Nirma Univ J Pharm Sci; 2019, 6(1) 55-68

ISSN 2348 –4012

ARTICLE

INHALED FLUTICASONE PROPIONATE DRY POWDER FOR THE EFFECTIVE MANAGEMENT OF ASTHMA

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Abstract:

Dry powder inhaler has become an attractive platform for pulmonary drug delivery. Dry powder inhalers are commonly used to treat asthma and other pulmonary diseases. Dry powder inhalers chiefly consist of micronized drug admixed with the carrier particles which aid in the flow of the drug in the respiratory tract. The dry powder formulations of fluticasone propionate were prepared with different coarse and fine lactose grades such as Respitose® SV003, Respitose® SV010, Respitose® ML001, Respitose® ML006 and Lactohale® LH 230, Inhalac® 230 and Inhalac® 400 and evaluated for flow properties, emitted and fine particle dose, content and blend uniformity. The final coarse and fine lactose grades were Inhalac® 230 and Inhalac® 400 based on the flow properties. 32 factorial design was applied for the formulation optimization. The final device used was Breezhaler®. The optimized batch showed a fine particle fraction of 8.99 ± 3.71 with a mass median aerodynamic diameter of 3.40 ± 0.02 thus showing the efficiency of dry powder inhalers in the delivery of fluticasone propionate deep into the lungs.

Keywords: Dry powder inhaler, fluticasone, fine particle fraction, cascade impactor.

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1. Introduction

Asthma is a chronic disease which is generally caused due to factors such as dust mites, common cold, air pollutants and irritants etc. It is a condition in which the airways of a person becomes inflamed and swollen up leading to excess mucus production due to which breathing becomes difficult. (1-3) About 334 million people suffer from asthma worldwide. (4) The current treatment of asthma involves the use of pressurized inhalers.

Nowadays, dry powder inhalers are prioritized now over pressurized formulations for asthma due to their several advantages, prior one is the safety due to absence of any propellants in the formulation. (5) Dry powder inhalers are mainly composed of blend of drug in micronized form and carrier particles. These work on fluidization mechanism in which the drug and carrier blend is fluidized in the lungs. The carrier particles are retained in the upper airways while the drug particles with an aerodynamic diameter between 1-5 μm undergo deposition deep into the lower airways. The disaggregation between drug and carrier particles plays a key role in the efficient delivery of the drug deep into the lungs. The key steps in the delivery of drug from DPI formulations are detachment of drug particles from carrier, dispersion of drug in the air flow and finally deposition of drug in the lungs. (6-8)

Fluticasone propionate is a corticosteroid which is highly effective against asthma. (9, 10) It is an essential component of asthma treatment which binds to the glucocorticosteroid receptors with high affinity. This results in down regulation of pro-inflammatory mediators (Interleukins) and up regulation of anti-inflammatory mediators (IkappaB). Fluticasone propionate has been chosen as the model drug due to high lipophilicity which will result in high retention in the lung tissues. (11, 12) Though researchers are working on the development of nanoparticles, microparticles etc. for the delivery of fluticasone propionate in the lungs. But, considering developing nations, dry powder inhaler formulations will serve as an economical alternative to the above listed expensive formulations.

In this research work, we have developed dry powder inhaler formulation of fluticasone propionate with a view to improve the aerodynamic properties of the drug for the successful treatment of asthma. The designing of powder of such a potent drug is a challenge which should meet the desired aerodynamic properties for the proper deposition into the lungs. The deposition is a key factor influencing the efficiency of any inhaled drug delivery system. The purpose of the investigation is to evaluate the lung deposition of fluticasone propionate via cascade impactor study.

2. Materials and Methods

2.1 Materials

Fluticasone propionate was obtained as a gift sample from Zydus Cadila Helathcare

Ltd. Rotahaler® and Breezhaler® were purchased from a local vendor. Capsules of size '3' were provided as gift sample from Cipla Ltd. Mumbai. Respitose® SV003, Respitose® SV010, Respitose® ML001, Respitose® ML006 and Lactohale® LH 230 were obtained as a gift sample from DMV-Fonterra Excipients GmbH & Co. and Inhalac® 230 and Inhalac® 400 were obtained as a gift sample from Meggle, Germany. All the chemicals and reagents used were of analytical grade.

