Advancing Inhaler Performance Through Airflow Management

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Summary:

Design of pressurized metered dose inhalers (pMDIs) has typically overlooked inhalation airflow management, a potentially useful parameter for enhancing aerosol performance. MAP Pharmaceuticals' Tempo® inhaler, a next-generation breath synchronous pMDI platform, is based upon an innovative air flow control chamber that seeks to decelerate the aerosol spray and to promote a continuous reduction in propellant droplet size through evaporation. The internal flow profile and its effect on spray properties and deposition in the Tempo inhaler was simulated using Computational Fluid Dynamics (CFD). The simulations showed that diverting a fraction of the inhalation airflow and redirecting it towards the spray (in an axially counter-current direction) decreased the spray velocity from 50 m/s at the nozzle down to 5 m/s at the mouthpiece. Experimental characterization using Andersen Cascade Impaction (ACI) showed USP throat deposition for the Tempo inhaler to be just 9% of the metered dose, a significant improvement over the standard pMDI which showed 24% of the metered dose deposited in USP throat.

Introduction:

Pressurized metered dose inhalers (pMDI) are one of the most widely used aerosol drug delivery platforms, primarily due to compactness , convenience and low cost. A conventional pMDI device consists of a one-piece plastic actuator that comprises an atomizing nozzle, a holder for the drug canister and a mouthpiece. Actuator designs have typically overlooked inhalation airflow management, a potentially useful parameter for enhancing aerosol performance. Few commercial attempts have been made to harness inhalation airflow to enable deceleration of pMDI sprays. For instance, the Spacehaler [1] and Vortex Nozzle Actuator [2] devices subjected airflow to gradual expansion along the mouthpiece to reduce its velocity, which in turn decelerated the spray. The Gentlehaler device was also shown to achieve a significant reduction in spray velocity through inventive airflow configurations, but the gain in overall delivery efficiency was marginal [3]. MAP Pharmaceuticals' Tempo® inhaler uses an innovative air flow control chamber (FCC) to decelerate the aerosol spray and to promote continuous propellant droplet size reduction through evaporation. The FCC in the Tempo inhaler (fig. 1) splits the inhalation airflow into 3 components: (1) an entraining component that enters the FCC through specially designed air inlets close to the spray orifice, (2) a cushioning component that enters the FCC through a porous element along the cylindrical wall, and (3) an impinging component that is directed at the spray in an axially-opposite direction. The entraining and cushioning airflow components help minimize the drug deposition within the inhaler, whereas the impinging airflow reduces the spray velocity. The design is highly tunable, as the relative strengths of the three flow components can be optimally balanced through geometry modifications to achieve desired performance. A comprehensive design optimization effort, involving both in vitro experimentation and CFD simulations, has presented some significant insights into the internal flow characteristics of the Tempo inhaler and revealed a path to further performance improvements. The objective of this work is to demonstrate, using the Tempo inhaler as an example, how aerosol performance of a pMDI can be optimized enhanced by managing inhalation airflow profiles within the inhaler.

Methods:

CFD Methodology:

Multi-physics CFD simulations coupling airflow with propellant flow, spray transport, heat transfer and evaporation were performed using the CFD-ACE+ software suite to evaluate the performance of the various configurations of the Tempo inhaler. Most simulations were performed using a steady 28.3 LPM inhalation flow. Spray at the nozzle orifice was assumed to have a Rosin-Rammler distribution with 15 µm Sauter mean diameter. Spray velocity at the orifice was set at 50 m/s (in equilibrium with the propellant flow), as confirmed through Particle Image Velocimetry (PIV) measurements with the Tempo inhaler nozzle. A 30° half-cone spray angle was used in the simulations. The porous spacer element within the Tempo inhaler was characterized using porosity (ratio of pore volume to total volume) and permeability (ratio of pore surface area to pore volume) of the medium, both determined experimentally. The particle deposition probability in the event of collision with internal device surfaces was assumed to be 100% for the porous spacer and 80% for all other plastic surfaces. HFA134a:HFA227 and HFA-134a:Ethanol propellant blends were simulated. In both cases, physical and thermodynamic properties of individual components were assumed to be additive and standard databases from the manufacturer were used. Airflow and spray evolution were simulated for each case.

