Digestion of Difficult APIs and Gel Capsules in Accordance with USP <233>

Abstract

The new USP Chapters <232> and <233> will become official on January 1, 2018. At that time, they will supersede the current Method <231>, which will no longer be valid. These new methods bring significant changes in sample preparation and analysis of pharmaceutical samples both in excipients and API's. Certain APIs pose challenges to traditional microwave digestion methods as they are very stable compounds and not easily broken down.

CEM recently introduced the iPrep vessel with a patented dual-seal technology that allows the vessel to hold much higher temperatures and pressures than typical digestion vessels. Digestion of difficult API's and large gelatin capsules was achieved using this vessel and iWave advanced temperature control.

Introduction

The new USP Methods <232> and <233> call for total digestion of pharmaceutical samples and quantification of individual elements typically by ICP-OES or ICP-MS analysis. Many pharmaceutical materials can be easily digested but APIs with multiple aromatic ring structures can be very difficult to completely break down and obtain a clear digestion, as prescribed in the new chapters. In addition, large gelatin capsules can prove challenging because of the amount of oil they typically contain. A large amount of gas is released once the capsule is dissolved and the acids begin to attack the contained oil which can lead to loss of volatile elements if not properly contained.

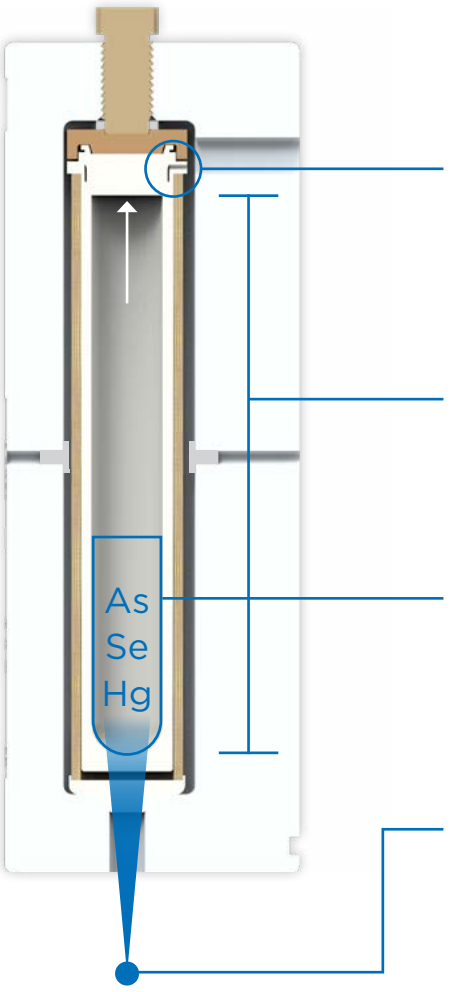
This application note will focus on the use of the CEM MARS 6 microwave digestion system with iPrep vessels to completely digest both difficult active pharmaceutical ingredients and large gelatin capsules. Sample structures of APIs are shown to illustrate complexity. Sample sizes are given as maximum allowable to achieve clear digest.

Instrumentation:

Three different APIs as well as large (approx. 1.0 g) fish oil gelatin capsules were prepared using a CEM MARS 6 microwave digestion system equipped with iWave technology. iWave is a novel technological advancement that utilizes Light Emitting Technology™ to measure the temperature of the actual sample solution inside the vessel and does not require an internal probe.

Samples were prepared using CEM iPrep vessels. The patented dual-seal design (**Figure 1**) provides for higher temperatures and fine control of the vent and reseal process necessary for these sample types. iPrep is a simple to use three piece vessel which uses a hand torque device at only 21 inch pounds.

Figure 1: iPrep Vessel Diagram



Dual-Seal Design

The high temperature and pressure conditions afforded by this seal and vessel design provide for the complete digestion of difficult organics, such as APIs, PET, bunker oil, organic dyes, toner, thermoplastics, and many other difficult to digest materials.

2X Capacity

In addition, its large 110 mL volume allows for larger sample sizes, as compared to other high performance vessels.

Elemental Integrity

The dual-seal function provides for unmatched control of the byproducts from digestions such as CO_2 and NO_x fumes. These are precisely vented outside the vessel, while maintaining the full integrity of all elements. Even volatile analytes such as As, Se, and Hg.

iWave Light Emitting Technology (LET)

iWave utilizes the emission of light from the sample (solution) to rapidly and accurately measure temperature. It reads the temperature of the solution itself, instead of reading the temperature of the vessel. This makes iWave the most accurate temperature sensor.

Procedure and Method

Multiple samples of each API were weighed and added to separate iPrep liners with 10 mL of a 9:1 HNO_3 and HCl solution. The API sample names, structures, and sample weights are recorded in **Table 1** below. The vessels were capped, assembled, and placed in the MARS 6 for digestion. Digestion parameters for a custom method are recorded in **Table 2**. In a separate run, 12 fish oil capsules were added, as received, to 12 liners. A predigestion step was performed to completely dissolve the gelatin capsule and release the entrapped oil. Failure to perform this step can result in fire inside the vessel, which can cause permanent damage to the vessel liner.