2.2 Preformulation studies

2.2.1 Drug excipient compatibility studies by Fourier transform infrared spectroscopy (FTIR)

In a dry powder inhaler formulation, the drug and carrier are in contact with each other. Hence, FTIR (Jasco FTIR 6100, Japan) studies were carried out in order to determine the compatibility of fluticasone propionate with the lactose. The powder blend was mixed with KBr in 1:1 ratio and spectrum was recorded in range of 4000-400 cm^{-1} after 24 hours using Spectra Manager II™ software.

2.2.2 Differential scanning calorimetry (DSC)

The drug excipient compatibility was determined using DSC. The DSC of pure drug and the blend of the micronized drug and the lactose were carried out using Mettler Toledo. The sample was sealed and was heated at 10°C at a temperature in the range of 25-250°C.

2.3 Preparation of formulation

2.3.1 Preliminary batches

Several coarse lactose grades such as Inhalac® 120, Inhalac® 230, Respitose® SV010, Respitose® SV 003, Respitose® ML 001 and fine lactose grades such as Inhalac® 250, Inhalac® 400, Respitose® ML006 and Lactohale® LH 230 were used for the preparation of preliminary batches. After preparation, these batches were further evaluated for flow properties, emitted and fine particle dose, content and blend uniformity. The functionality of devices, Rotahaler® and Breezhaler® were evaluated and the final selection was done based on the amount of drug left in the device. The selection criterion was based on the fact that less the amount of drug left in the device, the more efficient it is.

2.3.2 Preparation of fluticasone propionate dry powder formulation

The preblend of Inhalac® 230 and Inhalac® 400 was prepared using vortex mixer (Eie Instruments Pvt. Ltd., Ahmedabad). [13] After 24 hrs, the micronized drug was added into the lactose preblend and mixed for about 10 mins. The capsules were filled with blend equivalent to 50 mg of fluticasone propionate. The prepared batches were evaluated for flow properties, emitted and fine particle dose, blend and content uniformity.

2.3.3 Optimization of fluticasone propionate DPI

3^2 factorial design was used for optimizing process parameters of dry powder inhaler

formulation as well as develop the optimized formulation as given in **Table 1** and **Table 2**. Using this design, one can determine the effect of independent variables such as the amount of coarse lactose (X1) and fine lactose (X2) on dependent variables- flow properties, content uniformity, blend uniformity, emitted dose and fine particles dose. The independent variables were set at three levels. Nine batches were prepared as per the design. The experimental responses can be determined by the polynomial equation as given below:

Table 1 Independent and dependent variables of 3^2 full factorial design

Independent variables	Level 1 (-1)	Level 2 (0)	Level 3 (1)
Amount of coarse lactose	45.0	47.5	50.0
Amount of fine lactose	0.0	2.5	5.0
Y_1: Flow properties, **Y_2:** Content uniformity, **Y_3:** Blend uniformity, **Y_4:** Fine particle dose			

Table 2 Optimization of design batches using 3^2 full factorial design

Batch	X_1: Amount of coarse lactose	X_2: Amount of fine lactose
A1	-1	-1
A2	-1	0
A3	-1	1
A4	0	-1
A5	0	0
A6	0	1
A7	1	-1
A8	1	0
A9	1	1

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2 + B_1X_1^2 + B_2X_2^2 \quad (1)$$

Where, Y represents the response (dependent variable) and X_1 and X_2 represents the factors (independent variables) and B_0, B_1 and B_2 represents the coefficients of respective factors.

2.4 Evaluation of the batches

2.4.1 Flow properties of drug and carrier preblend

The bulk and tapped volumes were determined as per United States Pharmacopoeia (USP) [14]. From these

volumes, tapped and bulk densities were calculated (n=3). Hausner's ratio was calculated to determine the type of flow using the formula:

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \quad (2)$$

2.4.2 Content uniformity

Contents of ten capsules were individually dissolved in 100 mL of solvent (phosphate buffer pH 7.4: methanol (90:10)) via sonication for 5 minutes. The sample was analyzed using US-Vis spectrometer (Model 1800 UV-Visible spectrophotometer, Schimadzu, Japan) at a wavelength of 236 nm. The sample was considered homogenous if not more than one capsule was outside 85-115% of mean fluticasone propionate content and none was outside 75-125% of mean content. (n=3)

2.4.3 Blend uniformity

Weighed quantity of blend was dissolved in phosphate buffer pH 7.4: methanol (90:10) via sonication for about 5 minutes. The drug content was analyzed using UV-Vis spectrophotometer at 236 nm. The analysis was done in triplicates.

