CEM CORPORATION

APPLICATION NOTE

Microwave Digestion of Pharmaceutical Samples Via Proposed USP Chapter <233>

Updated September 2014

Introduction

Known limitations with USP Chapter <231> – Heavy Metals, which was written in 1905, have led to the development of new methods for the preparation and analysis of pharmaceutical samples. The proposed replacements, USP Chapters <232> and <233>, were first published in January of 2010 with subsequent updates made in 2011, 2012, and 2013. The implementation date has been further delayed due to harmonization efforts with the IEC. The final method is now expected to be published in August 2015 with implementation to begin in December 2015 at which time, USP Chapter <231> will be removed completely.

USP Chapter <232> identifies fifteen elements to be tested with concentration limits set based upon how they are introduced to the body. Arsenic, mercury, cadmium and lead, also known as the "big four," are the elements of chief concern due to their toxicity and pervasiveness. Testing will be required for raw materials, excipients, contaminants introduced during the manufacturing process of API's, metals added as catalysts and leachable metallic impurities from packaging materials. Additional elements will need to be tested based upon the manufacturing process, added catalysts, and the environment from which the raw materials were extracted. This paper will discuss the preparation and analyte recovery of three pharmaceutical samples spiked with As, Cd and Hg.

USP Chapter <232>

Elemental Impurities – Limits

USP Chapter <232> outlines the maximum limits for heavy metals in active pharmaceutical ingredients and drug products based on three routes of administration which include oral, parenteral, and inhalation. There are several avenues by which these elements can find their way into drug products: they may be naturally occurring in the components, they may be added intentionally during the manufacturing process, or they can be transferred via contact with the processing equipment.

USP Chapter <233>

Elemental Impurities – Procedures

USP Chapter <233> discusses the sample preparation and analysis procedures for the determination of heavy metals in pharmaceutical raw materials and finished products. The chapter outlines four sample preparation techniques: Neat, Direct Aqueous Solution, Direct Organic Solution, and Indirect Solution. Most pharmaceutical raw materials and finished products will require the Indirect Solution technique, a closed vessel digestion in a concentrated acid solution that solubilizes the sample for analysis via an inductively coupled plasma optical emission spectrometer (ICP-OES) or an inductively coupled plasma mass spectrometer (ICP-MS).

Microwave digestion instrumentation offers several advantages over other digestion techniques, such as hot plates and hot blocks, including rapid heating in sealed containers to provide greater control of volatile elements, more complete destruction of background organics, and lower acid consumption. Temperature and pressure control options available on microwave digestion systems allow for more reproducible digestion conditions, as well as rapid turnaround of digested samples. In addition, it allows for precise documentation of the preparation conditions of every sample.

CEM offers two microwave systems for acid digestion: the **MARS 6**™ provides high-throughput batch processing of samples, while the **Discover® SP-D** offers an automated, sequential platform. Both systems are 21 CFR Part 11 compliant.

Discover SP-D

Instrumentation

The first set of samples was digested in the **Discover® SP-D**. The SP-D family has been the primary instrument of choice for the pharmaceutical industry, as it combines the flexibility to run a variety of individual samples from raw materials to tablets with automation. The addition of the autosampler allows for different samples to be prepared sequentially-each with its own methodology, if required, allowing lab personnel to perform other tasks while the instrument independently prepares samples for analysis. Using CEM's patented Focused™ Microwave technology, the Discover SP-D can prepare samples in as little as 10 minutes including cool down. This compact system provides temperature and pressure control and documentation of every sample. The samples were digested in a 35 mL Pyrex® vessel with a snap-on cap for ease of operation.

MARS 6

The second set of samples was prepared in the **MARS 6™** with One Touch Technology®, which uses sensors located in the bottom of the cavity to identify the number and type of vessels. The system then calculates the optimum power conditions needed to achieve the desired temperature and ensure complete digestions. Pre-programmed methods allow for the user to simply select the method that matches their sample type and the instrument does the rest. This system provides for large throughput batch analysis of up to forty samples simultaneously.

The samples were digested in the easy-to-assemble, high temperature and high-pressure **Easy Prep™ Plus** vessels. The temperature was monitored and controlled using **DuoTemp™**, a proprietary feature that incorporates both a fiber optic probe and **Contactless All-Vessel IR Temperature Sensors.** DuoTemp automatically selects the control vessel based upon reaction conditions and will dynamically adjust during the run, so that the temperature is always controlled based on the most reactive vessel, providing reproducible, safe digestions every time by eliminating exothermic reactions.

