Drug Development and Industrial Pharmacy, 34:90–94, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701484205

informa
healthcare

Comparative Measurements of Pressurised Metered Dose Inhaler (pMDI) Stem Displacement

Paul M. Young
Advanced Drug Delivery Group, Faculty of Pharmacy, University of Sydney, Australia

Robert Price
Pharmaceutical Technology Research Group, Department of Pharmacy, University of Bath, Bath, UK

A technique was developed to enable direct measurement of a pressurised metered dose inhaler actuation cycle. Three commercially available 250 μg.dose^{-1} beclomethasone diproprianate formulations were chosen for analysis; Becloforte (Glaxosmithkline, Sussex), Clenil Forte (Chiesi, Parma, Italy), and BDP-Modulite (Chiesi-Glaxosmithkline). The compression cycle of each device was analyzed and the point of drug actuation (force at which drug was released as an aerosol) was determined. Quantitative analysis of three devices from each product suggested no significant variation in inter-batch actuation force (ANOVA, $p < 0.05$) ($N = 3$). Interestingly, a significant variation between product type actuation force was observed (ANOVA, $p < 0.05$) ($N = 3$). Actuation forces ranged from 22.33 N ± 1.44 N for Becloforte to 31.12 N ± 2.73 N for Clenilforte. In general, such observations suggested a maximum difference of 8.7 N between the two extremes, equivalent to a 39% increase in force required to receive a dose.

Keywords pMDI; CFC; HFA; compression force

INTRODUCTION

Pressurized metered dose inhalers (pMDI) are the most popular delivery mechanisms for respiratory ailments (Rossand & Gabrio, 1999) and have been marketed to the public as a medicament since the mid 1950's. In simple terms, pMDIs operate by rapidly aerosolizing a micronized particulate suspension or solution using a pressurized (super-cooled) liquid propellant. Upon actuation, a metered volume of the suspension or solution is exposed to atmospheric pressure, and rapidly expands through the valve and actuator orifice to produce a vaporized drug system (Dunbar, Watkins, & Miller, 1997).

There are many formulation routes to develop such a system, which will be dependent on many factors including company strategy (i.e., solution or suspension and specific patent issues), drug type, valve types, and dose. Furthermore the specific formulation has become more diverse due to the switch from chlorofluorocarbon (CFC) propellants to hydrofluoroalkane (HFA) propellants, following the Montreal protocol in 1989.

Such formulation variables may ultimately lead to variation in patient compliance, when switching between devices. Inter-patient variation has been reported in previous studies (Chapman, Love, Brubaker, 1993; Connolly, 1995), when using a device produced from the same manufacturer or different technologies (i.e., breath actuated vs. conventional). However, compliance between similar devices has not been investigated as per the authors' knowledge.

Variations in valve type, propellant, and co-solvents may directly influence the force required to actuate the device or change the actuation cycle (resulting in a different "feel" during use). Furthermore the complexity of the valve construction (Figure 1) and choice of specific polymers, elastirmers, and compression spring will directly influence the compression and de-compression properties of the valve. For example variations in vapor pressure of the order of 100×10^3 Pa exists between the different HFA and CFC propellant systems (without even considering the addition of liquid excipients such as ethanol co-solvents). Where such variations occur, it would be expected that an increased vapor pressure would result in an increased force required to actuate a pMDI device. Similarly, different seal material (such as nitrile or ethylene propylene diene monomer (EPDM) rubbers) will increase or decrease the force required to initiate and actuate a pMDI depending on their relative hardness and degree of swelling. Obviously, the spring component will also play a major role in the compression force required for actuation.

Such variation between devices may directly affect elderly patients with poor dexterity (e.g., arthritis) (Connoly, 1995) or children. These factors have already led to the development of pMDI aids such as Haleraid® (GlaxoSmithKline) and breath actuated devices (Chapman et al., 1993).

