Spray-granulated mannitol as a viable alternative to lactose in DPI formulations: Preparation of ordered mixtures and storage stability

A study of the influence of blend preparation and storage stability of a mannitol carrier material in DPI formulations

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Introduction

The use of dry powder formulations for inhalation is common. Active pharmaceutical ingredient (API) particles should have an aerodynamic particle size less than 5 µm to reach the lung. Yet these micronized powders come with some disadvantages such as high cohesiveness, which can lead to poor flowability so they can be very difficult to handle. The most common method to improve these challenging powders is to formulate ordered mixtures in which large carrier particles are blended with micronized API particles to improve their bulk properties like flowability, powder homogeneity and uniformity of dose. During inhalation, the small API particles become detached from the carrier and follow the inspiration airflow to reach the lung. These carrier-based blends are a well-known formulation strategy in local treatment of asthma and chronic obstructive pulmonary disease.[1]

Currently, lactose is the most established carrier in such carrier-based powder blends.[2] This material is mainly used as crystalline alpha lactose monohydrate, which is stable and not very susceptible to water vapor, but it is known that amorphous content can be introduced via processing such as milling or spray drying.[3] In addition, lactose is a reducing sugar, which could cause product stability concerns. It is also of animal origin, requiring certification as BSE/TSE-free.

Mannitol as an alternative to lactose has been discussed for quite some time.[4] Mannitol is interesting because it is a non-reducing sugar, animal-origin-free and listed as a GRAS (generally recognized as safe) material by the United States Food and Drug Administration (FDA).[5] Previous studies have shown that mannitol is generally suitable as a carrier in various formulations.[4,6,7] Important aspects of carriers for dry powder inhalation (DPI) formulation are particle size distribution, flowability, dosability,[8] crystallinity and hygroscopicity,[9] as all of them can influence the aerodynamic behavior of the blend. Furthermore, the process of preparing the ordered mixture may also influence aerodynamic performance. Depending on the blending conditions, the powder blend is exposed to differing degrees of mechanical stress, which may influence these characteristics, especially over certain storage times. Electrostatic charge, which is introduced by the mixing process, can be reduced during storage so that API particles can be detached more easily from the carrier. Inversely, adsorption of moisture during storage can adhere API particles on the carrier particles, therefore it will be more difficult to detach them. Both factors influence fine particle fraction (FPF).

The study presented in this article investigated the influence of blend preparation, using a low shear Turbula® tumble blender and a Picomix® high shear mixer, on the aerodynamic performance of blends containing mannitol for inhalation (Parteck® M DPI). It is known from lactose-based blends, that the choice of blender type and blending conditions can strongly influence aerodynamic properties,[10] whereas this has not yet been examined with mannitol-based blends. In addition, lactose-based blends are sensitive to humidity and their physical properties, as well as their aerodynamic behavior, may change depending on storage conditions.[11] Therefore, the stability of mannitol-based blends stored under three different conditions for 14 months with mannitol as a carrier and two model APIs—namely budesonide (BUD) as a hydrophobic example and sal-

butamol sulphate (SBS) as a hydrophilic example—was examined with respect to aerodynamic performance during storage.

Material and methods

This study was carried out with Parteck M DPI (Merck KGaA, Darmstadt, Germany) as a mannitol carrier material. Micronized budesonide (BUD, mean particle size: 1.45 ± 0.03 µm; Farmabios SpA, Cropello Cairoli, Italy) and micronized salbutamol sulphate (SBS, mean particle size: 1.61 ± 0.03 µm; Lusochimica SpA, Peschiera Borromoo, Italy) were selected as model APIs. To reach a typical market product dose of 200 µg (Novopulmon® 200 µg Novolizer®, MEDA Pharma GmbH & Co. KG or (Cyclocaps® 200 µg Salbutamol, PB Pharma GmbH), the API content was set to 2 wt% for all blends.

In the first part of the study, two blends were prepared with a Turbula low shear tumble blender (Type T2C, Willy A. Bachhofen AG Maschinenfabrik, Muttenz, Switzerland) and two blends were prepared with a Picomix high shear mixer (Hosokawa Alpine, Augsburg, Germany). BUD or SBS, respectively, were weighed into the mixing vessel using a double-weighing method. For both blender vessels, a filling volume of 54% was achieved. Each preparation in the Turbula tumble blender was blended three times and each blend in the high shear mixer was blended once. The rotation speed for the low shear tumble blender was 42 rpm with a blending time of 5 minutes compared to the high shear mixer which used 500 rpm and 30 seconds of blending time. To destroy potential blend-agglomerates, a sieving step (with a 710 µm sieve) was introduced. The blends were sieved after every 5 minutes for the preparations in the low shear tumble blender and after 30 seconds for preparations in the high shear mixer.