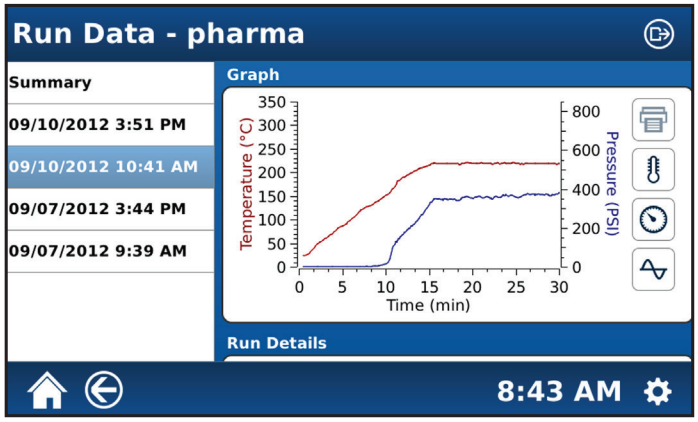
Digested samples were analyzed with using ICP-MS technology.

Analytical Procedure

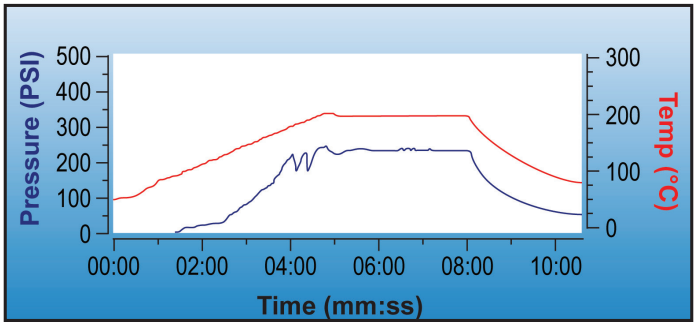
Three finished product samples were analyzed including a tablet containing the active ingredient acetylsalicylic acid, a second tablet containing the active ingredient loratadine, and a liquid gel capsule containing the active ingredient diphenhydramine HCl. Each tablet or capsule was added to an EasyPrep Plus vessel or Discover SP-D 35 mL vessel. A total of 9.0 mL of concentrated ultra-pure nitric acid and 1.0 mL of a spike solution of deionized (DI) water containing 50.0 ppb of arsenic, mercury, and cadmium was added to all of the vessels. Moreover, a 1.0 mL addition of hydrogen peroxide was added to each Easy Prep vessel, while 0.5 mL was added to each SP-D vessel. Each of the samples and blanks was prepared in triplicate using the digestion parameters shown in Table I.

Table I: Digestion Parameters for MARS 6 and Discover SP-D

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



Onboard temperature and pressure graph for a pharmaceutical sample digested in the MARS 6.



Temperature and pressure graph for Discover SP-D digestion of loratadine sample.

Samples were cooled to room temperature and diluted to 50.0 mL with DI water and transferred to autosampler vials. Calibration standards containing arsenic, mercury, and cadmium at concentrations of 0.10, 0.50, 1.00, 5.00, 10.00 ppb were prepared in 20% nitric acid. The samples were run on the Thermo Scientific iCAP Q ICP-MS using the following analysis conditions:

Forward Power	1500 W
Nebulizer Gas	1 L/min
Auxiliary Gas	0.8 L/min
Cool Gas Flow	14.0 L/min
Collision Cell Gas	He at 4.5 L/min
Sample Uptake/Wash Time	45 seconds each
Dwell Times	Optimized per analyte
Number of Points Per Peak	1
Replicates	3
Internal Standard	1.00 ppm yttrium

Results and Discussion

The results of the spike recovery study of pharmaceutical finished products are shown in the tables: MARS 6 Spike Recovery Results (ppb) of 50.0 ppb As, Cd, and Hg and Discover SP-D Spike Recovery Results (ppb) of 50.0 ppb As, Cd, and Hg.

