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EFFECT OF LACTOSE FINES, USP IPs AND GLASS SAMPLING APPARATUS ON THE AERODYNAMIC BEHAVIOR OF THE FLUTICASONE PROPIONATE DPI

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ABSTRACT

DPIs use many techniques to produce effective drug dispersion, with passive dispersion and turbulent dispersion being notable methods. Passive dispersion depends on the patient's inhaling force to fragment the powder aggregates and distribute the medication into particles that may be breathed in. Conversely, turbulent dispersion refers to the interaction between the carrier particles and the turbulent airflow during inhalation, which results in the separation of the drug particles for efficient administration. Comprehending these complex systems is crucial for enhancing medication administration, guaranteeing patient adherence, and enhancing treatment results in respiratory disorders. Continuous research in the domain of DPIs persists in improving and introducing new features to these devices, facilitating the advancement of inhalation treatments that provide improved accuracy, effectiveness, and patient contentment. Understanding the processes that control DPIs is crucial for the development of respiratory drug delivery devices.

KEYWORDS: Lactose Fines, Aerodynamic Behavior, Fluticasone Propionate, drug dispersion, drug delivery devices.

INTRODUCTION

The current research aims to clarify the impacts on the FP DPI's aerodynamic behavior by adding lactose fines (ranging from 0% to 25%), a USP modified IPs, and a USP modified glass sample device (DDU apparatus). A medium resistance inhaler device, namely the Revolizer, was used to conduct the aerodynamic evaluation at a constant flow rate of 60 L/min. This study uses USP-modified IP and DDU equipment to provide the first comprehensive description of the aerosolization performance of a pre-blended lactose carrier. Hence, these results can have significant implications for

researchers in academia and business. A multistage cascade impactor with a USP IP has been the tool of choice for the majority of research publications that have sought to understand how the aerodynamic performance of medications is affected by the addition of lactose fines. Unfortunately, there hasn't been much research on using a multistage cascade impactor with a USP modified IP to study how the APSD pattern of DPIs changes with the addition of lactose fines. The majority of research has also neglected to examine how drug DDU is affected by the addition of lactose penalties. Given this and the paucity of data in the published scientific literature, it is crucial to comprehend the effects of lactose fines on the APSD and DDU of DPIs when using a USP modified IP and a USP modified glass sampling apparatus, respectively. This knowledge is important for both academia and industry. Therefore, in this study, FP, a prototype medication, was aerosolized utilizing lactose carriers with varying concentrations of lactose fines (ranging from 0% to 25%). The effectiveness of the aerosolization process was assessed using the USP modified IP and modified DDU equipment.

GENESIS AND OUTLINE OF THE WORK

An inhaler device that is suited for a DPI is combined with a micronized medicine (0.5-5 µm), suitable carrier particles (90-150 µm), and other unique components. Because the final formulation contains a modest amount of medication (e.g., 18 to 500 µg), carrier molecules are a crucial component of a drug carrier formulation, which is known as a DPI. Which means that the drug's aerodynamic efficiency is very sensitive to even little changes in the carrier's physicochemical properties. Consequently, there has been a surge of interest in the scientific literature on the changing of the carrier physicochemical features. A wide variety of particle engineering approaches have been investigated in the past with the aim of improving the aerodynamic performance of DPIs by altering their carrier physicochemical characteristics. Adding a third element, such as tiny particulates, amino acids, metal stearates, or natural or synthetic lung surfactants, has also shown unique ability to improve the physicochemical features of the carrier particles, in addition to these particle engineering strategies. Adding lactose fines, however, is the most appropriate approach to altering the DPI aerodynamic performance among these strategies.

Tertiary blends are the powder combinations that come from adding lactose fines to DPI formulations; the first method by adding intrinsic lactose fines to coarse lactose particles. The second method involves adding an extrinsic fraction to a final blend. In terms of the dosage given, these tertiary mixes significantly enhance the aerodynamic efficiency of the DPI. The enhanced aerodynamic performance with lactose fines has been explored using several theories, including active site (hot spots) theory, agglomeration, buffer, fluidization, and case-dependent theories. Lactose fines, according to these theories, significantly affect three parameters: electrostatic charge (columbic forces), moisture content (capillary actions), and van der Waals forces (molecular forces). All of these processes significantly alter the dispersion/DE agglomeration pattern that occurs during inhalation by influencing the equilibrium between the adhesion/cohesion forces of drug-carrier particles. The influence of lactose fines on drug-carrier adhesion/cohesion and aerosolization has been well-documented, but few studies have investigated how concentration, particle size, and shape affect this effect. To further investigate the interactions between the drug-carrier particles and the added lactose fines, a combination of Raman spectroscopy, X-ray microanalysis, and scanning electron microscopy has been used. In addition, a range of aerodynamic and non-aerodynamic techniques, including as microscope image analysis and laser diffractometry, have been used to comprehend how the addition of lactose fines impacts the APSD of DPIs.

