

Achieving Consistent MDI Drug Delivery Data: The Role of the Rockstar Automation Platform in Through-Can-Use-Life Characterization

Daniel I. Lewis, Josh Carter, Rob Johnson, & David A. Lewis

Oz-UK Ltd, Unit 15a, Lansdowne Court, Bumpers Way, Chippenham, Wiltshire, SN14 6RZ, UK.

Summary

Metered Dose Inhalers (MDIs) are commonly used for treating respiratory conditions, but suspension formulations are prone to sedimentation or creaming, requiring consistent shaking for uniform drug delivery [1]. Manual testing introduces variability and operator fatigue, impacting comprehensive through-can-use life characterization.

To overcome this, the novel automated in-vitro drug delivery characterization system, Rockstar (Lewis Jonsen Limited), was developed. Its novelty lies in providing precise digital control and visual feedback over the kinematic parameters applied to the MDI during shaking.

Rockstar enables precise control over critical MDI actuation parameters, including diverse shake methodologies (e.g., 90°, 180°, up/down) and the temporal profiles of rotational speed (i.e., acceleration and deceleration during the shake and return movement). The system provides real-time visualization of shake metrics, enabling researchers to adjust, simulate, and correlate manual operator shaking characteristics with the automated process. Furthermore, it provides exact control of shake number, shake-to-fire delay, and actuation duration. Importantly, it rigorously fires all doses (including waste shots) under consistent conditions to maintain representative in-canister drug homogeneity throughout the MDI's use-life.

In this study, Rockstar systematically fired all 200 doses from three generic salbutamol sulphate MDIs (>600 total actuations, including priming doses), with drug delivery quantified for a subset of 10 doses per MDI at Beginning, Middle, and End of Life using a Dosage Unit Sampling Apparatus (DUSA) and validated HPLC assay.

Results demonstrated high consistency in delivered dose across individual MDIs and through their lifecycle; the overall delivered salbutamol dose observed was $99 \pm 5 \mu\text{g}$. This highly reproducible, USP-compliant data confirms Rockstar's capability to provide reliable MDI performance measurements. Its automation advances high-throughput testing, significantly reduces human variability, and offers a critical tool for characterizing current and next-generation MDI products.

Key Message

Rockstar is a novel automated MDI characterization system that uses precise digital control of shake kinematics and real-time on-screen metrics to eliminate manual variability. This platform facilitates the collection of highly reproducible, USP-compliant drug delivery data essential for robust MDI development and lifecycle evaluation.

Introduction

Metered Dose Inhalers (MDIs) are commonly used in the long-term management of chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD). These devices deliver medication directly to the lungs, and their efficacy hinges on consistent dose delivery. MDI formulations are broadly categorized into solutions, where the drug is homogeneously dissolved, and suspensions, where the active pharmaceutical ingredient (API) is dispersed as fine micronized particles within the excipient-propellant system. Both solution and suspension formulations are utilized in the treatment of asthma and COPD. Suspension formulations, may include excipients like co-solvents or surfactants, but remain inherently prone to physical instability, with particles tending to settle or cream due to density differences between the suspended drug particles and the liquid propellant [1].

Consequently, proper shaking is a critical pre-use step for suspension MDIs, ensuring the uniform distribution of the drug and thus a consistent dose is presented to the metering valve. Research has previously demonstrated that insufficient shaking or even brief delays between shaking and actuation can lead to significant variability in the emitted dose and detrimental alterations in the aerodynamic particle size distribution, ultimately compromising therapeutic efficacy and patient outcomes [2].

Specifically, studies have shown that while solution pressurized MDIs (pMDIs) remain unaffected by not shaking or shake-fire delays in terms of respirable dose (Fine Particle Mass and Mass Median Aerodynamic Diameter), suspension pMDIs exhibit substantial variability. For suspension pMDIs, not shaking can lead to extreme changes in Fine Particle Mass, ranging from -82% to 363% compared to control values, and significant shifts in Mass Median Aerodynamic Diameter, such as from approximately 3 μm to 4.2-5.1 μm [3, 4].

Recognising the importance of reliable in-vitro MDI performance testing, this study evaluates the drug delivery characteristics of a generic salbutamol sulphate MDI. We present data on delivered dose obtained throughout an MDI's can use-life. The consistent results achieved underscore the precision and robustness of our experimental methodology, demonstrating its capability to obtain reliable drug delivery measurements in full accordance with United States Pharmacopeia (USP <601>) guidelines. In the study presented here our investigation is limited to a single shake-fire method; however, these robust findings lay a strong foundation, with further exploration of diverse shaking protocols planned for future work.

Experimental Methods

The study utilized generic marketed salbutamol sulphate Metered Dose Inhalers (MDIs), each nominally containing 200 metered doses with a nominal 100 μg salbutamol delivered dose (as 120 μg Salbutamol sulphate per actuation). To characterize product performance through its lifecycle, three MDIs from the same batch were evaluated, with drug delivery characteristics assessed at three distinct stages: beginning of life (BOL), middle of life (MOL), and end of life (EOL) of the canister.

