White Paper

Drying Oven vs. Halogen Moisture Analyzer

A Practical Guide to Compare Methods

This white paper will be of interest to anyone involved in moisture analysis applications in pharmaceutical, chemical, food and other industries.

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METTLER TOLEDO

Moisture affects the quality, shelf-life and usability of many products, including pharmaceutical substances, plastics and foodstuffs. Therefore, monitoring and determination of the moisture content in samples is an important application. Typically, loss on drying (LOD) using a drying oven is used as reference method, but this can be slow with many manual steps. Faster determination of moisture content can be achieved with new methods, such halogen moisture analyzers (HMA), which are easy to use and give a direct result in a fraction of the time. The challenge has been how to validate the HMA method and prove that the results are comparable with the drying oven method. This white paper will describe how.

In some industries, such as plastics, the HMA method has already been established as the new standard test method by ASTM (formerly the American Society for the Testing of Materials, now known as ASTM International)

1 Introduction

In the field of moisture determination using loss on drying techniques, a common question is:

"Can the drying oven method be replaced by fast halogen moisture analysis?"

The simple answer is yes, as long as the results obtained by the two methods are comparable. This means that it is necessary to show evidence that the results are equivalent within specific tolerances, which is not such a straightforward question to answer.

This white paper guides the analyst through this process. It explains the key decision criteria surrounding the choice of method and provides practical guidance on how to demonstrate that the two different methods (drying oven and halogen moisture analyzer) for establishing the moisture content of a sample deliver comparable results. In addition, two alternative and acceptable comparison approaches are outlined here: the first approach is based on specific process requirements (tolerances), and the second approach is based on statistical analysis of the data obtained.

2 Overview of moisture analysis

2.1. The importance of moisture content

Moisture content is a key quality parameter in most industries, including food, chemical, and pharmaceutical industries. Moisture content determines the quality and the cost of raw materials; it affects product quality (e.g. shelf life) and often influences the financial margin of finished goods. Moisture is also a key parameter for process control in many production processes. For these reasons, monitoring of moisture content is very important. These moisture determinations need to be carried out rapidly and reliably so that any interventions in the production process can be made promptly, to avoid costly interruptions.

2.2 Loss on drying using the drying oven method

For many substances the admissible moisture limits and the applicable measurement method have been established by government agencies (e.g. USP monographs [1,2]) or industry commissions (e.g. ICUMSA method for sugar [3]). Therefore, the specific measurement method for a given sample is called reference method. Typically, loss on drying using the drying oven method is used as reference method. LOD is robust and reliable, providing good results and only requires standard laboratory equipment (a drying oven and typically an analytical balance). The LOD method however is slow, usually requiring 2-3 hours or more for a measurement to be concluded and tedious due to many manual steps in the process. LOD is not suited for use on the factory floor, as the it takes too long to achieve a result and qualified lab personnel are required.

2.3 Halogen moisture analysis: a fast alternative

Halogen moisture analyzers also operate on the principle of LOD, but offer a much faster alternative to the drying oven method. Measuring moisture with an HMA normally takes 5 to 15 minutes. The other important advantage of the HMA is that they are easy to operate, providing a direct measurement with no calculations necessary. This makes halogen moisture analyzers well-suited for conducting reliable measurements both in the laboratory environment and at the production line by factory staff during shift operations. In some industries the halogen moisture analyzer method has already been established as an accepted method. For example, the ASTM published in 2012 a standard test method for determination of moisture in plastics use of an HMA [4].
A comparison of the two methods, along with advantages and disadvantages is presented in Table 1.

	Drying Oven	**Halogen Moisture Analyzer**
Principle	Thermogravimetry	Thermogravimetry
Measuring method	Heating of sample by convection. Sample is dried in the oven for a defined period of time at constant temperature. Mass is determined before and after drying. The moisture content percentage is determined from the difference in weight before and after drying.	Heating of sample through absorption of IR radiation from a halogen radiator. Continual determination of mass during drying process. The moisture content percentage is determined from the difference in weight before and after drying.
Advantages	• Often reference procedure (for historical reasons this procedure often forms part of legislation) • Several samples can be determined at the same time • Large sample volumes possible	• Quick measurement (typically 5 – 15 min.) • Simple handling, no calculations • Compact instrument. No balance or dessicator required • Suitable for at-line use
Disadvantages	• Very long determination period (hours) • Substances other than water may evaporate • Prone to errors because of the high level of handling and calculations involved • Unsuitable for at-line use - requires analytical balance and dessicator	• Substances other than water may evaporate

Table 1: Comparison of drying oven and halogen moisture analyzer methods for determining moisture content of a sample

3 Practical guide on how to replace the drying oven by a halogen moisture analyzer

The drying oven method can be replaced by the halogen moisture analyzer, if the results of the two methods are comparable. This chapter describes how to verify comparability. Two approaches are described to establish that the drying oven and HMA provide equivalent results: the first evaluates the comparability based on process requirements; the second is based on statistical data comparison.

