



# The role of intrinsic fines in the performance change of expired lactose carriers for DPI applications

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## ABSTRACT

Dry powder inhalation offers a well-established administration route for either local or systemic drug delivery. Lactose-based powder blends still build the basis of respiratory drug delivery, despite of numerous emerging formulation approaches. The amount of fine lactose excipients, either extrinsic or intrinsic, crucially influences the aerodynamic performance of the corresponding blend. This study highlights the role of intrinsic fines as a fundamental performance affecting parameter during storage and expiry of lactose carrier bulk. We showed that intrinsic fines play an inferior role after expiring compared to fresh batches. If strongly adhering or even merged fines regain their mobility and contribute to the dispersion (by removal and re-addition), it will significantly enhance drug delivery. Furthermore, we provide evidence for decreased mobility of intrinsic fines caused by humidity (e.g., during inappropriate storage) resulting in decreased powder fluidisation.

## 1. Introduction

Although well-established in the treatment of respiratory diseases, research on dry powder inhalation (DPI) still reveals new insights. There is ongoing research regarding new formulation strategies [1], digitalisation-focused therapeutic optimisations [2] or sustainability considerations [3]. Regardless of these future-oriented approaches, the quality of the current orally inhaled drug products needs to be constantly evaluated as well. Currently, most marketed products (US and EU) are lactose-based interactive blends [4]. These formulations are therapeutic cornerstones of the more than 500 million asthma and COPD patients worldwide [5].

Lactose serves as a carrier particle to enable the processing and dose metering of the micronised ( $< 5 \mu\text{m}$ ), highly cohesive active pharmaceutical ingredient (API) particles. These interactive blends are obtained by mixing drug and carrier. This straightforward formulation strategy enables respiratory drug delivery but has still room for improvement regarding drug delivery performance [6]. The reason for insufficient drug delivery is mainly due to too high adhesion between drug and carrier [7]. To decrease this adhesion, scientists use particle engineering techniques such as dry particle coatings or modify carrier roughness and hence contact area [8,9]. A different approach to enhancing formulation performance is to use fine lactose excipients to create ternary blends for

inhalation. Those ternary blends are known to be superior in terms of aerodynamic performance compared to the respective binary blends [10]. But adding a ternary component to the bulk carrier represents an additional processing step, which needs quality control and is money- and time-consuming.

Carrier materials initially contain fines to a certain extent, depending on the production technique of the inhalation grade lactose. These intrinsic fines are known to enhance delivery performance following the same principles as added extrinsic fines [11]. Therefore, intrinsic fines are a critical quality attribute of lactose for inhalation.

This study highlights the role of intrinsic fines in lactose-based blends for inhalation. Furthermore, we investigated how intrinsic fines influence the performance of their corresponding interactive blends depending on age and storage.

## 2. Materials and methods

### 2.1. Materials

The carrier material investigated in this study was a highly crystalline, inhalation grade lactose (InhaLac® 230, IH230, Meggle, Wasserburg, Germany). In the following sections, we refer to a *fresh batch* as a batch that was still ahead of its retest date ( $< 12$  months) and stored in

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its commercial packaging (sealed aluminium bag) at non-monitored benchtop conditions. Furthermore, we used an expired batch of the same carrier quality, stored batch. “Expired” refers to InhaLac 230, which was stored outside of its commercial packaging (wide neck screw top drum) at non-monitored benchtop conditions (IH230 (ex)) for more than 36 months.

To investigate the role of intrinsic fines in the expiry process, we removed and re-added intrinsic fines in this study. Lactose batches with removed intrinsic fines are denoted with the suffix “rF”; the ones where we added the initially removed fines in their initial concentration are denoted with “rF-F”. In all interactive blends we used ipratropium bromide as a model drug ( $d_{90} < 5 \mu\text{m}$ , Boehringer Ingelheim, Ingelheim, Germany).