Address correspondence to Paul M. Young, Advanced Drug Delivery Group, Faculty of Pharmacy, University of Sydney, Australia, NSW 2006. E-mail: py@pharm.usyd.edu.au

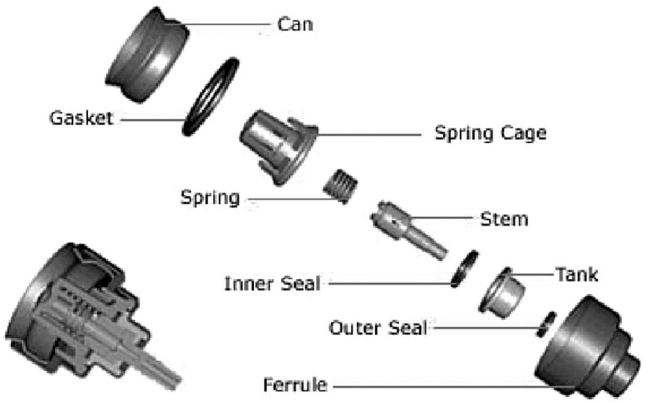

FIGURE 1. Schematic of a typical valve construction. Used with permission by 3M Drug Delivery Systems.

Here the authors describe the development of a technique to directly measure the actuation cycle (compression/de-compression) of pMDI devices and compare three marketed beclomethasone dipropionate (BDP) formulations. This approach would be of clear advantage, when evaluating formulations performance in terms of patient feel and compliance and allow a greater insight into how specific formulation variables and valve components influence the actuation performance of a pMDI system

MATERIALS AND METHODS

Materials

250 mg BDP formulations of CFC Becloforte (Glaxosmithkline, Sussex: batch E050), CFC Clenil Forte (Chiesi, Parma, Italy: batch 42) and HFA BDP-Modulite (Chiesi-Glaxosmithkline: batch 7M601) were used as supplied.

Design and Operation of the pMDI Load Cell

Compression force relative to stem displacement measurements were conducted using a TA-HDi/500 Texture Analyzer with a modified 4900 N pMDI load cell (Figure 2). The pMDI testing cell was constructed of stainless steel, and was bolted directly onto the load cell mount. The primary cell contained a lathed circular recess of 23 mm diameter and 23 mm depth. pMDI canisters were mounted, inverted, into this cell recess and were secured with two PTFE mounting screws. An actuation block, was manufactured with a 0.30 mm orifice and stem connection/sump geometries similar to that used in conventional plastic actuators. The actuator block was secured to the pMDI metering valve, such that the block base was parallel with the bottom load cell base of the Texture Analyzer (where device contact, compression, and actuation would occur).

The Texture Analyzer apparatus had a Z-displacement resolution of 1.0 μm and a force resolution of 0.1 N, which was calibrated using known masses. The apparatus was connected to a

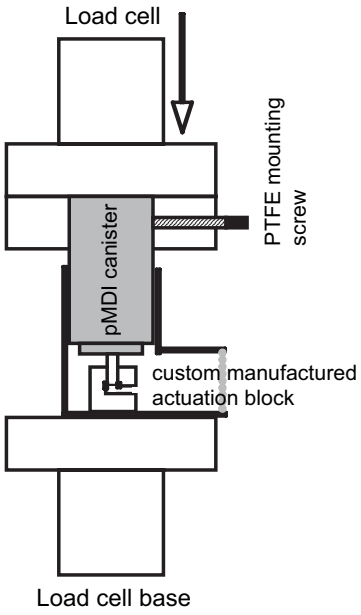

FIGURE 2. Schematic of the pMDI load cell apparatus.

personal computer, which monitored the Z position, force, and time (at a frequency of 200 s^{-1}). The apparatus was used in a cycling program with constant vertical probe speed and maximum applied load (controlled by a feedback loop). Measurements were exported as force, distance, and time data sets and analyzed/treated to produce force vs. displacement curves.

