Effect of Texture and Surface Chemistry on Deagglomeration and Powder Retention in Capsule-Based Dry Powder Inhaler

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Abstract
Pulmonary delivery systems should administer a high dose of the required formulation with the designated dry powder inhaler (DPI) to achieve therapeutic success. While the effects of device geometry and individual components used on powder dispersion are described in literature, potential effects of DPI surface properties on powder retention within the device and deagglomeration have not been adequately studied, but could impact inhalation therapy by modifying the available dose. For this, inner parts of a model DPI were modified by plasma treatment using various processes. Since both the hydrophilic-hydrophobic and structural properties of the surface were altered, conclusions can be drawn for future optimization of devices. The results show that surface topography has a greater influence on powder deposition and deagglomeration than hydrophilic or hydrophobic surface modification. The most important modification was observed with an increased rough surface texture in the mouth piece, resulting in lower powder deposition in this part (from 5 to 1% quantified amount of powder), without any change in powder deagglomeration compared to an untreated device. In summary, increasing the surface roughness of DPI components in the size range of a few nanometers could be an approach for future optimization of DPIs to increase the delivered dose.

Keywords capsule-based dry powder inhaler · plasma treatment · powder deposition · surface modification · surface roughness

Introduction
Capsule-based dry powder inhalers (DPIs) are devices commonly used to treat respiratory diseases [1]. In general, the therapeutic success is linked to adequate deposition of the powder in the lower respiratory tract. Therefore, the device should be able to deagglomerate the formulation during inhalation so that the powder particles have an aerodynamic diameter of < 5 µm [2]. Despite the progress and optimization achieved, the development and realization of an “ideal DPI” is challenging, as many mechanisms are not yet fully understood and require further investigation [2, 3]. However, to minimize potential sources of error (e.g., insufficient inspiratory air flow, duration) and to ensure sufficient powder deposition in the lungs, delivery systems are marketed in a fixed combination of the DPI and formulation [4, 5].

In order to identify the impact of device layout or components on powder retention in the DPI and also for the subsequent deagglomeration, numerous studies have been carried out. For capsule-based DPIs, the opening mechanism (e.g., size, number, and position of holes in pin-based systems) prior to actuation, as well as the capsule material, size, and movement during actuation (rotation, vibration, shaking), can affect the deagglomeration and ejection of the powder [6–9]. The grid, which primarily separates the capsule chamber from the mouth piece, is intended to prevent fragments of the opened capsule from entering the patient’s oropharynx during the inhalation flow and causing local irritation or aborting inhalation. In addition, the grid can straighten the passing air flow, which reduces the tangential flow behavior in the mouth piece and results in reduced powder deposition in this area, thus increasing the fine particle
fraction (FPF) [10]. While modifying the mouth piece by
reducing its length from the original geometry had no effect on powder retention within the DPI or powder deagglomeration, increasing the diameter of the circular mouth piece exit resulted in lesser powder deposition in the induction port (IP) due to a lower air flow and particle exit velocity [11, 12].

In addition to the general device geometry and the specifically dedicated components (e.g., classifier, vortex breaker) for improving powder aerosolization, minimizing powder retention in the device is an issue that has become increasingly important in recent years. Powder retention in inhalation devices can significantly affect therapeutic outcomes due to mechanical anchoring of the powder to the device surface and/or electrostatic charge generated during powder dispersion. Triboelectrification is an unavoidable consequence of contact or friction between particles and devices during actuation [13]. One focus for overcoming this problem is the “dry powder coating” method through the use of force control agents such as amino acids or metal stearates. As the safety profile is well known, magnesium stearate and leucine are widely used and numerous studies have been conducted to improve device retention and aerosolization performance by coating drugs and/or carrier particles with these pharmaceutical lubricants [14, 15]. In the last decade, an alternative strategy has been pursued, aimed at lower powder retention, by coating the inner surface of the DPI and also of the capsule with lubricants. It has been shown that, depending on the concentration of the magnesium stearate suspension used for surface modification, significant differences in powder retention can be achieved in both compartments [16]. In addition to the use of classic lubricants, the coating of DPI plastic with a polytetrafluoroethylene (PTFE) film has also been tested in recent years to create a hydrophobic surface characterized by a high water contact angle and low surface energy. In previous studies, the capsule and device were coated with a commercial PTFE suspension (LU™ 708; Sprayon™ Products, OH) [17–19]. It was shown that this surface modification resulted in a higher emitted fraction without affecting the FPF.