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Figure 1 Revolizer inhaler device and US Pharmacopoeia (USP) induction ports (IP) i.e. USP IP and USP modified IP.

EXPERIMENTAL WORK

Induction ports and glass sampling apparatus

Two distinct IPs were used in this investigation. This new product-specific monograph for FP inhalation powder and the USP general monograph (601) are the sources for the USP IP and USP modified IP designs, respectively. A new monograph for FP inhalation powder is referred to as USP modified glass sampling instrument. Figures 1 and 2 illustrate the USP IP, USP modified IP, and USP modified glass sample equipment, correspondingly.

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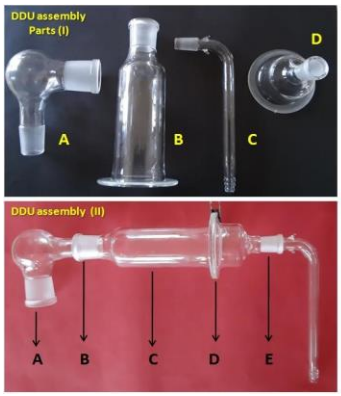

Parts	Description for I
A	Throat (modified round bottom flask)
B	Sample collection chamber with neck and base
C	Glass tube to connect vacuum pump
D	Filter-support base with neck

Parts	Description for II
A	Mouthpiece adaptor
B	Glass joint
C	Sample collection chamber
D	Filter support with holder
E	Connector

Figure 2 USP modified glass sampling device parts [I] and USP modified glass sampling device [II].

METHODS

Sieving

The lactose samples were filtered using a wire-mesh brass test sieve to remove any clumps or fragments. To summarize, a coarse lactose sample was passed through a set of 80 and 100 mesh sieves, measuring 180 and 150 µm, respectively. The resulting fraction was then placed in a stainless-steel container, followed by an aluminum pouch containing a desiccant (1 g, Tyvek pouches, India), and left to dry at room temperature. We used this stored fraction that had been sieved for future studies. The whole sieving procedure was carried out in a controlled environment with temperatures (25 °C ± 2% and humidity levels (50 % ± 5%).

Preparation of lactose pre-blends

It was mixed with sieved coarse lactose (Lactohale 200) at five different concentrations with micronized fine lactose (Lactohale 300). To summarize, roughly measured quantities of fine (ranging from 0% to 25%) and coarse (from 0 to 25%) lactose were mixed for 30 minutes at a low speed (50 rpm) in an in-house cone blender [17]. Stainless steel containers were used to preserve the pre-blends that were obtained. After that, aluminum pouches containing a desiccant (5 g, Tyvek pouches, India) were used until further experiments were required. Similar to the sieving experiment described above, the blending experiment was also conducted in a controlled atmosphere.

CHARACTERIZATION

Particle size distribution

We used a Sympatec Helos system (Sympatec GmbH-System, Germany) with the Sympatec software Windox for data processing and analysis to conduct the PSD analysis of lactose samples in RODOS mode. The dry powder feeding rate (vibri) was maintained at 85% and the disperser pressure (Oasis dry) at 1.5 bar. An R4 lens (0.5-350 µm) was used to conduct PSD analysis on the lactose samples. Three measurements were averaged to get the PSD findings. In addition, the steps outlined by Molina et al. (2018) were used to calculate the PSD spans.

Loss on drying and moisture content

A moisture analyzer (HE53, MettlerToledo AG, Switzerland) and the Karl Fischer titration (Veego Karl Fischer Matic III, Mumbai, India) were used to find the percentage LOD and percentage MC values of the lactose samples, respectively. Two grams of each lactose sample was precisely measured and put into the aluminum pan of the moisture analyzer for % LOD determination. The usual drying procedure was then run under ambient environmental conditions. A slightly modified version of the Karl Fischer titration technique as reported by Li et al. (2016) was used for % MC analysis [18]. For every lactose sample, the percentages of LOD and MC were computed by averaging three separate measurements.