2.4.4 Emitted dose and Fine particle dose

The emitted and fine particle dose was determined using twin stage impinge fabricated as per European Pharmacopoeia[15]. It is a two stage device used for the assessment of aerosolized formulations. The coarse part of the formulation remains on the upper stage whereas fine fraction of the drug is collected in the lower stage. The upper stage was filled with 30 mL of solvent (phosphate buffer: methanol (90:10)) and the lower stage was filled with 7 mL of the solvent in order to resemble the respiratory tract of the lungs.

2.4.5 *In vitro* deposition studies of the optimized batch using eight stage non viable cascade impactor

2.4.5.1 Mass balance and *in vitro* deposition studies

The mass balance is necessary to be determined in order to ensure no drug loss in the system. The recovery of the total amount of active pharmaceutical ingredient from an impactor represents the mass balance.[16] After mass balance determination, *in vitro* deposition studies were carried out using eight stage nonviable cascade impactor (Tisch Environmental Inc TE-20-800). For mimicking the human throat, a throat piece was attached on the inlet cone which was placed on Stage '0' of the impactor. The mouthpiece adaptor was used according to Breezhaler® design. The adaptor was fitted on the throat piece and the impactor was connected to vacuum pump set at 28.3 L/min. Inspiration of single formulation

dose was done for about 8 sec. After the experimentation, the particles on each stage were washed with phosphate buffer: methanol (90:10) and analyzed using UV-Visible spectrophotometer. The cumulative percentage dose from stages 2 to 5 represents the fine particle fraction. (n=3)[17]

2.5 Scanning electron microscopy (SEM)

The surface morphology studies of coarse and fine lactose preblend was carried out using SEM (Oberkochen, Germany). The method used was plasma deposition in which gold coating was done under argon atmosphere onto the sample to make it conductive to scanning electron beam. The SEM was carried out at a working distance of 17.5 mm and at a voltage of 30 kV.

2.6 Statistical analysis

The batches were prepared three times each, and the results were expressed as mean ± standard deviation. A difference between means (Pd"0.05) was considered significant.

3.0 Results and Discussion

Dry powder inhalers comprise of formulations in which the micronized drug is admixed with the carrier particles. However, coarse carrier particles possess both high and low adhesion sites. The high adhesion sites do not allow easy detachment of drug which may lead to improper dosing of the formulation. Hence, the coarse lactose is firstly admixed with fine lactose so that most of the high adhesion sites are covered by the fines and major part of the drug adheres to the low adhesion sites which may facilitate the separation of the drug from the coarse lactose.[18]

3.1 Preformulation studies

3.1.1 Drug excipient compatibility studies

FTIR studies were carried out to determine the compatibility between the drug and the carrier. The FTIR spectra of pure futicasone propionate and its mixture with lactose has been shown in **Fig.1** which indicated the presence of identical peaks (3329 cm^{-1}, 2939.31 cm^{-1}, 1618 cm^{-1}, 1271 cm^{-1} and 736 cm^{-1}) in both pure drug and the mixture thus showing the compatibility between the drug and the carrier.

3.1.2 Differential Scanning Calorimetry

The DSC thermograms of drug and mixture are shown in **Fig.2.** The pure fluticasone propionate exhibited an endothermic peak at 290°C, representing the melting point of the drug. The representing peak was also seen in the mixture thus showing the compatibility of the drug with the carrier.

3.2 Preliminary batches

Preliminary batches were prepared using various coarse and fine lactose grades such as Respitose® SV003, Respitose® SV010, Respitose® ML001, Respitose® ML006, Lactohale® LH 230, Inhalac® 230 and Inhalac® 400. Out of these, Inhalac® 230 and Inhalac® 400 were the final coarse and fine lactose selected on the basis of flow properties.

