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Short communication

Improvements in soft gelatin capsule sample preparation for USP-based simethicone FTIR analysis

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ABSTRACT

Due to the absence of a significant chromophore, Simethicone raw material and finished product analysis is achieved using a FTIR-based method that quantifies the polydimethylsiloxane (PDMS) component of the active ingredient. The method can be found in the USP monographs for several dosage forms of Simethicone-containing pharmaceutical products. For soft gelatin capsules, the PDMS assay values determined using the procedure described in the USP method were variable (%RSDs from 2 to 9%) and often lower than expected based on raw material values. After investigation, it was determined that the extraction procedure used for sample preparation was causing loss of material to the container walls due to the hydrophobic nature of PDMS. Evaluation revealed that a simple dissolution of the gelatin capsule fill in toluene provided improved assay results (%RSDs $\leq$ 0.5%) as well as a simplified and rapid sample preparation.

1. Introduction

Simethicone, a mixture of polydimethylsiloxane (PDMS) and silicon dioxide (SiO_2), is the active ingredient found in many over-the-counter gas relievers. The PDMS component of Simethicone acts as a surfactant to allow gaseous bubbles in the digestive system to conglomerate and, therefore, pass more easily [1,2]. For quality control analysis of Simethicone raw material and of Simethicone-containing finished products, a United States Pharmacopeia (USP) FTIR-based method is often used [3].

The USP assay methods quantify the PDMS component of Simethicone using FTIR. This is accomplished by comparing the spectral band attributed to the symmetric CH_3 deformation of the PDMS methyl—silicon—methyl (CH_3—Si—CH_3) bond [4] to that of an external standard of known concentration. The CH_3—Si—CH_3 band ($\sim$1261 cm^{-1}) is used for quantification because its response is linear with respect to PDMS concentration and the band is specific to the PDMS component in the Simethicone mixture. Additionally, for simple formulations that contain few excipients, the CH_3—Si—CH_3 band in the FTIR spectrum is isolated from interfering bands from the placebo and sample diluent (toluene). The SiO_2 component of Simethicone usually constitutes approximately 4–7% of the Simethicone total weight and can also be quantified through a separate testing procedure; however, it is sufficient to only quantify the PDMS component and correct for the SiO_2 content.

Due to the high viscosity of Simethicone, it lends itself well to a soft gelatin encapsulation delivery method. Formulations are simple, with gelatin capsules containing either a neat fill of Simethicone or Simethicone and small additions of a flavoring agent. The current USP includes a monograph specific for the analytical analysis of Simethicone-containing capsules [3]. The sample preparation procedure involves dissolving a single capsule in 6 N HCl, followed by extraction of the Simethicone from the 6 N HCl aqueous layer into a toluene organic layer. Any residual water in the toluene layer is then removed using anhydrous sodium sulfate. An aliquot of the dried toluene layer is analyzed by FTIR and the peak height of the CH_3—Si—CH_3 band is used to determine the PDMS, and thus Simethicone, content of the capsule. Standards are prepared via the same extraction procedure using known quantities of PDMS USP reference standard.

For soft gelatin capsule dosage forms, inconsistencies in the analysis of PDMS content using the USP monograph procedure were often observed. High variability between triplicate preparations of the same sample was common. Examples of PDMS content variability for triplicate preparations of two different product formulations are shown in Table 1.

During the capsule dissolution step in 6 N HCl, sample material was observed along the walls of the glass container used for the preparation. Because PDMS is highly hydrophobic, the material sticking to the container walls was most likely the Simethicone capsule fill. Adhesion of sample material to the container walls was still

Abbreviations: USP, United States Pharmacopeia; PDMS, polydimethylsiloxane.

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Table 1
Example %PDMS values obtained using the USP monograph for Simethicone analysis of soft gelatin capsules. Triplicate sample preparations were made for each of the three lots of each finished product formulation.

%PDMS						
	Formulation 1			Formulation 2		
Sample Prep	Lot #1	Lot #2	Lot #3	Lot #1	Lot #2	Lot #3
1	88.2	87.4	94.7	82.0	86.1	90.1
2	84.6	86.7	102.7	87.0	84.3	84.4
3	87.8	100.5	98.7	80.7	87.8	85.6
Average	86.9	91.5	98.7	83.2	86.1	86.7
%RSD	2.3	8.5	4.1	4.0	2.0	3.5

observed despite extensive shake times during the extraction step with toluene. Therefore, the high variability between sample preparations for Simethicone-containing gelatin capsules was attributed to the extraction procedure, which appeared to cause sample loss due to hydrophobic adhesion to the preparation container walls. The goal of the work described here was to improve the sample preparation procedure to allow for more accurate and reproducible PDMS quantification in soft gelatin capsule finished products.

