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Research paper

# Air permeability of powder: A potential tool for Dry Powder Inhaler formulation development

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ABSTRACT

Dry Powder Inhalers have drawn great attention from pharmaceutical scientists in recent years in particular those consisting of low-dose micronized drug particles associated with larger carrier particles and called interactive mixtures. However, there is little understanding of the relation between bulk powder properties such as powder structure and its aerodynamic dispersion performance. The aim of this work was to develop a simple method to measure the air permeability of interactive mixtures used in Dry Powder Inhalers by using Blaine's apparatus – a compendial permeameter and to relate it to the aerodynamic behaviour. The study was done with fluticasone propionate and terbutaline sulphate as drug models that were blended with several lactoses having different particle size distribution thus containing different percentages of fine particle lactose. The quality of the blends was examined by analysing the drug content uniformity. Aerodynamic evaluation of fine particle fraction was obtained using a Twin Stage Impinger. A linear correlation between a bulk property – air permeability of packed powder bed – and the fine particle fraction of drug was observed for the tested drugs. The air permeability reflects the quantity of the free particle fraction in the interparticulate spaces of powder bed that leads to fine particle fraction during fluidization in air flow. A theoretical approach was developed in order to link the air permeability of powder bed and drag force acting on powders during aerosolization process. The permeability technique developed in this study provides a potential tool for screening Dry Powder Inhaler formulations at the development stage.



## 1. Introduction

Dry Powder Inhalers (DPI) have drawn great attention in recent years because of various advantages, such as being free from propellants, ease of use with a portable small device and overcoming the problem of patient coordination [1–3]. The typical size of respirable particles is generally less than 5 μm. In this size range, the intrinsic cohesiveness of small particles opposes their conversion from a bulk powder to an aerosol by air flow. Formulations with fine drug particles and coarse carrier particles, usually lactose, have been commonly used to facilitate dispersion and flow [4]. In this so-called ordered mixture or more recently interactive mixture [5], the fine drug particles are expected to adhere to the carrier surface to produce a homogenous mixture. In reality, perfect examples of ordered mixture are rarely found and the powder structure is much more complex. In a mixture of very cohesive micronized drug particles, agglomerates of drug may occur and the mixture contains ordered units and also drug agglomerates. Additionally, a concept "total mix" was developed [6]. Total mix is composed of both random (drug particles alone and carrier particles alone) and ordered units (drug particles adhered onto carrier particles surface and carrier particles onto drug particle surface). In order to effectively deliver drug into the lungs, the turbulent air stream created by any Dry Powder Inhaler must provide adequate power to disperse the powder and to produce a cloud of respirable particles [1,4]. The fluidization of cohesive powder was researched in recent years. The fluidization of fine particle powders was characterized by the direct transition from rigid-plastic state to a gas-fluidized state without passing through an inertial step [7]. In order to fluidize a cohesive powder, the gas flow has to overcome not only the weight of the powder, but also its tensile strength. When particles are very fine, the interparticulate cohesive forces become dominant and the minimum velocity for fluidization becomes less dependent on the particle diameter [7,8]. Nevertheless, the understanding of the interaction between bulk powder and air stream and the transformation from a powder state to a disperse state are still lacking [9]. Recently, some authors have examined the dynamic and bulk powder properties in order to explain the

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mechanisms that dominate Dry Powder Inhaler performance. The increased resistance to air flow of powder was found to enhance the intensity of the dispersion process. [10]. However, no further investigations have been performed in order to elucidate the relationship between these parameters and the performance.

