Method Validation

16
Application Brochure

METTLER TOLEDO
Titrators

Validation of Titration Methods

A Guideline for Customers

METTLER TOLEDO

Validation of Titration Methods

This bulletin includes selected examples for the validation of titration methods. These have been tested with all possible care in our lab with the analytical instruments mentioned in this bulletin. The experiments were conducted and the resulting data evaluated based on our current state of knowledge. However, this bulletin does not exempt you from personally testing its suitability for your intended methods, instruments and purposes. As the use and transfer of an application example are beyond our control, we can therefore not accept any responsibility.

When chemicals and solvents are used, the general safety rules and the directions of the producer must be observed.

Editorial

Dear Reader

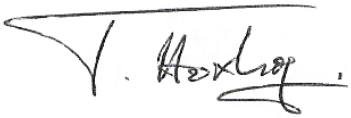
The quality of your product depends on the analyses performed in quality control. That is why you rely on first-rate analytical instruments for the most accurate and precise results, and product quality.

This application brochure addresses analysts from regulated laboratories in the various industries. It provides not only an explanation of the key aspects of the validation of titration methods but also gives details of strategies and specific recommendations. A good analytical method is simple and accurate; various degrees of automation might be considered for increased productivity and reducing human errors. Such a thorough approach also brings added advantages of cost-savings and environmental protection. In this document you will find universal protocols for method development explained by means of three common titration applications.

As every laboratory is unique the approach and main emphasis might vary. We intend to inspire you to think of ways to validate your specific titration methods. Do not hesitate to contact your local Mettler-Toledo representative for tailored support.

We thank you for your trust in our analytical Solutions and wish you great success in titration with METTLER TOLEDO instruments.

Schwerzenbach, March 2015



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1 Summary

The goal of all measurements and determinations is to generate correct results. Correct results are accurate compared to the true value and precise in their statistical deviation [1]. By validating the analytical methods an important step is taken in achieving this goal. A detailed method is compiled and applied in order to obtain correct results.

A method must describe every step, from the sampling to the final result. The outcome from the method validation can be used to judge the quality and consistency of analytical results, which is an integral part of any good analytical practice. In other words, the validation of a method proves whether or not the developed method fulfills the specific requirements for the intended analytical application.

Validation of analytical methods is required by most regulations and quality standards that impact laboratories. Consider the USP and ICH guidelines: Here eight parameters have to be considered when validating analytical methods, namely accuracy, precision, specificity, linearity, limit of detection, limit of quantitation, range and robustness [1,2]. Both the USP and ICH guidelines are universal and apply to any analytical procedure and technique used in a regulated environment.

Three different titration methods are validated in the examples that follow starting with the determination of sulfuric acid (acid/base titration), followed by the determination of chloride (precipitation titration) and finally the determination of water content (Karl Fischer titration). These applications serve as a nonbinding guideline, as a means of showing how a titration method can be validated.

2 Basics of Validation

Validation is a requisite of any regulated environment and the foundation of quality in the laboratory. The overall validation process consists at least of four distinct steps, starting with software validation/qualification and the hardware (instrument) validation/qualification. This is followed by the method validation and finally rounded off by the system suitability [3]. The basic steps in the validation process are shown in the *Figure 1* below.

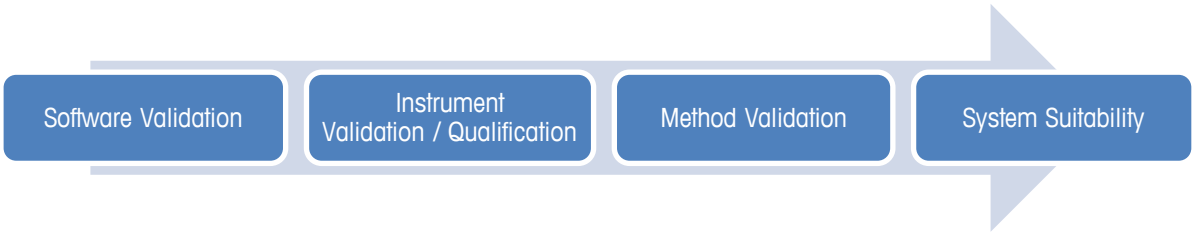


Figure 1. The basic steps in the validation process.

A correctly documented and well-defined validation process serves as evidence for the regulatory agencies that the system (software, instrument, method and controls) is suitable for its intended use.

The method validation is a critical part of the whole validation process. It is used to provide documented evidence that the analytical procedure applied for a specific test is suitable for its intended use.

The correct sequence of validation experiments is not predefined in any guideline, and the optimal sequence may depend on the method itself. The most significant parameters for the validation of titration method are accuracy, precision, linearity and systematic errors, limit of quantification, and robustness. The other parameters are mostly predefined as the measurement range and specificity of standard substances (ensured by the choice of the adequate titrant). For quantitative methods such as titration the limit of detection is not a crucial parameter to be validated (only in very special cases).

The complete analytical procedure from taking the sample to result calculation and documentation include the following evaluation procedure:

- Use of a standard substance (primary standard) allows the assessment of accuracy.
- Statistical evaluation of multiple sample series shows precision and repeatability.
- Varying the analyte concentration indicates the linearity and systematic errors.
- If the results show no deviations by being perturbed by small but deliberate variations, then the method can be considered as robust.
- The smallest amount of sample that can be titrated with a good precision gives the limit of quantification.

Recommended acceptance criteria (limits) for different parameters are subject to the tested methods. Other methods e.g. analysis of foods and drugs may require much stricter limits.

3 Steps of Method Validation and Recommended Limits

The titrant to be used has to be standardized first against a primary standard. Primary standards are commercially available substances with the following characteristics [4-6]:

- Clearly defined composition and high degree of purity.
- Large equivalent mass (minimizing weighing errors).
- Accurately weighable by being not hygroscopic, insensitive to oxygen and/or CO_2.
- Chemically stable in solutions and easily soluble in adequate solvents.
- Fast and stoichiometric reaction with the titrant.

The typical combination of titrant and primary standard is shown in the Appendix.

3.1 Accuracy

Accuracy can be described as the closeness of agreement between the value that is adopted, either as a conventional, true or accepted reference value, and the value found. Multiple series of standard samples or of samples with exactly known concentration are titrated. The analyte concentration therein should cover the complete determination range, including concentrations close to the quantitation limit, one in the middle and one at the high end of the determination range. Therefore, the sample size should be varied randomly, resulting in a consumption of titrant of 20% to 90% of the burette volume. The refilling of the burette must be avoided.

The mean value of each series represents the result of the titration. The difference between this mean value and the true value (i.e. the known concentration) allows the determination of accuracy. For a better understanding of the definitions, an illustration of accuracy and precision is shown in *Figure 2*.

Recommendation

Results obtained should not deviate from the true value by more than 0.3%.

3.2 Precision

The definition of ICH for precision of an analytical procedure is the closeness of agreement among a series of measurements obtained from multiple sampling of the same homogeneous sample [2]. Precision may be subdivided into three levels: repeatability, intermediate precision and reproducibility. Repeatability expresses the precision under identical operating conditions over a short interval of time (also termed as intra-assay precision). Intermediate precision expresses variations within laboratory variation, such as different days, different analysts or equipment. Reproducibility expresses the precision among different laboratories, involved in collaborative studies. In the following validation examples, the sub-parameter repeatability is chosen to express the precision of the method.

Multiple series of a sample are titrated, where the analyte concentration cover the complete determination range. This is done by varying the sample size in order to have a wide range of titrant consumption of 20% to 90% of the burette volume. An outlier test according to Grubbs [4] is performed on the results of these sample series in order to eliminate distinct outliers. Then a statistical

evaluation is performed on each sample series to get the mean value and the relative standard deviation (RSD). The RSD expresses the precision of the method.

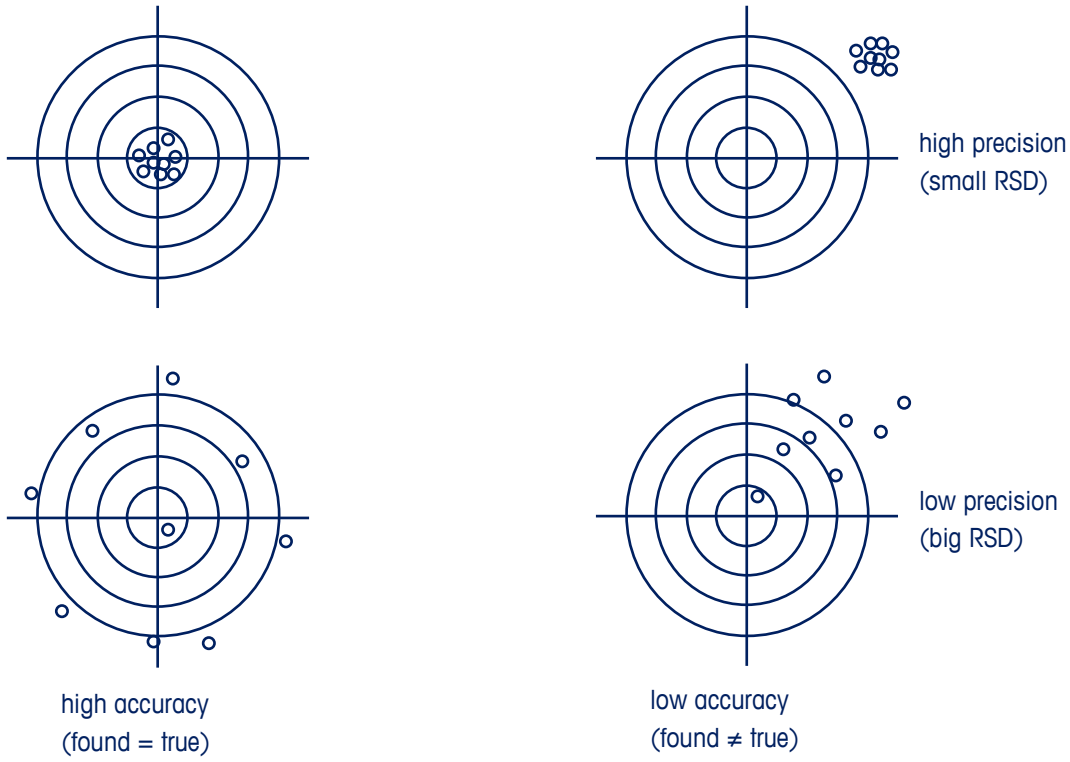


Figure 2: Illustration of accuracy and precision.

Recommendation

The RSD obtained from individual sample series should not be greater than 0.3%.

3.3 Specificity

Specificity can be defined as the ability to measure unequivocally the analyte in the presence of components which may be expected to be present in the sample. Other reputable authorities such as IUPAC and AOAC use the term "selectivity" for the same meaning. This reserves the use of "specific" for those procedures that produce a response for a single analyte only. Specificity is demonstrated by the ability to discriminate between other compounds in the sample or by comparison to reference substances. Specificity studies should also evaluate interferences that may be caused by the matrix, e.g., other acids for acid base titration, or similar ions by using ion selective sensor, etc. The absence of matrix interferences for a given method should be demonstrated by the analysis of several independent sources of control matrix.

3.4 Linearity and Systematic Errors

Linearity is the ability of the analytical method to obtain test results that are directly proportional to analyte concentration within a given range [1,2,7]. Traditionally, the recommended range is between 20% and 90% of the burette volume. In titration the analyte concentration depends on the sample size, sample concentration and on the solvent volume added for the analysis. By varying the sample size and thereby the analyte concentration, the linearity of a titration method may be detected in the range of interest and reported as the variance of the slope of the regression line. The regression line is described by the formula $y = a + bx$, where a represents the intercept on the y-axis and b is the slope of the regression line.

Systematic errors of a titration are for example disturbing influences due to the method itself or to solvent blank values. In the linear regression systematic errors show up as a significant deviation of the y-axis intercept a of the regression line from the zero point coordinates (see *Figure 3*), i.e. a_{sys} is clearly different from zero.

Recommendation

The systematic error a_{sys} should be smaller than 15 µL. If this systematic error cannot be avoided by optimizing the method or the reagents, then the a_{sys} must be included in the calculations in order to generate results that are free from the influence of a systematic error.

There are two practical ways to check the linearity of the analytical procedure:

A) The regression coefficient (R^2) of the linear regression (graphical evaluation of the titrant consumption vs sample size) must be greater than the recommended limit, depending on the demanded accuracy for the specific determination, i.e. $R^2 > 0.995$.

B) A significant positive or negative slope b (resp $\Delta R/\Delta V$) of the regression line in *Figure 4* (graphical evaluation of the determined concentration vs. sample size) indicates a non-linearity of the titration method, meaning that the result depends on the sample size.

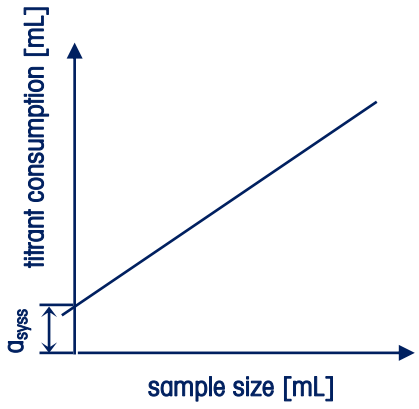


Figure 3. Interception of the regression line with the y-axis.

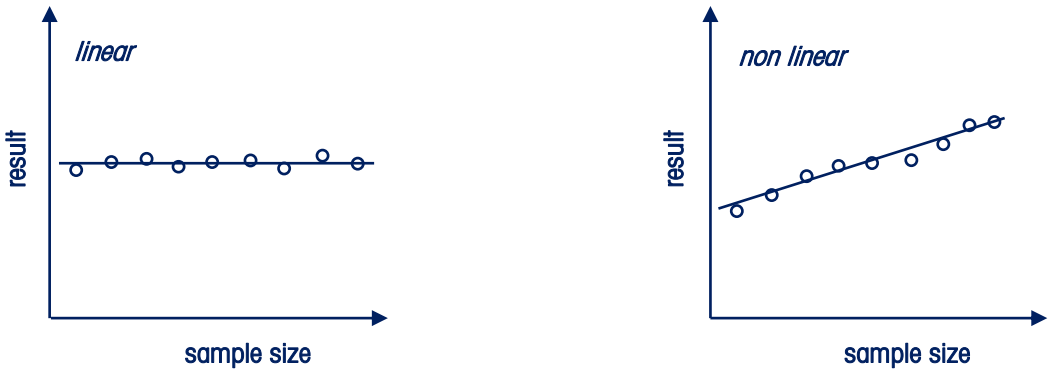


Figure 4. Determination of linearity by graphical evaluation of the results vs. sample size.

Recommendation

If ΔR/ΔV is greater than 0.1%, a non-linearity has to be assumed.

3.5 Limit of Detection

The limit of detection (LOD) is defined as the lowest concentration of analyte in the sample that can be detected but not necessarily quantified as an exact value. It is mostly expressed as the concentration of analyte as mol/L or ppm. There are various possible approaches for determining LOD. One method is visual examination. Here it is expected that no detectible color change should occur when using a photometric sensor in complexometric titrations.

3.6 Limit of Quantitation

Limit of quantitation (LOQ) is defined as the minimum concentration of the analyte in the sample that produces quantitative measurements with acceptable precision and accuracy. LOQ is determined by titrating several sample series. Each series is titrated with a continuously reduced amount of sample. The relative standard deviation (RSD) of the precision of six repetitive injections is plotted against the analyte amount. The amount that corresponds to the below defined required precision is equal to the limit of quantitation. The approach is illustrated in *Figure 5*.

Recommendation

The Limit of Quantitation is the smallest amount of substance in mmol, which can be titrated with a good precision, expressed as RSD ≤ 0.3%.

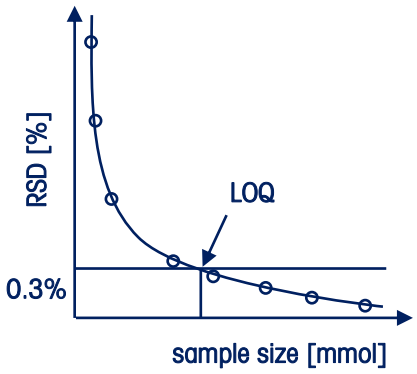


Figure 5. Limit of quantitation based on selected precision.

3.7 Range

Range is the interval between the upper and lower concentration of the analyte in the sample for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. In titration it is recommended that the analyte size should correspond to a titrant consumption of 20% to 90% of the burette volume. One of the examples in this brochure, demonstrates that the linear measurement range of the current METTLER TOLEDO titrators is even better, namely from 10% to 90% of the burette volume.

3.8 Robustness and Ruggedness

Robustness describes whether a titration method is sensitive to small, but deliberate variations in procedural parameters listed in the documentation such as pH, analyte volume, cleaning and conditioning procedures of the sensor, ambient conditions, etc. Robustness provides an indication of the method's suitability and reliability during normal use.

Ruggedness is not addressed in ICH documents. In past USP guidelines it was defined as the degree of reproducibility of results by analyzing the same samples under a variety of conditions such as different analysts, different laboratories, instruments, days, etc. Ruggedness is determined by the analysis of aliquots from homogeneous lots in different laboratories. The ICH is addressing ruggedness in the guideline part where the intermediate precision and reproducibility is discussed.

4 Practical Hints

4.1 Preparation and Precautions

In order to obtain good results it is essential to observe the following points:

- The primary standard must be dried in a drying oven, e.g. 2 hours at 105°C, depending on the type of primary standard. It must then be cooled to ambient temperature in a desiccator for at least 1 hour. The standard should always be stored in a desiccator.
- For acid/base endpoint titrations, it is necessary to calibrate the pH sensor. Certified buffers from METTLER TOLEDO may be used for this purpose.
- The experimental setup must be protected from direct sunlight and should be in thermal equilibrium with the environment.
- The analytical balance must have a vibration free stand and should be calibrated regularly. METTLER TOLEDO analytical balances offer FACT (Fully Automatic Calibration Technology), which automatically executes a calibration whenever needed. All steps to ensure proper weighing must be observed [8].

4.2 Titration Control Parameters

The control parameters are subject to the titration performed. Titrations with primary standards should be executed with the same or very similar parameters as the titrations of the sample [4]. This is especially important for the basic settings such as:

Titration mode	Endpoint Equivalence point	
Titrant addition	Dynamic Continuous	Incremental
Measure mode	Equilibrium Fixed time interval	

4.3 Titration Evaluation Parameters

The evaluation procedure is subject to the type of the titration reaction and the indication. For acid/base titrations and by default, the standard evaluation procedure is applied.

