

# Room Temperature Stable Formoterol Metered Dose Inhaler Systems with Consistent Delivery Characteristics

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## Summary

Formoterol fumarate is a long acting  $\beta_2$  agonist that has proved difficult to formulate as a Metered Dose Inhaler (MDI) product, due to both physical and chemical stability challenges. Formoterol MDIs that have made it to the market place have done so with limited shelf-life. This poster shows that by employing a novel bulking agent excipient, that formoterol fumarate MDI systems can be achieved with both stable content assay and consistent delivery characteristics.

## Introduction

Formoterol fumarate is indicated in the management of asthma and/or Chronic Obstructive Pulmonary Disease (COPD). Inhaled formoterol causes bronchodilation by relaxing the smooth muscle of the airways, thereby alleviating the symptoms of asthma and COPD.

Formoterol has proved problematic to formulate in MDIs due to its relatively low dose requirements (12mcg per dose) and chemical instability. This chemical instability can lead to a decrease in formoterol content on storage allowing only a limited shelf life.

## Historic Formulation Approach

Formoterol fumarate has previously been marketed as Foradil® Inhaler. This was a chlorofluorocarbon (CFC) based MDI solution formulation and provided a shelf life of 12 months refrigerated storage (2 to 8°C) prior to use, followed by a 3 month ambient/in use period<sup>[1]</sup>. However, with the phase out of CFCs and their replacement with HFAs (hydrofluoroalkanes), an opportunity arose to reformulate and at the same time improve on the performance of the older CFC products.

## Currently Marketed HFA Formoterol Products

Currently the only formoterol fumarate HFA-based MDI products available on the European market are 12mcg per actuation solution inhalers marketed as Atimos®/Forair®, Chiesi Pharmaceutica and Foradil® HFA, Novartis Pharma. The formulations contain the following components:

- Formoterol fumarate dihydrate (12mcg/actuation)
- HFA Propellant 134a
- Ethanol
- Hydrochloric acid

The hydrochloric acid is included to maintain a low solution pH of the formulation<sup>[1]</sup> which is believed to prevent the oxidative and/or hydrolytic degradation of certain Active Pharmaceutical Ingredients (APIs)<sup>[1]</sup> including formoterol fumarate dihydrate (FFDH).

Although this product addresses the environmental need for transition from a CFC to a HFA based product, the shelf life issue does not appear to have been addressed. Hence the non-ideal stability characteristics of the product remain evident from the proposed 15 months refrigerated shelf life prior to dispensing and the limited 3 month ambient shelf life.

## The 3M Drug Delivery Systems Approach

There are two categories of HFA MDI formulation; solutions and suspensions. Drugs formulated as solutions have the advantage of being fully homogenous and are likely to provide the best dosing uniformity. However, chemical degradation is more likely to occur with a solution system and this is evident with the solution formulation systems of formoterol discussed above. Suspension formulations on the other hand are less prone to drug degradation but can exhibit inconsistencies in dosing behaviour<sup>[2]</sup> that are especially apparent with low dose products such as formoterol fumarate. One way to overcome the drawbacks of suspension formulations is to include a sub-micron bulking agent that is widely compatible with both formulation and hardware components. 3M Drug Delivery Systems has previously demonstrated the applicability of this approach in overcoming dosing issues<sup>[2]</sup> seen in suspension formulations of formoterol. The latter approach has now been built on through careful

container closure system and excipient selection and further formulation optimisation, with the achievement of a highly stable formoterol fumarate MDI system with excellent dosing characteristics. Details of the system and its performance characteristics will now be highlighted.

### System Manufacture

A formoterol fumarate dihydrate (FFDH) MDI suspension formulation product batch was prepared at a laboratory scale using a cold filling procedure. The system was designed to deliver 200 actuations (i.e. 100 doses as a two actuation per dose product). The formulation details were as follows:

- 0.121mg/ml FFDH (12 mcg per dose)
- Sub-micron-lactose<sup>[2]</sup> as a bulking agent
- 3M DDS canister
- 50 mcl 3M DDS valve
- Ethanol (2%w/w)
- P227

Units were placed on stability storage at 40°C/75%RH for 6 months (figure 1) and 25 °C/75%RH for 13 months (figure 2) in the valve down orientation and tested employing a stability indicating HPLC assay method . A sample size of 5 units was used for each test point.

