doi.org/10.52568/001555/JCSP/46.05.2024

Assessment of Critical Quality Attributes of Budesonide and Formoterol Fumarate Dihydrate in Dry Powder Inhalers Marketed in Pakistan

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(Received on 18th April 2022, accepted in revised form 17th May 2024)

Summary: Dry powder inhalers (DPIs) have been well established and recognized for the delivery to the lungs. It provides better drug stability, less irritable, easy to use with deep penetration of drugs in the lungs. Budesonide (BDS) and formoterol fumarate dihydrate (FFD) indicated in pulmonary diseases.

The main aim of the study is to evaluate BDS, FFD and their marketed DPIs product in Pakistan were compare in quality and performance with the reference product. The particle size distribution and aerodynamic characterization were analyzed by laser diffraction and multi stage liquid impinger, respectively. The particle density and delivered dose uniformity were also determined. HPLC was also used for the qualitative and quantitative estimation of BDS and FFD along with its marketed products. Laser diffraction particle size analyzer revealed D_v50 53.27 to 56.34 µm having surface area 1815 to 2304 cm^3/g. The percentages of emitted dose (%ED) and fine particle fraction (%FPF) was found 98.19 to 99.23% and 31.57 to 34.87%, respectively. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated 2.62 to 2.89 µm and 1.99 to 2.54, correspondingly. The quantitative assay of BDS and FFD in all the commercial DPIs and reference product were well within the pharmacopeial limit i.e. 97.26 to 101.36%. The average of ten units results of delivered dose uniformity for BSD and FFD were also found in the range i.e. 97.97 to 103.19% and 98.48 to 104.41 %, respectively.

The results of evaluation of parameters of DPIs like D_v50, %ED, %FPF, MMAD, GSD has shown compliance with the pharmacopeial standards. It is concluded that the all DPIs of BDS/FFD marketed in Pakistan has revealed conformance with the standard of pharmacopoeia and meet the requirements of drug regulatory authority of Pakistan.

Key words: Marketed; Dry Powder Inhalers, Budesonide, Formoterol Fumarate Dihydrate, Physical Characterization.

Introduction

Globally the pulmonary diseases like asthma, chronic obstructive pulmonary disease (COPD), bronchiolitis and bronchiectasis are one of the major non-communicable diseases contributing to the highest mortality and morbidity [1]. Asthma is mainly characterized by inappropriate level of airway obstruction and hyperresponsiveness due to multiple factors like airborne allergens, environmental pollution, smoking, some food and fragrance [2]. According to global asthma report, 4.3% of population in Pakistan may suffer from asthma. [3]. Similarly, COPD is also characterized by the swelling of airways. It is mainly caused by air pollution and smoking and its prevalence in Pakistan is reported 2.1% [4].

The useful interventions for the management of asthma and COPD are included bronchodilators for symptomatic management, corticosteroids inhalers for nearly all patients suffering from asthma and particular patients with COPD, glucocorticoids prescribed for severe exacerbations, smoking cessation with annual influenza vaccination. The asthma and COPD is mainly treated by bronchodilators, steroid inhalers, cough suppressants, anti-inflammatory drugs, antibiotics, antiallergics, decongestants, expectorants [5]. The chronic inflammatory pulmonary diseases are mainly treated by glucocorticoids like ciclesonide, dexamethasone, budesonide, beclomethasone dipropionate, flunisolide, fluticasone, triamcinolone, prednisolone and prednisone [6].

The main advantage of glucocorticoids is not only reducing the inflammation but also reduce the pain. It is generally available in metered dose inhalers (MDI) or in dry powder inhalers (DPI) directly inhaled by the patients. The inhalers possessed more efficacy as compared to other dosage forms such as pills, capsules or syrups [9]. The major advantage of MDIs and DPIs is to deliver a fix dose of medication directly to the lungs [10].

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The DPI formulations are gaining more attraction with time due to their precision and convenience in use [9, 10]. The physical properties of powder like particle size, shape and surface morphology, hygroscopicity and moisture content in the DPI formulations plays an important role in drug delivery at the site of action. The physiological conditions of the patients such as breathing patterns and the general health of the lungs may affect the quality and performance of these inhalers [11-14].