Evaluation procedure	Standard Maximum Segmented	Asymmetric Minimum

4.4 Titration

- Samples should be titrated immediately after weighing and dissolution. Enough solvent must be added to cover the sensor.
- When performing a series of titrations, the interval time between samples should be kept to a minimum.
- In sample series, the sensor as well as stirrer and temperature sensor should be rinsed between two measurements.
- Temperature compensation is essential for pH endpoint titrations.

5. Possible Sources of Error

Primary standard	unsuitable, impure, moist, inhomogeneous, no guaranteed primary standard quality, contaminated (e.g. by CO_2, O_2 or H_2O[1]).
Sample size / Balance	balance not accurate, air humidity too high or too low, contaminated balance, temperature changes or gradient from titration vessel to balance, careless weighing, sample weight, concentration or volume too low or too high, sample inhomogeneous, improper sampling.
Titration vessel	contaminated, unsuitable, electrostatically charged.
Dispensing unit	tube connections not tight, contaminated burette cylinder (visible corrosion marks), leaky piston (liquid film or crystals below the piston), leaking burette tip, air in tubing system, three-way stopcock leaking.
Sample	matrix effects from similar species.
Reaction kinetics	too slow.
Solvent	Solvent impure (blank value), poor solubilizing power, not stable, contaminated (e.g. by CO_2, O_2 or H_2O[1]), wrong pH value or ionic strength.
Titrant	impure, decomposed, contaminated (e.g. by CO_2, or H_2O[1]), light sensitive, wrong pH value or ionic strength, very high or low concentration.
Measurement	unsuitable sensor type, contaminated sensor, blocked diaphragm, loose contact at connector, poor mixing of sample solution, unfavorable arrangement of burette tip and sensor, excessive response time of sensor, insufficient rinsing of sensor and stirrer before the next titration.
Titration parameters	unsuitable titration mode, wrong measure mode parameters, titration rate too fast or too slow, unsuitable evaluation procedure.
Temperature	temperature fluctuations, especially perceptible with titrants in organic solvents, highly endothermic or exothermic reaction.
Environment	changing, fluctuating, adverse conditions (humidity, temperature, UV light).

[1] for Karl Fischer Titration

6. Recommendations for Troubleshooting

6.1 Relative Standard Deviation too high (poor repeatibility)

- Ensure complete dissolution of the weighed sample in the solvent.
- Optimise the arrangement of burette tip, sensor and stirrer.
- Regenerate or replace the sensor.
- Optimise titration parameters (see METTLER TOLEDO Application Brochures).
- Remove the burette, clean and possibly change tubing and possibly piston and cylinder.
- Weigh the sample only after establishing temperature equilibrium between balance, titration vessel and sample.
- Increase the sample size if possible.
- Select bigger or smaller burette size.
- Check temperature of sample solution (e.g. use water bath).
- Optimize pH value of sample solution (e.g. add buffer).

6.2 Relative Systematic Deviation too high (accuracy unsatisfactory)

- Use pure solvent (without blank value), degas the water if necessary.
- Dry the primary standard substance.
- Ensure complete dissolution of the weighed sample in the solvent before titration starts.
- Visual inspection of the burette and its replacement if need be.
- Check sensor. Clean properly, regenerate or replace.
- Check titration parameters.
- Increase the sample size if possible.
- Check the balance.
- Optimize solution temperature using a water bath, and pH value adding a buffer.
- Reduce, if not eliminate possible influences, e.g. filtration, centrifugation, extraction etc.

7. Results not conforming to specifications

If inaccurate or imprecise results, systematic errors, non-linearity or problems with the robustness or repeatability are found, an attempt must be made to optimize the titration method in order to meet the required limits. In some cases it may be necessary to use an unchanged method. However, systematic errors and non-linearity must be then compensated in the calculations.

All non-conforming values must be reported and commented on in the validation record and the subsequent procedure noted and explained.

If relevant deviations are found, the sections "Possible Sources of Error" and "Recommendations for Troubleshooting" must be checked carefully in order to avoid the disturbing influences. It is essential to repeat the validation afterwards.

The titrators of METTLER TOLEDO have undergone various intensive tests during development and manufacturing. Furthermore, they have been time tested by numerous users in different applications all over the world and considered to be robust and reliable. If irregular results are obtained, primary consideration should be given to the working technique of the operator or to wrong or accidentally altered titration parameters.

8. Examples

8.1. Determination of Sulfuric Acid

The developed method for the determination of the sulphuric acid by titration with sodium hydroxide is compiled below.

Sample	Sulphuric acid solution $c(H_2SO_4)$ = 0.05 mol/L
Compound	Sulphuric acid, H_2SO_4 M = 98.079 g/moL, z = 2
Chemicals	40 mL deionized water
Titrant	Sodium hydroxide, NaOH c(NaOH) = 1.0 mol/L
Standard	Potassium hydrogen phthalate, KHP, M = 204.23 g/moL, z = 1
Indication	DGi111-SC combined pH glass sensor
Chemistry	Titer determination: $NaOH + HOOC\text{-}C_6H_4\text{-}COOK \rightarrow Na^+ + K^+ + {}^-OOC\text{-}C_6H_4\text{-}COO^-$ Titration: $H_2SO_4 + 2NaOH \rightarrow Na_2SO_4 + H_2O$
Instruments	METTLER DL 77 Sample Changer ST20A
Accessories	DT120 T-sensor Printer HP Deskjet

Method

001 Title	
Type	General Titration
ID	Determination of H_2SO_4
002 Sample	
Number of Samples	6
Titration stand	ST20 1
Entry type	Fixed Volume U
Volume	30.0 mL
ID1	H_2SO_4
Molar mass M	98.079
Equivalent number z	2
Temperature sensor	TEMP A
003 Pump	
Auxiliary reagent	H2O
Volume	30.0 mL
004 Stir	
Speed	50%
Duration	10 s
005 Titration	
Titrant	NaOH
Concentration	0.1 mol/L
Sensor	DG111-SC
Unit	mV
Titration Mode	EQP
Predispensing 1	mL
Volume	2 mL
Titrant addition	DYN
ΔE(set)	8.0 mV
Limits ΔV	Absolute
Measure mode	EQU
ΔE	1.0 mV
Δt	1.0
t(min)	3.0 s
t(max)	15.0 s
Threshold	3.0
Maximum volume	10.0
Termination	
after n EQPs	Yes
n =	1
Evaluation procedure	Standard

006 Rinse	
Auxiliary reagent	H_2O
Volume	10 mL
007 Calculation	
Result Name	H_2SO_4 Conc.
Formula	R1=Q*C/U
Constant	C=M/z
Result unit	g/L
Decimal places	5
008 Record	
Output unit Printer	
Raw results last sample	Yes
Table of values	Yes
E – V curve	Yes
009 Conditioning	
Interval	1
Time	10 s
Rinse	Yes
Auxiliary reagent	H_2O
Volume	10.0 mL
010 Statistics	
Ri (i = index)	R1
Standard deviation s	Yes
Rel. standard deviation srel	Yes
Outlier test	Yes
011 Record	
Output unit	Printer
All results	Yes

8.1.1. Titer Determination

The titer of 1M NaOH titrant was determined against the primary standard potassium hydrogen phthalate (dried for 2 h at 150°C). The titration results are summarized in *Table 1* and the plot of titer vs. sample size is shown in *Figure 6*.

Sample	Sample size [g]	Titer
1	0.94376	1.00110
2	0.69729	1.00140
3	1.44905	1.00150
4	0.76393	1.00030
5	1.28186	1.00120
6	0.91697	1.00020
7	1.09282	1.00150
8	0.61858	1.00440
9	1.73847	1.00240
10	1.32274	1.00110
11	1.63289	1.00080
12	1.1767	1.00110
13	0.64051	1.00180
14	1.52071	1.00170
15	1.30135	1.00040
16	0.72725	1.00120
17	1.04305	1.00100
18	0.62867	1.00240
19	1.79993	1.00090
20	1.68623	1.00170
21	1.77458	1.00100
22	1.38162	1.00240

Mean Value	1.0014
Standard deviation (SD)	$9.07 \cdot 10^{-4}$
Relative standard deviation (RSD)	0.0905%

Table 1. Titer determination of 1M NaOH titrant with potassium hydrogen phthalate as standard.

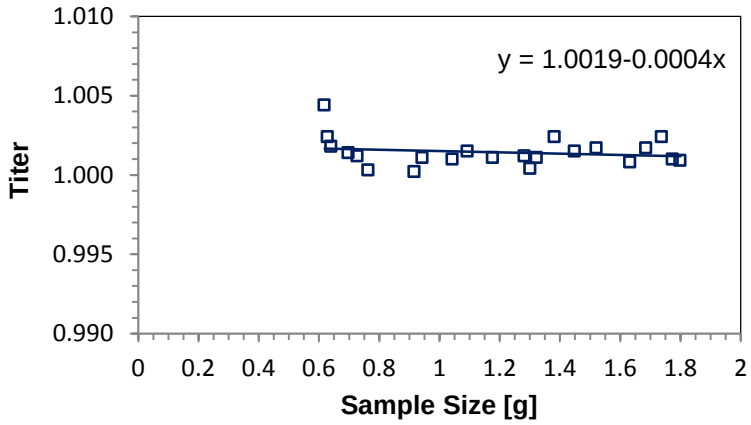


Figure 6. Variation of titer value with the sample size.

Conclusion

The standardization is highly reproducible and linear with a RSD of 0.0905%. Results do not depend on the sample weight.

8.1.2. Precision and Accuracy

A commercially available H_2SO_4 solution with a concentration of 0.05 mol/L was titrated with 1M NaOH standardized titrant, as shown in the previous chapter. The results were compared with the true value (compensated for a temperature of 21°C) in order to determine the accuracy. The precision was evaluated with help of relative standard deviation obtained from the statistics. The titration results are summarized in *Table 2* and the variation of results with the sample size is shown in *Figure 7*.

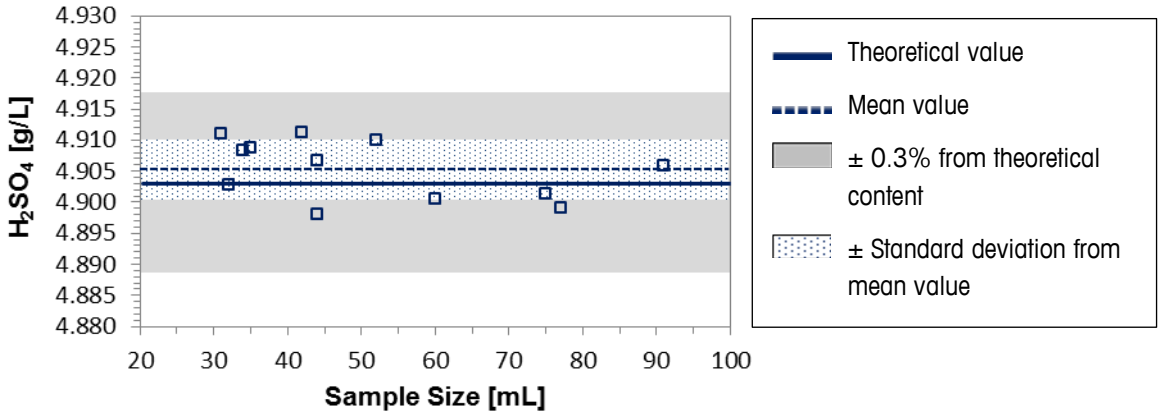


Figure 7. Determined analyte concentration vs. sample size.

Sample	Sample Size [mL]	Result [g/L]
1	75	4.90143
2	34	4.90828
3	44	4.89803
4	60	4.90046
5	35	4.9087
6	44	4.90672
7	77	4.89912
8	32	4.90273
9	52	4.90995
10	91	4.90584
11	31	4.91109
12	42	4.91117

Theoretical value	4.9030 g/L
Mean value found	4.90529 g/L
Deviation from theoretical value	0.00229 g/L
Relative deviation from theoretical value	0.0467%
Standard deviation	0.004752 g/L
Relative standard deviation	0.0968%

Table 2. Titration of H_2SO_4 solution with 1M NaOH as titrant.

Conclusion

Both precision as well as accuracy are excellent. The RSD is less than 0.1% and the RSD relative deviation to from theoretical value is less than 0.05%. The requirements for precision and accuracy are easily met.

8.1.3. Systematic Errors, Linearity

The equivalence volumes (VEQ) and the determined concentration were plotted versus the sample size as shown in *Figure 8a* and *8b* respectively. A linear regression was performed on these data to determine systematic errors. In this case, systematic errors manifest themselves in a significant

deviation of the y axis intercept of the regression line from the zero point coordinates (see diagram below). The results of titration are shown in *Table 3*.

Sample Size [mL]	VEQ [mL]	Result [g/L]
75	7.4871	4.90143
34	3.3989	4.90828
44	4.3894	4.89803
60	5.9885	4.90046
35	3.4492	4.9087
43	4.3972	4.90672
77	7.6831	4.89912
32	3.1953	4.90273
52	5.2001	4.90995
91	9.0925	4.90584
31	3.1008	4.91109
42	4.2011	4.91117

Systematic error	9.7 µL
Correlation coefficient R^2	0.9997
Non-linearity	$1 \cdot 10^{-4}$ (g/L)/mL

Table 3. Titration of H_2SO_4 solution with 1M NaOH as titrant.

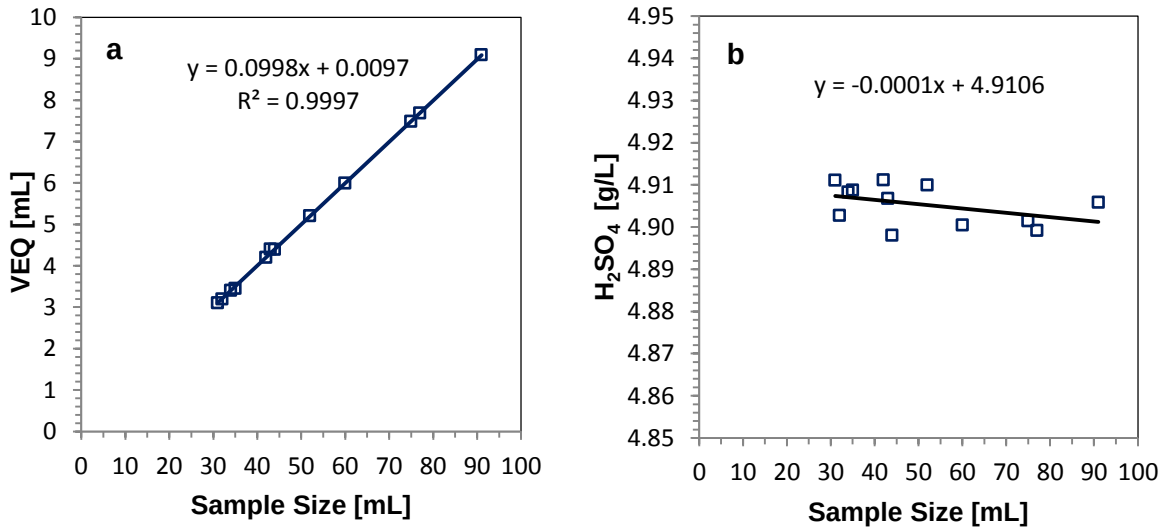


Figure 8 : a) VEQ vs. sample size. b) Determined analyte concentration vs. sample size.

Conclusion

The results show a systematic error and non-linearity. Presumable causes are pipetting errors when preparing the samples. Both values are very small and well below the recommended limits.

8.1.4. Robustness

In this example the robustness of the method was tested against the carbon dioxide uptake of the titrant only. The uptake of carbon dioxide CO_2 from ambient air is the major threat of alkaline titrants. The dissolved CO_2 in water generate carbonates to CO_3^{2-}. Carbonate precipitation and the decrease of the titrant concentration are the consequences.

The robustness of the sulphuric acid method was evaluated by exposing the titrant to air and thereby also to CO_2. Batches of NaOH titrants were exposed to air for 7 days in a row. The CO_3^{2-} content of each sample was determined by titration with sulphuric acid solution. The amount of absorbed carbonate is shown in *Table 4* and plotted vs. days of exposure to air in *Figure 9*.

Air exposure [days]	Result CO_3^{2-} [mg/L]
1	2526
2	5026
3	8793
4	14422
6	20684
7	24568

Table 4. Absorbed CO_3^{2-} on the exposed NaOH titrant to air.

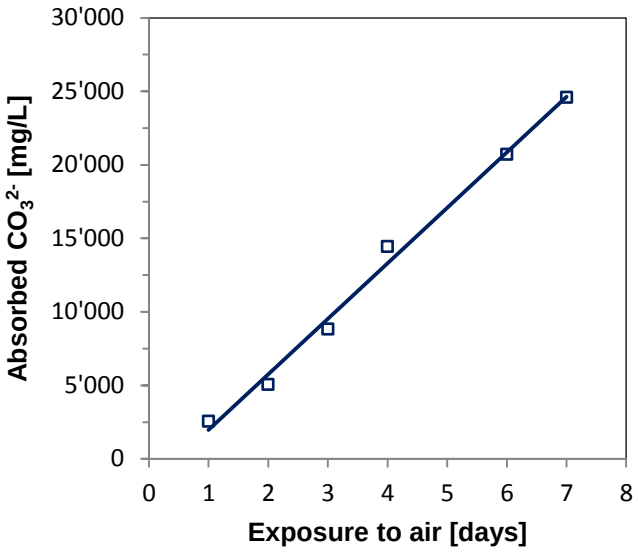


Figure 9. Absorbed CO_3^{2-} vs. days of exposure to air

The uptake of carbon dioxide is almost linear and very fast! After 2 days of exposure to air already 5 g/L CO_3^{2-} are present in the NaOH titrant. The NaOH concentration (as to OH^-) thereby was reduced from the initial 40 g/L to ca. 37 g/L.

After exposure to air, each batch of NaOH titrant was first standardised against potassium hydrogen phthalate and then used to determine the known concentration of a H_2SO_4 solution. The *Table 5* shows the corresponding results.

By titrating a strong acid as H_2SO_4 with NaOH solution that is contaminated with CO_3^{2-}, a typical double jump of the titration curve is found, caused by the following reactions:

1st EQP	$NaOH + H_3O^+$	$Na^+ + 2\ H_2O$
	$Na_2CO_3 + H_3O^+$	$NaHCO_3 + H_2O + Na^+$
2nd EQP	$NaHCO_3 + H_3O^+$	$Na^+ + 2\ H_2O + CO_2$

However, this double jump does not occur when titrating weak acids such as potassium hydrogen phthalate, which is mainly used for the titer determination. Therefore, the carbonate error cannot be compensated by frequent standardization of the titrant. It is advisable to periodically check the carbonate content by a specific titration and dispose of the titrant if a significant amount of carbonate is found.

