DEVELOPMENT AND EVALUATION OF PHARMACEUTICALLY EQUIVALENT LEVOSALBUTAMOL DRY POWDER INHALER WITH INCREASED *IN VITRO* DEPOSITION

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(Received 19 August 2023) (Accepted 23 April 2024)

ABSTRACT

The advancement and assessment of an efficient and safe dry powder inhaler formulation for levosalbutamol are critical for optimizing its therapeutic potential in managing chronic obstructive pulmonary disease (COPD). This study aims to provide an overview of the development process and evaluation outcomes of a levosalbutamol dry powder inhaler, including formulation development, physicochemical characterization and *in vitro* performance assessment. It employed a stepwise approach to develop and evaluate the inhaler. Initially, different excipients (Respitose®SV010, Respitose®ML006, Respitose®SV003, Lactohale LH100, Lactohale LH300) and particle size distributions were evaluated to optimize the formulation. Physicochemical characterization, such as particle size, shape and density were conducted using appropriate techniques. *In vitro* performance assessments, together with fine particle fractions, emitted dose and aerodynamic particle size distribution was determined using validated methods. The formulation development process resulted in an optimized levosalbutamol dry powder inhaler with desirable physicochemical properties, including uniform particle size distribution and suitable density for effective inhalation. *In vitro* assessments demonstrated favourable aerodynamic characteristics, with a high emitted dose and significant fine particle fraction, indicating efficient lung deposition and therapeutic efficacy. These findings support the potential of the levosalbutamol dry powder inhaler as an effective treatment option for respiratory conditions such as asthma and COPD.

Keywords: Levosalbutamol, dry powder inhaler, formulation development, physicochemical characterization, *in vitro* performance assessment, lung deposition

INTRODUCTION

Currently, increasing focus of researchers has been seen on pulmonary drug delivery system due to its potential to produce maximum therapeutic effect[1]. Administering active pharmaceutical ingredients (APIs) through pulmonary delivery facilitates the treatment of various conditions, including local ones like chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) as well as systemic diseases such as agitation linked to schizophrenia and diabetes mellitus[2]. Primarily, the increased focus is due to the highly absorptive tissues of the lung, which has large excellent blood supply, surface area and thin adsorption membrane. Secondly, the pulmonary path requires lesser dose and gives faster onset of action in comparison of oral route of administration[3,4]. There are various types of Pulmonary Drug Delivery Devices such as –"Nebulizer", "Metered Dose Inhalers" (MDIs) and "Dry Powder Inhalers"(DPIs)[5]. The dry powder inhaler (DPI) stands out as the preferred device among available options for treating an expanding array of diseases[6].

The utilization of dry powder inhalers for pulmonary drug delivery has emerged as the most promising non-invasive method of administering drug formulations[7]. Dry powder inhalers (DPIs) rank among the most commonly utilized systems for administering therapeutic agents to treat COPD and asthma[8]. They are extensively employed due to their ease of use, superior drug stability and environmental friendliness. The disadvantage of MDIs is that they use chloro-fluro-carbons (CFCs) which causes lot of environmental damage, and this is solved by the use of DPIs[9–11]. Usually, DPI formulations consist of a micronized active ingredient along with an inert carrier or

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https://doi.org/10.53879/id.61.06.14295

Table I: Formulation of inhalable dry powder

Trial formulation	Levosal - butamol	Respitose® SV010	Lactohale® LH100	Respitose® ML006	Micronized Respitose® SV010	Lactohale® LH300
Trial 1						
F1	0.1313	24.87	-	-	-	-
F2	0.1313	18.75	-	-	6.12	-
F3	0.1313	18.75	-	6.12	-	-
F4	0.1313	18.75	-	-	-	6.12
Trial 2						
F5	0.1313	-	24.87	-	-	-
F6	0.1313	-	18.75	-	6.12	-
F7	0.1313	-	18.75	6.12	-	-
F8	0.1313		18.75	-	-	6.12
Trial 3						
F9	0.1313	12.5	-	12.368	-	-
F10	0.1313	15	-	9.868	-	-
F11	0.1313	20	-	4.8687	-	-
F12	0.1313	22.5	-	2.3687	-	-
Trial 4						
F13	0.1313	14.86	-	6	-	4
F14	0.1313	14.86	-	6	4	-
Reproducible batches						
F15	0.1313	14.86	-	6	-	4
F16	0.1313	14.86	-	6	-	4