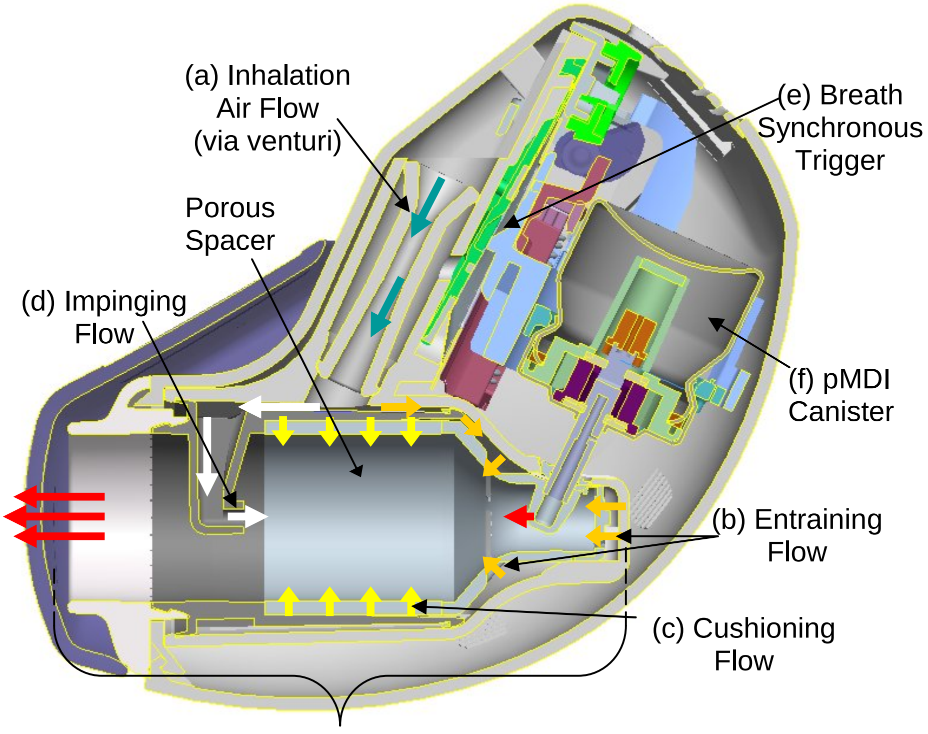


Figure 1: Tempo Inhaler schematic with generalized air flow paths. Inhalation air flow is routed via a venturi (a) into the FCC through entraining (b), cushioning (c) and impinging (d) flows. Air flow through the venturi creates a vacuum that pulls on a diaphragm coupled to a trigger (e). On trigger release, the pMDI canister (f) is actuated to release the aerosol plume

Experimental Methods:

Experimental testing used Tempo inhalers produced using validated manufacturing processes. Bespak actuators were used reference actuators without active airflow management. The pMDI canisters contained 0.5 mg/actuation drug suspension (engineered particles formulation, Dv_{50} =1.8µ) in a HFA134a:HFA227 propellant blend. Andersen Cascade Impactor (ACI) methodology, as described in USP <601>, was used to measure aerodynamic size distribution, as well as USP throat deposition. All testing was performed using at least 5 inhalers (2 determinations for each), at a steady airflow rate of 28.3 LPM. After testing, each inhaler was disassembled and components assayed to elucidate device deposition profiles. All test samples were analyzed using HPLC.

Results:

