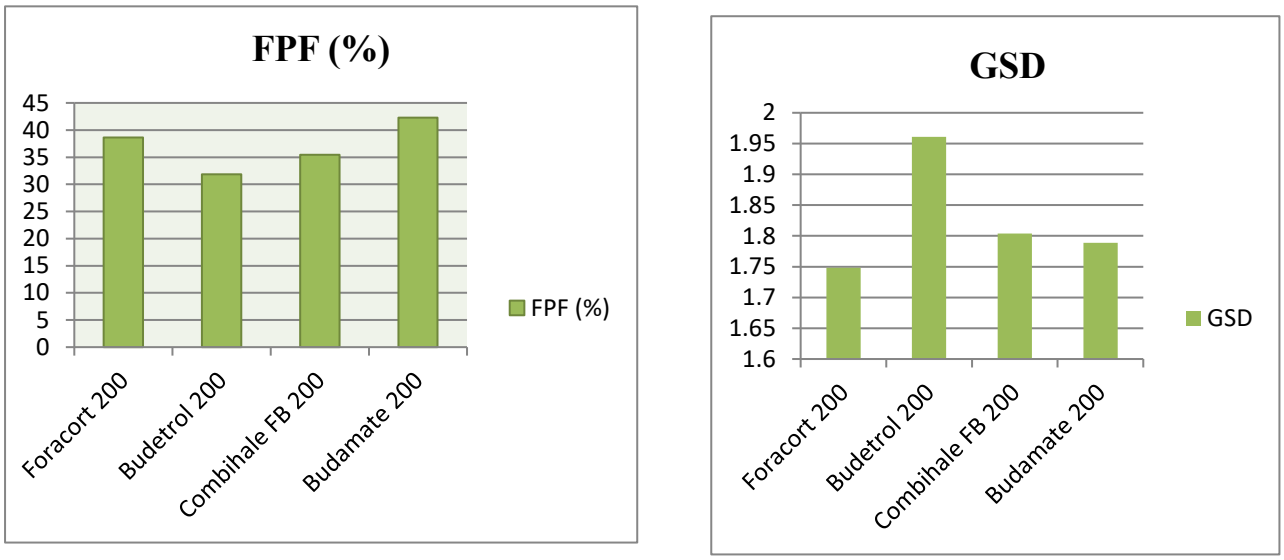


Fig:9 Particle characterization of **Formoterol Fumarate**in (Fine Particle Fraction (FPF), Fine Particle Dose (FPD), Mass Median Aerodynamic Diameters (MMAD), and Geometric Standard Deviation (GSD) of NGI