diluent, such as lactose. Incorporating carrier excipients aids in improving the flow and dispersibility of drug particles, which is particularly important when they are micronized and tend to be highly cohesive. The inclusion of the carrier excipients favours the flow and dispersibility of the drug particles, which can be very cohesive when they are micronized. If fractions of a milligrams of a powerful medication are to be administered, including a carrier also solves the issue of dosage metering[12].

The micronized drug particles have a big surface area and are easily agglomerated. The carrier particles in this environment lessen agglomeration and enhance flow. The ideal aerodynamic particle size for drug deposition in the alveoli, the primary target location, is 1 to 5 µm. Since the air velocity in the lower airways is so low, many

Table II: Preformulation study results

Sr. No.	Parameter	Observation	
		API	Inhalable Powder Formulation
1	Bulk density (g cc^{-1})	0.764	0.501
2	Tapped density (g cc^{-1})	0.867	0.700
3	Compressibility index	10.69	15.00
4	Hausner's ratio	1.13	1.18
5	Angle of repose (°)	30.15	29.45

of these particulates fail to be cleared by the mucocilium and settle there, where they experience sedimentation due to gravitational forces. The oropharyngeal region is where particles larger than 5 µm experience impaction before being further eliminated by swallowing. For the drug to settle in alveoli, which is the primary target location, the ideal aerodynamic particle size is 1 to 5 micrometres[13,14,15].

Salbutamol, a beta2-adrenoceptor agonist, has an *R*-enantiomer called levosalbutamol. It may have a higher therapeutic index than racemic salbutamol, according to certain research. Racemic salbutamol's therapeutic benefits are thought to be mediated by levosalbutamol, because it has a substantially higher receptor affinity than the *S*-enantiomer. As levosalbutamol's toxicity is unrelated to its ability to bind to β2-receptors, racemic salbutamol's *S*-enantiomer may greatly increase its toxicity[16,17]. Levosalbutamol, also known as levalbuterol, is a bronchodilator drug which is used in the treatment of COPD and asthma[18,19,20]. There are various marketed DPI products available of this drug. It is observed that lactose is the most frequently carrier in DPI formulations due to historical reasons, physicochemical and pharmaceutical properties[21]. It is used in order to improve the flow of the particles. This results in raised delivery efficiency of formulations[22,23]. As lactose is marketed in various grades and particle sizes, it is easily available. The particle size of the lactose considerably affects the DPI formulation.

Table III: Particle size distribution of LST and Lactose

Particles	D_{10}	D_{50}	D_{90}	Size distribution
Levosalbutamol	0.689	1.791	3.890	1.7872
Lactohale® LH100	43.65	122.32	203.12	1.303
Lactohale® LH300	0.75	2.89	6.91	2.1314
Respitose® SV003	31.98	58.52	89.86	0.9890
Respitose® SV010	51.23	109.25	178.89	1.1685
Micronized Respitose® SV010	0.99	3.22	6.85	1.8198
Respitose® ML006	2.43	25.62	50.23	1.8657

Table IV: Particle size distribution of formulation batches

Batch No.	D10	D50	D90	Size distribution
F9	3.109	49.82	158.69	3.122
F10	3.343	53.382	152.535	2.7947
F11	2.304	49.881	157.427	3.1098
F12	2.950	37.786	150.278	3.8987
F13	3.055	44.865	154.62	3.33782
F14	2.959	50.074	157.071	3.0776
F15	3.099	52.778	157.096	2.9178
F16	3.127	51.345	156.812	2.9931
Innovator	2.553	52.139	151.773	2.8619