Budesonide (BDS), a glucocorticoid is successfully used in the form of DPI, alone and in combination with other drugs like albuterol or formoterol fumarate dihydrate (FFD) in the management of asthma and COPD. The combination of BDS and FFD in DPI has not only produced anti-inflammatory action but also act as bronchodilator. It relieves the pain and inflammation in pulmonary diseases [15].

A number of workers have been studied various aspects of BDS and FFD on DPI formulations [16-20]. Several workers worked to determine the effect of particle size in drug delivery by DPIs [21-26]. The importance of physical properties of powder in DPIs were also reported. [27-31]. The chemical structures of BDS and FFD have been shown in Fig. 1.

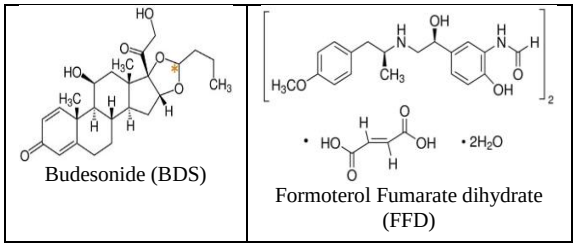

Fig. 1: Chemical structures BDS and FFD.

The present study reveals the geometric particle size distribution and aerodynamic particle size distribution of BDS and FFD in DPIs marketed in Pakistan. by using laser diffraction (LD) and multi stage liquid impinger (MSLI) cascade impaction measurements, respectively. Moreover, the particle density, emitted dose (% ED), fine particle fraction (% FPF) (≤5 μm), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were also calculated for BDS and FFD DPI. The critical quality attributes like content of BDS and FFD, delivered dose uniformity and uniformity of dose with the reference of pharmacopeial requirement has also been determined. Similar studies were also performed with the reference product (Symbicort, Astra Zenica, Canada) to explore quality and relative efficiency of the locally manufactured DPIs.

Experimental

Material

Budesonide (BDS) and formoterol fumarate dihydrate (FFD) were gifted by Getz Pharma (Pvt) Limited. The samples of the marketed BDS and FFD DPIs and reference product (Symbicort, Astra Zenica, UK) were purchased from local pharmacies. All chemicals were of analytical grade or of purest form available from Merck & Co, Whitehouse Station, NJ, USA. Freshly boiled distilled water was used for the preparation of solutions. All solvents and reagents were of HPLC grade form Merck (USA). Deionized water (16.5 MΩ resistance) from milli-Qpore system (Bedford, USA) was used for HPLC work. The solvents and the solutions were filtered using a Millipore filtration unit and then degassed before use.

Particle size distribution studies were performed on laser diffraction particle size analyzer (Anton Paar, USA). Assays for determination of content, aerodynamic particle size distribution, uniformity of dose and delivered dose uniformity were performed on HPLC system equipped with PDA detector (Prominence Series, Shimadzu, Kyoto, Japan). Multistage liquid impenger (Copley Scientific, UK) and Dosage Unit Sampling Apparatus (Copley Scientific, UK) were used as sampling devices, respectively.

Measurements of Particle Size Distribution

Laser diffraction (LD) measurement was performed on particle size analyzer (Atton Paar, USA) equipped with dry jet dispersion technology for dispersion and efficient analysis of powder particles. Powder sample was picked up with a micro spoon and incorporated in the sample holder. The dry powder sample was blown (dry dispersion method), using compressed air, through the laser beam. The particle size of the DPIs was determined by laser diffraction technique by using particle size analyzer, PSA 1190, (Anton Paar, USA). The instrument was equipped with dry jet dispersion technology aids in dispersion and efficient analysis of DPIs particles. The data were analyzed using KALLIOPE™ software (Anton Paar, USA) provided with the instrument.

The DPIs sample was placed in the sample holder. The sample was blown by dry dispersion method by using compressed air. The particle size distribution was measured by laser diffraction technique. The particle size distribution was measured

ever 0.02 ms for 2 sec by the scattered laser passed through 300 mm lens. In the cumulative particle size distribution, the percentage of fine particles of 5µm or less was defined as LD FPF% ≤5µm, and the geometric particle size of the cumulative percentage of 50% was defined as D_v50. The measurements and settings were made with KALLIOPE™ Software. The mean of five measurements was noted.