### 2.1.1. Stressed lactose storage

We stored fresh IH230 samples in open aluminium jars at different conditions for 4 months in different conditioning units (Weiss Umwelttechnik, Reiskirchen-Lindenstruth, Germany) to recreate the condition of the IH230 (ex). The conditions were constantly monitored using data loggers (TFA Dostmann, Wertheim-Reicholzheim, Germany). We chose the conditions according to the ICH guideline CPMP/QWP/609/96/Rev 2 as I) long term (25 °C, 60% RH) II) accelerated (40 °C, 75% RH and III) high humidity (25 °C, 90% RH). The high humidity conditions were chosen separately from the well-established ICH guideline to provide information on humidity influence dissociated from higher temperatures.

## 2.2. Measurement of particle size distributions

We analysed all batches using laser diffraction to ensure similar particle size distributions (PSD) and adequate removal of intrinsic fines. The automatically fed powder (VIBRI) was dispersed using compressed air within the dry powder dispersion unit (RODOS) of the helium-neon laser optical system (HELOS®, Sympatec, Clausthal-Zellerfeld, Germany) at a dispersion pressure of 2 bar for carrier batches and 4 bar for the fines, respectively. We used the R4 lens for all measurements and evaluated the raw data based on the Fraunhofer enhanced equation using the PAQXOS software. Displayed data is average of three measurements.

## 2.3. Extraction and removal of intrinsic fines

IH230 and IH230 (ex) were both sieved on a sieve shaker (mesh size: 32  $\mu\text{m}$ , RETSCH, Haan, Germany) to extract and collect the corresponding intrinsic fines. Due to high agglomeration tendencies of such small excipients, we additionally used an air-jet sieve (mesh size: 32  $\mu\text{m}$ , Hosokawa Alpine, Augsburg, Germany) with a negative pressure of 4 kPa and 29 min sieving time to ensure complete removal of loose intrinsic fines in the respective carrier batches.

## 2.4. Assessment of specific surface area (SSA)

We measured the SSA using octane adsorption isotherms in the Surface Energy Analyser (SEA, Surface Measurement Systems, London, UK). Samples were packed into silanised glass columns (inner diameter: 4 mm) and fixed with silanised glass wool on both ends. By tapping the columns using the SMS Column Packer Accessory (Surface Measurement Systems) for 5 min, we excluded voids within the powder bed. The packed columns were conditioned for 60 min at 0% RH and 10  $\text{cm}^3/\text{min}$  nitrogen flow prior to the SSA measurement. After a double injection of methane (determination of dead volume) we conducted a range of octane injections, which resulted in an adsorption isotherm. The SEA Analysis software (Surface Measurement Systems) enabled the calculation of the SSA according to the BET theory.

## 2.5. Preparation of interactive blends

All interactive blends in this study were prepared using the Picomix® high-shear mixer (Hosokawa Alpine). All excipients were pre-sieved (mesh size carrier: 250  $\mu\text{m}$ ; mesh size drug: 180  $\mu\text{m}$ ; mesh size fines: 180  $\mu\text{m}$ ) to remove agglomerates. Ahead of the blending process, the excipients were weighed into the mixing vessel using the sandwich-weighing method (1% w/w drug concentration). The mixing process comprised two mixing steps at 500 rpm as well as a sieving step (mesh size: 250  $\mu\text{m}$ ) in between. For ternary blends, fines were added in the first mixing step and the drug in the second one. All blends were tested for homogeneity using high-performance liquid chromatography (HPLC, see section 2.7). A blend was considered homogeneous at a drug content of 90% – 110% and a relative standard deviation of drug content < 5%. Prior to the following experiments, we conditioned the blends at 44% RH for at least one week to decrease process-induced electrostatic charging.

## 2.6. Aerodynamic assessment

The assessment for aerodynamic performance was conducted using the Next Generation Pharmaceutical Impactor (NGI, Copley Scientific, Nottingham, United Kingdom). The powder blends were transferred into Novolizer® devices (MEDA Pharma, Bad Homburg, Germany) and dispersed at an airflow which corresponds to a 4 kPa pressure drop over the device (78.3 L/min). After emitting eight doses, the drug content was quantified using HPLC (see section 2.7). We evaluated the raw data using the CITDAS software (V3.1, Copley Scientific). All data displayed as an average of triplets.