Despite these findings, the critical factor of reducing powder adhesion to the inhaler wall is still not fully understood, so there is no commercially approved surface modification for DPIs to reduce powder adhesion. The present study aimed to investigate the influence of a modified inner DPI surface firstly on the powder deposition within the device and secondly on the deagglomeration behavior for the tested formulation. For the surface modifications described above, it is not clear whether the low surface energy or the surface texture achieved by the deposited magnesium stearate particles or the PTFE suspension is the important parameter for reducing powder retention within the DPI, so this study aimed to investigate the influence of both surface modifications on powder ejection and also powder aerosolization.

In order to modify the chemical surface properties as well as the nanotexture of the DPI surface, various cold-plasma processes were developed and applied to the DPI surface using a low-pressure plasma unit. In general, the species generated during the process, such as ions, radicals, neutrals, or metastables, which have a temperature close to room temperature, can interact with the surface of the starting material. For this reason, this modification method is generally preferred for thermolabile materials in industry [20]. Since the modified materials are only changed at a depth of a few nanometers, only the outer layer is affected, while the bulk properties are not changed. This allows in the ability to produce desired surface properties depending on factors such as gas type, pressure in the chamber, gas ignition power, treatment time, and the type of starting material used. In general, four basic processes can be distinguished. Surface activation is intended to create new functional groups on the material surface, leading to a different surface energy usually preparing the surface for a subsequent plasma polymerization step by coating the surface through polymerization of a monomer. While surface cleaning by plasma aims to remove contaminants from the substrate surface, surface etching aims to remove and degrade material from the treated surface by physical and chemical reactions, producing volatile products [21–23].

For oxygen, numerous effects are described in the literature, including the mentioned surface activation, cleaning, and etching [24, 25]. On this basis, oxygen plasma was used to create hydrophilic surfaces, while an octafluorocyclobutane (OFCB) process was intended to create hydrophobic surfaces. Both processes also cause the surface topography to become irregular and the roughness to increase (26—30). In order to estimate not only the effects of a plasma-induced rough surface, but also the extent of a smooth and non-sticking surface produced by the plasma coating, the monomer hexamethyldisiloxane (HMDSO) was used for in situ polymerization [26–28]. The results obtained were compared with those of untreated DPIs, which also have a smooth surface due to the injection molding process used during manufacturing. The study here was run with a DPI type composed of individual components which allows for a clearer identification of which surface modifications may have an impact on powder deposition, as DPI components can be plasma treated separately. To demonstrate differences in powder retention within the DPI or in deagglomeration behavior, an unmodified device was used as control and an in-house-developed spray-dried particle formulation of the active pharmaceutical ingredient rifampicin was actuated. Since therapy with classical asthma and chronic obstructive pulmonary disease (COPD) drugs is well known and there is a growing interest in the pulmonary use of antibiotics, this
formulation was focused on [29–31]. While it was initially assumed that the hydrophilic or hydrophobic surface properties produced by plasma treated could reduce powder deposition within the DPI, the surface topography of the inhaler revealed its impact on the aerosolization of the drug powder.

Materials and Methods

Materials

Rifampicin (> 98.0%, lot number: 6K4AF-RO) was ordered from TCI (Tokyo, Japan). With the exception of water, which was purified in-house (Merck-Millipore Biocel A10, Burlington, MA, USA), all solvents were HPLC grade. Oxygen (99.99%), the octafluorocyclobutane (OFCB) (99.99%), and nitrogen (N₂) (99.99%) gases were purchased from Air Liquide (Paris, France), and hexamethyldisiloxane (HMDSO) was ordered from Sigma-Aldrich (St. Louis, MO, USA). Polyamide (PA) plastic material used to develop the plasma processes was kindly provided by Hadi-Plast (Hadi-Plast GmbH & Co. KG, Hövelhof, Germany). The Presspart prototype DPI (PP DPI) tested was provided by Heitkamp & Thumann Ltd. (Blackburn, UK). The set-up of this novel DPI was described and explained in a previous study [32].

