



SAMPLE PREPARATION OF PHARMACEUTICAL SAMPLES FOR TRACE METAL ANALYSIS

Ensuring high-quality and productivity in elemental analysis of pharmaceutical samples using the Milestone ETHOS UP

| INTRODUCTION

New USP chapters <232> and <233> for the measurement of inorganic contaminants in pharmaceutical samples have been implemented. While samples that are soluble in aqueous and organic solvents may be analyzed directly, a large proportion of samples will require digestion, and in fact digestion may be preferred for ICP-MS analysis even if the sample is soluble in organic solvent.

Closed vessel digestion is stipulated by USP and it is expected that microwave digestion will be the predominant digestion technique used. Microwave digestion can achieve high temperatures and pressures and offers many

benefits when compared to traditional sample preparation techniques such as hot plate.

Milestone's ETHOS UP, microwave digestion system, incorporates all of the benefits of closed vessel microwave digestion while making sample preparation fast, easy, effective, and of the highest quality.

| EXPERIMENTAL

In this technical note, a recovery study on spiked Avicel PH-101, magnesium stearate, capsules and dietary materials has been performed to prove the efficacy of the ETHOS UP the sample preparation for metals analysis.



INSTRUMENT

The ETHOS UP meets the requirements of today's pharmaceutical labs. It offers several unique benefits including:

- Increased ease of use and productivity
- Enhanced control in all vessels
- Fast, accurate and traceable
- Superior safety and digestion quality

The ETHOS UP is a flexible and high performing platform used for elemental analysis and routine determinations in many applications. Its construction of stainless steel coated with five PTFE layers and accommodates both high-pressure and high-throughput rotors.



Figure 1 – Milestone's ETHOS UP

easyTEMP

Milestone's easyTEMP contactless sensor directly controls the temperature of all samples and solutions, providing accurate temperature feedback to ensure complete digestion in all vessels and high safety.

The superior temperature measurement of easyTEMP allows the processing of different

samples of similar reactivities, thus reducing labor time and increasing overall throughput.

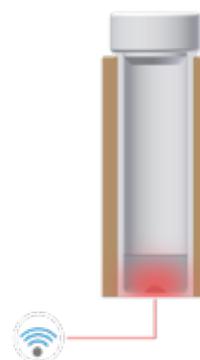


Figure 2 – easyTEMP contactless direct temperature sensor

This technology combines the fast and accurate reading of an in-situ temperature sensor with the flexibility of an infrared sensor. The ETHOS UP software provides digestion history traceability and temperature measurement for every sample. The temperature diagram and profiles are displayed real-time, and can be subsequently saved on the ETHOS UP terminal.

SK-15 HIGH PRESSURE ROTOR

The SK-15 rotor perfectly matches the needs of a modern analytical lab to determine trace elements, thanks to its capability for digesting large sample amounts at high temperature (up to 300 °C) and pressure (up to 100 bar).



Figure 3 – SK-15 easyTEMP High Pressure Rotor



The 15-position rotor is controlled by a contactless direct temperature sensor that controls the internal temperature of all vessels throughout the digestion cycle. This ensures complete and reproducible digestions of even the most difficult and reactive samples. The SK-15 also features Milestone’s patented “vent-and-reseal” technology for controlling the internal pressure of each vessel.

USER INTERFACE

The ETHOS UP comes with a dedicated touch screen terminal and easyCONTROL software which incorporates our expertise and know-how in microwave sample preparation. The ETHOS UP user-interface fully control all the digestion parameters, provides complete documentation and expedites the overall digestion procedure. The terminal is equipped with multiple USB and ethernet ports for interfacing the instrument to external devices and the laboratory network. The ETHOS UP controller is user-friendly, icon-driven, multi-language and 21 CFR Part 11 compliant.

To find the method which best suits your application simply select from the vast library of pre-stored methods. Included with the ETHOS UP is a unique web-based application: Milestone Connect. This app allows you to become a part of the Milestone community and gain exclusive access to a robust library of information: lists of parts, technical notes, user manuals, video tutorials, continuously updated application notes and all relevant scientific articles.