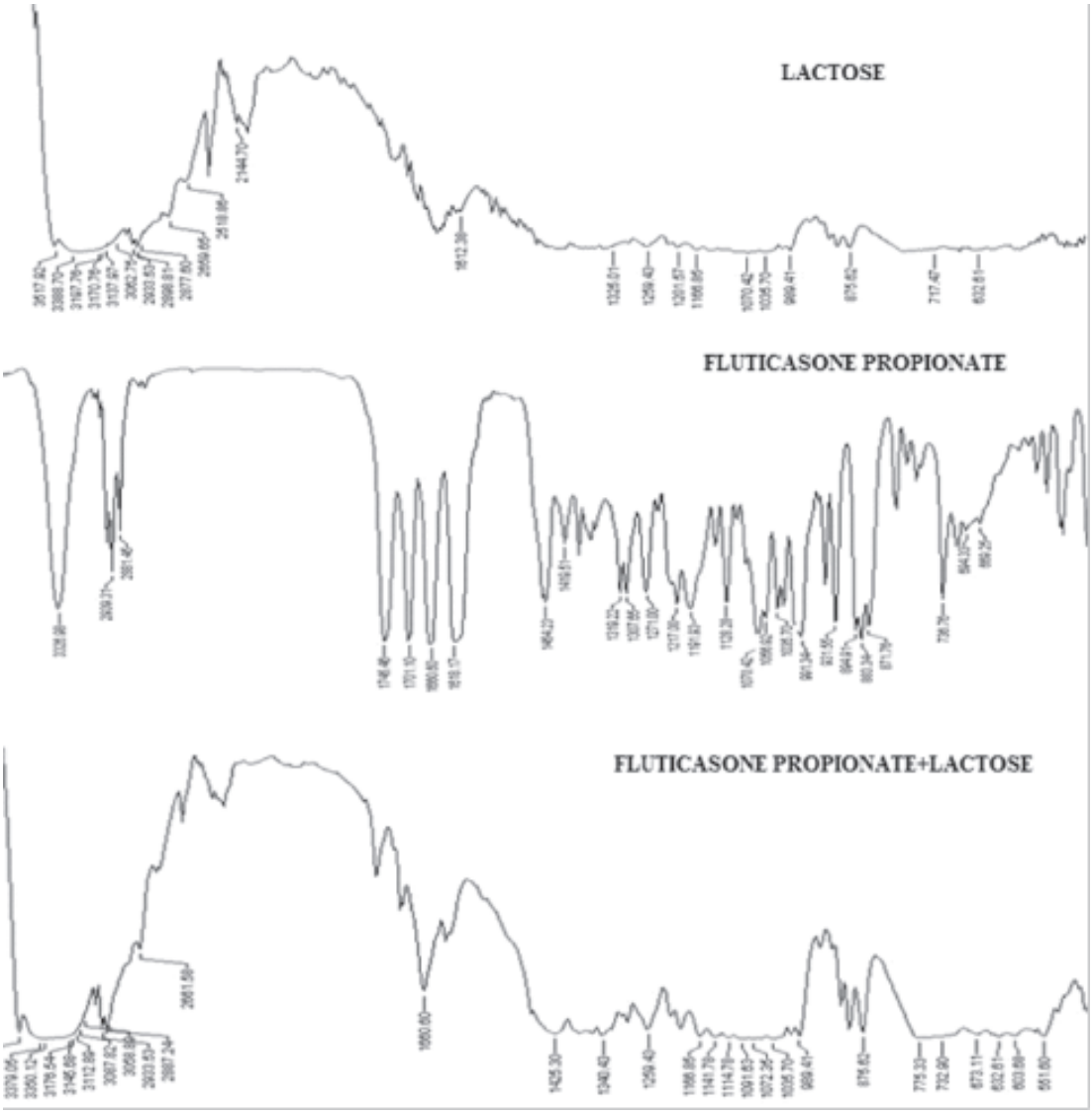

Figure 1. FTIR spectrum of lactose, Fluticasone propionate and combination of lactose and Fluticasone propionate