Ten samples (8-12 mg) of each powder mixture were randomly selected for homogeneity testing and API content was analyzed by reverse phase high performance liquid chromatography (RP-HPLC). Blends were judged to be homogeneous at a relative standard deviation (RSD) of less than 3% and a recovery above 95%. Before performing the impaction analysis, the blends were stored for a minimum of two weeks in open plastic bottles at 45% relative humidity (RH) and room temperature (RT, 20-23°C).

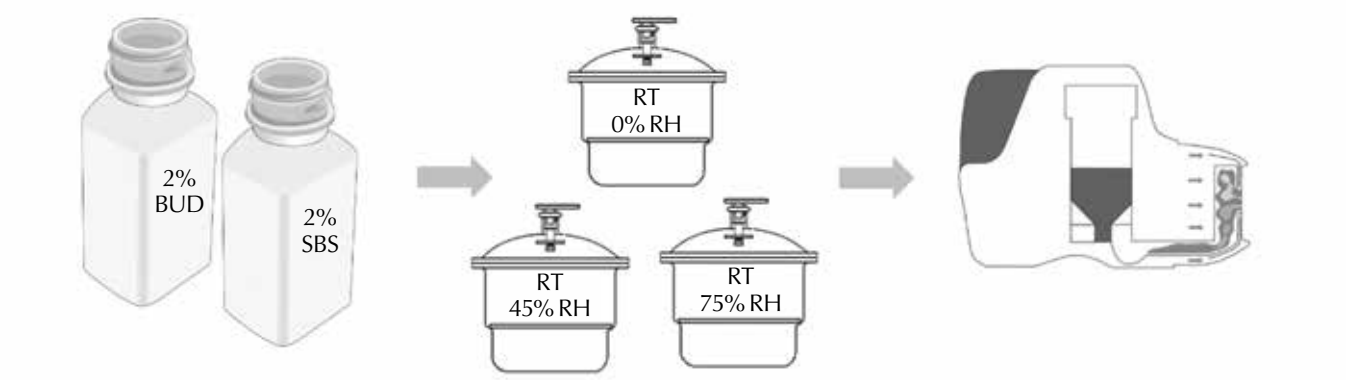
Investigation of the aerodynamic particle size distribution was performed with the Next Generation Impactor (NGI®) (Copley Scientific, Nottingham, United Kingdom), according to the European Pharmacopoeia 9.0) utilizing two commercially available inhaler devices (one reservoir-based device (Novolizer) and one capsule-based device (Cyclohaler®)). Flow rates were adjusted to ensure a 4 kPa pressure drop over the devices, according to the Ph. Eur. (the flow rate for the 4 kPa pressure drop of the Novolizer was 78.3 L/min and for the Cyclohaler was 100 L/min). BUD and SBS content were quantified by RP-HPLC. Data were evaluated with CITDAS 3.0 software (Copley Scientific, Nottingham, United Kingdom). The FPF below 5 µm (of emitted dose) was calculated from the resulting aerodynamic particle size distribution. All impaction tests were done in triplicate and measured at constant conditions (21°C and 45% RH).

In the second part of the study, two more blends, consisting of a new batch of Parteck M DPI and BUD or SBS, respectively, were prepared. The mixing process was carried out as described for the first adhesive mixtures in the Turbula tumble blender. The two powder blends were placed in open plastic bottles at room temperature in three different desiccators with 0%, 45% and 75% RH (Figure 1). The aerodynamic behavior of the ordered mixtures was tested directly after they were blended, as well as after 1 week and 1, 2, 3, 6 and 14 months under each storage condition, by using the Novolizer.

Geometric particle size distribution of the APIs and the carrier was measured by laser light diffraction (HELOS, Sympatec GmbH, Clausthal-Zellerfeld, Germany) using an R1 lens for the APIs and an R5 lens for the carrier. The powder was dispersed at 3.0 bar by the RODOS system (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The data was evalu-

Figure 1

Schematic drawing of the storage stability method



ated using Windox 5.4.2.0 software (Sympatec GmbH, Clausthal-Zellerfeld, Germany). Span values were calculated by: span = $(x_{90}-x_{10})/x_{50}$). Reported data is the average of six measurements.

