



MICROWAVE DIGESTION FOR PHARMACEUTICAL SAMPLE PREPARATION IN ACCORDANCE WITH USP <232>/<233>

Introduction



The new USP chapters <232> and <233> for the measurement of inorganic contaminants in pharmaceutical samples will be implemented on January 1, 2018. While samples that are soluble in aqueous and organic solvents may be analyzed directly, a large proportion of samples will require digestion. In fact, digestion is expected to be the preferred technique 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 due to its high pressure and temperature capability.

Single reaction chamber (SRC) microwave digestion is a relatively new type of closed vessel microwave digestion technique that significantly differs from traditional closed vessel microwave digestion. A commercially available benchtop SRC digestion system can digest up to 15 samples simultaneously, at high temperature and pressure conditions. This high temperature and pressure capability enables the complete digestion of virtually every pharmaceutical sample type, producing digested solutions with a very low total organic carbon (TOC) content, which in turn is beneficial for ICP-MS analysis.

Three sample types, dietary supplement, fish oil pill and magnesium stearate, were digested using a Milestone UltraWAVE (SRC) microwave digestion system and analyzed for the toxic USP elements using ICP-OES.

Since all samples are digested together in a single chamber with SRC, blank and spike recoveries were performed to confirm the retention of volatile elements and the absence of cross contamination.

Instrumentation

The SRC features a large 1 L pressurized stainless steel reaction chamber, which also serves as the microwave cavity.

This enables the intensity and distribution of the delivered microwave energy to be optimized to the shape of the reaction vessel, ensuring even heating without the need to rotate samples during the digestion program.

Samples are placed inside the SRC together and digested simultaneously. Because the samples are placed inside a pressurized vessel, individual pressure vessels are not needed. Samples are weighed into auto sampler-type vials with the appropriate digestion acid and loaded into a rack.



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The rack is loaded into the chamber, which is then sealed and pre-pressurized with nitrogen to 40 bar prior to microwave heating. Pre-pressurization prevents splashing or boiling of the sample solutions, avoiding cross contamination or loss of volatiles.

The SRC can operate at very high temperatures and pressures – up to 300 °C and 200 bar, enabling the complete digestion of every sample type.

The higher pressure capability of the UltraWAVE allows greater sample quantities to be digested – up to 1 g of sample using a 15 position rack.

With SRC technology, a variety of sample types can be run simultaneously. There is no need to “batch” digestion runs into identical sample types as needed with traditional microwave digestion systems. For example, raw materials and finished products can all be digested together in the same run. Furthermore, the UltraWAVE requires less digestion acid (typically 2-4 mL), thus decreasing the potential for contamination.

Upon completion of the digestion program, the chamber is vented and rack removed. Samples are diluted to volume and ready for measurement.

Analytical Procedure

The table below details the UltraWAVE microwave program and the pharmaceutical samples used for this test.

Sample	Weight	Spike added to samples	Reagents	Vial
Fish Oil	1.2 g	50 ppb	7 mL HNO ₃ + 3 mL H ₂ O	Quartz
Magnesium Stearate	1.0 g	50 ppb	6 mL HNO ₃ + 3 mL H ₂ O	Quartz
Dietary Supplement	1.0 g	50 ppb	6 mL HNO ₃ + 3 mL H ₂ O	Quartz

Microwave Program:

Step	Time	T1	Power
1	00:10:00	120 °C	1500 W
2	00:03:00	120 °C	1500 W
3	00:08:00	160 °C	1500 W
4	00:05:00	160 °C	1500 W
5	00:10:00	250 °C	1500 W
6	00:10:00	250 °C	1500 W



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ICP-OES Parameters:

Power	1.30 kW
Plasma Flow	15.0 L/min
Auxiliary Flow	1.50 L/min
Nebulizer Flow	0.75 L/min
Replicate read time	10 s
Instrument stabilization delay	15 s
Sample uptake delay	30 s
Pump Rate	15 rpm
Rinse Time	10 s
Replicates	3

ICP-OES Results

The samples were completely digested, forming a clear digestate, which was diluted to 50 mL with DI water. The samples were analyzed for toxic elements lead (Pb), cadmium (Cd), mercury (Hg), arsenic (As) and selenium (Se).

The table below illustrates the excellent recoveries obtained for the spiked samples.

Full recoveries for Hg demonstrate the effectiveness of pre-pressurization of the SRC prior to the digestion sequence. Volatile elements such as Hg are not lost and no cross contamination of samples occurs due to sample splashing or boiling.

	Fish Oil		Magnesium Stearate		Dietary Supplement	
	ppb	recovery	ppb	recovery	ppb	recovery
As	56.35	112.7%	52.75	105.5%	56.20	112.4%
Se	56.70	113.4%	44.80	89.6%	48.80	97.6%
Cd	50.55	101.1%	44.20	88.4%	45.70	91.0%
Hg	49.36	98.7%	47.70	95.4%	50.11	100.2%
Pb	50.40	100.8%	46.20	92.4%	49.30	98.6%

Conclusion

Milestone's UltraWAVE SRC microwave digestion system offers multiple benefits for sample preparation and subsequent analysis.

The UltraWAVE's higher sample capacity, use of disposable vials, and faster cooling time allows for increased sample throughput by a factor of 2 - 3 over conventional closed vessel systems. Furthermore, the higher temperature and pressure capabilities of the UltraWAVE provide superior digestion quality, a critical capability for multi element analysis.

The ability of the UltraWAVE to simultaneously digest a variety of sample types and weights, with minimum acid volume (1-4 mL per sample), make it the ideal solution for trace metals analysis of pharmaceutical samples.

