Validation of Moisture Determination for Pressurized Metered Dose Inhalers – An Alternative Approach
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Purpose
A novel approach was taken to validate a method for the determination of water content in pressurized metered dose inhalers (pMDI) containing a single active and combination therapies. The approach used is a streamlined version of the traditional approach, and consists of determining moisture values of spiked water additions and plotting the data to determine accuracy, linearity, and specificity. Moisture determination was assessed using a Karl Fischer coulometric titrator and the method was validated for method precision, linearity, range, and accuracy in two simple experiments.

Methods

Materials:
• Two different products, one containing Albuterol Sulfate (Product 1) (90 mcg Albuterol sulfate per actuation) and one containing two API’s (Product 2) were used in this study.
• Karl Fischer coulometric titrator (Mitsubishi Chemical Corporation
• Moisture meter CA-100 with Coulometric Option
• Mettler Toledo analytical balance (Model AX205 DeltaRange®)

Analysis Method:
1. Prime the canister and take initial weight (W1).
2. Actuate the canister (15 actuations) into the titration cell using an adaptor fitted to the valve stem.
3. Weigh the canister (W2) to confirm weight of product actuated.
4. Calculate the amount of water in the sample using the quotient of the weight of water titrated and the difference in the weight of the canister (W1-W2).

Results and Discussion

Protocol:
• The endogenous (baseline ppm) moisture level in each product was first determined for six replicate measurements from a single canister. The calculated RSD was used to evaluate precision.
• Three canisters of each product were then tested by actuating and spiking with water at an amount equivalent to 100, 800, and 1500 ppm of water in the product.
• The spike addition approach provides comprehensive data in fewer experiments than a traditional approach evaluation one parameter at a time (precision, accuracy, linearity, specificity, and range).
• Endogenous Amount Results:
The endogenous amount of water was similar between the two products despite the difference in active. Both products utilize HFA-134a as the propellant system. One product contains ethanol as a co-solvent while the other contains no co-solvent. Collection of this data also demonstrated precision of the method as indicated by the low RSD results.
Product 1 contained an endogenous amount of 476 ppm water with a 3% RSD (n=6)
Product 2 contained an endogenous amount of 440 ppm with a 2% RSD (n=6)

Figure 1: Plot of Actual versus Theoretical ppm Values for Product 1 and Product 2

Table 2: Statistical Results for Product 1

<table>
<thead>
<tr>
<th>Concentration Level (ppm)</th>
<th>Theoretical</th>
<th>Actual</th>
<th>Theoretical</th>
<th>Actual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline + 100 ppm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theoretical</td>
<td>576</td>
<td>680</td>
<td>633</td>
<td>696</td>
</tr>
<tr>
<td>Actual</td>
<td>576</td>
<td>724</td>
<td>633</td>
<td>601</td>
</tr>
<tr>
<td>Baseline + 600 ppm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theoretical</td>
<td>1276</td>
<td>1351</td>
<td>1322</td>
<td>1372</td>
</tr>
<tr>
<td>Actual</td>
<td>1276</td>
<td>1298</td>
<td>1333</td>
<td>1556</td>
</tr>
<tr>
<td>Baseline + 1500 ppm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theoretical</td>
<td>1976</td>
<td>1869</td>
<td>1958</td>
<td>2050</td>
</tr>
<tr>
<td>Actual</td>
<td>1976</td>
<td>2127</td>
<td>2028</td>
<td>2167</td>
</tr>
</tbody>
</table>

R2 = 0.9854

R2 = 0.9865

TABLE 3: Statistical Results for Product 2

<table>
<thead>
<tr>
<th>Confidence Interval</th>
<th>Y-Intercept</th>
<th>Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower 95%</td>
<td>-193.34</td>
<td>0.95</td>
</tr>
<tr>
<td>Upper 95%</td>
<td>140.26</td>
<td>1.18</td>
</tr>
</tbody>
</table>

The data presented in Table 1 were plotted (Actual Water Content (ppm) vs. Theoretical Water Content (ppm)) and the y-intercept, slope, and r² value were evaluated against the specifications presented below:

1. If the 95% confidence interval for the y-intercept from this plot includes zero then the data indicate that there was no matrix bias/effect and the method is specific for moisture determination and free from interferences.
2. If the 95% confidence interval for the slope includes 1 then the method is shown to be accurate over the range of moisture determinations from 100 ppm to 1500 ppm moisture.
3. If the coefficient of determination (r²) is between 0.9 and 1.1 then the method is shown to be linear over the range of 100 to 1500 ppm moisture.

Conclusions:
• The method provided the same results regardless of the active in the product. Each product evaluated includes zero indicating that the method was specific for water in the presence of Albuterol Sulfate in the case of Product 1 and in the presence of both actives in the case of Product 2. The inclusion of zero within the 95% confidence interval of the y-intercept also indicates that there were no matrix bias effects associated with the results generated by this method. In addition, the y-intercept values associated with both products is smaller than the endogenous amounts of water present in the products lending further evidence that the method is free from bias associated with the API present in the product.
• The value of 1 was within the 95% confidence interval for the slope for both products, indicating the method was accurate for both products and had a range from 100 through 1500 ppm spiked moisture. In addition, the slope of Product 1 was 0.99 and the slope of Product 2 was 1.07 indicating that very little divergence between theoretical and actual values exists for this method.
• Finally the coefficient of determination (r²) value was between 0.9 and 1.1 for both products indicating that the method was linear over the range of data evaluated. In addition, since the 95% confidence interval for the y-intercept of each product evaluated includes zero this indicated that the method had an implied linearity from the highest level evaluated down to the sensitivity limit of the instrument. Therefore, the linearity of the method had been shown to encompass values between the sensitivity limit of the instrument and 2167 ppm which was the highest level measured during spike addition experiments. In practice, moisture levels of less than 100 ppm are unlikely to be observed with ethanol containing products and as a result the practical linear range of the method is 100 ppm to 2167 ppm moisture for products with an ethanol co-solvent.
• Method validation for the determination of water content in pressurized metered dose inhalers has been streamlined to provide five conclusions from two experiments (method precision/endogenous amount determination and spike addition). Overall, it was shown that this novel approach provides more comprehensive results in a shorter amount of time than the traditional approach.