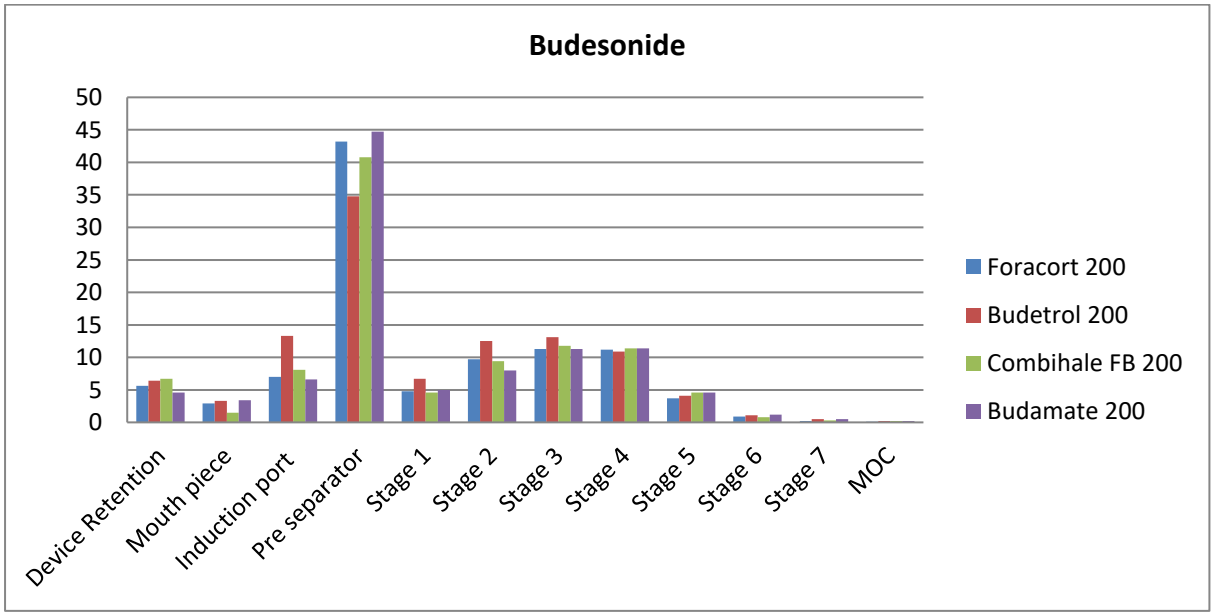
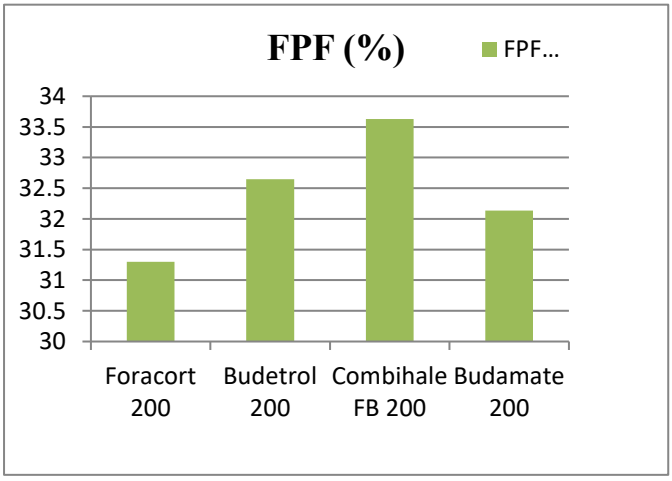
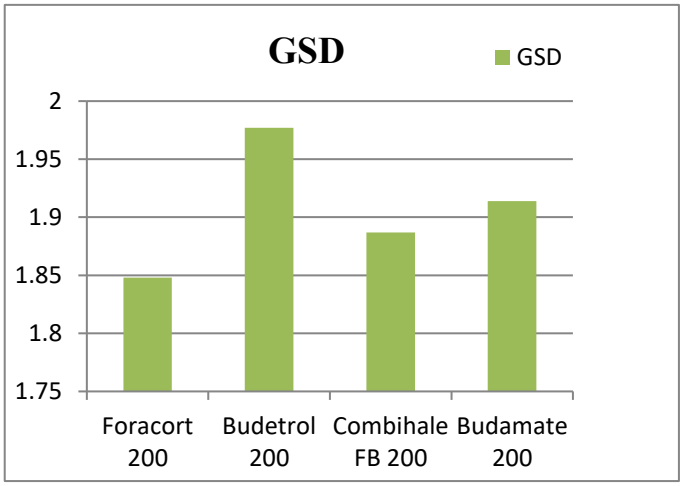
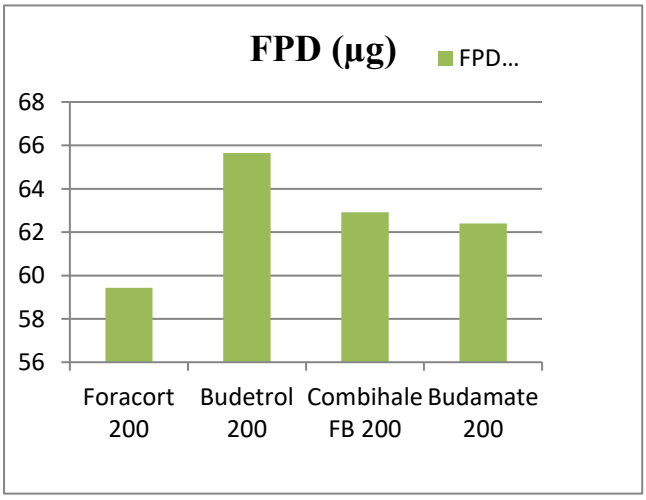


Fig:10 overall deposition of Budesonide in various stages

Budesonide				
Parameter	**Foracort 200**	**Budetrol 200**	**Combihale FB 200**	**Budamate 200**
FPF (%)	31.30145	32.64495	33.62965	32.13294
MMAD(µm)	3.428	3.709	3.31	3.199
FPD (µg)	59.43217	65.64701	62.90961	62.39883
GSD	1.848	1.977	1.887	1.914