Powder flow properties

Dhumal et al. (2008) detailed a procedure for measuring the powder flow characteristics of pre-blended lactose samples. In order to comprehend the powder flow characteristics of the control and preblended lactose samples, the following parameters were calculated: bulk density (BD), tapped density (TD), Carr's compressibility index (CI), and Hausner ratio (HR). Every single sample had three values computed.

Surface area analysis

Each lactose sample was subjected to a surface area study utilizing an automated gas sorption system developed by Quanta chrome Instruments (Anton Paar GmbH, Germany, IIT Bombay, India). In particular, the SSAs of the lactose samples were calculated using the multipoint Brunauer-Emmett-Teller (BET) technique. The analytical parameters were as follows: bath temperature, 77.30 K; outgas temp., 300.0 °C; outgas time, 1.0 h; X sect. area, 16.2 Å2 per mole.; P/P0 tolerance, 9; and non-ideality, 6.58 X 10^-4. The 50 mg of lactose sample was precisely weighed and added to the surface area analyzer's loop. In addition, the pore diameters of the different lactose samples were measured using the same gas sorption apparatus.

Surface roughness

The SR values of lactose samples were determined using a method illustrated by Du et al. (2014). The BET SSA and theoretical volume-specific areas were used to determine the surface roughness values of the lactose samples. The SR of each lactose sample was calculated using the following equation:

$$SR = \frac{BET\ SSA}{Theoretic\ \ volume\ -specific\ \ area} \ldots\ldots \text{Eq. 1}$$

where SR is the surface roughness, BET SSA is the Brunauer-Emmett-Teller specific surface area and the theoretical volume-specific area is the sphere surface area over the unit weight of the particle.

Field emission scanning electron microscopy

An FESEM (FEI Nova NanoSEM, Thermo ScientificTM) was used to image the surface of every lactose sample. Surface imaging was performed at an acceleration voltage of 15 kV after individual lactose samples were adhered to the circular aluminum stub using double-sided adhesive black carbon tape and sputtered with gold. An image and analysis program developed by Thermo ScientificTM called xT was used for controlling the microscope (Version 1.0).

PREPARATION OF DPI FORMULATIONS

Micronized FP was used to produce model DPI formulations in accordance with the method outlined by Dhumal et al. (2008). A stainless-steel container was used to

combine FP and lactose in a geometrical fashion. After that, a cone blender was used to blend the mixture at a low speed (50 rpm) for 30 minutes. A stainless-steel container was used to keep the resultant mixes in a controlled environment. The controlled environment allowed for the hand filling of Size 3 HPMC capsules with 25 mg ± 1% of each formulation, which corresponds to 100 mg of FP. In addition, the filled capsules were kept in a double polybag, then in an aluminum pouch containing a desiccant (1 g, Tyvek Pouches, India), until the next test was run.

Content uniformity

Samples were taken from the top, middle, and bottom of the container to ascertain the CU of every batch. We collected 100 mg of FP powder from each site, dissolved it in an 80:20 methanol: water diluent, and then tested it for FP content. Three measurements were used to calculate the CU values. There was also an expression for the CU level in each batch using the % CV.

Energy-dispersive X-ray spectrometry

The FP distribution on the surface of the pre-blended lactose sample was investigated using energy dispersive spectroscopy (Bruker XFlash, 6I30). The data collecting and analysis were carried out using the Esprit 1.9 software, while the EDS detector operates based on the concept of silicon drift. EDS analysis was performed with an elemental detection range of 4Be to 95Am, with an outstanding energy resolution of 123 eV for Mn Ka and 45 eV for C Ka.

Aerodynamic particle size distribution

All batches were subjected to in-vitro deposition experiments utilizing a non-viable ACI (Westech Scientific Instruments, UK) that is eight stages long. A vacuum pump and a critical flow controller (Innovative Sampling Technologies, Westech Scientific Instruments, UK) are integral parts of the ACI setup, which also includes a PS and cascade stages. In accordance with the approved monograph for FP inhalation powder, the ACI assembly was also supplied with a USP modified IP (Fig. 1). The PS was immersed in 15 mL of methanol before to each experiment, and a combination of n-hexane and silicone oil (1% w/v) was evenly coated onto the cascade stages to

guarantee effective sample collection and enhanced sample recovery. The lactose mixture (five capsules) was introduced into the ACI assembly in each experiment using a Revolizer inhaler device at a steady flow rate of 60 L min-1 (± 5%). Following dosage activation, the ACI assembly was carefully removed and immersed in a known volume of methanol: water (80:20), together with the device, capsules, mouthpiece, IP, PS, and cascade stages. A high-performance liquid chromatography (HPLC; PU-2080, Jasco, Japan) system was used to examine and quantify the quantities of FP retained in the various components. The analysis was carried out at 235 nm following appropriate dilution. Recovery dose (RD), exposure dose (ED), mass balance (MB), percent of particles (FPD), and fine particle fraction (FPF) were all determined after a thorough analysis of the collected data. The MMAD and GSD were also determined with the use of a no-cost online tool, the MMAD calculator.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