Although the load cell had a capacity of 4900 N, a maximum applied force of 50 N was chosen for routine analysis since forces in excess of 100 N suggested signs of valve component failure. Accurate force measurement was obtained by pre-calibrating the load cell with known calibration weights. During measurement, a vertical probe speed of 3 $mm.s^{-1}$ was chosen for the comparative studies as this was estimated to be similar to the rate applied during patient use. Measurements were conducted in a saw-tooth sequence with each cycle commencing when a force trigger threshold of 0.05 N was obtained. Approach and retraction speeds prior to and post measurements were 3 $mm.s^{-1}$. It is important to highlight that all these experiments were conducted at the same settings to allow comparison of the compression cycle and actuation force. Variations in, for example, the compression rate may influence actuation cycles and should be considered in future investigations.

During testing, each device was shaken and five actuations were performed using the test conditions before measurements were recorded. This ensured that the pMDI valve stem was correctly seated in the actuator block. Measurements were conducted by cycling the test five times (five actuations). All measurements were conducted into an open-ended ‘waste’ dose unit sample apparatus (DUSA) (British Pharmacopoeia), which was connected to a pump, such that the flow rate was 28.3 $L.min^{-1}$. In this case the DUSA was used only as an

active-drug filter, (however it may be incorporated into the valve testing apparatus in the future). In addition, it is important to note no shaking protocol was instigated between shots.

All measurements were performed in triplicate (three cans) and randomised for product type. Statistical analysis of different measurement parameters (for example actuation force) was compared using one-way ANOVA with post-hoc Fishers pair wise comparison. The results were found to be significantly different based upon 95% probability values ($p < 0.05$).

RESULTS AND DISCUSSION

Representative force vs. displacement curves for shots 6–10 of a Becloforte, Clenil Forte, and Modulite pMDI canister are shown in Figure 3A, B, and C, respectively. In simple terms, the upper curves represent the valve actuation of the canister while the lower curves represent the closing of the valve and resetting of the actuation pin (stem), with the hysteresis between compression and decompression being the energy loss. In general, little variation was observed for five consecutive shots, and between different canisters of the same product. However, clear variations between "actuation curves" from separate products were observed (Figure 3).

To quantify such differences, the compression cycles of each device were analyzed in more detail to obtain information regarding the actuation force, distance for actuation, and maximum stem displacement. An example of such analysis is shown in Figure 4A for a Modulite canister. Similar analysis was performed for each product.

Figure 4A shows a single actuation, i.e., compression-decompression cycle of a Modulite pMDI canister. In general terms, the compression cycle of the device will be dependent on the mechanical properties of each of the components in the valve housing, shown in Figure 1 (rubber seals, valve chamber, valve, compression spring gaskets, and outer crimped housing), and the pressure difference, i.e., reservoir content, throughout the cycle. For simplicity, the compression can be broken down into three components, which can be described as follows.

It is suggested that point (1) in Figure 4A is the point at which the first "yield point" of the device is reached. The load between origin to point (1) probably represents the initial resistance of the valve components and a small displacement of the valve stem. After point (1) the spring in the valve begins to compress and displacement of the stem is achieved until point (3) in Figure 4A is reached. At his point the spring is fully depressed and any further displacement is due to deformation of the compressed components. This was exemplified by the mechanical failure of the device when compressed in excess of 100 N, representing a stress of over 15 MPa on the stem. Therefore a 50 N maximum load force was applied in all cycles, with point (3) being described as the maximum stem displacement.

