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APPLICATION NOTE 42162

CHN determination in Fluorine-Compounds with the Thermo Scientific Flash*Smart* Elemental Analyzer

Authors

Dr. Liliana Krotz, and
Dr. Guido Giazzi,
Thermo Fisher Scientific,
Milan, Italy

Keywords

CHN, Fluorine Compounds, IQ/OQ, Organic Synthesis, Pharmaceuticals

Goal

This application note shows the accuracy and robustness of the Thermo Scientific Flash*Smart* EA used for fluorine applications.

Introduction

Fluoro-organic compounds exhibit unique properties and their potential is increasingly being exploited in various areas of life sciences, particularly in pharmaceutical and crop-protection fields.

For example, many of the fluoro-compounds, the fluorosilicate $(SiF_6)^{-2}$, are used in industrial solutions such as insecticides and antiseptics, and at low concentrations are used in toothpaste and mouthwash preparation. Applications have also been found using Teflon® (PTFE–polytetrafluoroethilene), a fluoro-polymer which is very resistant to acid attack and is used in the car industry and in the production of special vessels such as non-stick looking utensils. Furthermore, some per-fluorate hydrocarbons are used as very stable lubricant oils.

However, in the last fifteen years fluorine-containing drugs have become an important tool in medicinal chemistry, as shown by its widespread use in the drugs currently available on the market. Many fluorine compounds have been developed and tested to enhance metabolic stability, which influences acidity and basicity levels in the human body.

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This application note was developed with the great support of Dr Keiko Bando of DaiNippon, Osaka, Japan, who has supplied us with many of the samples evaluated, and supported us with her wide experience in fluorine-compounds analysis.

Fluorine compounds in OEA analysis

Fluorine is very reactive. It reacts with catalysts, the tin container and with the silica present in the quartz reactor.

Consequently, it affects the robustness of the analytical system and the resistance time is proportional to the fluorine concentration in the molecule.

Figure 1. Thermo Scientific Flash*Smart* Elemental Analyzer.

The fluorine compounds, which were analyzed for this application have a concentration range from 3% to 55%. Although fluorine reaction affects the analytical system, the Thermo Scientific™ Flash*Smart*™ Elemental Analyzer provides a solution to overcome this challenge.

A short layer of **FluoAdso**, constituting a mixture of different oxides, was placed in the hot area of the oxidation reactor where the flash combustion occurs. The adsorber reacts with the fluorine-compounds, saving catalysts and the quartz reactor wall.

Method

The Flash*Smart* Elemental Analyzer is based on the dynamic combustion of the sample. The materials to be analyzed are weighed in tin containers and introduced into the combustion reactor via the Thermo Scientific™ MAS Plus Autosampler with oxygen. After combustion of the sample, the gases produced are carried by a helium flow to the combustion reactor filled with the FluoAdso, then through the oxidation reduction catalysts, a GC column. They are finally detected by a Thermal Conductivity Detector (TCD).

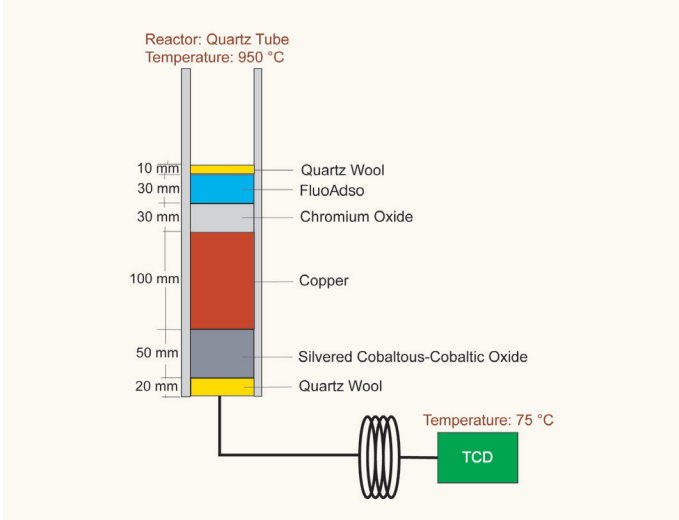
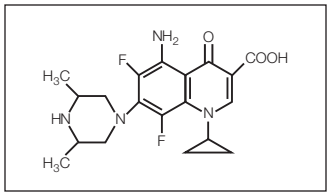


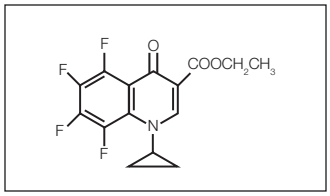
Figure 2. CHN configuration for Fluorine-Containing Compounds.

