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**Review Article**

# Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers

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## Abstract

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States with a significant economic burden related to hospital admissions for exacerbations. One of the primary treatment modalities for COPD is medications delivered through breath-actuated dry powdered inhalers (DPIs). For users to successfully receive inhaled medication, they must inhale with enough flow to overcome the internal resistance of the device, leading to deaggregation of the medication powder. Peak inspiratory flow rate (PIFR) is the maximal flow rate obtained during an inspiratory maneuver. PIFR measurement can be impacted by the internal resistance of the device, which varies with device design. Many devices require a PIFR >60 L/min for adequate medication dispersal, while others appear to have adequate drug deaggregation with a PIFR >30 L/min. Studies have shown PIFRs are reduced among females and decrease with age, without a clear correlation between forced expiratory volume in 1 second and PIFR. PIFR can be reduced at the time of COPD exacerbation. Recent data suggest that reduced PIFR may be associated with worse COPD-related symptom burden, increased odds of COPD-related hospital readmissions, and improved responsiveness to nebulized therapy. This review article aims to examine the physiology and clinical correlations of PIFR, as well as review published studies related to PIFR with DPIs used to treat COPD.

**Keywords:** COPD, dry powder inhaler, peak inspiratory flow

## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common pulmonary diseases throughout the United States, with nearly 16 million Americans reporting a diagnosis in 2014.[1] COPD remains the third leading cause of death in the United States, with a significant economic burden due largely to hospital admissions for exacerbations.[2] One of the primary treatment modalities for COPD is medications delivered through dry powdered inhalers (DPIs). As of 2014, DPIs made up 60% of the $39 billion worldwide market of inhaled medications.[3] The availability of these devices has been increasing in the last decade, with over 10 now available in the United States.

DPIs are breath-actuated devices. For users to successfully receive a dose, they must inhale with enough flow to overcome the internal resistance of the device, leading to deaggregation of the medication powder.[4] The internal resistance varies with device design, and subsequently the flow required to overcome the internal resistance also varies. Peak inspiratory flow rate (PIFR) is the maximal flow rate, typically expressed in liters/minute, obtained during an inspiratory maneuver. PIFR measurement can be impacted by the internal resistance of the device. For a lower resistance device, a given pressure gradient will produce a higher PIFR than in a higher resistance device.[4–6] This review article aims to examine the physiology and clinical correlations of PIFR, as well as review published studies related to PIFR with DPIs used to treat COPD.

### *Pharmacologic treatment options for COPD*

While pharmacologic therapy for COPD has not been shown to slow decline in lung function over time, maintenance inhalers can reduce exacerbation frequency as well

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as improve symptoms and exercise tolerance.[7] Three pharmacological classes, bronchodilators, antimuscarinic agents, and corticosteroids, can be administered via nebulizers, pressured metered dose inhalers (pMDIs), mist inhalers, or DPIs.[8] There is no clear evidence that one mode of delivery is superior to the other[9,10]; however, each has its advantages and disadvantages.

Nebulized medications are more commonly used in the inpatient setting and require the least patient participation and synchrony. These agents are the easiest to deliver in patients unable to follow commands, patients with significant hand arthritis, and those with uncontrolled dyspnea.[11] However, nebulizers present many barriers, including increased time of administration, need for cleaning after each use, reduced portability, and inavailability of nebulized formulations of long-acting muscarinic antagonists.[11,12] Additionally, differing medication formulations and nebulizer performance contribute to variability in drug delivery and can lead to significant wasting of drug.[11] Newer devices, such as vibrating mesh nebulizers and dosimetric nebulizers, are more efficient and portable than the traditional pneumatic jet nebulizers, but may be limited by increased costs.[12]

pMDIs are portable, rapid in administration, and have reproducible drug doses.[12] However, these require the most patient coordination, with hand–breath synchronization for appropriately timed actuation and inhalation. These limitations can be decreased with the appropriate use of a reservoir device (spacer). High rates of erroneous pMDI use continue to be observed from inappropriate rapid inhalation rates, improper priming, and incorrect dosing.[11–13] Additionally, spacers do not mitigate technical difficulties in those with significant arthritis of the hands.