Measurements of Aerodynamic Particle Size Distribution

The aerodynamic characteristics of DPIs of all samples were assessed by using multi stage liquid impinger (MSLI) (Copley Scientific, UK). The method of analysis is described in USP-NF [32]. The mouthpiece of product was kept horizontally into the induction port i.e. mouthpiece adaptor. The solenoid valve was closed by both ends while running the vacuum pump. The two-way solenoid valves were opened for 5 s and the powder was discharged from capsule. The process was repeated by 4 more samples.

The filter was removed carefully and the sample was extracted with diluent. The adaptor of mouthpiece and induction port was rinsed and diluted a required amount of diluent. The drug presented in the inner valve was also rinsed. The collection plat of each of the four upper stages of the apparatus into the solution in the respective stage by tilting and rotating apparatus while it was ensured that no liquid transfer was occurred between the stages. The percentages of emitted dose (% ED) and fine particle fraction (% FPF) were calculated by Eq. 1 and 2, respectively [33]. ED is the amount of drug exit from the device and is expressed in percentage. FPF of the DPIs is the mass of drug contained in an aerosol cloud that may be small enough to enter the lungs and exert a clinical effect. The geometric standard deviation (GSD) was calculated from the deposition data by the Eq. 1 and 2, as expressed in Fig. 2 [33].

$$\% \text{ ED} = \frac{\text{Initial mass capsule – Final mass remaining in capsule}}{\text{Initial mass in capsule}} \times 100 \quad \text{Eq. (1)}$$

$$\% \text{ FPF} = \frac{\text{Mass of particles on terminal stages of apparatus}}{\text{Total mass on all stage}} \times 100 \quad \text{Eq. (2)}$$

The MMAD and the D_v50 values were obtained from MSLI and LD measurements, respectively. The mass median aerodynamic diameter (MMAD) and D_v50 of the particles of DPIs on inhalation was calculated by Eq.-3 [33]. The value of Dv50 indicates that the particle size in micrometer is half of the total amount of dry powder delivered from the device during aerosolization. In other words, D_v50 divides the measured distribution into two halves, smaller and larger particle size [34].

