Permeability as a performance descriptor of dry powder inhalation carriers: Investigation of several lactose grades

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Summary

Background: Dry powder inhalers (DPIs) have captured the interest of several research groups, for the purpose of solving the performance prediction dilemma. Several studies reported linear inverse relationship between permeability and inhalation performance, while others found no simple relationships. The carrier particle sizes used in these studies were different, that may have resulted in viewing only a part of the whole pattern in each study.

Aim: This study aimed to investigate the relationship between the carrier permeability and the performance of the DPIs and to utilize this relationship in formulation development.

Methods: We prepared inhalation mixtures from six different lactose grades. Carriers and inhalation mixtures were characterized for their particle size distribution using laser diffraction, crystallinity using differential scanning calorimetry, particle shape using image analysis, moisture contents using loss on drying, pore size distribution and permeability using mercury porosimetry. We assessed the in vitro performance of the inhalation mixtures.

Results: The results show that carriers were crystalline with low moisture contents. However, carriers differed in their size distributions, permeabilities and performance ($FPF_{8.06}$ 5 - 21 %).

Conclusions: Initially at low permeabilities, the increase in performance was associated with increasing carrier permeability, until an optimum performance was reached. At higher permeabilities, a decrease in performance was associated with increasing carrier permeability. The findings explain reported controversies between carrier permeability and performance. Carriers with excessive amount of fines become highly resistant to air flow with lower dispersion/performance. Permeability can account for carrier size distribution, shape and packing in a more performance-relevant manner, it also allows identifying a carrier's optimum fines content to meet device dispersion requirements.

Introduction

Inhalation aerosols are generally designed to deliver a therapeutic payload with an aerodynamic diameter D_{ae}~1-5 µm, so that the resulting aerosol may penetrate to reach the lower and peripheral airways. For carrier-based inhalation mixtures, fines addition is generally known to improve DPI inhalation performance up to a certain limit [1, 2]. Several theories have been proposed to explain the effect of fines on performance, including blocking of active sites, formation of hybrid (drug-fines) agglomerates, increasing bulk carrier cohesivity/tensile strength. However, none of the proposed theories can explain all the reported observations. One example is the decrease in performance associated with excessive fines addition. Recently permeability has been proposed as a performance predicting property [3, 4]. Permeability takes into account carrier particle size , shape, and macroscopic surface textural properties [5]. A linear relationship was recently proposed between permeability and performance [4, 6]. However, that relationship was based on a rather limited permeability range. Other groups more recently reported that, no apparent relationship found between permeability and performance [2], using an FT-4 powder rheometer. Therefore, carrier permeability has had a rather controversial role regarding its performance prediction capability. This study aimed to investigate the performance of a variety of lactose carrier grades possessing a wide range of permeability values and particle size distributions.

Materials and Methods

Carriers were prepared by sieve fractionation of six different lactose grades. Carriers were evaluated for their particle shapes, crystallinity and moisture contents using optical microscopy, differential scanning calorimetry and loss on drying, respectively. Carriers were mixed with and without 1% fluticasone propionate (FP) to make inhalation mixtures. The porosity profiles of the prepared carriers were acquired using mercury intrusion porosimetry. Blend uniformity, in vitro performance and particle size distribution of the inhalation blends were assessed using UV-VIS spectrophotometry, cascade impaction analysis and laser diffraction, respectively.

Results

The DSC thermograms suggested that carriers were all crystalline. All carriers had moisture contents below 1.3%. The carriers were slightly elongated, with aspect ratios, between 1.49 and 1.76. The carriers had different median pore diameters ranging from 5.35 to 24.15 µm. As a result permeabilities of the carriers varied more than 30 folds, from 0.40 Darcy to 13.0 Darcy. For the inhalation mixtures, blend uniformity showed RSD values below 6%. Size distribution analysis of the inhalation mixtures showed modal diameters ($D_{v, mode}$) values ranging from 33 to 88 µm. The mixtures also remarkably differed in their fine particle contents below 10 and 25 µm in diameter. Fine contents below 10 µm in diameter ranged from 4.8 to 11.6 µm. However, the fine contents below 25 µm in diameter ranged from 8.7 % to 42 %. Fluticasone propionate had a median diameter ($D_{v, 0.5}$) of 4.49 µm. Performance of the inhalation mixtures varied widely; as $FPF_{8.06}$ ranged from 4.97% to 21%, while, $FPF_{4.46}$ ranged from 3.09 to 16%.

