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Elemental Analysis: CHNS/O characterization of pharmaceutical products by the Thermo Scientific Flash*Smart* EA

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Keywords

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Goal

Demonstrate the performance of the Thermo Scientific Flash*Smart* EA for the characterization of pharmaceutical products.

Introduction

Carbon, nitrogen, hydrogen, sulfur and oxygen analysis is commonly used for the characterization of raw and final products in pharmaceutical and cosmetics industries in synthesis, separation, purification and structural identification both for quality control and R&D purposes.

The organic elemental composition is periodically monitored for the characterization of materials. Rigorous quality control begins with the suppliers of the raw materials. Therefore, an accurate and precise analytical technique allowing fast analysis with excellent reproducibility is needed for quality control processes in pharmaceuticals applications.

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The Thermo Scientific™ Flash*Smart*™ Elemental Analyzer (Figure 1) enables the quantitative determination of the five elements. The system, which is based on the dynamic combustion of the sample, provides simultaneous CHNS analysis in a single run and oxygen determination by pyrolysis in a second run. The Flash*Smart* Elemental Analyzer is equipped with two totally independent furnaces allowing the installation of two analytical circuits that can be used sequentially and are completely automated through the Thermo Scientific™ MultiValve Control™ (MVC) Module (Figure 2). Each analytical circuit has its own autosampler. In this way the system copes effortlessly with the laboratory requirements such as accuracy, day to day reproducibility and high sample throughput. The proprietary MVC Module also ensures very low helium consumption by switching from helium to nitrogen or argon gas, when the instrument is in Stand-By Mode. In this way the cost of analysis is significantly reduced.

Figure 1. Thermo Scientific Flash*Smart* Analyzer.

Figure 2. MultiValve Control (MVC) Module.

Methods

For CHNS determination the Flash*Smart* Elemental Analyzer operates with the dynamic flash combustion of the sample. Samples are weighed in tin containers and introduced into the combustion reactor (left furnace) via the Thermo Scientific™ MAS Plus Autosampler with the proper amount of oxygen. After combustion the resulted gases are carried by a helium flow to a layer filled with copper, then swept through a GC column that provides the separation of the combustion gases. Finally, they are detected by the Thermal Conductivity Detector (TCD). (Figure 3).

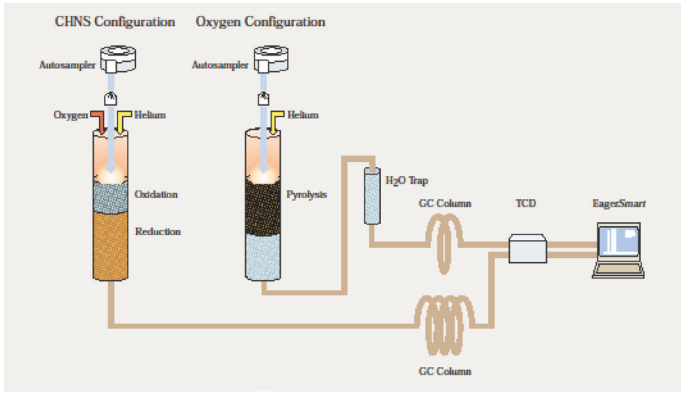

Figure 3. Flash*Smart* CHNS/O configuration.

For oxygen determination, the Elemental Analyzer operates in pyrolysis mode. Samples are weighed in silver containers and introduced into the pyrolysis chamber (right furnace) via the MAS Plus Autosampler. The reactor contains nickel coated carbon at 1060 °C. The oxygen in the sample, combined with the carbon, forms carbon monoxide which is then chromatographically separated from other products and detected by the TCD Detector (Figure 3). A complete report is automatically generated by the Thermo Scientific™ Eager*Smart*™ Data Handling Software and displayed at the end of the analysis.