In practice, the first approach is typically applied, as the acceptance criteria for comparability take the specific process context into account.

3.1 Evaluation of comparability based on process requirements

Broadly accepted guidelines for comparability are the pharmaceutical industry guidelines. For example, the United States Pharmacopeia (USP) Chapter <1010> "Analytical Data – Interpretation and Treatment" [5], states that an alternative method (in this case the HMA method) is comparable, if its results do not differ from the reference method (the drying oven method) by more than "an amount deemed important" [6]. To evaluate equivalency of the methods, their precision [7] and accuracy [8] should be compared. The decision on whether differ-

ences found between the two methods are within an acceptable range must be taken within the specific context of the application. This is based on the accepted tolerances in moisture content (%MC tolerances) of a production process, e.g. 'Statistical Process Control' [9]).

The typical and well-proven approach for comparison of drying oven versus HMA methods is to apply a range of acceptance to the mean value and standard deviation of the drying oven results, and then to verify that the HMA results are within this range (see example in Table 2).

Parameter	Unit	Acceptance criteria (formula / value)	Exemplary acceptance criteria
Accuracy	%MC	$\Delta\%MC_{(DO-HMA)} = \lvert\%MC_{DO} - \%MC_{HMA}\rvert$ (where '||' is the absolute value)	$\Delta\%MC_{(DO-HMA)} \leq 0.1\%MC$: excellent $\Delta\%MC_{(DO-HMA)} \leq 0.2\%MC$: good $\Delta\%MC_{(DO-HMA)} \leq 0.4\%MC$: acceptable $\Delta\%MC_{((DO-HMA)} > 0.4\%MC$: failed
Precision	SD	$Q = SD_{HMA}/ SD_{DO}$	$Q \leq 1.5$: good

Table 2: Exemplary tolerances applied as acceptance criteria for samples within a moisture range of ~2%MC to ~15%MC.

Note: these values are exemplary and it is the responsibility of the operator to verify their suitability for a specific process. For samples outside this moisture range other values may become applicable.

Definitions:

$\%MC_{DO}$ = mean of at least 6 measurements utilizing the drying oven method.
$\%MC_{HMA}$ = mean of at least 6 measurements utilizing the HMA method
Q = the quotient of SD_{HMA} and SD_{DO}
SD_{DO} = the standard deviation of at least 6 measurements utilizing the drying oven method
SD_{HMA} = the standard deviation of at least 6 measurements utilizing the HMA method

As demonstrated in the method collection for Pharma Excipients [10], a precision of the HMA method that is equal or less than 1.5 times the precision of the DO method is typically achievable (see section 4.1 below for further information).

Please refer to Appendix 1 for an exemplary method comparison for Ethyl Cellulose based on process comparability. If the comparability of drying oven and HMA methods shall be verified over a moisture range (e.g. between 1.00%MC and 8.00%MC), it is recommended to verify accuracy and precision at multiple (typically three, e.g. at 1.00%MC, 4.50%MC, 8.00%MC) moisture values representing the moisture range of interest.

Analysts, however, will often decide to focus on accuracy and precision at the critical moisture content only.

3.2 Evaluation of comparability by statistical means

Statistical methods may be applied to evaluate comparability of drying oven and HMA methods of LOD, as discussed in USP <1010> [5]. A proven statistical method for method comparison at a specific moisture content is to apply the generic statistical tool Student t-test [11, 12] which tests the statistical significance of the differences between the drying oven and HMA methods. If the differences are not found to be significant, the methods are considered equivalent. For method comparison over a moisture range, the linear regression analysis is often applied.

Other than the process requirement based approach described above (chapter 3.1), the statistical methods (e.g. Student t-test, linear regression analysis) compare two sets of data (results), testing if they are statistically equivalent. Statistical methods only look at the population of the samples and cannot take acceptable differences between the drying oven and HMA methods into account (typically process requirements allow for some differences in the results of the methods). The use of statistical methods may therefore lead to unnecessary restrictive acceptance criteria for the HMA method; subsequently the HMA method may be unnecessarily rejected, leading

to the loss of its benefits (speed, simplicity).