Point (2) in Figure 4A shows an inflection in the compression cycle. It is suggested that this may be due to the release of the propellant from the device, through the metering orifice,

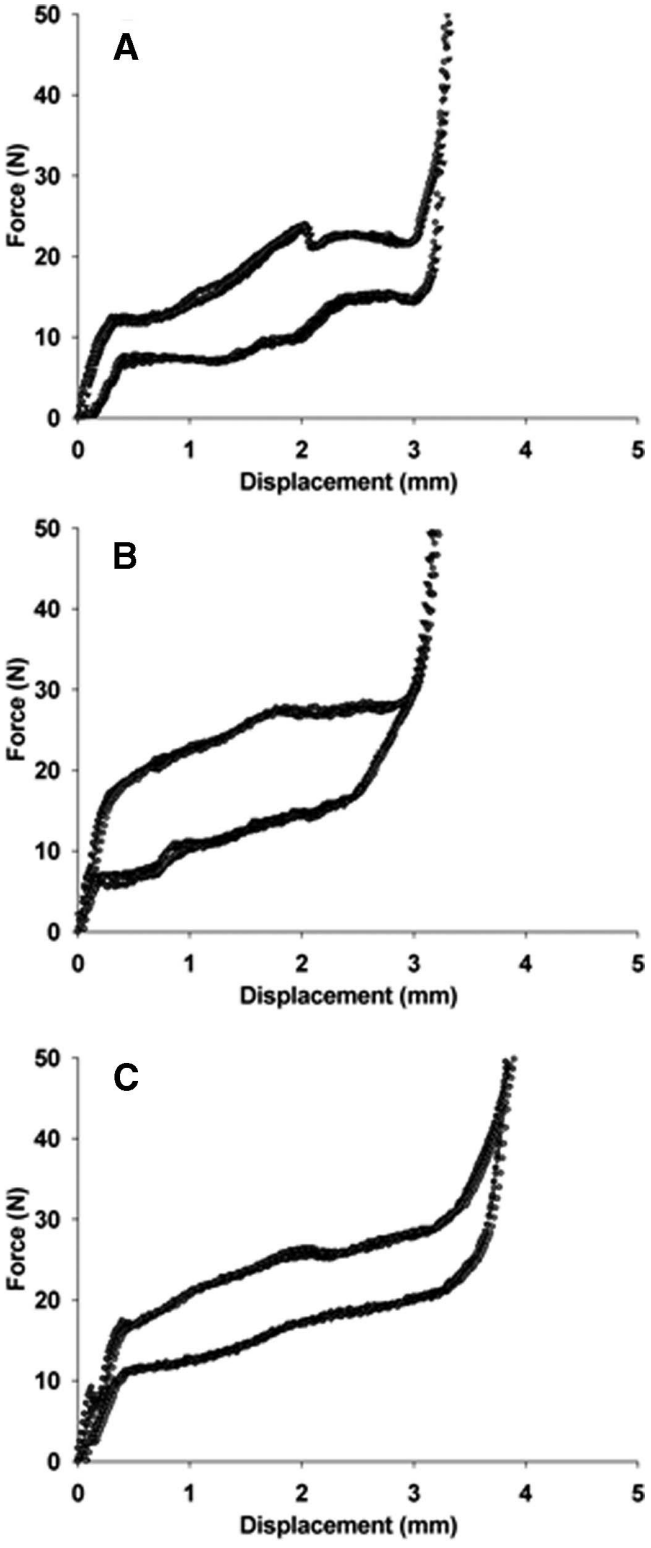

FIGURE 3. Representative force vs. displacement curves for (A) becloforte, (B) clenil forte, and (C) modulite pMDIs ($N = 5$ actuations).