With just minor adjustments, the HPLC technique described above was lifted from an earlier publication. A ChromNAV data collection system was linked to the PU-2075 plus UV detector, AS-4050 auto-sampler, and PU-2080 plus pump that made up the PU-2080 Jasco HPLC system. Analysis was carried out using an Agilent Eclipse Plus C18 column (5 µm, 250 X 4.6 mm, Agilent, USA).

At a flow rate of 1.0 mL min-1, the isocratic mobile phase was mixed with methanol, acetonitrile, and water in a ratio of 40:30:30, v/v. The detection wavelength was set at 235 nm. For FP, the retention time was 12.02 minutes. After collecting the chromatographic data, they were analyzed using ChromNAV HPLC software (Version 2.0, Jasco, Easton, USA).

STATISTICAL ANALYSIS

We give the data as the mean ± SD, and all studies were done three times. In order to do statistical analysis, the findings were submitted to Student's t-tests and the program used was Graph Pad Prism (Ver. 8, San Diego, CA, USA). The data that have been evaluated are shown as follows: $p < 0.01$ indicates statistical significance, while $p \leq 0.001$ indicates very significant statistical results.

RESULTS

Particle size distribution

In Table 1, you can see the PSDs for several samples of lactose. There were notable variations in the PSD profiles of the control and pre-blended lactose samples. The control lactose sample (128.22 mm) had an average particle size (d90) of 1.12 times larger than the pre-blended samples with 5% fines and 10% fines, with mean particle sizes of 144.39 and 156.31 µm, respectively.

The average particle size (d90) values for pre-blended lactose samples containing 15, 20, and 25% fines were 134.67, 147.88, and 130.93 µm, respectively. Additionally, in the preblended lactose samples, the percentages of particles smaller than 10 mm in size were 11.54, 12.99, 14.91, 14.46, and 17.98%.

Additionally, there were notable disparities in the span values between the control and pre-blended lactose samples.

The following is the sequence of the span values for the lactose samples: control lactose (1.96), pre-blend 5% (1.96), pre-blend 15% (2.30), pre-blend 10% (2.43), pre-blend 25% (2.65), and pre-blend 20% (2.71). Kaialy et al. (2012) similarly found that pre-blended lactose samples had larger span values.

Loss on drying and moisture content

The lactose samples' % LOD and % MC values may be shown in Table 1. In comparison, the control lactose sample had a % MC of 4.10% and a LOD of 0.10%. When comparing the pre-blended lactose samples to the control lactose sample, there were no discernible variations in the % LOD and % MC values.

Table 1 Physiochemical characterization of control and pre-blended lactose carrier (n=3).

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Batches	PSD (µm)			LOD	MC	BD	TD	CI	HR
	d_{10}	d_{50}	d_{90}	(%)	(% w/w)	g/mL	g/mL	(%)	
Control	4.40 ± 1.31	63.10 ± 2.09	128.22 ± 12.99	0.10 ± 0.02	5.10 ± 0.20	0.58 ± 0.01	0.95 ± 0.10	38.75 ± 2.13	1.63 ± 0.10
05 % fines	8.80 ± 2.76	69.31 ± 3.82	144.39 ± 7.98	0.11 ± 0.01	5.00 ± 0.11	0.62 ± 0.03	1.00 ± 0.11	37.49 ± 3.10	1.59 ± 0.11
10 % fines	7.70 ± 1.09	61.22 ± 4.21	156.31 ± 6.66	0.12 ± 0.01	5.10 ± 0.21	0.67 ± 0.02	0.89 ± 0.12	24.35 ± 2.19	1.32 ± 0.13
15 % fines	6.00 ± 2.09	56.45 ± 2.87*	135.67 ± 8.14	0.10 ± 0.02	5.10 ± 0.20	0.63 ± 0.01	0.89 ± 0.10	28.74 ± 3.20	1.40 ± 0.11
20 % fines	6.20 ± 1.98	52.54 ± 3.01$^{\Delta}$	147.88 ± 9.19	0.10 ± 0.01	5.10 ± 0.19	0.62 ± 0.03	0.87 ± 0.11	28.70 ± 1.89	1.40 ± 0.12
25 % fines	5.40 ± 1.86	47.81 ± 3.07$^{\Delta}$	130.93 ± 10.88	0.10 ± 0.01	5.10 ± 0.18	0.62 ± 0.01	0.90 ± 0.10	31.24 ± 3.08	1.45 ± 0.11