Permeability methods are well known for measurements of specific surface area of fine particulate materials in different industries. In reality, the permeameter does not measure surface area but the structure of the air pathways through the powder mixture. Permeability studies of powder mixture can actually generate information on the changes in the internal pore structure of the mixture as the ingredients of the mixture intermingle [11]. Permeametry was used to study the ordered mixture structure of drug of larger size and glidants of smaller size [12]. The authors stated two distinct behaviours of glidants. After a threshold of glidant concentration, the powder permeability decreases. They speculated that for small quantity of glidant, their particles are principally adhered onto the surface of drug and there are not enough fine particles present in the pore of powder bed. So the permeability remained unchanged. Above this threshold, the glidant particles are dispersed in the mixture and fill the interparticular space that generates the decrease in permeability. In the second type of glidants, a progressive decrease in powder permeability is noted with its addition. The glidant particles do not adhere to the larger particles and distribute into the pore systems of the powder bed. Thus, the structure of a binary mixture was elucidated. Developing this technique, Traisnel et al. [13] studied the distribution of different component in ternary mixtures of lactose, sodium salicylate and magnesium stearate. It is shown that magnesium stearate can bring out two types of distribution of components depending on the order in which it is added.

The aim of this work was to develop a simple method to measure the permeability of interactive mixtures used in Dry Powder Inhalers by using Blaine's apparatus – a compendial permeameter [14]. Then, the relationship between the air permeability of powder and Dry Powder Inhaler performance was investigated.

## 2. Theoretical considerations

In the 19th century, Darcy (1856), when observing the laminar flow of water through a packed bed of sand, proposed the relationship [15]:

$$U = \frac{K}{\eta} \times \frac{-\Delta P}{L} \tag{1}$$

where $U$ is the superficial fluid velocity through the bed and the $\Delta P$ is the pressure drop across a bed depth $L$. $K$ is designed as the intrinsic permeability of packed bed and $\eta$ is the fluid viscosity. If this equation is applied to a fixed weight of powder bed and noted the sample permeability $K'$, $K'$ can be determined as:

$$K' = \frac{K}{L} \tag{2}$$

The Eq. (1) can be rewritten as the following equation:

$$U = \frac{K' \times (-\Delta P)}{\eta} \tag{3}$$

In Blaine's apparatus, $U$ and $\Delta P$ vary in function of time. In the time interval $\Delta t$, the fluid flow is $\alpha \Delta H$, where $\Delta H$ is the decrease in the pressure head in time $\Delta t$ and $\alpha$ is the cross-sectional area of the manometer [16,17]. In the Eq. (1), $U$ represents the fluid volumetric flow rate ($Q$) per cross-sectional area of powder bed ($A$). Therefore, the quantity flowing per unit time is given by the term $\alpha \Delta H/\Delta t$. Substituting this expression in the Eq. (3) and rearranging terms, we have

$$\frac{\Delta H}{H} = \frac{A}{\alpha} \times \frac{K' \times \rho_f}{\eta} \times \Delta t \tag{4}$$

with $\rho_f$ is the fluid density.

Integrating this equation within the time $T$ of fluid fall from $H_1$ to $H_2$ of Blaine's apparatus, we obtain

$$\ln \frac{H_1}{H_2} = \frac{A}{\alpha} \times \frac{K' \times \rho_f}{\eta} \times T \tag{5}$$

In the Blaine apparatus, $H_1$, $H_2$, $A$, and $\alpha$ are constant. The relationship between the powder permeability and air time flow through powder bed can be described as following equation:

$$K' = C \times \frac{\eta}{\rho_f \times T} \tag{6}$$

with $C$ being a constant, taking into account Blaine's apparatus parameters $H_1$, $H_2$, $A$, and $\alpha$. The permeability has then a reciprocal relationship with air flow time.

## 3. Materials and methods

Micronized fluticasone propionate (FP) and terbutaline sulphate (TBS) were used as supplied. Inhalac 230 (Meggle, Wasserburg, Germany) and Lactohale 200 (Borculo Domo, Zwolle, The Netherlands) were used as carrier. Furthermore, 2 grades of carrier lactose without fines were prepared from Inhalac 230 and Lactohale 200 by air-jet sieving through a 32-μm sieve for 30 min with an air flow that produces a pressure drop of 4 kPa. Inhalac 230 without fines and Lactohale 200 without fines were only used after at least 24 h following sieving so that the electrostatic charges, if there is any, may decay.