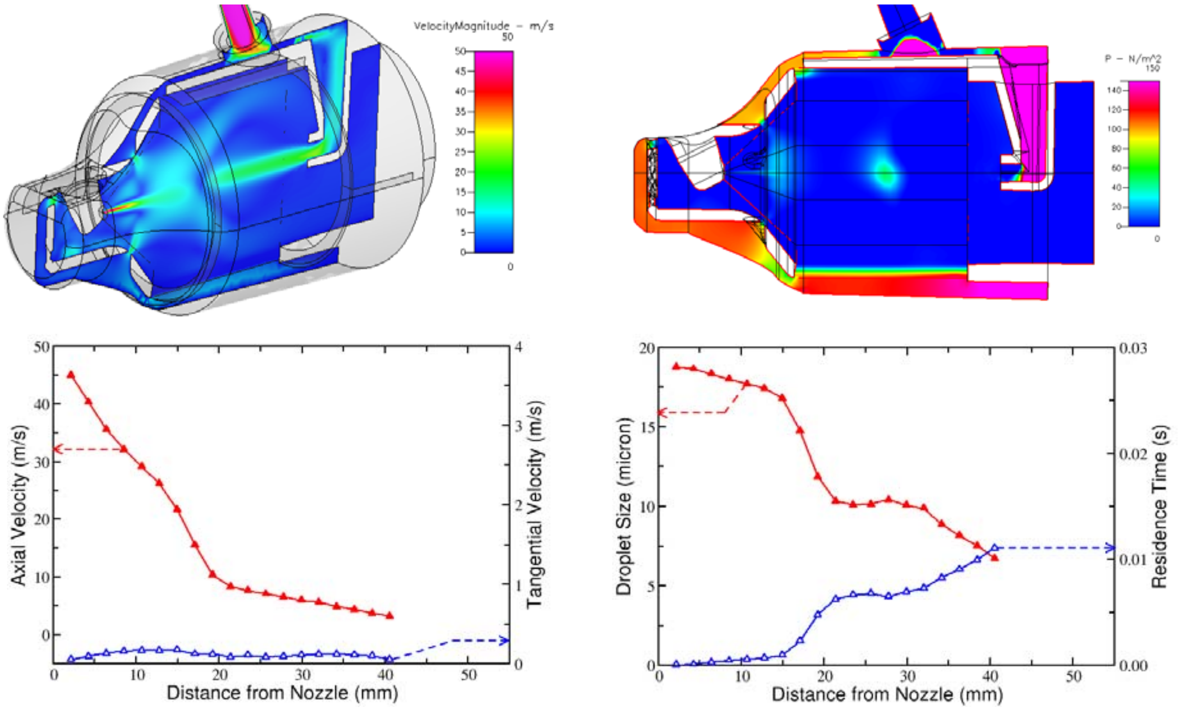
Figure 2a shows the simulated the airflow within the FCC of the Tempo inhaler. The flow velocities across the porous spacer were evenly distributed along the circumference, and were much less in magnitude compared to the impinging flow. The impinging airflow was axially-centered and impinged upon the spray in a head-on manner as desired. Figure 2b shows the static pressure distribution plot within the FCC. The collision point between the spray and the impinging flow, marked by the high-pressure zone at the center of the FCC, was almost equidistant from both the spray orifice and the impinging flow outlet. As a result, a rapid reduction in axial spray velocity, from 50 m/s at the spray orifice down to 5 m/s leaving the inhaler mouthpiece, was observed (fig 2c). The average residence time of the spray droplets increased noticeably around the collision point, indicating the droplets were slowed and veered around the impinging flow. A corresponding sharp drop in the average droplet size (fig 2d) was observed prior to the collision point between the spray and impinging airflow.

Figure 3 compares the results of ACI-based testing of the Tempo inhaler with that for the standard pMDI actuator. The device deposition for the Tempo inhaler was higher than the standard pMDI, likely resulting from larger surface area available for deposition. The Tempo inhaler was successful in reducing the throat deposition to just 1/3rd (44 ± 15 µg/act.) of that observed with the standard pMDI (120 ± 23 µg/act.). As a result, although the emitted dose for the Tempo inhaler was marginally lower (327 ± 28 µg/act.) than that for the standard pMDI (368 ± 39 µg/act.), the fine particle dose (<4.7µ) actually showed a modest but statistically significant increase over the standard pMDI (from 207

± 42 µg/act. to 241 ± 21 µg/act., p<0.004). The magnitude of difference was likely reduced due to use of the particle engineered formulation optimized to yield a high performance plume. The large reduction in throat deposition, to <10% of the metered dose, in Tempo inhaler was most likely achieved through a combination of a significant reduction in the spray momentum as well as preferential deposition of larger droplets within the device. The unique flow profiles in Tempo inhaler result in a softer plume with increased fine particle fraction.