## 2.7. Quantification of drug content

To quantify drug content in this study, we used HPLC. The analytical method comprised a cyanopropyl-substituted stationary phase (LiChrospher® 100 CN, Merck) and a mobile phase consisting of 71% bidistilled water, 29% acetonitrile and 1.42 g/L heptane sulfonic acid, adjusted to pH 3.2. We validated the method in terms of system suitability, specificity, precision, repeatability, and linearity and calculated the limit of quantification according to the ICH guideline CPMP/ICH/381/95 as 0.08  $\mu\text{g}/\text{mL}$ . All drug concentrations used for further calculations were within a calibrated range (external standard calibration curve ranging from 0.21  $\mu\text{g}/\text{mL}$  to 104.80  $\mu\text{g}/\text{mL}$ ). Solvents used in this study were supplied by Honeywell Riedel-de Haën (Chromasolv, Seelze, Germany) as chromatographic grade solvents.

## 2.8. Powder rheometry

Different powder properties were measured using the FT4 Powder Rheometer (Freeman Technology, Tewkesbury, United Kingdom). We used two different methods: The aeration method and powder permeability tests.

### 2.8.1. Aeration method

The aeration setup comprised an aeration base (perforated base connected to an air control unit), a borosilicate vessel and a stirring blade. The powder sample passes different conditioning and test phases during this test with increasing air flow through the powder bed. The instrument monitors the force which is needed to stir through the powder in helical movements. The range of air velocities needs to be adjusted to the powder behaviour, resulting in an energy plateau at the end of the corresponding method (aeration energy). We used 10 g sample mass per measurement and increased the air velocity up to 20 mm/s to ensure a complete fluidisation for all samples. In contrast to the aeration energy (plateau energy), the aeration ratio allows levelling out of parameters like sample mass deviations. The aeration ratio (AR) is calculated following equation (1).

$$AR = \frac{\text{Total energy at } 0 \frac{\text{mm}}{\text{s}} \text{ air velocity}}{\text{Aeration energy at } 20 \frac{\text{mm}}{\text{s}} \text{ air velocity}} \quad (1)$$

### 2.8.2. Permeability method

The permeability setup uses the same aeration base as the aeration energy test. In contrast to aeration, the powder sample is filled into a borosilicate split vessel. This split vessel allows (after conditioning by the stirring blade) a levelled sample surface. The conditioned sample was compressed at different pressures by a vented piston. During compression, air passes through the sample and the instrument measures the pressure drop over the powder bed. Using the pressure drop at 15 kPa compaction pressure, we calculated the permeability according to equation (2).

$$\text{Permeability} = \frac{\text{Air velocity} \times \text{Air viscosity} \times \text{Length of the powder bed}}{\text{Cross-sectional area of the powder bed} \times \text{Pressure drop}} \quad (2)$$

All FT4 data in this work is based on triplicate measurements.

## 2.9. Carrier surface morphology

### 2.9.1. Scanning electron microscopy (SEM)

A Hitachi TM3030 tabletop SEM (Hitachi, Chiyoda, Japan) equipped with a backscatter detector was used to depict lactose surface appearance at 5 kV acceleration voltage. Ahead of SEM imaging, samples were fixed onto carbon stickers and sputter-coated with gold to minimise charging effects (Cressington 108, Tescan, Dortmund, Germany).

### 2.9.2. Atomic force microscopy (AFM)

Morphology mapping of lactose particles has been conducted using a cypher atomic force microscope (Oxford Instruments, Abingdon, United Kingdom) in tapping mode. The scan size was  $25 \mu\text{m}^2$  at a scan rate of 1 Hz and a resolution of  $256 \times 256$  pixel. The spring constant of the cantilever was 457.5 pN/nm. AFM raw data was processed using Igor Pro software (Wavemetrics, Lake Oswego, OR, USA). We probed at least two different spots on the surface of three different particles. Shown data is picked as representative for these particle qualities.

## 2.10. Statistical evaluation

Statistical calculations were performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). We stated differences between measurement results to be significant at a p-value < 0.05 (depicted as “\*\*”).