Both pneumatic circuits for CHNS and oxygen determination are preset in the system in order to switch automatically from one to the other through the MultiValve Control (MVC) Module managed by the dedicated Eager*Smart* Data Handling Software without the need for manual intervention. The Eager*Smart* Data Handling Software window page, which controls the MVC Module (Figure 4), shows how to switch from the left to the right furnace to pass from CHNS determination by combustion to oxygen analysis by pyrolysis. It indicates also how to switch from helium carrier gas to nitrogen or argon gas when the instrument is in Stand-By Mode.

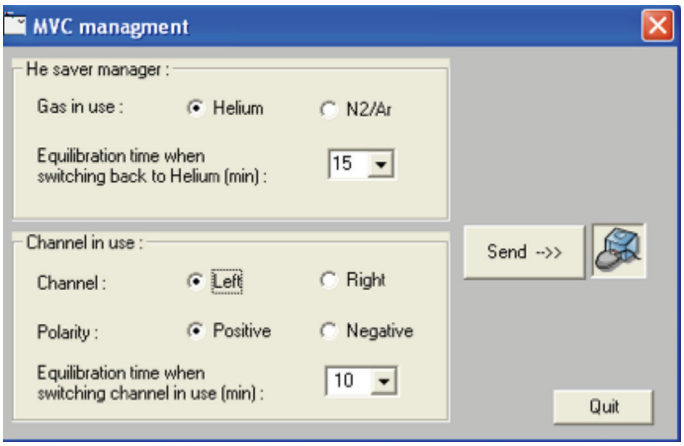

Figure 4. MVC Module window on the Eager*Smart* Data Handling Software.

Results

Different pharmaceutical samples were chosen to show the performance of the Elemental Analyzer. The samples were analyzed in different configurations according to the element of interest. Table 1 shows the information of the pharmaceutical products tested including the medical use, the empirical formula and the theoretical element percentages. Figure 5 shows the relative chemical formula.

Table 1. Pharmaceutical products information.

Name	Medical use	Formula	N%	C%	H%	S%	O%	Cl%	F%
Agomelatine	Melatonergic antidepressant	$C_{15}H_{17}NO_2$	5.76	74.05	7.04	-	13.15	-	-
Apixaban	Anticoagulant	$C_{25}H_{25}N_5O_4$	15.24	65.35	5.48	-	13.93	-	-
Dofetilide	Antiarrhythmic agent	$C_{19}H_{27}N_3O_5S_2$	9.52	51.70	6.12	14.51	18.12	-	-
Fesoterodine fumarate	Antimuscarinic	$C_{30}H_{41}NO_7$	2.65	68.29	7.83	-	21.22	-	-
Ivabradine hydrochloride	For stable angine pectoris	$C_{27}H_{37}ClN_2O_5$	5.55	64.21	7.38	-	15.84	7.56	-
Perampanel	Antiepileptic	$C_{23}H_{15}N_3O$	12.03	79.07	4.33	-	4.58	-	-
Rivaroxaban	Anticoagulant	$C_{19}H_{18}ClN_3O_5S$	9.64	52.35	4.16	7.36	18.35	8.13	-
Teriflunomide	Multiple sclerosis	$C_{12}H_9F_3N_2O_2$	10.37	53.34	3.36	-	11.84	-	21.09