Predigestion was performed by adding of 5 mL of H_2O_2 to the liner and capsule in a fume hood. The samples were allowed to stand uncapped for 10 minutes. This allowed the peroxide to soften the capsule and break it open to expose the oil. **Figure 2** and **Figure 3** illustrate what the samples should look like prior to adding acid, sealing the vessel, and performing the digestion. After 10 minutes, 10 mL of a 9:1 HNO_3 and HCl solution was added to each liner. The HNO_3 and HCl solution must not be added before predigestion is complete, or the samples will excessively foam out of the liner. The One Touch Pharmaceutical Method was selected for the Fish Oil Capsule.

Table 1: Samples and Approximate Weights

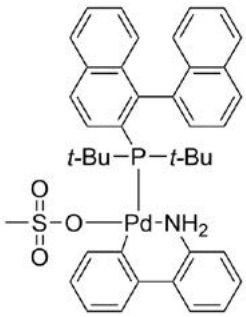
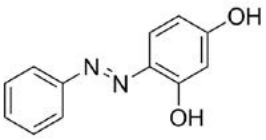
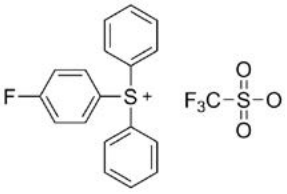
Sample & Structure	TrixiPhos Pd 	Sudan Orange 	4-Fluorophenyldiphenyl-sulfonium triflate 	Fish Oil
Max Sample Weight (mg)	100	500	250	1 Capsule (approx. 1.0 g)

Table 2: MARS 6 Digestion Parameters for APIs

Stage	Ramp Time (min)	Hold Time (min)	Temperature (°C)
1	25	30	250

Acid used: 9 mL HNO_3, 1 mL HCl per sample

Figure 2:
Photos of Fish Oil Capsule after Peroxide Addition

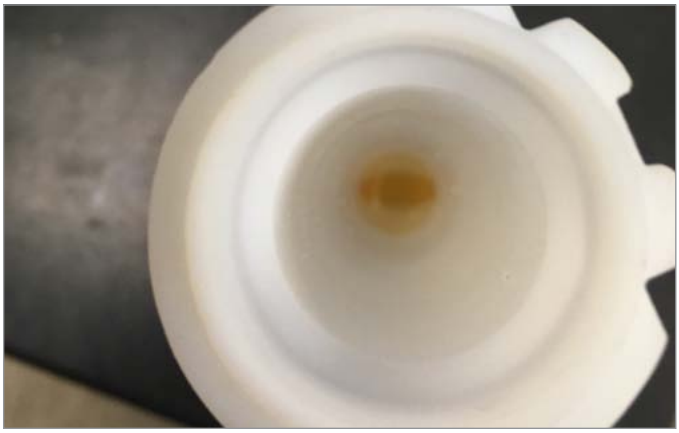
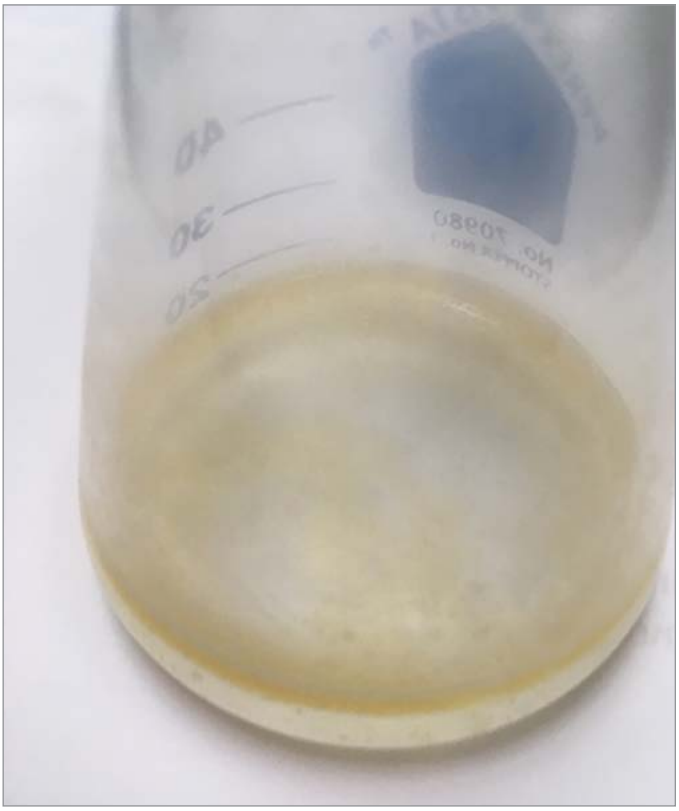