2. Material and methods

2.1. Chemicals

Unless otherwise noted, all chemicals were purchased from Sigma–Aldrich (St. Louis, MO). Simethicone and PDMS reference standards were purchased from the USP (Rockville, MD). Qorpax 125-mL glass jars were purchased from Thomas Scientific (Swedesboro, NJ). The jars were made of flint glass with thermoset F217 and PTFE lined caps.

2.2. Procedures

2.2.1. USP monograph for capsules [3]

A single gelatin capsule, whose formulation contained either 133.3 mg or 180 mg Simethicone, was placed in a 125-mL glass jar. Next, 20.0 mL of 6 N HCl was added to the jar and swirled until the capsule was dissolved. For the extraction, either 50.0 mL or 72.0 mL of toluene (for 133.3 mg and 180 mg dosage forms, respectively) were added to the jar and the jar was mechanically shaken for 10 min. After allowing the layers to separate overnight, 10.0 mL of the toluene layer were transferred to a test tube containing approximately 0.5 g of anhydrous sodium sulfate. The test tube was shaken well and allowed to settle. The toluene layer was then analyzed by FTIR. For quantification, standards were prepared similarly by weighing PDMS USP reference standard to a jar and performing the same extraction described for the samples.

2.2.2. New sample preparation procedure

Using a capsule cutter (custom fabricated by Nelson's Garage and Fabrication, Stokesdale, NC), five gelatin capsules, containing either 133 mg or 180 mg Simethicone, were cut directly into a 250-mL volumetric flask. The capsule cutter was rinsed with 4–5 mL of toluene directly into the flask to remove any Simethicone that may have adhered to the cutter blade. The flasks were filled to volume with toluene and mixed well by shaking and inversion until the capsule shells appeared clean of fill material.

Standards were prepared by weighing approximately 133 mg Simethicone USP reference standard directly to a 50-mL volumetric flask on an analytical balance. The flasks were then filled to volume with toluene and mixed well by shaking and inversion.

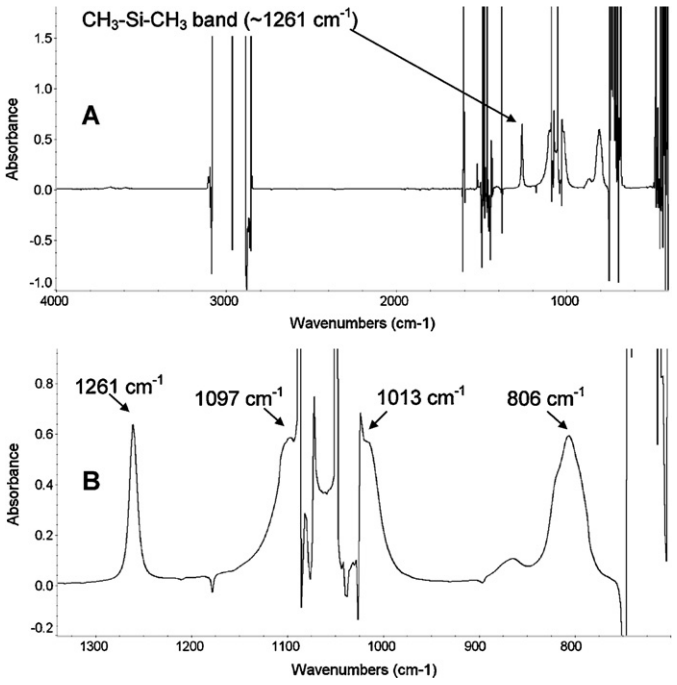

Fig. 1. Infrared spectra of Simethicone. (A) Spectrum from 400 cm^{-1} to 4000 cm^{-1}. (B) Spectral features used for PDMS identification. The 1261 cm^{-1} band is isolated and used for quantification of PDMS.

2.2.3. FTIR analysis

Spectra for all samples were collected using a 0.5 mm NaCl sample cell transmission accessory (PerkinElmer, Waltham, MA) on a ThermoFisher Nicolet 6700 FTIR (ThermoFisher, Waltham, MA). Toluene was used as the background and a fresh background was collected every 15 min to correct for background drift. System suitability was established by comparing the 1261 cm^{-1} band height response factor between two prepared standards. Additionally, a working standard was analyzed five times in succession to ensure system precision (RSD $\leq$ 2%). Additional working standard spectra were collected after the analysis of every six samples and at the end of the analysis to bracket the samples. The overall PDMS response factor %RSD for all standards analyzed was required to be $\leq$2% to establish system suitability.