A complete CHN report is automatically generated by the Thermo Scientific™ Eager*Smart*™ Data Handling Software and displayed at the end of the analysis.

Analytical Conditions	
Oxidation/Reduction Furnace	950 °C
GC Column Oven	75 °C
Helium Carrier Flow	140 ml/min
Helium Reference Flow	100 ml/min
Oxygen Flow	250 ml/min
Oxygen Injection Time	5 sec
Sample Delay Time	12 sec
Total Run Time	less than 8 min
Standard	Acetanilide
Standard Weight	0.8-1.2 mg
Sample Weight	0.8-1.2 mg
Calibration Method	K factor



NACC 001



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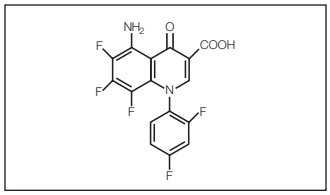

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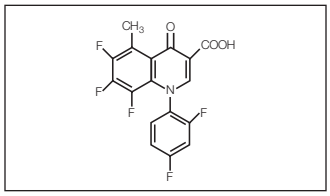

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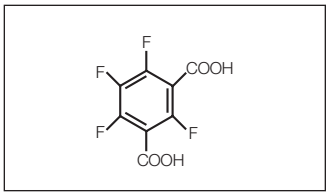

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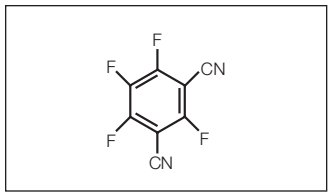

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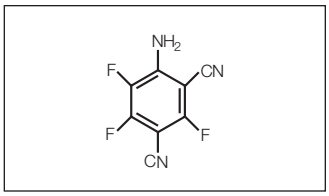


NACC 011

Results

To validate the system, organic compounds with different concentrations of fluorine were chosen. Instrument calibration was performed with acetanilide using K factor as calibration method.

Table 1 shows the theoretical and experimental data of a Reference Material, BRC 73, analyzed in three series of a large number of runs to evaluate the reproducibility, accuracy and precision.

Table 1. CHN determination of BCR 73 Reference Material.

Theoretical Data							
N%		C%		H%			
8.89		50.81		3.84			
Experimental Data							
Series	N. of runs	N%	RSD%	C%	RSD%	H%	RSD%
1	40	8.78	0.34	50.81	0.38	3.84	1.21
2	15	8.81	0.42	50.84	0.38	3.82	0.80
3	35	8.83	0.40	50.96	0.03	3.87	0.89

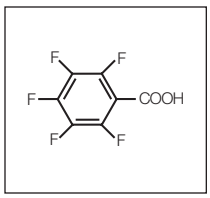
BCR 73: 1-[1-(-4bromophenylmethyl)-4-piperidinyl] - 5-chloro-2 (trifluoromethyl)-1H-benzimidazole

Table 2, 3 and 4 show the comparison of theoretical and experimental values of different fluorine containing compounds analyzed 5 times, in which the concentrations of fluorine is from 2 to 60%. The data obtained demonstrates the repeatability capabilities of the system for this matrix. No memory effect was observed, meaning that there were no interference of the fluorine.

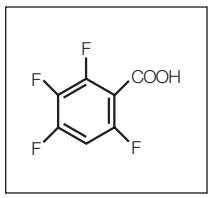
Table 2. Accuracy of CHN determination.

Sample	Calculated %		Experimental Data	
			%	RSD%
NACC 001*	F	9.68		
	N	14.28	14.28	0.283
	C	58.16	58.35	0.179
	H	5.65	5.68	0.269
NACC 002	F	23.08		
	N	4.25	4.24	0.136
	C	54.72	54.90	0.038
	H	3.37	3.34	0.173
NACC 003	F	25.66		
	N	7.57	7.40	0.135
	C	51.91	52.18	0.067
	H	1.91	1.97	0.155
NACC 004	F	25.73		
	N	3.79	3.77	0.153
	C	55.3	55.44	0.101
	H	2.18	2.10	0.262
NACC 005	F	31.92		
	N	0	0.00	0.000
	C	40.36	40.59	0.384
	H	0.85	0.84	0.690
NACC 008	F	37.98		
	N	14.00	13.95	0.504
	C	48.02	47.88	0.588
	H	0	0.00	0.000
NACC 011	F	28.91		
	N	21.31	21.01	0.595
	C	48.75	48.99	0.470
	H	1.02	0.98	0.591

* The NACC 001 sample is an antibiotic traded as Spara®.



