RESEARCH ARTICLE

A Novel Metered Dose Inhalation Formulations with Formoterol 6 Mcg and Beclomethasone 200 Mcg by Using Breath Actuated Inhaler

Musale VP[1*], Shah PJ[2]

[1]*Department of Quality Assurance, Rubicon Research Private Limited, Thane, Maharashtra, India.*
[2]*Department of Pharmaceutics, Maliba College of Pharmacy, Bardoli, Surat, Gujarat, India.*

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ABSTRACT

Metered spray inhalers represent a broadly utilized dosage form for delivering anti-asthmatic drugs to the pulmonary system. The drug-device combination formulation, which includes beclomethasone dipropionate (BDP) and formoterol fumarate (FF), are widely employed for the treatment of bronchial asthma and chronic obstructive pulmonary diseases (COPD). The current formulation available in the market contains both active ingredients, FF and BDP, dissolved in a mixture of hydrofluoroalkane (HFA) 134a and ethanol are commonly used together as a co-solvent. However, individuals with religious or cultural concerns may opt to avoid using inhalers containing alcohol. In such cases, they may prefer non-alcoholic alternatives that are also accessible in the market. This study presents an innovative formulation strategy for metered-dose inhalers based on HFA that are non-alcoholic in combination therapy of FF and BDP inhalers. The novelty of the recently developed formulation lies in the substitution of ethanol with PEG 1000 as a co-solvent. Additionally, PEG 1000 serves the dual function of acting as a dispersing agent, thereby stabilizing the developed formulation. Moreover, it facilitates the delivery of synergistic effects by lubricating the valve components, ensuring smooth and flawless spray performance. The assay results for FF were 99.7 and 98.4%, while for beclomethasone, they were 101.0 and 99.7%, respectively, for pMDI and breath actuated inhaler (BAI). The percentage of emitted dose was 43.7 and 44.2% for pMDI, and 42.9 and 49.8% for BAI. Overall, both the developed conventional pMDI formulations and BAI exhibited efficient performance characteristics with equivalent performance.

Keywords: Formoterol fumarate, Beclomethasone, Hydrofluoroalkane, Asthma, pMDI, Breath actuated inhaler, Drug-device combination.

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INTRODUCTION

Asthma is a chronic condition resulting from airway inflammation, manifesting in symptoms such as coughing, wheezing, chest tightness, and breathing difficulties. This inflammation heightens the sensitivity of the airway's smooth muscles, leading to forceful contractions (bronchospasm) when exposed to various triggers. Asthma typically involves periods of symptom remission interrupted by sudden exacerbations. Recent studies highlight the significant synergistic effect of combining formoterol fumarate (FF) and beclomethasone dipropionate (BDP) is administered through pressurized metered dose inhalers (pMDIs) to manage and control asthma effectively. BDP is classified as a glucocorticosteroid and is employed to assist in mitigating inflammation associated with COPD. FF dihydrate belongs to the class of LABA-2 agonists. class, aiming to widen the air passages in the lungs for enhanced respiratory ease. This action aids in relaxing the smooth muscles encircling the airways, thereby facilitating smoother breathing. The combined effects of BDP and FF dihydrate collaboratively contribute to keeping the airways unobstructed and promoting improved respiratory function.

Currently, pharmaceuticals are administered through various routes into the body, utilizing diverse forms of dosage that facilitate drug delivery. A relatively modern advancement in pharmaceuticals involves administering drugs through the lungs. The onset of action through inhalation is notably rapid compared to oral and additionally, metered dose inhalers provide one of the external routes of administration are extensively employed in the management of respiratory airway diseases, as reported by Bisgard (2002) and Williams (2008).[1,2]

**Author for Correspondence: vinsweet1915@gmail.com*

Medicated inhaler formulations usually consist of a drug component combined with one or more propellants. They may also include formulation additives such as co-solvents and surfactants. The propelling liquified gas system plays a fundamental role in formulations, acting as dispersion medium and a solvent for the active substance and other excipients. The passage explains how the aerosol cloud is generated when activated, with an energy source enabling the release of the dose *via* the metering valve, a mechanism detailed by Williams (1998).[2]