### 3.1. Powder characterization

Particle size was measured by laser diffraction (Malvern Mastersizer 2000®, Malvern Instrument Ltd., Orsay, France) in liquid dispersion using the 300 RF lens and the small volume sample presentation unit.

For lactose, the dispersing medium was 0.5% Polysorbate 80 (Tween 80) in absolute ethanol saturated by lactose over 24 h and filtered through 0.25-μm filter prior to analysis. Lactose was dispersed in the dispersing medium for 3 min by magnetic agitation. The sample was further treated with sonication in a water bath for 1 min. Sample was added into sample cell containing the dispersing medium in order to obtain an obscuration between 10% and 30%. For fluticasone propionate, the dispersing medium was ethanol/water 10/90 (% v/v) with 0.1% Polysorbate 80, saturated by fluticasone propionate. In the case of terbutaline sulphate, 0.1% Sorbitan oleate 85 in cyclohexane saturated with terbutaline sulphate was used. Size measurement of each sample was performed using 2000 sweeps. Size distribution and summary statistics are the average of at least three determinations. For each measurement, the mean diameter, the median diameter, the diameter under which 10% particles ($d_{v,0.1}$) and 90% particles ($d_{v,0.9}$) were in consideration.

The true density of powder was assessed by helium pycnometer (AccuPyc 1330, Micromeritics, USA) using a 3 $cm^3$ sample cell. The results are expressed as the average of ten determinations.

### 3.2. Mixing conditions and evaluation

Terbutaline sulphate (TBS) and lactose were mixed in a ratio of 1:67.5 w/w, in a Turbula mixer (Bachofen Maschinenfabrik, Basel, Switzerland) for 2 h at 90 rpm. Each blend was prepared in 100 g quantities in glass vessels adapted for Turbula mixer. The mixing was performed at controlled ambient conditions (40 ± 5% relative

humidity and 20 ± 2 °C). Fluticasone propionate (FP) and lactose were mixed at a concentration of 2.5% w/w in the same conditions.

The quality of the blends was expressed by the coefficient of variation (cv) of sample drug content. In case of FP mixtures, fifteen randomly selected samples (20.0 ± 0.2 mg) were dissolved in methanol/water 70/30 (% v/v) using 25-mL volumetric flasks. Sonication ensured the total dissolution of drug. All fluticasone propionate samples were analysed by a validated HPLC method using an ODS chromatographic column, 50 × 4.6 mm × mm 5 μm (Phenomenex). Mobile phase is composed of methanol/0.1% acetate buffer in 80/20 (% v/v) ratio and was passed through a filter of 0.25 μm prior to use. The flow rate was 1 mL/min and fluticasone propionate was detected at 336 nm. A linear range was obtained from 0.01 to 23.0 μg/mL ($R^2$ = 0.996). Quantitative analysis was carried out by BeckMann spectrophotometer at a wavelength of 276 nm for terbutaline sulphate. Fifteen randomly selected samples (34.25 ± 0.25 mg) were dissolved in water using 25-mL volumetric flasks. A linear range was obtained from 0.001 to 0.1 mg/mL ($R^2$ = 0.9999).

### 3.3. Aerodynamic evaluation

Each formulation was manually loaded into size 3 gelatine capsules (donated by Capsulgel, France). Fill weight was 20.0 ± 0.2 mg for fluticasone propionate mixtures and 34.25 ± 0.25 mg for terbutaline sulphate mixtures giving the nominal dose of 500 ± 5 μg drug per capsule. Following filling, capsules were stored at 40 ± 5% relative humidity and 20 ± 2 °C for at least 24 h prior to analysis.

Aerodynamic evaluation of fine particle fraction and emitted dose were obtained using a Twin Stage Impinger (TSI, Apparatus A, European Pharmacopoeia, 2008). Each deposition experiment involved the aerosolization at 60 l/min via an Inhalator Ingelheim of five capsules. All stages of the Twin Stage Impinger were filled with water/methanol 30/70% v/v for fluticasone propionate and water for terbutaline sulphate. The quantity of drug was determined by the methods previously described in mixture quality evaluation. For each blend, the assays were performed in triplicate. All experiments were performed in controlled temperature and relative humidity (40 ± 5% relative humidity and 20 ± 2 °C).