Flow Field within the FCC, showing air flow (right) impinging on the aerosol spray (left)

(b) Pressure distribution within the FCC, showing high pressure zone (center) at “collision point”



(c) Decreasing axial & steady tangential spray velocity during transport through the Tempo Inhaler

(d) Droplet size reduction (through evaporation) & residence time progression through the Tempo Inhaler

Figure 2: CFD Simulation Results for the Tempo Inhaler

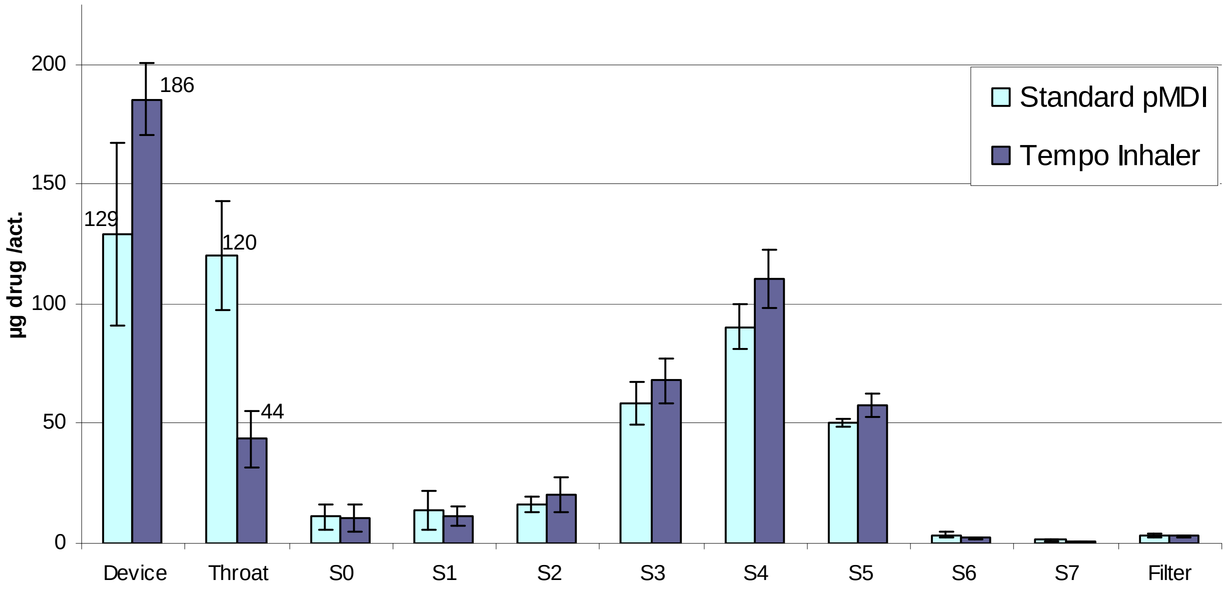
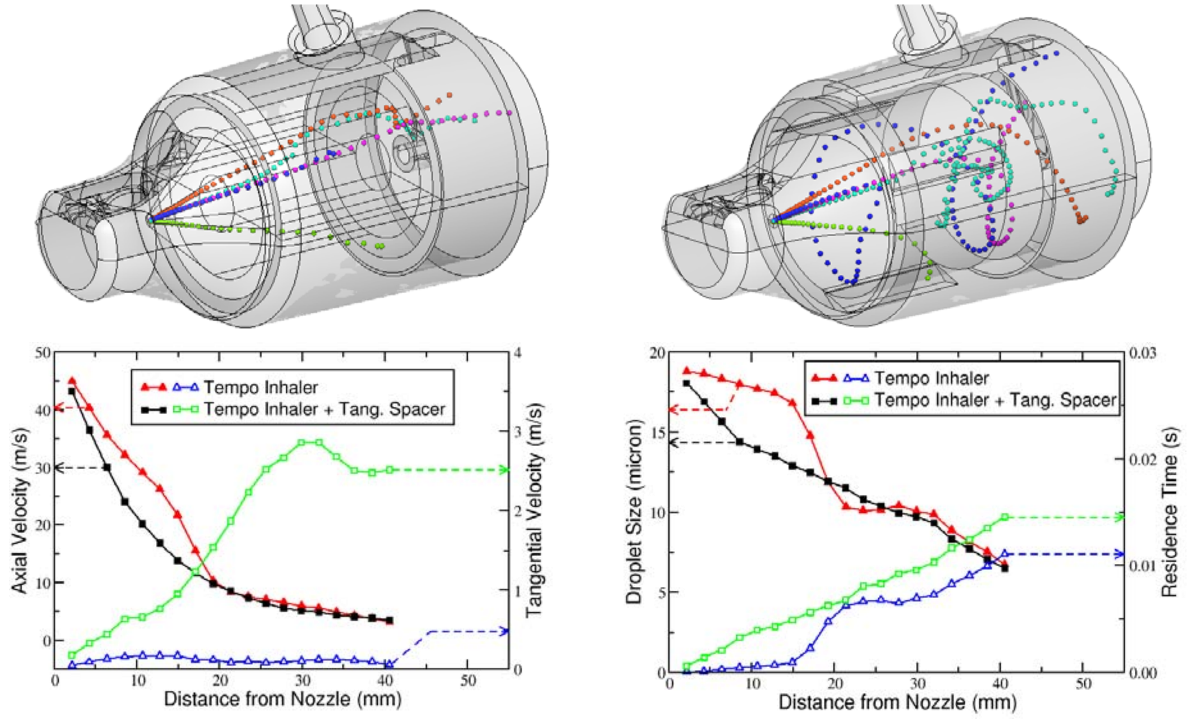