Spray-Drying Process for the Rifampicin Formulation

Rifampicin was spray-dried as described in [32, 33]. The powder was dispersed in a predefined amount of ethanol (38 mg/mL) and the suspension was sonicated with an ultrasonic bath (type DT 106, Bandelin Electronic, Berlin, Germany) under controlled temperature conditions (25°C) to homogeneously disperse the particles. A thermostat (DC 10, Haake Technik GmbH, Vreden, Germany) was used to keep the temperature constant during the water exchange. For spray-drying under inert atmosphere (N₂), a B-290 spray-dryer equipped with a high-performance cyclone, a B-295 inert loop, a B-296 dehumidification unit (all Buchi), and an anemometer (AF89-AD1AA13C0AA, Fluid components Int'l., San Marcos, CA, USA) were used. Throughout the manufacturing process, the suspension was continuously stirred until atomization using a modified three-fluid nozzle with a blocked inner channel (Buchi).

Test Procedure for the Aerosol Classification with the Next Generation Impactor

A total of 5 mg of the rifampicin formulation was filled into size 3 gelatin capsules. A Next Generation Impactor (NGI) connected with two vacuum pumps (HCP 5) (all Copley Scientific Limited, Nottingham, UK) was used to characterize the aerosol properties obtained with the untreated and the plasma-treated devices. Prior to the experiments, 15 mL of the diluent was added to the preseparator, and each cup was coated with 1% glycerol-methanol solution (m/v). To analyze the powder deagglomeration behavior of unmodified and different modified DPIs by quantifying the active ingredient at the different stages (capsule—MOC), the rifampicin particles were dissolved in a solution of ascorbic acid in methanol (0.5% m/v). For each experiment, an actuation volume of 4 L was used in combination with a flow rate of 50 L/min, corresponding to USP conditions at a pressure drop of 4 kPa [34, 35].

Developing the Plasma Processes

To modify the surface of the plastic samples, a low-pressure system unit (Diener Plasma GmbH & Co. KG, Ebhausen, Germany) with a radiofrequency generator (13.56 MHz, 0–200 W) was used. For treating the surface, the samples were placed inside a heatable vacuum chamber (rectangular, aluminum, H: 240 mm × D: 600 mm × W: 240 mm) at a specified position to obtain uniform and reproducible process conditions. The development of the various plasma processes was carried out on PA material. In the case of oxygen, a flow rate of 44 sccm, resulting in a pressure of 0.3 mbar, was ignited with a generator power of 90% and a duration of 60 min. For OFCB, to obtain hydrophobic surfaces, the C₄F₈ gas was used as a Teflon film precursor after an oxygen treatment step to polymerize the fluorocarbon units on the surface at a flow in the chamber of 9 sccm, a pressure of 0.1 mbar, and a generator power of 20%.

For the HMDSO process, the monomer was heated to 110°C to convert the liquid to the gas state. For the plasma process, the monomer was mixed with oxygen in a ratio of 1:4, resulting in an oxygen gas flow in the chamber of 21–25 sccm at a pressure of 0.3 mbar. To ignite the plasma, 80% of the generator power was used for a duration of 5 min.

Contact Angle Measurements and Surface Energy Calculation

In order to verify the applied surface modifications by the plasma treatment and to analyze potential aging effects of a generated hydrophobic (OFCB) or hydrophilic (oxygen) surface as an extreme case under the plasma modifications tested here, contact angles were determined at ambient conditions with deionized water using a FM40 Easy Drop – drop shape analyzer (Krüss GmbH, Hamburg, Germany). The sessile drop measurement principle was applied, and drops of 10 µL were analyzed. The method of Owens, Wendt, Rabel, and Kaelble (OWRK method) was used to calculate the surface energy directly after plasma treatment and after storage times of 3 and 6 weeks [36]. Deionized water as the
polar component and diiodomethane as the lipophilic component were used as test fluids. Using the linearized equation of Owens and Wendt, the surface energy was calculated as follows:

$$\sigma_s = \frac{(1 + \cos \theta) \cdot \sigma_s}{\sqrt{\sigma^D))^2 + \sigma^P)) + \sqrt{\sigma^D}) \cdot \sigma^P + \sqrt{\sigma^P})$$  

(1)

$\sigma_s$: surface free energy of the solid surface [mJ/m²].
$\sigma_l$: surface tension of the wetting medium [mN/m].
$\theta$: contact angle [°].
$\sigma^D$: dispersed fraction of the wetting medium [mN/m].
$\sigma^P$: polar fraction of the wetting medium [mN/m].
$\sigma^D$: dispersed fraction of the wetting surface [mJ/m²].
$\sigma^P$: polar fraction of the wetting surface [mJ/m²].