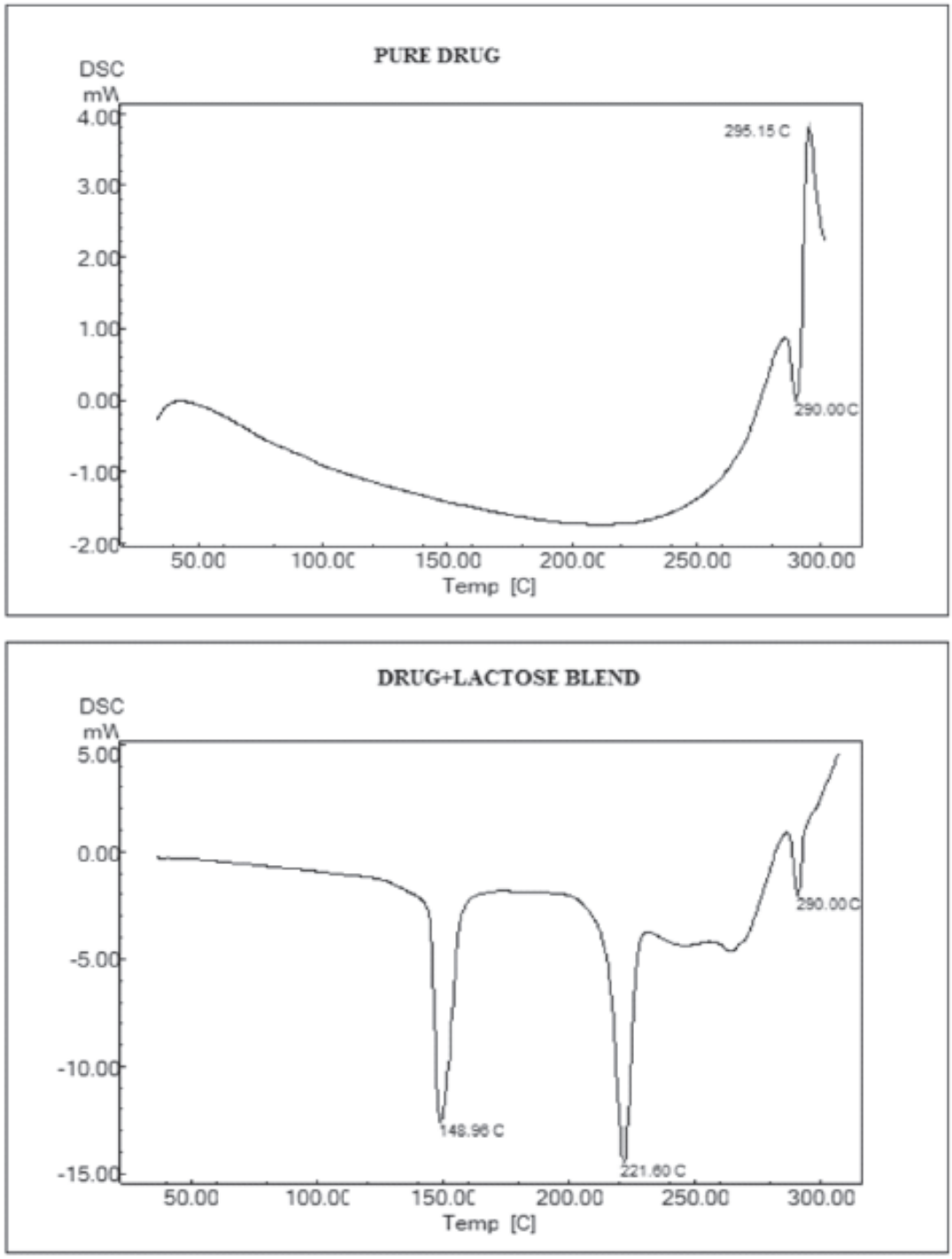

Figure 2. DSC of Fluticasone propionate alone and dry powder inhaler blend (optimized batch)

3.3 Optmization of the formulation

Design of Experiments (DOE) is used from a long time for optimizing the formulations. Numerous designs can be used for the optimization based on the data of the preliminary batches. Since few components are required in dry powder inhaler formulations and the amount of coarse and fine lactose were the important factors influencing the dry powder inhaler performance. Hence, 3^2 factorial design was used for the optimization considering amount of coarse lactose (X_1) and amount of fine lactose (X_2) as the independent variables. Nine batches were prepared and evaluated for following parameters:

3.3.1 Flow properties of the drug and carrier preblend

The micronized fluticasone propionate showed Hausner's ratio of 1.87, whereas design batches showed values between 1.18-1.21. The drug flow can be categorized as 'exceedingly poor' and 'fair flow' for the design batches as per USP [16] except batch A9 showed 'poor' flow. The poor flow might be due to the presence of high amount of fine lactose due to which large amount of drug remain unbound to low adhesion sites, thus leading to 'poor' flow. The results have been shown in **Table 3**.

