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# Quantitative Determination of Simethicone in Antacid Suspension and Chewable Tablet Using FTIR Spectroscopy

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**Abstract:** Fourier transform infrared (FTIR) spectroscopy has been employed for the quantitative analysis of simethicone (SMT) in chewable tablet and suspension. Analysis of SMT is achieved by determination of polydimethylsiloxane (PDMS). Analysis of SMT-containing preparations especially suspension and chewable tablet is difficult to get reproducible results using FTIR spectroscopy. The extraction procedure used for sample preparation causes SMT loss, therefore, a sample preparation procedure for FTIR spectroscopy has been developed and validated. Some validation parameters namely llinearity, sensitivity, accuracy and precision are presented for the modified method. Some wavenumbers were also optimized to get the best results. Finally, the intensity (absorbancies) at wavenumber of 1261 $cm^{-1}$ was used during validation and sample analysis. The developed method was linear over the concentration range of 0.05 – 1.0 % (wt/v) with the acceptable precision and recoveries. The developed method was used for quantifying SMT in tablet and suspension formulation. The SMT found was in the acceptable range as stated in Indonesian Pharmacopeia (85 – 115 % from the stated amount in label).

**Key words:** FTIR Spectroscopy · Simethicone · Antacid · Validation

## INTRODUCTION

Antacids are medicines containing aluminum hydroxide [$Al(OH)_3$] and magnesium hydroxide [$Mg(OH)_2$] which relieve the symptoms of heartburn and reflux of gastric fluid [1]. Many antacid preparations use the combination of those hydroxides with simethicone (SMT) in order to reduce the side effects of carbon dioxide, as a byproduct from the gastric fluid neutralization [2]. SMT (Figure 1) is a mixture of polydimethylsiloxane (PDMS) and silicon dioxide ($SiO_2$) which is used to relieve flatulence, abdominal discomfort due to excessive gas, colic in infants and ulcer disease [3]. SMT constitutes approximately of 90.5 to 99.0 % of PDMS and 4 - 7% of $SiO_2$ [4].

Some analytical methods have been reported for determination of SMT in pharmaceutical preparations such as reversed phase-high performance liquid chromatography [5], gas chromatography [6], size exclusion chromatography [7] and atomic absorption spectrophotometry [8]. However, this method is impractical and time consuming, therefore, for routine quality control, rapid method such as FTIR spectroscopy is used for determination of SMT in some compendia.

In analytical field, Fourier transform infrared (FTIR) spectroscopy is the powerful method for analysis of pharmaceuticals, especially for those having no chromophores. Besides, FTIR spectroscopy is fingerprint technique offering good specificity over the other spectroscopic tehniques [9]. With the advancement of computer software, the use of FTIR spectroscopy in pharmaceutical analysis is common [10]. FTIR spectroscopy has been employed for the quantitative analysis of simethicone based on several compendium such as USP, Indonesian Pharmacopeia and Indian pharmacopeia. SMT analysis is carried out by FTIR

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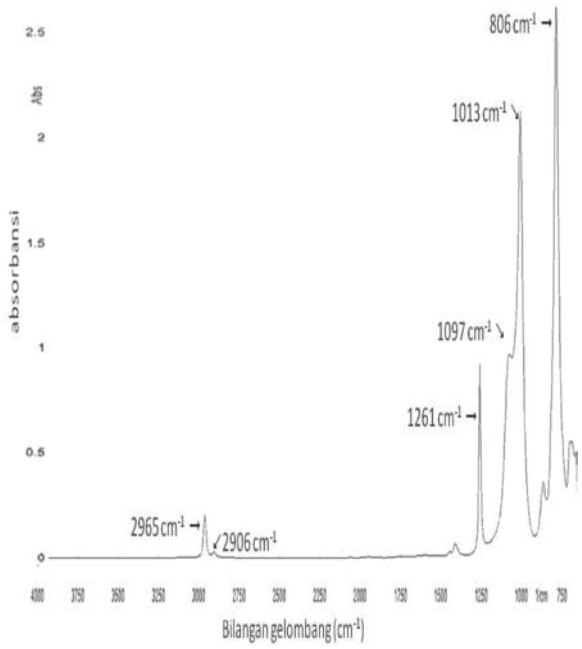


Fig. 1: FTIR spectra of simethicone scanned over wavenumbers of 4000 - 650 ccm-1.