In this study, we have tried to formulate levosalbutamol dry powder for inhalation using various grades of lactose and in-house micronized levosalbutamol. Respitose®SV010, Respitose®ML006, Lactohale® LH100, and Lactohale® LH300 grades of lactose were used. The main aim of this study was to develop pharmaceutical equivalent levosalbutamol dry powder for inhalation to be administered with Instahaler-P device. To compare pharmaceutical equivalence, Levolin Rotacaps was used as innovator product. The prepared formulation exhibits more *in vitro* deposition as compared to the marketed innovator sample.

MATERIALS AND METHODS

Materials

Levosalbutamol tartarate (LST) was gifted by Melody Healthcare Pvt. Ltd., Mumbai, was commercially available. Alpha lactose monohydrate of various particle sizes was used. Various inhalation grade lactoses such as Respitose®SV010 coarser grade, Respitose®ML006, Lactohale LH300 and Lactohale LH100 coarser grade, were supplied by DFE Pharma, Germany. In the above-mentioned grades of lactose, Respitose®SV010 as well as Lactohale® LH100 are the coarser grades lactoses with higher particle size whereas Respitose®ML006 and Lactohale® LH300 are finer grade lactoses with finer particle size. Micronisation of Respitose®SV010 was done with Spiral Jet Mill to get the required particle size. Hard gelatin and HPMC capsule shells were purchased from Natural Capsules Ltd. Bengaluru and Associated Capsules Pvt. Ltd., Mumbai respectively.

PREFORMULATION STUDY

Bulk density[24,25]

The LST and dry powder formulation underwent sieving through a 20# sieve. Subsequently, 15 g was precisely weighed and transferred into a 50 mL graduated cylinder. After leveling the powder carefully, the unsettled volume was recorded, and the apparent bulk density (g mL^{-1}) was calculated:

$$\text{Bulk density} = \frac{\text{weight of powder}}{\text{volume of powder}}$$

Tapped density[26,27]

The LST and inhalable dry powder formulation were sifted through a 20# sieve. Then, precisely 15 g was accurately weighed and transferred into a 50 mL graduated cylinder. Using a mechanical tapping device set to provide a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times and the tapped volume was recorded. Subsequently, an additional 750 taps were applied, and the tapped volume was noted again. Finally, the following formula was used for measuring the tapped density:

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{tapped volume}}$$

Hausner's ratio[28,29]

This metric reflects the material's flowability. It is determined by dividing the tapped density by the apparent density and is computed using the formula:

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Compressibility index[29]

This property refers to a powder's capacity to reduce in volume under pressure. The alteration in volume due to packing reorganization during tapping serves to evaluate the drug's packing capability. Termed as the compressibility index (CI), it can be computed using the formula:

$$\text{Compressibility index:} \frac{\text{tapped density-bulk density}}{\text{bulk density}} \times 100$$

Angle of repose[30,31,32]

The angle of repose denotes the angle formed between the edge of a pile, resembling a cone, and the horizontal surface of the bench. Poor powder flow results from frictional forces among particles and is quantified by the angle of repose.

$$\tan\theta = \frac{h}{r}$$

Where, h= height, r= radius ɵ=angle of repose

Particle size distribution (PSD) of LST and lactose[33,34,35]

Particle size stands out as the primary design factor in DPI formulation. Utilizing Malvern Mastersizer 2000, particle size was assessed via laser diffraction. The designated powder quantity passed through the measurement zone, where an extended laser beam interacted with the sample in motion. Diverse particle sizes diffracted light at varying angles. A computer algorithm, varying among manufacturers, interpreted the diffraction pattern to compute particle size distribution. These algorithms, rooted in Fraunhofer or Mie theory, determined particle sizes. Dry powder dispersion throughout the sample cell utilized air as the medium. Roughly 250 mg of product was loaded into the feeder tray. PSD was described by D10, D50, and D90.