In order to measure the hygroscopicity of the carrier material, dynamic vapor sorption (DVS) was used (DVS1, Surface Measurement Systems Ltd., London, United Kingdom). Measurements were executed at isothermal conditions (25°C). In one run, relative humidity starts at 0% RH and rises to 90% RH in 10% increments. After, it declines in 10% increments to 0% RH and then the process begins again. Therefore, one run consists of two cycles.

By using scanning electron microscopy (SEM), particle surface and morphology were visualized. Powder was fixed with a carbon sticker and coated with gold using a BAL-TEC SCP 050 Sputter Coater (Leica Instruments, Wetzlar, Germany). Samples were evaluated with a Zeiss Ultra 55 plus (Carl Zeiss NTS GmbH, Oberkochen, Germany) using the SE-2 detector and a working voltage of 2 kV.

Results and discussion

Carrier characterization

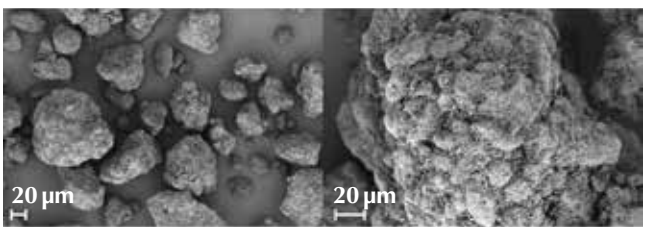
Parteck M DPI is a spray-granulated mannitol with a wide particle size distribution (mean particle size 114 ± 9 µm, span: 2.3) and a unique, large and rough surface area (Figure 2). Despite its irregular structure and broad particle size distribution, its powder flowability appears to be free-flowing and comparable to lactose (ffc Parteck M DPI = 46, ffc Lactose = 39). When subjected to moisture, it adsorbed a small amount of water (1.65% ± 0.20% at 90% RH). Pronounced adsorption of water vapor did not start below 80% RH (Figure 3). This low amount of water indicates a very slightly hygroscopic and crystalline[9] material with high physical stability. Consequently, Parteck M DPI possesses an important characteristic for storage stability.

Influence of blender type

During the blending process, coarse API agglomerates should break up and be distributed homogenously over the surface of the carrier material. In this study, the results from a low shear tumble blender were compared to those from a high shear mixer. In preliminary experiments, blending conditions were explored to achieve a homogeneous blend with high recovery. Homogenous blends with a maximum RSD < 2.87% and a minimum recovery of 96.32% for the Picomix mixer and a maximum RSD < 1.44% and a minimum recovery of 98.43% for the Turbula blender were prepared.

Figure 2

SEM images of Parteck M DPI, representing an overview of the powder (left, magnification 250x) and a detailed surface image (right, magnification 500x)



However, the blending conditions for the two instruments were very different. The total mixing time of 15 minutes required for the Turbula blender is about 30 times longer than the blending time needed in the Picomix mixer. This is due to the efficient mixing principle used in the Picomix instrument. The powder changes position in the mixing vessel not only horizontally but also vertically (Figure 4). This so-called "Cyclomix principle" leads to high shear forces acting on the powder. Therefore, a decreased blending time of 30 seconds was sufficient to prepare homogenous powder blends.

Furthermore, it was assumed that the Picomix mixer could affect the particle size distribution of the carrier, due to its blending tool and high mechanical stress. This hypothesis was verified via laser light diffraction, measuring particle size distribution after 1, 2 and 5 minutes at 500 rpm in the Picomix instrument. Figure 5 depicts the x_{10}, x_{50} and x_{90} values as well as the percentage of particles < 15 µm from Parteck M DPI, unmixed and after blending. A blending time up to 120 seconds at a rotation speed of 500 rpm showed no significant influence on all of these values ($p > 0.435$). For the shorter mixing time of 1 minute, a significantly ($p = 0.003$) lower percentage of particles < 15 µm could be detected. This may be due to the fact that fines adhered to the mixer's walls and blending tool, or were pressed to the carrier and thus were not detected by laser diffraction. After 5 minutes, a significantly ($p = 0.0005$) higher percentage of particles < 15 µm could be observed, caused by the effect of abrasion of the carrier. Increasing blending times led to further particle size reduction and a shift of x_{90} to lower sizes. Therefore, diminution during blending should be observed carefully and the shortest blending time possible should be used in a high shear mixer. For the high shear mixer, a twelve-times-faster rotation speed was used, which was the lowest possible rpm setting. Nevertheless, the total number of rotations was 1.5 times greater than in the tumble blender.

