International Journal of Medical and Pharmaceutical Sciences
Open access peer-reviewed Journal
Volume 2, Issue 8, Page 797-803.
https://doi.org/10.5281/zenodo.22171061

Research Article

Formulation Development and Evaluation of Fluticasone Propionate and Salmeterol Xinafoate Powder for Inhalation

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Pulmonary drug delivery provides a direct route for treating respiratory disorders such as asthma and chronic obstructive pulmonary disease. Dry powder inhalers offer rapid pulmonary delivery, patient convenience and avoidance of first-pass metabolism. The present study aimed to develop and evaluate a dry powder inhalation formulation containing fluticasone propionate, an inhaled corticosteroid, and salmeterol xinafoate, a long-acting β_2-adrenergic agonist. Preformulation studies included organoleptic evaluation, solubility, melting point, UV spectrophotometric analysis and ATR-FTIR compatibility studies. Eight formulations (F1–F8) were prepared using different ratios of fine- and coarse-grade lactose monohydrate, with or without magnesium stearate. The formulations were evaluated for flow properties, capsule net content, locking length, moisture content, assay, uniformity of delivered dose and aerodynamic particle-size distribution using a Next Generation Impactor. The formulations exhibited acceptable physical characteristics, with angle of repose of 34–47°, Carr's index of 11.71–32.30% and Hausner's ratio of 1.17–1.48. Net capsule content ranged from 23.98–26.13 mg, while moisture content ranged from 4.12–6.32%. Assay values ranged from 99.8–115.4% for fluticasone propionate and 97.1–101.7% for salmeterol xinafoate. F3 and F7 showed better overall flow and drug-delivery characteristics and were selected for aerodynamic evaluation. F7 demonstrated superior aerodynamic performance, with a fine particle fraction of 42.29%, mass median aerodynamic diameter of 2.90 µm and geometric standard deviation of 1.78. The optimized formulation demonstrated satisfactory stability and improved aerosolization characteristics. Thus, optimization of lactose grade ratio and omission of magnesium stearate may improve the performance of fluticasone propionate–salmeterol DPI formulations.

Keywords: Fluticasone propionate, Salmeterol xinafoate, Dry powder inhaler, Lactose monohydrate and Fine particle fraction.

INTRODUCTION

Pulmonary drug delivery is an important route of administration for the treatment of respiratory disorders because it enables direct delivery of the active pharmaceutical ingredient to the lungs. The large surface area and extensive vascularization of the pulmonary system provide favourable conditions for local and systemic drug absorption. Inhalation therapy can also reduce the influence of gastrointestinal degradation and first-pass metabolism associated with oral administration[1,2]. Dry powder inhalers (DPIs) are breath-actuated pulmonary drug-delivery systems in which the drug is formulated as a dry particulate powder[3,4]. Their performance is strongly influenced by particle size, powder flow, drug–carrier interactions, formulation composition and inhaler/device characteristics. Particles in the

respirable range are required for effective deposition in the lower respiratory tract[3-5]. Asthma and chronic obstructive pulmonary disease are chronic respiratory disorders associated with airway inflammation and airflow limitation. Combination therapy involving an inhaled corticosteroid and a long-acting β2-adrenergic agonist is widely used to provide both anti-inflammatory and bronchodilator effects. Fluticasone propionate acts primarily as an inhaled corticosteroid, whereas salmeterol xinafoate produces prolonged bronchodilation through β2-adrenergic receptor stimulation. The thesis literature review identifies the combination of these two drugs as an established therapeutic approach in asthma and COPD[6-9]. The performance of a DPI depends not only on the properties of the drug but also on the carrier system. Lactose monohydrate is commonly used as a carrier in DPI formulations. Fine lactose can assist drug-carrier interactions and dispersion, whereas coarse lactose can contribute to powder handling and flow characteristics[4,5,10]. Magnesium stearate may also influence powder flow, but its presence can alter aerosolization and drug deposition characteristics[10,11]. In the present investigation, different ratios of fine-grade lactose monohydrate (Lactose 200) and coarse-grade lactose monohydrate (Lactose 300) were investigated, with and without magnesium stearate. The objective was to identify a formulation with improved powder flow and aerodynamic performance suitable for pulmonary drug delivery.

1. AIM AND OBJECTIVES

AIM

The aim of the present study was to develop and optimize a dry powder inhalation formulation containing fluticasone propionate and salmeterol xinafoate with improved powder-flow characteristics and pulmonary drug deposition.