## 3. Results and discussion

### 3.1. Air-jet sieving could remove intrinsic fines without changing carrier particle size

This study is based on different sieve fractions. We removed the intrinsic fines of inhalation grade lactose batches to investigate if and how this will affect carrier performance in the corresponding interactive blends. To obtain valid results, we verified the success of the sieving process by measuring the PSDs. The PSDs of the carrier substances used are displayed in Fig. 1.

Based on Fig. 1, we state that the PSDs within the lactose batches before and after sieving were equivalent (IH230 = IH230 (ex)). Furthermore, the PSDs (Fig. 1 A and B) served as proof for the successful removal of intrinsic fines. Table 1 displays the  $d_{10}$ ,  $d_{50}$  and  $d_{90}$  values before and after air-jet sieving. The values did not differ statistically significant before the removal of intrinsic fines (p-value > 0.05), whereas they did after (p-value < 0.05). The mass concentration of the removable fines (via air-jet sieving) was higher for the fresh batch (IH230: 3.2%) compared to the expired batch (IH230 (ex): 2.2%), which is in line with the differing d-values. Nevertheless, the differences in PSD of the “rF” batches have no influence on the comparability in section 3.2, since we are comparing changes within batches, not total values.

Furthermore, Table 1 presents the percentage of particles smaller than  $30 \mu\text{m}$ . Both batches decreased by approximately 65% in particles <  $30 \mu\text{m}$  after air-jet sieving, even though the removed mass concentration was different. This hints at fines, which were not removable by air-jet sieving, but dispersible at high pressures in HELOS measurements. It must be stated that particle sizing by laser diffraction differs from the results obtained by sieving. The reason is a lack of precision for small sizes when using laser diffraction, different measurement principles and crucially different dispersion forces between air-jet sieving and laser diffraction [12].

Using the original bulk materials and these sieve fractions, we produced adhesive mixtures for inhalation. We additionally rebuild the original batches by adding the previously removed intrinsic fines in their initial concentration to the carrier sieve fractions without intrinsic fines, respectively. We proportioned the re-added concentration to the removable fines' concentrations.

### 3.2. Removal of intrinsic fines caused changes of fine particle fraction depending on the carrier storage

All six blends were homogeneous (RSD < 3%) after blending and

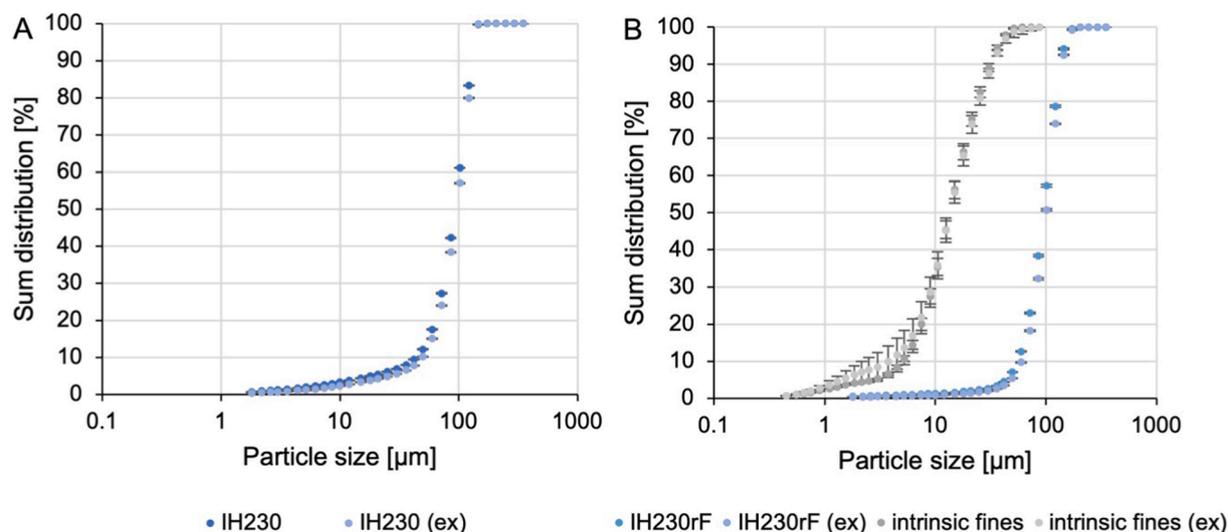


Fig. 1. PSDs of (A) InhaLac 230 and InhaLac 230 (ex) as bulk and (B) after the removal of the respective intrinsic fines. n = 3, error bars show SD.