Table 3 Evaluation of responses for design batches

Batch	X_1: CL	X_2: FL	Y_1: CU (%)	Y_2: BU (%)	Y_3: FPD (%)
A1	-1	-1	99.32 ± 1.26	98.30 ± 1.43	6.60 ± 0.41
A2	-1	0	100.79 ± 0.82	98.76 ± 4.59	7.10 ± 1.69
A3	-1	1	89.78 ± 2.37	88.89 ± 5.81	8.67 ± 2.31
A4	0	-1	111.02 ± 5.68	99.64 ± 4.28	6.50 ± 7.86
A5	0	0	109.98 ± 9.81	99.89 ± 0.67	7.40 ± 3.91
A6	0	1	85.01 ± 1.71	86.92 ± 5.83	8.50 ± 0.76
A7	1	-1	115.67 ± 4.82	101.87 ± 0.65	6.70 ± 3.62
A8	1	0	110.11 ± 4.36	101.2 ± 0.89	6.97 ± 4.21
A9	1	1	87.68 ± 2.21	91.98 ± 1.82	8.70 ± 5.31

* CL= coarse lactose, FL=fine lactose, CU= Content uniformity, BU=blend uniformity, FPD= fine particle dose

$$Y_{CU} = 99.72 + 1.52X_1 + 0.16\,X_2 - 0.12\,X_1X_2 + 0.35\,X_1^2 + 0.15\,X_2^2 \quad (3)$$

3.3.2 Content uniformity

The content uniformity of all the batches was within 85-115% of the label claim as per USP. The batches A3, A6 and A9 having the highest fine lactose content showed low content uniformity. This might be due to improper binding of the drug to the lactose due to high amount of fines which might have covered both high as well as low adhesion sites thus leading to low content uniformity. The results have been shown in **Table 3**.

The complete polynomial equation for content uniformity was described as follows:

From the above equation, it can be seen that the amount of coarse lactose and fine lactose both have a positive effect on the content uniformity. This might be due to the increase in number of high adhesion sites with the increase in the amount of coarse lactose. In order to cover these high adhesion sites, the fine lactose has to be increased which will lead to proper binding of drug to the low adhesion sites thus leading to proper content uniformity.

3.3.3 Blend uniformity

The blend uniformity of all the batches was within 85-115% of the label claim as per USP. However, again the batches A3, A6 and A9 with high amount of fines showed poor blend uniformity. This might be again due to insufficient binding of drug to the coarse lactose due to high amount of fines. The results have been shown in **Table 3**.

The polynomial equation for the blend uniformity was described as follows:

$$Y_{BU} = 108.83 + 6.69\,X_1 - 0.090\,X_2 - 0.12\,X_1X_2 - 3.35\,X_1^2 + 1.75\,X_2^2 \quad (4)$$

The above equation states that amount of coarse lactose has a positive effect on blend uniformity whereas the fine lactose amount has a negative impact on the blend uniformity. This might be due to improper binding of drug and coarse lactose due to increase in fines above certain extent, thus resulting in poor blend uniformity.

3.3.4 *In vitro* drug deposition studies by twin stage impinger

Twin stage impinger is a simple device which comprises of two stages and is used for the assessment of inhalation formulations. The powder is fractionated via upper impinger stage (simulated oro-pharynx) and then into lower impinger stage having defined aerodynamic particle size cut-off. The fraction of the drug which is accumulated in the lower impinger stage, is the fine particle fraction. This fraction undergoes deposition deep into the lower respiratory tract of the lungs. The results have been shown in **Table 3**.

The polynomial equation for fine particle fraction was described as follows:

$$Y = 7.16 + 0.10\,X_1 + 1.01\,X_2 - 0.018\,X_1X_2 - 0.010\,X_1^2 + 0.45\,X_2^2 \quad (5)$$

From the above equation, it can be seen that as the amount of coarse lactose and fine lactose are increased, they may lead to high fine particle fraction. This might be due to easy detachment of the drug from the coarse lactose due to its high adhesion onto the low adhesion sites of the coarse lactose. Thus lung deposition majorly depends on the optimum ratio of coarse and file lactose as well as mixing time or lactose with drug.

