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Research paper

Powder flow analysis: A simple method to indicate the ideal amount of lactose fines in dry powder inhaler formulations

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ABSTRACT

Many efforts have been made in the past to understand the function of lactose fines which are given as a ternary component to carrier-based dry powder inhaler formulations. It is undisputed that fines can significantly improve the performance of such formulations, but choosing the right amount of fines is a crucial point, because too high concentrations can have negative effects on the dispersion performance. The aim of this study was to indicate the optimal concentration of fines with a simple test method. For this purpose, mixtures with salbutamol sulfate and two different lactose carriers were prepared with a high shear mixer, measured with a FT4 powder rheometer and tested for fine particle delivery with two different inhaler devices. A correlation between the fluidization energy, measured with the aeration test set up, and the fine particle fractions (FPF) could be proven. This also applied for the aeration ratio, as well as the permeability of the powder samples. In addition, drug-free mixtures hardly differed in their rheological properties from mixtures containing the active pharmaceutical ingredient (API), which indicates that the method could be suitable for cost-saving screening trials. Furthermore, important aspects that explain the function of fines, such as the saturation of active sites, the formation of agglomerates and an increase in fluidization energy, could be shown in this study.

1. Introduction

The addition of lactose fines in dry powder inhaler (DPI) formulations is well known to increase the FPF. Numerous theories like the active sites hypothesis (Hersey, 1975; Jones and Price, 2006; Lucas, 1998), agglomeration hypothesis (Kinnunen et al., 2015; Lucas, 1998), fluidization hypothesis (Shur et al., 2008) and the buffer hypothesis (Dickhoff et al., 2006) have been discussed. Grasmeijer et al. further suggest that all of these above-mentioned theories act simultaneously and can be taken into consideration to explain the beneficial effect of fines (Grasmeijer et al., 2014). However, the addition of extrinsic lactose fines can not only improve the performance of DPI formulations. Young et al. (Young et al., 2007) and Louey et al. (Louey et al., 2003) proposed a linear increase in FPF with increasing amounts of excipient fines up to a certain threshold value. Further addition of fines resulted in a clear decrease in fine particle fraction. Young et al. assumed that above this threshold value, drug-lactose fines agglomerates fail to adhere to the larger lactose carrier particles and become segregated. The authors further assumed that this biphasic system can be seen as a cause for the decrease in FPF. Numerous efforts have been made to predict the performance of DPI formulations, but unfortunately, it is not possible to predict at which concentration these effects occur. An approach by Saleem et al. is based on the use of surface energy measurements and blending dynamics to predict the FPF (Saleem et al., 2008). An inverse relationship with the surface energy and a positive correlation with the root mean square of blending rates could be determined. However, routine use of inverse gas chromatography (iGC) measurements may be limited by time and only little data is available for blending studies which reduces the suitability for screening of DPI formulations. In addition, the study does not take into account that with high concentrations of fines the FPF decreases again or reaches a plateau. A study by Le et al. exhibited a linear correlation of air permeability of binary mixtures and the FPF by using Blaine's apparatus (Le et al., 2010). However, this study also does not take the behavior at very high concentrations of fines into consideration. A similar approach to predict the performance of DPI powder mixtures was carried out by Cordts and Steckel (Cordts and Steckel, 2012). The authors determined a correlation between the permeability of ternary adhesive mixtures measured

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Nomenclature

A	Cross-section area of the powder bed [cm^2]
ACU	Aeration control unit
API	Active pharmaceutical ingredients
AR	Aeration ratio
$carrier_{large}$	InhaLac® 70
$carrier_{small}$	InhaLac® 230
CAB	Cohesion-adhesion balance
CBD	Conditioned bulk density
dd	Double-distilled
DPI	Dry powder inhaler
FPF	Fine particle fraction
HPLC	High performance liquid chromatography
iGC	Inverse gas chromatography
k	Permeability [cm^2]
L	Length of the powder bed [cm]
MMAD	Mass mean aerodynamic diameter
NGI	Next generation impactor
Q	Air velocity [cm^3/s]
RSD	Relative standard deviation
SBS	Salbutamol sulfate
SD	Standard deviation
SEM	Scanning electron microscopy
x_{50}	Volumetric diameter, where 50% of the particles are smaller [µm]
µ	Viscosity of the air [$1.74 \cdot 10^{-5}$ Pas]
ΔP	Pressure drop across the powder bed [Pa]

with an FT4 powder rheometer and the concentration of fines, but no correlation with FPF could be detected. This is also the case for aeration test measurements, which were carried out, too. Price et al. used the same aeration test method and the authors found a correlation between the fluidization energy of different lactose carriers with different intrinsic concentrations of fines (Price, 2010). But again, the special behavior at high concentration of fines within DPI mixtures was not taken into consideration.