Spectra were collected using Omnic Software (Version 8.1.11, ThermoFisher, Valencia, CA). The spectra were collected from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. For each spectra, 32 scans were performed. All spectra were background corrected and automatic baseline corrected. The height of the band at ~1261 cm^{-1} was determined by drawing a baseline from 1319 cm^{-1} to 1219 cm^{-1}.

3. Results and discussion

3.1. Development of a simplified sample preparation procedure for soft gelatin capsules

Examples of typical FTIR spectra obtained for Simethicone are shown in Fig. 1 with the identification region shown in Fig. 1B. Toluene has over-ranging bands in several regions (e.g., 1500 cm^{-1}, 1050 cm^{-1}, and 700 cm^{-1}) of the spectrum which results in a large amount of noise after background subtraction around these wavenumbers. As can be seen from the spectra in Fig. 1, the band at 1261 cm^{-1} is isolated from the noise and other interferences. This band is unique to PDMS and is, therefore, used for quantification.

The variability associated with the current USP monograph for PDMS content in capsules was believed to be caused by the loss of material during both standard and sample preparation. To test

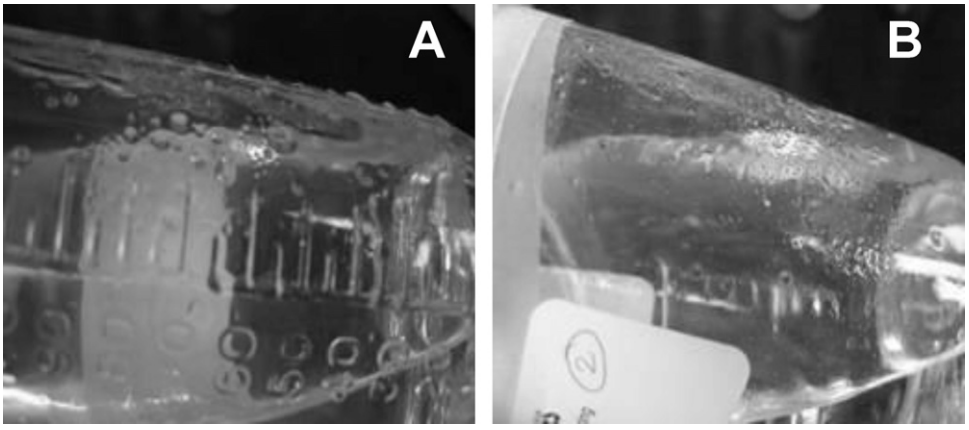

Fig. 2. Images of PDMS (A) and Simethicone (B) sticking to the sides of the glass containers during the extraction procedure.

whether or not the observed material on the container walls results from the dissolved gelatin capsule shell or the capsule fill, an extraction was performed using only Simethicone USP reference standard and one extraction using PDMS USP reference standard. The same material adhesion to the container walls was observed for both extractions indicating that the material is from the capsule fill. Images of material adhering to the glass container walls during the extraction procedure are shown in Fig. 2.

In order to improve the analysis of Simethicone-containing gelatin capsules, the sample preparation procedure was investigated. Initial experiments were aimed at determining what, if any, components of the gelatin capsule finished products might interfere with the quantification of PDMS by FTIR. First, it was found that the gelatin capsule shells were not soluble in toluene. Capsules shells were left in toluene for greater than 14 days and did not show signs of deterioration or degradation. The toluene containing the capsule shells was analyzed by FTIR and no interfering peaks were present in the collected spectra. Thus, the capsule shell components will not interfere with the detection of PDMS by FTIR when samples are prepared in toluene.

For capsule formulations that are not neat fills of Simethicone, the excipients were found to dissolve in toluene; however, the resulting solution spectra did not show interferences with the CH_3—Si—CH_3 band at 1261 cm^{-1} used for PDMS quantification or the other bands and spectral features used for identification of PDMS (1261 cm^{-1}, 1097 cm^{-1}, 1013 cm^{-1}, and 806 cm^{-1}). Because no placebo components interfere with the detection of PDMS when the sample is prepared in toluene, it was determined that an extraction is not necessary for the sample preparation of gelatin capsules.