Mist inhalers are a form of handheld nebulizer in which a metered dose of nebulized medication is delivered at a low velocity.[11] Similar to pMDIs, these are trigger actuated, but require less patient coordination due to slower delivery. While mist inhalers have greater portability and shorter administration time than traditional nebulizers, there is still variability in drug delivery and actuation requires intact patient cognition, participation, and dexterity.

The primary benefit of DPIs, when compared with pMDIs and mist inhalers, is medication delivery through breath actuation, therefore decreasing issues related to patient synchrony. DPIs are also faster to use and more portable when compared with nebulizer therapy. Nevertheless, the wide variety of DPIs, each with unique mechanics, leads to frequent device-dependent technical errors (e.g., exhaling into device, holding device incorrectly, etc.). Additionally, optimal flow is required to actuate the device as well as properly deliver the medication.[12,14]

### *Peak inspiratory flow rate*

The PIFR is the maximal flow generated during a forced inspiratory maneuver. It is regularly measured without resistance during standard pulmonary function testing. When inhaling through a DPI, high internal resistance impacts the PIFR generated and needed for drug dispersion.[4,6] During an inspiratory maneuver, PIFR is not reached until after drug release, making acceleration and duration of inhalation as important as the peak value for drug delivery.[15,16] There is a significant correlation between the acceleration of the inhalation profile and the PIFR, indicating that PIFR is a good marker for acceleration during the inhalation profile.[17] As flow is a metric proportional to pressure differentials, the PIFR is directly related to the pressure difference generated during inhalation.[18] Maximal inspiratory pressure, also measured during spirometry, has also been shown to correlate with PIFR.[18,19] PIFR serves as a good surrogate for acceleration and maximal inspiratory flow pressure, but has the advantage of ease of measurement.

### *Device Resistance Profiles of DPIs*

To actuate most DPIs, a minimal flow of 30 L/min is required. Sufficient flow is also required to appropriately deaggregate the dose into fine particles, allowing for inhalation. *In vitro* testing of various drugs has demonstrated that higher flow rates generate smaller particle sizes, thereby allowing for better drug deposition within the lung.[5,16,20,21] Importantly, turbulent energy required for deaggregation is a product of the inhaler's resistance and subsequent flow generated.[6,22] Thus, high resistance devices may require lower PIFRs for deaggregation.[6]

Deaggregation is also determined by the resistance of the DPI, potentially leading to more consistent dose emission.[22] Achieving goal PIFR in a high resistance DPI can lead to more consistent drug delivery.[5,22] Inhaled agents can have different dose–response curves and the approved dosages can vary along that dose–response curve. The clinical impact of reduced drug deposition associated with low PIFR will be more substantial for drugs with steep dose–response curves or those approved at the lower end of the curve.

### *Optimal flow rates by device*

The minimum and optimal PIFRs for DPIs vary by device. The following section highlights the key publications regarding PIFRs for specific devices when measured with specific device resistance (Table 1).

Turbuhaler®/Flexhaler® (US): *In vitro* studies comparing drug delivery through the Turbuhaler® have shown increased variability at lower flow rates.[5,23,24] In one study, drug delivery at flow rates of 60 L/min was 88%

Table 1. Minimal and Optimal Peak Inspiratory Flow Rates (L/min) for Dry Powder Inhalers

| *Device* | *Minimal* | *Optimal* |
|---|---|---|
| Turbuhaler®/Flexhaler® | 30 | 60 |
| Easyhaler® | 30 | 30 |
| Diskus® | 30 | 60 |
| HandiHaler® | 20 | 30 |
| Ellipta® | 30 | 60 |
| Aerolizer® | 40 | 65 |
| Genuair® | 40 | 45 |
| Breezhaler® | 50 | 50 |
| Spiromax® | 40 | 40 |
| Novolizer® | 35 | 50 |
| NEXThaler® | 35 | 35 |

See article for inhaler references.