Microsoft® Excel™ offers standardized tools (Add-Ins) facilitating the statistical analyses by Student t-test or by linear regression analysis. This white paper shows how to perform step-by-step a Student t-test for measuring data at specific moisture content (single sample comparison, see Appendix 2) and a linear regression analysis for data over a range of moisture content (multi-sample comparison, see Appendix 3). This white paper does not elaborate on the statistical tools applied. Please refer to corresponding statistical textbooks for further information [13].

The added-value of statistical methods versus a process requirement based evaluation is rather limited, as moisture tolerances are typically quite large (process requirements) and allow for some differences between the methods (differences within the acceptance range). For this reason statistical methods are not regularly applied in practice.

4 Accurate moisture determination with halogen moisture analyzers

The pre-requisite for a successful method comparison is a good moisture method that delivers precise and accurate results. A sound drying method, good sample handling and accurate instrument calibration ensures accurate and consistent results.

4.1 Sound drying method and good sample handling

Well-suited (with respect to the sample) method parameters (drying temperature, drying program, sample weight, switch-off criterion) determine the precision and accuracy of the HMA method. Smart and consistent sample preparation improves both speed and repeatability. Please refer to the Guide to Moisture Analysis [14] for further information.

4.2 Accurate instruments

The most important factor influencing the accuracy of the moisture analyzer instrument is the variability of the heating temperature: the differences between the programmed target temperature and the actual temperature. Therefore accurate temperature adjustments and periodic testing with SmartCal and the temperature calibration kit are of critical importance in order to detect potential deviations early. Please refer to the white paper Moisture Analyzer Routine Testing [15] for further information. Well-suited (with respect to the sample) method parameters (drying temperature, drying program, sample weight, switch-off criterion) determine the precision and accuracy of the HMA method. Smart and consistent sample preparation improves both speed and repeatability. Please refer to the Guide to Moisture Analysis [14] for further information.

5 Conclusion

The drying oven method can be replaced by a fast halogen moisture analyzer for loss on drying (LOD) if the comparability of the two methods is demonstrated. This can be achieved by a straight-forward method comparison requiring less than 20 measurements and the evaluation of precision and accuracy based on process requirements. Typically, less than a day's work is required to establish documented evidence that halogen moisture analyzers provide comparable results to the drying oven method - but are much faster and easier-to-use.

Appendix 1: Exemplary method comparison at a specific moisture content based on process requirements

A1.1. Key Information and assumptions

- Sample: Ethyl Cellulose
- Drying oven and halogen moisture analyzer methods are described in the Method Collection Pharma Excipients available from METTLER TOLEDO [10]. The maximum moisture content of Ethyl Cellulose is 3.0 per cent determined by drying in the oven at 100-105°C for 2 hours; European Pharmacopoeia [16].
- The method comparison is conducted at a specific moisture content of ~1%MC

A1.2. Acceptance Criteria

The drying oven and HMA methods are considered comparable when fulfilling following acceptance criteria:

- Accuracy
  The differences of the mean values of drying oven and HMA method is less than 0.1%MC: $\Delta\%MC = ¦\%MC_{DO} - \%MC_{HMA}¦ \leq 0.10\%MC$
- Precision
  The standard deviation of the HMA method is smaller than 1.5 x that of the drying oven method:
  $Q \leq 1.5 = SD_{HMA} / SD_{DO}$

A1.3. Measurement data

A single homogenous batch of sample material with ~1%MC is measured both ten times with the drying oven method and the halogen moisture analyzer (HMA).

Measurement	**Moisture Content [%MC]**	
	HMA	Drying Oven
1	1.09	1.08
2	1.09	1.03
3	1.03	1.10
4	1.07	1.09
5	1.05	1.09
6	1.09	1.08
7	1.12	1.12
8	1.11	1.04
9	1.09	1.04
10	1.06	1.05

Table 3: Moisture content of Ethyl Cellulose measured with HMA and drying oven methods

A1.4. Data Evaluation

1. Mean value and standard deviation of the measurements for HMA and drying oven are calculated:

	Moisture Content	
	HMA	Drying Oven
Mean [%MC]	1.08	1.07
SD	0.027	0.029

Table 4: Mean values and standard deviation of moisture content measured using HMA and drying oven methods

