



Approaching USP Method 233 – Results of Sample Preparation and Analysis of Several Pharmaceutical Sample Types

Jason D. Keith, Daniel Iversen, Tina Restivo, Ivana Mrvalj, Elaine Hasty: CEM Corporation, 3100 Smith Farm Rd., Matthews, NC 28104 www.cem.com

Abstract

The current USP Method 231 is to be replaced with USP Methods 232 and 233. Conformance to USP Methods 232 and 233 will be required on May 1, 2014 as part of the General Notices revision that appears in USP 37-NF 32. During the process of developing the new methods, several changes were made to the sample preparation and sample analysis procedures, as well as the limits of accuracy and precision.

The official USP Method 233 requires that samples be completely dissolved prior to analysis. The sample can be directly dissolved in water or organic solvent or by closed vessel microwave digestion. The dissolved samples are then analyzed with an ICP-OES or ICP-MS.

A study was completed to compare accuracy and precision of the closed vessel microwave digestion of several pharmaceutical sample types. The samples were spiked with a solution of volatile and non-volatile metals and were analyzed with an ICP-MS to compare accuracy and precision. Although impurities must be monitored in all raw materials used for drug manufacturing, such as APIs, excipients, and finished products, this study focused solely on finished products. The spike recovery results are discussed.

Instrumentation



The MARS 6 with EasyPrep Plus vessels processes up to 12 samples simultaneously. The EasyPrep Plus vessel is an easy to assemble, high-temperature, high-pressure vessel that is capable of venting and resealing if the vessel over pressurizes. The temperature of the control vessel is monitored and controlled with a fiber optic probe and Contactless All-Vessel Sensors. The temperature of the standard vessels is monitored and controlled with Contactless All-Vessel IR Temperature Sensors.

The Discover SP-D System features a simple vessel with a snap-on cap. The system digests each sample sequentially, which allows for different sample types and acid matrices with individually programmed digestion conditions for each sample. When equipped with an optional automated sample deck, the Discover SP-D can run unattended, processing different sample types without operator intervention. Samples are processed at a rate of 6/hour (48/day), or it can be run overnight. The system is compatible with hydrofluoric acid.



Analytical Procedure

Three finished product samples were analyzed including a 0.1 g whole tablet containing the active ingredient acetylsalicylic acid, a 0.1 g whole tablet containing active ingredient loratadine, and a 0.3 g whole liquid gel capsule containing active ingredient diphenhydramine HCl. Each unprepared tablet or capsule was added to an EasyPrep Plus or Discover SP-D 35 mL vessel. A total of 9 mL of concentrated ultra-pure nitric acid and 1.0 mL of a spiked solution of deionized (DI) water containing 50.0 ppb of arsenic, mercury, and cadmium was added to all of the vessels. In addition, 1.0 mL of hydrogen peroxide was added to each EasyPrep vessel and 0.5 mL was added to each SP-D vessel containing the diphenhydramine HCl liquid gel capsule. Each of the samples and blanks was prepared in triplicate using the digestion parameters shown in the table below. Samples were cooled to room temperature and diluted to 50.0 mL with deionized water and transferred to autosampler vials. Calibration standards containing arsenic, mercury, and cadmium at concentrations of 0.1, 0.5, 1.0, 5.0, 10.0 ppb were prepared in 20% nitric acid. The samples were run on a Thermo Scientific ICP Q ICP-MS.

Digestion Conditions

	Ramp Time (minutes)	Hold Time (minutes)	Digestion Temperature (°C)
MARS 6 with EasyPrep Plus vessel	15	15	210
Discover SP-D with 35 mL vessel	5	3	210

Results

MARS 6 Spike Recovery Results of 50.0 ppb As, Cd, and Hg

	As	Hg	Cd
Acetylsalicylic Acid Finished Product			
Average	55.18	56.70	48.10
% Recovery	110.36	113.40	96.19
RSD	9.68	15.05	3.50
Loratadine Finished Product			
Average	68.02	51.33	55.67
% Recovery	136.04	102.66	111.34
RSD	7.23	12.00	6.95
Diphenhydramine HCl Finished Product			
Average	56.28	60.71	47.02
% Recovery	112.55	121.42	94.04
RSD	10.38	14.16	9.07

Discover SP-D Spike Recovery Results of 50.0 ppb As, Cd, and Hg

	As	Hg	Cd
Acetylsalicylic Acid Finished Product			
Average	54.90	50.45	51.84
% Recovery	109.80	100.90	103.67
RSD	3.04	6.13	2.86
Loratadine Finished Product			
Average	53.94	54.60	51.09
% Recovery	107.87	109.19	102.18
RSD	7.82	2.33	0.48
Diphenhydramine HCl Finished Product			
Average	59.38	53.70	57.11
% Recovery	118.77	107.41	114.23
RSD	9.99	0.89	7.21

Discussion

The accuracy of proposed USP Method 233 is 70 to 150% with a Relative Standard Deviation of not more than 20% for each element.

As shown in the results, the MARS 6 achieved good recoveries of both the volatile and non-volatile elements.

Mercury 101-122%
Arsenic 110-137%
Cadmium 94-112%

Also, easily demonstrated by the data, were the good recovery results for volatile and non-volatile metals in the Discover SP-D.

Mercury 100-110%
Arsenic 107-119%
Cadmium 102-115%

The accuracy and precision results of this study show that pharmaceutical samples prepared with the MARS 6 and Discover SP-D are well within the requirements of USP chapter 233 for each element.

Accuracy and precision can be improved by reducing interferences in the ICP-MS and utilizing acid mixtures that solubilize and stabilize the elements of interest.

Minimize the acid concentration in the final dilution

To stabilize mercury, add approximately 2 ppm gold to the standards and samples.

HCl will solubilize Fe, Zn, Al, Sn

Conclusions

Microwave closed vessel digestion instrumentation allows for fast, simple, and safe preparation of pharmaceutical samples for metals analysis.

Both the MARS 6 and the Discover SP-D meet or exceed their requirements of proposed USP Method 233 and are well suited to prepare pharmaceutical raw materials and finished products.

MARS 6 and Discover SP-D are simple-to-operate, offering a choice in instrumentation based on laboratory work flow and sample throughput.

The MARS 6 and Discover SP-D use easy-to-assemble, completely sealed vessels that eliminate the possibility of cross contamination and improve the