Figure 5 – easyCONTROL built-in library

ANALYTICAL PROCEDURE

ETHOS UP – SK-15 easyTEMP

SAMPLE	SAMPLE AMOUNT	ACID MIXTURE
Avicel PH-101 (Cellulose microcrystalline)	0.5 g	4 mL of HNO ₃ 65%, 1 mL of H ₂ O ₂ 30%
Magnesium Stearate	0.5 g	10 mL of HNO ₃ 65%
Capsules	0.7 g	4 mL of HNO ₃ 65%, 1 mL of H ₂ O ₂ 30%
Dietary supplement	0.9 g	4 mL of HNO ₃ 65%, 1 mL of H ₂ O ₂ 30%

Table 1 – Sample amount and acid mixture used for the microwave digestion run



STEP	TIME	T2	POWER
1	00:20:00	210 °C	1800 W
2	00:15:00	210 °C	1800 W

Table 2 – Microwave program used for digestion of samples

- Final dilution: 50 mL with dionized water

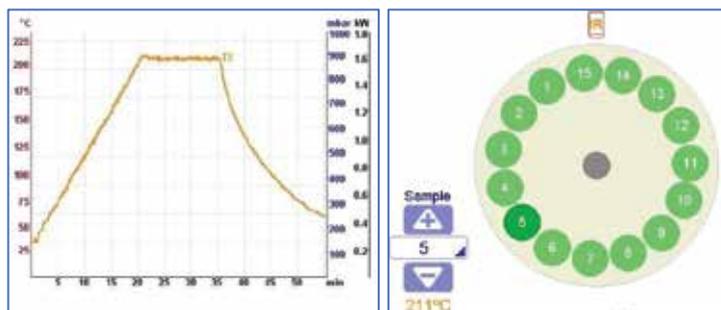


Figure 6 – SK-15 Microwave Run Report and multiple temperature traceability

QUANTIFICATION

ICP-OES Instrumental Parameters: RF power (W): 1300; Plasma flow (L/min): 15.0; Auxiliary Flow (L/min): 1.5; Nebulizer Flow (L/min): 0.75; Replicate read time (s): 10; Instrument stabilization delay (s): 15; Sample Uptake Delay (s): 30; Pump Rate (rpm): 15; Rinse Time (s): 10; Replicates: 3.

RESULTS AND DISCUSSION

The performance of the Milestone ETHOS UP equipped with SK-15 easyTEMP rotor was

evaluated through a recovery study on samples of interest for the pharma industry. All samples were fortified with a spike solution (Elemental Impurities according to ICH Q3D parenteral, Standard 1, ICP standard. Sigma-Aldrich code 89118-100ML) containing As, Cd, Co, Pb, Hg, Ni, Se, Ag, Tl and V (see spike concentration in Table 3). The sample were digested with Milestone's Ethos UP and subsequently analyzed via ICP-OES

	As	Cd	Co	Pb	Hg ^a	Ni	Se	Ag	Tl	V
Spike value (mg/L)	15	2	5	5	3	20	80	10	8	10
Avicel PH-101										
Recovery % (n=3)	97.3	90.1	92.7	95.6	98.2	101.3	102.4	91.8	89.2	98.9
RSD (%)	0.6	1.8	0.8	2.5	1.3	1.6	0.4	1.7	2.4	2.6
Magnesium Stearate										
Recovery % (n=3)	107.2	94.2	93.6	97.6	95.3	98.4	103.8	97.5	91.4	97.3
RSD (%)	1.0	0.6	1.8	0.4	0.9	1.3	0.8	1.6	2.1	1.6
Capsules										
Recovery % (n=3)	91.1	92.3	95.3	102.3	97.6	93.4	104.3	96.2	92.2	98.3
RSD (%)	1.4	1.4	2.0	1.4	0.3	1.1	2.4	1.5	1.9	0.5
Dietary Supplement										
Recovery % (n=3)	100.2	95.4	94.3	95.2	97.5	96.7	101.6	93.4	92.3	101.2
RSD (%)	0.6	1.6	0.9	1.3	1.5	1.2	2.1	1.9	1.7	1.4

Table 3 – Data of the recovery study on spiked samples of interest for Pharma

^a Analyzed with ICP cold vapor generator module.



The analytical results are shown in table 3 with good recoveries of all elements and RSDs below 3%. This demonstrates the robustness and reproducibility of microwave digestion using the ETHOS UP equipped with SK-15 easyTEMP technology.

CONCLUSION

The data shown in this technical note demonstrates full recovery of the elements spiked in the samples.

Samples, such as those from the pharmaceutical industry, can be completely digested, even in large sample amounts along with samples of similar reactivities. The digestion process was accurately controlled by the easyTEMP sensor, ensuring superior digestion quality and reliable results. In addition to full analyte recovery, microwave digestion using the Milestone ETHOS UP provides the highest level of reproducibility, great ease of use and high productivity in alignment with the new USP requirements.

ABOUT MILESTONE

At Milestone we help chemists by providing the most innovative technology for metals analysis, direct mercury analysis and the application of microwave technology to extraction, ashing and synthesis. Since 1988, Milestone has helped chemists in their work to enhance food, pharmaceutical and consumer product safety, and to improve our world by controlling pollutants in the environment.