(SD 19%), compared with 72% (SD 19%) at 30 L/min.[5] A small *in vivo* study with 10 participants showed similar differences, with 27% drug deposition at faster flow rates (60 L/min) compared with 15% deposition at slower flow rates (35 L/min).[25] Studies since then have defined optimal PIFR as >60 L/min, however no clinical correlation has been observed.[26–28] Given the limited clinical correlation, we recommend a minimal PIFR of 30 L/min and optimal PIFR of 60 L/min. It should be noted that a PIFR of 30 L/min, while described as minimum flow, is likely not fully sufficient given the sharp drop-off of drug delivery observed in the range of 30 L/min to 60 L/min.[29]

Easyhaler®: *In vivo* studies have shown that drug delivery through the Easyhaler,® a high resistance device, is consistent across various resistance profiles with an SD of only 4.5%.[5] Given less variability in drug delivery, recommended minimal and optimal flow rates are 30 L/min.

Diskus®: Drug delivery across the Diskus® resistance has been shown to be 92% (SD 9%) at higher flows of 60–90 L/min compared with 76% (SD 12%) at flow rates of 30 L/min.[5] While a separate study did not show significant differences in drug delivery, differences in fine particle fraction delivery were observed, with 21% at 60 L/min and 16% at 28.3 L/min.[24] More recently, an *in vivo* study showed higher serum peak levels of inhaled salbutamol in those with PIFR >60 L/min, suggesting that this increase in fine particle fraction delivery may contribute to better drug delivery.[30] Given these discrepancies, while 30 L/min is the minimal flow required for Diskus®, we recommend defining optimal PIFR as >60 L/min.

HandiHaler®: Few studies currently exist regarding the optimal flow for HandiHaler®. As shown through *in vitro* testing, the drug delivery occurs at flow rates as low as 20 L/min. However, the fine particle dose delivery is decreased at flows <28.3 L/min. Therefore, 30 L/min is most commonly considered the optimal flow rate for HandiHaler® use.[31]

Ellipta®: The Ellipta® inhaler has been designed to have a similar resistance profile to the Diskus®, with few studies characterizing drug delivery across PIFR with Ellipta.®[32] One study did evaluate the *in vitro* drug delivery of four different drug formulations with the Ellipta® inhaler. Across the range of flow rates from 30 to 90 L/min, delivered dose ranged from 71% to 97% depending upon the drug. At 60 L/min, the mean delivered dose ranged from 81% to 94%.[33] Dose delivery did increase with increasing PIFR. Given the minimal change of drug delivery from 60 to 90 L/min, as well as the limited data available, we would recommend 60 L/min for optimal flow.

Aerolizer®: The Aerolizer® is an older single-dose capsule DPI. This device has been studied across flows of 28.3 to 120 L/min. Deaggregation is not sufficient at 28.3 L/min and the fine particle fraction delivery is optimized at flows >40 L/min, with the highest fraction occurring at 80 L/min.[34] One study showed maximum dose delivery at flows of 60 L/min (when compared with 28.3, 40, and 80 L/min), with another showing delivery plateauing at a flow of 65 L/min.[34,35] Given the increase in fine particle fraction delivery seen at this threshold of 65 L/min, optimum flow has been defined as 65 L/min and minimum flow as 40 L/min for the Aerolizer®.[27,35]

Genuair®: The Genuair® inhaler has an acoustic trigger for medication delivery that is not activated until the flow reaches a minimal threshold.[27] *In vitro* data have shown constant fine particle dose delivery with flows between 45 and 90 L/min. Optimal flow has been defined as 45 L/min.[36,37]

Breezhaler®: The Breezhaler® DPI has been studied across flows of 50–100 L/min with one study showing consistent drug delivery within 15% of target dose, as well as consistent fine particle mass, at all flow rates >50 L/min.[38] Given these limited data, 50 L/min for both minimal and optimal flow is recommended.[27]

Spiromax®: The Spiromax® inhaler has been studied *in vitro* at flow rates of 40, 60, and 90 L/min. There was a statistically significant increase in dose delivered with each increase of flow; however, all values were within 15% of the labeled dose.[39] Given that 30 L/min has not been studied and the clinical significance of the 15% variability of dose delivery is not yet established, we recommend a minimum and optimal flow of 40 L/min.