Measurement of the Frequency of the Capsule Oscillation During Actuation

To determine the oscillation frequency of the capsule during actuation within an untreated and a plasma-treated DPI, the capsule motion was recorded for 1 s using the camera of a cell phone (Samsung Galaxy s20, 960 fps). For this purpose, the DPI was connected to the NGI and a flow rate of 50 L/min was applied. A frame-by-frame analysis was performed to count the oscillations of the capsule.

Scanning Electron Microscopy (SEM)

The samples were fixed with carbonaceous conductive paste on an aluminum sample holder and then coated with gold for two cycles of 2 min each. Subsequent imaging was performed in high vacuum using a Hitachi SU-3500 SEM (Hitachi Ltd., Tokyo, Japan). The accelerating voltage was 5 kV, and the magnification and working distance were adjusted as needed and are indicated on the SEM images.

Laser Diffractometry (LD)

The particle size distribution of the formulation was determined with a LA-940 laser scattering particle size distribution analyzer (Horiba ltd., Kyoto, Japan) using the following procedure: Rifampicin was suspended in a solution of 0.1 w/w (%) Span 80 in n-hexane in an amount that resulted in suitable attenuation of the laser beams. The suspension was stirred in a quartz cuvette during analysis (suitable attenuation of the laser beams. The suspension was

High-Performance Liquid Chromatography Analysis

Quantification of the drug deposited in the different NGI stages was performed by high-performance liquid chromatography (HPLC) analysis (Shimadzu, LC-2030C 3D Plus, Kyoto, Japan) using an RP18 column (LiChrospher 100 RP 18-5µ EC, 250 × 4.6 mm). To detect the rifampicin, the photodiode array detector was set to 337 nm. The mobile phase consisted of a mixture of a phosphate buffer pH 5.2/methanol/acetonitrile (33/50/17% v/v/v), and an isocratic flow rate of 1.0 mL/min was set in combination with a column temperature of 25°C [32]. The values of the intercepts and the slope of the calibration curve were used to calculate the limit of detection (LOD) and limit of quantification (LOQ). The LOD and LOQ for rifampicin were determined to be 0.30 µg/mL and 0.90 µg/mL.

Data Processing and Statistics

The NGI plots show the relative powder deposition of the drug on the different stages (capsule—MOC). Error bars indicate one standard deviation. All experiments were performed in triplicate, unless otherwise reported. To determine statistically significant differences in the contact angle measurements, in surface energy calculation, and in relative powder deposition in the different stages of the NGI (capsule—MOC) after actuation with untreated and plasma-treated DPIs, results were compared using the Kruskal–Wallis test followed by Dunn’s test ($p < 0.05$) (Prism 8.0.2, GraphPad software).

Results

Characterization of the Surface Structures and Chemical Changes of the Surface Obtained by Plasma Treatment

Comparison of the surfaces of the mesh in the initial state and after modification by the various plasma treatments revealed differences in their nanostructures. The surface texture of the untreated and HMDSO plasma–treated surface is smoother compared to the other two treated surfaces. For the untreated material, residues probably originating from injection molding are characteristic [37–39]. In the case of HMDSO, a thin layer covered these residues and also the interstices, resulting in a flatter surface structure. Increased roughness in the nanometer range is observed on the plastic surfaces treated with oxygen and OFCB compared to the structure of the untreated surface. This nanotexturing is more dominant in the case of the oxygen process than for the OFCB-treated surface (Fig. 1).

To characterize the change of the chemical surface properties due to plasma modification, the contact angle was measured and the surface energy was calculated over a storage period of 6 weeks after plasma treatment with measurement steps of 3 weeks (initial, 3 weeks, 6 weeks) (Fig. 2). In the case of the oxygen plasma treatment, it was observed
that the wettability of the surface increased, resulting in a lower contact angle with water directly after surface modification. After 3 and 6 weeks, the wettability decreased until the initial condition of the untreated material was regained after 6 weeks to a contact angle of about 60°, so that this effect was reversible. The OFCB-treated surfaces were found to be hydrophobic, characterized by a contact angle with water of 120°, which remained constant over time, unlike the hydrophilic surface modification (Fig. 2a).