OBJECTIVES

The study was designed:

1. To characterize fluticasone propionate and salmeterol xinafoate using physicochemical and spectroscopic techniques.
2. To evaluate the solubility and compatibility of the drugs with selected excipients.
3. To develop different DPI formulations using different ratios of fine and coarse lactose monohydrate.
4. To investigate the influence of magnesium stearate on formulation performance.
5. To evaluate the prepared formulations for flow properties, physical characteristics, moisture content, assay and uniformity of delivered dose.
6. To determine the aerodynamic particle-size distribution of selected formulations using a Next Generation Impactor.
7. To identify the optimized formulation based on its overall physicochemical and aerodynamic performance.
8. To assess the stability of the optimized formulation.

MATERIALS AND METHODS

3.1 MATERIALS

Fluticasone propionate and salmeterol xinafoate were used as active pharmaceutical ingredients. Lactose monohydrate of fine and coarse grades was used as the carrier system, while magnesium stearate was incorporated as a flow-modifying excipient in selected formulations. Size 3 hard gelatin capsules were used for filling the prepared powder.

3.2 Preformulation Studies

3.2.1 Organoleptic Evaluation

The active pharmaceutical ingredients were examined for colour, odour and physical nature. Fluticasone propionate was observed as a white-to-off-white crystalline powder and salmeterol xinafoate as a white crystalline powder. Both were reported to be odourless.

3.2.2 Solubility Studies

The solubility of fluticasone propionate and salmeterol xinafoate was investigated in water, ethanol, dimethyl sulfoxide and acetone. Fluticasone propionate was insoluble in water, sparingly soluble in ethanol and freely soluble in dimethyl sulfoxide, while salmeterol xinafoate was very slightly soluble in water, soluble in ethanol and dimethyl sulfoxide. Both drugs showed solubility in acetone.

3.2.3 Melting Point

The melting points of the active ingredients were determined using a suitable capillary method. The melting point of fluticasone propionate was reported as approximately 238°C, while that of salmeterol xinafoate was approximately 154°C.

3.2.4 UV Spectrophotometric Analysis

UV spectra were recorded in the range of 200–400 nm. The maximum absorption wavelength was observed at 239 nm for fluticasone propionate and 252 nm for salmeterol xinafoate. Calibration curves were subsequently prepared over the concentration range of 1–10 µg/mL. Both drugs showed good linearity over the investigated range, with regression coefficients of 0.9967 and 0.9964 for fluticasone propionate and salmeterol xinafoate, respectively.

3.2.5 ATR-FTIR Compatibility Study

ATR-FTIR spectra were recorded over 4000–400 cm^{-1}. Characteristic functional-group peaks of fluticasone propionate and salmeterol xinafoate were identified. The spectra of the drug–excipient mixture did not show evidence of significant chemical interaction, supporting the compatibility of the selected formulation components.

4. FORMULATION DEVELOPMENT

Eight formulations, designated F1–F8, were developed by varying the ratios of fine-grade and coarse-grade lactose monohydrate. F1–F4 contained magnesium stearate, whereas F5–F8 were prepared without magnesium stearate. The quantities of the active ingredients were maintained constant across all formulations.

4.1 Preparation of DPI Formulations

The formulation components were accurately weighed and handled under controlled environmental conditions. Lactose monohydrate 200, lactose monohydrate 300 and magnesium stearate were passed through a 60# sieve. The active ingredients and carrier materials were blended using geometric dilution. The powder mixture was transferred to a DPI mixing vessel and blended for one hour using forward and reverse mixing cycles. Following blending, the powder was allowed to equilibrate before evaluation and capsule filling. The prepared powder was filled into size 3 capsules with a target fill weight of approximately 25 mg per capsule.

5. EVALUATION OF DPI FORMULATIONS

The prepared formulations were evaluated for:

Flow properties
Physical appearance
Average net content
Capsule locking length
Moisture content
Assay of active ingredients by HPLC
Uniformity of delivered dose
Aerodynamic particle-size distribution using NGI
Stability

5.1 Flow Properties

Angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index were determined. The results were used to compare the flow characteristics of the formulations.

5.2 Physical Appearance

The filled capsules were visually examined for particulate matter, colour change, sticking of powder to the capsule shell and softening. The formulations generally showed acceptable physical characteristics. However, sticking/lump formation was noted in some formulations, particularly F1 and F5, which was attributed in the thesis to the higher proportion of coarse lactose.