Powder flow properties

In Table 1, you can see the outcomes of the powder flow properties. The BD values ranged from 0.58 to 0.67 g mL-1, whereas the TD values ranged from 0.87 to 1.00 gm/L. Between 24.35% and 38.55% was the CI range, while between 1.32% and 1.63% was the HR range.

A lackluster flow profile is indicated by higher CI (> 38) and HR (> 1.60) values. No lactose sample had good flow characteristics, as shown in Table 1, with the exception of the 10% lactose fines pre-blended with lactose.

Compared to the control lactose, which had CI values of 38.75 and HR values of 1.63, the pre-blended lactose fines containing 10% lactose had the lowest values at 24.35 and 1.32, respectively.

Except for the 10% lactose fines pre-blended with lactose, all of the lactose samples exhibited poor flow characteristics.

Surface area analysis

SSA was evaluated using multipoint BET analysis for both the control and pre-blended lactose samples. The lactose samples' multipoint BET SSA values are shown in Table 2. The SSA values showed considerable variations between the control and pre-blended lactose samples, ranging from 0.21 to 3.98 m2g-1.

The SSA values changed significantly when lactose penalties were added; for samples with 15% fines, they dropped to 0.20 m2 g-1, while those with 10% fines dropped to 0.70 m2 g-1. Additionally, for samples with 5% penalties and 20% fines, the SSA values rose to 3.95 and 3.98 m2 g-1, respectively.

As an interesting aside, the SSA value of the 25% lactose fines sample (1.43 m2g-1) remained relatively unchanged when contrasted with the control lactose sample (1.62 m2g-1). Table 2 also shows the findings of the pore diameter analysis of the lactose samples. Pore diameter measurements for the lactose samples varied significantly, ranging from 0.15 to 7.18 µm, just as they did for the SSA samples.

The control lactose sample had 969.1 nm macro-pores (pore size more than 50 nm), however as indicated in Table 2, the pore size was dramatically reduced with the addition of lactose

fines. Pore size (7187 nm) was substantially larger in the 15% lactose fines sample than in the control lactose and other pre-blended lactose samples. The pattern of drug deposition in the pulmonary airways is greatly affected by changes in the SSA and pore size.

Surface roughness

Table 2 displays the SR values for each lactose sample. The BET SSA and the sphere surface area over the particle weight unit were used to determine SR in this study. Preblended lactose samples had much lower SR values than the control lactose samples. The SR values were 2.41 times higher in the pre-blended lactose samples that included 5% and 20% fines than in the control lactose sample.

Also, when comparing the control lactose sample, the pre-blended lactose sample with 15% fines, and the pre-blended lactose sample with 5% and 20% fines, the SR value was lowest for the 15% fines sample. In addition, FESEM research was carried out to comprehend the qualitative variations in the surface characteristics.

Table 2 Specific surface area, average pore diameter and content uniformity of control and pre-blended lactose carrier (n=3).

Batches	SSA (m^2/g)	Average pore diameter (µm)	SR	CU (%)	CV (%)
Control	1.62 ± 0.19	0.97 ± 0.01	0.34 ± 0.01	96.47 ± 1.05	1.08
05 % fines	3.95 ± 0.16»	0.25 ± 0.02»	0.82 ± 0.01»	96.93 ± 1.39	1.44
10 % fines	0.70 ± 0.01»	0.15 ± 0.01»	0.16 ± 0.00»	98.07 ± 0.90	0.91
15 % fines	0.21 ± 0.01»	7.18 ± 0.01»	0.04 ± 0.02»	98.10 ± 1.87	1.91
20 % fines	3.98 ± 0.32»	0.38 ± 0.02»	0.82 ± 0.01»	98.35 ± 1.76	1.79
25 % fines	1.43 ± 0.29	0.60 ± 0.02»	0.30 ± 0.02*	99.91 ± 0.51	0.51

*$p \leq 0.01$ (statistically significant) and »$p \leq 0.0001$ (statistically highly significant) when compared to the control group.

