

Cold-Stage MDRS Investigation of Beclomethasone Dipropionate: In Situ Monitoring Morphological and Chemical Stability of Nasal Spray API Across Different Temperatures

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Summary

This study investigated the impact of temperature on the particle size, shape and chemical identity of beclomethasone dipropionate (BD) in a commercial nasal spray formulation using a novel cold-stage coupled with morphologically-directed Raman spectroscopy (MDRS). A bespoke temperature-controlled platform was designed, manufactured and combined with MDRS to enable in situ analysis of particle size and shape across a clinically and environmentally relevant ranges (25, 37 and 50 °C). Results confirmed temperature-dependent morphological changes in BD API, including particle agglomeration and shape distortion at elevated temperatures, whilst cellulose excipients remained morphologically stable. Number- and volume-based size distributions highlighted clear differences in thermal response, with BD API exhibiting increased Dv(0.9) values and formation of larger agglomerates at 50 °C. These findings demonstrate the utility of cold-stage MDRS as a powerful orthogonal technique for characterising thermally sensitive nasal formulations under real-world storage and use conditions.

Key Message

The integration of cold-stage MDRS provides a powerful analytical platform to support the quality and stability assessment of OINDPs, particularly under storage and use reflective of real-world scenarios. These findings contribute to the broader understanding of API-excipient behaviour under thermal stress and inform generic product development in much shorter time.

Introduction

The nasal route for drug administration has garnered increasing interest in recent years, primarily due to its capacity for rapid and efficient systemic drug absorption¹. Compared to oral or parenteral delivery, intranasal administration offers distinct advantages, including the bypassing of first-pass hepatic metabolism, a faster onset of action, and the benefit of being non-invasive features particularly valuable in both acute and chronic therapeutic contexts¹. Their efficacy, however, hinges on the precise control of particulate characteristics – size, shape, crystallinity, and chemistry – which critically influence dose delivery, mucosal deposition and subsequent absorption.

Beconase nasal spray (Boots Pharmacy, UK), a widely prescribed formulation for the treatment of allergic rhinitis (hayfever) and other inflammatory conditions of the nasal mucosa, contains beclomethasone dipropionate (BDP) as its active pharmaceutical ingredient (API). As an exemplar of an Orally Inhaled and Nasal Drug Product (OINDP), its therapeutic efficacy is intimately linked to the physicochemical attributes of the API – particularly particle size, shape and polymorphic transitions. These attributes critically influence intranasal deposition patterns, mucociliary clearance rates, dissolution behaviour (kinetics), and ultimately, both local and systemic drug bioavailability². In Beconase, BDP is suspended in a multi-dose aqueous vehicle and delivered via a metered-dose nasal actuator. Given the nature of suspension-based delivery, it is essential that particle characteristics remain within tight specifications throughout manufacturing, storage, and administration². Variability in critical attributes such as particle agglomeration, polymorphic transitions, and API-excipient interactions can profoundly influence product performance, often manifesting as clinically relevant issues including spray quality, nozzle blockage, sedimentation, and dose non-uniformity. These risks are amplified under variable environmental conditions - particular temperature fluctuations – that may induce agglomeration, phase transitions, or morphological changes in both API and excipient particles.

Traditional particle characterisation techniques, such as laser diffraction (LD) and cascade impaction, offer valuable ensemble or aerodynamic particle size data. However, these techniques offer limited insight into heterogenous particle populations and LD is inherently incapable of distinguishing API from excipients or from other API particles in complex formulations. As such, advanced, particle size and shape characterisation are essential – not only for product development and quality control, but also, to evaluate potential bioequivalence for generic OINDPs. Notably, morphologically directed Raman spectroscopy (MDRS) has been validated for characterising mometasone furoate in nasal suspensions and accepted as a surrogate for clinical bioequivalence studies³. MDRS uniquely integrates automated static image analysis with Raman spectroscopy to enable simultaneous morphological and chemical identification analysis of individual particles within multicomponent formulations⁴. This dual capability

addresses one of the key analytical challenges highlighted in recent FDA product specific guidance's for nasal suspensions. As a result, MDRS has gained considerable traction as a powerful orthogonal technique for OINDP characterisation, particularly in distinguishing APIs from morphologically similar excipients in generic complex products ⁵. Moreover, when coupled with a temperature-controlled cold-stage, MDRS allows the characterisation of thermally sensitive formulations under storage-relevant conditions, reducing the risk of morphological transformation due to sublimation, crystallisation, or melting during analysis, storage and/or transportation.