5.3 Average Net Content

The average net content of the capsules ranged from 23.98 to 26.13 mg. The values were reported to be within the target specification of 25 ± 5%.

5.4 Capsule Locking Length

The locking length of the filled capsules was determined using a suitable measuring device. The observed values were within the reported specification range of 14.90–15.30 mm.

5.5 Moisture Content

Moisture content was determined using Karl Fischer titration. The values ranged from 4.12 to 6.32% among the formulations.

5.6 Assay by HPLC

The assay of fluticasone propionate and salmeterol xinafoate was determined using HPLC.

5.7 Uniformity of Delivered Dose

The uniformity of delivered dose was evaluated for the prepared DPI formulations. The reported values for all formulations were within the range of 80–120% of the assay value, indicating acceptable dose-delivery uniformity. Based on the combined evaluation of flow properties, assay and delivered-dose uniformity, F3 and F7 were selected for further aerodynamic assessment.

6. Aerodynamic Assessment Using Next Generation Impactor

The aerodynamic performance of F3 and F7 was evaluated using a Next Generation Impactor. Drug deposition was determined across the different stages of the impactor, and the aerodynamic performance was expressed in terms of fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD).

7. Stability Study

The optimized F7 formulation was subjected to stability evaluation under accelerated conditions of 40°C ± 2°C/75% RH ± 5% RH. Physical appearance, particulate matter, capsule softening, sticking, moisture content and assay were monitored.

RESULTS AND DISCUSSION

The present investigation focused on developing a combination DPI containing fluticasone propionate and salmeterol xinafoate with improved powder-flow and aerosolization characteristics. Preformulation studies confirmed the physical identity and suitability of the selected drugs. The UV maxima were found at 239 and 252 nm for fluticasone propionate and salmeterol xinafoate, respectively, and both drugs showed good linearity over the investigated concentration range.

Table 01: Composition of Fluticasone Propionate–Salmeterol DPI Formulations

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
Fluticasone propionate (mg)	0.275	0.275	0.275	0.275	0.275	0.275	0.275	0.275
Salmeterol xinafoate (mg)	0.0798	0.0798	0.0798	0.0798	0.0798	0.0798	0.0798	0.0798
Lactose monohydrate 200 (mg)	12.08	18.33	20.83	22.08	12.15	18.40	20.90	22.15
Lactose monohydrate 300 (mg)	12.50	6.25	3.75	2.50	12.50	6.25	3.75	2.50
Magnesium stearate (mg)	0.0625	0.0625	0.0625	0.0625	—	—	—	—
Capsule size	3	3	3	3	3	3	3	3

The ATR-FTIR investigation indicated that the characteristic functional groups of the active ingredients were retained and no significant interaction was observed in the drug–excipient mixture. Eight formulations were developed by varying the proportions of fine and coarse lactose and by incorporating magnesium stearate in selected batches. The flow-property results demonstrated considerable differences between formulations. F3 and F7 showed substantially better flow characteristics than the other formulations. F7 demonstrated the lowest Carr's index (11.71%) and Hausner's ratio (1.13), indicating improved powder flow.

Table 02: Results for Flow Properties of DPI Formulations

Formulation	Angle of repose (°)	Bulk density (g/mL)	Tapped density (g/mL)	Hausner's ratio	Carr's index (%)
F1	46	0.61	0.846	1.39	27.89
F2	42	0.59	0.798	1.35	26.06
F3	34	0.50	0.585	1.17	14.52
F4	38	0.48	0.620	1.29	22.58
F5	47	0.57	0.843	1.48	32.30
F6	44	0.51	0.655	1.31	22.14
F7	35	0.49	0.555	1.13	11.71
F8	40	0.38	0.508	1.33	25.19

F7 demonstrated the most favourable flow characteristics, with a Hausner's ratio of 1.13 and Carr's index of 11.71%. The physical evaluation demonstrated that the formulations maintained acceptable capsule characteristics. The average net content ranged from 23.98 to 26.13 mg, while locking length remained within the reported specification. Moisture content was between 4.12 and 6.32%.

Table 03: Moisture Content of DPI Formulations

Formulation	Moisture content (%)
F1	5.19
F2	4.12
F3	6.09
F4	4.47
F5	5.22
F6	6.32
F7	5.18
F8	4.58

The assay results demonstrated acceptable drug content across the formulations. Fluticasone propionate showed values approximately between 99.8 and 115.4%, whereas salmeterol xinafoate ranged from 97.1 to 101.7%. Delivered-dose uniformity was reported to remain within 80–120% of the assay value.