Formulation of inhalable powder

The inhalable powder of levosalbutamol tartrate and α-lactose monohydrate was prepared in four trial batches, as given in Table I. The concentration of lactose is varied as given in the Table I. In trials 1 and 2, coarser grade of lactose varied is Respitose® SV010 and Lactohale LH100 respectively, keeping all other grades constant. In trial 3, the ratio of fine grade lactose Respitose® ML006 is finalised. In trial 4, two intermediate grade lactoses were added.

Methodology

1) An accurately weighed quantity of drug and fine grade lactose were mixed geometrically in stainless steel container.
2) Blend prepared in step 1 was sifted through 60# sieve and mixed with coarser grade lactose and blended in Alphie Terbula Blender at 30-32 rpm for 15 minutes.
3) Blend prepared in step 2 was sifted through 40# sieve and mixed in Terbula blender for 30 minutes at 30-32 rpm.
4) The above blend was kept at room temperature for 24 h.
5) The blend was filled manually using Profiller Capsule

filling machine in HPMC capsule with fill weight 25 mg.

Powder properties of DPI formulation

Powder properties were not performed for trial 1 and 2 batches, as these trials were only taken to finalise the grades of lactose. Particle size of trial 3, trial 4 and reproducible batches DPI formulation was determined using Malvern Mastersizer 2000. The method for determination has been described above.

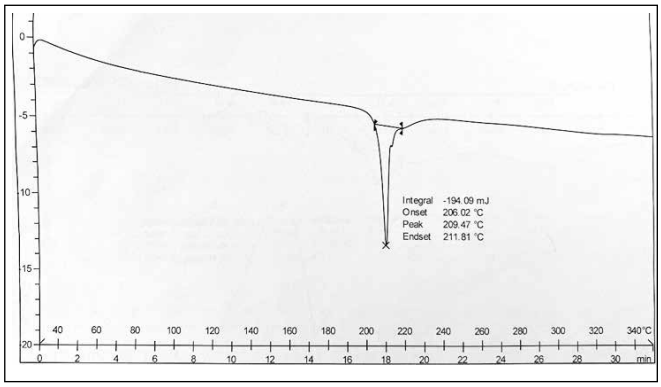

Fig. 1A: DSC curve of levosalbutamol

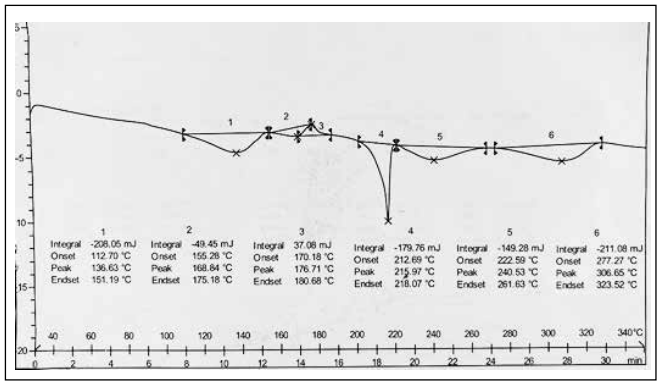

Fig. 1B: DSC curve of α-lactose monohydrate

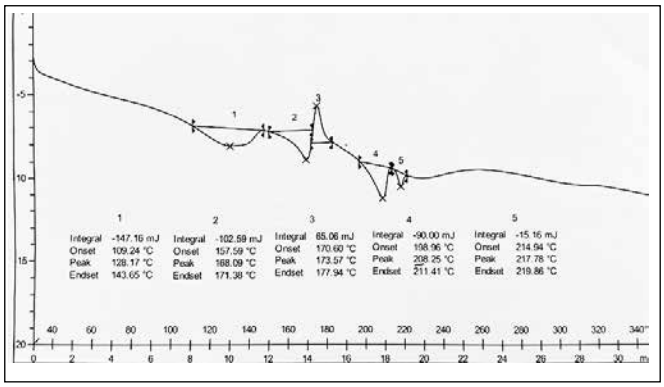

Fig. 1C: DSC curve of pharmaceutically equivalent batch

Differential scanning calorimetry (DSC)[36,37]