The aim of this study is to detect the amount of fines, from which on a further addition of fines becomes disadvantageous, by using a powder rheometer, different sized carriers and different test inhalers. Both, the carrier properties and the used test inhaler directly affect the performance of DPI formulations (de Boer et al., 2012). Therefore, a capsule-based and a multi-dose reservoir based inhaler were selected, employing different dispersion mechanisms to prove the robustness of the developed method.

2. Materials

Different grades of alpha-lactose monohydrate (carrier: InhaLac® 70 also referred to as $carrier_{large}$, InhaLac® 230 also referred to as $carrier_{small}$; fines: InhaLac® 400) were provided by Meggle (Wasserburg, Germany). Micronized salbutamol sulfate (SBS) was obtained by Lusochimica S.P.A (Lomagna LC, Italy). Detailed particle size distributions of the components are listed in Table 1. As devices the Novolizer® (MEDA Pharma GmbH & Co. KG, Köln, Germany) and the Cyclohaler® (PB Pharma GmbH, Meerbusch, Germany) were used. HPMC capsules (Quali-V® HPMC Capsule size 3) were obtained by Qualicaps Europe S.A.U (Madrid, Spain). All other chemicals were of analytical grade and have been purchased from common suppliers.

3. Methods

3.1. Preparation of model DPI formulations

An Alpine Picoline equipped with the Picomix® high shear mixer module (Hosokawa Alpine, Augsburg, Germany) was used to prepare adhesive mixtures.

3.1.1. Preparation of ternary formulations

SBS concentration was set to 1.5 wt%. The content of fines was increased in 5.0 wt%-steps to a maximum of 45 wt% for the large carrier InhaLac® 70 and 30 wt% for the smaller carrier InhaLac® 230. The blending process consisted of two steps. In the first blending step, the fines were added and the drug was added in the second blending step. A sandwich-weighing-method was used at a batch size of 30 g for blending. The blender was operated with a rotation speed of 500 rpm for one minute. After every blending step, the mixtures were passed through a 355 µm sieve to break-up agglomerates. Homogeneity and recovery were assessed for all formulations by measuring the SBS content of ten randomly drawn samples by a high performance liquid chromatography (HPLC) method. The requirements for homogeneity of blends were set to a relative standard deviation (RSD) of less than 5% and a recovery of 95%. Each formulation was prepared and stored at ambient conditions (20–23 °C and 30–65% relative humidity). The blends were stored for at least seven days before any further work was performed to ensure the reduction of electrostatic charge. In stability studies (data not shown) no worsening of the powder dispersion behavior due to due to capillary forces or solid bridging could be observed at these conditions.

3.1.2. Preparation of binary formulations

To prepare placebo powder blends the mixing process was carried out as described for the ternary formulations.

3.2. Shot weight test

The cartridge of the Novolizer® was filled with powder and the channel below the dosing slide was removed. By pressing the dosing button, it was possible to determine the separated dose directly with an analytical balance (AT106 Comparator, Mettler Toledo, Switzerland). Employing this method, falsification by electrostatic charging of the inhaler can be excluded. Results are given as the mean of 10 shots with standard deviation (SD).

3.3. Determination of in vitro fine particle delivery

Aerodynamic particle size distribution was determined using a Next Generation Impactor (NGI) equipped with a critical flow controller

Table 1
Particle size distribution of the mixture components (average with SD; n = 3).

Material	Function	x_{10} [µm]	x_{50} [µm]	x_{90} [µm]	Particles < 5 µm [%]
InhaLac® 70	Carrier	126.9 ± 0.6	218.7 ± 1.0	302.4 ± 1.3	0.0 ± 0.0
InhaLac® 230	Carrier	55.7 ± 0.1	101.3 ± 0.1	142.6 ± 0.1	1.6 ± 0.0
InhaLac® 400	Fines	1.0 ± 0.0	6.3 ± 0.0	23.9 ± 0.4	45.1 ± 0.1
SBS	API	0.6 ± 0.0	1.8 ± 0.0	3.9 ± 0.0	96.3 ± 0.3