Novolizer®: The Novolizer® inhaler has an acoustic trigger indicating actuation at 35 L/min; it is unclear how much drug is delivered below this threshold. Studies have shown increasing drug deposition with increasing flow, which plateaus with PIFR >54 L/min.[40] Optimal PIFR has been defined at 50 L/min.[27,41]

NEXThaler®: The NEXThaler® is a medium resistance device with a breath-activated mechanism that allows drug release only after a threshold flow >35 L/min is reached.[28,42] *In vitro* studies showed no significant difference in drug delivery between flows ranging 30–90 L/min, therefore both minimal and optimal PIFRs are 35 L/min.[27,28]

### *Measurement of peak inspiratory flow rate*

PIFR is measured without resistance during standard spirometry. Various studies have tried to correlate spirometric PIFR measurements with PIFR measured with DPI-imposed resistances. A 1999 study measuring PIFR through a portable spirometer attached to an empty Turbuhaler® DPI observed a weak correlation between PIFRs from standard spirometry compared with those obtained through a spirometer with Turbuhaler® attachment ($r = 0.35$).[43] The correlation was not strong enough to predict the PIFR through the Turbuhaler.®

Seheult et al. found a moderate correlation between spirometric PIFR without resistance compared with Diskus® PIFR.[44] In this study, 85 participants with asthma, COPD, neuromuscular disease, and other nonrespiratory conditions had standard spirometry collected, in addition to PIFR measurements through a pneumotachograph connected to the Diskus® inhaler. All participants with a spirometric PIFR above 196 L/min had a Diskus® PIFR >30 L/min (the minimal flow needed for Diskus®). Other studies have also attached DPIs to spirometry to replicate PIFR measurements against DPI resistance; however, no reliable spirometric predictor of DPI PIFR has been established.[32]

Due to the cumbersome nature of obtaining these measurements and the lack of consistent correlation between

spirometry and device PIFRs, alternative methods have been developed to measure PIFR. The vitalograph Aerosol Inhalation Monitor™ is a battery-powered patient training device that assesses a user's inhalation rate, inhalation time, and breath-hold time using a DPI or MDI simulator.[45] After each inhalation, the device reports if the measured three variables are either optimal or suboptimal. Many publications have used the In-Check™ Dial (Alliance Tech Medical, Granbury, TX) to measure PIFR against various resistances.[20,26,46–49] The In-Check™ Dial is a handheld, low-range inspiratory flow device that measures PIFR through a brief inspiratory maneuver. The device includes adapters that mimic the resistance of the DPIs currently available in the marketplace. The In-Check™ Dial is calibrated using an ATS waveform generator, with a reported accuracy rate of 10% or 10 L/min.[50]

Broders et al. correlated In-Check™ Dial measurements of the Diskus® and Turbuhaler® against an inhalation profile recorder that converts pressure profiles into flow profiles. Among 45 patients, they found a difference of 3.9 L/min for the Diskus® ($p = 0.03$) and 3.5 L/min for the Turbuhaler® ($p = 0.056$) between the In-Check™ Dial and flow profile recorder, with two participants being classified incorrectly as optimal on the In-Check™ Turbuhaler® resistance.[51] In patients with stable COPD, PIFRs appear to be reproducible; one study showed that there was no significant difference in measurements obtained through the In-Check™ Dial between visits occurring $317 \pm 225$ days later.[20]