Air exposure [days]	Result CO_3^{2-} [mg/L]	Theoretical content [g/L]	Systematic deviation [%]	Reproducibility RSD [%]
1	2526	4.9017	1.31	0.051
2	5026	4.9017	6.44	0.139
3	8793	4.9020	12.11	0.178
4	14422	4.9017	15.20	0.108
6	20684	4.9040	20.35	0.162

Table 5. The influence of absorbed CO_3^{2-} on the accuracy of the titration results.

Conclusion

The method was found not to be robust against NaOH titrant exposure to air. Even by exposing the NaOH titrant for only one day to air, the correct determinations of the sulphuric acid concentration failed.

8.1.5. Limit of Quantitation

The limit of quantitation was examined using NaOH titrant with a concentration of 0.005 mol/L in order to avoid the limitation factor of the burette resolution by using a titrant with high concentration of 1 mol/L. Series of 3 to 6 samples each were titrated. Note that low amounts of sample were used. The

relative standard deviation was then calculated for each series to measure repeatability. The results are summarized in *Table 6*.

Decreasing the amount of sulphuric acid in the sample to less than 0.01 mmol leads to the continuous increase of the relative standard deviation, while the absolute standard deviation remains more or less constant. The uptake of CO_2 from the air has a significant impact in the low concentration range of the titrant. Therefore the titrant has to be protected from CO_2 intake with an absorption tube filled with NaOH on a carrier. Even then, it remains usable only for one day.

Number of samples per series	Mean value [mmol]	Standard deviation [mmol]	Relative standard deviation [%]
3	0.013135	0.000012	0.092
5	0.005380	0.000022	0.408
5	0.004065	0.000038	0.944
6	0.002735	0.000037	1.369
6	0.001335	0.000048	3.581
5	0.000785	0.000031	3.945

Table 6. The influence of H_2SO_4 amount in the sample on the precision of the titration results.

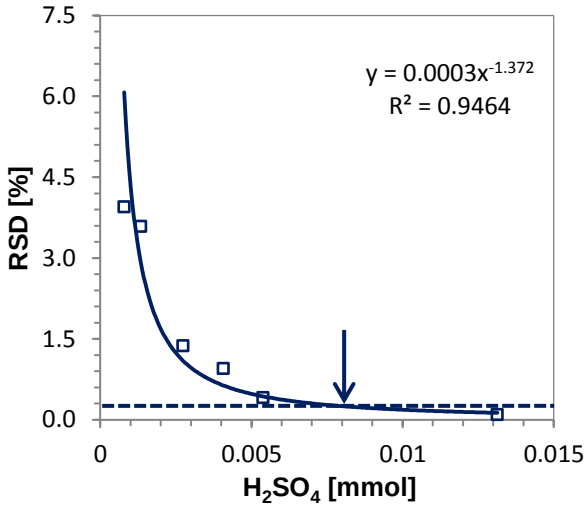


Figure 10. Determination of limit of quantitation by interpolation.

Conclusion

The smallest amount of substance that can be titrated with a repeatability of less than 0.3% RSD was determined by interpolation, as shown in *Figure 10*, and is less than 0.01mmol H_2SO_4 per sample. In this case, the determination limit was obtained with a titrant of very low concentration, c(NaOH) = 0.005 mol/L. In the standard validation procedure the method parameters, the setup (as burette size) and chemicals (as titrant concentration) are kept unchanged, in order to avoid e new validation of the modified method.

8.2. Chloride Content Determination

The below described titration method represents a general purpose chloride (salt) titration with parameters set to ensure a high sample throughput by fully automated analysis on Titration Excellence and InMotion Max Autosampler.

Sample	Sodium chloride standard solution, NaCl c(NaCl) = 0.1 mol/L
Compound	Chloride, Cl^- M = 35.453 g/moL, z = 1.
Chemicals	0.02 mol/L Sulfuric acid, H_2SO_4 5% Non-ionic surfactant (TritonX-100) 0.1% NH_3 in water 50 mL deionized water
Titrant	Silver nitrate, $AgNO_3$ c($AgNO_3$) = 0.1 mol/L
Standard	NaCl, 30-50 mg
Indication	DMi141-SC Combined silver ring sensor.
Chemistry	Titration: $AgNO_3$ + NaCl → AgCl + $NaNO_3$ Cleaning procedure: AgCl(s) + NH_3(aq) → $Ag[(NH_3)_2]^+$(aq) + Cl^-(aq)
Instruments	Titration Excellence T70/T90 InMotion Max Autosampler XP 205 Analytical Excellence Balance
Accessories	LabX® Titration 2014 PC Software 3 additional dosing units 2 x 10mL DV1010 burette Optional: 1 x 1mL DV1001 burette (for dosing purposes of the NaCl standard solution) 1 x 5mL DV1005 burette (for dosing purposes of the NaCl standard solution) Titration Beaker 100mL 3 x SP280 Peristaltic Pump

Comments

- This application has been developed for a fully automated analysis of sample series by using additional burette drives and pumps. The method parameters have been developed and optimized for the above mentioned sample.
- The method can be modified for other autosamplers with different beaker sizes and manual addition of required reagents.
- A 5% non-ionic surfactant solution (e.g. Triton X-100) can be added to avoid formation of larger silver chloride particles and to slow down the adhesion of the precipitate on the sensor, stirrer and tubing.
- In order to prevent the deposition of the AgCl precipitate on the sensor ring (leading to malfunction of the sensor), the conditioning in the NH_3 water solution after completion of each sample is recommended.

Method

001 Title

Type	General Titration
Compatible with	T70 / T90
ID	Chloride InMotion Max
Title	Chloride Determination
Author	METTLER TOLEDO
Modified at	--
Modified by	--
Protect	No
SOP	None

002 Sample

Number of IDs	1
ID 1	NaCl Solution
Entry type	Fixed Volume
Volume	8.0 mL
Density	1.0 g/mL
Correction factor	1.0
Temperature	25.0°C

003 Titration stand

Type	InMotion T/Tower A
Titration stand	InMotion T/1A

004 Pump

Auxiliary reagent	0.02 M sulfuric acid
Volume	50 mL
Condition	No

005 Dispense(normal) [1]

Titrant	5% TritonX-100
Concentration	5%
Volume	2.0 mL
Dosing rate	60.0 mL/min
Condition	No

006 Dispense(normal) [2]

Titrant	NaCl Solution
Concentration	0.1 mol/L
Volume [mL]	8.0
Ranges	0
Add. EQP criteria	No
Dosing rate [mL/min]	60.0
Condition	No

007 Stir

Speed	40%
Duration	15 s
Condition	No

008 Titration (EQP) [1]

Titrant	
Titrant	$AgNO_3$
Concentration	0.1 mol/L
Sensor	
Type	mV
Sensor	DM141-SC
Unit	mV
Temperature acquisition	
Temperature acquisition	No
Stir	
Speed	40%
Predispense	
Mode	None
Wait time	0 s
Control	
Control	User
Titrant addition	Dynamic
dE (set value)	9.0 mV
dV (min)	0.008 mL
dV (max)	0.4 mL
Mode	Equilibrium controlled
dE	0.5 mV
dt	1.0 s
t (min)	3.0 s
t (max)	30.0 s
Evaluation and recognition	
Procedure	Standard
Threshold	200 mV/mL
Tendency	Positive
Condition	No

Termination	
At Vmax	10 mL
At potential	No
At slope	No
After number of recognized EQPs	1
Combined termination criteria	No
Accompanying stating	
Accompanying stating	No
Condition	
Condition	No

009 Calculation R1

Result	Consumption
Result unit	mL
Formula	R1=VEQ
Constant	C=M/z
M	M[None]
z	z[None]
Decimal places	4
Result limits	No
Record statistics	Yes
Extra statistical func.	No
Send to buffer	No
Write to RFID	No
Condition	No

010 Calculation R2

Formula	R1=Q*C/M
Constant	C=M/z
M	M[Chloride]
z	z[Chloride]
Decimal places	5
Result limits	No
Record statistics	Yes
Extra statistical func.	No
Send to buffer	No
Write to RFID	No
Condition	No

011 Rinse

Auxiliary reagent	Water
Rinse cycles	1
Vol. per cycle	10 mL
Position	Current position
Drain	Yes
Drain Pump	SP280
Condition	No

012 Line rinse

Interval	1
Position	Conditioning beaker
Drain Pump	SP280
Descent rate	Medium
Refill	Yes
Auxiliary reagent	0.1% NH_3 in water

013 Conditioning

Type	Fix
Interval	1
Position	Conditioning beaker
Time	60 s
Speed	60 %
Lid handling	No
Condition	No

014 Titration stand

Type	Auto stand
Titration stand	Auto stand 1

015 Drain

Drain pump	SP280
Drain volume	100 mL
Condition	No

016 Titration stand

Type	InMotion T/Tower A
Titration stand	InMotion T/1A

017 Conditioning

Type	Fix
Interval	1
Position	Special beaker 1
Time	60 s
Speed	50 %
Lid handling	No
Condition	No

018 Conditioning

Type	Fix
Interval	1
Position	Special beaker 1
Time	60 s
Speed	50 %
Lid handling	No
Condition	No

019 Rinse

Auxiliary reagent	Water
Rinse cycles	1
Vol. per cycle	10 mL
Position	Current position
Drain	Yes
Drain Pump	SP280
Condition	No

020 Line rinse

Interval	10
Position	Special beaker 1
Drain Pump	SP280
Descent rate	Medium
Refill	Yes
Auxiliary reagent	0.02 M sulfuric acid
Volume	60 mL
Condition	No

021 Park

Titration Stand	InMotion T/1A
Position	Special beaker 2
Condition	No

022 Record

Report	
Report template	Titration report
Print	No
Condition	No

023 End of sample

8.2.1 Titer Determination

The titer of 0.1M $AgNO_3$ titrant was determined against the primary standard Sodium Chloride (dried for 2 h at 150 °C). The titration results are summarized in *Table 7* and the plot of titer vs. sample size is shown in *Figure 11*.

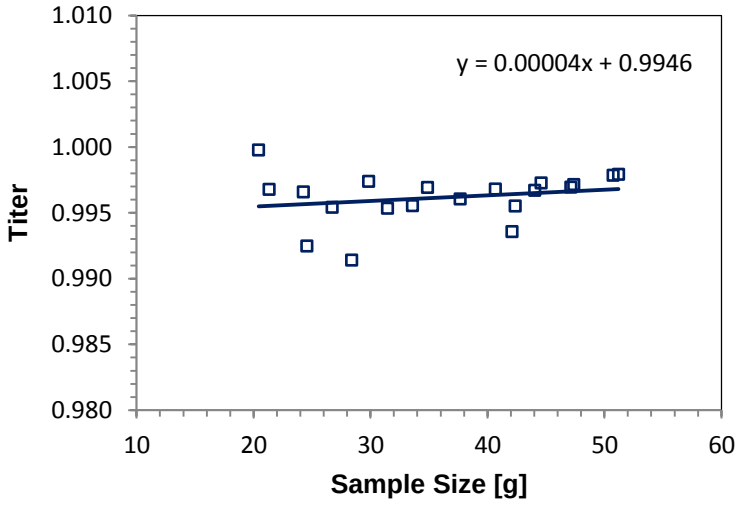


Figure 11. Variation of Titer value with the sample size

Conclusion

The standardization of 0.1 mol/L $AgNO_3$ titrant is highly reproducible and linear with a RSD of 0.1930%. Additionally, the results are not dependent on the sample weight.

Sample	Choride amount [mg]	Titer
1	21.32	0.99676
2	24.55	0.99246
3	28.38	0.9914
4	31.46	0.99533
5	33.58	0.99554
6	37.68	0.99603
7	42.10	0.99356
8	44.04	0.99669
9	47.39	0.99714
10	51.20	0.9979
11	50.75	0.99783
12	47.13	0.99694
13	44.60	0.99725
14	42.36	0.99551
15	40.69	0.99679
16	34.87	0.99691
17	29.85	0.99737
18	26.71	0.99541
19	24.25	0.99657
20	20.43	0.99976

Mean Value	0.99616
Standard deviation (SD)	$1.92 \cdot 10^{-3}$
Relative standard deviation (RSD)	0.1930%

Table 7. Titer determination of 1M NaOH titrant with potassium hydrogen phthalate as standard.

8.2.2 Precision and Accuracy

A commercially available ampule of NaCl solution was used to prepare the NaCl standard solution with a concentration of 0.1 mol/L. In order to avoid the pipetting error of the analyte, the NaCl standard solution was dosed to the titration beaker with help of an additional dosing unit and various burette sizes (1, 5 and 10mL) depending on the analyte volume. Finally, the 50 mL sample volume was titrated with 0.1 mol/L $AgNO_3$ standardized titrant, as shown in the previous chapter. The results were compared with the true value in order to determine the accuracy. Additionally, precision was evaluated with help of relative standard deviation obtained from the statistics. The titration results are summarized in *Table 8* and the plotting of found concentration vs. sample size is shown in *Figure 12*.

Sample	Analyte volume [mL]	Result [g/L]
1	9	3.53813
2	8.5	3.54022
3	8	3.54073
4	7.5	3.54078
5	7	3.54098
6	6.5	3.53914
7	6	3.53952
8	5.5	3.54334
9	5	3.54181
10	4.5	3.53717
11	4	3.53906
12	3.5	3.54198
13	3	3.53609
14	2.5	3.53400
15	2	3.53832
16	1.5	3.53618
17	1	3.54090

Theoretical value	3.54176 g/L
Mean value found	3.53932 g/L
Deviation from theoretical value	0.00229 g/L
Relative deviation from theoretical value	0.0689%
Standard deviation	0.002442 g/L
Relative standard deviation	0.0690%

Table 8. Titration NaCl standard solution with 0.1M $AgNO_3$.

Conclusion

Precision as well as accuracy are excellent. The RSD of the results and the RSD to theoretical value are less than 0.07%. The requirements for precision and accuracy are easily met.

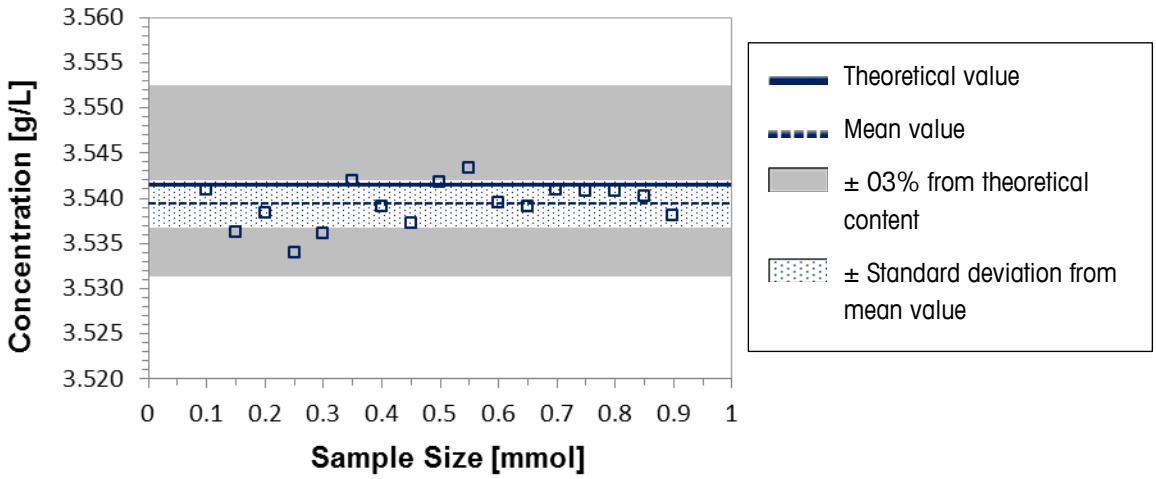


Figure 12. Determined analyte concentration vs. chloride amount.

8.2.3. Systematic Errors, Linearity

The equivalence volumes (VEQ) were plotted versus the sample size. A linear regression was performed on these data to determine systematic errors. The systematic error is represented as deviation of the *y* axis intercept of the regression line from the zero point coordinates (see *Figure 13b* below). The variation of result with the analyte volume is plotted in *Figure 13a*. The results of titration are shown in *Table 9*.

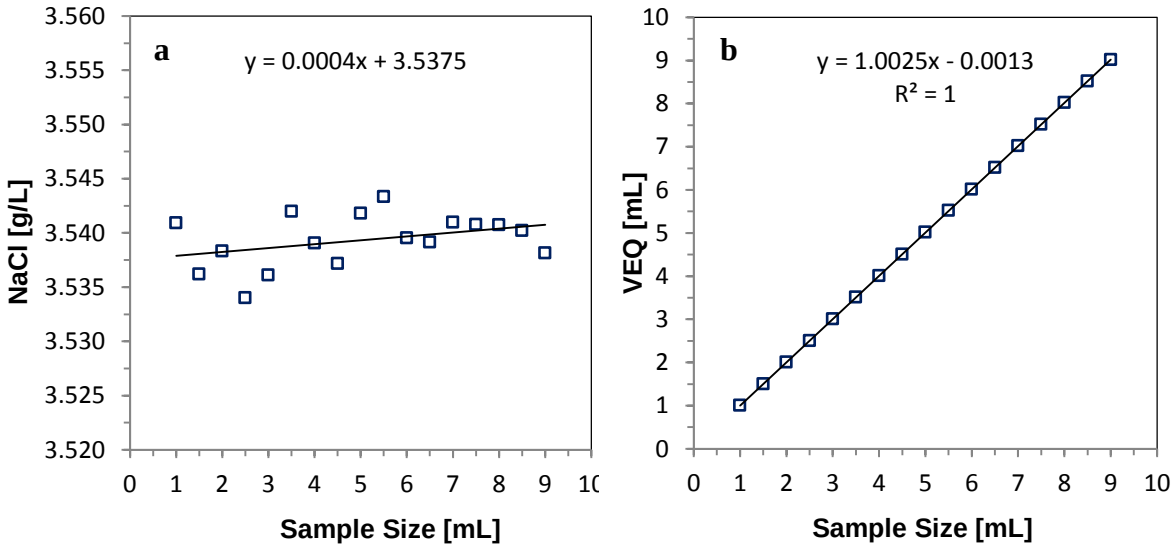


Figure 13. a) Determined NaCl concentration vs. sample size. b) VEQ vs. sample size.