The contour plots and the overlay plot with the design space has been shown in **Fig. 3**.

3.3.5 Scanning electron microscopy

The SEM studies of preblend of coarse and fine lactose were done to see whether the fine lactose occupies the high adhesion sites of coarse lactose or not. The SEM images as shown in **Fig. 4** show that the fine lactose has covered majority of the high adhesion sites of the coarse lactose.

3.3.6 *In vitro* deposition studies of optimized batch using eight stage nonviable cascade impactor

3.3.6.1 Mass balance and *in vitro* deposition studies

The mass balance study of the optimized batch was done prior to *in vitro* deposition studies. The mass balance was 98.63% which was within the acceptable range of 85-115%, showing no drug loss in the system. Cascade impactor is the best tool for the *in vitro* evaluation of the inhalation products due to several merits. It helps in the determination of mass median aerodynamic diameter which plays a significant role in determining the

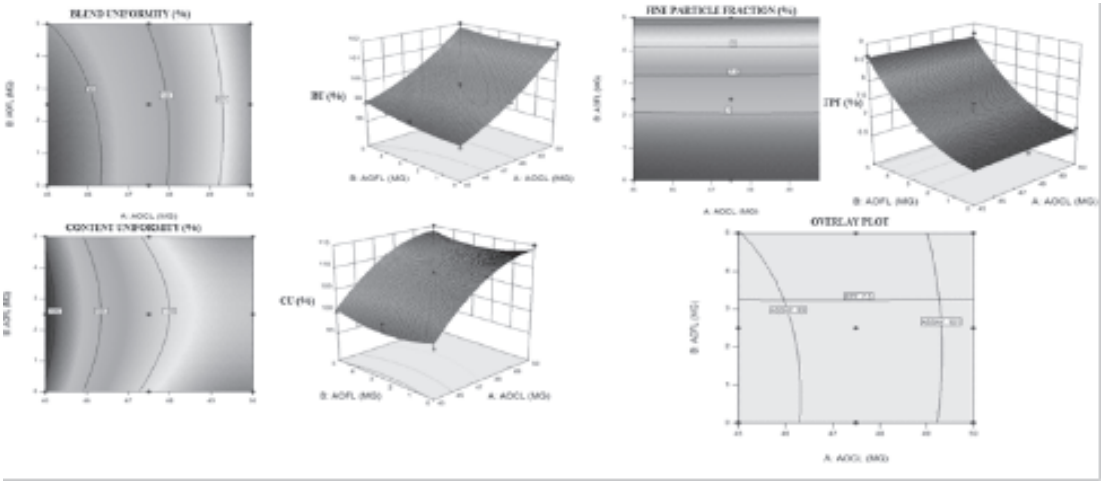

Figure 3. Response surface plots of design batches and overlay curve

Table 4 Mass balance and fine particle fraction of the optimized batch

Optimized batch	Mass Balance (%)	Fine particle fraction (%)	Mass median aerodynamic diameter (µm)
A_{10}	98.63 ± 3.41	8.99 ± 3.71	3.40 ± 0.02

