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PROCESS VALIDATION OF FORMOTEROL FUMARATE AND BUDESONIDE DRY POWDER INHALATION

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ABSTRACT

Quality and quantity of the drug is one of the main aspects of any formulation. The export of the prepared formulations depends upon the factors like money, quality and product specification. The parameters are being evaluated using the process validation techniques. The present research article represented the validation of Formoterol fumarate and Budesonide dry powder inhalation as per ICH guidelines.

INTRODUCTION

Formoterol is a long-acting β_2-agonist used in the management of asthma or chronic obstructive pulmonary disease (COPD). This drug has extended duration of action up to 12 hours in comparison to short-acting β_2 agonists which are effective for 4–6 hours. This category of drug acts by treating the exacerbation of asthma by relaxing the smooth muscles of airway. Formoterol have a faster onset of action as a result of lower lipophilicity, and is more potent in comparison to other drugs of this category such as salmeterol and bambuterol [1-2].

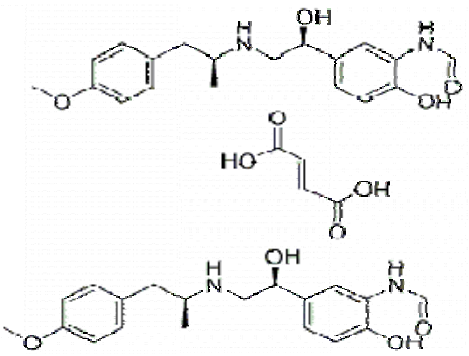

Figure 1 Chemical Structure of Formoterol Fumarate

Budesonide is a glucocorticoid steroid for the treatment of asthma and non-infectious rhinitis. In addition, it is used for Crohn's disease and for treatment and prevention of nasal polyposis. When compare to prednisolone it shows fewer bone density losses therefore can be used for longer duration.

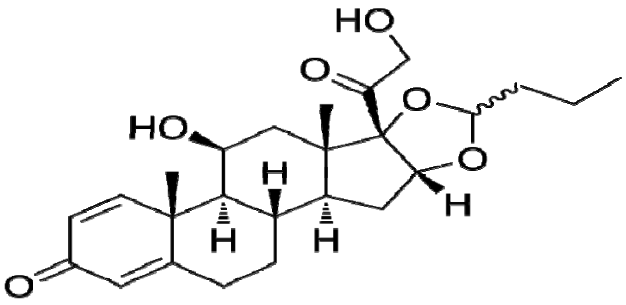

Figure 2 Chemical Structure of Budesonide

Process validation is establishing documented evidence which provides a high degree of assurance, for a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics[3]. Validation is a concept that has been evolving continuously since its first formal appearance in the United States in 1978. The concept of

validation has expanded through the years to encompass a wide range of activities from analytical methods used for the quality control of the drug substances and drug products to computerized systems for clinical trials. A validated process assures that the final product has a high probability of meeting the standards for identity, strength, quality, purity and stability of the drug product [4-5]. In this research article, the process validation of Formoterol fumarate and Budesonide dry powder inhalation was carried out to establish efficacy of combination product.

MATERIALS AND METHOD

Formoterol fumarate and Budesonide was obtained as a gifted sample from Finar chemicals, Ahmedabad. Lactose was purchased from the local market. All the ingredients were used as received. Vibratory sifter, Mechanical Stirrer, Fluid bed granulator, Turbula mixer blender, Air Jet mill, Vernier caliper, Capsule filling Machine were used as per specified in ICH guidelines

To conduct the process validation of the manufacturing process for product Formoterol Fumarate and Budesonide Powder for Inhalation IP 6+400 mcg. Three consecutive batches of Formoterol Fumarate and Budesonide Powder for Inhalation IP 6+400 mcg shall be taken up for Process Validation.