**Table 1**

Particle size parameters before and after removing intrinsic fines via air-jet sieving. n = 3, SD in parentheses.

Material	IH230		IH230 (ex)		IH230rF		IH230rF (ex)	
d <sub>10</sub> [µm]	44.2	(4.0)	49.2	(0.2)	55.3	(0.2)	60.5	(0.2)
d <sub>50</sub> [µm]	93.4	(3.2)	96.0	(0.1)	95.8	(0.3)	101.3	(0.2)
d <sub>90</sub> [µm]	134.2	(0.0)	134.1	(0.1)	139.5	(0.3)	142.7	(0.1)
Particles < 30 µm [%]	6.9	(0.1)	5.6	(0.0)	2.6	(0.0)	2.0	(0.0)

assessed for their aerodynamic performance after conditioning. We refer to aerodynamic performance as fine particle fraction (FPF). We depicted the results of the NGI assessments in Fig. 2.

After removing the intrinsic fines of IH230, the FPF of the corresponding blend decreased significantly from 39.9% to 33.6%. Since fines crucially influence the aerodynamic performance of an interactive blend [10], the significant performance decrease can be explained solely by the absence of fines. But performing the same removal step with the IH230 (ex) batch, the performance did not change statistically significant. Hence, we concluded that the fines in the expired batch did not significantly contribute to the blend performance of IH230 (ex).

When re-adding the removed fines of IH230 to IH230rF, we reached a comparable FPF as before the removal (no significant difference, p-value > 0.05). This indicates that the fines had the same performance-enhancing characteristics in the original bulk as in the IH230rF-F blend. Contrarily, the addition of the initially removed fines to the IH230rF (ex) batch resulted in a significantly enhanced FPF. Restoring the same concentration and type of fines present in the original IH230 (ex) batch, the FPF increased from 23.2% to 28.4%.

Based on these observations, we assume the intrinsic fines in the expired batch to be strongly bound to the carrier or even fused. Nevertheless, it is possible to remove (at least parts of) them using high dispersion pressures (during the laser diffraction measurements) or extensive dispersion times (during air-jet sieving). Comparably low pressures within short timeframes during aerodynamic assessment were not able to loosen the fines to include them into the dispersion mechanism. But if these fines are removed and then blended with the initial carrier, they will be available again to meet their role as contributors in the dispersion of the blend.

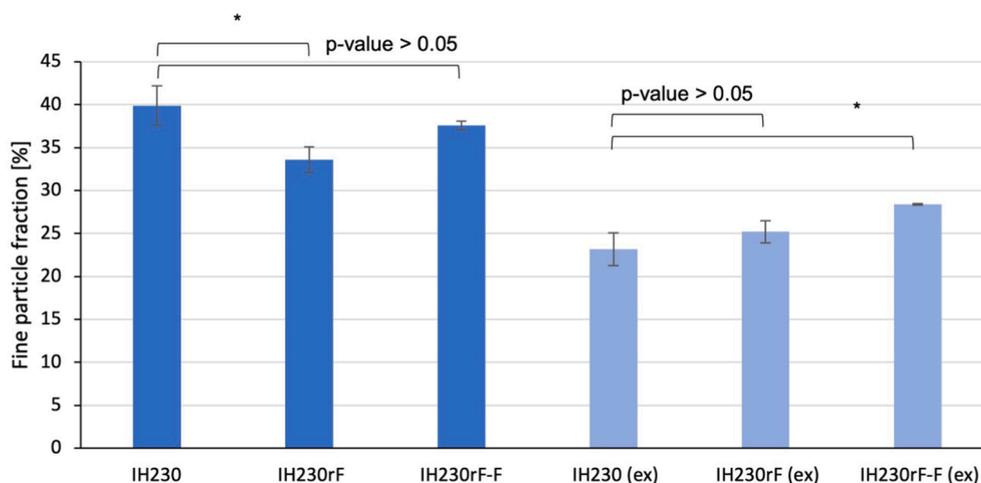
Additionally, we observed a statistically significant higher FPF for IH230 blends compared to IH230 (ex) or IH230rF-F (ex) blends. This hints at FPF influencing factors apart from the content and availability of intrinsic fines. Fused fines (Fig. 3) may lead to a micro-roughness, which was shown to decrease drug detachment, due to mechanical interlocking [8].