The results of aerodynamic characterization of the SBS blends prepared with the two blenders did not show significant differences; fine particle fraction (FPF): $p_{Novolizer} > 0.388$; $p_{Cyclohaler} > 0.059$; fine particle dose (FPD): $p_{Novolizer} > 0.256$; $p_{Cyclohaler} > 0.241$ (Figure 6). In theory, a more intensive blending of the powder (with the Picomix mixer) could lead to higher press-on forces and therefore to a lower inhalable fraction. In contrast, shear forces are needed to overcome API cohesion and distribute individual API particles on the carrier surface. The impact of these two theories seems to be balanced here because none of the influencing factors was predominant in the results.

Similarly, the BUD blends did not exhibit significant differences using the Cyclohaler ($p_{FPF} > 0.440$; $p_{FPD} > 0.146$), but it should be noted that the FPF and FPD of the mixture from the Picomix tested with the Novolizer was 16% or 28 µg higher than from the Turbula blender. The delivered dose between these BUD blends did not show a significant difference ($p = 0.925$).

Figure 3

DVS measurement of Parteck M DPI; mass in percent is depicted in gray

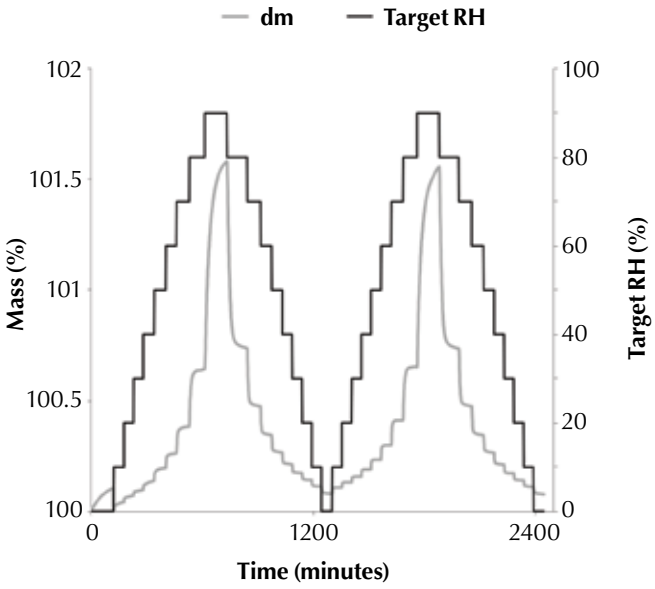
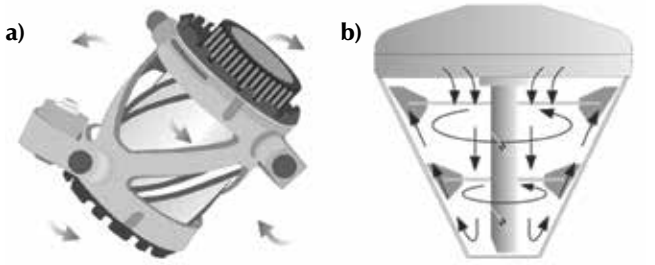


Figure 4

Schematic drawings of the blender principles used in a) the Turbula low shear tumble blender and b) the Picomix high shear mixer



A reason for the difference in FPF and FPD could be the changes in particle size, as shown in Figure 5. The particle size distribution exhibited a greater amount of larger particles due to the already-described decrease of fine particles (< 15 µm). In the Novolizer, the main dispersion principle is inertial forces, which are very strong and thereby able to disperse the adhesive mixture, even if particles adhere quite intensely to the carrier.[12] Larger particles have a higher inertia and therefore increase the inhalable fraction. That this effect was not observed for the SBS blends was possibly due to the higher adhesion forces between SBS and mannitol.[13] In summary, the two blender types produced comparable results with the selected parameters. Consequently, a production of ordered mixtures based on Parteck M DPI with both methods is equally possible.