- the emitted dose (ED) was the sum of drug collected from the upper and lower stages,
- the fine particle dose (FPD) is defined as the amount of drug deposited in the lower stages of the TSI, since their aerodynamic diameter was less than the cut-off diameter of the TSI (6.4 μm at an air flow rate of 60 L/min),
- the percentage emission was calculated as the ratio of ED to the average capsule content,
- the fine particle fraction was calculated as the ratio of FPD to the emitted dose.

### 3.4. Air permeametry

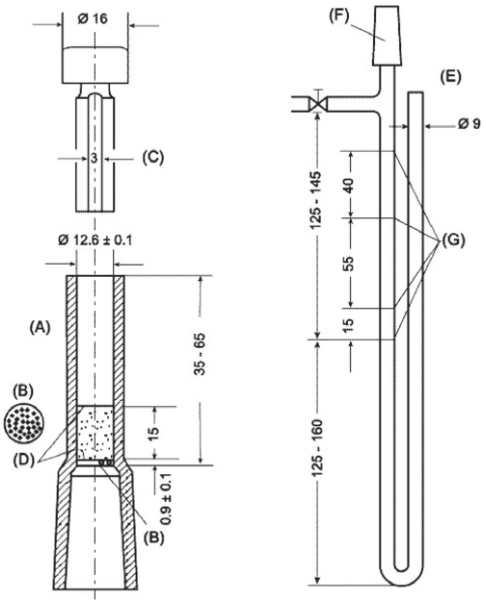
The air permeability of powder mixtures was measured by means of a Blaine apparatus – the permeameter described in European Pharmacopoeia 6.0, normally used for determination of specific surface area [14]. The apparatus consists of 2 parts: (I) a permeability cell and (II) *U*-tube manometer (Fig. 1).

A modified procedure for investigating the structure of powder was developed. A critical point of this procedure is that no force is exerted on the powder bed in order to maintain the un-modified powder structure.

Place a filter paper disk on top of the perforated metal disk of the permeability cell. Weigh and carefully transfer 1.590 (± 0.005) g of the examined powder into the permeability cell. Carefully tap the cell five times so that the surface of the powder bed is levelled and cover it with a second filter paper disk by means of a 10-g pencil without applying pressure. Attach firmly the permeability cell to the tube of manometer and carefully prevent an air pulse moving up through the powder bed when mounted. Check that the system is airtight. Evacuate the air from the manometer by means of a rubber bulb until the level of liquid is at the highest mark. Using a timer, measure the time taken for the liquid to fall from second to third mark of the manometer. Repeat eight times for measuring the air flow time through each powder bed. Three samples are analysed. The results are calculated as the mean of the 24 measurements.

### 3.5. Powder permeability by mercury porosimetry

Powder permeanility was assessed by mercury intrusion porosimetry (Micromeritics® Autopore IV 9500). Mercury pressure working range was from 0.0034 MPa to 15 MPa in order to avoid




(A) Cylinder
(B) Perforated Metal Disk
(C) Plunger
(D) Filter Paper Disk
(E) U-tube manometer
(F) Connection to permeability cell