2. Verification of acceptance criteria:

a. Accuracy
   $\Delta\%MC_{(DO-HMA)} = |1.08\%MC - 1.07\%MC| = 0.01\%MC$
   Conclusion: The acceptance criteria for accuracy (<0.10%MC) is fulfilled.

b. Precision
   $SD_{HMA} = 0.027$, $SD_{DO} = 0.029$;
   $Q = SD_{HMA} / SD_{DO} = 0.027 / 0.029 = 0.93$
   Conclusion: The acceptance criteria for precision ($SD_{HMA} \leq 1.5 \times SD_{DO}$) is fulfilled

A1.5. Conclusion

The differences between the results of the HMA method compared to the drying oven method do not differ by more than an amount deemed important and are acceptable. Therefore, the halogen moisture analyzer method is comparable to the drying oven method.

Appendix 2: Exemplary method comparison at a specific moisture content by statistical means

A2.1. Introduction

This appendix shows how to conduct a method comparison for a single sample by statistical means. For this test, a number of replicate samples from a single homogenous batch are measured by both drying oven method and moisture analyzer. The results are then compared by applying the Student t-test.

This chapter provides step-by-step guidance, however it does not explain the statistical theory applied. Please refer to the corresponding literature for further information [13].

A2.2. Comparison of measurement results

Sample size determination is the act of choosing the number of observations to include in a statistical sample and an important feature of any empirical study. In practice, the sample size used is determined based on the experience of data collection and the need to have sufficient statistical power. For further information please refer to "ASTM E122 - 09e1, Standard Practice for Calculating Sample Size" [17]. Experience shows a minimum number of six measurements per method (for drying oven and for HMA) are required. Larger sample sizes will lead to higher statistical power of the analysis.

A2.3. Measurement data

A minimum of six measurements of a single homogeneous batch using the drying oven and a minimum of six measurements of the same batch using the halogen moisture analyzer must be made. It is not necessary to have the same number of measurements for both methods. In the following example, a laboratory performs ten measurements using the HMA and eight using the conventional oven drying method. The results are shown in Table 5.

Measurement number	**Moisture Content [%]**	
	HMA	Drying Oven
1	5.77	5.51
2	5.55	5.72
3	5.49	5.58
4	5.64	5.62
5	5.90	5.56
6	5.89	5.64
7	5.60	5.67
8	5.96	5.84
9	5.82	
10	5.63	

Table 5: Results of two measuring methods using replicate samples from a single homogeneous batch

A2.4. Data Evaluation using Microsoft® Excel™

Microsoft® Excel™ can be used to compare the results of these two methods. Firstly, ensure that the Add-In called "Data Analysis" is installed. If not, it can be installed in Excel 2010 by:

a) Click on File → Options → Add-Ins → Excel Add-Ins → Go

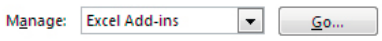

Figure 1: Add-Ins selection box in Excel

b)Select "Analysis ToolPak – VBA"

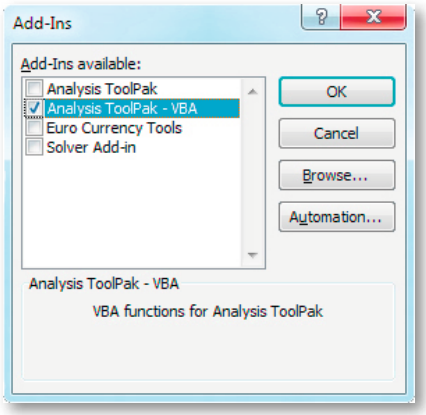

Figure 2: Add-Ins window in Excel

c) Press "OK" to finish the installation

d) Click on "Data" and select "Data Analysis"

Figure 3: Menu bar for Data Analysis

e) Select "t-Test: Two-Sample Assuming Unequal Variances" in the Data Analysis window and press "OK".

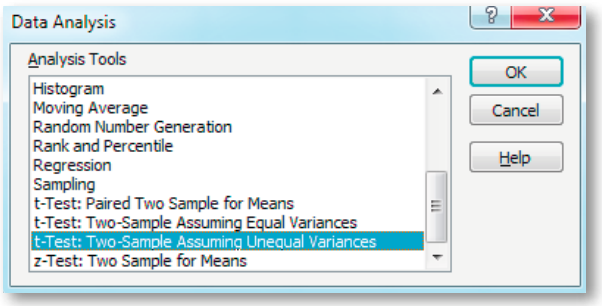

Figure 4: t-Test selection in Data Analysis window

This option is selected, as the variance of drying oven and HMA methods typically is not the same as they are different methods.