Sample	Analyte volume [mL]	VEQ [mL]
1	9	9.01644
2	8.5	8.52055
3	8	8.02047
4	7.5	7.51930
5	7	7.01842
6	6.5	6.51372
7	6	6.01330
8	5.5	5.51815
9	5	5.01433
10	4.5	4.50698
11	4	4.00835
12	3.5	3.51020
13	3	3.00375
14	2.5	2.50164
15	2	2.00375
16	1.5	1.50191
17	1	1.00261

Systematic error	1.3 µL
Correlation coefficient R^2	1
Non-linearity	$4 \cdot 10^{-4}$ (g/L)/mL

Table 9. Titration of NaCl standard solution with 0.1M $AgNO_3$ as titrant.

Conclusion

An excellent linear regression is shown in *Figure 13b*. The found value of systematic error (SE) is only 1.3 µL and more than tenfold smaller than the recommended 15 µL. For this method the value of SE is assumed to be negligible. Additionally, within the burette volume range from 10% to 90% the non-linearity is very small and well below the recommended limits.

8.2.4. Robustness

The formation of the silver chloride (AgCl) precipitate is a well-known characteristic of the argentometric titration. During titration procedure, the adhesion of the AgCl precipitate on the sensor, stirrer and tubing cannot be avoided even by addition of surfactants (formation of small AgCl particles) and high stirring speed. Generally, it is recommended to clean manually the sensor, the stirrer and the titration tubes

with a paper tissue soaked with deionized water after each sample in order to completely remove any AgCl residue.

A challenging situation is to develop a method to ensure high sample throughput by fully automated analysis with help of a sample changer, where the interaction of the operator between the samples is not wished. The use of InMotion autosampler from METTLER TOLEDO offer several cleaning options as:

- rinsing between the samples with help of power shower option.
- conditioning the sensor in dedicated conditioning beaker
- usage of additional beakers for deep cleaning by immersion of the sensor, stirrer and tubing into distilled water (or other solutions) with or without stirring for any defined time.

In this aspect, the robustness of the fully automated method for chloride determination is evaluated with regards to the cleaning procedure, especially the type of solutions used for deep cleaning procedure after each sample measurement, namely distilled water vs. diluted ammonia solution.

Referring to the method description in Chapter 8.2, the deep cleaning procedure corresponds to the method functions:

- 012 Line rinse: Addition of 60 ml cleaning solution of 0.1% ammonia into the conditioning beaker and
- 013 Conditioning: Deep cleaning of the immersed sensor, stirrer and tubing in 0.1% ammonia solution with stirring for 60s.

In the presence of ammonia solution, the silver is transformed to water soluble diamine silver ion $Ag[(NH_3)_2]^+$, preventing the formation of silver chloride precipitate. Due to this procedure the sensor is kept clean and free of AgCl deposition.

The performance of the "default" titration method (deep cleaning procedure with 0.1% NH_3 solution) is compared with the "modified" method, where distilled water is used for the cleaning procedure, as previously described. The other method parameters, including chemicals and setup were not changed, inclusive the two post-conditioning procedures with 0.02M H_2SO_4 solution followed by conditioning in distilled water (method functions 017 and 018 respectively, see Chapter 8.2).

Several series of more than 10 samples of NaCl standard solution were titrated with the "default" and "modified" method and the results are discussed below.

The results of the "modified" method were astonishing. The rinsing of the tubes and the deep cleaning of the electrode, tubing and stirrer in the absence of ammonia was not sufficient to prevent the deposition of AgCl on the sensor ring. The state of the sensor, tubing and stirrer directly after the run of one series (15 samples in total) with the "modified" method is shown in the *Figure 14*.

The continuous deposition of AgCl on the sensor ring with the number of titrated samples slows down the response of the sensor. The negative influence of this phenomenon with regards to titration curve is drastic, leading to scattering E/V curve and finally to false results. The results of the first 7 samples are very accurate and within the limits of ± twofold standard deviation of their mean value (red lines), as shown in the *Figure 15*. From the 8th sample the results are out of limits and in case of samples 13 and 14 no equivalent point could be found, due to the heavy coverage of the sensor ring with AgCl, leading to very scattering titration curves.

Figure 14. The condition of the sensor after measurement of 15 samples with the "modified" method.

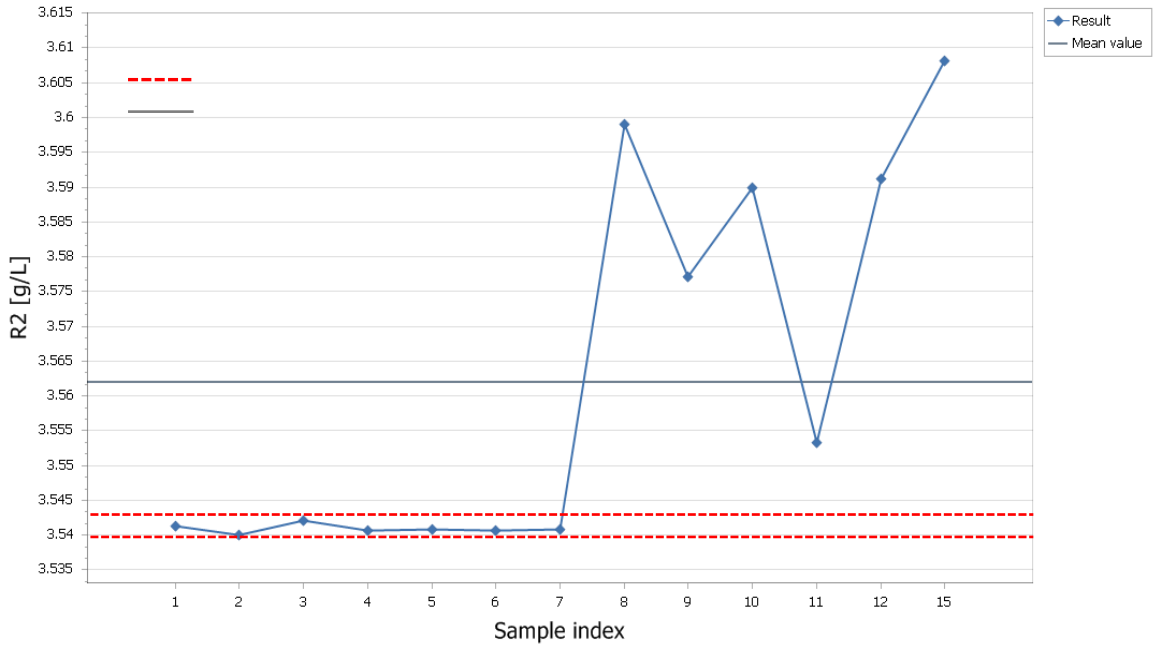


Figure 15. Titration results of the series with 15 samples that have been measured with the "modified" method.

----- ± Twofold standard deviation of mean value of the first 7 samples.

——— Mean value of all 15 samples in the series.

Figure 16 shows a comparison of the titration curves of two samples of the above mentioned series that have been measured with the "modified" method. The titration curve of the 1st sample of the series (Figure 16a) has a perfect first derivative curve dE/dV leading to correct determination of the equivalent point. In opposite, the profile of the dE/dV curve of the 12th sample (Figure 16b) is not adequate for an accurate equivalent point determination, due to the poor E/V titration curve. In this case a fail result (out of limit) was generated.

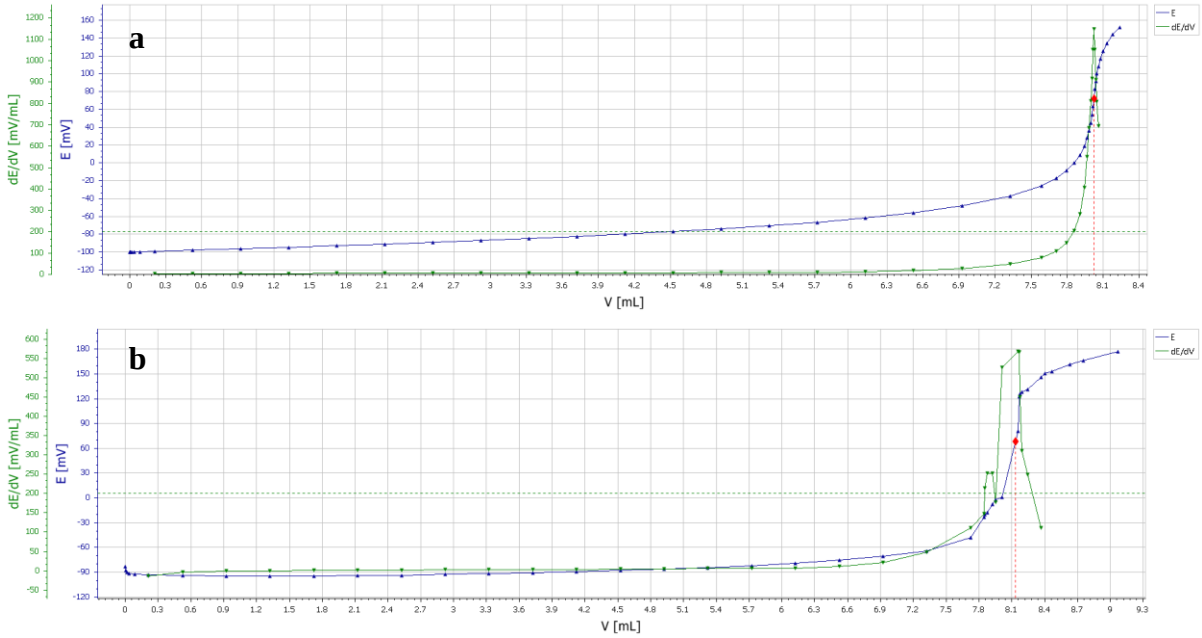


Figure 16. Titration curve of the 1st (plot **a**) and 12th (plot **b**) sample of the same series that has been measured with the "modified" method.

In order to emphasize the role of the proper cleaning of the sensor from the residue of AgCl with ammonia solution, four series of at least 20 samples each were measured within two days with the "standard" method (deep cleaning procedure with 0.1% NH_3 solution). Additionally, there was no operator interaction between the series in order to simulate the real situation with high sample throughput and fully automated analysis.

The high precision and excellent repeatability are the two characteristics of the results shown in *Table 10*. The standard deviation between the mean values is less than 0.5 ppm (0.47 µg/L) with a RSD between the series of only 0.013%.

Series	Samples per series	Mean value [g/L]	SD [g/L]	RSD [%]	SD between mean values [g/L]	RSD between mean values [%]
1	50	3.53387	0.0011	0.0297	0.0005	0.0132
2	22	3.53397	0.0005	0.0150		
3	20	3.53460	0.0024	0.0670		
4	20	3.53347	0.0031	0.0880		

Table 10. Titration of 8 mL NaCl standard solution (0.1 mol/L) with 0.1M $AgNO_3$ titrant by "standard" method.

Conclusion

The developed method is robust and suitable for fully automated measurement of a large number of samples per day with help of InMotion sample changer. Special care should be taken in the cleaning of the sensor between the samples in order to guarantee faultless results.

8.2.5 Limit of Quantitation

For the determination of limit of quantitation the setup and method parameters, burette size, chemicals quality and concentration were not changed. Series of 6 samples were analyzed, in order to check the repeatability with help of RSD by titrating low amount of sample. The NaCl standard solution with a concentration of 0.1 mol/L was dosed with help of 1 mL burette in order to avoid the pipetting errors. The results are summarized in *Table 11*.

Series	Analyte volume [mL]	Mean value [mmol]	Standard Deviation [mmol]	Relative standard deviation [%]
1	0.9	0.09003	0.0040	0.045
2	0.7	0.07002	0.0037	0.103
3	0.5	0.05021	0.0104	0.103
4	0.4	0.03991	0.0124	0.292
5	0.3	0.02997	0.0218	0.347
6	0.2	0.01995	0.0191	0.612
7	0.1	0.00892	0.1230	3.897

Table 11. The influence of choride amount in the sample on the precision of the titration results.

Decreasing the chloride amount in the sample leads to increases of the relative standard deviation continuously, while the absolute standard deviation remains almost constant (except the last series). The measurement of the last series is neither accurate nor precise anymore, indicating the resolution limitation of the 10 mL burette with the 0.1M $AgNO_3$ titrant with regard to the analyte amount.

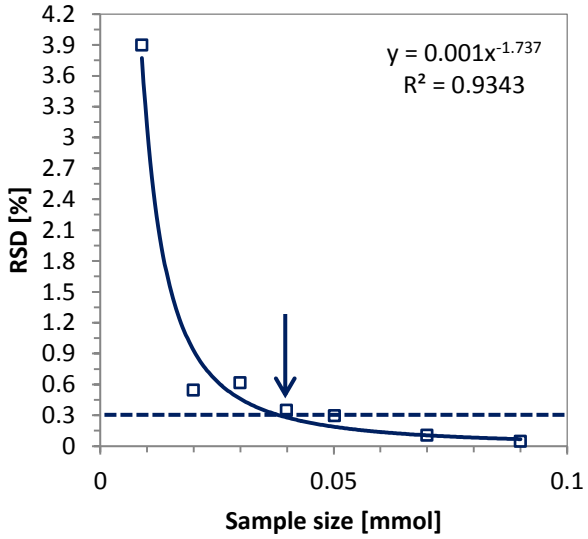


Figure 17. Determination of Limit of Quantitation by interpolation.

Conclusion

The smallest amount of substance, which can be titrated with a good reproducibility of less than 0.3% RSD with the predefined titrant concentration of 0.1 mol/L $AgNO_3$ and burette size of 10 mL, was determined by interpolation and is about 0.04 mmol NaCl (see Figure 17 below).

Other methods can be found in the application notes of METTLER TOLEDO where concentrations of 5 and 0.5 ppm of chloride are determined with high degree of precision with potentiometric and voltametric titration respectively.

8.2.6 Closing Remarks

In this example it has been shown how a precipitation titration method can be validated. The method gives excellent results in all areas, and ensures a high sample throughput by fully automated analysis with a linear range of the measurement from 10% to 90% of the burette volume.

The acceptance criteria for different parameters or the order of priorities in the validation process have to be adapted by the user depending on the method and the specifications for a given task (e.g. additional tests for the determination of specificity with real samples, reproducibility, etc.). This example may well serve as a guideline for further method validations of this type.

8.3. Water Content Determination by Volumetric Karl Fischer Titration

The following method describes the measurement and validation of water content determination by volumetric Karl-Fischer titration. Water-standards were used as model samples. The general procedure for the method validation can also be applied to other samples. The method used is based on the METTLER TOLEDO application note M300 including more strict termination criteria (drift stop relative 5 µg/min). The measurement time for one sample was about 4 min. In order to have a stable drift value, the titrator was run in standby mode for about 5 min after each sample measurement.

Sample	0.5 – 2.5 g Water Standard 10.0 mg/g (HYDRANAL® - Water Standard 10.0) Certified value: 10.02 mg/g (expanded uncertainty = 0.11 mg/g, k = 2)
Compound	Water, H_2O M = 18.01 g/mol
Chemicals	HYDRANAL® - Methanol dry
Titrant	HYDRANAL® - Composite 5 (5 mg H_2O/mL)
Standard	Water Standard 10.0 mg/g
Indication	DM143-SC
Chemistry	$CH_3OH + SO_2 + 3\ RN + I_2 + H_2O \rightarrow (RNH)\bullet SO_4CH_3 + 2\ (RNH)I$
Instruments	V30 5 mL DV1005 burette XP205 and XS205 Balance with syringe holder
Accessories	LabX® 2014 Software Solvent Manager

Comments
- Before aspirating the sample, rinse the syringe with about 1 mL of sample. - After rinsing the syringe aspirate the whole volume of sample needed for the series. Add a suitable portion of the sample to the titration vessel for each measurement.

Method

001 Title

Type	Karl Fischer titration Vol.
Compatible with	V30 / T70 / T90
ID	Validation Precision
Title	Water Standard 10.0 mg/g
Author	PredefinedUser
Date/Time	12/18/2014 02:04:32 pm
Modified on	12/18/2014 02:04:45 pm
Modified by	PredefinedUser
Protect	No
SOP	None

002 Sample (KF)

Sample	
Number of IDs	1
ID 1	--
Entry type	Weight
Lower limit	0.0 g
Upper limit	5.0 g
Density	1.0 g/mL
Correction factor	1.0
Temperature	25 °C
Autostart	Yes
Entry	After addition
Concentration	
Titrant	KF1-Comp5
Nominal conc.	5 mg/mL
Standard	Water-Standard 10.0
Entry type	Weight
Lower limit	0.0 g
Upper limit	2.0 g
Temperature	25 °C
Mix time	10 s
Autostart	Yes
Entry	After addition
Conc. Lower limit	4.5 mg/mL
Conc. Upper limit	5.6 mg/mL

003 Titration stand (KF stand)

Type	KF stand
Titration stand	KF stand
Source for drift	Online
Max. start drift	25 µg/min

004 Mix time

Duration	15 s

005 Titration (KF Vol) [1]

Titrant	
Titrant	KF1-Comp5
Nominal conc.	5 mg/mL
Reagent type	1-comp
Sensor	
Type	Polarized
Sensor	DM143-SC
Unit	mV
Indication	Voltametric
Ipol	24.0 µA
Stir	
Speed	35%
Predispense	
Mode	None
Wait time	0 s
Control	
End point	100.0 mV
Control band	400.0 mV
Dosing rate (max)	5 mL/min
Dosing rate (min)	80 µL/min
Start	Normal
Termination	
Type	Drift stop relative
Drift	5.0 µg/min
At Vmax	10.0 mL
Min. time	0 s
Max time	∞ s

006 Calculation R1

Result type	Predefined
Result	Consumption
Result unit	mL
Formula	R1=VEQ
Constant C=	1
Decimal places	4
Result limits	No
Record statistics	Yes
Extra statistical functions	No

007 Calculation R2

Result type	User defined
Result	Content
Result unit	mg/g
Formula	R2=(VEQ*CONC-TIME*DRIFT/1000)*C/m
Constant C=	1
Decimal places	4
Result limits	No
Record statistics	Yes
Extra statistical functions	No

008 Calculation R3

Result type	User defined
Result	Content
Result unit	%
Formula	R3=(VEQ*CONC-TIME*DRIFT/1000)*C/m
Constant C=	0.1
Decimal places	4
Result limits	No
Record statistics	Yes
Extra statistical functions	No

009 End of sample

Open series	Yes

8.3.1 Concentration Determination

The concentration of the one component Karl Fischer titrant with a nominal concentration of 5 mg/mL was determined using water standard (HYDRANAL® - Water Standard 10.0). The sample size was varied between 0.5 g and 1.5 g (corresponds to a burette volume of 20% to 60%). The results are plotted against the sample size as shown in *Figure 18*.