Importantly, all MDI shaking and firing sequences for dose collection were performed entirely by the automated Rockstar (Lewis Jonsen Limited) system at a sampling flow rate of 30L/min. This ensured consistency and reproducibility of pre-actuation shaking and subsequent actuation parameters for every single dose. MDIs were shaken by 180° rotational inversion (600ms per shake), ten times between each actuation, and fired 1s after shaking with the metering valve held open for 500ms. Delivered doses were collected into individual Dosage Unit Sampling Apparatus (DUSA) tubes, adhering to established pharmacopoeia methodologies (USP <601>). Following collection, the delivered drug was quantitatively recovered from each DUSA using precisely known volumes of diluent. The salbutamol content in each test sample was subsequently quantified using a previously validated High-Performance Liquid Chromatography (HPLC) assay.

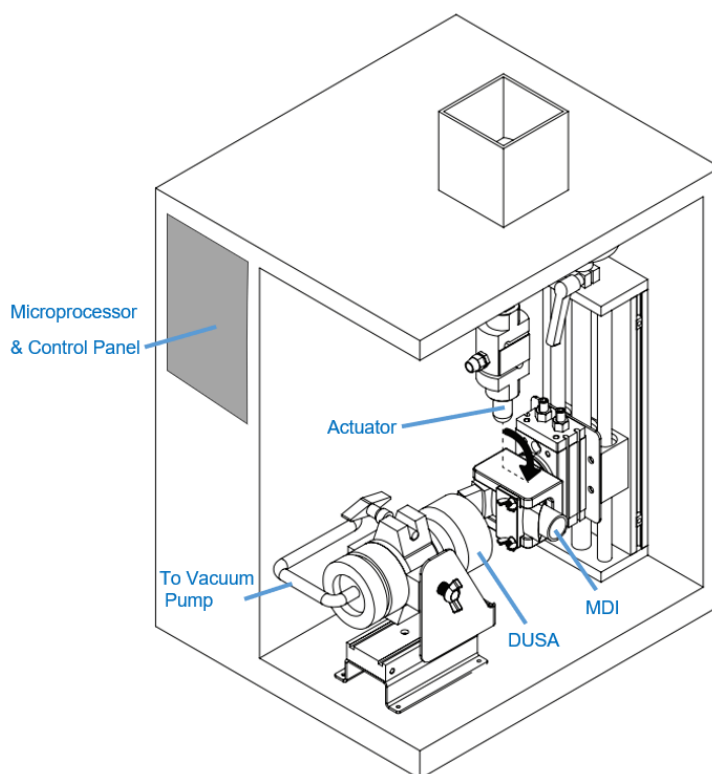


Figure 1, Diagram of the Rockstar shake fire system, MDIs in this study were shaken using a 180°, inverted shake; 10 shakes within 6 seconds. Shake-Fire Delay & Dose Duration were controlled.

For this specific investigation, the Rockstar system was employed to systematically fire all 200 doses from each of the three test MDIs, accounting for a total of > 600 actuations (including priming doses). This comprehensive firing, including the necessary 'waste' shots, was critical to maintain the in-canister drug homogeneity and representative behaviour throughout the MDI's life, accurately mimicking patient usage conditions. Actuators were cleaned following waste shots and prior to MOL and EOL drug delivery collection to ensure consistent spray performance. From this sequence, drug delivery was quantitatively assessed for a subset of 10 doses from each MDI: specifically, three doses at the beginning of life, four doses at the middle, and three doses at the end of life.

Figure 1 presents a schematic of the experimental setup and the specific Rockstar settings employed. MDIs were consistently shaken ten times within six seconds, followed by a 1-second delay between shake and fire. The actuation duration (metering valve open time) was 0.5 seconds, and the time between consecutive actuations was 10 seconds. This scale of testing vividly highlights the advantages of automation in MDI characterization. It is particularly beneficial for rigorous studies involving large numbers of canisters, multiple batches, or diverse test conditions (e.g., varying shake protocols, MDI storage conditions) routinely conducted during extensive stability programs or product development phases, where manual methods would be prohibitively time-consuming and susceptible to operator fatigue.