This study presents a systematic investigation into the impact of temperature on the particle size and shape of BDP API-containing particles within the Beconase nasal spray formulation. A bespoke fit-for-purpose cold-stage was developed and coupled with MDRS to enable controlled analysis across a temperature range of 5 to 50°C. This novel method was used to assess in-line monitor potential morphological changes and evaluate the robustness of the suspension formulation under conditions representative of global storage, transport, and patient use across varying climatic zones. By replicating these real-world scenarios, the study provides novel insights into the structural stability of BDP API particles and support more informed decisions during product development.

Experimental methods

Materials and Reagents

Commercial Beconase nasal spray was purchased from Boots Pharmacy (Leeds, UK) and used as a model nasal spray suspension product to conduct method development and evaluate, for the first time, cold-stage MDRS to inline measurement of particle size, shape and chemical composition of the BD API. Beconase is a manually actuated metered-dose nasal spray containing an aqueous suspension of BDP API (50 micrograms per spray), formulated with microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, polysorbate 80, purified water, benzalkonium chloride and phenylethyl alcohol. BDP was selected as it is an over-the-counter product readily available and containing API and excipients commonly used in other formulations.

Cold-Stage MDRS Setup and Method Optimisation

The cold-stage accessory has been custom-designed and built for use with the Malvern Panalytical Morphologi4-ID instrument (Malvern, UK). An image of the cold-stage coupled with MDRS setup is shown in Figure 1.



Figure 1. Photograph of the Cold-Stage MDRS Setup Used

The method development began with the optimisation of sample preparation and particle dispersibility. Once the method was optimised, a fresh sample slide prepared for in-line monitoring of particle size, shape and chemical identity (ID) across different temperatures (25, 37 and 50 °C).

Sample Preparation

Prior to use, Beconase nasal spray was shaken vigorously for 30 seconds, and the first 4 actuations were discarded. The subsequent 10 actuations were collected into a scintillation vial. A 10 µL aliquot of this undiluted suspension was then transferred onto a quartz slide, and a clean quartz coverslip was carefully placed over the sample. The edges were promptly sealed with an appropriate amount of silicone grease. The prepared slide was placed onto the cold-stage and allowed to equilibrate for 10 minutes prior to initiating particle size, shape analysis and chemical ID.

Results and Discussion

According to the patient information leaflet, Beconase nasal spray should not be stored in a refrigerator or exposed to temperatures above 30 °C. To investigate the instability of the suspension, prepared sample slides were tested at three different temperatures; 25, 37 and 50 °C – representing typical pharmacy or supplier shelf conditions, body temperature during use, and extreme transport scenarios in regions where such nasal sprays are not properly stored and monitored. By understanding the temperature sensitivity of the formulation, it is hoped to accelerate the de-formulation workflow for complex generic products. Furthermore, such studies should enhance both patient safety and product efficacy. The dissolution rate and extent of absorption of BD drug in the nasal cavity following intranasal delivery via the Beconase nasal spray, are directly related to the particle size and shape of the BD API within the formulation. Prior to analysis using the optimised method, manual microscopy on the Morphologi4-ID instrument was used to capture particle images at various pre-defined temperatures. An example of representative images is presented in Figure 2.