Figure 3:
Photos of Fish Oil Capsule after Nitric Acid Addition



Results and Discussion

The MARS 6 using iPrep vessels and iWave temperature control was able to completely digest each of the API materials as well as manage the pressures during the digestion of the gelatin capsule. Each API sample was run in duplicate in order to confirm the success of the sample preparation. An example of the digestion conditions of the TrixiePhos material is illustrated in **Figure 4**. The conditions of the gelatin capsule are illustrated in **Figure 5**. The system automatically and instantly adjusts the power to precisely control the digestion conditions at the high temperatures required for this process. All samples were completely digested and are clear as shown in **Figure 6**. The MARS 6 system with iPrep vessels is an ideal option for working with these difficult pharmaceutical materials.

Figure 4:
Power and Time Graph of Digestion of TrixiePhos

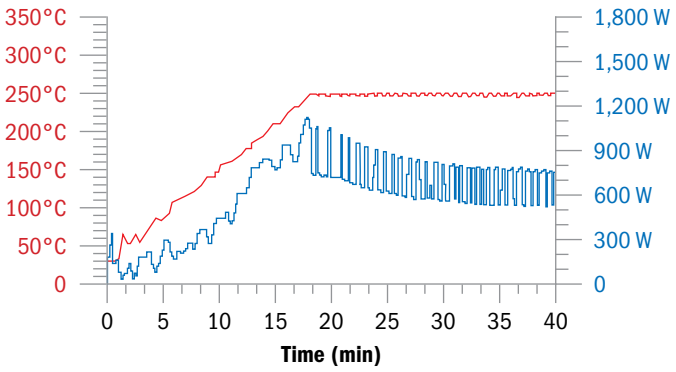


Figure 5:
Power and Time Graph of Digestion of Fish Oil Capsule

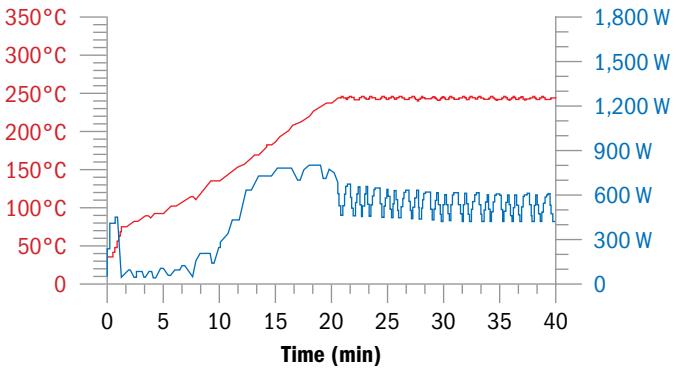
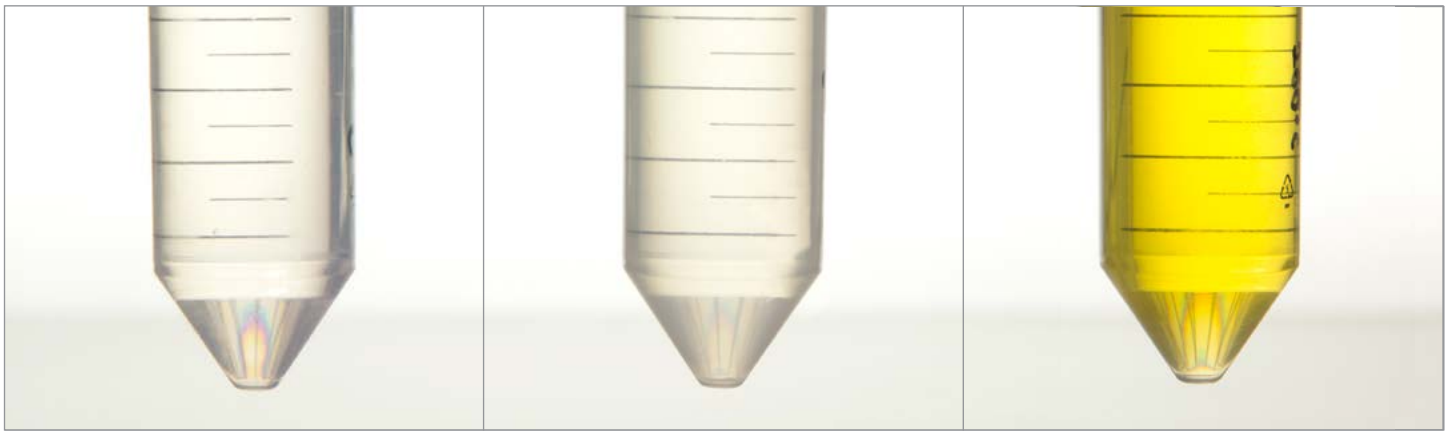


Figure 6:
Solutions after Digestion and Dilution



Note the yellow color of the third sample is due to the palladium catalyst in the TrixiePhos sample.