### 3.3. Powder rheometry detected changes in fines-related blend characteristics

We performed powder aeration tests to check on the hypothesis of worse fluidisation with or without available intrinsic fines. A worse fluidisation may indicate a worse dispersion of the respective powder blend and thus a worse FPF. Multiple properties influence the aeration behaviour of a powder sample: Particle adhesion/cohesion, surface texture, morphology, and particle size distribution. As adhesion should be comparable (expired and fresh batches are still chemically identical), as well as PSD, morphology and the availability of intrinsic fines could mainly influence aeration. In this study, we used the aeration ratio (AR) as a representative value for the aeration behaviour. Based on previously published data [13], a lower aeration ratio correlates with higher amounts of (available) fines and higher FPFs of the corresponding interactive blends, respectively. We displayed the measured AR in Table 2.

When comparing IH230 and IH230 (ex), one can observe increased ARs after expiry. Increased ARs can be caused by decreased availability of fines resulting in decreased fluidisation and dispersion characteristics. The batches with removed fines, in turn follow the same trend, whereas it will be most likely caused by fused fines on the carrier surface of IH230rF (ex). Since the aeration method is based on a blade stirring through the air-penetrated powder bed, the friction of particles will affect the measured energy. In the scenario of particles without intrinsic fines and comparable PSDs, the fused fines could result in increased surface roughness causing more friction while stirring through the powder bed, resulting in higher ARs of the IH230rF (ex) sample.

The permeability of a powder bed depends on the particle size distribution, particle morphology and interaction strength of the particles. If a powder is little cohesive and has narrowly distributed, large, smooth particles, air will penetrate the powder bed easily. A low permeability, in opposite, will lead to the powder being lifted by the dispersing airflow as a plug, fractured and subsequently dispersed [14]. In the past, Hertel et al. used the permeation method in powder rheometry to figure out the ideal amount of extrinsic fines [13]. They reported decreasing



**Fig. 2.** Results of NGI assessment (FPF at a cut-off of 5 µm). IH230 batches coloured in dark blue, IH230 (ex) batches coloured in light blue. n = 3, error bars indicate SD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

**Table 2**

Results of FT4 powder rheometer tests of the carrier materials in terms of aeration energy and permeability. Also, permeability data on lactose samples after stressed storage is shown.  $n = 3$ , SD in parentheses.

Material	IH230	IH230 (ex)	IH230rF	IH230rF (ex)
AR	9.3 (0.4)	11.3 (2.2)	10.2 (0.6)	13.0 (1.5)
Permeability [ $\bullet 10^{-9} \text{ cm}^2$ ]	94.2 (0.8)	134.8 (3.4)	112.8 (0.9)	131.8 (3.9)
Material (conditioned)	IH230 60% RH	IH230 75% RH	IH230 90% RH	
Permeability [ $\bullet 10^{-9} \text{ cm}^2$ ]	108.0 (3.0)	127.0 (1.4)	133.7 (11.2)	

permeability with an increasing percentage of extrinsic fines. If the particle size distribution is comparable (as shown in Fig. 1 for InhaLac 230 and InhaLac 230 (ex)), the permeability should be mainly dependent on the carrier morphology. In Table 2, we displayed the permeability of the respective powder samples.