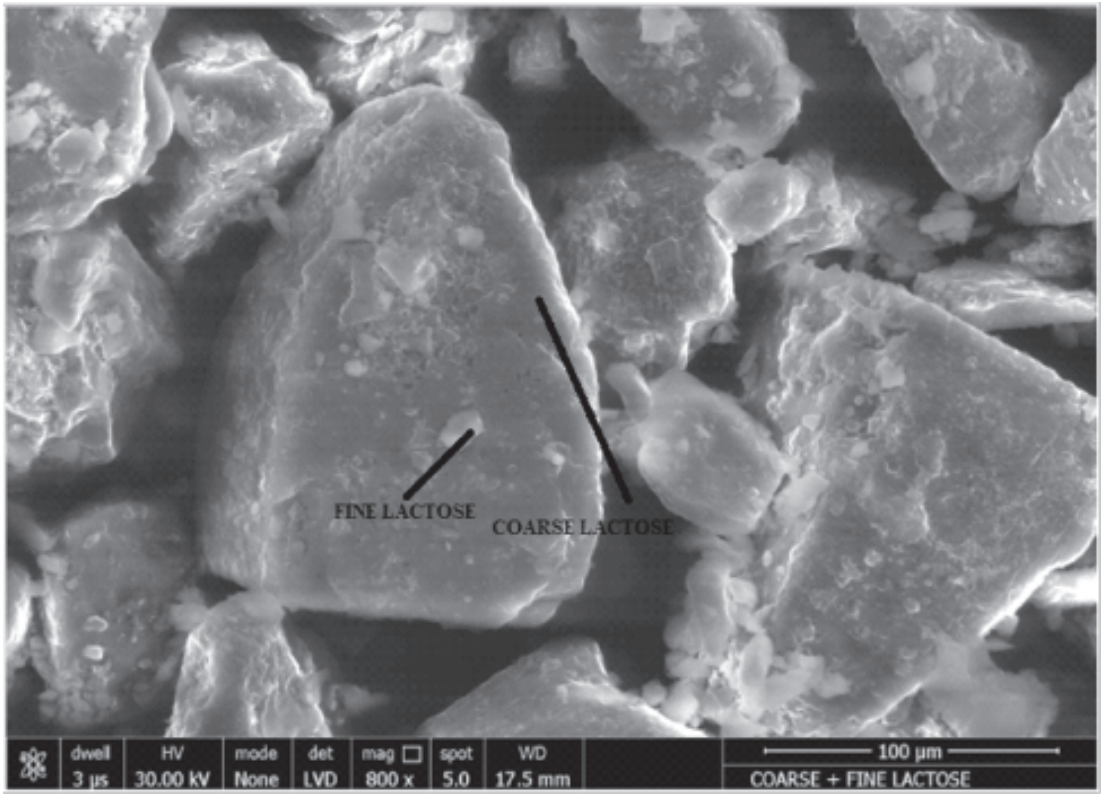

Figure 4. SEM image of dry powder inhaler blend (optimized batch)

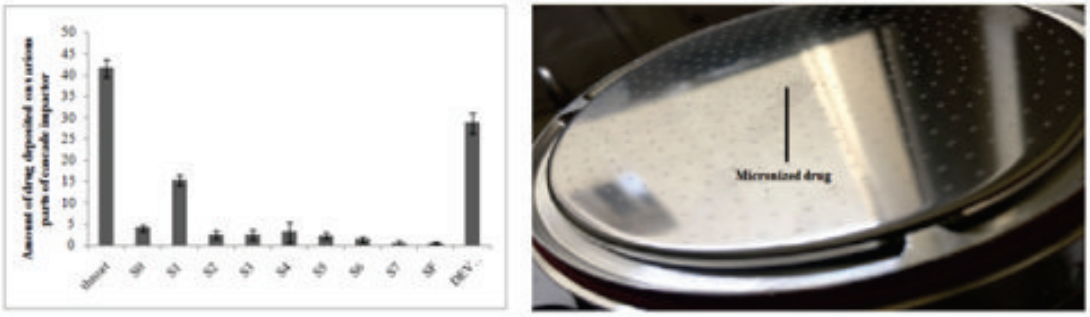

Figure 5. Amount of drug deposited on various stages of cascade impactor and image of S1 plate

deposition of the drug in several parts of the lungs. It also helps to determine the fine particle fraction of the drug. [19,20] It consists of eight stages with a cut-off diameter ranging between 0.7 and 10 µm. The mass median aerodynamic diameter as well as fine particle fraction of the optimized batch has been shown in **Table 4** and the amount of drug deposited at various stages has been shown in **Fig.5**.

Conclusion

The fluticasone propionate dry powder formulation was prepared and evaluated systematically. The optimized formulation showed mass median aerodynamic diameter between 1-5 µm and fine particle fraction of 8.99% using Breezhaler® device. This represents the effectiveness of the dry powder inhalation formulation in the efficient delivery of fluticasone propionate into the lungs which can be useful for the successful treatment of severe disease such as asthma.

Acknowledgement

The authors would thank Institute of Pharmacy, Nirma University for providing all the facilities for carrying out our research work. We also thank **Meggle Germany** and **DFE Pharma** for providing us inhalable lactose grades.

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