

Optimization of Fluid Flow in pMDI Valves

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INTRODUCTION

In a pressurised metered dose inhaler (pMDI) the active pharmaceutical ingredient (API) is dissolved or suspended in hydrofluoroalkane (HFA) propellant and is dispensed by a valve that isolates and then delivers the dose. Therefore the valve is one of the most critical components in a pMDI. Most valves currently on the market pre-meter the dose immediately following delivery, retaining the dose until required. This approach can, however, lead to the phenomena known as Loss of Prime and Loss of Dose (LoP/LoD) when left for extended periods. To overcome this, patients are recommended to fire priming shots to waste if the inhaler has been unused for a set period of time. However, aside from being wasteful, many patients do not follow their instructions properly, and do not prime their inhalers as directed.

OPTIMIZING VALVE DESIGN FOR FLUID FLOW

One way of overcoming LoP/LoD issues is to design a valve that fills as the pMDI is operated. Assuming proper shaking of the pMDI prior to actuation, such an approach would result in a homogeneous dose, no matter how long the inhaler has been left unused. For this approach the formulation must flow in and out of the metering region freely and fast enough for the chamber to fill prior to shut off from the bulk formulation. Flow of formulation into the metering region after a dose has been dispensed is relatively easy, as it is driven by the pressure difference between the bulk formulation and the metering region. The challenge comes, however, in the situation where formulation may have migrated over time. For the patient to re-homogenize the next dose by shaking, substantial interchange of formulation between the metering region and the bulk formulation must be able to occur, without the benefit of a driving pressure difference. The effectiveness of a free flow pMDI valve thus relates to how well liquid can move in one direction through the valve's filling port at the same time as vapor moves in the other. The ease of liquid/vapor transfer can be related to the relative magnitude of gravitational and electromagnetic forces. For example, in a large filling port (consider the "hole" when a bucket of water is upturned), gravity dominates, liquid flows out and gas (air) flows in. For a small port (consider water in a capillary tube, closed at the top), electromagnetic forces (surface tension) dominate, and liquid and gas cannot readily be made to interchange.

Rayleigh-Taylor instability theory (1) is able to shed some light on the size of filling port required to ensure that gravity dominates and liquid flow occurs. The theory describes the interplay of opposing forces acting on the random fluctuations that will always form at any interface between two fluids of different densities. The equation

$$\text{Critical Wavelength}(\lambda_{\text{crit}}) = \sqrt{\frac{\sigma}{a(\rho_1 - \rho_2)}}$$

describes a critical wavelength related to the stability of the interface between a denser fluid and a less dense one below it. In this equation, σ represents surface tension, a represents acceleration (which will be g , the acceleration due to gravity, in the absence of shaking), ρ_1 represents the density of the upper fluid layer, and ρ_2 the density of the lower fluid layer. Surface tension will dominate for interfacial fluctuations on a scale below λ_{crit} , pulling the interface back towards planarity. The fluids will not be able to interchange or mix readily. Above this wavelength, gravity will dominate, and incipient instabilities will tend to grow when the denser fluid is above the less dense one. The size of the filling port opening of a free flow pMDI valve should thus be significantly above λ_{crit} to ensure the ready formation of fluctuations large enough to grow into liquid fingers, droplets and vapor bubbles. If the valve filling port opening is inadequate, it can be hard to ensure that surface tension will always be overcome and formulation flow assured.

Table 1.

Physical properties of HFAs at 20 °C. (Vapor densities at saturated vapor pressure. HFA 134a data from ²; HFA 227 data from ³; λ_{crit} calculated by authors.)

	Density (kg/m ³)		Surface Tension (N/m)	λ_{crit}
	Liquid	Vapor		
HFA 134a	1224	27.8	8.92x10 ⁻³	0.87 mm
HFA 227	1415	31.1	6.96x10 ⁻³	0.72 mm

The critical wavelength given by the above equation turns out to be on the order of 1 mm for HFA propellants, which is around the width of the free opening in pMDI valve filling ports (using the properties listed in Table 1). This means that the exact size (and shape) of the filling port design becomes critical to a valve's performance.

Although λ_{crit} represents the approximate balance point between forces, in practice the prospects for Rayleigh-Taylor instability growth do not change abruptly at this wavelength. Instead, there is a more gradual change as the filling port opening size increases in the range around λ_{crit} . The greater the amount by which the dimensions of a filling port opening exceeds λ_{crit} , the better the valve's filling is likely to be. For filling port openings closer to λ_{crit} , filling may be more dependent on the value of a (where vigorous shaking can increase the value of a to significantly more than 9.81 m/s², leading to liquid movement into or out of the metering chamber). In such cases, the dependence of flow behavior on acceleration is likely to make the valve excessively sensitive to patient handling.

THE 3M™ FACE SEAL VALVE

Empirical testing at 3M has shown that a filling port opening of around 1mm is realistically required in order to ensure free flow of liquid upon even the gentlest inversion of the valve. These observations were applied in the design of the 3M™ Face Seal Valve (Figure 1), a next generation valve in development at 3M Drug Delivery Systems. Its design thus ensures that metering of homogeneous doses is facilitated, with consequent benefit to the dose consistency data obtained, even with “difficult” suspension formulations.