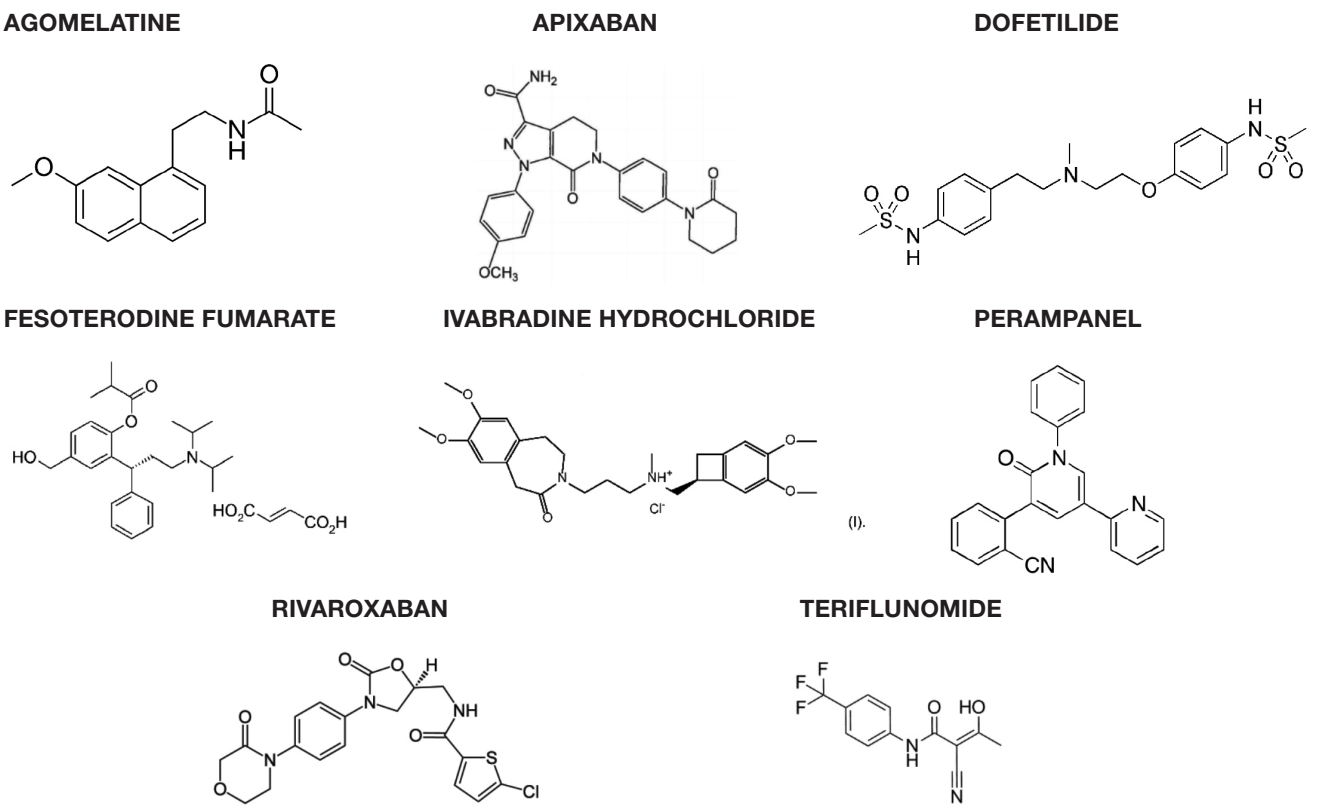

Figure 5. Chemical formula of pharmaceutical products tested.

Agomelatine and **Apixaban** were analyzed by CHN configuration. The calibration was performed with 2-3 mg of acetanilide standard, and the standard and sample weight was 2-3 mg. Table 2 shows the data obtained which are comparable to the theoretical values.

Table 2. CHNS/O data of Agomelatine and Apixaban.

Sample	N%	RSD%	C%	RSD%	H%	RSD%
Agomelatine	5.75 5.74 5.76	0.17	73.95 74.03 73.93	0.07	7.04 7.05 7.05	0.08
Apixaban Batch 1	15.25 15.23 15.24	0.07	65.35 65.45 65.43	0.08	5.46 5.47 5.49	0.28
Apixaban Batch 2	15.27 15.25 15.28	0.10	65.39 65.46 65.41	0.06	5.47 5.46 5.48	0.18

For Dofetilide, two different batches were analyzed in CHNS configuration. The calibration was performed with 2-3 mg of BBOT (2,5-bis (5-tert-butyl-benzoxazol-2-yl) thiophene) standard and the sample weight was 2-3 mg. Table 3 shows the data obtained which are comparable to the theoretical values.