Table 04: Assay of Fluticasone Propionate and Salmeterol Xinafoate

Formulation	Fluticasone propionate (%)	Salmeterol xinafoate (%)
F1	109.2	99.6
F2	105.5	97.1
F3	112.8	100.3
F4	99.8	99.3
F5	109.4	97.7
F6	103.7	99.8
F7	114.0	101.7
F8	110.3	98.5

F3 and F7 were therefore selected for aerodynamic characterization. The NGI results indicated superior performance of F7, particularly in terms of fine particle fraction. The thesis reports an FPF of 42.29%, MMAD of 2.90 µm and GSD of 1.78 for the best-performing formulation. These characteristics are favourable for aerosol particles intended to reach the lower respiratory tract.

Table 05: Results of APSD of Formulations F3 & F7

Stages	Fluticasone propionate		Salmeterol xinafoate	
	F3	F7	F3	F7
Device retention	4.6	6.7	11.7	10.2
Mouth piece	3.4	1.5	1.5	4.1
Induction port	6.6	8.1	6.2	4.8
Pre separator	44.7	40.8	38.4	35.3
Stage 1	5.0	4.6	3.8	3.7
Stage 2	8.0	9.4	8.7	7.3
Stage 3	11.3	11.8	12.3	14.1
Stage 4	11.4	11.4	11.4	15.2
Stage 5	4.6	4.6	4.0	5.7
Stage 6	1.2	0.8	0.7	1.4
Stage 7	0.5	0.3	0.3	0.6
MOC	0.2	0.2	0.2	0.3
Copley data				
FPF (%)	32.13	33.62	35.43	42.29
MMAD (µm)	3.19	3.31	3.27	2.90
GSD (µm)	1.91	1.88	1.80	1.78

Table 06: Stability studies of optimized formulation F7 at room temperature 40^0C.

Parameters	Controlled	After 1 month	After 2 months	After 3 months
Particulate matter	Not observed	Not observed	Not observed	Not observed
Colour change	Not observed	Not observed	Not observed	Not observed
Sticking of blend inside the capsule shell	Not observed	Not observed	Not observed	Not observed
Softening of the capsules	Not observed	Not observed	Not observed	Not observed
Moisture content %	5.18	5.18	5.17	5.16
Assay of Fluticasone propionate	114.0%	110.7%	113.2%	112.2%
Assay of Salmeterol xinafoate	101.7%	99.8%	102.8%	100.7%

The improved performance of F7 may be related to its optimized balance of fine and coarse lactose in the absence of magnesium stearate. The thesis similarly concludes that the formulation without magnesium stearate demonstrated improved flow and drug-deposition characteristics compared with the corresponding formulation containing magnesium stearate.

CONCLUSION

The present study successfully developed and evaluated dry powder inhalation formulations containing fluticasone propionate and salmeterol xinafoate using different grades and ratios of lactose monohydrate, with and without magnesium stearate. Preformulation studies confirmed the suitability and compatibility of the selected formulation components. Among the eight formulations, F3 and F7 exhibited comparatively favourable flow and dose-delivery characteristics and were therefore subjected to aerodynamic evaluation. F7 demonstrated the superior overall performance, with favourable flow characteristics, acceptable drug content and improved aerodynamic properties. The reported fine particle fraction, MMAD and GSD values demonstrated the potential of F7 for improved pulmonary deposition. The improved performance of F7 was associated with optimization of the lactose grade ratio and the absence of magnesium stearate. The formulation exhibited good physical stability with minimal changes in moisture content and assay during the reported stability assessment. Overall, the findings demonstrate that appropriate optimization of carrier

grade and formulation composition can significantly influence the performance of fluticasone propionate–salmeterol DPI formulations. F7 may therefore be considered the optimized formulation from the investigated batches, subject to confirmation of the original aerodynamic and stability records.

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Cite: Tirumala Devi K.*, Prasada Rao M., Manikanta P., Formulation Development and Evaluation of Fluticasone Propionate and Salmeterol Xinafoate Powder for Inhalation, Int. J. Med. Pharm. Sci., 2026, 2 (8), 797-803. https://doi.org/10.5281/zenodo.22171061