$$\text{MMAD} = \frac{D_v50}{\sqrt{Particle\ Density}} \quad \text{Eq. (3)}$$

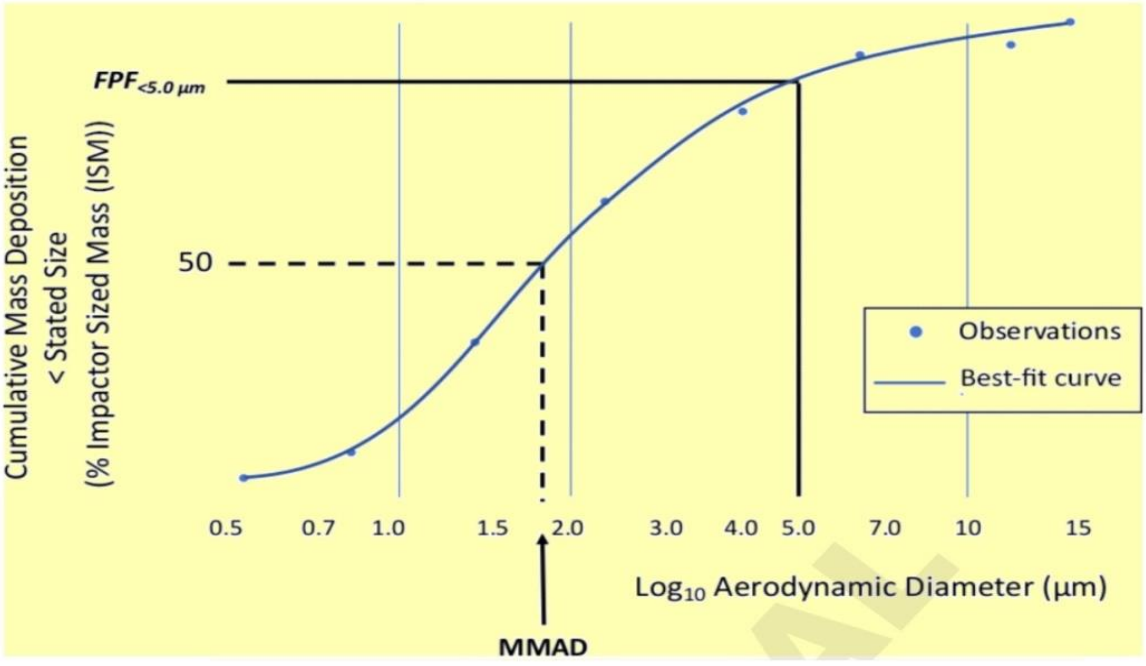

Fig. 2: MMAD and FPF <5.0µm calculations from MSLI data.

Assay of Budesonide and Formoterol Fumarate Dihydrate

The HPLC was used for the assay of BDS and FFD, alone and in combination by using a Shimadzu (Japan) LC-10ATVP instrument equipped with a UV detector (model SPD-10 AVP) connected to a micro system. The mobile phase was composed by acetonitrile and buffer solution (sodium dihydrogen phosphate – sulfonic acid) ((7:3 *v/v*). The pH 3.0 was adjusted by phosphoric acid. The analysis was performed at 25 ± 1 °C using isocratic condition. A volume of 25 µl was used for injection. The flow rate was 1.5 ml min^{-1}. All the solutions and mobile phase were sonicated for 25–30 min before use. The detection of BDS and FFD was carried out at 214 nm by C-18 column. The method was validated as per ICH guidelines [35].

The buffer was prepared by adding 1.38g of sodium dihydrogen phosphate and 1g of sulphonic acid in 1L distilled water. The pH was adjusted to about 3.0 with phosphoric acid. The mobile phase was prepared by adding buffer in acetonitrile (7:3 *v/v*). The stock solution of BDS and FFD was prepared by adding 50 mg and 60 mg, respectively, in 100 ml distilled water. A 4- and 5-ml solution was taken from of BDS and FFD, respectively, were taken in 50 ml volumetric flask. The volume is adjusted by distilled water. The mixture was filtered through 0.45 µ filter paper. The sample was sonicated before analyzed through HPLC.

A total of 10 capsules of budesonide and formoterol fumarate 400 µg /12 µg and transfer into 100ml flask and make up the volume with diluent to the mark to make concentration 40 µg/ml and 1.2 µg/ml respectively. The solution was filtered through 0.45 µ membrane filter paper and sonicated before HPLC analysis. Similarly, the reference product was processed in the same way as the sample. The final concentration of BDS and FFD was kept same i.e. 40 µg/ml and 1.2 µg/ml, respectively was maintained. The results were obtained by the Eq. 4

$$\%\text{Assay} = \frac{AU}{AS} \times \frac{CS}{CU} \times 100 \quad \text{Eq. (4)}$$

where,
AU = Area of sample
AS = Area of standard
CS = Concentration of standard
CU = Concentration of sample

Determination of Delivered Dose Uniformity

The delivered dose uniformity test was performed as per described by USP [32]. The device was loaded with capsule or powder for inhalation. The mouthpiece of sample was inserted horizontally into the mouthpiece adapter. The solenoid valve was closed and the vacuum pump was run. The powder was discharged into the sampling apparatus by activating the timer controlling the solenoid valve and withdrawn 2L of air from the product at the rate 60L/min air flow rate. The whole operation was repeated *n-1* times, where, n is the number of times defined in the labeling as the minimum recommended dose. The inhalation powder device was detached form the sampling apparatus and disconnected the vacuum tubing. The assay was made for the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with the diluent as described earlier.

Results and Discussion

Particle Size Distribution

Geometric particle size and size distribution studies are generally performed on inhalation powders to gather data on some basic properties of the powders. The geometric particle size distribution is measured by laser diffraction (LD). The density of the particle is not affected by the geometric particle size [36]. The LD is used to measure the D_v10, D_v50, and D_v90 (corresponding to the cumulative percentage particle undersize values for 10%, 50% and 90% of the particles by volume), and the % volume <5 µm were used for analysis [37]. The particle size and size distribution obtained from LD measurement for raw BDS, FFD, three locally manufactured DPIs and the reference DPI are shown in Table-1.