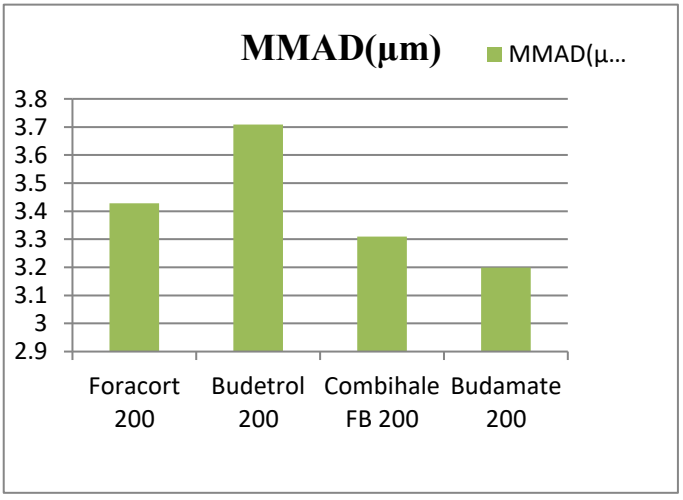


Fig:11 Particle characterization of **Budesonide** in (Fine Particle Fraction (FPF), Fine Particle Dose (FPD), Mass Median Aerodynamic Diameters (MMAD), and Geometric Standard Deviation (GSD)) of NGI

DOED Study

GTI apparatus has been arranged properplyand GTI study was carried out at a fixed flow rate of 60.0 L/min. Load the 10 DPI capsule in each sample with an Aerolizer-type device. The fractions from both the chambers (T1 and T2) were collected carefully and analysed using the validated HPLC method.

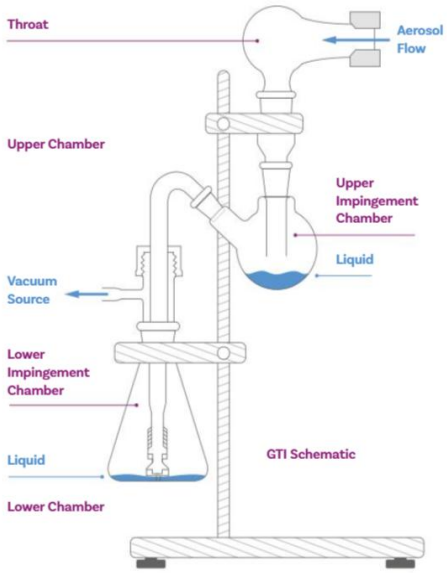


Fig 12: Deposition Of Emitted Dose

Comparison of DOED Results in Different Marketed Products (Formoterol Fumarate)

ED Stages	**Formoterol Fumarate**			
	Foracort 200	**Budetrol 200**	**Combihale FB 200**	**Budamate 200**
Device Retention	5.4	21.8	21.8	9.2
T1	49.4	51.7	52.4	46.4
T2	31.1	37.6	37.7	40.3
Mass Balance	**80.5**	**89.3**	**90.1**	**86.7**

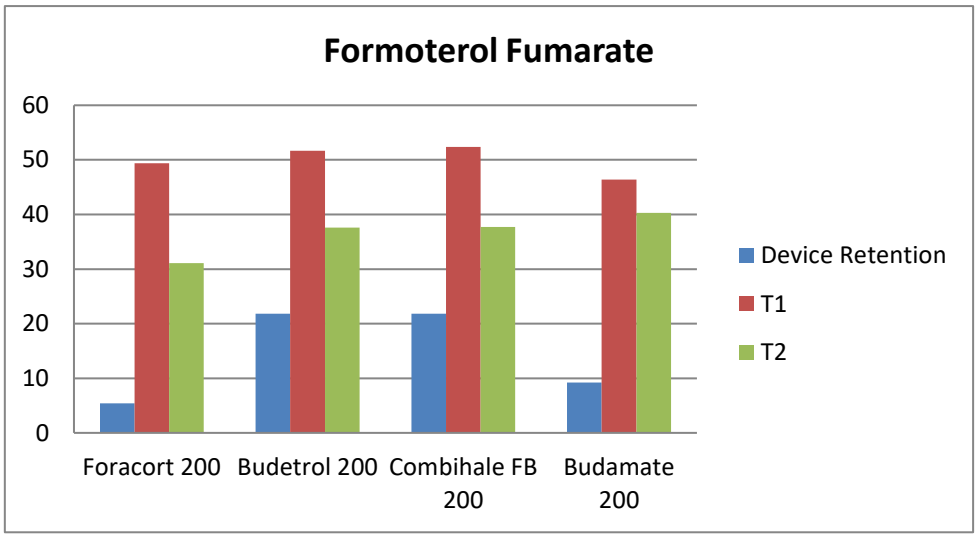


Fig:13overallComparison of DOED of Formoterol Fumarate in DOED

Comparison of DOED Results in Different Marketed Products (Budesonide)