Table 3. CHNS data of Dofetilide.

Sample	N%	RSD%	C%	RSD%	H%	RSD%	S%	RSD%
Batch 1	9.51 9.51 9.47	0.24	51.71 51.76 51.79	0.08	6.14 6.13 6.12	0.16	14.54 14.53 14.55	0.07
Batch 2	9.44 9.44 9.45	0.06	51.77 51.73 51.79	0.06	6.13 6.10 6.11	0.25	14.58 14.59 14.58	0.04

Fesoterodine fumarate, Ivabradine hychloride and **Perampanel** were analyzed by CHN/O configuration. For CHN analysis, the calibration was performed with 2-3 mg of acetanilide standard, and the standard and sample weight was 2-3 mg. While for oxygen determination, the calibration was performed with 1-2 mg of atropine, nicotinamide and methionine, sample weight 1-2 mg. Table 4 shows the data obtained which are comparable to the theoretical values.

Table 4. CHNS/O data of Fesoterodine fumarate, Ivabradine hydrochloride and Perampanel.

Sample	N%	RSD%	C%	RSD%	H%	RSD%	O%	RSD%
Fesoterodine fumarate	2.64 2.65 2.65	0.22	68.27 68.27 68.28	0.00	7.84 7.85 7.85	0.07	21.25 21.25 21.27	0.05
Ivabradine hydrochloride	5.50 5.51 5.50	0.10	63.97 64.02 64.00	0.04	7.39 7.38 7.40	0.14	15.80 15.84 15.80	0.15
Perampanel	11.98 12.01 11.99	0.13	79.12 79.03 79.08	0.06	4.29 4.28 4.28	0.13	4.58 4.58 4.57	0.13

For Rivaroxaban, two different batches were analyzed in CHNS/O configuration. For CHNS, the calibration was performed with 2 -3 mg of BBOT (2,5-bis (5-tert-butyl-benzoxazol-2-yl) thiophene) standard and the sample weight was 2-3 mg. While for oxygen determination, sulfanilamide was used to calibrate the system, standard and sample weight was 1-2 mg. Table 5 shows the data obtained which are comparable to the theoretical values.

Table 5. CHNS/O data of Rivaroxaban.

Sample	N%	RSD%	C%	RSD%	H%	RSD%	S%	RSD%	O%	RSD%
Batch 1	9.67 9.67 9.64	0.18	52.43 52.42 52.43	0.01	4.15 4.17 4.15	0.28	7.33 7.36 7.37	0.28	18.31 18.32 18.31	0.03
Batch 2	9.66 9.66 9.63	0.18	52.44 52.41 52.42	0.03	4.15 4.13 4.14	0.24	7.37 7.33 7.37	0.31	18.37 18.36 18.35	0.05

Two batches of **Teriflunomide** were analyzed by CHN configuration which reactor contains an absorber for trapping the fluorine. The calibration was performed with nicotinamide, standard and sample weight was 1-1.2 mg. Table 6 shows the CHN data which are comparable with the theoretical values.

Table 6. CHN data of Teriflunomide.

Sample	N%	RSD%	C%	RSD%	H%	RSD%
Batch 1	10.32 10.36 10.30 10.35 10.35 10.33	0.22	53.28 53.29 53.26 53.37 53.30 53.16	0.15	3.33 3.33 3.33 3.34 3.34 3.34	0.16
Batch 2	10.34 10.33 10.33 10.36 10.34 10.36	0.13	53.34 53.33 53.34 53.27 53.31 53.34	0.05	3.34 3.33 3.32 3.33 3.34 3.34	0.24

Along with controlling the instrument parameters and evaluating the unknown concentration, the dedicated Eager*Smart* Data Handling Software automatically calculates the Empirical Formula, by using the experimental data obtained. Figure 6 shows the dedicated window of Rivaroxaban sample analysis indicating on the left the relative information.