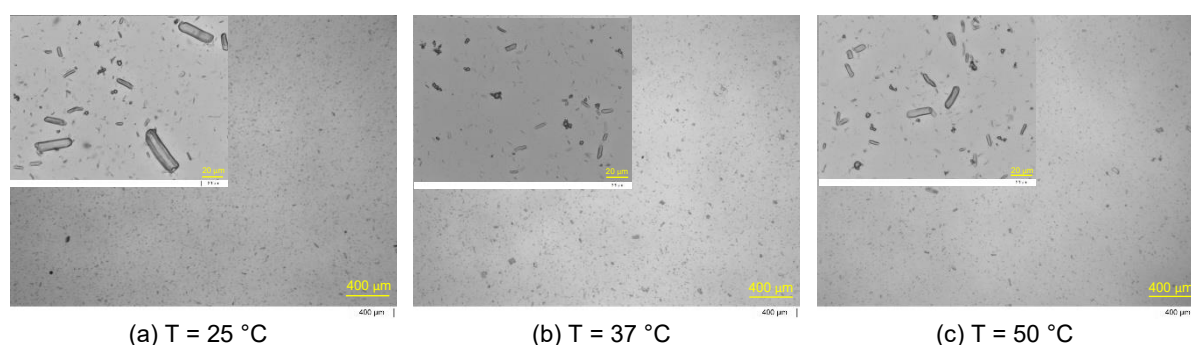


Figure 2. Example of Microscopic Images of Captured Particles at Various Temperatures

Figure 2 shows two distinct visible and undissolved particle populations within the formulation: elongated, rod-shaped particles matched with microcrystalline cellulose, and darker, irregular to near-circular particles majority identified as BD API. The static images of particles captured at all three different temperatures are shown in Figure 3.

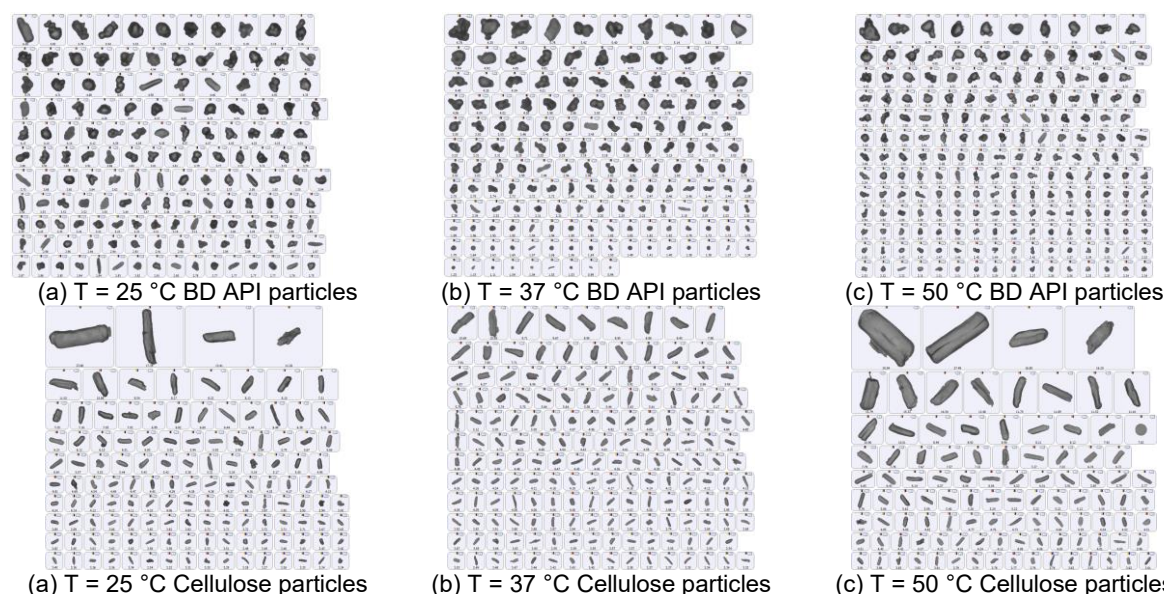


Figure 3. Example of Captured Images of Particle at Various Temperatures from Beconase Nasal Spray Prepared Slides

Figure 3 shows that the BD particles appeared predominantly irregular to rounded in morphology. Increasing the temperature resulted in a noticeable degree of agglomeration and partial particle fusion. In contrast, the cellulose particles were elongated and retained a relatively consistent morphology across all three tested temperatures, suggesting greater thermal stability in shape compared to the BD particles.

The overlaid number-based size distributions of BD API particles as well as cellulose excipient particles for samples at all three different temperatures are shown in Figure 4.