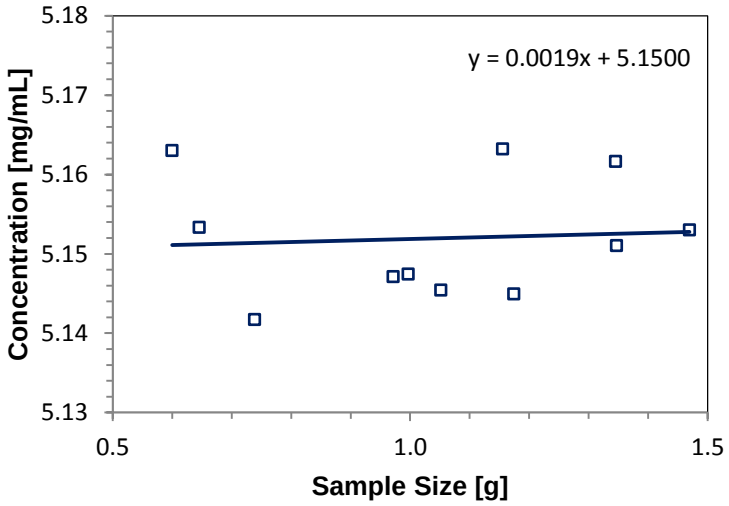


Figure 18. Titrant concentration vs. sample size.

Sample	Sample size [g]	Titrant concentration [mg/mL]
1	1.0518	5.1454
2	0.7388	5.1417
3	0.6457	5.1533
4	0.5999	5.1630
5	1.347	5.1510
6	0.9715	5.1471
7	0.9966	5.1474
8	1.1743	5.1449
9	1.3454	5.1616
10	1.4694	5.1530
11	1.1554	5.1632

Mean value	5.1520 mg/mL
Standard deviation (SD)	0.0077 mg/mL
Relative standard deviation (RSD)	0.15%

Table 12. Concentration determination of Karl Fischer titrant using water standard.

Conclusion

The results from the concentration determination are repeatable (RSD 0.15%) and no significant dependency on the sample size is visible.

8.3.2 Precision and Accuracy

The same certified water standard (as described in the previous chapter) was used to perform 11 measurements. The sample size was varied from 0.5 g to 2.25 g, corresponds to a burette volume of 20% to 90%. The relative standard deviation (RSD) of these measurements is used to check the precision. The accepted RSD value is less than 0.3%. The accuracy is determined by comparing the measured mean water content to the certified value of the water standard (10.02 mg/g, expanded uncertainty: 0.11 mg/g). The uncertainty stated on the water standard certificate was used as criteria for the accuracy. The measured value should be within the limits 10.02 mg/g ± 0.11 mg/g, which corresponds to a maximum relative deviation of 1.1%.

Sample	Sample size [g]	Result [mg/g]
1	1.1414	9.9652
2	0.7461	9.9867
3	1.1932	10.0065
4	0.7490	9.9923
5	1.0291	9.9689
6	2.0227	9.9910
7	1.8023	9.9939
8	1.7323	10.0093
9	1.5560	10.0184
10	2.4909	9.9993
11	2.0201	10.0006

Theoretical value	10.02 mg/g
Mean value found	9.994 mg/g
Deviation from theoretical value	0.026 mg/g
Relative deviation from theoretical value	0.26%
Standard deviation	0.016 mg/g
Relative standard deviation (RSD)	0.16%

Table 13. Water content determination of water standards by Karl Fischer titration.

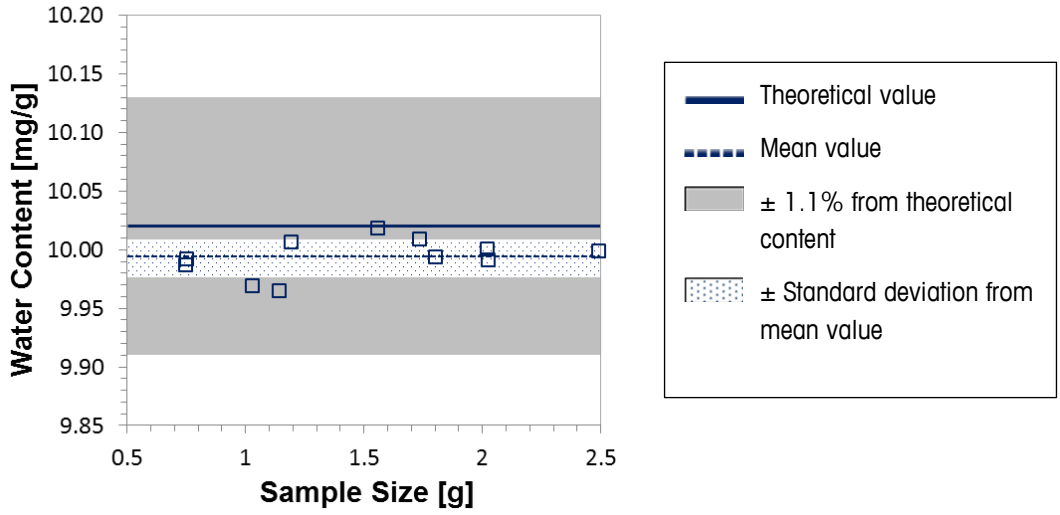


Figure 19. Determined water content vs. sample size.

Conclusion

The acceptance criteria for precise and accurate measurement are fulfilled. The relative standard deviation and the relative deviation from the theoretical (certified) water content are below the limits of 0.3% and 1.1%.

8.3.3. Systematic Errors and Linearity

The determined water content and the volume at the equivalence point (VEQ) from the measurements of the previous chapter were plotted versus the sample size. To reveal any systematic errors and non-linearity a linear regression is applied.

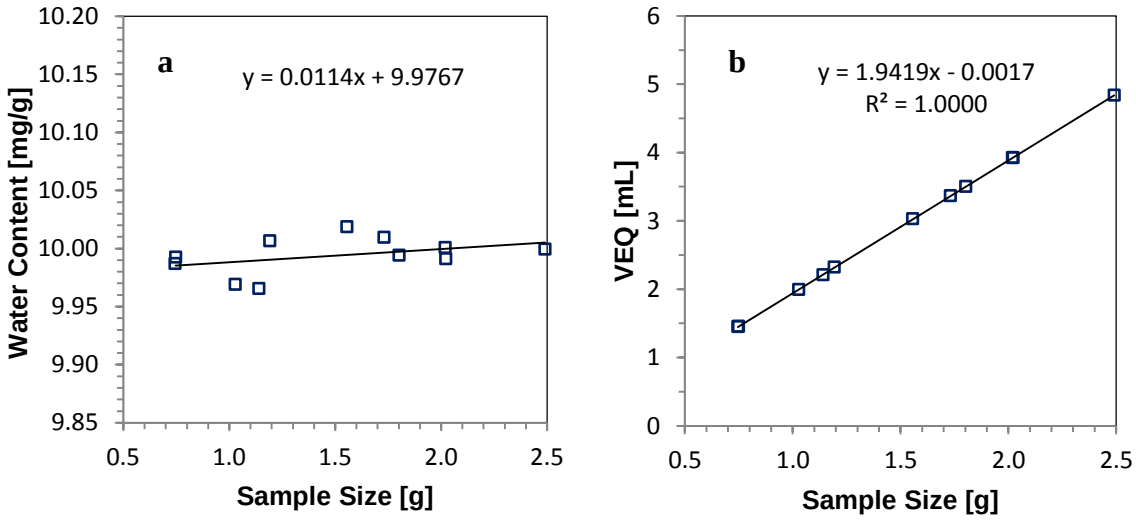


Figure 20. a) Water content vs. sample size
b) Titrant volume at the equivalence point (VEQ) vs. sample size.

Sample	Sample size [g]	VEQ [mL]
1	1.1414	2.2078
2	0.7461	1.4485
3	1.1932	2.3175
4	0.7490	1.4548
5	1.0291	1.9922
6	2.0227	3.9225
7	1.8023	3.4985
8	1.7323	3.3655
9	1.5560	3.0258
10	2.4909	4.8345
11	2.0201	3.9212

Systematic error	1.7 µL
Correlation coefficient R^2	1.000
Non-linearity	$1.1 \cdot 10^{-2}$ (mg/g)/g

Table 14. VEQ, sample sizes and numbers for systematic error and linearity of the water content determination.

Conclusion

The correlation coefficient shows an excellent linear correlation between the sample size and the volume at the equivalence point (*Figure* 20b). The systematic error is negligible and far below the recommended value of 15 µL. A non-linearity of 0.11% (0.0114 mg/g relative to a content of 10 mg/g and a sample size of 1 g) is observed from the *Figure* 20a. This value is just 0.01% above the recommended value of 0.1%. The main reason for the non-linearity is limited accuracy caused by sample addition into the titration vessel with a syringe.

8.3.4. Robustness

A Karl Fischer titration vessel is never completely tight and always a certain amount of moisture enters continuously into the vessel. This is the reason why the drift value is one of the most important and critical parameter of a Karl Fischer titration. For a good titration this value should be low (typically < 25 µg/min) and constant. Due to the fact that the water which enters the titration vessel comes from ambient air a dependency between the humidity and the drift value is assumed. Since the drift value is a critical parameter for a good Karl Fischer measurement, the humidity may have a direct influence on the result of the water determination. This is the reason why this method was tested against the robustness to air humidity variations. For this purpose the titrator was placed in a climate chamber at constant temperature (23°C ± 0.5°C) and 5 different humidity levels were tested, starting from 10% and finishing at 80% ± 2% of relative humidity. For each humidity value a series of six measurements

were performed. For these measurements the relative standard deviation and the relative deviation from the theoretical (certified) water content (10.02 mg/g, expanded uncertainty: 0.11 mg/g) were determined. These values should fulfill the same criteria as defined in chapter 8.3.2 (relative standard deviation < 0.3%, relative deviation from the theoretical value < 1.1%). The results for these measurements are shown in *Figure 21* and *Table 15*.

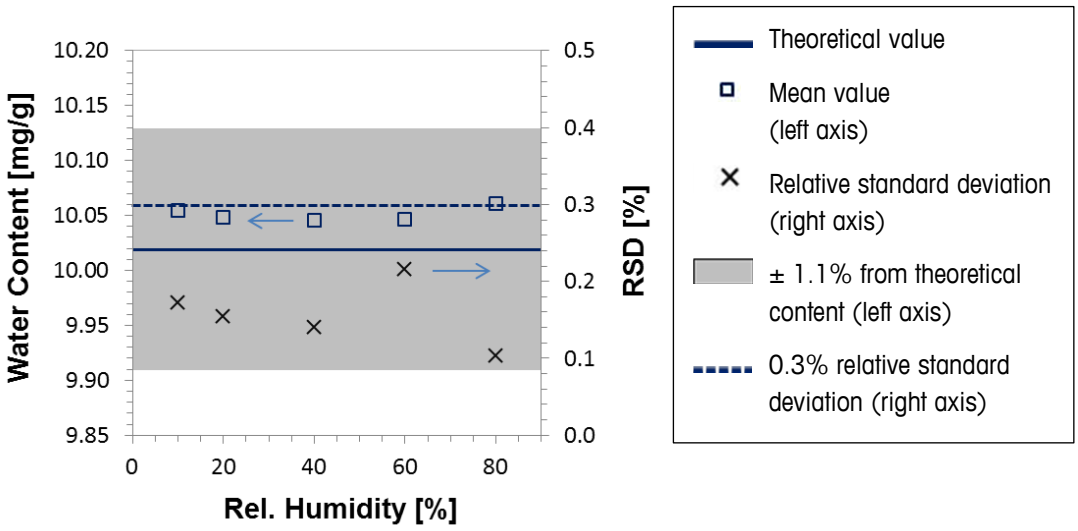


Figure 21. Water content and relative standard deviation (RSD) measured at different humidity.

Series	Rel. humidity [%]	Mean value [mg/g]	RSD [%]	SD [mg/g]	SD between mean values [mg/g]	RSD between mean values [%]
1	10	10.0549	0.172	0.0173		
2	20	10.0482	0.154	0.0155		
3	40	10.0455	0.140	0.0141	0.0067	0.066
4	60	10.0460	0.216	0.0217		
5	80	10.0610	0.103	0.0103		

Table 15. Water content, mean value and standard deviation (SD, RSD) measured at five different relative humidity levels.

Conclusion

The relative standard deviation is below the specified limits and the relative standard deviation between the mean values is very low. There is no significant influence of the humidity on the precision and accuracy of the results. The results in *Table 15* clearly prove that this method is robust against variations of air moisture between 10% and 80% relative humidity. Furthermore, repeatable results were gained by keeping the titrator for longer time (overnight) in the standby mode at the given humidity and repeating the measurements.

To achieve such robust results one has to make sure that always freshly regenerated molecular sieve (as drying agent for the titration vessel, titrant and solvent manager) is used. At higher humidity the molecular sieve will exhaust faster and has to be regenerated / exchanged more often.

8.3.5 Limit of Quantitation

To determine the limit of quantitation 4 series of 5 samples each were measured. For each series the amount of water standard added was lowered to simulate lower water contents. For the last series a standard (HYDRANAL® - Water Standard 1.0) with low water content of 1.001 mg/g and expanded uncertainty of 0.003 mg/g was used. For each series the absolute and relative standard deviation was determined. As defined for the other examples, the limit of quantitation is reached as soon as the relative standard deviation is higher than 0.3%. The results for these measurements are shown in the *Table 16* and *Figure 22*.

Series	Water standard [mg/g]	Sample size [g]	Amount of water [mg]	SD [mg/g]	RSD [%]
1	10.02	2.25	22.5	0.0164	0.163
2	10.02	1.00	10.0	0.0153	0.153
3	10.02	0.50	5.0	0.0326	0.324
4	1.003	1.00	1.0	0.0076	0.766

Table 16. Absolute (SD) and relative standard deviation (RSD) measured for different amount of water in the titration vessel.

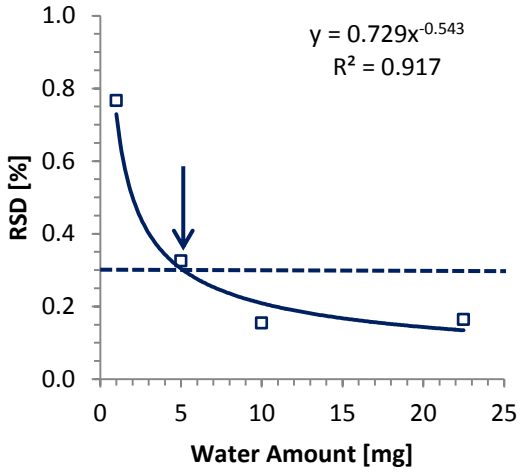


Figure 22. Relative standard deviation (RSD) vs. water amount.
The dashed line shows the limit of quantitation at 0.3% relative standard deviation.

Conclusion

From the graph it can be seen that the limit of quantitation for this method is 5 mg of water. This means that the sample size has to be chosen such that at least 5 mg of water is added into the titration vessel. If a sample contains 1 mg/g water this means that at least 5 g of sample has to be added.

To improve the standard deviation for low water contents the method has to be adapted (e.g. lower titrant concentration, lower titration speed, etc.). If we would change the method, the newly created method has to be validated again.

With the method used, lower water amounts of 1 mg could not be measured due to the titration parameters (too fast titrant addition). For such low water amounts coulometric Karl Fischer titration would be the method of choice.

8.3.6 Closing Remarks

The above example showed how the method for the volumetric Karl Fisher titrator can be validated. This procedure can be applied to any other volumetric Karl Fischer analysis by substituting the water standard, which was here used as a sample, by a representative sample. In order to get good results the user should take care about the following points:

Sample handling	The sample should be handled and added as described in the Good Titration Practice™ brochure for Karl Fischer Titration. The sample should be added carefully and the back weighing technique should be used.
Desiccant	Use always fresh or regenerated desiccant to protect the titration cell and the titrant against the ingress of moisture. The drying capacity of the desiccant is limited and it depends on the humidity (regeneration needed after 2 – 4 weeks). Silica gel can be regenerated over night at 150°C, whereas molecular sieves require temperatures up to 300°C.
Drift value	Before starting the measurements the drift value should be low (max. 25 µg/min, preferable: < 10 µg/min) and stable.
Time between measurements	Between every measurement a waiting time should be applied to ensure that the drift value is within the optimal range and stable.

By considering these points one should be able to get very precise and accurate results.

8.4 Coulometric Karl Fischer Titration: 1.0 mg/g Liquid Water Standard

The following method describes the measurement and validation of water content determination by Coulometric Karl-Fischer titration by means of a generating cell with diaphragm. 1.0 mg/g water standards were used as samples. The general procedure for the method validation can also be applied to other samples.

Sample	0.2 – 2.2 g Water Standard 1.0 mg/g (Hydranal® - Water Standard 1.0) Certified value: 1.003 mg/g ± 0.003 mg/g (expanded uncertainty k = 2)
Compound	Water, H_2O - M = 18.01 g/mol
Chemicals	HYDRANAL® Coulomat AG HYDRANAL® Coulomat CG
Standard	HYDRANAL® Water Standard 1.0 mg/g (Fluka product No. 34826)
Indication	DM143-SC
Chemistry	$CH_3OH + SO_2 + 3RN + I_2 + H_2O \rightarrow (RNH)SO_4CH_3 + 2(RNH)I$
Instruments	Compact Karl Fischer Coulometer C30D (Generator cell with diaphragm) XP205 Balance
Accessories	LabX® 2016 Software Solvent Manager 2, 5 & 10 mL syringes

Comments

- Before aspirating the sample, rinse the syringe with 1 mL of sample and discard it into a waste container.
- After rinsing the syringe aspirate the whole volume of sample needed for the series. Add a suitable portion of the sample to the titration vessel for each measurement.
- The weight is determined by back-weighing.
- Ensure that the pulling of syringe piston after injecting must be at equal distance for every sample injected. This is due to the fact that unknowingly we are removing the moisture present in the coulometric vessel.
- The instrument should not be set up in rooms subject to drastic temperature variations. It must not be placed beside heating sources or cooling thermostats.
- When carrying out the KF water determination gloves must be worn, as skin moisture could otherwise influence the precision of the results.
- Accurate weighing is required to achieve accurate and precise results. Thus, a 5-decimal digits analytical balance is used.
- The greatest error in KF coulometer titration of this water standard sample arises from the sample handling. For instance, the balance reading has to be perfectly stable when the weight is taken. The slight drift in weight leads to significant deviations in results due to the low water content expected.