Table-1: Particle size and size distribution of raw BDS, FFD, commercial DPI formulations and reference product [a]

Material / Formulation	D_v10 (µm)	D_v50 (µm)	D_v90 (µm)	Span	Specific Surface Area (cm^2/g)
Raw BDS-1	0.5825	1.311	2.5305	2.202	7964
Raw BDS-2	0.1968	1.123	2.332	2.016	7531
Raw BDS-3	0.6465	1.061	2.3965	1.848	6339
Raw FFD-1	0.38695	1.48405	2.918	2.004	6977
Raw FFD-2	0.3363	1.3886	3.05	1.729	5216
Raw FFD-3	0.6006	1.5542	3.3360	1.76	4728
Commercial DPI-1	1.9979	54.234	79.072	1.421	2300
Commercial DPI-2	2.646	53.272	77.801	1.411	1815
Commercial DPI-3	1.9337	53.984	79.068	1.429	2304
Reference DPI	2.201	56.342	68.454	1.311	1917

[a]The values are mean of five determinations

Table 2: Aerosol performance parameters of raw BDS, FFD, commercial DPIs and reference product[a]

3		ED (%)	FPF (%)	MMAD (µm)	GSD
Raw BDS-1		**97.33±0.73**	**56.105±1.12**	**2.472±0.12**	**2.276±0.08**
Raw BDS-2		**96.9±0.84**	**55.865±0.98**	**2.614±0.39**	**2.411±0.12**
Raw BDS-3		**96.98±0.56**	**58.416±1.22**	**2.746±0.15**	**2.530±0.31**
Raw FFD-1		**95.45±1.23**	**35.459±1.03**	**2.677±0.22**	**2.150±0.44**
Raw FFD-2		**96.15±0.98**	**36.108±1.15**	**2.952±0.16**	**2.655±0.19**
Raw FFD-3		**95.23±1.52**	**36.091±0.99**	**2.815±0.28**	**2.110±0.09**
Commercial DPI-1	**BDS**	**98.19±0.98**	**31.568±0.86**	**2.699±0.32**	**1.998±0.08**
	FFD	**96.57±1.18**	**33.574±1.11**	**2.814±0.15**	**2.267±0.17**
Commercial DPI-2	**BDS**	**99.23±0.73**	**34.871±0.88**	**2.859±0.25**	**2.199±0.51**
	FFD	**98.65±1.11**	**32.162±0.43**	**2.761±0.19**	**2.541±0.34**
Commercial DPI-3	**BDS**	**97.53±0.87**	**32.155±0.87**	**2.741±0.32**	**2.223±0.15**
	FFD	**96.15±0.58**	**33.112±1.31**	**2.889±0.26**	**2.331±0.17**
Reference Product	**BDS**	**99.15±0.91**	**32.011±1.13**	**2.468±0.37**	**2.174±0.21**
	FFD	**98.27±1.01**	**32.341±0.81**	**2.616±0.34**	**2.214±0.34**

Mean ± standard deviation
[a]The values are mean of five determinations

It was noted that the particle size of all samples was within the range. The particle size for drug powder should be in range of 0.5 to 5 µm in size. Furthermore, the particles in the range of 0.5 to 3 µm are the most appropriate for the systemic absorption in alveoli and 3 to 5 µm for the localized terminal bronchioles [38].

It was found that D_v50 of raw material of drug contents was observed within the range 0.5 to 5 µm, whereas, the commercially available DPIs Dv50 was measured from 53.272 to 56.342 µm. The value of D_v50 of the particle size of DPIs powder has the shown the half of total amount of drug powder content delivered from device during aerosolization, basically a distribution between larger and smaller particle size [10]. Similarly, Parisini *et al.* has confirmed that the D_v50 of powdered in marketed DPIs was increased due to the blending of drug content with the carriers like fine lactose [37]. The particle size distribution of drug content in DPIs was increased by spray dried lactose mainly due to hydrolism [39], crystallization [40] and coarser carrier particles [41].