### Results and Discussion – Formoterol Fumarate Content Assay

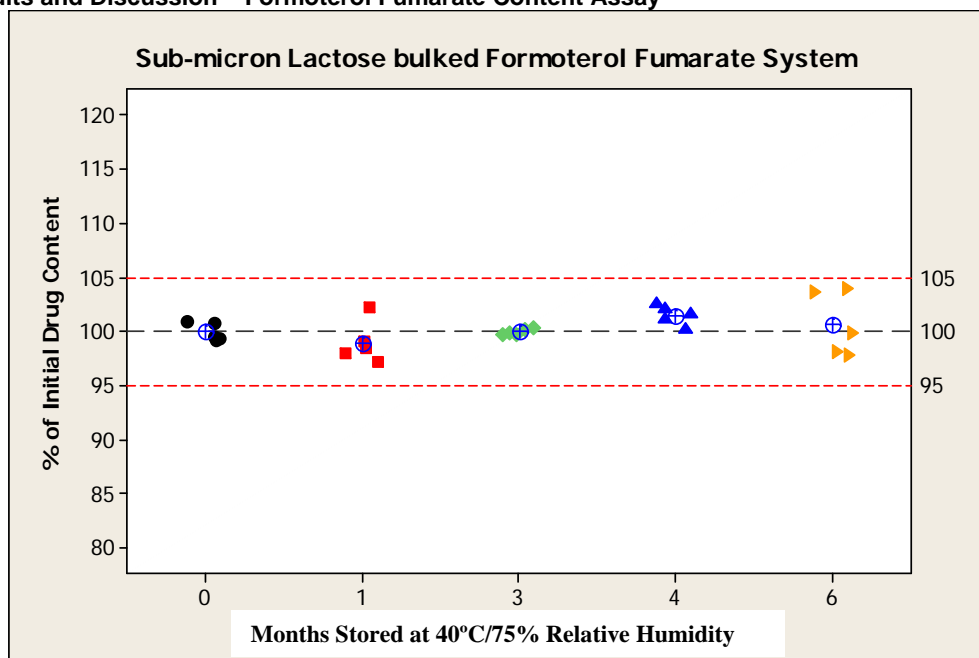
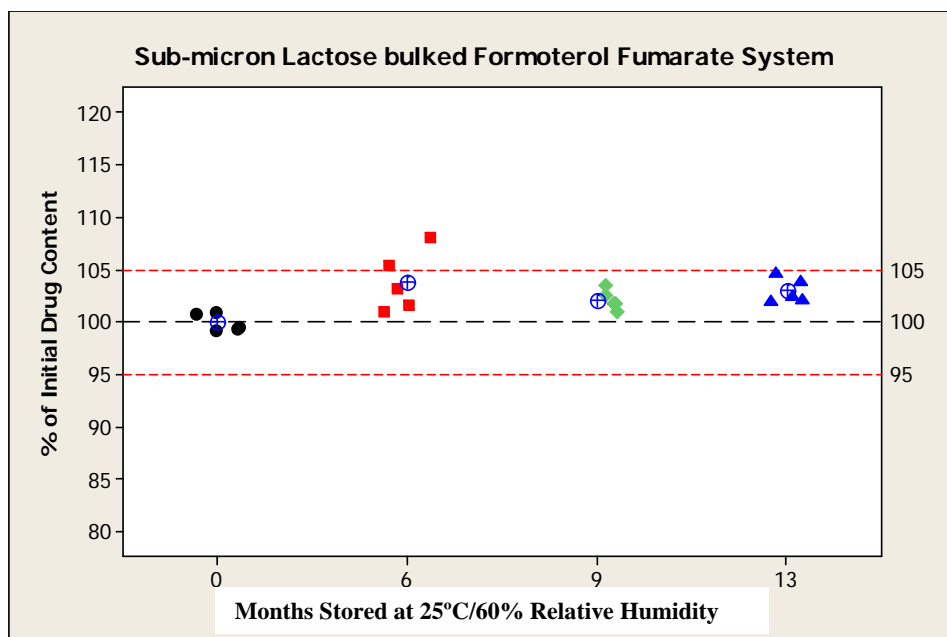


Figure 1: The FFDH content of a sub-micron lactose containing formulation over 6 months storage at 40°C/75% RH, expressed as a % of initial drug content

Time Point (Months)	0	1	3	4	6
% of Initial	100.0	99.0	100.0	101.2	100.7

Table 1: Data table showing average FFDH content over 6 months storage at 40°C/75% RH

The data generated employing the sub-micron lactose bulking agent show that the product exhibits no significant change<sup>[3]</sup> in FFDH content over 6 months storage at 40°C/75%RH.