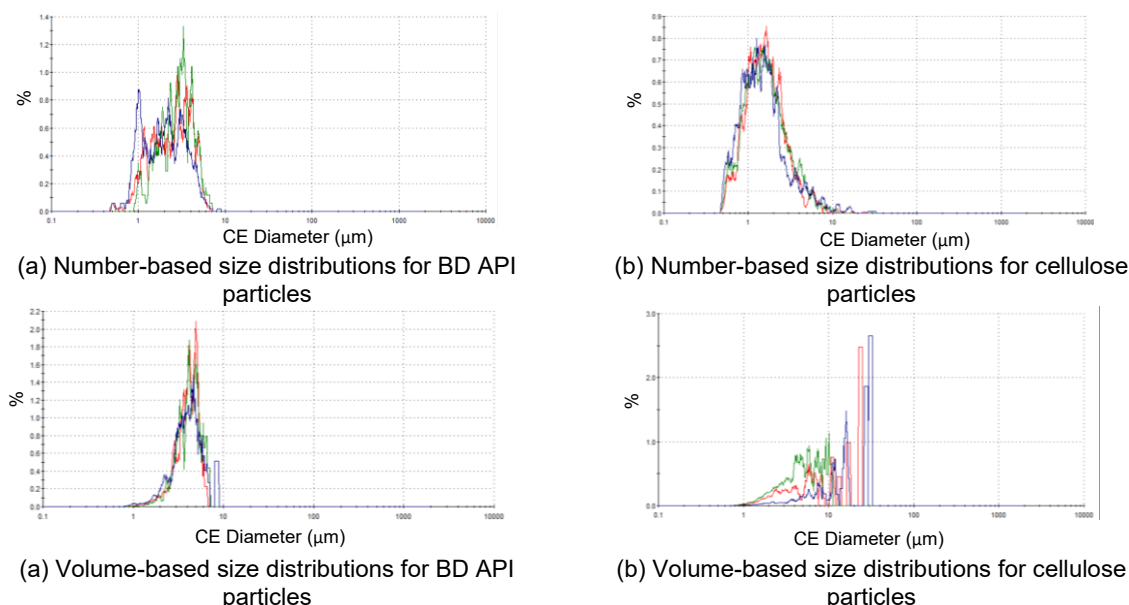


Figure 4. Overlaid Size Distributions of Different Particle Classes within the Beconase Nasal Spray at Different Temperatures. Colour-coded Lines: Red Line: 25 °C; Green Line: 37 °C; and Blue Line: 50 °C.

Figure 4 shows that temperature changes altered size distributions on both a number and volume basis. For BD particles, the number-based distributions showed a slight increase in particle size at 37 °C, followed by a reduction at 50 °C - indicating initial aggregation and subsequent deagglomeration or particle alterations. Volume-based data, however, confirmed a consistent increase in $D_v(0.9)$ values, suggesting the formation of larger agglomerates at higher temperatures that disproportionately influence the overall volume. On the other hand, cellulose particles demonstrated stable number-based sizes across temperatures, but a marked shift in volume-based metrics, with $D_v(0.9)$ increasing sharply at 50 °C up to ~31 μm. This suggests a degree of particle swelling or fusion occurred under the subjected thermal stress. It is important to highlight that the rise in unclassified fine particles at 50 °C implies temperature-driven deagglomeration.

Conclusion

This study demonstrated, for the first time, the application of a cold-stage MDRS for in situ monitoring particle size, shape and chemical ID of BD API particles in a commercial Beconase nasal spray formulation across clinically and environmentally relevant temperature conditions. The results highlight the temperature sensitivity of BD API, indicating a morphological change at elevated temperatures, whilst excipient cellulose particles exhibited greater structure resilience. Both number and volume-based size distributions suggest temperature-driven effects, particularly at 50 °C, where BD particles showed increased $D_v(0.9)$ values indicative of thermally induced agglomeration, and cellulose particles displayed marked volume expansion. Next steps and future direction will primarily focus on similar evaluations at lower temperatures, such as 5 °C. Furthermore, the evaluation of nasal spray bottles conditioned at various temperatures following inverted storage will be evaluated at different time periods to investigate the impact of temperature on nozzle positioning in nasal spray products. Alternative nasal spray products will also be evaluated.

References

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