The results showed low range values explaining very high portion of homogenous smaller particles (≤5µm) with larger surface area due to the particle agglomeration. This factor is due to the cohesive behavior of smaller particles as reported earlier [12]. The formulations of DPIs may carrier based with drug powders (0.5 to 5 µm) is mainly attached with coarser spray dried lactose (50 to 200 µm), sometimes the fine particle may agglomerate to form a corser particle due to static charges [42].

Aerodynamic Particle Size Distribution

The aerodynamic diameter of particles was determined the efficacy of medicaments delivered by DPIs formulations [43, 44]. The MSLI is used to determine the delivered dose uniformity by the aerodynamic particle size distribution of DPIs formulations [42, 45]. The most important criteria of the appropriate aerodynamic particle size distribution were the percentage of emitted dose (%ED) which was mainly depends upon the percentage of fine particle fraction (%FPF) [46]. The basic need of the aerodynamic particle size distribution is the amount of drug present in DPIs capsule having capability to reach at the lungs and employed the desired therapeutic effect [47]. The aerosol performance parameters of raw BDS, FFD, commercial DPIs and reference product were presented in Table-2.

The desirable FPF range of particles in the lung cavity is ranges from 1 to 5 µm, as a percentage of the total ED [48]. The percentage of emitted dose (% ED) recovered from all the stages of MSLI of all samples is ranges from 95.45 to 99.23%, whereas, the fine particle fraction (%FPF) of all samples was found to be in the range of 31.57 to 58.42%. The %ED of marketed product of reported by Behara *et al.* found %ED greater than 75%, [49] Farkas *et al.* 71% [50] Mehta found 85.40% [51]. It has shown that the marketed DPIs product in Pakistan has possessed better emission of dose. The role of FPF has major effect on the delivered dose delivered to patients. Moreover, the FPF is increased due to the increased in the airflow rate [52]. The FPF of DPIs were reported by Zheng *et al.* >40% [42], Mehta, 52.99% [51], Saldanha *et al.* 9.8 to 49% [53] and Lechanteur and Evrard reported 14% [54].

The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the samples was found to be in the ranges of 2.472 to 2.952µm and 1.998 to 2.655 µm, respectively. The half of cumulative mean aerodynamic particle size was defined as MMAD [36]. In commercial products the value of D_v50 is higher than MMAD value. Mainly, MMAD values were conceptional for lung delivery, whereas, theoretically, it can be determined from the

geometric particle size and tap density [12]. The greater particle deaggregation is represented by the decreased MMAD values [55]. The smaller the MMAD values enhanced the marginal lung deposition. The confidence on the use of DPIs based on the flow rate of particle size for a more consistent delivered dose to the lungs [56].

Suzuki *et al.* determined that the GSD values of DPIs were low (≤2.75 µm). The low value of GSD along with low MMAD values was revealed of a perfect size distribution. This may aid in efficient pulmonary delivery [57]. Generally, the GSD of monodisperse DPIs have value 1 and above 1.22 is considered for polydisperse aerosol. However, most commercial DPIs having GSD values 2 to 3 and are considered as polydisperse [58]. This is evident that the greater the value of GSD help in the increase in the spreading of the residual particles.

Particle Density

The aerodynamic properties of inhalation products directly depend on the particle density. Therefore, particle densities are needed to be considered before aerodynamic particle size measurement [59]. Particle densities were calculated by Eq. 3, using MMAD and D_v50 values and shown in Table-3. The high density and small geometric diameter particles possessed greater deposition fractions in lung cavity. Musante *et al.* [60] clarified by the statistic that particles with a decrease in geometric diameter deposited mainly by diffusion. It was observed that increased in the value of MMAD may be affected on the density on deposition was reduced marked because of the reduced in the efficiency of diffusion for large particles. These polydisperse inhalers contained a substantial proportion of submicron particles which was deposited in the pulmonary airways with better efficiency than aerodynamically similar inhalers contained of geometrically larger porous particles [60].