### *Factors that affect PIFR*

Many demographics have been correlated with PIFRs, with increasing age[19,20,22,44,47–49] and female gender[20,22,26,48] being the predominant two factors consistently shown to correlate with decreasing flow. Jansenn et al. measured PIFRs of different resistances in older males (70–87 years old), 14 of whom did not have COPD. PIFR was significantly lower with increasing resistance and age ($r = -0.5$; $p < 0.005$), regardless of the presence of COPD. While studies have found correlations with various spirometric data, maximal inspiratory pressure consistently correlates with PIFR.[19,26,52] There is a lack of consistent correlation between PIFR (measured against resistance) and both FEV1 and FEV1% predicted, reinforcing the notion that inhaler selection should not be based on FEV1 alone.[19,20,22,26,47]

In one of the few studies to include patients with severe COPD, Prime et al. observed a statistically significant correlation between FEV1 and PIFR through the resistance of an Ellipta® inhaler ($r = 0.73, p < 0.0001$).[32] While PIFR and FEV1 are not correlated across the spectrum of lung function, these findings suggest that in severe airflow obstruction (FEV1 < 30% predicted), PIFR is consistently reduced likely due to air trapping. Reduced vital capacity is also correlated with reduced PIFR in multiple studies, suggesting that other factors beyond airflow obstruction (i.e., respiratory muscle insufficiency, air trapping, or hyperinflation) may be good predictors of low PIFR.[19,20,26] Last, as detailed below, exacerbations of COPD have shown to decrease PIFR during the acute phase.

### *PIFRs during AECOPD*

Acute exacerbations of COPD (AECOPD) are associated with alterations in PIFR. In 2003, van der Palen measured PIFRs against resistance of the Diskus® and Turbuhaler® on 50 patients with asthma and COPD with or without exacerbation. They found that 50% of those participants with an active asthma or COPD exacerbation were unable to generate optimal flow (defined as PIFR >60 L/min) through the higher resistance of the Turbuhaler®, compared with 5% of those without an exacerbation ($p < 0.004$).[26] All patients were able to reach the optimal flow rate for the Diskus® (defined as PIFR >30 L/min).[26] More recently, a retrospective study done by Loh et al. measured PIFR measured without resistance in 123 patients admitted with an acute exacerbation of COPD. PIFRs were obtained on all patients at least once during their hospital course. Suboptimal PIFR (defined as PIFR <60 L/min) was present in 52% of participants during COPD exacerbation.[47] There was no difference in median PIFRs regardless of the day of evaluation, suggesting that PIFRs do not vary substantially in the acute exacerbation time frame.[47]

A study with 15 participants (10 with COPD) characterized PIFRs during days 1–9 of an inpatient exacerbation and compared these measures with those taken during stable respiratory status at day 50. PIFR was measured with four different resistance profiles: pMDI, pMDI with spacer, Diskus®, and Turbuhaler.®[52] During day 1 of an exacerbation, PIFRs were significantly lower with Diskus® and Turbuhaler® compared with day 5 and day 50 PIFRs ($p < 0.05$). There was no statistical difference between PIFR measured on day 5 of exacerbation versus day 50 for Diskus® or Turbuhaler®. All patients were able to reach goal PIFR on the Diskus® (defined as >30 L/min) at all study time points, but there was a statistically significant improvement of PIFR on follow-up day 50 compared with day 1 (101 L/min vs. 86 L/min, $p < 0.05$).

All patients were able to generate minimal PIFR (>30 L/min) for Turbuhaler,® but only 60% were able to generate optimal PIFR (>60 L/min) during the exacerbation (days 1–9). Mean PIFR through the Turbuhaler® improved from 59 L/min on day 1 to 72 L/min on day 50 ($p < 0.05$). There was no change in the prevalence of optimal PIFR measured during exacerbation compared with the stable phase (60% vs. 64%). While this study is limited by small sample size and inclusion of both asthma and COPD patients, it is the only study to date that has directly compared PIFRs during exacerbation with stable state in a cohort of patients.