Method

001 Title

Type	Karl Fischer titration Coul.
Compatible with	C30
ID	Validation
Title	Water Standard 1.0 mg/g
Author	PredefinedUser
Date/Time	....
Modified on	....
Modified by	PredefinedUser
Protect	No
SOP	None

002 Sample (KF)

Sample

Number of IDs	1
ID 1	--
Entry type	Weight
Lower limit	0.0 g
Upper limit	5.0 g
Density	1.0 g/mL
Correction factor	1.0
Temperature	25 °C
Autostart	Yes
Entry	After addition

003 Titration stand (KF stand)

Type	KF stand
Titration stand	KF stand
Source of drift	Online
Max. start drift	25 µg/min

004 Mix time

Duration	15 s

005 Titration (KF Coul) [1]

Sensor

Type	Polarized
Sensor	DM143-SC
Unit	mV
Indication	Voltametric
Ipol	5.0 µA

Stir

Speed	45 %

Control

End point	100.0 mV
Control band	250.0 mV
Rate	Normal
Generator current	Automatic

Termination

Type	Drift stop relative
Drift	3.0 µg/min
Min. time	90 s
Max. time	3600 s

006 Calculation R1

Result type	Predefined
Result	Content
Result unit	mg/g
Formula	R1 = (ICEQ/10.712-TIME*DRIFT)/(C*m)
Constant C =	1000
Decimal places	5
Result limits	No
Extra statistical functions	No

006 Calculation R2

Result type	Predefined
Result	Content
Result unit	ppm
Formula	R1 = (ICEQ/10.712-TIME*DRIFT)/(C*m)
Constant C =	1
Decimal places	5
Result limits	No
Extra statistical functions	No

007 End of sample

Open series	Yes

8.4.1 Precision and Accuracy

The certified water standard from the same batch was used to perform 10 measurements. The sample size was varied from 0.6 to 1.7 g. The relative standard deviation (RSD) of these measurements is used to check the precision. The accuracy is determined by comparing the measured mean water content to the certified value of the water standard (1.003 mg/g ± 0.003 mg/g, expanded uncertainty k = 2). The uncertainty stated on the water standard certificate was used as criteria for the accuracy. The measured value should be within the limits 1.003 mg/g ± 0.003 mg/g which corresponds to a maximum relative deviation of 0.3 %.

Sample	Sample size [g]	Result [mg/g]	Result [ppm]
1	0.89947	1.002188	1002.188445
2	0.77916	1.000998	1000.997663
3	1.4601	1.00135	1001.350409
4	0.66322	0.994836	994.835740
5	1.32674	1.000908	1000.907590
6	1.17647	0.998632	998.631508
7	1.69214	1.002141	1002.141209
8	1.61431	1.00082	1000.820171
9	0.79594	0.998426	998.425932
10	1.75454	1.00153	1001.530119

Theoretical value	1.003 mg/g	1003 ppm
Mean value found	1.002188 mg/g	1002.1882879 ppm
Deviation from theoretical value	0.000812 mg/g	0.817121 ppm
Relative deviation from theoretical value	0.08185 %	0.08147 %
Standard deviation	0.00228 mg/g	2.27831 ppm
Relative standard deviation (RSD)	0.228 %	0.228 %

Table 1. Water content determination of water standards by Coulometric Karl Fischer titration.

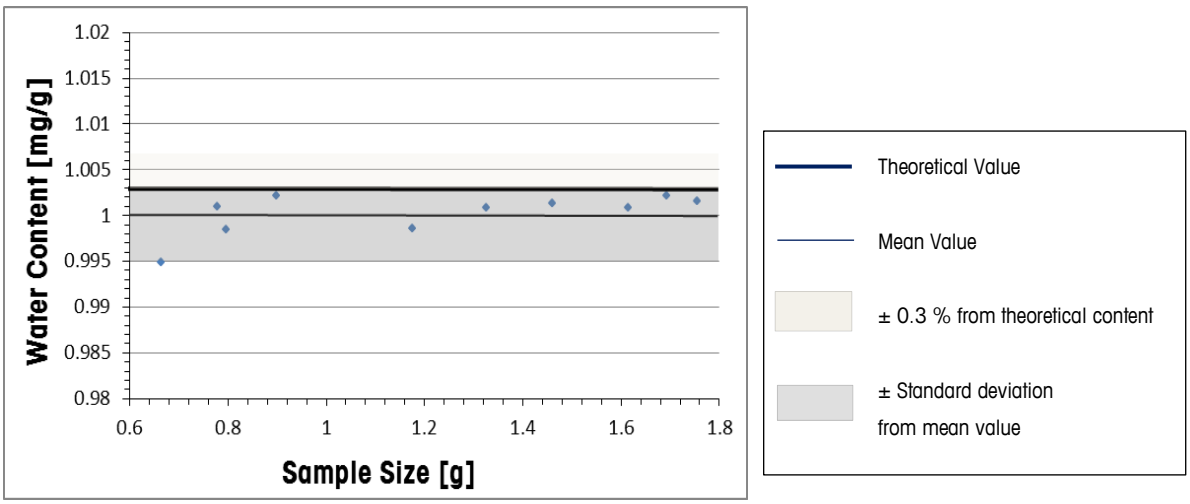


Figure 1. Determined water content vs. sample size.

Conclusion

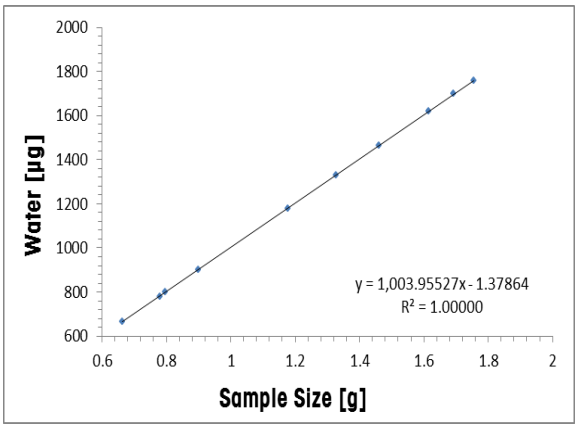
The acceptance criteria for the measurements are fulfilled. The relative standard deviation and the relative deviation from the theoretical (certified) water content are below the limits of 0.3%.

8.4.2 Systematic Errors and Linearity

To determine systematic errors such as method specific errors or working problems, a linear regression is calculated by plotting the water amount (µg) vs. the sample weight (g). In particular, the water amount (y-coordinate) is plotted as a function of sample weight (x-coordinate). The regression fits a straight line through the points. The regression line is described by the equation y = mx+c. Here, 'c' is the y-axis intercept whereas 'm' is the slope of the line.

Systematic errors are indicated by a significant deviation of the zero point coordinate of the y-axis (intercept), i.e. the regression line calculated from the pairs of values (µg water, sample weight) does not cut through the y-axis at exactly the origin of the coordinate system i.e. 0 µg water for a sample weight of 0 g.

To reveal any systematic error and non-linearity, a linear regression is applied:



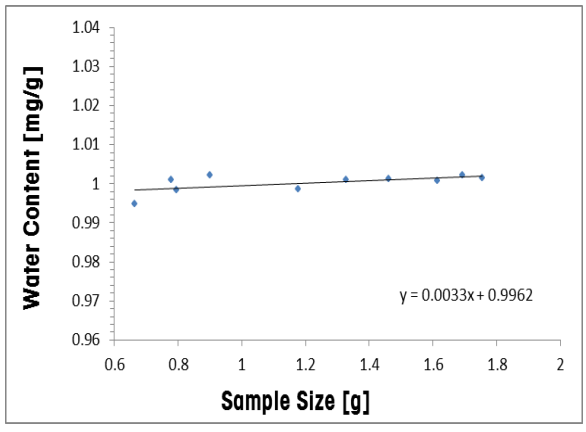


Figure 2. **a)** Systematic error: Water vs. sample size **b)** Linearity: Water content vs. sample size.

Sample	Sample size [g]	Water [µg]
1	0.89947	901.808
2	0.77916	780.665
3	1.4601	1463.892
4	0.66322	663.68
5	1.32674	1330.689
6	1.17647	1179.984
7	1.69214	1698.381
8	1.61431	1619.274
9	0.79594	798.614
10	1.75454	1759.421

Systematic error	-1.379 µg
Coefficient of determination R^2	1.00000
Non-linearity	$3.3 \bullet 10^{-3}$ (mg/g)/g

Table 2. Sample size and water amount (µg) are used to calculate the systematic error and coefficient of determination for the coulometric water content analysis.

A further possible method for measuring systematic error is the graphical representation of the regression line of the pairs of values (water amount µg, water content mg/g). A significant positive or negative slope of the regression line indicates a dependency of the water content on the amount of water. This can be an indication of a method–specific systematic error.

In fact, the slope m of the regression line y = mx+c should theoretically be m = 0, i.e. the curve should be a horizontal line through the y-intercept, where the intercept value is then given by the certified value of the standard.

Conclusion

The coefficient of determination R^2 shows an excellent correlation between the sample size and the water amount (in µg) at the end point (Figure 2a). The very good linearity of water content determination as a function of sample size and plotted in figure 2b is mainly due to the accurate sample handling entering the sample into the titration vessel with a syringe. The systematic error a_{sys} = -1.379 µg may be considered as negligible since it is below the expected limit of detection of 10 µg (see "GTP - Good Titration Practice in KF Titration" Brochure, chap. 8).

8.4.3 Robustness

The robustness of the method is the ability to reproduce the analytical method in different laboratories or under different circumstances without the occurrence of unexpected differences in the obtained results.

A Coulometric Karl Fischer titration vessel is never completely tight and always a certain amount of moisture enters continuously into the vessel. This is the reason why the drift value is one of the most important and critical parameter of a Karl Fischer titration. For accurate and precise titration this value should be at least below 25 µg/min before starting analysis, whereas in this case it is recommended to wait until the drift is below 15 µg/min in order to achieve accurate and precise results.

Due to the fact that the water which enters the titration vessel comes from ambient air, a dependency of humidity is responsible for drift variation. The results of water content determination are strongly influenced by the drift value. One of the reasons for testing robustness of this method is also a drift variation in drift value.

No.	Replicates	Drift Variation [µg/min]	Reproducibility RSD [%]
2	10	0.2 – 2.8	0.228
3	6	0.2 – 0.9	0.235
4	10	0.2 – 15.9	0.246
5	10	0.1 – 16.8	0.288
6	10	18.8 – 24.8	0.629

Table 3. Variation in drift leads to higher reproducibility expressed as higher relative standard deviation RSD.

Conclusion

This technique is robust with higher drift variation up to approx. 17 having a RSD of 0.3 %, and with lower drift variation the relative standard deviation RSD is 0.23%.

8.4.4. Ruggedness

The ruggedness is expressed as the degree of reproducibility of the test results obtained by analyzing the same samples under variety of normal test conditions i.e. different instrument, analysts, days etc.

A sample for ruggedness was assessed by multiple replicate determinations of sample from a single lot and percentage recovery of the results was calculated. The series have been measured on different days.

No. of days	Replicates	Sample size [g]	Drift Variation [µg/min]	Mean Water Content [mg/g]	Deviation from certified standard 1.003 mg/g ± 0.003 mg/g	Systematic error [µg]
4	10	0.66 – 1.75	0.2 – 2.8	1.00018	-0.00282	1.379
3	10	0.28 – 1.82	0.1 – 1.2	1.00101	-0.00199	3.318
2	6	0.69 – 1.67	0.2 – 0.9	0.99763	-0.00537	5.608
1	11	0.66 – 1.75	2.0 – 5.2	0.99953	-0.00347	7.286
11	10	0.78 – 1.71	3.1 – 7.9	1.00346	-0.00046	10.849
7	10	0.60 – 1.40	0.2 – 15.9	1.00022	-0.00278	12.759
8	10	0.53 – 1.68	3.0 – 8.8	1.00215	-0.00085	14.943
5	9	0.55 – 1.09	5.1 – 14.0	1.01432	0.01132	22.931
10	10	0.48 – 1.24	18.8 – 24.8	0.99867	-0.00433	33.705

Table 4. Systematic error increases only if the drift strongly varies

Conclusion

The method is rugged against the determinations performed on different days as well as by varying the sample size.

8.4.5 LOQ Limit of Quantitation

To determine the limit of quantitation few series of 6-11 samples each were measured. For each series the amount of water standard added was lowered to simulate lower water contents, and the absolute and relative standard deviation were determined. The limit of quantitation is reached as soon as the relative standard deviation is higher than 0.3 %. The results for these measurements are shown below:

Series	Water standard [mg/g]	Mean sample size [g]	Amount of water [µg]	SD [mg/g]	RSD [%]
1	1.003	1.15312	1151.763	0.00234	0.235
2	1.003	1.21621	1219.641	0.00228	0.228
3	1.003	0.82559	855.831	0.00749	0.738
4	1.003	0.99519	1006.824	0.00246	0.246
5	1.003	0.97471	988.0357	0.00382	0.381
6	1.003	0.79002	828.5715	0.00628	0.629
7	1.003	1.14479	1158.13	0.00161	0.160

Table 5. Relative standard deviation (RSD) measured for different amount of water.

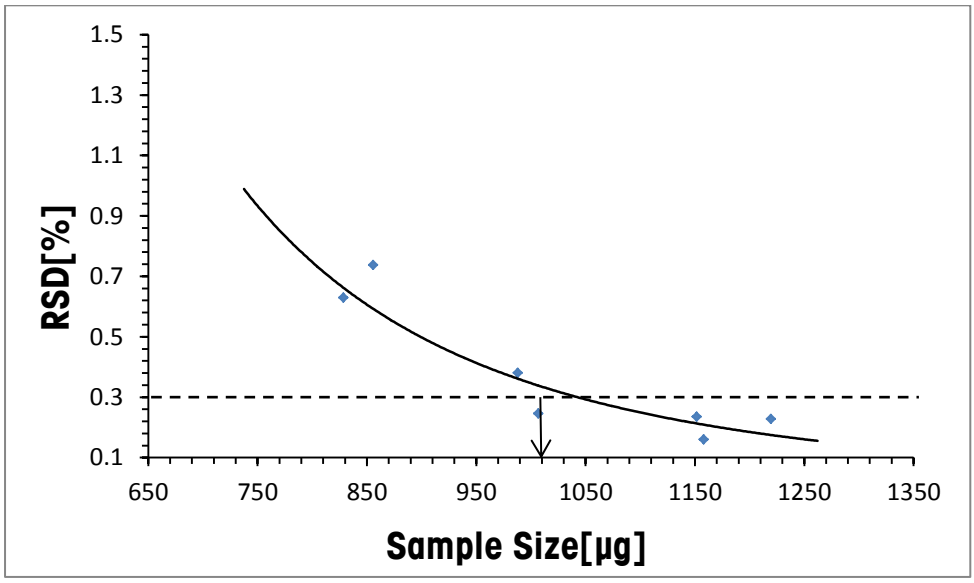


Figure 3. Relative standard deviation (RSD) vs. Amount of water.
The dotted line shows the limit of quantitation with the amount of water.

Conclusion

From the graph it can be seen that the limit of quantitation for this method is 1000 µg of water. This means that the sample size has to be chosen such that at least 1000 µg of water is added into the titration vessel in order to achieve a relative standard deviation of 0.3 %. If a sample contains 1.0 mg/g water this means that at least 1.000 g of sample has to be added to achieve accurate and precise results.

8.5 Coulometric Karl Fischer Titration: 0.1 mg/g Liquid Water Standard

The following method describes the measurement and validation of water content determination by Coulometric Karl-Fischer titration by means of a generating cell with diaphragm. 0.1 mg/g water standards were used as samples. The general procedure for the method validation can also be applied to other samples.

Sample	0.4 – 15 g Water Standard 0.1 mg/g (HYDRANAL® - Water Standard 0.1) Certified value: 0.102 ± 0.002 mg/g (expanded uncertainty = 0.002 mg/g, k = 2)
Compound	Water, H_2O M = 18.01 g/mol
Chemicals	HYDRANAL® Coulomat AG HYDRANAL® Coulomat CG
Standard	HYDRANAL® Water Standard 0.1 mg/g (Fluka product No. 34847)
Indication	DM143-SC
Chemistry	$CH_3OH + SO_2 + 3RN + I_2 + H_2O \rightarrow (RNH)SO_4CH_3 + 2(RNH)I$
Instruments	Compact Karl Fischer Coulometer C30D (Generator cell with diaphragm) XP205 Balance
Accessories	LabX® 2016 Software Solvent Manager 5, 10, 20 mL syringes

Comments

- Before aspirating the sample, rinse the syringe with about 1 mL sample and discard it into waste container.
- After rinsing the syringe aspirate the whole volume of sample needed for the series. Add a suitable portion of the sample to the titration vessel for each measurement.
- The sample mass is determined by back-weighing
- Ensure that the pulling of syringe piston after injecting the liquid standard in coulometer must be at equal distance for every sample injected. This is due to the fact that unknowingly we are removing the moisture present in the coulometeric vessel.
- The instrument should not be set up in rooms subject to drastic temperature variations. It must not be placed beside heating sources or cooling thermostats.
- When carrying out the KF water determination gloves must be worn, as skin moisture could otherwise influence the precision of the results.
- Accurate weighing is required to achieve accurate and precise results. Thus, a 5-decimal digits analytical balance is used.
- The greatest error in KF coulometer titration of this water standard sample arises from the sample handling. For instance, the balance reading has to be perfectly stable when the weight is taken. The slight drift in weight leads to significant deviations in results due to the low water content expected.