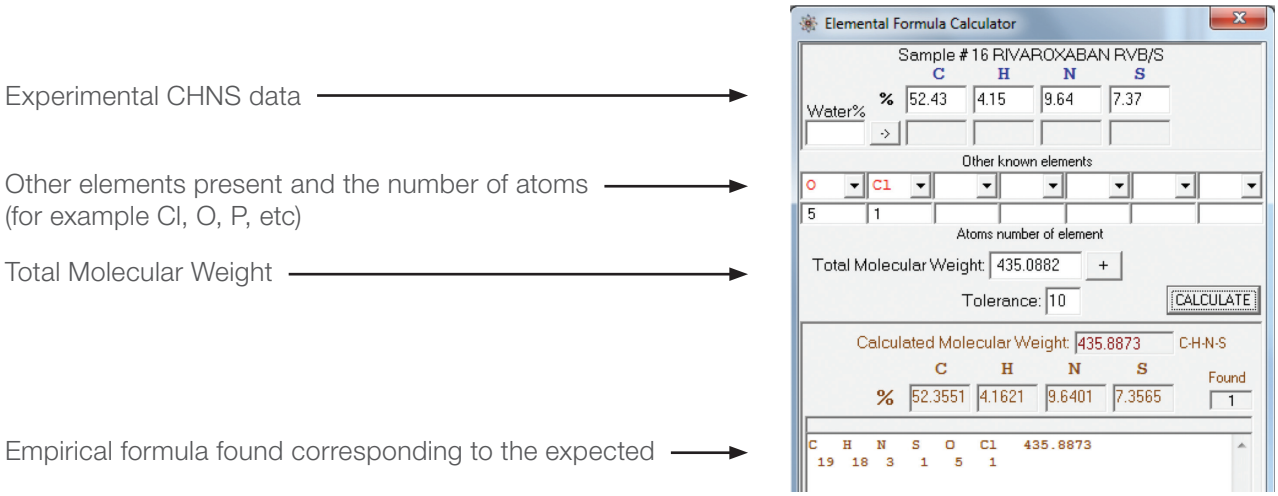

Figure 6. Empirical Formula of Rivaroxaban.

Conclusions

The Flash*Smart* Elemental Analyzer is a valuable solution for the analysis of CHNS/O in terms of accuracy, reproducibility, automation, speed of analysis and cost per analysis. All data showed were obtained with an acceptable repeatability and no matrix effect was observed when changing the configuration.

The presence of chlorine does not affect the data. The reactive fluorine in the Teroflunomide sample can be eliminated by adsorbing it after the combustion of the sample, without interference in the results.

The dual analytical configuration by the MVC Module allows performing the following functions:

- Automated control of two MAS Plus Autosamplers.
- Automated switch from the left channel to the right channel or vice-versa, increasing laboratory productivity.
- Reduction of helium consumption by switching from helium to nitrogen or argon when the system is in Stand-By Mode.
- Automated return to helium carrier gas from Stand-By Mode with the Auto-Ready function.
- Fully control of the workflow by the Eager*Smart* Data Handling Software.

Same system, hardware, autosamplers and software can be used for other combinations such CHN/O, CHN/S, CHNS/CHNS, CHN/CHN, NC/S, N-Protein / S, etc., using simple upgrade kits of consumables in which combustion and pyrolysis for oxygen determination can be performed. Another interesting combination of configurations could be CHNS on left furnace and CHN with the fluorine adsorber on the right furnace.

A dedicated Qualification (IQ, OQ) package for the Flash*Smart* EA is available. The qualification kit is configuration-specific and consists of consumables, standards or reference materials, filters and a GC separation column. These components are those required for the qualification process.

The Eager*Smart* Data Handling Software allows exporting and/or importing data to Microsoft Excel and LIMS.

Acknowledgments

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