Definition: the sample variance is the square of the variance of the standard deviation of the sample [13].

f) Select the input range and write "0.0" in the field "Hypothesized Mean Difference, as we test the assumption that the mean values are equal". An alpha of 0.05 indicates a confidence level of 95%. Press "OK" to continue.

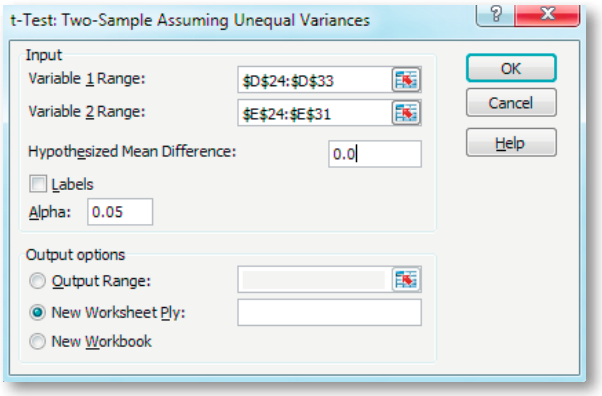

Figure 5: t-Test window

g) Excel calculates the t-Test and provides the results as shown in Figure 6.

	A	B	C
1	**t-Test: Two-Sample Assuming Unequal Variances**		
2			
3		*Variable 1*	*Variable 2*
4	Mean	5.725	5.6425
5	Variance	0.026872222	0.01065
6	Observations	10	8
7	Hypothesized Mean Difference	0	
8	df	15	
9	t Stat	1.30143794	
10	P (T<=t) one-tail	0.106371718	
11	t Critical one-tail	1.753050356	
12	P (T<=t) two-tail	0.212743435	
13	t Critical two-tail	2.131449546	

Figure 6: Summary output of t-Test analysis

A2.5. Description of Summary output of t-Test analysis

Figure 6 contains the mean values of the two measurement methods (HMA in cell B4 and drying oven in cell C4), the variances (cells B5 and C5), the number of observations (cells B6 and C6), the hypothesized mean difference (value = 0, meaning no difference between the two measuring methods is assumed, cell B7), the degree of freedom (df), cell B8), plus four other entries. The first two (lines 10 & 11) refer to a one-tailed t-Test and are not of interest here. The last two entries (lines 12 and 13) refer to the two-tailed test, which we are applying (see below). The probability of a higher value of t_{Stat} is shown in cell B12. The tabular t-value $t_{Critical}$ is shown in cell B13. Please refer to statistical textbooks for further information [13].

A2.6. Data Comparison

The data of the summary output (Figure 6) indicates that the mean values of the two measuring methods are slightly different and the variance of the oven drying method is smaller than the variance of the HMA method. Are these differences significant? Not necessarily. Slight differences can be caused by experimental error.

To check if the methods are comparable the "Student's t Test" method is applied (more specifically: two-tail Student t-test with a confidence level of 95%). It compares the calculated t_{Stat} value based on the measurements with the value $t_{Critical}$ (two-tail), a tabular value taken e.g. from a standard statistical textbook. If t_{Stat} is less than $t_{Critical}$, the methods are equivalent (by laws of statistics [13])

A2.7. Conclusion

The t_{stat} value of our example is 1.30 (see figure 6, line 9, t_{Stat}) and is less than $t_{Critical}$ (see figure 6, line 13, $t_{Critical}$ two-tail), which is 2.13.

In conclusion, based on the results obtained, the drying oven and halogen moisture analyzer methods are equivalent.

Appendix 3: Exemplary method comparison over a range of moisture content by statistical means

Linear regression analysis is widely used for comparison of measuring data over a range. It requires a series of samples covering the expected range of moisture content.

A3.1. Measurement Data

In order to perform a linear regression analysis, a variety of materials and multiple batches have to be measured in duplicate by HMA method and drying oven method. As an example, assume that a range of 0% to 10% moisture content is required. A laboratory examined 60 batches in duplicate for loss of moisture on drying using an HMA method and oven drying method.