spectroscopy due to the lack of chromophore. This method quantifies PDMS component of SMT by comparing the typical spectral band for PDMS with an external standard of known concentration. Because of the small silicon dioxide content of SMT, it is sufficient to only quantify PDMS component, although the silicone dioxide content can also be quantified through another testing procedure [11]. FTIR spectroscopy has been used for quantitative analysis of SMT in the cosmetics preparation such as lotions and cream [12], SMT in soft gelatin capsule [11] and dimethicon in commercial tablet and capsules [3]. Besides, FTIR spectroscopy is also used for quantification of lard in cosmetics preparation [13], analysis of medicinal herb of Warburgia ugandensis [14], studying the characteristics of polypyrrole and its composites [15], characterization of Tellurite-Vanadate Glasses [16].

From several publications, it is reported that analysis of SMT using FTIR spectroscopy method is difficult to get reproducible results due to the many variations in sample preparation and sample measurements [11]. A study showed that the extraction procedure for sample preparation has caused the material loss, because PDMS material sticks to the jar walls due to the hydrophobic nature of PDMS. The variations of the measurements may be attributed to the extraction procedure, so that the necessary modification of extraction method is developed by some researchers.

The procedure of sample preparation, as used in USP for analysis of SMT using FTIR spectroscopy method, has been modified and validated by Hargis and Whittall [11] for determination of SMT in gelatin soft capsule. The extraction involves acidification step to neutralise antacid components of the formulation, then a single extraction of the PDMS with toluene was performed. In this study, we validate the proposed extraction procedure by Hargis and Whittall [11] for determination of SMT in tablet and suspention formulation.

## MATERIALS AND METHODS

**Materials:** Simethicone reference standard was RS USP grade. The placebo sample was kindly obtained from Graha Farma (Surakarta, Indonesia). Toluene, hydrochloric acid and anhydrous sodium sulphate were obtained from E. Merck (Darmstadt, Germany). The chewable tablet sample was kindly given by PT Graha Farma, Indonesia, while suspension sample was kindly given by PT Nufarindo (Semarang, Indonesia).

**Preparation of Standard Solution and Reagent:** A 10 % SMT standard stock solution was prepared by diluting 5.0 ml of SMT USP RS to a final volume of 50.0 mL with toluene. The stock solution was used for preparing a series of working solution for making calibrration curve. Hydrochloric acid 6 N was prepared by diluting 50 ml of concentrated hydrochloric acid to a final volume of 100.0 mL with distilled water.

**Sample Extraction:** A certain sample of tablet or suspension equivalent to 66.67 mg of SMT was accurately weighed and transferred to a capped conical flask. For chewable tablet preparations, 20 tablets were weighed and finely powdered first for the evaluation of tablet homogenity. Then, 20.0 ml of HCl 6 N was added to the jar and swirled until SMT dissolved completely. Next, 25 ml of toluene was added for the extraction and the jar was mechanically shaken at a frequency 200 rpm for 10 minutes (suspension) or 20 minutes (chewable tablet preparations). After allowing the layers to separate, toluene layer was pipetted sufficiently and transferred to screw-capped tube. Any residual water in the organic layer was then removed using anhydrous sodium sulfate. Standards were prepared by the same extraction procedure using the known quantities of SMT. Toluene layer was then analyzed by FTIR spectrophotometer and the height of the band (absorbance) at ~1261, 1091 and 1014 $cm^{-1}$ were used to determine SMT content in sample preparations.

**FTIR Spectra Acquisition:** ABB MB3000 FTIR spectrophotometer (Montreal, Canada) was used in the mid infraed region of 4000 -650 $cm^{-1}$. Spectra were collected using Horizon MB (Version 3.1.24.2, ABB Analytical Measurement, Canada). For each spectra, 32 scans were performed with a resolution of 4 $cm^{-1}$. FTIR spectrum is read as absorbance.

**Validation of Analytical Method:** Analytical method validation was performed by evaluating several parameters namely linearity, sensitivity, precision dan accuracy according to the guidance from International Conference on Harmonization (ICH) [17] as described by Islam *et al*. [18]. Linearity was evaluated by preparing SMT standard in six different concentrations in the range of 0.05 to 1.00 % through the same preparation procedure used for sample. Each measurement in FTIR was performed 3 times. Linearity was evaluated by calculation the correlation coefficient (r) from the regression curve. Additionally, the wave number which showed the highest r value is used for subsequent measurement.