Discussion and Conclusions

At low permeability values (< 3.0 Darcy), the increase in inhalation performance (FPF) was associated with increasing carrier permeability, in a quasi-linear fashion ($R^2 > 0.97$), until a maximum performance was reached at a carrier permeability value of 3.0 Darcy. At higher carrier permeability values, performance decreased was associated with increasing carrier permeability, in a quasi-exponential fashion ($R^2 > 0.82$), Fig 1A-1B. Similar behaviour was observed for either cut-off diameters of fine particle fractions $FPF_{4.46}$ or $FPF_{8.06}$. Therefore, performance (FPF) generally had a direct relationship with carrier permeability till a certain permeability value is reached (3.0 Darcy), around which the two trends (direct and inverse relationships) intersected. Permeability of the carriers also had good agreement with carrier size distribution parameters such as cumulative particle diameters undersize 10 % v/v ($D_{v, 0.1}$) and carrier fine contents percentages below 10 or 25 µm in diameter. The following conclusions could be drawn from the relationships:

(1) The linear trend observed between performance and permeability, at low permeability values (< 3.0 Darcy), suggests that, the Aerolizer ® device, at flow rate of 60 $L.min^{-1}$, have reached its dispersion limit at this permeability value i.e. below this permeability value lower performance (FPF) will be obtained. The reason may be that too much fines will result in powders with very low permeability and high tensile strength/cohesivity that the device separation forces will not be adequate to disperse efficiently [3, 7, 8]. Therefore, optimal dispersion of the Aerolizer ® device at 60 $L.min^{-1}$, was recognized for carriers with permeabilities closest to 3.0 Darcy, Fig 1A-1B.

(2) The relationships between performance and permeability, direct then inverse relationships, may explain the lack of correlation reported earlier in literature. It can also explain the apparent linear direct relationship between performance and permeability at higher permeability values (> 3.0 Darcy). That could be attributed to limited ranges of carrier size or permeabilities employed in those studies [2, 4, 6].

(3) It is possible to find the optimum fines content for a carrier by adjusting its permeability to the device optimal dispersion permeability value (3.0 Darcy for Aerolizer® at 60 L.min-1), using the relationships between permeability and carrier size distribution parameters.

The permeability values correlated well with size distribution parameters, Fig 1C-1D. An exponential fit using the same function had adj. R^2 values of 0.61 and 0.99 associated with percentage of fines below 10 µm in diameter and percentage of fines below 25 µm, respectively. However, a direct linear relationship was found between $D_{V, 0.1}$ and carrier permeability, at permeability values higher than 2.5 Darcy, with an R^2 value of 0.999. The relationships are generalized as they belonged to different lactose carrier grades rather than a single coarse carrier with different fine additions. Therefore the relationships can be used for:

(1) customizing the carrier composition to adjust its permeability to the desired value.

(2) observing the influence of different types of fines on permeability; so as to select the best amount of fines required for optimum performance.

(3) preliminary selection among the offered carrier grades by roughly estimating carrier permeability from its micrometrics, assuming similar particle shapes and surface texture.