NACC 007



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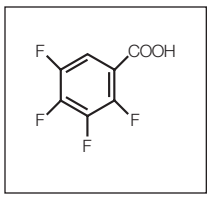

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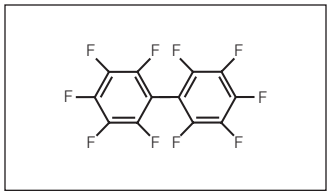

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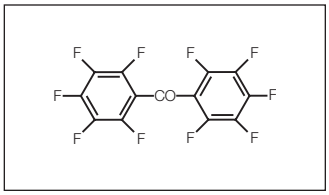
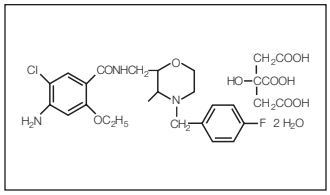
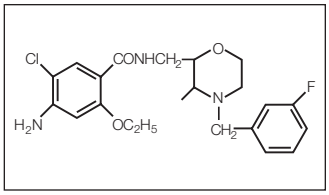


NACC 013



NACC 014



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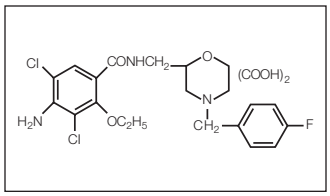

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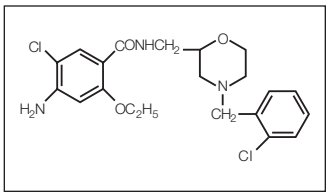

NACC 017

Table 3. Accuracy of CH Determination.

Sample	Calculated %		Experimental Data	
			%	RSD%
NACC 007	N% C% H% F%	- 39.64 0.48 44.79	- 39.28 0.52	- 0.291 0.794
NACC 009	N% C% H% F%	- 43.32 1.04 39.16	- 43.37 1.03	- 0.237 0.813
NACC 010	N% C% H% F%	- 43.32 1.04 39.16	- 43.51 1.01	- 0.216 0.351
NACC 012	N% C% H% F%	- 43.14 - 56.86	- 43.08 -	- 0.039 -
NACC 013	N% C% H% F%	- 43.12 - 52.46	- 43.21 -	- 0.264 -

Table 4: Accuracy of CHN determination.

Sample	Calculated %		Experimental Data	
			%	RSD%
NACC 014*	N% C% H% O% Cl% F%	6.46 49.89 5.74 29.54 5.45 2.92	6.44 50.11 5.73 - -	0.090 0.192 0.201 - -
NACC 015	N% C% H% Cl% F%	9.96 59.78 5.97 8.40 4.51	9.89 59.92 5.98 -	0.210 0.059 0.096 -
NACC 016	N% C% H% O% Cl% F%	7.69 50.56 4.80 20.49 12.98 3.48	7.62 50.68 4.78 - -	0.200 0.199 0.526 - -
NACC 017	N% C% H% O% F%	9.59 57.54 5.75 16.18 10.95	9.52 57.71 5.78 -	0.182 0.108 0.173 -

* The NACC 014 is a gastro movement acceleration pharmaceutical present in the market with Gasmotin® trade name.

Conclusion

Among halogens, only fluorine concentrations affects CHN determination as it causes tailing or splitting of the hydrogen peak. The use of a special FluoAdso, placed in the hot part of the combustion reactor eliminates the high activity of the fluorine compounds and it allows the quantitative determination of CHN with excellent accuracy and precision.

The lifetime of the reactor, when analyzing fluorine compounds, is 150 – 200 samples, depending on the sample nature and the fluorine concentration in the chemical compounds. The use of the adsorber in CHN configuration completely eliminates any interference of fluorine and other halogens atoms, chlorine, bromine and iodine do not influence CHN determination and no dedicated hanlding measures need to be taken.

Acknowledgments

Dr Keiko Bando, Nichiei Sangyo Co.,Ltd, Dainippon Pharmaceutical, Osaka, Japan

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