ED Stages	**Budesonide**			
	Foracort 200	**Budetrol 200**	**Combihale FB 200**	**Budamate 200**
Device Retention	5.1	4.7	4.7	4.1
T1	61.9	61.1	59.4	59.4
T2	33.3	38.2	31.4	31.4
Mass Balance	**95.20**	**99.30**	**90.80**	**90.80**

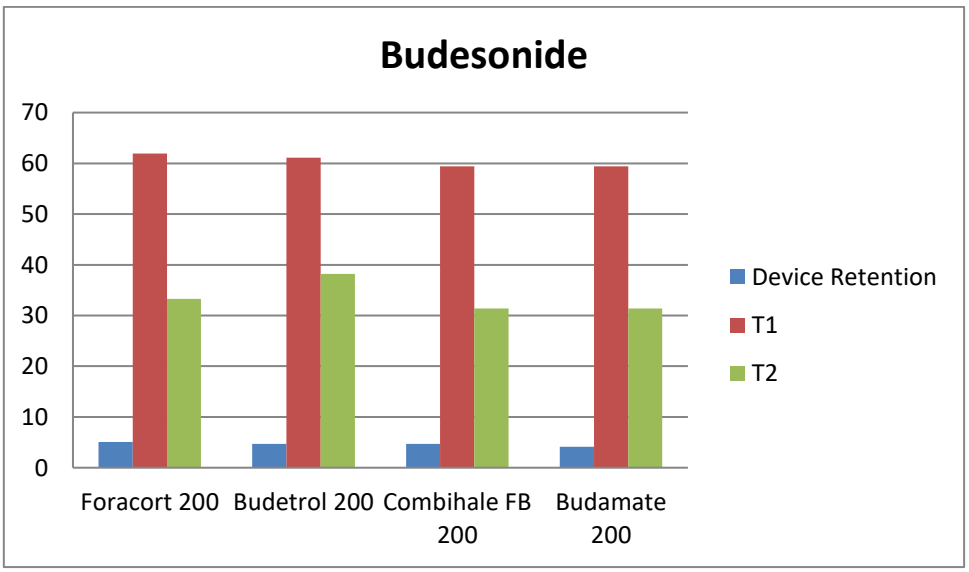


Fig:14 overall Comparison of DOED of Budesonide in DOED

Uniformity of delivered dose UODD Study

The uniformity of delivered dose (UODD) study was carried out in 10 individual DPI capsules with an Aerolizer type of device. The UODD study was performed at a fixed Flow rate of 60 L/min, and a filter paper was first placed in a DUSA cup. Place one DPI capsule into the aerolizer device, puncture the capsule shell, and activate the timer button. The dose discharged into the DUSA tube was collected by adding the 25ml diluent to the DUSA cup. The tube was vigorously shaken for about 10 min in a DUSA shaker, the dissolved content was then transferred to a volumetric flask, the volume was made up to the mark, filtered via a 0.45 _m nylon syringe filter, and used for the HPLC analysis. The study was repeated for the remaining 9 capsules. All 10 samples were analyzed for their active contents using the validated HPLC method.

Fig 15: Uniformity Of Delivered Dose

UODD	**Formoterol Fumarate**			
	Foracort 200	**Budetrol 200**	**Combihale FB 200**	**Budamate 200**
TOTAL UODD AVERAGE	**96.3**	**98.2**	**98.1**	**99.9**