Even though the PSDs of IH230 and IH230 (ex) are comparable (Fig. 1), the permeabilities showed significant differences.

We assume due to solid bridges between intrinsic fines and coarse carrier particles, the sample surface area decreased in the stored sample and hence the opportunities for interaction between air and lactose (see section 3.5; Fig. 3).

Furthermore, permeability is a measure of the void space in the powder if the fines are not able to move freely and thus do not occupy voids, the permeability increases.

We observed the same pattern for the batches with removed intrinsic fines. The permeability increased for IH230rF (ex) due to the irregularly shaped carriers being fused with fines. Fines that are fused could work as spacers between the particles which results in increased permeability. The fresh lactose batch without intrinsic fines, in turn, should contain less fused fines and hence resulted in less permeability.

An assessment of the SSA gave further insights into surface properties of the lactose samples. Table 3 contains the respective SSA values before and after removal of intrinsic fines of fresh and expired lactose batches. Especially the differences after air-jet sieving are interesting, since the fresh batch shows a significant decrease of SSA by removal of intrinsic fines. The SSA of the expired batch in turn, changed not statistically significant (less fines were removable). In general, the expired batch exhibited a smaller SSA compared to the fresh batch, indicating fused

fines and potentially a carrier smoothening by humidity [15].

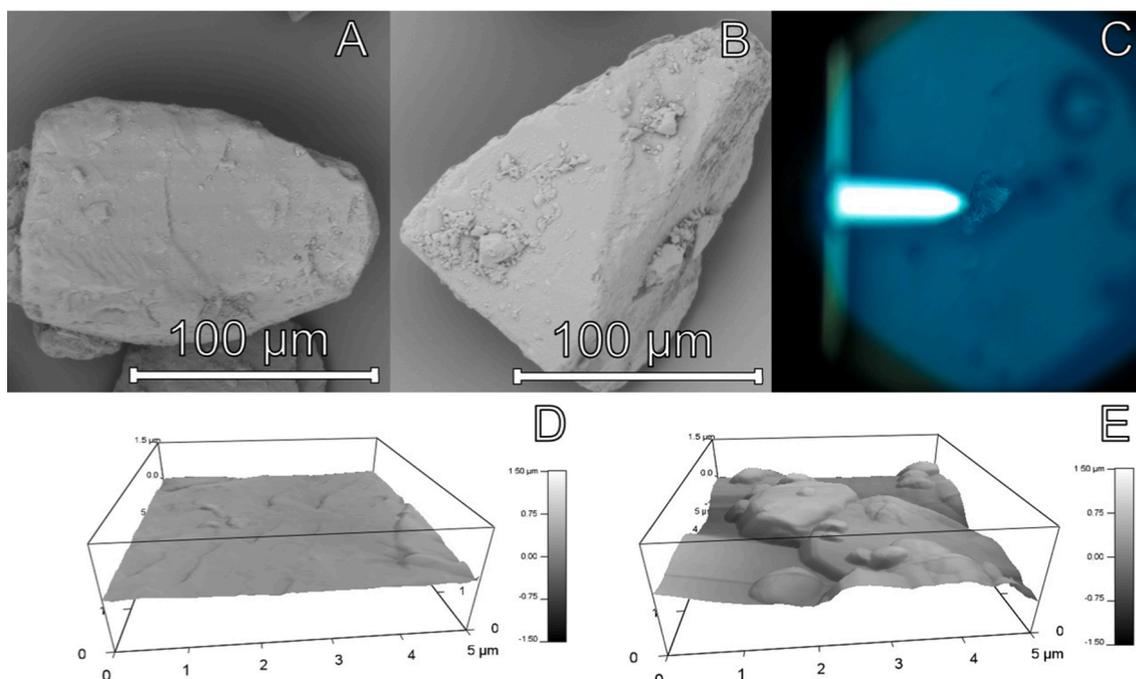
#### 3.4. Storage stability tests reveal the reason for changes upon storage

Following the findings of the NGI assessments and powder rheometry, we started storage tests to elucidate the conditions causing transfer the fresh lactose batch into the condition of the expired batch. Therefore, InhaLac 230 samples were stored at three different conditions and assessed for their powder properties afterwards. The permeability results of the stored samples are displayed in Table 2.