Method

001 Title	
Type	Karl Fischer titration Coul.
Compatible with	C30
ID	Validation
Title	Water Standard 0.1 mg/g
Author	PredefinedUser
Date/Time	….
Modified on	….
Modified by	PredefinedUser
Protect	No
SOP	None
002 Sample (KF)	
Sample	
Number of IDs	1
ID 1	--
Entry type	Weight
Lower limit	0.0 g
Upper limit	25.0 g
Density	1.0 g/mL
Correction factor	1.0
Temperature	25 °C
Autostart	Yes
Entry	After addition
003 Titration stand (KF stand)	
Type	KF stand
Titration stand	KF stand
Source of drift	Online
Max. start drift	25 µg/min
004 Mix time	
Duration	15 s
005 Titration (KF Coul) [1]	
Sensor	
Type	Polarized
Sensor	DM143-SC
Unit	mV
Indication	Voltametric
Ipol	5.0 µA
Stir	
Speed	45 %
Control	
End point	100.0 mV
Control band	250.0 mV
Rate	Cautious
Generator current	Automatic
Termination	
Type	Drift stop relative
Drift	3.0 µg/min
Min.time	90 s
Max. time infinite	No
Max.time	3600 s
006 Calculation R1	
Result type	Predefined
Result	Content
Result unit	mg/g
Formula	R1 = (ICEQ/10.712-TIME*DRIFT)/(C*m)
Constant C =	1000
Decimal places	5
Result limits	No
Extra statistical functions	No
006 Calculation R2	
Result type	Predefined
Result	Content
Result unit	ppm
Formula	R1 = (ICEQ/10.712-TIME*DRIFT)/(C*m)
Constant C =	1
Decimal places	5
Result limits	No
Extra statistical functions	No
007 End of sample	
Open series	Yes

8.5.1 Precision and Accuracy

The same certified water standard was used to perform 10 measurements. The sample size was randomly varied from 2.9 to 7.0 g. The relative standard deviation (RSD) of these measurements is used to check the precision.

The accuracy is determined by comparing the measured mean water content to the certified value of the water standard (0.102 mg/g ± 0.002 mg/g, expanded uncertainty, k = 2). The uncertainty stated on the water standard certificate was used as criteria for the accuracy. The measured value should be within the limits 0.102 mg/g ± 0.002 mg/g which corresponds to a maximum relative standard deviation of 2.0 %.

Sample	Sample size [g]	Result [mg/g]	Result [ppm]
1	2.91932	0.10222	102.22142
2	4.24256	0.10282	102.81876
3	6.80013	0.10276	102.75989
4	3.63112	0.10331	103.31100
5	7.08189	0.10222	102.22181
6	4.7424	0.10204	102.04185
7	6.00009	0.10229	102.29012
8	4.84465	0.10297	102.96565
9	4.11921	0.10331	103.31022
10	7.00708	0.10262	102.62409

Theoretical value	0.102 mg/g	102 ppm
Mean value found	0.10266 mg/g	102.65648 ppm
Deviation from theoretical value	0.00066 mg/g	0.65648 ppm
Relative deviation from theoretical value	0.0065%	0.0064 %
Standard deviation	0.00046 mg/g	0.45700 ppm
Relative standard deviation (RSD)	0.446 %	0.445 %

Table 1. Water content determination of 0.1 mg/g water standard by Coulometric Karl Fischer titration.

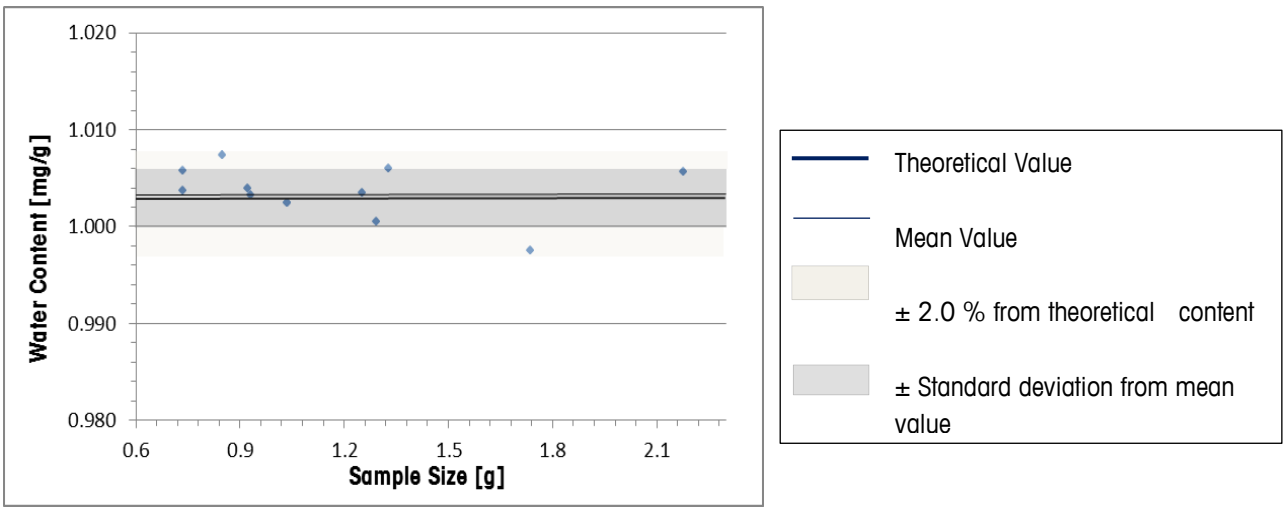


Figure 1. Determined water content vs. sample size.

Conclusion

The acceptance criteria for precise and accurate measurements are fulfilled. The relative standard deviation and the relative deviation from the theoretical (certified) water content are below the limits of 2.0 %.

8.5.2 Systematic Errors and Linearity

In order to determine systematic errors such as method specific errors and technical working problems, a linear regression is calculated by plotting the water amount (µg) against the sample weight (g). In particular, the water amount is plotted on the y-coordinate as a function of the sample weight (x-coordinate). The linear regression constructs a straight line through the measuring points. The regression line is described by the equation: y=mx+c. Here, 'c' is the y-axis intercept, whereas 'm' is the slope of the curve. Systematic errors are indicated by a significant deviation of the zero point coordinate of the y-axis (intercept), i.e. the regression line calculated from the pairs of values **µg water/sample weight** does not cut through the y-axis at exactly the origin of the coordinate system i.e. 0 µg water for a sample weight of 0 g. To reveal any systematic error and non-linearity, a linear regression is applied.

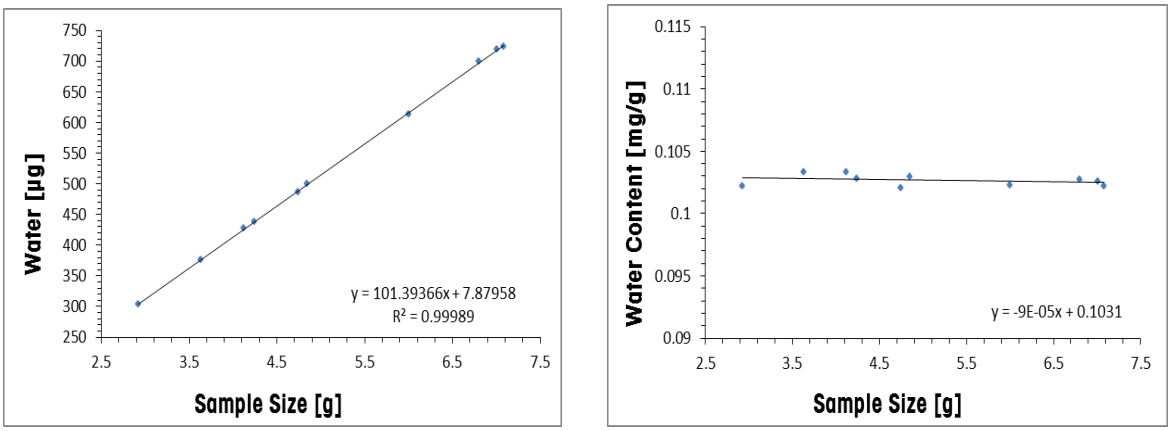


Figure 2. **a)** Systematic error: Water content vs. sample size **b)** Linearity: Water content vs. sample size.

Sample	Sample size [g]	Water [µg]
1	2.91932	303.695
2	4.24256	438.763
3	6.80013	699.509
4	3.63112	375.681
5	7.08189	724.47
6	4.7424	486.289
7	6.00009	614.114
8	4.84465	499.743
9	4.11921	427.536
10	7.00708	719.459

Systematic error	7.880 µg
Coefficient of determination R^2	0.99989
Non-linearity	$-9.0 \cdot 10^{-5}$ (mg/g)/g

Table 2. Sample size and water amount (µg) are used to calculate the systematic error and coefficient of determination for the coulometric water content analysis.

A further possible method for measuring systematic error is the graphical representation of the regression line of the pairs of values **(water amount µg, water content mg/g).** A significant positive or negative slope of the regression line indicates an apparent dependency of the mg/g water content on the amount of water. This can be an indication of a method–specific systematic error. In fact, the slope m of the regression line y = mx+c, should theoretically be m=0, i.e. the curve should be a horizontal line through the y-intercept, where the intercept value is then given by the certified value of the standard.

Conclusion

The coefficient of determination R^2 shows an excellent correlation between the sample size and the water amount (in µg) at the end point ***Figure 2a***. The very good linearity of water content determination as a function of sample size and plotted in ***Figure 2b*** is due to the accurate sample handling entering the sample into the titration vessel with a syringe. The systematic error a_{sys} = 7.880 µg may be considered as negligible since it is below the expected limit of detection of 10 µg (see chap. 8, GTP in KF Brochure).

8.5.3 Robustness

The robustness of the method is the ability to reproduce the analytical method in different laboratories or under different circumstances without the occurrence of unexpected differences in the obtained results. A Coulometric Karl Fischer titration vessel is never completely tight and always a certain amount of moisture enters continuously into the vessel. This is the reason why the drift value is one of the most important and critical parameter of a Karl Fischer titration.

For accurate and precise titration this value should be at least below 25 µg/min before starting analysis, whereas in this case it is recommended to wait until the drift is below 5 µg/min in order to achieve accurate and precise results. Due to the fact that the water which enters the titration vessel comes from ambient air, a dependency of humidity is responsible for drift variation. The results of water content determination are strongly influenced by the drift value. One of the reasons for testing robustness of this method is also a drift variation in drift value.

No.	Replicates	Drift Variation [µg/min]	Repeatability RSD [%]
1	10	0.2 – 3.0	0.446
2	10	0.7 – 4.9	0.772
3	12	0.6 – 3.7	0.786
4	10	1.9 – 9.5	1.483
5	10	2.1 – 8.0	1.656
6	10	13.8 – 18.1	2.280

Table 3. Variation in drift leads to lower repeatability expressed as higher relative standard deviation RSD.

Conclusion

This technique is robust with higher drift value up to approx. 22 having a RSD of max. 2.6 % and with lower drift value the relative standard deviation RSD is 0.4 %.

8.5.4 Ruggedness

The degree of reproducibility of the test results obtained by analyzing the same samples under variety of normal test conditions i.e. different instrument, analysts, days etc.

A sample for ruggedness was assessed by multiple replicate determinations of sample from a single lot and percentage recovery of the results was calculated. The series have been measured on different days.

No. of days	Replicates	Sample size [g]	Drift Variation [µg/min]	Mean Water Content [mg/g]	Deviation from certified standard 0.102 mg/g ± 0.002 mg/g	Systematic error [µg]
1	10	3.90 – 23.40	0.4 – 9.0	0.10224	0.00024	3.9056
2	7	2.82 – 14.38	0.4 – 2.8	0.10166	-0.00034	-4.6159
3	10	0.85 – 2.81	0.2 – 6.1	0.10464	0.00264	6.7808
4	10	2.91 – 7.08	0.2 – 3.0	0.10266	0.00066	7.8796
5	10	2.21 – 13.23	0.7 – 4.9	0.10470	0.00270	9.8645
6	12	0.80 – 15.39	0.6 – 3.7	0.10453	0.00253	12.152
7	10	1.91 – 5.42	2.1 – 8.0	0.10459	0.00259	12.924
8	10	2.32 – 8.31	1.9 – 9.5	0.10476	0.00276	18.509
9	10	1.55 – 7.32	13.8 – 18.1	0.10466	0.00266	20.035

Table 4. Systematic error increases only if the drift strongly varies

Conclusion

The method is rugged against the determinations performed on different days as well as by varying the sample size but the systematic error is increased due to strong variation of the drift value.

8.5.5 LOQ Limit of Quantitation

To determine the limit of quantitation few series of 10 samples each were measured. For each series the amount of water standard added was lowered to simulate lower water contents. For each series the absolute and relative standard deviation was determined. The limit of quantitation is reached as soon as the relative standard deviation is higher than 2.0 %. The results for these measurements are shown below:

Series	Water standard [mg/g]	Mean sample size [g]	Amount of water [µg]	SD [mg/g]	RSD [%]
1	0.102	8.89951	919.0342	0.00080	0.779
2	0.102	8.27080	866.173	0.00082	0.786
3	0.102	6.10507	643.1589	0.00081	0.772
4	0.102	4.51725	482.5879	0.00155	1.483
5	0.102	1.56759	170.1947	0.00401	3.833
6	0.102	3.39165	363.739	0.00173	1.656

Table 5. Relative standard deviation (RSD) measured for different amount of water.

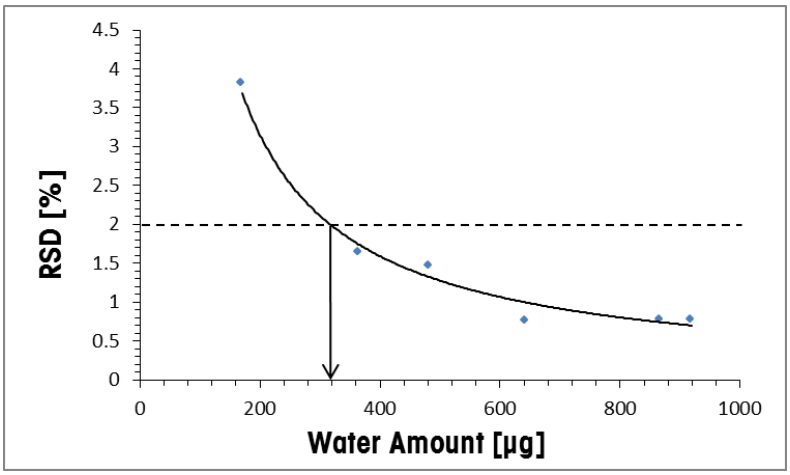


Figure 3. Relative standard deviation (RSD) vs. Amount of water.
The dotted line shows the limit of quantitation with the amount of water.

Conclusion

From the graph it can be seen that the limit of quantitation for this method is approx. 90 µg of water. This means that the sample size has to be chosen such that at least 90 µg of water is added into the titration vessel. If a sample contains 0.1 mg/g water this means that at least 0.9 g of sample has to be added.

9. Uncertainty of Measurement in titration

Beside the method validation, another important and supplementary approach in delivering trustworthy and reliable analytical data is the accomplishment of the results with the confidence interval. Only when this information is available the results obtained in other laboratories for the same samples and method can be comparable. In this aspect, a very useful and widely accepted concept is the uncertainty of measurement (or measurement uncertainty). The uncertainty of the analytical measurement is defined as a "parameter, associated with the result of a measurement that characterizes the dispersion of the values that could reasonably be attributed to the measurand" [9]. Calculation of measurement uncertainty is fundamental in many different fields of analytical chemistry ranging from production, quality control up to forensic investigations.

There are four steps to be considered in order to calculate the measurement uncertainty of results:
Step 1: Specifying the measurand.
Step 2: Identifying all the relevant sources of uncertainty.
Step 3: Quantifying the different uncertainty components.
Step 4: Calculating the combined measurement uncertainty.
The implementation of these four steps in practice is shown for the determination of chloride concentration for a series of 50 samples by using the former validated method from Chapter 8.2.

Step 1: The aim of this step is to describe the titration procedure. The information is usually found in standard operating procedure (SOP), as the preparation of the analyte, concentration and size of the analyte, type of equipment as titrator, sensor, stirrer, etc., titrant purity and concentration, burette size, expected titrant consumption, expected RSD, method parameters, etc. Additionally, the equation of measurand is written down and analyzed, with the units of each variable defined, as summarized in *Table 17*.

$$C = \frac{V_{Tit} * c_{Tit} * M_{Mol}}{V_s}$$

Symbols	Description	Unit
c	Concentration	g/L
V_{Tit}	Required Volume	mL
c_{Tit}	Concentration	mol/L
M	Molar Mass	g/mol
V_S	Volume	mL

Table 17: Description of the equation of measurand.

Step 2: The aim of the second step is to identify all single sources of uncertainty and to understand their effects on the uncertainty of measurement of the measurand. This is the most difficult step and brings the risk of neglecting important sources of uncertainty or double-counting of the other influences. In this case, the possible uncertainty sources are shown in so called cause and effect diagram (see *Figure 23*).

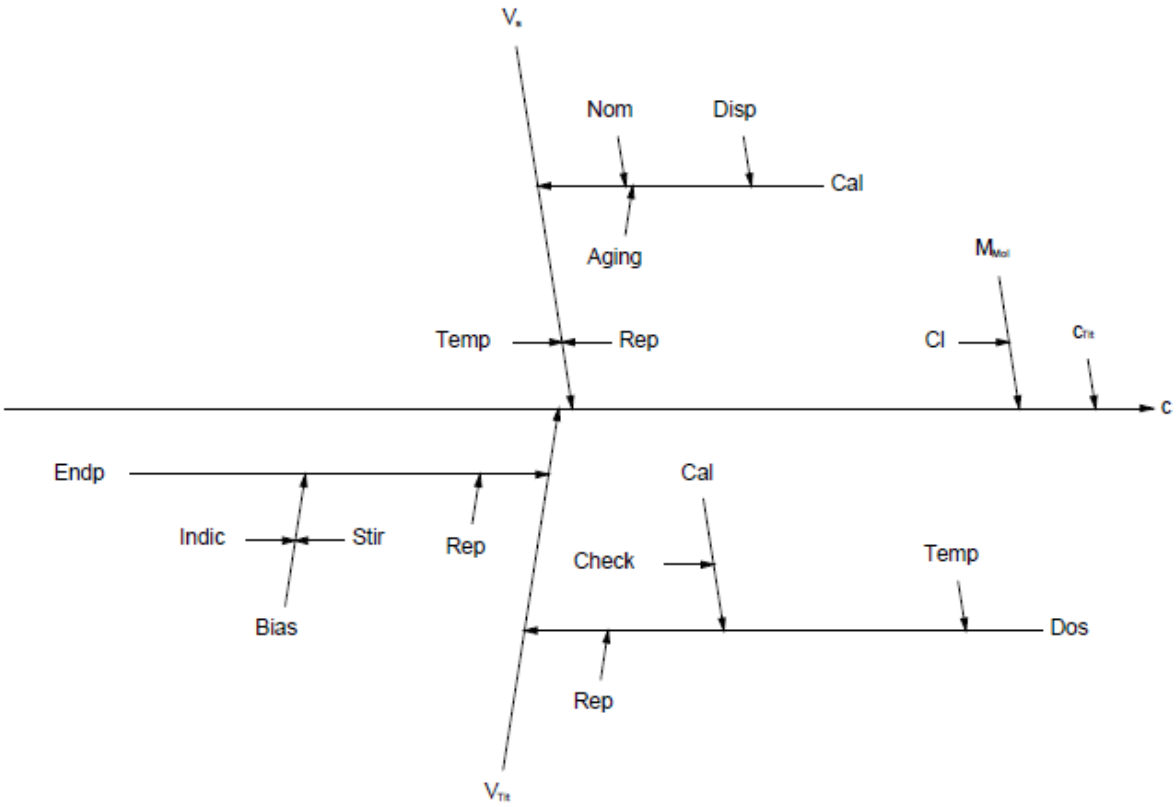


Figure 23. Cause and effect diagram of all the possible uncertainty sources.