The existing formulation available on the market includes both active ingredients, FF and BDP, dissolved in a blend of co-solvent (ethanol) and HFA 134a. However, due to religious or cultural considerations, some individuals may choose to avoid using alcoholic inhalers and may instead prefer non-alcoholic alternatives that are also available in the market. This research presents a innovative formulation strategy for non-alcoholic HFA-based inhalers formulations, particularly focusing on combination therapy involving FF and BDP inhaler. The research on integrating a developed formulation for Formoterol: Beclomethasone pMDI with a breath-actuated inhaler (BAI) device has shown the benefits of incorporating a BAI to enhance drug-device association. This inclusion in the non-alcoholic HFA suspension promotes patient preference for the device during administration, facilitating easier breathing and airway opening. A comparative evaluation was carried out among the conventional non-alcoholic MDI, and the breath actuated inhaler, revealing equivalent and comparable performance with demonstrated efficacy.[3-8]

MATERIALS AND METHODS

Materials

Samples for drug substances such as FF were sourced from Vamsi Labs Ltd., Solapur, while anhydrous BDP was obtained as a gift sample from Avik Pharma Pvt. Ltd., Vapi Gujarat. Polyethylene glycol 1000 was acquired from Croda Chemicals, Mumbai. Propellant HFA 134a (1,1,2,2 Tetrahydrofluoroethane) and 25 µL metering valves (stainless steel 3M), along with 14 mL aluminium canisters, were provided as gift samples by Medisol., Vapi Gujarat. Using the pressure filling method, the product was filled into the 14 mL aluminium canisters using a Pamasol 2045 machine from Switzerland *via* crimped metering valves. Autohaler samples were purchased from the local market (Cipla Ltd., India). The chemicals and reagents utilized for analytical determination meet the standards of analytical grade quality.

Methods

MDI formulations preparation method

The suspension was prepared by accurately weighing 0.00144 g of FF and 0.048 g of beclometasone dipropionate (equivalent to 200 doses delivering 6 and 200 mcg/dose, respectively). Each canister received a weighed quantity of the drug and the required excipients, with 0.003168 g of polyethylene glycol 1000 added to each. The canisters were then crimped with a 25 µL stainless steel metered valve using a crimper, and approximately 7.2 g of propellant HFA 134a (1,1,2,2 Tetrahydrofluoroethane) was forced under pressure into each canister using a filling crimping machine (Pamasol 2045, Switzerland) via the pressure filling method. After crimping and filling, the canisters were sonicated in a water bath containing cool water at 10°C for 15 minutes to check for any leakage and to ensure homogenous mixing of the contents, affix/installed the canister in Autohaler.[9-11]

Evaluation of physical parameters

The inhalers underwent evaluation for physical parameters, including crimp height and crimp diameter using a socage gauge, total height measured with a vernier calliper, vapor pressure assessed with a dome's gauge, and the number of deliveries determined by manually actuating the canister under a fume hood.

Content per canister

Place a stainless-steel holder with three legs and a central indentation with a hole (1.5 mm diameter, about 20 mm height) tapered downward within a 100 mL beaker. Add approximately 60 mL methanol such that discharge takes place at least 25 mm below the surface. Clean the valve with methanol. Shake the pressurized container in an inverted position for about 30 seconds and place it inverted in the vessel. Discharge one spray under the surface level of the solvent. Release the valve. Repeat the same procedure until the can is empty. Remove the pressurized container and wash it with methanol. Transfer the washings to 200 mL volumetric flask. Carefully cut the can using a cutter and wash the can. Transfer the washings in the same volumetric flask. Read and observe absorbance solution at 218.2 nm on a suitable spectrophotometer using methanol as blank in 1-cm cuvette. Calculate the content of formoterol & beclometasone and report the results.

Assay/Content per actuation

Place a teflon or steel base plate with a central circular indentation, including a 1.5 mm diameter hole, in a small beaker suitable for shaking (100 mL). Add 35 mL of diluent to the 100 mL beaker. Shake the pressurized canister vertically for approximately 30 seconds, then invert it into the 100 mL beaker. Actuate the first spray immediately, followed by 9 more sprays (totaling 10 sprays initially) under the surface level of the 35 mL diluent while maintaining the pressurized canister in a vertical position through the hole in the center of the base plate. Collect the initial 10 sprays, middle 10 sprays, and end 10 sprays from the container, and estimate the drug content per spray by measuring the absorbance of the solution at 218.2 nm on a UV spectrophotometer using methanol as a blank in a 1-cm cuvette.