DSC measurements of LST, lactose monohydrate and pharmaceutically equivalent batch was carried out using a Mettler Toledo DSC 821. Accurately weighed samples (approximately 5-10 mg) were placed into 40µL sealed aluminium pans with three vent holes. A heating rate of 10^0C/min and temperature range of 30-350 ^{0}C was used for all measurements. “Mettler Toledo STAR” software was used for capture and analysis of data.

In vitro deposition[38,39,40]

A twin stage impinger was employed to measure the aerodynamic particle deposition of LST. In the upper and lower impingement chambers of the emitted dose (ED) apparatus, 7 and 30 mL of mobile phase were respectively introduced. All components were interconnected and ensured to maintain a vertical position. A suitable pump was attached to the outlet apparatus without installing the device. The Instahaler P device, containing 25 mg premixed powder, was loaded and equipped with a moulded rubber mouthpiece. Piercing the device to create two emitting pores for particle dispersion followed loading. Subsequently, the Instahaler P device was affixed to the throat of the impinger. Experiments were conducted with an airflow rate of 60 L min^{-1}, where the pump was briefly activated for 5 s and then turned off. This discharge sequence was repeated for an additional 9 capsules. Post-experiment, the apparatus was cautiously disassembled, and the inner and outer surfaces of the inlet tube were washed. The washings were diluted, and the volume was adjusted to 100 mL. The prepared solution was thoroughly shaken and then filtered through a 0.45µ filter paper.

RESULTS

Preformulation study

The results of preformulation study of LST as well as the inhalable powder blend are shown in Table II. Bulk density of LST and blend was found 0.764 and 0.501 g mL^{-1}, respectively. The decrease in bulk density of LST in presence of lactose blend may signify increase aerosolization property of the drug in the prepared formulation. Bulk density is a deciding factor in selection of capsule size. Based on the results of the bulk density, size 3 capsule was selected. Tapped density values (Table II) of LST and its powder blend indicated that the powder blend is coarser as compared to pure drug. Angle of repose of LST and powder blend was found 30.15^0 and 29.45^0, respectively. The results of angle of repose shows that the powder blend flow is increased in

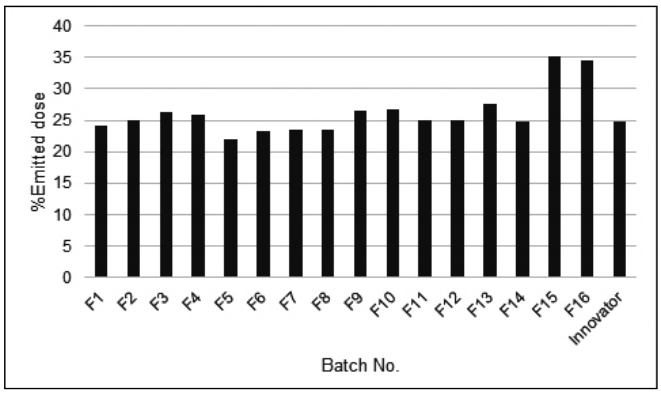

Fig. 2: Comparison of *in vitro* deposition of innovator against various prepared batches

comparison of pure drug, which is ultimately beneficial for its flow through the device.