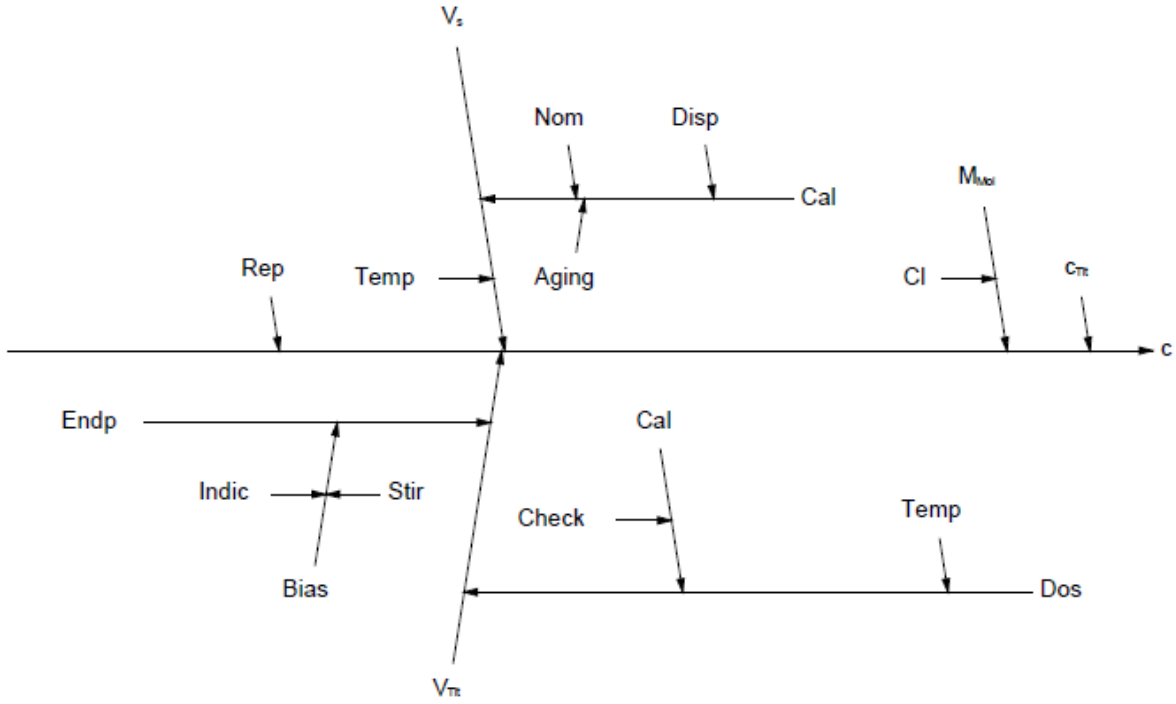


Figure 24. Simplified cause and effect diagram.

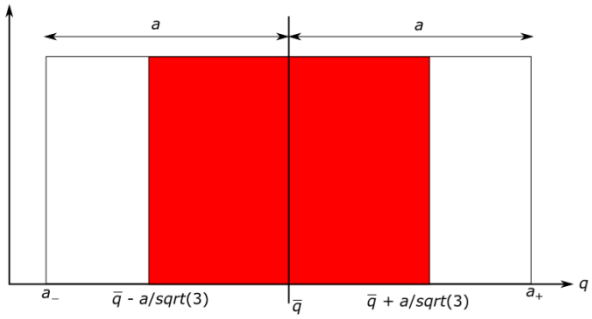
The diagram is a handy tool in daily practice to express the correlations between various sources of uncertainty in an analytical procedure. Individual variables of the equation are represented as main branches on the diagram. The contribution of each variable to the overall uncertainty is different and depends on the procedure/equipment used. Once the four main branches of the cause and effect diagram have been explored and recorded, individual titration steps are examined further and all other significant contributors to uncertainty are then also entered in the diagram as sub-branches.

The diagram can be further simplified by adding a new "repeatability" branch which represents all the repeatability sub-branches, as shown in *Figure 24* above. In this case the relative standard deviation (RSD) summarizes all repeatability effects.

Step 3: In this step, individual sources of uncertainty are quantified utilizing the technical specifications of the measuring instruments. For the missing information an adequate estimation can be used. Finally, these values are converted into standard deviations. To quantify the uncertainties a non-statistical approach is followed by using the rectangular and triangular distributions, as shown in the examples below.

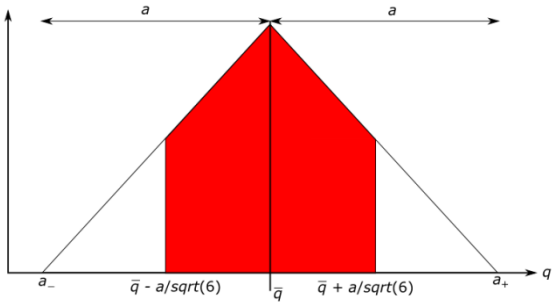
Example of rectangular distribution for the temperature:

$$\mathrm{u(Temp)} = \frac{3°\mathrm{C}}{\sqrt{3}} = 1.73°C$$



Example of triangular distribution for the burette:

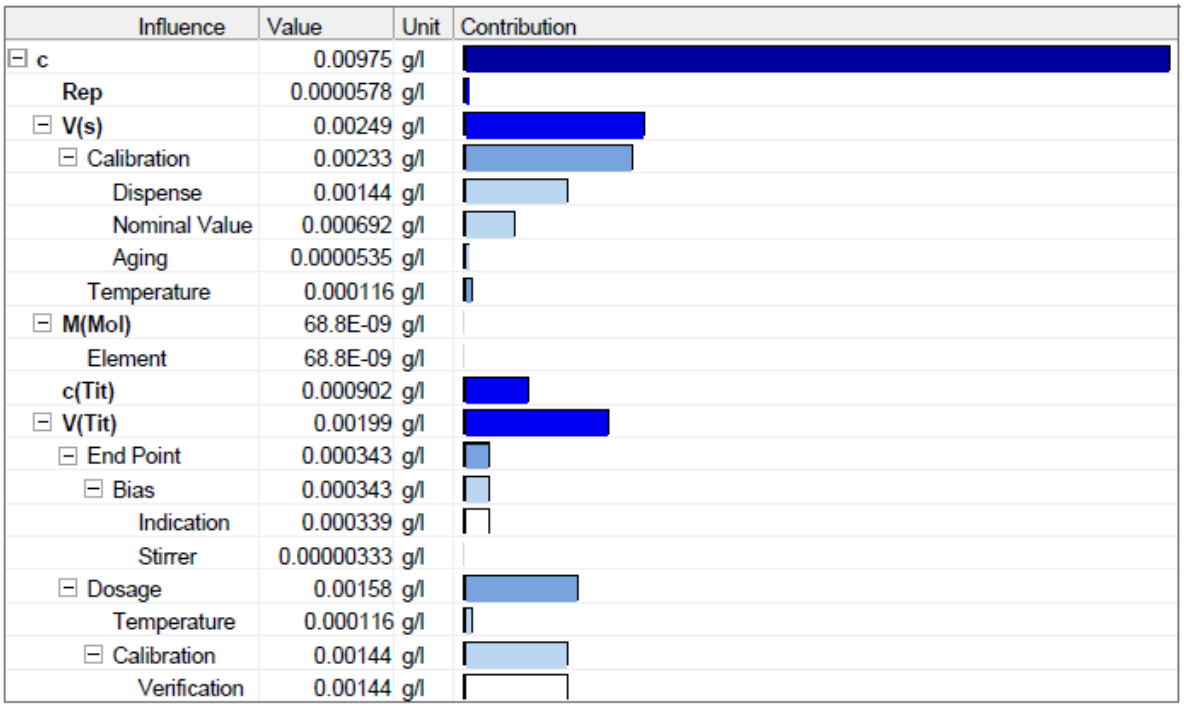
$$\mathrm{u(Vol)} = \frac{0.04\mathrm{mL}}{\sqrt{6}} = 0.0163mL$$



Step 4: In the final step, the overall (combined) uncertainty is calculated by using the principles of uncertainty propagation, as shown in the equation below.

$$\frac{u(R_1)}{R_1} = \sqrt{rep^2 + \left(\frac{u(V_{Tit})}{V_{Tit}}\right)^2 + \left(\frac{u(c_{Tit})}{c_{Tit}}\right)^2 + \left(\frac{u(M_{Mol})}{M_{Mol}}\right)^2 + \left(\frac{u(V_S)}{V_S}\right)^2}$$

The contributions of individual variables of the measurand for the determination of chloride concentration in the standard solution are described in *Figure 24*.



Influence	Value	Unit
c	0.00975	g/l
Rep	0.0000578	g/l
V(s)	0.00249	g/l
Calibration	0.00233	g/l
Dispense	0.00144	g/l
Nominal Value	0.000692	g/l
Aging	0.0000535	g/l
Temperature	0.000116	g/l
M(Mol)	68.8E-09	g/l
Element	68.8E-09	g/l
c(Tit)	0.000902	g/l
V(Tit)	0.00199	g/l
End Point	0.000343	g/l
Bias	0.000343	g/l
Indication	0.000339	g/l
Stirrer	0.00000333	g/l
Dosage	0.00158	g/l
Temperature	0.000116	g/l
Calibration	0.00144	g/l
Verification	0.00144	g/l

Figure 24: Contributions of the individual parameters of the equation of the measurand to the combined measurement uncertainty.

Conclusion

The calculated standard uncertainty (for a specimen result of 3.53378 g/L) is 0.00975 g/L. The corresponding relative standard uncertainty is then 0.276%. As shown in *Figure 24,* the main contribution in the overall uncertainty comes from the sample and titrant volume V_S and V_{Tit} respectively. It can be expected that the higher relative standard deviations (i.e. bad reproducibility) will lead to a higher uncertainty as well.

Additional extensive information about the calculation of the measurement uncertainty can be found in METTLER TOLEDO's Analytical Chemistry UserCom articles [10,11].

METTLER TOLEDO offers to our costumers the possibility to calculate the measurement uncertainty of volumetric titration applications (including KF) according to EN/ECN/ISO 17025 with an ISO 9000 validated software, called MuPac. MuPac is a unique service product, where the measurement uncertainty and compiled report is made by METTLER TOLEDO. MuPac generates a comprehensive report to provide knowledge and documentation to meet ISO audits. Furthermore, it helps to adjust specification limits accordingly, now that the titration uncertainty is known. It enables quantitative assessment of the titration (like a checkup) and derives recommendations to optimize SOP and hardware for the specific titration application.

10. Appendix: Standardisation of Titrants

Titrant	Standard Substance	Solvent and Auxiliary reagents	Intervall	Protection of Titrant / General Remarks
Alkalimetry				
Sodium hydroxide c(NaOH) = 1.0 mol/L	Potassium hydrogen phthalate $C_8H_5KO_4$; M = 204.23 g/mol Dry at: 150 °C	Deion. H_2O	weekly	Protect from CO_2 (tube filled with NaOH on carrier).
Sodium hydroxide c(NaOH) = 0.1 mol/L	Potassium hydrogen phthalate $C_8H_5KO_4$; M = 204.23 g/mol Dry at: 150 °C	Deion. H_2O	weekly	Protect from CO_2 (tube filled with NaOH on carrier).
Tetrabutyl ammonium hydroxide c(TBAH) = 0.1 mol/L	Benzoic acid $C_7H_6O_2$; M = 122.12 g/mol Dry at: 105 °C	Isopropanol	weekly	Protect from CO_2 (tube filled with NaOH on carrier).
Sodium methylate c($NaOCH_3$) = 0.1 mol/L	Benzoic acid $C_7H_6O_2$; M = 122.12 g/mol Dry at: 105 °C	Methanol	daily	Protect from CO_2 (tube filled with NaOH on carrier).
Potassium hydroxide c(KOH) = 0.1 mol/L	Benzoic acid $C_7H_6O_2$; M = 122.12 g/mol Dry at: 105 °C	Ethanol	weekly	Protect from CO_2 (tube filled with NaOH on carrier).
Acidimetry				
Sulfuric acid c(1/2 H_2SO_4) = 0.1 mol/L	Tris(hydroxymethyl)-aminomethane [THAM] $C_4H_{11}NO_3$; M = 121.14 g/mol Dry at: 105 °C	Deion. H_2O	Every 2 weeks	
Hydrochloric acid c(HCl) = 0.1 mol/L	Tris(hydroxymethyl)-aminomethane [THAM] $C_4H_{11}NO_3$; M = 121.14 g/mol Dry at: 105 °C	Deion. H_2O	Every 2 weeks	
Perchloric acid c($HClO_4$) = 0.1 mol/L	Tris(hydroxymethyl)-aminomethane [THAM] $C_4H_{11}NO_3$; M = 121.14 g/mol Dry at: 105 °C	Acetic acid	weekly	

Titrant	Standard Substance	Solvent and Auxiliary reagents	Intervall	Protection of Titrant / General Remarks
Precipitation				
Silver nitrate $c(AgNO_3)$ = 0.1 mol/L	Sodium chloride NaCl; M = 58.44 g/mol Dry at: 105 °C	Deion. H_2O acidify to pH 3.5	Every 2 weeks	Keep bottle in dark.
Barium chloride $c(BaCl_2)$ = 0.1 mol/L	Sodium sulfate Na_2SO_4; M = 142.05 g/mol Dry at: 105 °C	Deion. H_2O Buffer pH 4 Thorin	weekly	
Complexometry				
Complexone III c(EDTA) = 0.1 mol/L	Calcium carbonate $CaCO_3$; M = 100.09 g/mol Dry at: 105 °C	Deion. H_2O Indicatorbuffer-tablet	Every 2 weeks	Use PE bottles.
Complexone VI c(EGTA) = 0.1 mol/L	Calcium carbonate $CaCO_3$; M = 100.09 g/mol Dry at: 105 °C	Deion. H_2O Indicatorbuffer-tablet	Every 2 weeks	Use PE bottles.
Redox – Titration (Reducing titrants)				
Sodium thiosulfate $c(Na_2S_2O_3)$ = 0.1 mol/L	Potassium iodate KIO_3; M = 214.00 g/mol	Hydrochloric acid 0.1 M	biweekly	
Hydroquinone $c(C_6H_6O_2)$ = 0.1 mol/L	Potassium dichromate $K_2Cr_2O_7$; M = 294.19 g/mol	Sulfuric acid 5%	weekly	Keep bottle in dark.
Ammonium ferrous (II)sulfate c(FAS) = 0.1 mol/L	Potassium dichromate $K_2Cr_2O_7$; M = 294.19 g/mol	Sulfuric acid 5%	daily	Protect from oxygen.
Redox – Titration (Oxidizing titrants)				
Iron(III) chloride $c(FeCl_3)$ = 0.1 mol/L	Ascorbic acid $C_6H_8O_6$; M = 176.13 g/mol	Deion. water	biweekly	
Potassium dichromate $c(1/6\ K_2Cr_2O_7)$ = 0.1 mol/L	$(CH_2NH_3)_2SO_4 \bullet FeSO_4 \bullet 4H_2O$ M = 382.15 g/mol	Sulfuric acid 5%	biweekly	
Iodine $c(1/2\ I_2)$ = 0.1 mol/L	di-Arsenic trioxide As_2O_3; M = 197.84 g/mol	Deion. water $NaHCO_3$	daily	Keep bottle in dark. Keep cool.
Cerium sulfate $c(Ce(SO_4)_2)$ = 0.1 mol/L	di-Sodium oxalate $C_2O_4Na_2$; M=134.00 g/mol	Deion. water Sulfuric acid 5%	biweekly	

Titrant	Standard Substance	Solvent and Auxiliary reagents	Intervall	Protection of Titrant / General Remarks
Potassium permanganate c(1/5 $KMnO_4$) = 0.1 mol/L	di-Sodium oxalate $C_2O_4Na_2$; M=134.00 g/mol	Sulfuric acid 5%; 70 °C	biweekly	Keep bottle in dark.
Sodium nitrite c($NaNO_2$) = 0.1 mol/L	Sulfanilic acid $C_6H_7NO_3S$; M = 173.19 g/mol	HBr 0.5 mol/L	weekly	
Fehling solution	Glucose 1% in water $C_6H_{12}O_6$; M = 180.16 g/mol	Deion. water	weekly	Prepare Glucose solution daily.
2,6-Dichlorophenol-indophenol sodium salt c(DPI) = 0.01 mol/L	Ascorbic acid $C_6H_8O_6$; M = 176.13 g/mol	Deion. water	daily	Keep bottle in dark. Keep in PE bottles. Keep cool.
Turbidimetric Titrations				
Sodium dodecylsulfate c(SDS) = 0.01 mol/L	N-Cetylpyridinium chloride [CPC] monohydrate; M = 358.01 g/mol	Deion. water	biweekly	Rinse bottle and beakers with deion. water before use.
Hyamine c(Hyamine) = 0.01 mol/L	Sodium dodecylsulfate [SDS]; M = 288.4 g/mol	Deion. water	biweekly	Rinse bottle and beakers with deion. water before use.
N-Cetylpyridinium chloride c(CPC) = 0.01 mol/L	Sodium dodecylsulfate [SDS]; M = 288.4 g/mol	Deion. water	biweekly	Rinse bottle and beakers with deion. water before use.

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Notes

Notes

Method Validation Brochure

This applications brochure explains method validation using examples of three different common titrations. In this brochure METTLER TOLEDO summarizes the general method development protocols. These include accuracy, precision, limit of detection and quantitation, specificity, linearity, range and robustness.

The brochure is intended as a guide for analysts from regulated laboratories in the different industry segments, providing an explanation of the key aspects of titration method validation. As every laboratory is different this brochure is meant to inspire you to think of ways to validate your own titration method, in order to generate a high quality method that provides reliable data.

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