CRITICAL PROCESS PARAMETERS

Step No.	Process Stage	Specifications
1	Environmental conditions during processing % Relative Humidity Temperature	 Below 45% Below 25%
2	Preparation of Budesonide Solution	Clear Solution
3	Top Spray Granulation Inlet Temperature Product Temperature during top spray granulation Product Temperature during drying Exhaust Temperature during top spray granulation Exhaust Temperature during drying Atomization Air Drive Speed Pump RPM Air Flow Spray rate % LOD (at the end of drying)	 45±15˚C 30±10˚C 35±10˚C 30±10˚C 30±5˚C 0.1-0.5 bar 20±10 20±10 20±10 15±10 NMT 0.30%w/w at 105ºC for 5 min.
4	Micronization of Budesonide Air Pressure Screw feeder rate Grinding Pressure Ventury Pressure Particle size distribution	 8-12 bar 9 - 15 RPM 3.50 Kg/cm^2 1.00 Kg/cm^2 D90 value should be between 2-12 micron
5	Micronization of Lactose monohydrate Air Pressure Screw feeder rate Grinding Pressure Ventury Pressure Particle size distribution	 8-12 bar 24 - 27 RPM 3.5 Kg/cm^2 1.0 Kg/cm^2 D90 value should be between 15-30microns
6	Sifting	Through sieve #40

IN PROCESS SPECIFICATION

During Granulation, micronozation and blending

Sr. No.	Parameters	Description
Budesonide Granules		
1	Assay of Budesonide (by HPLC)	Not less than 90.0% and Not more than 115.0% of label claim
2	Residual Solvent	Isopropyl Alcohol: Not more than 5000ppm
Budesonide Micronised Blend		
1	Description	White to off White powder
2	Assay of Budesonide (by HPLC)	Not less than 90.0% and Not more than 115.0% of stated label claim
3	Loss on drying (By halogen moisture analyser)	NMT 1.2 % w /w
4	Particle Size Distribution (by Malvern)	D90 value should be between 2-12 microns
Formoterol Fumarate and Budesonide Blend		
1	Appearance	White to off white powder
2	Assay (by HPLC) a) Formoterol Fumarate b) Budesonide	NLT 90.0% and NMT 125.0% of Label Claim
3	Blend Uniformity Analysis (By HPLC) a) Formoterol Fumarate b) Budesonide	Each indivisual value is NLT 90.0% and NMT 125.0% of Formoterol Fumarate & Budesonide stated in the blend RSD is less than or equal to 6.0 %
5	Particle Size Distribution by Malvern	For information
6	Bulk Density	For information
7	Tapped density	For information

During Capsule Filling

Sr. No.	Parameters	Description
1	Description	Size '3' capsule with opaque brown cap having "G" logo and transparent body, filled with white to off-white powder.
2	Target fill weight	25.0 mg
3	Average weight of filled capsules	73.0 mg ± 5.0% (69.35 mg to 76.65 mg) Considering size '3' empty capsule average weight 48mg.
4	Average net content	25.0mg ± 4.0% (24.0 mg to 26.0mg)
5	Weight variation of net content	25.0mg ± 10.0% (22.5 mg to 27.5 mg)
6	Locked length	15.80mm ± 0.40mm (15.40mm to 16.20mm)

SAMPLING PROCEDURE AND TESTING PLAN

During Manufacturing and Capsule Filling

Product Name	Average Weight	Quantity	Test required
Granulation Stage (After 1 hour resting)			
Budesonide Blend	100 mg dried granules of Budesonide contains 10 mg of Budesonide	600 mg in one vial, 200 mg from each locations (total 3 locations) (In triplicate) i.e total 3 vials containing 600 mg each	Assay and Organic volatile impurities (Residual solvent)
Micronisation stage (At initial stage and after 30 min of micronisation)			
Budesonide Micronised Blend	100 mg micronised blend contains 10 mg of Budesonide	2 g in one vial	Particle size distribution
Micronisation stage (After 1 hour resting)			
Budesonide Micronised Blend	100 mg micronised blend contains 10 mg of Budesonide	5g in one vial, 1.66 g from each locations (total 3 locations) (In triplicate) i.e. total 3 vials containing 5 g each	Description, Assay, LOD and Particle size distribution
Micronisation stage (After 7 and 14 days of micronisation for hold time study)			
Budesonide Micronised Blend	100 mg micronised blend contains 10 mg of Budesonide	For Assay: 1 g For LOD: 1 g For Microbial analysis: 12 g	Assay, LOD and Microbial analysis