Measurement	Moisture Content [%]		Measurement	Moisture Content [%]		Measurement	Moisture Content [%]	
	Oven	HMA		Oven	HMA		Oven	HMA
1	0.2	0.1	21	4.9	5.1	41	8.5	8.6
2	3.1	3	22	1.3	1.4	42	7.2	7.5
3	4.4	4.5	23	2.6	2.7	43	8.2	8.4
4	4.1	4.3	24	1.6	1.7	44	5.6	5.8
5	4.5	4.6	25	2.2	2.3	45	0.1	0.2
6	5.5	5.5	26	2.7	2.7	46	1.6	1.9
7	0.1	0.1	27	5.2	5.4	47	2.6	2.5
8	0.6	0.6	28	1.7	1.7	48	2.4	2.7
9	3.2	3.3	29	0.1	0.2	49	4.3	4.3
10	0.1	0.1	30	5.9	6.1	50	9.4	9.7
11	0.1	0.2	31	9.1	9.1	51	1	0.6
12	0.1	0.1	32	5.9	6.2	52	9.6	9.7
13	0.1	0.2	33	0.6	0.2	53	9.1	9.3
14	0.2	0.3	34	4.6	4.7	54	0.1	0.1
15	0.7	0.6	35	5.5	5.2	55	0.3	0.3
16	8.8	8.6	36	4.8	4.9	56	0.1	0.1
17	1.1	1.1	37	0.2	0.2	57	3.5	3.6
18	0.8	0.9	38	3.2	3.3	58	4.6	4.6
19	0.9	0.9	39	0.1	0.1	59	3.3	3.2
20	4.3	4.1	40	4.5	4.3	60	7.1	7.1

Table 6: Measuring data of a variety of materials and multiple batches

A3.2. Data Evaluation using Microsoft® Excel™

Microsoft® Excel™ can be used to compare this data. Make sure the Add-In called "Data Analysis" is installed (see A2.4).

a. Click on "Data" and select "Data Analysis".

Figure 7: Menu bar for Data Analysis

b. Select "Regression" in the Data Analysis window and press "OK".

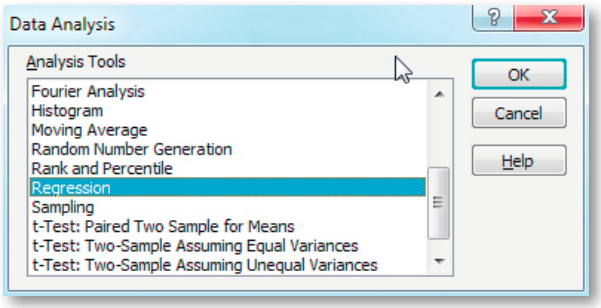

Figure 8: Regression selection in Data Analysis window

c. Select the input range of the data. Furthermore, select "Residuals", "Residual Plots" and "Line Fit Plots" as indicated in Figure 9.

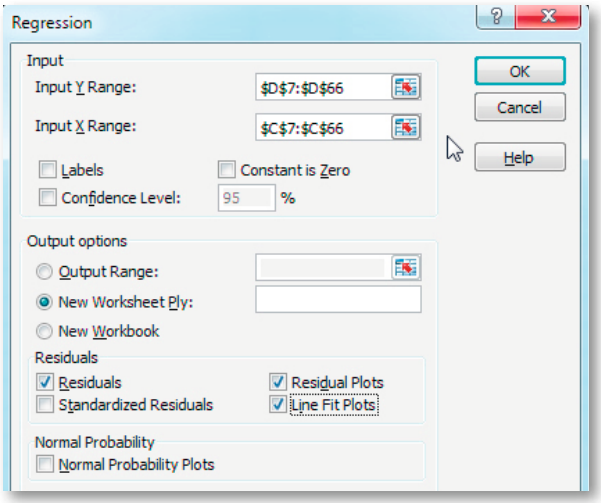

Figure 9: Regression window

d. Excel calculates the linear regression analysis and provides the results as shown in Figure 10.

	A	B	C	D	E	F	G	H	I
1	SUMMARY OUTPUT								
2									
3	*Regression Statistics*								
4	Multiple R	0.99874273							
5	R Square	0.99748704							
6	Adjusted R S	0.99744372							
7	Standard Error	0.14958648							
8	Observation	60							
9									
10	ANOVA								
11		*df*	*SS*	*MS*	*F*	*Significance F*			
12	Regression	1	515.151519	515.151519	23022.3841	4.2097E-77			
13	Residual	58	1.29781468	0.02237612					
14	Total	59	516.449333						
15									
16		*Coefficients*	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
17	Intercept	-0.0007937	0.0293199	-0.02707032	0.97849657	-0.05948387	0.05789647	-0.05948387	0.05789647
18	X Variable 1	1.01335833	0.00667864	151.731289	4.2097E-77	0.99998959	1.02672708	0.99998959	1.02672708

Figure 10: Summary output of regression analysis

A3.3 Data Comparison

On the summary output (Figure 10), the values of slope (cells F18 & G18), intercept (cells F17 & G17) and correlation coefficient (cell B5) are checked to access the equivalency of drying oven and HMA methods. The exemplary data of Table 6 is visualized as 'line fit plot' (Figure 11).