**Fig. 1.** EP apparatus for air permeability – *dimensions in millimeters.*

**Table 1**
Powder characteristics.

| | $D_{4,3}$ (μm) | $d_{v,0.1}$ (μm) | $d_{v,0.5}$ (μm) | $d_{v,0.9}$ (μm) | Density (g/mL) |
|---|---|---|---|---|---|
| Terbutaline sulphate | 3.40 (± 0.01) | 1.38 (± 0.02) | 3.07 (± 0.03) | 5.93 (± 0.15) | 1.37 (± 0.009) |
| Fluticasone propionate | 3.23 (± 0.04) | 0.51 (± 0.01) | 2.69 (± 0.03) | 6.69 (± 0.10) | 1.38 (± 0.004) |
| Lactohale 200 | 73.84 (± 0.84) | 10.75 (± 0.77) | 67.84 (± 0.45) | 143.64 (± 1.60) | 1.54 (± 0.0016) |
| Inhalac 230 | 69.13 (± 3.16) | 16.97 (± 2.97) | 67.54 (± 3.90) | 122.46 (± 2.54) | 1.5427 (± 0.001) |
| Lactohale 200 without fines | 91.32 (± 1.00) | 41.02 (± 1.08) | 88.81 (± 1.94) | 147.78 (± 1.67) | 1.5370 (± 0.0013) |
| Inhalac 230 without fines | 79.36 (± 3.99) | 34.26 (± 6.25) | 78.92 (± 3.92) | 126.64 (± 4.28) | 1.5383 (± 0.0012) |

particle compression or collapse due to high pressure. One (± 0.02) gram of powder sample was used. In order to avoid the influence of contact angle on the result, only lactose samples were measured. The values obtained will be compared with those obtained with Blaine's apparatus on the samples of lactose alone. This is to validate the method developed with the Blaine's apparatus. If we have a good correlation between the two methods for lactose, we can suppose that it will be the case for the drug/lactose blends. Permeability is calculated from characteristic length of sample by Katz and Thompson's equation [18]. The latter was experimentally determined based on pressure at which the percolation begins.

## 4. Results and discussion

### 4.1. Powder characterization

Saturation of the dispersing medium with sample prevents the possible dissolution during the measurements. Sonication is believed to aid the complete agglomerate separation into primary particles. Sample observation by optical microscope (40 and 100 times magnification) demonstrated the complete dispersion of fine particles, and no particle fragmentation was detected. Table 1 gives an overview of particle characterization of drugs and carriers. Air depression sieving removed successfully the fine fraction of lactose. The mass median diameter of drugs is about 3.23 μm for fluticasone propionate and 3.40 μm for terbutaline sulphate and is adequate for deep penetration into the lungs.

### 4.2. Air permeability by Blaine apparatus vs. permeability determined by mercury porosimetry

Permeability is an important property of porous materials. There have been many attempts to relate permeability to some relevant micro-structurally defined length scale. In a study of rock permeability using mercury injection measurements, Katz and Thompson have recently derived, using percolation theory, a prediction for the ratio of permeability to electrical conductivity. The permeability ($k$) was expressed as [18]:

$$k = \frac{1}{226}(L_c)^2\left(\frac{\sigma}{\sigma_0}\right) \quad (7)$$

where $L_c$ is characteristic length and $\sigma/\sigma_0$ is the conductivity formation factor.

The characteristic length was determined from the mercury intrusion in the following way. If the pore space is sequentially built up starting with the largest pores and working down, then $L_c$ is the diameter of the pore that just completes the first continuous pathway through the material. This pathway then consists only of pores with diameter greater than or equal to $L_c$. In practice, to obtain this characteristic length $L_c$, pressure is determined at the point of inflection in the rapidly increasing range of the cumulative intrusion curve. This inflection point corresponds closely to the pressure at which percolation begins. This pressure point is defined as the threshold pressure ($P_t$). The value of $L_c$ is the pore diameter calculated from the Washburn equation for $P_t$.

An estimation of conductivity formation factor $\sigma/\sigma_0$ makes the calculation of permeability from mercury intrusion possible.

The results of powder permeability determined by the Blaine apparatus and mercury porosimetry are presented in Table 2. As developed in Eq. (6), the permeability has a reciprocal relationship with time for air passing through the powder bed in the Blaine apparatus. The results in Fig. 2 demonstrates a good linear relationship ($R^2 = 0.9618$) between permeability determined by mercury porosimetry and the reciprocal of air flow time obtained with the Blaine apparatus. Thus, the Blaine apparatus is a good method to estimate the permeability of powder. However, air permeability avoids the influence of contact angle in interaction between mercury and sample, especially for a mixture of different materials. Consequently, the air permeability is the chosen method for further investigation into mixture behaviours.