Table-3: Particle densities calculated from MMAD and D_v50 [a]

Material / Formulation	MMAD (µm)	D_v50 (µm)	Particle Density (g/cm^3)
Raw BDS-1	**2.472±0.12**	**1.311**	**3.555**
Raw BDS-2	**2.614±0.39**	**1.123**	**5.418**
Raw BDS-3	**2.746±0.15**	**1.061**	**6.698**
Raw FFD-1	**2.677±0.22**	**1.4841**	**3.254**
Raw FFD-2	**2.952±0.16**	**1.3886**	**4.519**
Raw FFD-3	**2.815±0.28**	**1.5542**	**3.281**

Mean ± standard deviation
[a]The values are mean of five determinations

The particle density is directly proportional to the ability for the particles to reach deep into the lungs [61]. The importance of the particle density is for the determination of the correlation between mobility and aerodynamic diameter and mobility of particle. It aids to change in the number of particles distribution to mass concentration as early with the span of time. The variation in particle density is used to deduce the mechanism of aerosol formation. The density may help in the determination of the morphology of particles [62].

HPLC Assay of BDS and FFD

The analytical method was developed for simultaneous estimation of both the drugs by using constant flow method. The method was validated as per ICH Q2 R1 guidelines considering specificity, linearity, accuracy, precision, range and robustness [35]. Salem [63] developed a method with an accurate and validated ion-pairing HPLC method for the determination of budesonide epimers and formoterol fumarate simultaneously in metered dose inhaler. The wavelength was selected at 214nm. The proposed method was found rapid (7min), reproducible where relative standard deviation was found to be < 2.0% and effective resolution between FFD and BDS epimer B (resolution factor = 12.07). Nanasaheb and Kale [64] developed a method for simultaneous determination of BDs and FFD by using RP-HPLC method. The detection was carried out on dual wavelength detector at 214nm and 247nm for FFD and BDS, respectively. Forced degradation was used to establish stability indicating nature of the method. The method was satisfactorily validated as per the ICH Q2 (R1) guidelines. In another study, the workers explored the Quality by Design (QbD) approach in development of a new UHPLC method of testing for BDS/FFD and related substances using Fusion QbD® software. The gradient run time of 25 min was also appropriate. The same method produced similar separation in the sample solution of BDS and FFD prepared from a Symbicort® metered dose inhaler as compared to standard solution. Fadi and Alkhateeb concluded that application of QbD principles possessed advantage in development of analytical method. QbD provides in depth understanding for the effects of parameters along with acceptance and regulatory flexibility [65].

Budesonide is mixture of epimer A (BDS A) and epimer B (BDS B) [66], therefore, combined area of BDS A and BDS B was considered in calculation. The assay of BDS and FFD in raw, commercial DPIs and Reference product was made as per the validated assay method A typical chromatogram of assay is shown in Fig. 3. The assay data for raw BDS, FFD, commercial DPI formulations and reference products is presented in Table-4. All the assay results for raw BDS and FFD samples fall in the acceptable limit of 98%-102% [67] and 98.5% to 101.5% [68], respectively.