RESULTS

Finished Product Report (Certificate of analysis) of all the three batches of Formoterol Fumarate and Budesonide Powder for Inhalation IP (6+400 mcg) is tabulated below.

S. No.	Test	Acceptance Criteria	Batch No.		
			12110057	**12110058**	**12110059**
1.	Description	Size '3' capsule with opaque brown cap having "G" logo and transparent body, filled with white to off-white powder.	Size '3' capsule with opaque brown cap having "G" logo and transparent body, filled with white powder.	Size '3' capsule with opaque brown cap having "G" logo and transparent body, filled with white powder.	Size '3' capsule with opaque brown cap having "G" logo and transparent body, filled with white powder.
2	Identification for Formoterol Fumarate	**A) By HPLC:** In the test for assay, the retention time of principal peak from the sample should match with that from Formoterol Fumarate In- house	Complies	Complies	Complies
	Identification for Budesonide	**B) By HPLC:** In the test for assay, the retention time of principal peak from the sample should match with that from Budesonide In- house Reference/			
3	Average weight of filled capsules	73.0 mg ± 5.0%	Complies	Complies	Complies
4	Net Content a) Average net content b) Weight variation of net content	25.0mg ± 5.0% 25.0mg ± 10.0%	24.70 mg Complies	24.68 mg Complies	25.35 mg Complies
5	Assay (by HPLC) Formoterol Fumarate	NLT 90.0% and NMT 125.0% of Label Claim	100.3 %	101.6 %	100.4 %
	Assay (by HPLC) Budesonide	NLT 90.0% and NMT 125.0% of Label Claim	101.0 %	101.4 %	100.6 %

6	Uniformity of delivered dose of Formoterol Fumarate and Budesonide	Nine out of ten results lie between 75% and 125% of the average value and all lie between 65% and 135%. If 2 or 3 lie outside the limit of 75% to 125%, repeat the test for 2 more times (20 capsules). NMT 3 of the 30 capsules lies outside the limit of 75% to 125 % & no value lies outside the limit of 65 % to 135%	Complies	Complies	Complies
7	Uniformity of Content for Formoterol Fumarate and Budesonide(By HPLC)	NMT one individual value thus obtained is outside the limit 85% to 115% of the average value and none is outside the limit 75% to 125% when determined on 10 units.	Complies	Complies	Complies
8	Related Substances (By HPLC) Formoterol Fumarate	Single Maximum Impurity : NMT 3.0 % w/w Total Impurity : NMT 5.0 % w/w	0.03 % 0.06 %	0.02 % 0.02 %	0.05 % 0.13 %
	Related Substances (By HPLC) Budesonide	Single Maximum Impurity : NMT 3.0 % Total Impurity : NMT 5.0 %	0.22 % 0.69 %	0.19 % 1.57 %	0.16 % 0.56 %
9	Microbial Limits Total viable aerobic bacterial count **<u>Absence of Pathogenic organism</u>** *Escherichia coli* *Salmonella* *Staphylococcus aureus* *Pseudomonas aeruginosa*	Not more than 100 cfu / g Absent per 10 g Absent per 50 g Absent per 10 g Absent per 10 g	30 cfu / g Absent Absent Absent Absent	20 cfu / g Absent Absent Absent Absent	20 cfu / g Absent Absent Absent Absent

CONCLUSION

All the analytical data derived during process validation of Formoterol fumarate and Budesonide dry powder inhalation with reference to TDM. Hence process is validated.

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