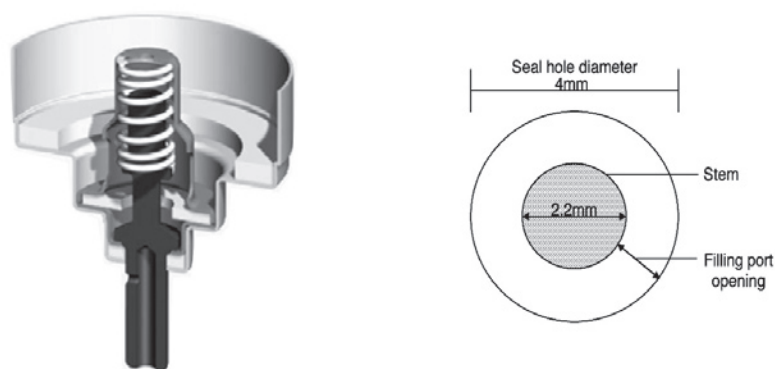


Figure 1. The 3M Face Seal Valve and filling port dimensions.

RESULTS

Figure 2 shows through life dose consistency from six 3M Face Seal Valves using an ethanol-free albuterol sulphate suspension formulation, a key performance factor that would be expected to be affected if fluid flow into the valve were to be impeded by a filling port opening of dimensions insufficiently larger than λ_{crit} . Results show excellent dose consistency through life with results within acceptance limits.

Figure 3 shows the doses of an ethanol-containing albuterol sulphate suspension formulation from five inhalers with 3M Face Seal Valves. For each inhaler, the first three shots were collected as normal, valve-down. Two shots were then fired valve-up, to ensure the metering chamber was empty, and the next three shots were then collected valve-down. Two more valve-up shots followed, and then three more valve-down. The doses from shots 6 and 11 from each valve thus represent doses from completely un-primed valves. The results demonstrate that fluid flow into this valve is adequately free to avoid Loss of Dose problems.

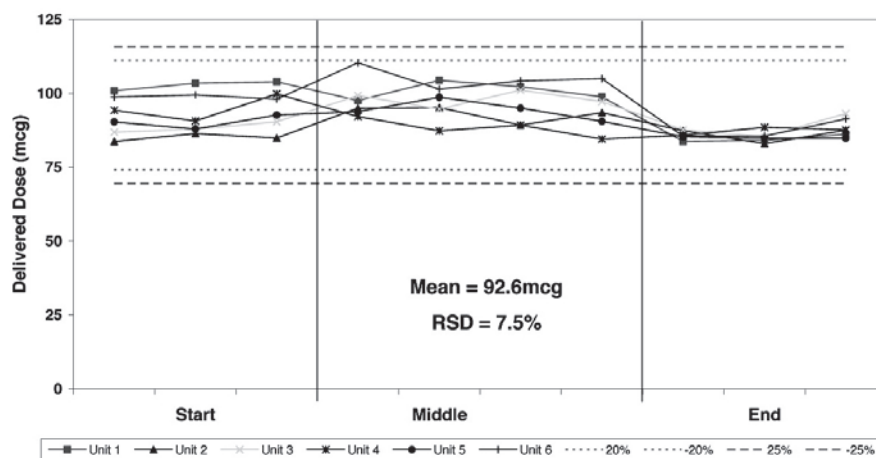


Figure 2. Through life dose consistency for the 3M Face Seal Valve, using a challenging ethanol-free albuterol sulphate suspension formulation.

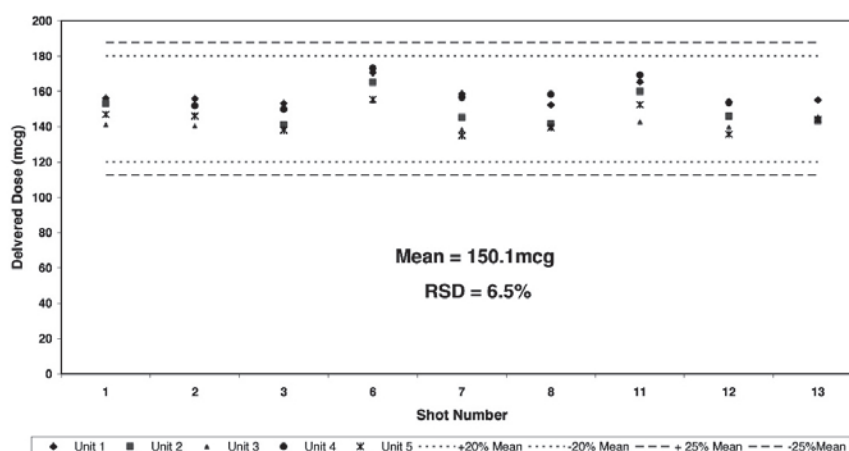


Figure 3. Effect of priming for the 3M Face Seal Valve.

CONCLUSION

The above data show that a valve designed around a metering chamber filling port opening with dimensions rather greater than the Rayleigh-Taylor critical wavelength can display good pharmaceutical performance and fast-fill fast-empty properties.

REFERENCES

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