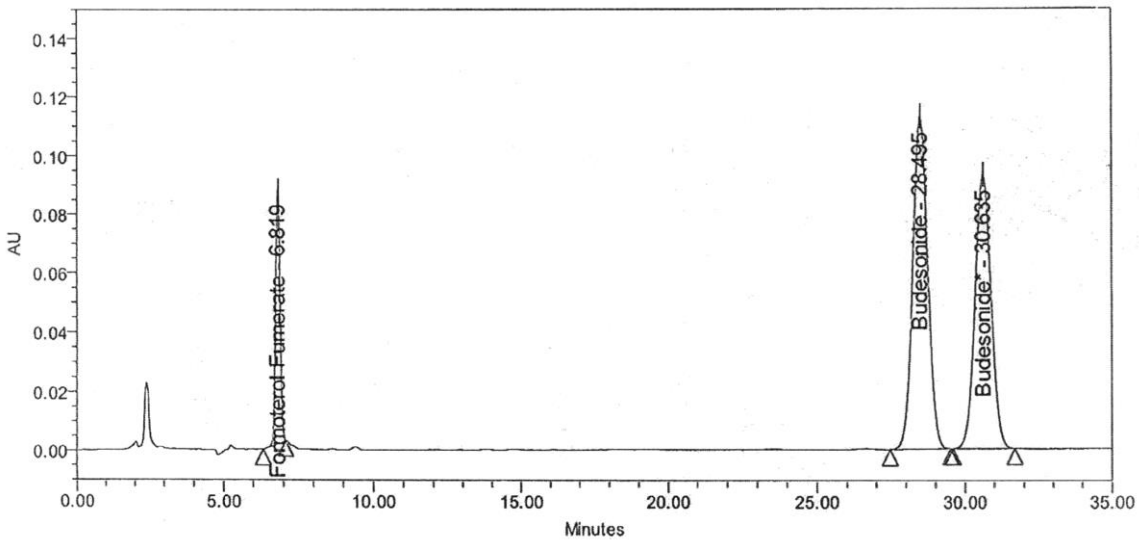

Fig. 3: Typical HPLC chromatogram of BDS and FFD.

Table-4: Results of Assay for raw BDS, FFD, commercial DPIs and reference products[a]

Material / Formulation		Assay (%)
Raw BDS-1		99.53±0.51
Raw BDS-2		100.1±0.43
Raw BDS-3		99.98±0.52
Raw FFD-1		100.25±0.44
Raw FFD-2		99.95±0.88
Raw FFD-3		99.63±0.11
Commercial DPI-1	BDS	99.99±1.35
	FFD	98.47±0.87
Commercial DPI-2	BDS	100.63±1.33
	FFD	100.25±1.18
Commercial DPI-3	BDS	99.835±1.49
	FFD	97.255±0.71
Reference Product	BDS	101.355±0.71
	FFD	99.67±1.34

Mean ± standard deviation
[a]The values are mean of five determinations

Delivered Dose Uniformity

The test for uniformity of delivered dose over the whole unit life is important for drug products packed in device-metered (multiple doses units) or in pre-metered dosage units (single dose units). For DPIs the products under study were in single dose form whereas the innovator product was in multi dose form hence, single reading was taken for locally manufactured DPIs samples whereas, two readings were taken for the innovator product [32]. The results of delivered dose uniformity for DPIs samples is shown in Table-5. The delivered dose uniformity of all the marketed products was compared to the innovator products and despite the difference. It was necessary to evaluate the delivered dose uniformity, which should be consistent so that the patient gets equal quantity of drug every time. The results were showed that of delivered dose uniformity were found comparable as the average content when sampled through sampling device for dry powder inhalers found to be well within range and no individual unit was below 85% and above 115% as required by USP general monograph for inhalation products [69].

Table-5: Results of Delivered Dose Uniformity for BDS and FFD in DPIs [a.]

Products	BDS		FFD
	Product No.	Average Results of 10 Units (mean ± SD)	Average Results of 10 Units (mean ± SD)
DPI	1	101.93 ± 4.12	100.12 ± 4.55
	2	103.19 ± 5.10	104.41 ± 3.77
	3	97.97 ± 3.72	99.39 ± 4.14
	Reference Product	100.76 ± 4.44	98.48 ± 3.35

Mean ± standard deviation
[a]The values are mean of five determinations

Conclusion

The use of DPIs is becoming popular, therefore, it is necessary to evaluate the performance characteristics of DPIs. In this study various physicochemical properties such as particle size and size distribution and density, of BDS and FFD powder along with performance of their commercial DPI formulations were evaluated. The study showed that the particle sizes and size distribution of raw BDS and FFD were in the range suitable for inhalation formulations. The delivery of BDS and FFD in suitable quantities to the deep lung tissues if properly used by the patient.

The geometric sizes of particles were comparably larger than the aerodynamic sizes. The commercial DPIs showed optimum quality parameters the performance test parameters of the commercial DPIs were found comparable to the reference product. Further,

studies are needed to explore other critical attributes like dissolution profiles and in-vivo performance etc.

Study Limitation

DPIs containing BDS and FFD are registered with few manufacturers in Pakistan, therefore, only three marketed samples could be considered in this study. Furthermore, same manufacturing dates formulations could not also be arranged from the market, therefore, samples with slightly different (± 03 months) manufacturing dates were used which is another limitation of this study.

Acknowledgments

The authors are thankful for the support of M/S. Scilife Pharma and Central Drugs Laboratory, Karachi for provision of testing equipment to conduct this study.

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