To estimate the effect of a hydrophilic or hydrophobic surface created by plasma treatment, as well as the effect of a nanotextured surface on the deagglomeration behavior of the device characterized with the NGI, a storage time of the plasma-treated inhaler of 3 weeks after treatment was complied before the device was tested. To verify the condition that after plasma treatment of the device with the different developed processes there are no changes in the movement of the capsule during actuation due to the changed surface energy, the oscillation frequency was measured for modified and untreated devices. The results show that the oscillation frequency of the capsule was about 45 Hz for the untreated and the plasma-treated devices, so no differences were found (Fig. S1).

Visual Characterization and Particle Size Distribution of the Spray-Dried Rifampicin Formulation

The spray-dried rifampicin particles have a flake-like and flocculated shape in the lower micrometer range with a d50 < 10 µm (Fig. 3).

Determination of the Influence of a Plasma-Modified Upper or Lower Unit of the DPI on Powder Aerosolization and Retention Within the Device

Figure 4 shows the NGI results obtained after treating the upper unit (comprising classifier, mesh, mouth piece) of the device with different plasma processes. Actuating the spray-dried rifampicin formulation showed increased powder deposition in the IP and also in the preseparator after surface modification with oxygen or OFCB plasma, with OFCB modification resulting in the highest deposition. For both plasma treatments, less powder deposition was observed in the modified mouth piece, with a rougher surface texture resulting in less powder deposition. A similar deagglomeration of the powder was achieved with the DPI treated with HMDSO and the untreated device. Despite a smooth surface, which was observed for both cases, the treatment with HMDSO resulted in a slightly increased powder deposition on the corresponding plastic parts (Fig. 4).

Plasma treatment of the capsule chamber showed no differences in aerosolization properties when characterizing the deagglomeration behavior of these devices for the rifampicin formulation compared to the untreated one, regardless of the surface modification applied. For the two processes that produced a rough surface texture, a decreased amount of powder was deposited in the capsule chamber shown as “lower unit” in the NGI diagram. For the part treated with HMDSO plasma, the powder deposition was similar to the original part (Fig. 5).

Identification of the Influence of the Surface Structure of the Mouth Piece on Powder Retention

Since differences in powder retention in the mouth piece were evident after treatment of the upper unit compared to the untreated unit, the DPIs were tested in a further experiment in which only the mouth piece was treated with plasma. The results in Fig. 6 show that for both processes, where a nanotextured surface was created in the mouth piece, less powder deposition was observed than for the untreated mouth piece. Of all the modifications, the lowest powder retention in this part was observed after treating with oxygen plasma. While no changes were observed in the deagglomeration of the powder between the oxygen-treated, HMDSO-treated, and untreated DPI, an increased power fraction was observed in the IP when using the OFCB-coated device, but not as high as shown in Fig. 4.

Determination of the Individual Effect of Each Component After Increasing the Surface Roughness by Plasma Treatment on Powder Deagglomeration

Since higher powder deposition occurred after oxygen or OFCB plasma treatment of the entire upper unit in the IP and preseparator, and oxygen gas was used in both processes, which increased the surface roughness of the treated parts, the following experiment was conducted to determine the components that could have a decisive influence on powder deagglomeration after surface treatment. Therefore, the focus was on the oxygen process, and for each experiment only one treated part was installed and tested, leaving the rest of the DPI untreated (Fig. 7). The results show that an oxygen plasma–treated mesh or classifier resulted in higher powder deposition in the IP and also the preseparator, although in both cases the observed amount was not as high as when the entire upper unit of the DPI was treated (Fig. 4). In addition, with the exception of the mouth piece, no reduced powder deposition was observed on the treated parts.
Fig. 1 Scanning electron microscopy (SEM) images of the untreated and the plasma-treated surfaces of the mesh after application of the above plasma modifications. HMDSO, hexamethyldisiloxane; OFCB, octafluorocyclobutane
Discussion

This study clearly demonstrated the effect of various DPI surface modifications by plasma treatment on powder deposition and deagglomeration. It was originally hypothesized that the different surface chemical properties obtained by the various plasma processes could minimize the hydrophilic-hydrophobic interactions between the DPI surface and the drug, resulting in less powder retention.