In-vitro deposition of emitted dose

The fine respirable fractions of the developed product were determined using an impactor apparatus, specifically the twin glass impinger apparatus from Copley Scientific Ltd, U.K. The collecting chambers of the twin impinger were assembled, and

methanol was used as the solvent (7 mL was added in stage I and 30 mL was added in stage II). The side arm tube of the twin apparatus was connected to a vacuum pump with a flow rate of 60 ± 5 L/min to simulate normal respiratory flow in patients. An adaptor mouthpiece was fitted to the device using a rubber collar and connected to the twin apparatus, and 10 sprays were fired into the apparatus with a 5-second gap between successive sprays. The MDI was thoroughly shaken before each spray. The reservoirs were rinsed with methanol and the quantity of drug deposited on the valve, adaptor, and collar (device, stage I, and stage II) was determined. The analysis involved calculating the proportion of the active substance in the solution retrieved from the lower impingement chamber (stage 2) per discharge, expressed as a percentage of the dosage indicated on the label, known as the labeled claim.

Comparison of conventional pMDI and BAI formulations

The conventional pMDI formulation (F1) was compared with the developed BAI (F2) formulation. The formulations were compared based on their assay and the drug deposition of the emitted dose.

RESULTS AND DISCUSSION[12-17]

Physical Properties

The characteristics of the formulations, including crimp height, crimp diameter, total height, vapor pressure, and number of deliveries, were assessed, and the findings are outlined in Table 1.

Based on the findings, the observed values for crimp height (6.50 ± 0.00 mm), crimp diameter (17.76 ± 0.01 mm), and total height (53.70 ± 0.01 mm) fall within acceptable limits. Similarly, the results for vapor pressure (85.2 ± 0.4 mm) and the number of deliveries per canister (237 ± 0.75 Nos) suggest that the observed values are within the specified ranges.

Content Per Spray (%Label claim), i.e., Assay

The test results affirm that the drug delivery corresponds to the labeled claim. Based on the average of three readings (Initial, Middle, and End) provided in Table 2, it is evident that the test formulation adheres to pharmacopeial standards. The drug content per spray falls within the acceptable range specified, which is not less than 80% and not more than 120% of the labeled claim. Specifically, FF demonstrated 98.4 ± 0.32% of the drug per spray, while beclometasone exhibited 99.7 ± 0.55%.

Content Per Canister (CPC)

Table 3 shows that all five test samples meet the specified criteria, with the drug content per canister falling within the acceptable range of not less than 90% and not more than 110% of the labeled claim. Specifically, FF exhibited a content of 1.43 ± 0.02 (99.3 ± 1.71%) per canister, while beclometasone showed 48.98 ± 0.56 (102.0 ± 1.18%) of the drug content per canister.

In-vitro Evaluation of BAI (Emitted Dose (Ed)

The deposition of the emitted dose was identified as a crucial factor influencing the therapeutic efficiency of inhalers. An emitted dose test was performed to predict the *in-vitro* availability of the drug content from the aerosolized product. Table 4 presents the results of the emitted dose.

The average net respirable fraction was observed to be 52.0% (3.12 mcg/actuation) for FF and 53.1% (106.10 mcg/actuation) for beclometasone, respectively. The mass balance of stage-I and stage-II combined fell within the acceptable range of 75 to 125%. The breath-actuated autohaler device was employed to evaluate the emitted dose of the developed formulation.

Comparative Evaluation of Conventional pMDI Vs BAI

The comparative assessment was carried out to evaluate the content per spray (%Assay) and the deposition of emitted dose (ED) as critical parameters. The results indicated equivalence and satisfactory performance between both test methods (Table 5). Figure 1 illustrates the graphical presentation of the comparative results for %assay and %emitted doses between conventional pMDI and BAI.