Sensitivity was determined by testing 10 pieces of blank samples added with a concentration of SMT standard having the smallest measurable response. Standard deviation (SD) of the responses ($Y_{samp}$) was then calculated (RSD $Y_{samp} \geq 33.3\%$). LOD was evaluated by calculation using the equation: $Y_{LOD} = Y_{blank} + 3 \times SD$. $Y_{blank}$ is the response for blank sample, in this case $Y_{blank} = 0$. SD is the standard deviation obtained from 10 sample absorbances. $Y_{LOD}$ value was used in order to obtain the value of x (concentration) with calibration curve equation obtained during the linearity determination. The value of x is the LOD. Furthermore, LOQ values can be calculated with formula: LOQ = 3.33 x LOD.

Analytical method precision was evaluated by repeatability procedure. A-10 blank samples were added with SMT standard under the same conditions, including the analysts, laboratory equipment and intra-day precision. Repeatability was evaluated by calculation of the relative standard deviation (RSD). Furthermore, inter-day precision was calculated by comparing the results obtained from 3 different repeatability tests in 3 different days.

Accuracy was evaluated by standard addition method. Three groups of sample in triplicate were spiked with SMT at 50, 100 and 150 % of the sample solution concentration, while the other group is without the addition of SMT standard. Recovery was calculated according to the following equation:

$$\text{Recovery} = (C_1-C_2)/C_3 \times 100\ \%$$

where $C_1$ is measured concentration of spiked sample, $C_2$ is the measured concentration of sample without spiking and $C_3$ is the actual concentration added to sample.

## RESULTS AND DISCUSSION

The USP 32 monograph employs the maximum wavelength of 7.9 μm (equivalent to wavenumbers of 1257 $cm^{-1}$) for quantitative determination of simethicone (SMT). FTIR spectrum of SMT dissolved in toluene (Fig. 1) showed a doublet at wave numbers of 1097 and 1013 $cm^{-1}$ due to the symmetric and asymmetric stretching vibrations of Si-O bond [3], sharp bands at wavenumbers around of 1261 $cm^{-1}$ due to the symmetric stretching vibrations of $CH_3$-Si and $CH_3$ rocking, at wavenumber of 806 $cm^{-1}$ [19]. Additionally, $CH_3$ group has 2 stretching vibrations of C-H at wavenumbers of 2965 $cm^{-1}$ (asymmetrical stretching) and 2906 $cm^{-1}$ (symmetrical stretching) [20].

**Method Validation:** Analysis of SMT in tablet and suspension formulation was carried out by determining the level of polydimethylsilicon (PDMS) present in SMT. Some wavenumbers namely ~1261, 1097 and 1013 $cm^{-1}$ were optimized during preparation of calibration curve. The linearity of the method for SMT assay was evaluated in the range of concentrations between 0.05-1.00 % wt/v at 3 different wavenumbers, namely of 1261, 1097 and 1013 $cm^{-1}$ (Fig. 2). The correlation coefficients (r) at 1261, 1097 and 1013 $cm^{-1}$ are 0.9989, 0.9858 and 0.9922, respectively. Based upon these result, it was decided to use the peak at 1261 $cm^{-1}$ for quantitative analysis of SMT, since it showed the best linearity than other wavenumbers. The slope at 1261 $cm^{-1}$ was 0.0437 with the intercept value of 0.0111 AU.

Sensitivity was determined by evaluating the limit of detection (LOD) and limit of quantification (LOQ). LOD is the smallest concentration of analyte that can still be detected in the presence of a significantly different response compared to blank response or noise [21], while LOQ is the lowest analyte level which can be determined quantitatively with acceptable precision values [18]. LOD and LOQ were evaluated by measuring the absorbance of 10 pieces of blank samples which spiked with SMT standard which still gives a measurable response. LOD values obtained were 0.009 % wt/v; 0.011 % wt/wt and the LOQ values were 0.031% w/v; 0.038 % wt/wt for antacid suspension and chewable tablet, respectively (Table 1).