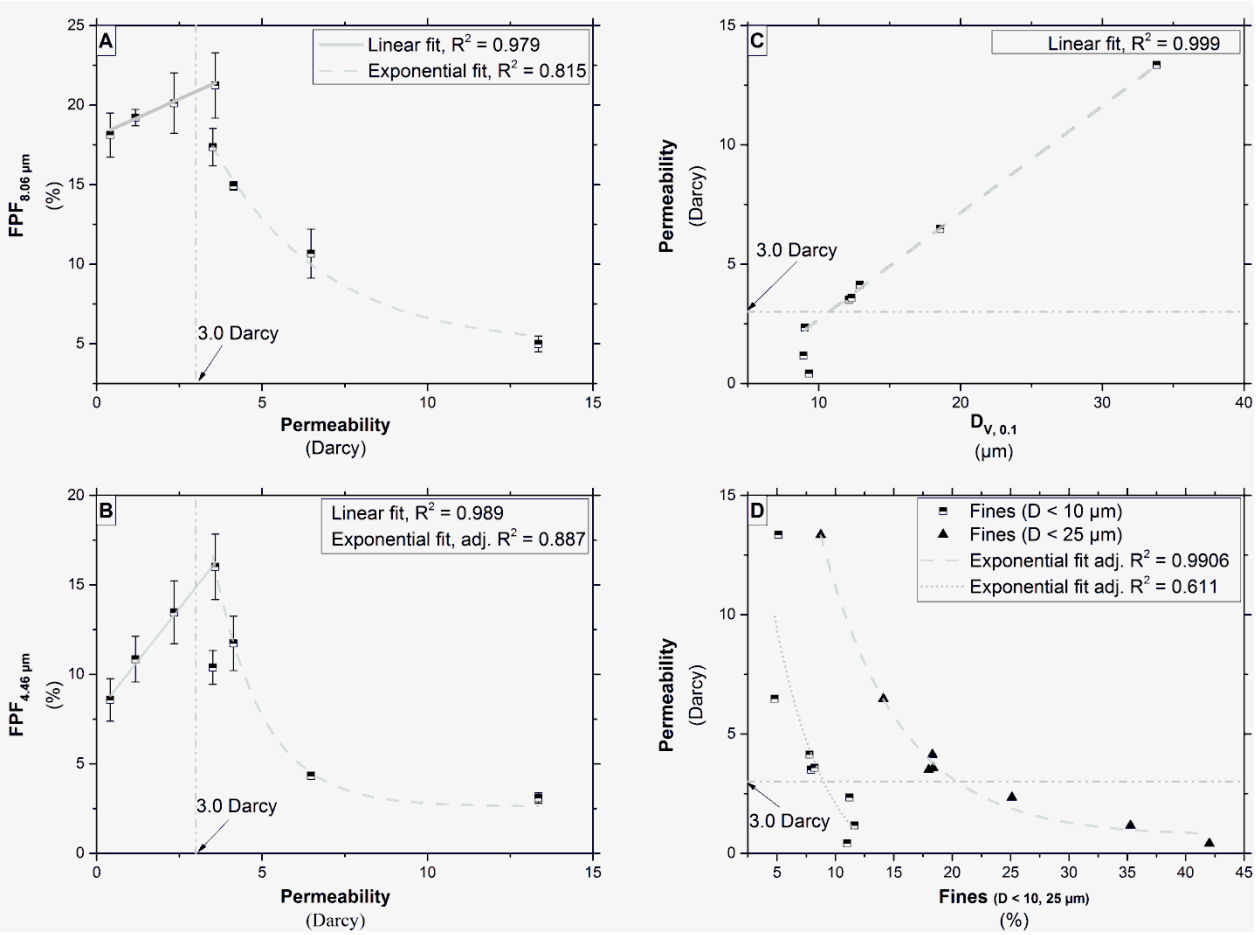

Figure 1 The relationships between (A) carrier permeability and fine particle fractions of the emitted dose below cut-off aerodynamic diameter of 8.06 µm ($FPF_{8.06}$), (B) carrier permeability and fine particle fractions of the emitted dose below cut-off aerodynamic diameter of 4.46 µm ($FPF_{4.46}$), (C) carrier permeability and cumulative particle diameters undersize 10% ($D_{v,\ 0.1}$), and (D) carrier permeability and fine contents percentages below 10 or 25 µm in diameter (Fines % (D < 10, 25 µm)). Note the dash-dot-dot cursors in all graphs (vertical in A and B, or horizontal in C and D) at 3.0 D value represent an optimum permeability value for dispersion using the Aerolizer® device at 60 $L.min^{-1}$.

References

1. Louey, M.D., S. Razia, and P.J. Stewart, *Influence of physico-chemical carrier properties on the in vitro aerosol deposition from interactive mixtures.* International Journal of Pharmaceutics, 2003. **252**(1-2): p. 87-98.
2. Cordts, E. and H. Steckel, *Capabilities and limitations of using powder rheology and permeability to predict dry powder inhaler performance.* Eur J Pharm Biopharm, 2012. **82**(2): p. 417-23.
3. Shur, J., et al., *The role of fines in the modification of the fluidization and dispersion mechanism within dry powder inhaler formulations.* Pharm Res, 2008. **25**(7): p. 1631-40.
4. Le, V.N.P., E. Robins, and M.P. Flament, *Air permeability of powder: A potential tool for Dry Powder Inhaler formulation development.* European Journal of Pharmaceutics and Biopharmaceutics, 2010. **76**(3): p. 464-469.
5. Shalash, A.O., A.M. Molokhia, and M.M. Elsayed, *Insights into the roles of carrier microstructure in adhesive/carrier-based dry powder inhalation mixtures: Carrier porosity and fine particle content.* Eur J Pharm Biopharm, 2015.
6. Le, V.N.P., E. Robins, and M.P. Flament, *Agglomerate behaviour of fluticasone propionate within dry powder inhaler formulations.* European Journal of Pharmaceutics and Biopharmaceutics, 2012. **80**(3): p. 596-603.
7. Valverde, J.M., et al., *The tensile strength of cohesive powders and its relationship to consolidation, free volume and cohesivity.* Powder Technology, 1998. **97**(3): p. 237-245.
8. Carman, P.C., *Fluid flow through granular beds.* Chemical Engineering Research & Design, 1997. **75**: p. S32-S48.