Table II: Recovery Results of 50 ppb Spike of As, Hg, and Cd in Finished Pharmaceutical Products

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

	As	Hg	Cd
Acetylsalicylic Acid Finished Product			
Analysis 1	49.04	60.93	48.63
Analysis 2	58.79	46.87	46.21
Analysis 3	57.71	62.29	49.45
Average	55.18	56.70	48.10
Percent Recovery	110.36	113.40	96.19
RSD	9.68	15.05	3.50
Loratadine Finished Product			
Analysis 1	73.22	45.93	51.37
Analysis 2	67.40	50.02	58.88
Analysis 3	63.44	58.04	56.75
Average	68.02	51.33	55.67
Percent Recovery	136.04	102.66	111.34
RSD	7.23	12.00	6.95
Diphenhydramine HCl Finished Product			
Analysis 1	55.01	67.64	43.60
Analysis 2	62.65	51.09	51.80
Analysis 3	51.17	63.40	45.67
Average	56.28	60.71	47.02
Percent Recovery	112.55	121.42	94.04
RSD	10.38	14.16	9.07

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

	As	Hg	Cd
Acetylsalicylic Acid Finished Product			
Analysis 1	56.16	52.53	53.50
Analysis 2	53.01	51.92	51.36
Analysis 3	55.53	46.90	50.65
Average	54.90	50.45	51.84
Percent Recovery	109.80	100.90	103.67
RSD	3.04	6.13	2.86
Loratadine Finished Product			
Analysis 1	58.08	55.76	51.07
Analysis 2	54.09	54.79	51.34
Analysis 3	49.65	53.24	50.85
Average	53.94	54.60	51.09
Percent Recovery	107.87	109.19	102.18
RSD	7.82	2.33	0.48
Diphenhydramine HCl Finished Product			
Analysis 1	66.23	53.78	61.64
Analysis 2	55.92	54.14	53.58
Analysis 3	55.99	53.19	56.12
Average	59.38	53.70	57.11
Percent Recovery	118.77	107.41	114.23
RSD	9.99	0.89	7.21

The accuracy of proposed USP Chapter <233> is 70 – 150% with a Relative Standard Deviation of not more than 20%. As shown in Table II, the MARS 6 achieved good recoveries of both the volatile and non-volatile elements with mercury at 101 – 122%, arsenic at 110 – 137%, and cadmium at 94 – 112%. Also, easily demonstrated by the data in Table II were the good results for volatile and non-volatile metals in the Discover SP-D with 100 – 110% mercury, 107 – 119% arsenic, and 102 – 115% cadmium recoveries achieved. The accuracy and precision results of this study show that the pharmaceutical samples prepared with the MARS 6 and Discover SP-D are well within the requirements of USP Chapter <233>.

Conclusion

Microwave closed vessel digestion instrumentation allows for fast, simple, and safe sample preparation of pharmaceutical samples for metals analysis. Both the MARS 6 and the Discover SP-D are well suited to prepare pharmaceutical raw materials and finished products and offer a choice in instrumentation based upon laboratory workflow and sample throughput. Each system provides significant time savings and operates to a large degree unattended, freeing analysts to complete other tasks. Since both systems use completely sealed vessels as opposed to caps, the possibility of cross contamination is eliminated and the recovery of both non-volatile and volatile metals is possible. As demonstrated by the data above, the recovery results are well within the upcoming USP Chapter <233> requirements.

APPLICATION NOTES

CEM Corporation
United States
Tel: (800) 726-3331 [USA & Canada]
e-mail: info@cem.com
www.cem.com

FRANCE
CEM μWave S.A.S.
Tel: (33-1) 69 35 57 80
e-mail: info.fr@cem.com
www.cemfrance.fr

GERMANY
CEM GmbH
Tel: (49) 2842-9644-0
e-mail: info@cem.de
www.cem.de

IRELAND
CEM Technology (Ireland) Ltd
Tel +353 (0)1 885 1752
Email: info.ireland@cem.com
www.cemmicrowave.co.uk

ITALY
CEM S.R.L.
Tel: (39) 35-896224
e-mail: info.srl@cem.com
www.cemmicroonde.it

JAPAN
CEM Japan K.K.
Tel: +03-5368-2507
e-mail: info@cemjapan.jp
www.cemjapan.jp

UNITED KINGDOM
CEM Microwave Technology Ltd.
Tel: (44) 1280-822873
e-mail: info.uk@cem.com
www.cemmicrowave.co.uk