Given the reduction of PIFR during COPD exacerbations, as well as the high prevalence of suboptimal PIFR during hospitalization, consideration can be given to transitioning to non-DPI therapies (i.e., nebulizers) during and after exacerbations. In the study by Loh et al., patients with suboptimal PIFR who were discharged on nebulizers had significantly lower rates of COPD readmission when compared with those discharged on DPIs (22.7% and 50%, respectively, $p = 0.005$).[47]

A recent prospective study enrolled participants admitted with COPD exacerbation and measured PIFRs against Diskus® resistance on the day of discharge and found that 31.7% of patients had a low PIFR (<60 L/min) on the day of discharge.[48] Those with low PIFR were older (66.2 vs. 62.1 years old, $p = 0.006$) and more likely to be female (61.2%, $p = 0.014$). When compared with the optimal PIFR groups, ischemic heart disease (14.1% vs. 3.5%, $p = 0.015$) and pneumonia (38.8% vs. 22.4%. $p = 0.02$) were more common in the low PIFR group. While there were differences between groups in medication prescription at discharge (increased DPI

prescriptions in the low PIFR group and more nebulizers in the high PIFR group), there were no differences in readmission rates. Given that PIFR decreases during acute exacerbations of COPD, prescribers should be cognizant that a PIFR measured during stable disease may not be reflective of PIFR during acute exacerbations. It may not be appropriate to prescribe DPIs in the situation where patients are able to only achieve the minimal optimal PIFR while stable, as PIFR may be insufficient during AECOPD (acute exacerbations of COPD).

### *PIFR and COPD outcomes*

The clinical significance of patients not achieving their target PIFR has not yet been fully elucidated. Limited data currently exist on this topic. A small study defining suboptimal PIFR across Diskus® resistance as <60 L/min found that patients with suboptimal PIFRs had significantly higher spirometric volume changes with beta agonists given through nebulizer versus DPI inhalation [forced vital capacity (FVC) change at 2 hours: 268 vs. 164 mL, respectively; $p = 0.02$].[53] While this study included only 20 patients, it helps to highlight the possible benefits of using PIFR to determine optimal drug delivery and identify patients who may not be good candidates for DPIs.

Loh et al.'s is the first study to show that suboptimal PIFR (defined as <60 L/min without resistance) had significant clinical outcomes.[47] Of the 123 patients enrolled, 64 were suboptimal on the day of discharge. When compared with the optimal group, the suboptimal group had fewer days to both all-cause admission (65.5 vs. 101 days, $p = 0.009$) and COPD readmission (63.5 vs. 144 days, $p = 0.002$).[47] In the study analysis, PIFR was the only significant variable associated with readmission. Suboptimal PIFR could lead to decreased lung deposition and higher oropharyngeal deposition. While the degree of oropharyngeal deposition has not yet been studied, the adverse effects of oropharyngeal deposition, most importantly thrush with corticosteroids, are well known.

When examining symptom burden, Sharma et al. did not detect a difference in scores on the modified Medical Research Council score nor the COPD Assessment Test (CAT) scores in those with a low PIFR (<60 L/min against the Diskus® resistance).[48] Loh et al., however, showed significantly higher CAT scores in the suboptimal group when compared with those with PIFR >60 L/min without resistance (29.1 vs. 25.3, $p = 0.0073$).[47] These data suggest that patients with low PIFR may be more symptomatic; however, this information is limited to two studies and currently only available for those admitted with exacerbations. Given that these patients are all admitted with AECOPD, the higher symptom scores seen in the Loh et al. study may be more related to their disease process, and PIFR may merely be a marker of exacerbation severity.

## Conclusions

At this time, there is limited guidance on prescribing devices,[12] and much of the selection process is based on insurance constraints and prescriber familiarity. PIFRs can be easily measured in a clinical setting and may be a useful tool when selecting an inhaler device for patients.[14,54] PIFR is an important metric in patients with obstructive lung disease, with suboptimal values frequently under-recognized in COPD patients who are prescribed DPIs. Further research is still necessary to determine predictors for suboptimal PIFR, which may be a valuable tool to identify patients who will not benefit from DPIs. Ultimately, PIFR measurement may help providers personalize DPI selection based on patient physiology as well as predict those at highest risk for increased healthcare utilization.

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