To confirm this sample preparation procedure, Simethicone-containing gelatin capsules were cut, using a capsule cutter, directly into a volumetric flask and dissolved to volume in toluene. Only a few minutes of vigorous shaking were required to completely dissolve the Simethicone capsule fills while the capsule shells remained intact in the flask. For quantification, standards were prepared using Simethicone USP reference standard with a known SiO_2 content. The standard was weighed directly to a volumetric flask and diluted with toluene. Reference standards were always prepared in duplicate to confirm the PDMS response factor. The standards were then used to quantify the PDMS content of the samples. Six sample preparations were made of two different finished product formulations and the results are shown in Table 2. The %RSD of the PDMS content for the six replicate preparations was $\leq$0.5% for both formulations. According to the vendor certificate of analysis, the Simethicone raw material lots used in these finished products formulations had %PDMS values of 94.3% and 92.7% for formulation 1 and 2, respectively. The finished product analysis of PDMS content agreed closely with that of the raw material indicating that the direct dissolution of the capsule fill in toluene provides accurate %PDMS values.

3.2. Validation of the new sample preparation procedure

Using the new sample preparation, in which the capsules are cut and dissolved directly in toluene, an assay method was validated according to ICH guidance. The validation included an assessment of specificity, linearity, accuracy, system precision, method precision, and intermediate precision. Sample and standard stability was also determined.

As noted above, the capsule shell does not dissolve in toluene. Also, the excipients do not interfere with the PDMS FTIR band (1261 cm^{-1}) used for quantification. Therefore, specificity of the method was established. Linearity of the 1261 cm^{-1} band height was confirmed for Simethicone concentrations between 1.3 mg/mL and 5.6 mg/mL. These Simethicone concentrations correspond to PDMS concentrations of 1.2 mg/mL to 5.3 mg/mL when the 5.5% SiO_2 content of the standard is taken into consideration. The coefficient of determination over this concentration range was 1.0 (0.99997) and the %*y*-intercept was 0.9%.

An accuracy assessment was performed by spiking known amounts of Simethicone into solutions containing capsule shells and any fill excipients at nominal concentrations. Recovery was assessed from 50% of the lowest dosage form concentration to 150% of the highest dosage form concentration. The recovery for triplicate preparations of samples spiked with 62.5 mg, 133 mg, and 270 mg showed >99% recovery and %RSD values of <1.0%. The %RSD for six replicate analyses (i.e., system precision) of a formulation 1 sample, a formulation 2 sample, and a standard was 0.06%, 0.11%,

Table 2
Analysis of six preparations of a single lot of Formulation 1 and Formulation 2 to determine the %PDMS variability between sample preparations using direct dissolution of the capsules in toluene.

%PDMS		
Sample preparation	Formulation 1	Formulation 2
1	94.5	92.6
2	93.7	92.9
3	94.4	93.1
4	93.8	93.3
5	94.1	94.0
6	93.6	93.6
Average %PDMS	94.0	93.3
%RSD	0.4	0.5

Table 3
Analysis of 10 production lots of Simethicone-containing gelatin capsules for two product formulations using direct dissolution of the capsule fills in toluene.

%PDMS		
Lot #	Formulation 1	Formulation 2
1	92.4	95.4
2	95.0	93.0
3	93.4	92.8
4	93.1	93.0
5	92.2	93.1
6	91.6	92.7
7	94.8	93.9
8	93.3	94.3
9	93.8	94.6
10	95.6	94.0
Average	93.5	93.7
%RSD	1.4	1.0

and 0.06%, respectively. For the two different product formulations, the analysis of six different sample preparations (i.e., method precision) gave PDMS assay values with %RSDs of ≤0.5%. Additionally, intermediate precision was assessed by a second analyst at a different laboratory using different equipment. The second analyst assayed two finished product formulations (six replicate preparations). The average PDMS content of the samples between the two analysts had absolute percent differences of ≤1.0%.

Based on the validation results, the new sample preparation procedure returns accurate and precise PDMS content values. The changes to the sample preparation procedure were implemented for routine analysis in a quality control laboratory. The results of analyzing ten finished product lots for both formulation 1 and 2 using the improved preparation procedure are shown in Table 3. The %PDMS results are consistent from lot to lot of finished product with %RSD values <2.0%. Since implementation of the improved sample preparation procedure, large sample assay variability has been eliminated.

4. Conclusion

For Simethicone-containing soft gelatin capsules, a new, simplified sample preparation procedure has been confirmed and validated for analysis of capsules that have neat fills or fill excipients that do not interfere with PDMS quantification by FTIR. By simply cutting the capsules and dissolving the fill directly in toluene, the new preparation eliminates a lengthy and unnecessary extraction process. Direct dissolution provides more accurate sample analysis results by reducing or eliminating loss of material caused by hydrophobic adhesion of Simethicone to the glass container walls.

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