Particle size distribution of LST and lactose

The particle characteristics of LST and inhalation-grade lactose particles, including size distribution and particle size, were examined to determine suitable carriers. Lactohale® series (LH100, LH300) and Respitose®series (SV003, SV010, ML006, and micronized SV010) were utilized as inhalation-grade lactose particles. Particle size distribution was calculated using the equation (D90-D10)/ D50[41]. The results, outlined in Table III, indicate that among the lactose particles tested, Lactohale® LH300 exhibited the highest particle size distribution value of 2.1314. Lactohale® LH100 demonstrated the highest D50 value at 122.32. Respitose® SV003 and Respitose® SV010 displayed the narrowest particle size distribution values of 0.9890 and 1.1685, respectively. Based on these findings, lactose grades listed in Table III were chosen for formulating the dry powder for inhalation.

Formulation of inhalable dry powder

In formulation of inhalable dry powder, four trial batches were taken, as shown in the Table I. Based on the results of trial batches, two reproducible batches of the optimised formulation were also prepared. In the given trials, in trial 1 we varied the various finer grade lactose (Respitose® ML006, Lactohale® 300 and Micronized Respitose® SV010) and kept the Coarser grade constant (Respitose® SV010). In trial 2, variations of the finer grade lactose were as mentioned above, but coarser grade lactose was constant i.e., Lactohale® 100. Based on the results of the two trials, we selected Respitose® ML006 as the finer grade lactose and Respitose® SV010 as coarser grade lactose. Based on this, third trial batch was conducted by varying the ratio of fine and coarse grade lactose from 50:50, 60:40, 80:20 to 90:10. Based on the results of emitted dose of the batches, the ratio of coarse grade lactose to fine grade lactose were finalised as 60:40. In the fourth trial, we added two more intermediate size lactose grade i.e., Lactohale® LH300 and micronized Respitose® SV010. Reason behind adding the intermediate size lactose was to increase the emitted dose. So, in the fourth trial, two batches were conducted in which we added two intermediate grade lactose and analysed the batches for its emitted dose. Based on the results of the % emitted dose batch F13 was finalised as the optimized batch. In order to check reproducibility of optimized batch two batches, F15 and F16 were checked. Reproducible batches are also important factor for scaling up the batches at industrial level.

Powder properties of DPI formulation

The powder properties of prepared DPI formulation are shown in the Table IV. The formulation containing the Respitose® SV010 and Respitose® ML006 in the weight ratio 60/40 i.e., F10 has shown desired D10, D50 and D90 which concludes that the proper ratio of coarse to fine grade lactose yields desired results. The batch containing Respitose® SV010, Respitose® ML006 and Lactohale® LH300 in weight ratio 60/16/24 i.e., F13, F15, F16 has shown nearly same particle size distribution as they contain the lactose grade in proper ratio, which in turn results into particle size distribution which shows better *in vitro* release.

DSC

The DSC scan of the LST has shown the sharp endothermic peak at 209.47 ^{0}C which shows the crystalline nature of the drug (Fig. 1A). The lactose monohydrate has shown multiple peaks at 136.63^{0}C, 168.84^{0}C, 176.71^{0}C, 215.97^{0}C (Fig. 1B). The pharmaceutically equivalent batch has retained all the peaks of the LST and lactose monohydrate peaks, which shows that there is no interaction between the excipients and drug; also no change in nature of drug is observed (Fig. 1C).

In vitro deposition

The aerodynamic characteristics of the DPI powder formulations were evaluated using the twin stage impinger, contrasting with the commercial product. The results depicted in Fig. 2 illustrate the outcomes of *in vitro* deposition.