For this purpose, an oxygen process was developed and used to produce hydrophilic and activated surfaces, while the OFCB plasma process yielded inert-hydrophobic surfaces. Since no differences in the oscillation frequency of the capsule were observed in the experiment, the storage period of 3 weeks seems to have been sufficient to counteract possible altered interactions between capsule and DPI due to the increased surface energy (oxygen plasma process), since otherwise a decrease in the oscillation frequency would

![Fig. 2](image1.png)

**Fig. 2** a) Contact angle measurement with deionized water for untreated and plasma-treated polyamide (PA) samples. b) Calculation of the surface energy for the defined time points. OFCB, octafluorocyclobutane. \( *p < 0.05 \)

![Fig. 3](image2.png)

**Fig. 3** Scanning electron microscopy (SEM) images (a) and particle size distribution (b) of the rifampicin formulation

![Fig. 4](image3.png)

**Fig. 4** Next Generation Impactor (NGI) results obtained with the rifampicin formulation actuated with a dry powder inhaler (DPI) with untreated and plasma-treated upper unit. cps, capsule; IP, induction port; Pres, preseparator. \( *p < 0.05 \)
have been found. It can be argued that a reduction in surface energy (OFCB plasma process) does not result in minimized interaction between the capsule and the inhaler wall during actuation, since a similar frequency of oscillation was also observed with this modification. The unaffected capsule oscillation confirmed the results of the NGI experiments obtained after plasma treatment of the lower part of the DPI. Since no differences in powder aerosolization were obtained after applying the different plasma modifications to the capsule chamber, hydrophilic-hydrophobic interactions do not seem to affect the deagglomeration of the powder during actuation in this DPI in the experiments performed.

In addition to the chemical surface modifications, it was shown that the plasma processes used in the experiments led to different surface structures with regard to their nano-texture. While the HMDSO process resulted in a smooth surface structure that was similar to the initial surface, the use of oxygen with or without OFCB plasma resulted in a nanotextured surface texture in two different size ranges of roughness.

The formulation of spray-dried rifampicin as a model drug was chosen because a higher amount of active ingredient was deposited in the DPI compared to commercially available interactive blends. This made it easier to detect differences in powder deposition due to surface modification by the plasma treatment. Moreover, the aerosolization of the powder by the device resulted in low drug deposition in the preseparator but high deposition in stages S1—MOC. Thus, a changed deagglomeration behavior of the device after surface modification can also be observed directly.

Comparison of the NGI results obtained using devices with plasma-treated parts of the upper unit suggests that the surface properties affect powder deposition within the DPI and also powder deagglomeration, since differences were observed in the experiments. The use of an untreated DPI or a DPI treated with HMDSO plasma resulted in similar deagglomeration of the powder, which was different from the results obtained with the DPIs treated with oxygen or OFCB plasma, raising the possibility that surface texture rather than hydrophilic or hydrophobic surface properties influenced powder deposition within the DPI and deagglomeration behavior. This is also underlined by the fact that similar
powder deagglomeration and deposition were obtained for the DPIs modified with oxygen or OFCB plasma, although a hydrophilic or hydrophobic surface was created.

While increasing the surface roughness of the mouth piece or capsule chamber resulted in lower powder deposition on the respective surfaces, modifying the classifier or mesh seems to be critical, as this resulted in higher powder deposition in the IP or preseparator. The observations can be compared with the results of previous studies, where a device coated with a PTFE suspension spray resulted in a higher emitted fraction, but also in a higher powder deposition in the IP or preseparator, since the fine particle fraction was not increased compared to the untreated device [17–19]. Here, it was found that a hydrophobic coating can increase the emitted fraction without changing the aerosolization properties of the device for the powder. Similar trends for a higher emitted fraction after surface modification were also observed after coating the device and capsule with an ethanol-based magnesium stearate suspension [16]. Compared to these studies, the work described above focused only on the generated surface properties of the device and not on the combined effect of a modified capsule and the device. Furthermore, it should be investigated which modified DPI component could be responsible for lower powder retention and which part seems to be critical for the surface modification. Since the DPI selected for this study can be decomposed into four main parts, it was possible to identify the most important surfaces for plasma modification. Unlike previous studies, this work did not focus exclusively on forcing agents to achieve friction-reducing or antistatic coatings. Therefore, a more neutral perspective was chosen for the study. Thus, in addition to a hydrophobic coating, the influence of the surface texture was also investigated, which represents a significant difference from the studies conducted so far. Since not only a hydrophobic surface in the mouth piece created by plasma treatment resulted in lower powder retention in this part, it seems logical that the chemical modification is not the main factor for the lower powder retention. This underlines the results of the previous studies, so that a PTFE and a magnesium stearate coating reduces powder deposition. Despite the low surface energy or antistatic surface properties obtained with these methods, the fact that in all cases a suspension was used so that the sprayed particles settled on the surface of the inhaler supports the idea that surface texture, rather than chemical properties, influences aerosolization behavior.