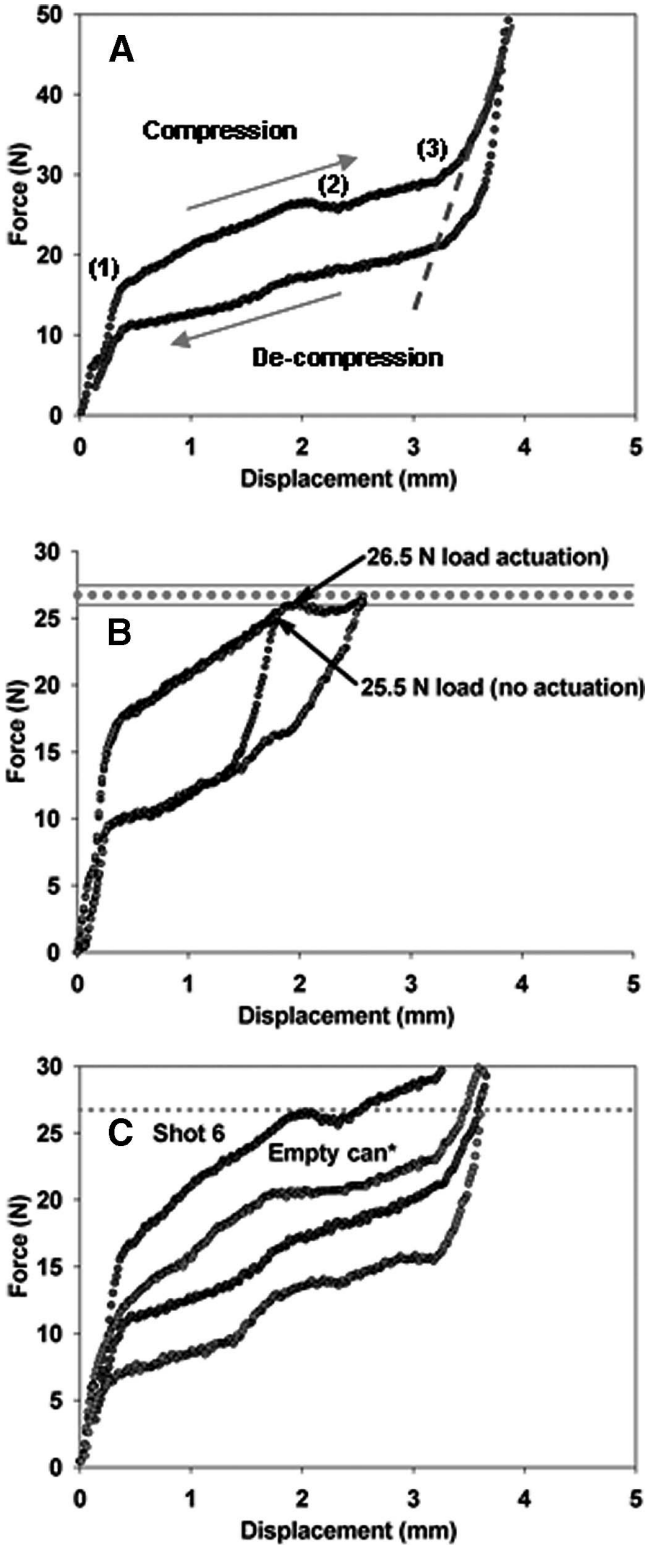

FIGURE 4. Force vs. displacement curves for modulite devices tested at a loading force of 50 N. (A) Example of one compression cycle (refer to text); (B) At maximum loading forces of 25.5 N and 26.5 N. (Dotted and straight lines indicate *M* firing force and *SD* of modulite cans tested under 50 N loading cycle [$N = 3$]); (C) Shot 6 from new modulite can (dark circles) and an empty pierced can (light circles).

resulting in a decrease in pressure and resistance and thus applied force. For the modulate pMDI, the maximum force value prior to the negative deflection (Figure 4A, point 2) in the compression cycle was observed at approximately 26.5 N. To test the hypothesis that the inflection point was related to propellant release, a series of cycles were conducted at increasing maximum loading forces (20 to 30 N at 0.5 N increments). For the canister studied, a force of ≤ 25.5 N resulted in no actuation, and ≥ 26.5 N in actuation (Figure 4B). In all cases, cycles that underwent actuation also exhibited the characteristic negative deflection after the maxima (point [2]). Furthermore, analysis of a Modulite canister that had been pierced and emptied (to insure no residual pressurised propellant) suggested no such negative deflection to occur at the actuation point (Figure 4C). The modulations in Figure 4C probably represent uneven resistance by the valve housing on the stem during compression.