Table 1: Physical characteristics of breath actuated inhaler

Test parameter	*Limits*	*Min*	*Max*	*Mean ± SD*	*% RSD*
Crimp height (mm)	6.50 ± 0.20	6.50	6.51	6.50 ± 0.00	0.06
Crimp diameter (mm)	17.70 ± 0.10	17.75	17.77	17.76 ± 0.01	0.04
Total height (mm)	53.70 ± 030	53.69	53.71	0.92 ± 0.06	0.01
Vapour pressure (psi)	70 - 95	85	86	85.20 ± 0.4	0.47
Number of deliveries	NLT 200	236	238	236.8 ± 0.75	0.32

Table 2: Assay/Content per actuation results of breath actuated inhaler

Stages	*Formoterol fumarate*			*Beclometasone dipropionate*		
	mcg/Actuation	*%Assay*	*Mean*	*mcg/actuation*	*%Assay*	*Mean*
Initial	5.93	98.8		198.52	99.3	
Middle	5.90	98.3	98.4 ± 0.32	200.51	100.3	99.7 ± 0.55
End	5.89	98.2		198.79	99.4	

Table 3: Content per canister results for 5 repetitions

Sample No.	*Formoterol fumarate*		*Beclometasone dipropionate*	
	mg/Canister	*%CPC*	*mg /Canister*	*%CPC*
1	1.45	100.7	48.68	101.4
2	1.40	97.2	49.38	102.9
3	1.45	100.7	48.01	100.0
4	1.40	97.2	49.35	102.8
5	1.45	100.7	49.49	103.1
Mean	1.43	99.3	48.98	102.0
SD	± 0.02	± 1.71	± 0.56	± 1.18
%RSD	1.71	1.73	1.15	1.16

Table 4: Deposition of the emitted dose results of breath actuated inhaler

Stages	*Formoterol fumarate*		*Beclometasone dipropionate*	
	mcg/actuation	*%Emitted dose*	*mcg/actuation*	*%Emitted Dose*
Stage-I	2.26	37.7	64.41	32.2
Stage-II	2.65	44.2	99.61	49.8
Mass balance		81.9	Mass balance	82.0

Table 5: Comparative evaluation of conventional pMDI and BAI

Test parameter	*Conventional pMDI (F1) (%)*	*Developed BAI (Autohaler) (F2) (%)*
% Assay/Content per spray		
Formoterol fumarate	99.70	98.40
Beclometasone dipropionate	101.0	99.7
In-vitro emitted dose (ed)		
Formoterol fumarate	43.7 (2.62 mcg/Spray)	44.2 (2.65 mcg/Spray)
Beclometasone dipropionate	42.9 (85.84 mcg/ Spray)	49.8 (99.61 mcg/Spray)

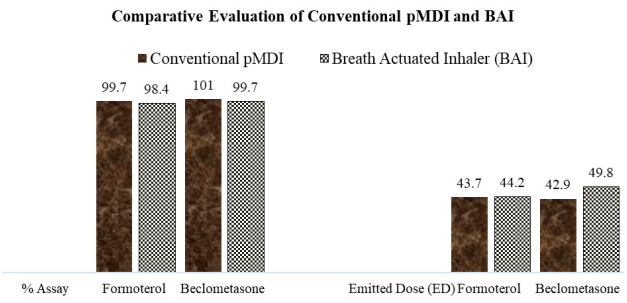

Figure 1: Graphical presentation of evaluation of pMDI and BAI (Autohaler)

The assay results for FF were 99.7 and 98.4%, and for beclomethasone, they were 101.0 and 99.7%, respectively, for pMDI and BAI. The percentage of emitted dose was 43.7 and 44.2% for pMDI, and 42.9 and 49.8% for BAI. Overall, both the developed conventional pMDI formulations and BAI demonstrated efficient performance characteristics with equivalent effectiveness.

CONCLUSION

The development and optimization of non-alcoholic metered dose inhalation formulations for formoterol and beclomethasone combination inhaler, utilizing HFA134a as the propellant system, have been successfully achieved. The developed formulation has demonstrated the desired properties through evaluation tests and *in-vitro* drug deposition studies. Comparative analysis with the conventional pMDI formulation revealed equivalent performance characteristics, suggesting its potential as an environmentally friendly substitute for alcoholic formulations of metered dose inhalers containing formoterol and beclomethasone. This investigation has successfully developed a substitute pMDI for the efficient administration of beclomethasone and formoterol.

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