Since increasing the surface roughness of the mesh or classifier resulted in high powder deposition in the IP, increased turbulent flow behavior could occur at these generated nanotextured surfaces after plasma modification, which could not be straightened in the mouth piece. This altered airflow could therefore cause the particles to move differently, so that they could no longer follow the air flow. Compared to the mesh and classifier, the modification of the mouth piece had no real influence on the overall aerosolization behavior of the device for the powder, which could be explained by the fact that for this component, the characteristic dimension of the air flow channel is much larger than for the mentioned components. This results in the overall flow profile being less affected by the near-wall turbulence created by the surface roughness generated by the plasma treatment (11, 12, 45).

In summary, this study pointed out that surface properties affect the deagglomeration and deposition of the powder in the DPI, and surface structure appears to have a greater influence on aerosolization behavior than the created hydrophilic or hydrophobic surface properties. In the experiments carried out, the mouth piece proved to be an interesting screw for these surface changes with regard to an unchanged deagglomeration behavior of the DPI for the powder with simultaneously reduced powder deposition. Modifying this component by increasing its roughness could be an interesting point for future device optimization and development, as a higher amount of drug could be available for pulmonary therapy. Increasing the amount of therapeutically available drug surely would improve the therapeutic effect. In addition, a decreased amount of drug formulation would need to be loaded into the device if more powder exits the DPI during an inhalation procedure. This could increase efficacy and patients’ compliance by reducing the number of inhalations required per day.

The use of a suitable method that only changes the surface topography could be an interesting way to clarify what influence the dimensions of the surface profile and the degree of roughness (height or width of the elevations) have on the powder deposition in the device. Whether there is an optimum surface roughness or whether it depends on formulation aspects like particle size, shape, and the formulation technique used (e.g., binary mixture, spray-dried) should be analyzed. In subsequent preliminary experiments with another formulation, a binary blend of albuterol sulfate and lactose monohydrate (Asthalin Rotacaps®, Cipla Ltd., Mumbai, India), we observed trends similar to the results with rifampicin (data not shown) which indicated that the effects were rather independent from the formulation but mainly depended on the modified DPI surface.

However, the aspect of formulation properties and the interaction of different formulations with rough surfaces of different size ranges surely needs to be clarified in more detail in subsequent studies. Besides, numerous parameters such as the potential influence of the DPI wall material and the dimensions of the airflow channel used in the different DPI components need to be analyzed. This is in view of a potential optimum dimension of the air flow channel for each component used in the respective device, so that an
increase in the surface roughness of this component leads to reduced powder deposition without altered deagglomeration behavior.

**Conclusion**

This study has shown that surface structure has a high impact on the deagglomeration and retention of the powder in the device, which has not been sufficiently considered so far and could be used for device optimization in the future. It has been shown that a nanotextured surface of the mouth piece can reduce powder deposition inside the inhaler, resulting in a higher emitted fraction. Since the development of pulmonary delivery systems usually focuses on the aspect of formulation development and optimization, this study has shown that the surface structure can have a major impact on the overall deagglomeration behavior and offers another opportunity to improve this form of therapy.

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**Declarations**

**Conflict of Interest** Christoph Schulte and Anselm Ebert are employees of Presspart GmbH & Co. KG; Sunita Sule and Ameet Sule are employees of H&T Presspart Manufacturing Ltd. The direction of the company had no role in the design of the study and in the collection, analyses, or interpretation of the data. The other authors declare no conflict of interest.

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