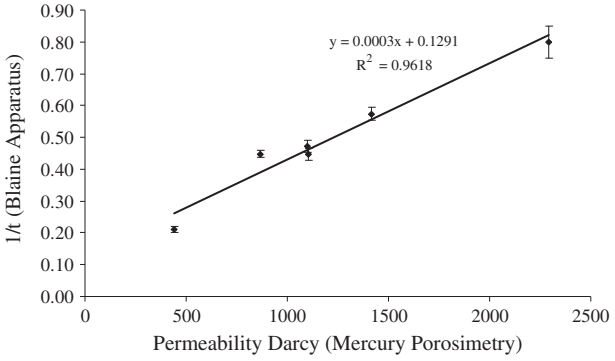



**Fig. 2.** Relationship between permeabilities of powders, Darcy (mercury porosimetry) and $1/t$ (Blaine apparatus) (mean ± SD, $n = 24$).

**Table 2**
Air permeability by the Blaine apparatus and by mercury porosimetry.

| | Pore structure summary | | | Blaine apparatus | |
|---|---|---|---|---|---|
| | Threshold pressure (calculated MPa) | Characteristic length (μm) | Permeability (Darcy) | Permeability (s) | $1/t$ (1/s) |
| Lactohale 200 total | 0.071 | 17.58 | 440.02 | 4.73 | 0.21 |
| Fraction 125–90 μm | 0.037 | 33.62 | 2290.44 | 1.25 | 0.80 |
| Fraction 90–63 μm | 0.048 | 26.07 | 1415.91 | 1.74 | 0.57 |
| Fraction 63–40 μm | 0.058 | 21.36 | 864.72 | 2.23 | 0.45 |
| Lactohale 200 > 32 μm | 0.051 | 24.55 | 1096.57 | 2.12 | 0.47 |
| Inhalac 230 | 0.052 | 23.84 | 1102.47 | 2.24 | 0.45 |

### 4.3. Mixture characteristics

All blends are acceptably homogenous with coefficient of variation less than 5%. The recovered drug contents are close to the theoretical values (Table 3), 1.46% in the case of TBS and 2.5% for FP. All individual recovery was comfortably within 85–115% of label claim, suggesting that homogenous blends were obtained for both drugs and lactose.

Table 4 presents air flow times for the different blends with terbutaline sulphate. The air permeability values are similar for the mixtures with Lactohale 200 without fines and Inhalac 230 with or without fines, whereas the mixture with Lactohale 200 provides greatest resistance to air flow. Lactohale 200 has the highest percentage of fine particles. The performance of powder blends, in terms of fine particle fraction (FPF), is also presented in Table 4. A good linear correlation between the air flow time through the powder mixture bed and FPF of terbutaline sulphate can be seen in Fig. 3, when plotting FPF vs. air flow time ($R^2$ = 0.9892).

The same observation is found with the interactive mixtures of fluticasone propionate. The Table 5 lists the values of air flow time and fine particle fraction for the different blends of fluticasone propionate. A good correlation between air resistance of powder mixtures and the fine particle fraction of drug is observed in Fig. 4 ($R^2$ = 0.9971).

In order to check the supposed relationship between air flow time through the powder bed and *in vitro* DPI performance, a mixture of fluticasone propionate with a ternary agent was performed. For this purpose, 0.5% w/w of magnesium stearate (MgSt) was blended with Lactohale 200 in a Turbula mixer for 3 h at 90 rpm. Then, 2.5% w/w of fluticasone propionate was added and mixed for 3 h. The Table 6 presents the characteristics of this mixture.

Interestingly, when the values of this blend of Lactohale 200–0.5% Magnesium Stearate and 2.5% FP are considered together with values of previous FP mixtures, a linear relationship between the air flow time and DPI performance is respected with a coefficient $R^2$ of 0.9981, which indicates a good correlation between these two parameters.