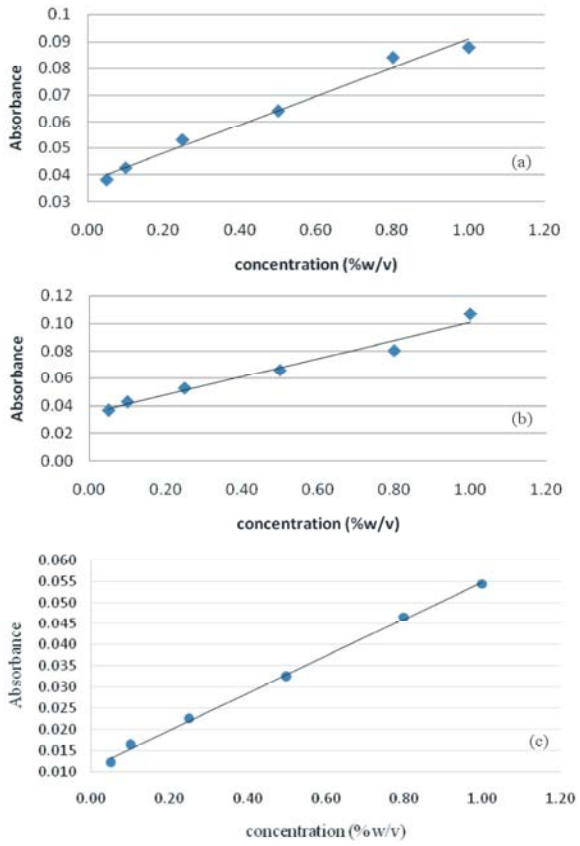


Fig. 2: Calibration curve of simethicone at three wavenumbers, namely ~1014 cm-1 (a); ~1097 cm-1 (b); ~1261 $cm^{-1}$ (c)

Table 1: Analysis of 10 blank samples spiked with 0.01 %w/v of simethicone standard to determine LOD and LOQ value

| | Absorbance (A.U) | |
|---|---|---|
| Samples | Suspension | Chewale Tablet |
| 1 | 0.01319 | 0.00465 |
| 2 | 0.00706 | 0.00444 |
| 3 | 0.00696 | 0.01397 |
| 4 | 0.00673 | 0.00862 |
| 5 | 0.01499 | 0.01167 |
| 6 | 0.00381 | 0.00755 |
| 7 | 0.01497 | 0.01481 |
| 8 | 0.01162 | 0.01408 |
| 9 | 0.01183 | 0.01134 |
| 10 | 0.01019 | 0.01291 |
| Average | 0.01013 | 0.0104 |
| % RSD | 37.86 | 37.16 |
| LOD (%w/v) | 0.0094 | 0.011 |
| LOQ (%w/v) | 0.0314 | 0.038 |

Precision assay was performed with repeatability assay and intermediate precision by spiking known amounts of SMT standard into 10 blank samples. In this study, samples were spiked with 0.6 % w/v of SMT for antacid suspension and 0.5 % w/v for antacid chewable tablet. The results for precision assay are shown in Table 2. Repeatability assay gave RSD value of 3.09 % for antacid suspension and 3.33 % for chewable tablet. Meanwhile, the intermediate precision was evaluated from three different days of measurement and gave RSD value of 2.71 % for antacid suspension and 3.04 % for chewable

Table 2: Analysis of 10 blank samples to determine repeatability and intermediate precision

| Day | Actual concentrations (%w/v) | Predicted concentrations (%b/v) (n=10) | Repeatability (% RSD) | Intermediate precision (% RSD) |
|---|---|---|---|---|
| | | Antacid Suspension | | |
| 1 | 0.60 | 0.58±0.040 | 3.09 | 2.71 |
| 3 | 0.60 | 0.58±0.030 | 2.32 | |
| 8 | 0.60 | 0.57±0.032 | 2.52 | |
| | | Antacid Chewable Tablet | | |
| 1 | 0.50 | 0.50±0.040 | 3.33 | 3.04 |
| 3 | 0.50 | 0.52±0.030 | 2.12 | |
| 8 | 0.50 | 0.51±0.030 | 2.79 | |