As previously stated, each product canister was tested through shots 6–10 using a 50 N maximum load cycle at a compression rate of 3 $mm.s^{-1}$. The data was subsequently processed to produce maximum force values at actuation, distance for actuation and maximum stem displacement. These data values were produced by recording points (2) and (3), described above (shown in Figure 4), for each test cycle. A summary of the results for each product is given in Table 1.

Statistical analysis of the data obtained for the three products indicated significant variation in the force required for actuation (ANOVA, Fisher's pairwise, $p < 0.05$) ($N = 3$ cans) In general, the force required followed the rank order of Clenil Forte > Modulite > Becloforte. The difference between the two extremes (Clenil Forte-Becloforte), would result in an increase of approximately 8.7 N required by the patient for actuation when switching between devices (this can be approximated to 0.9 Kg). The distance required for actuation were similar (1.85–2.06 mm), however, the Modulite device was higher than Becloforte and Clenil-Forte (which were not significantly different) (ANOVA, Fisher's pairwise, $p < .05$). It is interesting to note, however, that the total compression distance for the Modulite device was significantly greater than both Becloforte and Clenil-Forte (ANOVA, Fisher's pairwise, $p < .05$), resulting in similar percentage actuation

TABLE 1
Comparative Analysis of Becloforte, Clenil Forte, and Modulite pMDIs. (Data is Based Upon Shots 6–10) ($N = 3$ cans)

	Actuation Force (N) (± *SD*)	Distance to Actuation (mm) (± *SD*)	Total Compression Distance (mm) (± *SD*)
Becloforte	22.33 ± 1.44	1.91 ± 0.12	3.00 ± 0.07
Clenil-Forte	31.12 ± 2.73	1.85 ± 0.04	3.00 ± 0.02
Modulite	26.71 ± 0.73	2.06 ± 0.08	3.60 ± 0.11

distances relative to full stem displacement (63.6 ± 2.7, 61.7 ± 1.3, and 57.3 ± 2.9% for Becloforte, Clenil-Forte, and Modulite, respectively). Obviously, the differences in actuation load and energy may be a consequence of valve geometries and may not represent the stress in the system. However, it will be the absolute load and total energy required to receive the medicament (exerted by the patient) which will contribute towards "acceptability."

Another point to consider is variation in compression cycle profile beyond actuations 1–10, as used in this study. To investigate this, one device from each product type was tested in a continuous cycle for 180 cycles. In general, the compression and decompression cycles did not change noticeably during this short fatigue test; typical test data for a Modulite device is shown in Figure 5. Similar short fatigue tests and actuation point tests were conducted for Becloforte and Clenil forte. Analysis suggested similar negative deflections at the point of actuation (being most noticeable for Becloforte, as shown in Figure 3A).

As previously stated, patients with poor dexterity or weak grip strength (such as the young or elderly), may find it difficult to actuate a pMDI device. Indeed, a previous report by Connolly (1995), (studying 19 elderly patients with an average age of 78 yeas) suggested that ~10% were unable to trigger a conventional pMDI device.

Primary prescribers may regularly change a product through discontinuation, recommendation from sales representatives or financial reasons. In addition, when a generic device is prescribed, the particular product received will be dependent on the patients chosen pharmacy. Furthermore, a patient may be using multiple medicaments (e.g., a ß-antagonist in combination with a steroid) with different device properties.

For patient compliance, a variation in the force required to actuate different devices from different manufactures should be considered. In this study, three devices suggested a maximum difference of 8.7 N between products. From a patient perspective this is equivalent to a 39% increase in force required to receive a dose.