Initially, we assessed the impact of Respitose® SV010, a coarser grade lactose, on drug deposition. Among the various trial batches, F3 batch displayed higher deposition rates. Subsequently, we explored the

influence of Lactohale® LH100, another coarser grade lactose, on drug deposition in trial two. Results revealed that Respitose® SV010 achieved a higher percentage of emitted dose compared to Lactohale® LH100. This discrepancy can be attributed to the favourable particle size distribution of the lactose grades. Overall, our findings indicate that incorporating fine lactose particles into the DPI formulation enhances product performance, consistent with prior investigations. Based on this literature data, we opted to utilize the finer grade lactose. In the results of trial 3, F10 batch exhibited the highest % emitted dose compared to F9, F11, and F12. F10 batch comprised "Respitose® SV010" and "Respitose® ML006" in a 60:40 ratio, maintaining the ratio of fine grade lactose to coarse grade lactose at 60:40 for further trials. In trial 4, we comparatively analysed the effect of "Lactohale® LH300" and "micronized Respitose® SV010" on the emitted dose of the drug. Lactohale®300 demonstrated a superior emitted dose compared to micronized Respitose® SV010, even surpassing the innovator. Finally, two reproducible batches, F15 and F16, containing the same formulation as optimized batch F13, were analysed. Both F15 and F16 showed the highest % emitted dose.

Considering all results and observations, it was concluded that the appropriate ratio of fine grade to coarse grade lactose can enhance aerodynamic properties and drug emission from the DPI product formulation. This improvement is attributed to the presence of finer grade lactose. As fine grade lactose saturates the active sites of coarser carrier particles to which micronized drug is aligned, consequently, the drug adheres to passive sites (i.e., lower energy sites). This facilitates the deaggregation of the micronized drug during inhalation. This leads to a boosted respirable fraction and emitted dose[42].

DISCUSSION

Levosalbutamol is the active enantiomer of salbutamol (albuterol), a bronchodilator frequently employed in the treatment of ailments such as chronic obstructive pulmonary disease (COPD) and asthma. In this article, by focusing on the levosalbutamol enantiomer, the study was aimed for the development of more targeted and efficient therapeutic effect. Preformulation properties like angle of repose, tapped density and bulk density, which impact the drug's aerosolization, capsule size selection and flow properties through the inhaler device were studied. These results are essential for designing an effective dry powder inhaler formulation for delivering the drug to the respiratory system. The bulk density of LST was found as 0.764 g mL^{-1}, while the bulk density of the blend (containing LST and lactose) was 0.501 g mL^{-1}. Bulk density refers to the mass of a powder divided by its volume, indicating how closely the particles pack together. Here, the decrease in bulk density of LST in the presence of lactose suggests that the drug's aerosolization property was improved in the formulated product.

Particle size characterization of DPIs was important to consider aspects like the aerodynamic particle size distribution (APSD), which relates to the particle sizes that are maximum expected to be accumulated in the respiratory tract. This can impact the drug's therapeutic effect and safety. The equation (D90 - D10) / D50 was used to calculate the width of particle size distribution, providing insights into the variability of particle sizes within a distribution. In the context of a dry powder inhaler (DPI), understanding the particle size distribution is crucial for optimizing the inhalation performance and drug delivery efficiency. The size of the particles affects how they deposit in different parts of the respiratory tract. For effective inhalation, the particles should ideally be within a specific range to ensure that they can reach the desired target in the lungs.

CONCLUSION

Levosalbutamol, a bronchodilator medication, is extensively utilized in managing COPD and asthma. The DPI formulation containing this formulation is the best way to treat these pulmonary diseases as it is easy and cost effective. The results of preformulation study have showed that flow properties of levosalbutamol have improved in the formulation, which is an essential parameter of drug to be formulated in DPI to ease its flow through device. The results of particle size distribution signified that the prepared formulation has respirable fraction, so it will be deposited in the lungs at the desired site. Based on the results of *in vitro* deposition study, Respitose® SV010, Respitose® ML006 and Lactohale® LH300 were selected as excipients for preparation levosalbutamol DPI. Using these carriers, pharmaceutically equivalent product to Levolin Rotacaps was developed. In this equivalent product, the ratio of Respitose® SV010, Respitose® ML006 and Lactohale® LH300 is found to be 60/16/24, which shows increased emitted dose as compared to innovator.

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