The correlation coefficient r^2 (Figure 10: "R Square" cell A5) indicates the closeness of fit of the HMA values versus drying oven values. As per laws of statistics [13], the correlation coefficient ranges from 0 to +1. An r^2 of 1.0 indicates that the regression line perfectly fits the data (see Figure 10: "Coefficients, X Variable 1" in cell B18) and that the intercept (Figure 10: "Coefficients, Intercept" in cell B17) is zero.

However, real data always shows some variability. A typical minimal value for the correlation coefficient to be used for method comparison as addressed in this white paper is 95%. This indicates that with a probability of 95% a HMA result corresponds to the drying oven result, taking two margins of error into account (these correspond to approx. two standard deviations).

For the purpose of comparing moisture methods (drying oven vs. HMA), the typical minimal acceptable correlation coefficient r^2 is 0.95. A correlation coefficient r^2 of 0.99 indicates an excellent correlation of the methods [18].

At 95% confidence, the slope varies from 0.99 to 1.02 (see Figure 10: "Lower 95%" and "Upper 95%", "X Variable 1" in cells F18 and G18) and therefore encompasses unity. The intercept varies from -0.05 to 0.05 (Figure 10: "Lower 95%" and "Upper 95%", "Intercept" in cells F17 and F18) and encompasses zero (by laws of statistics [18]).

Line Fit Plot

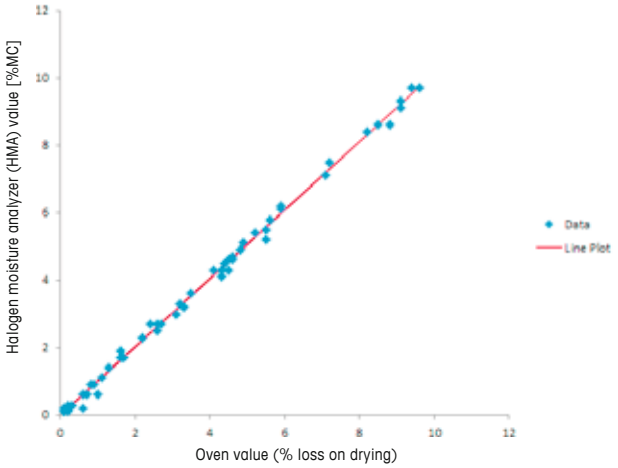

Figure 11: Regression analysis line fit plot

A3.4 Assessing the Quality of Regression Models

It is recommended not to rely on a high value of the correlation coefficient, r^2, e.g. > 0.99, and slope and intercept values on their own. It is good practice to additionally examine the plot of the residuals of the regression model to ensure that the scatter is reasonably uniform (homoscedastic) over the range and does not show a structured pattern (heteroscedastic - see Figure 13) [17]. The residual plot from our example is shown in Figure 12. The plot shows a uniform, random pattern and no structure is detectable. For this reason it is acceptable.

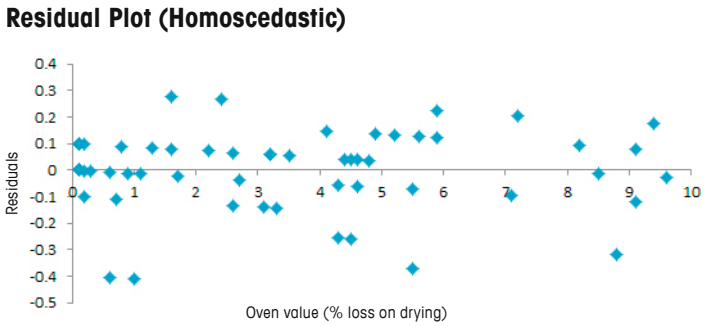

Figure 12: Uniform, random pattern (homoscedastic) of the example, indicating a good fit for a linear model. In other words, no structure is detectable.