Table 1, Delivered Dose Consistency of Generic MDIs Across Can-Use Life

	Delivered Dose (μg); presented as Salbutamol			
	MDI 1	MDI 2	MDI 3	Mean $\pm$ Standard Deviation
Beginning of Can-Use Life	102	106	95	98 ± 5
	104	96	92	
	101	96	94	
Middle of Can-Use Life	89	97	110	101 ± 6
	107	105	103	
	97	100	97	
	98	92	94	
End of Can-Use Life	96	96	104	98 ± 3
	95	94	97	
	102	101	99	
Mean $\pm$ Standard Deviation	99 ± 5	98 ± 5	99 ± 6	99 ± 5

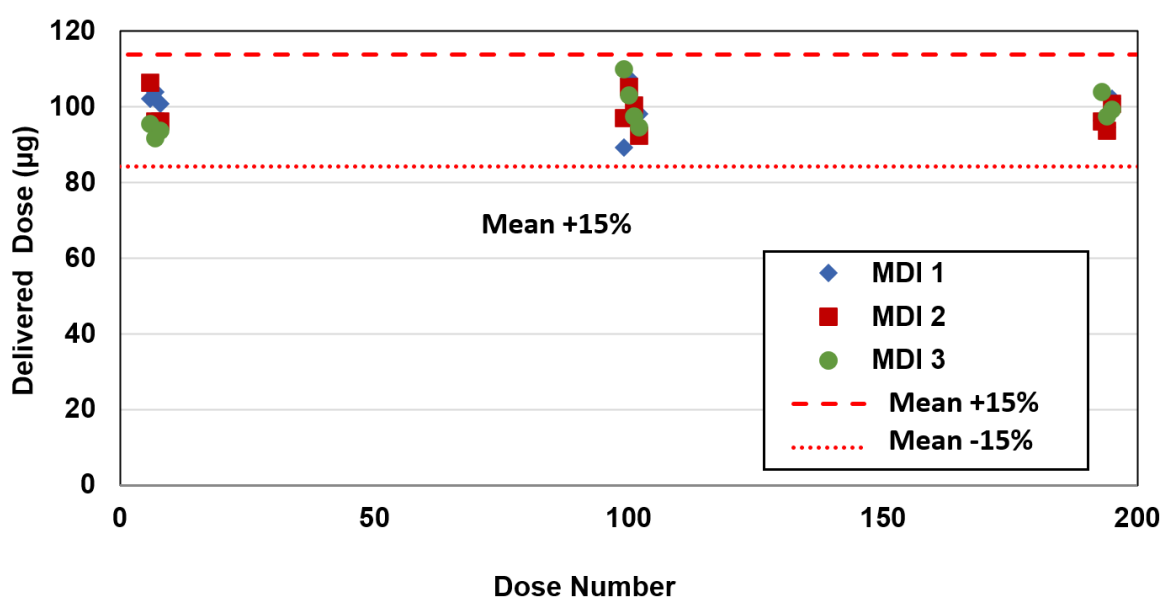


Figure 2 - Delivered Dose (μg); Beginning, Middle, and End of Can-Use Life, Facilitated by Automated Rockstar System

Results and Discussion

Table 1 and Figure 2 present the measured delivered dose data, directly demonstrating the high precision and consistency achievable in MDI characterization utilizing the automated Rockstar system.

The mean delivered dose obtained from each of the three individual MDIs, evaluated throughout their nominal 200-actuation lifespan, exhibited remarkable consistency: $99 \pm 5 \mu\text{g}$, $98 \pm 5 \mu\text{g}$, and $98 \pm 5 \mu\text{g}$, respectively. This consistency was rigorously maintained across the different stages of can-use life for which doses were quantified, with mean delivered doses of $100 \pm 4 \mu\text{g}$ at the Beginning of Life (BOL), $100 \pm 6 \mu\text{g}$ at the Middle of Life (MOL), and $97 \pm 3 \mu\text{g}$ at the End of Life (EOL).

The overall delivered dose observed across all 30 quantified samples was highly consistent at $99 \pm 5 \mu\text{g}$. This reproducibility demonstrates the precision of the automated methodology. By controlling all shaking and firing parameters for each actuation—including the waste shots used to maintain in-canister homogeneity—the system accurately simulates consistent patient use and enables the collection of low-variability drug delivery data in accordance with United States Pharmacopeia (USP <601>) guidelines. These results confirm that automation can effectively minimise the variability associated with manual testing, providing a reliable platform for quantitative evaluation of MDI performance.

Conclusion

This study successfully demonstrated the highly consistent delivered dose of a generic salbutamol sulphate MDI throughout its can-use life. This precision was directly attributed to the novel Rockstar automated system, which rigorously controlled all pre-actuation shaking and firing parameters, thereby eliminating human variability and ensuring representative in-canister drug homogeneity for every actuation. The remarkably reproducible data obtained, in full accordance with United States Pharmacopeia (USP) guidelines, demonstrates Rockstar's capability to provide robust and reliable drug delivery measurements. This automation significantly benefits the pharmaceutical industry by enabling high-throughput testing, reducing operator fatigue, and providing a critical tool for the thorough characterization and development of both current and next-generation MDI products, including those with novel propellants. Future work will leverage Rockstar's advanced capabilities to explore the impact of diverse shaking protocols and shake-to-fire delays on MDI performance.

References

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