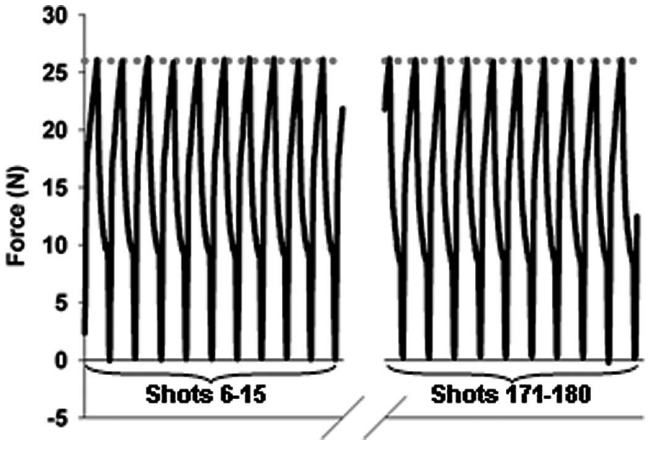

FIGURE 5. Representative through life compression cycle of modulite device with a maximum loading force of 26.5 (determined sufficient to actuate particular can).

As previously discussed, reasons for such variations in pMDI compression are very complex. Factors influencing the compression and de-compression cycle (as well as choice of suspension or solution) include propellant, excipient, and valve components. For example, different propellants with different vapour pressures may alter the compression force required to actuate a device (Vervaet & Byron, 1999). Likewise the addition of stabilising polymers, co-solvents, and low boiling point fluorinated carbons will lower the vapor pressure (Vervaet & Byron, 1999) as well as altering the lubrication properties of the formulation on the valve components. In addition, the regulatory bodies' interest in valve component molecules leaching into formulations has spurred the development of new polymer components and/or reduction of release agents and low molecular weight plastersizers (Howlett, Colwell, Goldsmith, & McCallion, 2002). Again, such variation in valve properties may influence the device actuation.

CONCLUSIONS

This study was concerned with the development of an analytical technique to compare the actuation properties of commercially available devices. Clear variations in actuation cycle between different product formulations containing BDP were observed. The maximum difference in actuation force of 8.7 N highlights the importance of measuring pMDI compression cycles as a means to evaluate final patient acceptability and compliance. In this study, it was not possible to elucidate which components caused such variations, since there were multi-variant factors between devices. However, such variables clearly warrant further study and should be considered during future product development.

REFERENCES

Chapman, K. R., Love, L., & Brubaker, H. (1993). A comparison of breath-actuated and conventional metered-dose inhaler inhalation techniques in elderly subjects. *Chest, 104*, 1332–1337. www.chestjournal.org/cgi/reprint/104/5/1332.pdf

Connolly, M. J. (1995). Inhaler technique of elderly patients—Comparison of metered-dose inhalers and large-volume spacer devices. *Age and Ageing, 24*, 190–192. 10.1093/ageing/24.3.190

Dunbar, C. A., Watkins, A. P., & Miller, J. F. (1997). An experimental investigation of the spray issued from a pMDI using laser diagnostic techniques. *Journal of Aerosol Medicine, 10*, 351–368. www.liebertonline.com/doi/pdf/10.1089/08942680252908601

Howlett, D., Colwell, J., Goldsmith, S., & McCallion, O. (2002). Correlation of extractables and leachables from marketed pMDIs. *In Proceedings from Respiratory drug delivery VIII*. Dalby, R.N., Byron, P.R., Peart, J., Farr, S.J. Davis (Eds.) Howard Int'l Publishing, Surrey, UK. (Vol. 1, pp. 129–136). taylorandfrancis.metapress.com/index/L032761K7G400708.pdf

Rossand, D. L., & Gabrio. B. J. (1999). Advances in metered dose inhaler technology with the development of a chlorofluorocarbon free drug delivery system. *Journal of Aerosol Medicine, 12*, 151–160. www.rcjournal.com/contents/09.05/09.05.1177.pdf

Vervaet, C., & Byron, P. R. (1999). Drug-surfactant-propellant interactions in HFA-formulations. *International Journal of Pharmaceutics, 186*, 13–30. linkinghub.elsevier.com/retrieve/pii/S0378517306003425