Field emission scanning electron microscopy

Control and preblended lactose samples are shown in Fig. 3 via exemplary FESEM photomicrographs. The morphologies and variations in shape of the control and pre-blended lactose samples were examined using FESEM analysis. Photomicrographs taken with a field emission scanning electron microscope reveal striking variations in the lactose samples'

forms, surface morphologies, and roughness. Using the FESEM photomicrographs, the surface morphologies and forms of the lactose samples at three distinct length scales can be readily identified. There were more aggregated particles and several asperities in the control lactose sample. Clusters of both tomahawk-shaped and otherwise haphazardly formed particles make it up. On the other hand, the tomahawk-shaped and surface-free lactose samples that were pre-blended had less agglomerated particles. And as can be seen from the FESEM images, the pre-blended lactose samples had surface asperities that the lactose particles stuck to. To summarize, the qualitative data provided by FESEM imaging of the lactose samples was very valuable; nonetheless, surface area analysis was the only method that could study more specific variations in the surface features. This was followed up by an analysis of how changes in the lactose samples' surface properties—their forms, sizes, morphologies, and surface areas—could affect FP's aerosolization performance in an in vitro drug deposition experiment.

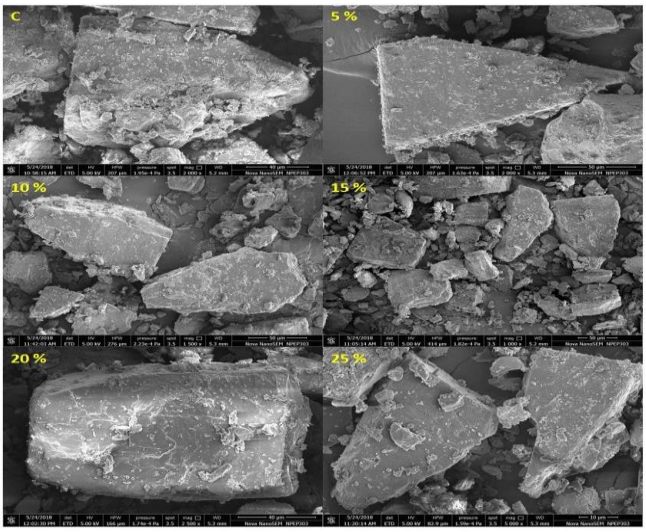

Figure 3 FESEM micrographs of control lactose (C) and pre-blended lactose samples i.e. 5 % lactose fines (5 %), 10 % lactose fines (10 %), 15 % lactose fines (15 %), 20 % lactose fines (20 %) and 25 % lactose fines (25 %).

Content uniformity

As a measure of batch quality, CU is an important quality feature of DPI products. In order to keep a product's strength within specified acceptability standards, CU assessments are useful. Both the percentage CU and CV values need to fall within the range of 100 ± 4.5% and 4.5%,

respectively, in order for CU to be confirmed. For every batch, Table 2 shows the proportion of CU and CV values. For FP, the percentages of CU and CV vary from 99.47% to 99.91%, and from 0.51% to 1.91%, respectively. The batch with 25% penalties had the highest CU values, followed by the batch without fines and the lactose control, which had the lowest CU values. All batches have adequate FP CU, as seen by the lower % CV readings. To summarize, all batches met the specified acceptance requirements for FP content and % CV values.

CONCLUSION

The field of materials science is actively investigating novel, high-performance materials for use in DPI components, with the goal of improving both device functionality and the user experience for patients. In order to build dependable and user-friendly DPIs, it is essential to choose materials that have enhanced mechanical qualities, are biocompatible, and have a long lifespan. One potential use for biodegradable materials in DPIs is to reduce their environmental effect and provide long-term sustainability. Another factor that helps DPI technology advance is the creation of new inhaler designs with ergonomic features and easy-to-use interfaces. By streamlining the administrative procedure, these developments hope to make DPIs more approachable and easy to use for people of all ages. In addition, DPIs will have potential applications outside the conventional management of respiratory diseases. Investigations on the feasibility of DPIs for the delivery of other prescription pharmaceuticals, not limited to pulmonary treatments, are now ongoing. With the advent of systemic drug delivery, new avenues for treatment have opened up, especially for conditions that might respond well to non-invasive, targeted medication delivery. Because of their adaptability, DPIs may be used as a drug delivery platform to create new and better therapies for illnesses and conditions including diabetes, heart disease, and certain neurological disorders. This expanded reach highlights the revolutionary potential of DPI technology to change the way pharmacological treatments are conducted. Another promising area of research is the use of personalized medical principles into DPI creation.

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