One can observe, that the permeabilities approached the value measured for IH230 (ex) with increasing storage humidity. The permeability of the sample stored at 90% RH showed no statistically significant difference to IH230 (ex). The RH most likely caused the fusion of adhering fines with the carrier surface. Based on this observation, it was possible to reproduce the condition of IH230 (ex) permeability-wise.

#### 3.5. SEM and AFM detected fused fines

To check on the hypothesis of intrinsic fines being fused on the carrier surface, we used SEM and AFM. Since neither SEM imaging nor the tapping mode of the AFM allows a clear differentiation between fines being fused or just loosely adhering, we investigated the surfaces of IH230rF and IH230rF (ex). The SEM images in Fig. 3 A and B indicate fewer residual fines on the surface of IH230rF than on the surface of IH230rF (ex).



**Fig. 3.** SEM and AFM images of IH230rF (A, D) and IH230rF (ex) (B, E). C shows a light microscopic picture of an exemplary lactose crystal under investigation by AFM.

**Table 3**

Results of SSA assessments using octane adsorption isotherms before and after removing intrinsic fines from the respective lactose batches. n = 3, SD in parentheses.

Material	IH230	IH230 (ex)	IH230rF	IH230rF (ex)
SSA [m <sup>2</sup> /g]	0.22 (0.00)	0.15 (0.02)	0.10 (0.01)	0.09 (0.00)

AFM provides 3-dimensional morphology maps of the non sputter-coated carrier surface. For the sake of comparability and feasibility, we always probed the same crystal facets of tomahawk shaped, flat-lying lactose crystals (Fig. 3 C). In Fig. 3 D and E, the surface of IH230rF (ex) exhibits protrusions that can be caused by fused intrinsic fines. The surface of IH230rF showed comparably small protrusions and to a lesser extent. Furthermore, the analysis software provides RMS values (root mean square of a surface) by calculating the average height deviations from the mean height line of the mapped area [16]. The higher the RMS value, the rougher the surface. The RMS values supported the SEM and AFM measurements as the fresh batch resulted in crucially lower roughness values (IH230: 3.92 nm) than the expired batch (IH230 (ex): 10.16 nm).

#### 4. Conclusion

In this study, we assessed the decreasing aerodynamic performance of expired lactose batches and attributed this behaviour to the availability of intrinsic fines. We were able to show that FPFs of old, expired batches did not change significantly after removing their intrinsic fines.

The shrinking role of intrinsic fines after expiry in powder fluidisation was confirmed in powder rheometric measurements. Furthermore, we were able to reproduce the powder characteristics of the IH230 (ex) batch by high RH storage. We hypothesised, fines began to fuse with the carrier particle in a humid environment, which prevents the respective fines from contributing to the powder dispersion [17].

This work highlights the need to control the storage conditions of excipients used in DPI applications. Even though it was possible to release strongly bound fines by means of high-pressure dry dispersion (e. g., in laser diffraction measurement), the expired batches still reached significantly lower FPFs than the fresh ones. Consequently, the intrinsic fines are not the only detrimental change after long-time storage. Nevertheless, our study emphasises the present risk of solely relying on well-established characterisation techniques such as PSD measurement in quality control or re-test analysis as this may show fines that, however, are not able to contribute to the aerodynamic performance. PSD measurements at more realistic dispersion pressures may be a promising approach in future studies and eventually to be implemented in quality control.

Additionally, this study provides further insights into the crucial role of fine excipient fractions in lactose for inhalation. Whether to work with qualities containing higher ratios of intrinsic fines, or to manually add micronised lactose to a quality without intrinsic fines, is multifactorial: Depending on regulatory requirements, device specifications and many more, formulation scientist will make their choice. Both strategies allow for a full exploitation of the beneficial effects of fine excipients. Nevertheless, we conclude from this study that both strategies may be vulnerable to humidity dependent performance loss. Thus, lactose carriers containing fine fractions should always be used as fresh as possible.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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