**Figure 2: The FFDH content of a sub-micron lactose containing formulation over 13 months storage at 25°C/60% RH, expressed as a % of initial drug content**

Time Point (Months)	0	6	9	13
% of Initial	100.0	103.8	102.1	103.0

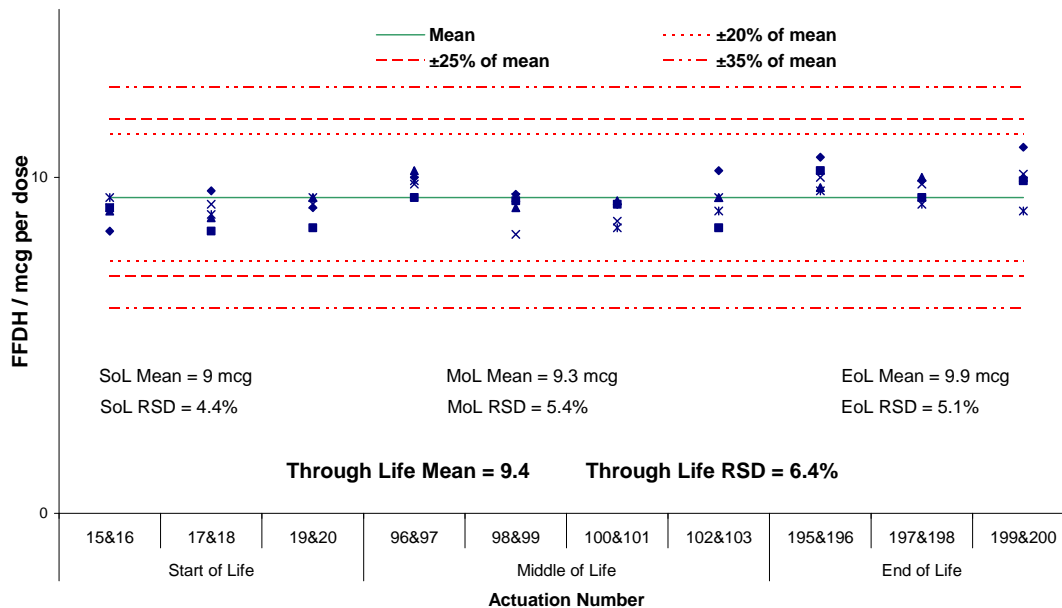
**Table 2: Data table showing average FFDH content over 13 months storage at 25°C/60% RH**

Since the high stress 40°C/75% RH data (figure 1) show no significant change out to 6 months (and minimal variability), when this data is evaluated in accordance with the International Committee of Harmonisation (ICH) guidelines<sup>[4]</sup>, the system would not require refrigerated storage and would have a shelf life of at least 12 months ambient/in use period. The data at 40°C/75% RH is supported by the 13 months storage data generated at 25°C/60%RH (figure 2), which similarly indicate that an ambient shelf life of more than 13 months is achievable. This in-use/ambient period is substantially longer than both the previously available Foradil® CFC and the currently marketed Atimos®/Forair® and Foradil® HFA products.

### Results and Discussion – Formoterol Fumarate Through Life Uniformity of Delivered Dose Testing

Samples were taken after storage at 40°C/75%RH for 13 months in the valve down orientation and tested at initial, 3, 6, and 13 month. 13 months data is shown below to demonstrate the consistent dosing profile and robustness of the sub micron lactose and the system as a whole even after extreme storage conditions.

Five units were tested through life (3 doses at start, 4 at middle and 3 at end of life) by firing 2 actuations (equating to one dose) into an USCA tube and analysing by HPLC.



**Figure 3: Through Life Uniformity of Delivered Dose (3, 4, 3 regime) after storage at 40°C/75%RH for 13 months. Chart shows all doses collected and +/- 20, 25 and 35% limits for a 100 dose product.**

The through Life Uniformity of Delivered Dose data show that all doses for the 100 dose product are within +/- 20% with low RSD values both for the overall performance and for performance at the start, middle and end of unit life.

### Results and Discussion – Formoterol Fumarate Fine Particle Dose & Fine Particle Fraction

Samples were taken after storage at 40°C/75%RH for 13 months in the valve down orientation. Five units were tested at start of life by firing 2 actuations (equating to one dose) into an Andersen Cascade Impactor and analysing by HPLC.

	Fine Particle Dose (mcg)	Fine Particle Fraction (%)
<b>13 Months Storage 40°C/75%RH (n=5)</b>	4.1	49.9
<b>% RSD</b>	7.6	5.4

**Table 3: Table of FPD (mcg) and FPF (%) after 13 months storage at 40°C/75%RH.**

### Conclusions

The formoterol fumarate system described is a HFA-based MDI product that unlike its predecessors, does not require refrigeration. The combined characteristics of the long shelf-life of the product and the consistent dosing behaviour make the product highly attractive in terms of manufacturing and supply logistics as well as patient use requirements.

### References

- [1] US Patent 6,716,414
- [2] Jinks P (2003). Preparation and Utility of Sub-micron lactose, a novel excipient for HFA MDI suspension Formulations. Conference proceedings from Drug Delivery to the Lungs XIV.
- [3] FDA draft Guidance For Industry Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Product, Section IV Drug Product Characterization Study defines a significant change as 'a 5 percent change from initial drug content assay value of the batch'
- [4] ICH Guidelines, Q1E, Evaluation of Stability Data, section 2.4.1.1 & Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf Life Estimation for Drug Substance or Products (excluding Frozen Products)