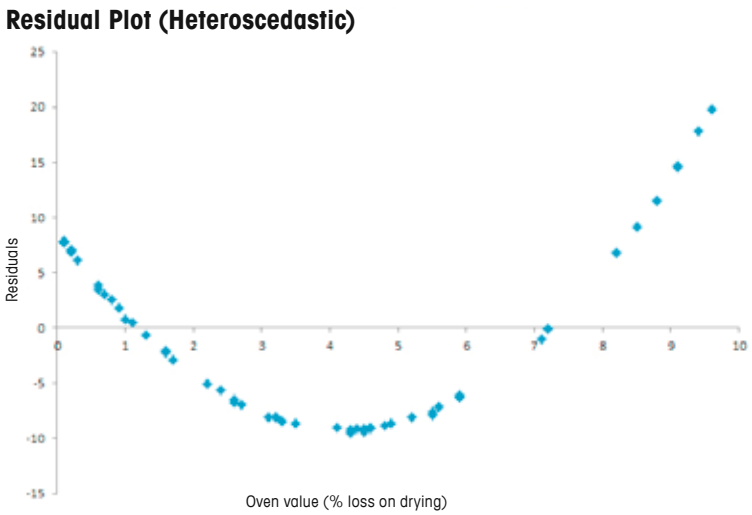

Figure 13: Structured, non-random pattern (heteroscedastic), suggesting a better fit for a non-linear model.

A3.5 Conclusion

In the summary output of the example (Figure 10), the correlation coefficient is >0.99, which is very good. Furthermore, the residual plot shows a uniform, random pattern.
In conclusion, based on the results obtained, the drying oven and halogen moisture analyzer methods are equivalent.

6 References

1. USP Monograph: 2013 The United States Pharmacopeial Convention; Methylcellulose, May 1, 2014; Specific Tests; section 'Loss on Drying (731)'
2. USP; General Chapter; <731> Loss on Drying
3. ICUMSA (International Commission for uniform Methods of Sugar Analysis); Methods Book (2013); Method GS2/1/3/9-15 (2007); The Determination of Sugar Moisture by Loss on Drying – Official
4. ASTM (American Society for Testing and Materials) International; D6980 – 12; Standard Test Method for Determination of Moisture in Plastics by Loss in Weight (2012)
5. USP General Chapter <1010>, Analytical Data - Interpretation and Treatment, 2007
6. USP General Chapter <1010>, Analytical Data - Interpretation and Treatment, 2007, section: Comparison of analytical methods
7. USP General Chapter <1010>, Analytical Data - Interpretation and Treatment, 2007; section: Precision: "Precision is the degree of agreement among individual test results when the analytical method is applied repeatedly to a homogeneous sample."
8. USP General Chapter <1010>, Analytical Data - Interpretation and Treatment, 2007; section Accuracy: "Comparison of the accuracy (…) of methods provides information useful in determining if the new method is equivalent, on the average, to the current method."
9. Statistical Process Control: NIST/SEMATECH, e-Handbook of Statistical Methods, http://www.itl.nist.gov/div898/handbook, April 2012
10. Method Collection 'Pharma Excipients', Mettler-Toledo AG, Greifensee 2014, doc.11795695
11. Student t-test reference: Richard Mankiewicz (2004). The Story of Mathematics (Paperback edition). Princeton, NJ: Princeton University Press. p. 158. The t-test was devised in 1908 as a cheap way to monitor the quality of stout in the Guinness brewery in Dublin, Ireland by a chemist named "William Sealy Gosset" whose pen name was "Student"
12. Hazewinkel, Michiel, ed. (2001), "Student test", Encyclopedia of Mathematics, Springer, ISBN 978-1-55608-010-4
13. John A. Rice (2006), Mathematical Statistics and Data Analysis, Third Edition, Duxbury Advanced
14. Guide to Moisture Analysis, Mettler-Toledo AG, Greifensee 2012, doc.11796096
15. Moisture Analyzer Routine Testing, White Paper, Mettler-Toledo AG, Greifensee 2012, doc. 30029586
16. European Pharmacopoeia 5.0, Ethylcellulose, 01/2005:0822
17. ASTM E122-09e1: Standard Practice for Calculating Sample Size to Estimate, With Specified Precision, the Average for a Characteristic of a Lot or Process
18. Data Fitting and Uncertainty. "A practical introduction to weighted least squares and beyond", T. Strutz, Vieweg,Teubner, ISBN 978-3-8348-1022

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