Storage stability

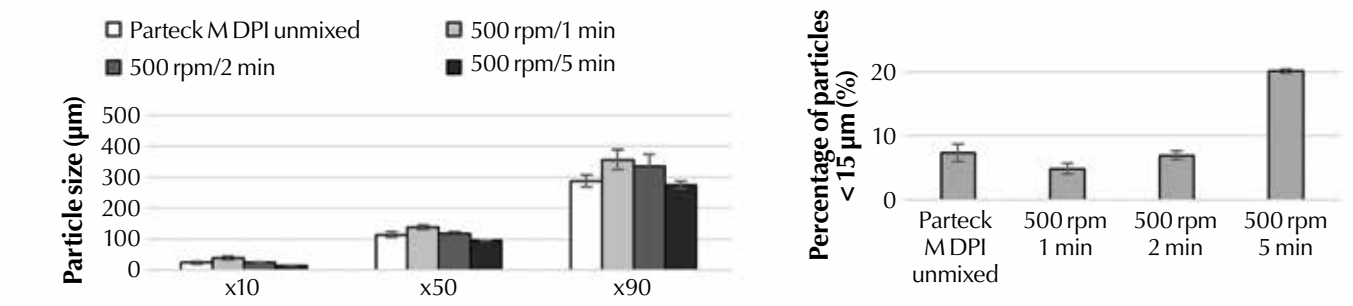
Given that previous experiments did not show any difference between the two preparation methods, blends for storage stability assessment were prepared with the Turbula blender. Again, both blends reached suitable homogeneity, comparable to the first set of blends (RSD < 1.45% and recovery > 97.06%).

For the BUD blend, there was no significant difference in FPF over storage time, irrespective of storage conditions (Figure 7). It was observed that the FPF decreased after two months at 75% RH but this effect was not significant due to a higher standard deviation. This shows that for BUD as a model substance for hydrophobic APIs, the high physical stability of the mannitol carrier can be a decisive factor in providing constant FPF values over a long storage period.

In the SBS blend, the effect of storage at increased humidity was more pronounced because a hydrophilic carrier was blended with a hydrophilic API. Price, et al.[14] were able to demonstrate that interparticulate forces were more dominant between SBS and a hydrophilic carrier (lactose) in comparison to BUD and lactose. SBS acquired counteracting electrostatic charges,[15] which were expected to disappear with an uptake of humidity over storage time. It was seen that at 0% RH, FPF remained at the same level over storage time. At 0% RH, no water adsorption can take place;

Figure 5

Overview of the x_{10}, x_{50} and x_{90} values as well as the percentage of particles < 15 µm from Parteck M DPI unmixed and after blending in the Picomix mixer; mean values with standard deviation; n = 6



therefore the influence of electrostatic charge is more important. At 45% RH, FPF initially increased until the one-month data point due to reduction of electrostatic charge and therefore reduced particle adherence. Over prolonged storage time, the adsorption of water and, consequently, the adherence of SBS particles on the mannitol carrier increased so that FPF was reduced again to the starting level (i.e., no significant difference between values at day 0 and after 14 months). This was different at the increased humidity of 75% RH where FPF continuously decreased. Here, the effect of water adsorption increases capillary forces and therefore adhesion of API particles to the carrier is predominant. Similar results, also using mannitol as a carrier, could be seen by Harjunen, et al.[16]

Conclusion

Physico-chemical characterization of Parteck M DPI demonstrated that it is a suitable carrier for DPI formulations. This mannitol substance is a crystalline, slightly hygroscopic and solid material. Homogeneous blends with a low API content were produced with a tumble blender as well as with a high shear mixer and resulted in suitable FPFs. Generally, blends exhibited good storage stability with constant FPF values, if they were stored under moderate relative humidity (< 45% RH for SBS and < 75% RH for BUD). These results underline the suitability of the mannitol carrier Parteck M DPI as an alternative in DPI formulations.

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Figure 6

Fine particle fraction (FPF) (%), fine particle dose (FPD) (µg) and delivered dose (µg) from all four blends (BUD = gray, SBS = blue) tested with the Novolizer (N) and with the Cyclohaler (C); mean values with standard deviation; n = 3