An increase in the *in vitro* DPI performance is observed with an increase in resistance to air flow through powder bed, regardless the active ingredient in the mixture. The air permeability of packed bed reflects the powder structure. In the interactive mixtures, only a fraction of fine drug particles adheres to the high-energy sites on the carrier. When these sites are saturated, the remaining particles adhere to other sites of lower energy from which they are more easily dislodged, or distribute themselves in a random way in the blend. The free fine particles in the interparticular spaces of a packed powder bed lead to greater resistance to air flow. Thus, the powder structure is very complex but can be assessed by the permeability technique. Because the free fine particle fraction can be easily entrained in the air flow, a better fine particle fraction is produced when a more air resistant powder bed is observed.

Furthermore, an explanation of this finding is that the force induced by air flow through a packed bed is linked to the latter's air resistance. The greater the air resistance of the powder bed is, the greater the importance of the force exerting on powder plug is.

In turbulent regime of air stream (high Reynolds number), the Darcy's equation is empirically modified as follows [19]:

$$-\Delta P = \frac{\eta U}{K'} + \frac{F\rho_f |U| U}{\sqrt{K'}} \quad (8)$$

From this relationship, we can observe that the greater the air stream velocity is and the smaller the permeability is, the greater is the pressure drop across the powder bed when aerosolization

**Table 3**
Quality of powder blends.

| Blends | Average drug content (%) | CV (%) |
|---|---|---|
| Lactohale 200 + TBS | 1.44 | 3.05 |
| Inhalac 230 + TBS | 1.46 | 0.86 |
| Lactohale 200 without fines + TBS | 1.43 | 0.62 |
| Inhalac 230 without fines + TBS | 1.46 | 0.58 |
| Lactohale 200 + FP | 2.47 | 2.17 |
| Inhalac 230 + FP | 2.43 | 3.87 |
| Lactohale 200 without fines + FP | 2.42 | 2.06 |
| Inhalac without fines + FP | 2.45 | 3.39 |

CV: coefficient of variation.

**Table 4**
Air flow time and fine particle fraction (FPF) of terbutaline sulphate (TBS) blends (mean ± SD).

| Blends | Air flow time (s) | FFP (%) |
|---|---|---|
| Lactohale 200 + TBS | 5.95 (± 0.42) | 46.02 (± 2.77) |
| Inhalac 230 + TBS | 3.20 (± 3.20) | 30.63 (± 2.26) |
| Lactohale 200 without fines + TBS | 2.72 (± 0.09) | 26.60 (± 1.28) |
| Inhalac 230 without fines + TBS | 2.44 (± 0.10) | 23.43 (± 0.95) |

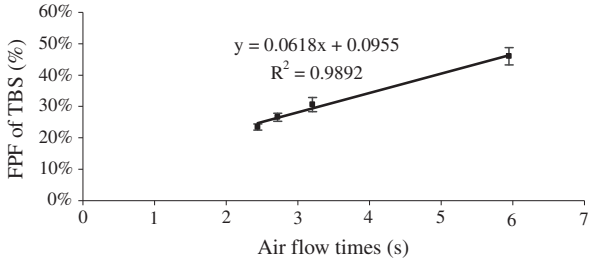



**Fig. 3.** Fine particle fraction of terbutaline sulphate vs. air flow time (mean ± SD, $n$ = 3).

**Table 5**
Air flow time and fine particle fraction (FPF) of fluticasone propionate mixtures (mean ± SD).

| Blends | Air flow time (s) | FFP (%) |
|---|---|---|
| Lactohale 200 + FP | 9.37 (± 0.48) | 25.25 (± 3.70) |
| Inhalac 230 + FP | 4.36 (± 0.09) | 11.02 (± 0.99) |
| Lactohale 200 without fines + FP | 3.38 (± 0.10) | 9.41 (± 2.78) |
| Inhalac without fines + FP | 2.89 (± 0.08) | 7.34 (± 0.19) |