Table 3: Analysis of 10 blank samples to determine accuracy

| Spiked content (% w/v) | Actual concentrations (%w/v) | Predicted concentrations (%w/v) (n=3) | Recoveries (%) | RSD (%) |
|---|---|---|---|---|
| | | Antacid Suspension | | |
| None | 0.20 | 0.15±0.0073 | - | - |
| 0.10 | 0.30 | 0.25±0.0014 | 100.95±1.36 | 0.42 |
| 0.20 | 0.40 | 0.35±0.0031 | 98.44±1.55 | 0.50 |
| 0.30 | 0.50 | 0.46±0.0070 | 101.64±2.32 | 0.72 |
| Range of recovery (%) | | | 98,44-101,64 | |
| | | Antacid Chewable Tablet | | |
| None | 0.20 | 0.15±0.0073 | - | - |
| 0.10 | 0.30 | 0.25±0.0014 | 102.10±6.43 | 0.61 |
| 0.20 | 0.40 | 0.35±0.0031 | 100.09±6.72 | 0.98 |
| 0.30 | 0.50 | 0.46±0.0070 | 101.63±3.36 | 0.59 |
| Range of recovery (%) | | | 100.09-102.10 | |

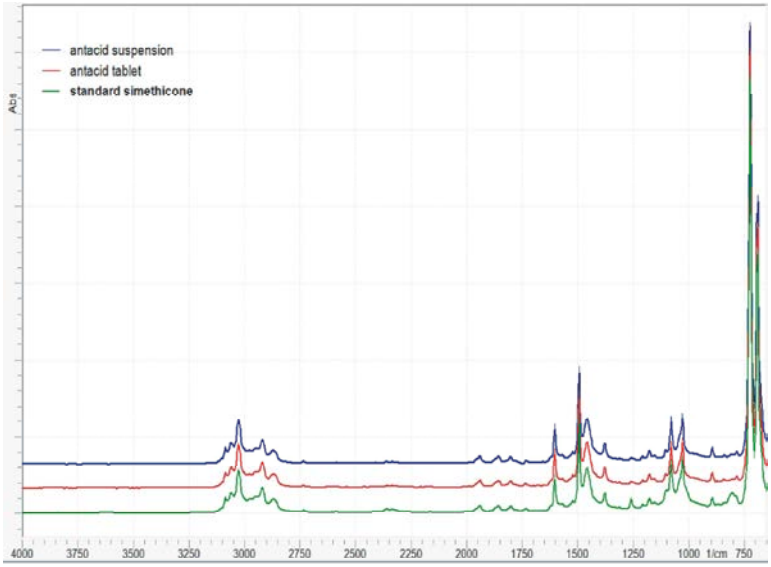


Fig. 3: Simethicone spectrum from standard simethicone, antacid suspension and chewable tablet

tablet. Based on the range of RSD according to Horwitz [23], RSD value allowed for the level of analyte of 0.5-0.6 % is ≤ 4.3 % [18]. It can be stated that the FTIR spectroscopy method had a good precision.

The accuracy evaluation of the used method was performed by spiking known amounts of SMT into solutions containing the sample preparation. Recovery was assessed from 3 different concentrations, namely 50, 100 and 150 % of SMT target. The recovery results obtained are shown in Table 3. The recovery values for antacid suspension were 100.95±1.36 %; 98.44±1.55 %; and 101.64±2.32 %, for 50, 100 and 150 % of SMT target, respectively; while the recoveries of chewable tablet samples were 102.10±6.43; 100.09±6.72; 101.63±3.36 %, respectively. The recovery value allowed for a concentration range of 0.1-1.0 % wt/v is between 95-105 % [22]. From this study, it can be concluded that the FTIR method has good accuracy.

**Analysis of Simethicone in Sample Preparation:** FTIR spectroscopy, which has been previously validated, was used for quantitative analysis of SMT in antacid suspension and chewable tablet. Both samples showed similar FTIR spectra to that of SMT standard, as can be seen in Fig. 3. The mean concentrations of SMT obtained from the study were 45.43 mg/5 ml for antacid suspension and 47.57 mg/antacid chewable tablet or equivalent to as much as 90.86 % and 95.14 % of the claimed label, respectively. These results indicated that the concentration of SMT in suspension and chewable tablet fall into the range of concentration allowed based on USP, which is between 85-115 %. It can be concluded that the method can be used for quantitative analysis of SMT, both in antacid suspension and chewable tablet.

## CONCLUSION

For SMT-containing antacid suspension and chewable tablet, a modified method has been validated for analysis of SMT with FTIR spectrophotometry. The validated method had good validation parameters according to ICH. The method gave content of SMT in the antacid suspension and chewable tablet preparations within the USP 32 limits for SMT in pharmaceutical preparation.

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