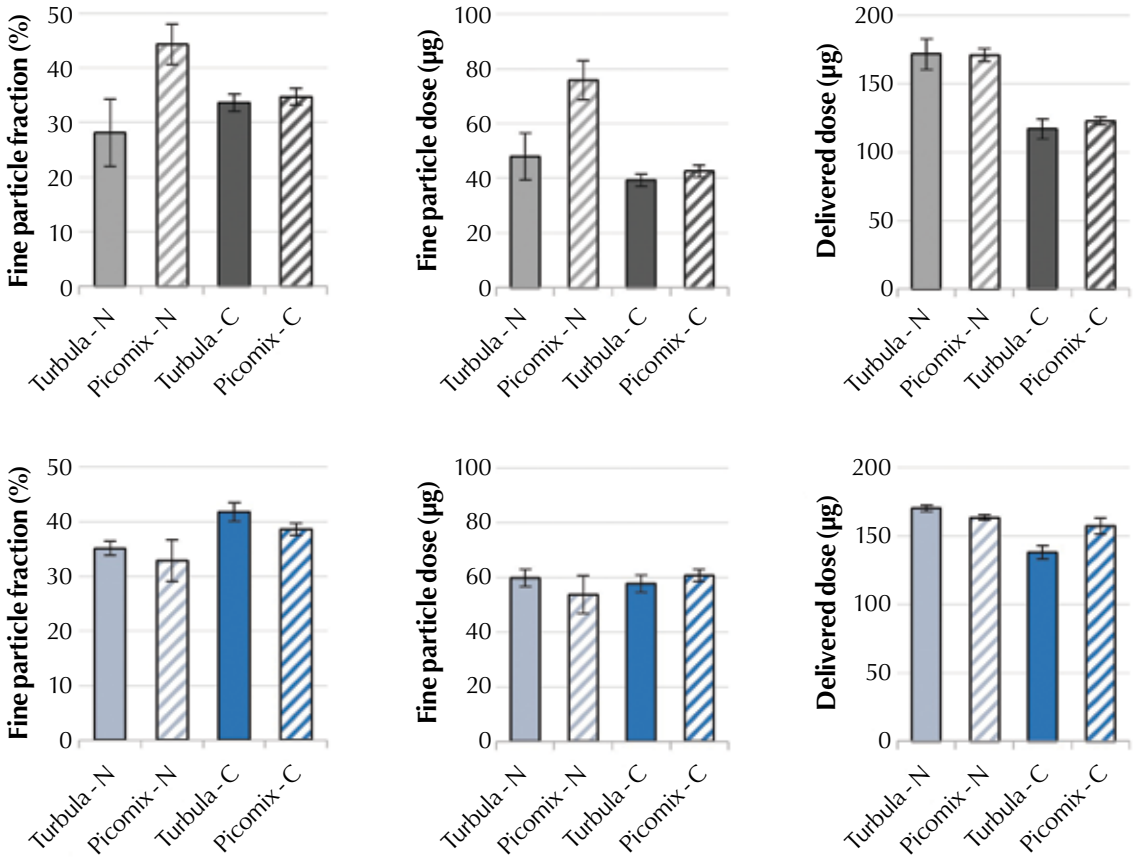
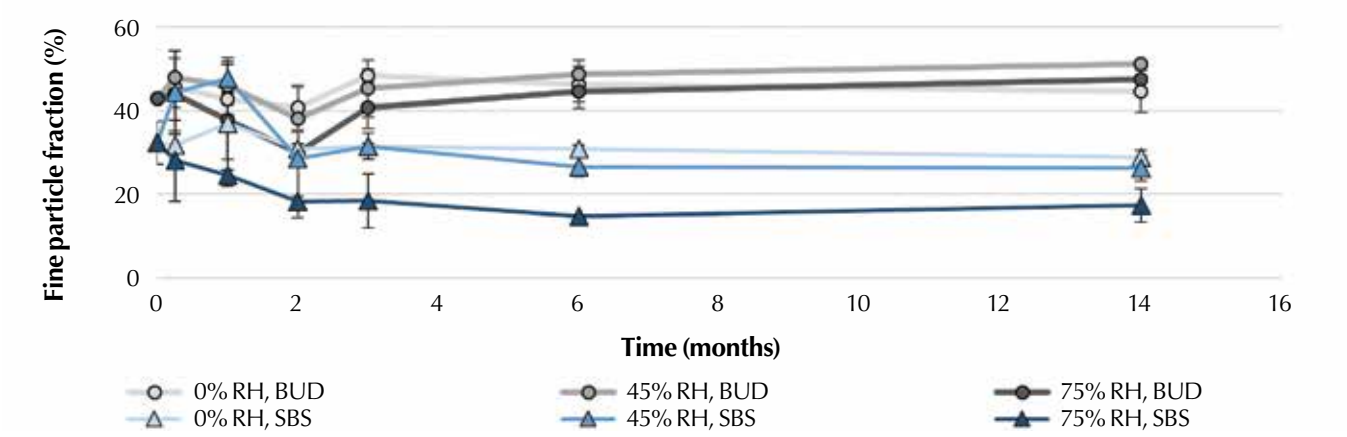


Figure 7

Fine particle fraction of the two formulations (BUD = gray, SBS = blue) tested with the Novolizer in up to 14 months of storage at three different relative humidities; mean values with standard deviation; n = 3



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