Figure 3: ACI Data showing markedly reduced throat deposition for the Tempo Inhaler relative to the standard pMDI

Ethanol, often used as a co-solvent in HFA-based pMDI formulations, reduces volatility of the resultant propellant blend. To effectively deliver such low volatility formulations and enhance versatility of the Tempo inhaler, recent optimization efforts were focused towards improving the vortexing motion of the droplets and thus enhancing their evaporation within the inhaler. One promising approach used a 'tangential flow spacer' instead of the porous spacer used in earlier Tempo inhaler versions. This spacer directs the airflow through the spacer in a tangential manner, thus promoting a vortical flow pattern inside the FCC. The number of air inlet slots and their length (as fraction of total spacer length) were used to modulate and understand the effects of tangential flow spacer design. CFD simulations on the Tempo inhaler containing the tangential flow spacer showed a slight misalignment between the spray and the impinging flow. Nevertheless, the tangential air flow generated by the spacer was found to be more effective in entraining the spray droplets by imparting significantly higher tangential velocities (Fig 4c), thereby leading to lower device deposition. Sample spray trajectories shown in Fig 4b clearly show the significant increase in vortical motion relative to that in standard Tempo inhaler (Fig 4a). The longer trajectories increased the average residence time for spray droplets, which in turn decreased droplet size (Fig. 4d) through evaporation. CFD predictions on the fate of droplets showed a modest decrease in device deposition and also a noticeable increase in evaporation when tangential spacer is used.

Tempo Configuration	Device Deposition (%)	Emitted Mass (%)	Evaporated Mass (%)
Tempo Inhaler	**49.0**	**15.2**	**35.8**
Tempo Inhaler + Tangential Spacer	**46.6**	**13.3**	**40.2**

Table 1: CFD Predictions on Fate of Spray Droplets for Two Tempo Inhaler configurations



(a) Sample Droplet Trajectories in Tempo Inhaler- relatively low vortical (tangential) flow

(b) Tempo Inhaler with Tangential Spacer significantly enhanced vortical (tangential) flow in droplets

(c) Similar decrease in axial velocity, but marked increase in tangential velocity when tangential spacer is used

(d) Droplet size reduction and residence time progression through the Tempo inhaler

Figure 4: CFD Predictions of Droplet Trajectories and Spray Properties in Tempo Inhaler Designs

Discussion:

The unique flow profiles within the Tempo inhaler reduce the spray momentum, as evidenced by CFD simulations as well as the low throat deposition observed in ACI-based testing. The 9% throat deposition shown by Tempo inhaler is significantly lower than that for conventional pMDIs (42 ± 2% throat deposition was recently reported for Proventil

HFA [4]). Apart from reducing oral thrush risks, reduced throat deposition is advantageous as it is reported to reduce variability in the lung deposition as well [5]. This, coupled with the breath synchronous trigger and a higher fine particle dose of the Tempo inhaler, is expected to enhance drug delivery efficiency as well as consistency. Based on the CFD results, further design improvements that impart vortical motion to spray droplets, while at the same time slowing them through the impinging flow action, may be possible. Additional in-vitro experimentation is underway to qualify these findings. Spray characterization within the inhaler through PIV or similar techniques is expected to enhance to the understanding of the flow profiles and assist in validating CFD models to enable further design improvements.

Conclusions:

The Tempo inhaler, with its markedly reduced spray velocity and breath-synchronous trigger, offers substantial improvements over conventional pMDIs, while retaining many of the core advantages of the pMDI platform. Using CFD modeling as a guide, this platform can be further improved for specific applications. Inhalation airflow can similarly be harnessed to improve aerosol performance in other inhaler platforms as well.

References:

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