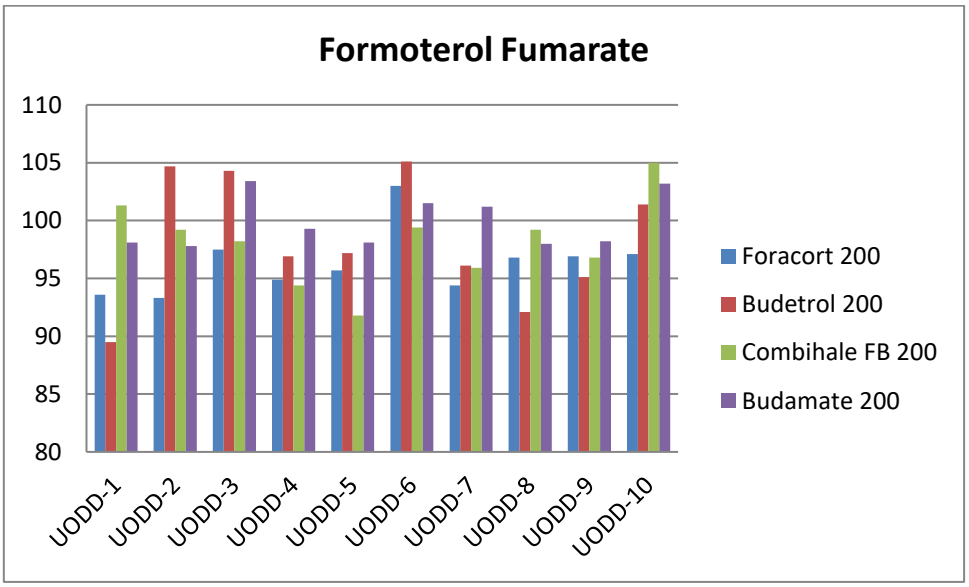


Fig:16overall Comparison of Formoterol Fumarate inUODD

Comparison of UODD Results in Different Marketed Products (Budesonide)

UODD	Budesonide			
	Foracort 200	Budetrol 200	Combihale FB 200	Budamate 200
TOTAL UODD AVERAGE	100.6	98.4	96.7	98.7

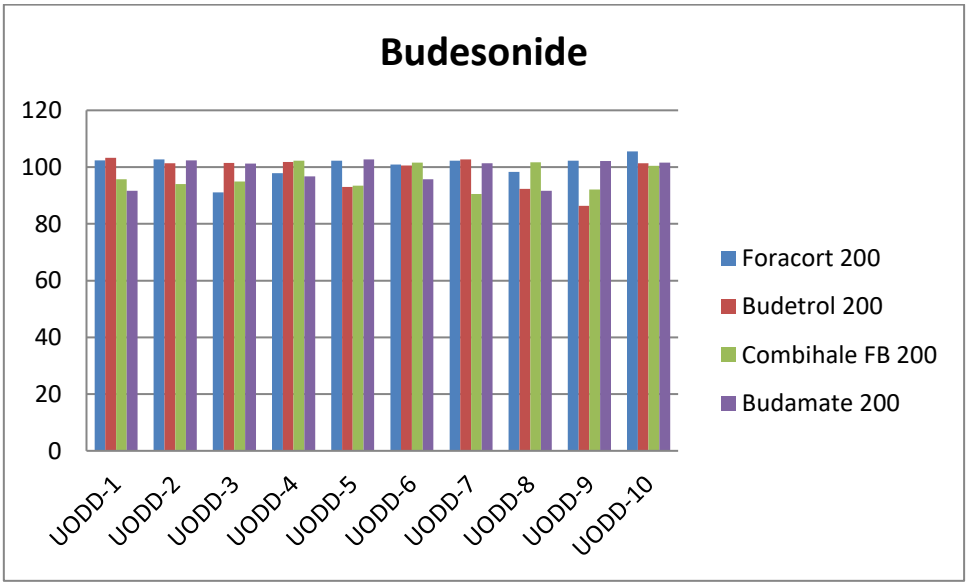


Fig:17 overall Comparison of Budesonide in UODD

Data analysis

The INHALYTIX (Copley Scientific Ltd., UK) software was used for the calculation of NGI. The statistical significance of generated data was evaluated using the Graph.

Conclusion

In this in vitro evaluation, we assessed the aerodynamic characteristics of various marketed products with Aerolizer-type devices: Foracort 200, Budetrol 200,Combihale FB 200, and Budamate 200, utilizing the Next Generation Impactor (NGI), Deposition of Emitted dose (DOED), and Uniformity of delivered dose (UODD) techniques. Typical chromatograms of diluent, standard solution, and sample solution are shown. In vitro aerodynamic characterisation data generated after the NGI, GTI, and UODD analysis for both Formoterol Fumarate and Budesonide with the Aerolizer type of device are reported . We found a statistically significant difference in the above marketed products available on the Indian market. All the results are within the limits.

Future research should continue to build on these findings, incorporating real-world conditions and further validating in vitro results with clinical performance to enhance therapeutic strategies in respiratory care.

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Author contribution:

- ✓ **Sekar Alexandar :** Conceptualization, data collection, manuscript drafting.
- ✓ **S.Sangeetha:** Methodology, data collection, writing assistance
- ✓ **J.Karisma** : Manuscript Editing
- ✓ **S.Nithya :** Writing Assistance
- ✓ **C.Pasupathi:** Project supervision.
- ✓ **P.Nallakumar :** writing and editing support.
- ✓ **M.Ravisankar :** Methodology development,
- ✓ **Rajkumar:** Data analysis, manuscript editing.

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Availability of data and material: All data are present in the manuscript

Competing Interests (Conflict of Interest): The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper."

Ethical approval and consent to participate: Not applicable

Consent for publication: Not applicable

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