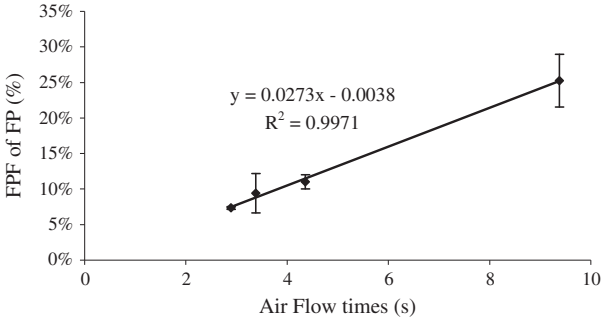



**Fig. 4.** Fine particle fractions of fluticasone propionate vs. air flow time (mean ± SD, $n$ = 3).

**Table 6**
Characteristics of the 0.5% w/w magnesium stearate/2.5% w/w FP/Lactohale 200 blend.

| | Mean | SD |
|---|---|---|
| Drug content (%) | 2.05 | 13.55 |
| Air flow times (s) | 17.24 | 1.13 |
| FPF (%) | 50.28 | 2.46 |

occurs. The increase in the pressure drop gives rise to a bigger aerodynamic drag force that can be exerted upon the powder. As a consequence, when the flow rate increases and the air permeability of powder bed decreases, the aerodynamic dispersion of a DPI powder is improved.

Further studies on permeability of powder beds can give a deeper understanding of powder structure. The Kozeny–Carman equation was established as a formula for interpreting the data from permeability measurements [16].

$$U = \frac{\varepsilon^3}{(1-\varepsilon)^2}\frac{\Delta P}{B\eta L S_w^2 \rho^2} \tag{9}$$

where $\varepsilon$ is the porosity of powder bed, $S_w^2$ is surface area per unit weight of the powder, $\rho$ is the density of powder and $B$ is the constant, taken the aspect factor.

By the rearrangement of the (3) and (9), the powder permeability can be expressed as follows:

$$K' = \frac{\varepsilon^3}{(1-\varepsilon)^2 B S_w^2 \rho^2} \tag{10}$$

Thus, the powder permeability depends on bed porosity, density of powder and surface area of powder, which depends on particle size.

This equation could explain the relationship between the carrier size and aerodynamic performance of DPI formulations. The smaller the particle size of the carrier, the larger the surface area is. That produces a more air resistant powder bed and greater pressure differential across the powder bed when aerosolized. This supports the fact that the FPF increased with decreasing carrier size as observed in previous papers [20–22]. However, finer particles can produce agglomerates that decrease the real surface area of the powder exposed to the air stream. This hypothesis was consistent with previous findings where FPF increased with increasing percentage of added fine lactose but further additions of fine lactose greater than a threshold, decreased FPF [21].

This finding leads to an interesting approach to improve the aerodynamic dispersion of DPI formulations based on powder structure. Higher density, non-agglomerate and easy packing carriers could be used to produce a more air resistant powder bed.

In this case, we can say that the relationship between air permeability of powder bed and aerodynamic dispersion depends on drug properties. In the case of terbutaline sulphate, a small resistance to air flow of the powder bed can result in a good *in vitro* DPI performance, i.e., air flow time of 5.95 s of mixture Lactohale 200 – TBS can give a FPF of 46.02%. However, a longer air flow time of FP mixture with magnesium stearate, 17.24 s is required to give a similar FPF of drug, e.g. 50.28%. More research is needed to relate the drug properties and its aerosolization.

This novel method provides a potential tool for Dry Powder Inhaler formulation development work. Here, permeability measurements are used in order to investigate the influence of ternary component on *in vitro* DPI performance.

## 5. Conclusion

In this study, we found a good linear correlation between a bulk property of powder – air permeability of powder bed – and the fine particle fraction of drug. An increase in the *in vitro* Dry Powder Inhaler performance is noted with an increase in air flow time through the powder bed. An explanation of this finding is that the force induced by air flow through a packed bed is linked to the latter's air resistance. The powder structure also plays an important role in the interaction between air flow and the powder bed. Air permeability reflects the quantity of the free particle fraction in the interparticular spaces of powder bed that leads to fine particle fraction during fluidization in air flow. More fundamental research is needed to elucidate the aerodynamic dispersion of powder, linking it with their bulk properties. The permeability technique provides a potential tool for screening Dry Powder Inhaler formulations at the development stage.

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