# Quantitation of Methanol, Ethanol and Isopropanol in Gel Hand Sanitizer Products by GC-FID

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## Abstract

The COVID-19 outbreak and pandemic resulted in an increase in the number of firms producing hand sanitizers and an increase in the numbers of hand sanitizers requiring analysis in U.S. FDA laboratories. The analysis was necessitated by initial screenings of imported hand sanitizers by Customs and Border Protection that tested positive for methanol. Due to the anticipated workload, OMPSLO determined that a single method was needed that could quantitate ethanol or isopropanol active ingredient and quantitate methanol adulterant if present. The analytical procedure developed uses GC-FID for quantitation of ethanol, isopropanol and/or methanol in hand sanitizer from levels as low as 0.25% v/v up to 100% v/v. The limit of detection of methanol is 0.0625% v/v. The method is an extension of the USP <611> Alcohol Determination method for ethanol, and now includes methanol and isopropanol in the analysis. This method was successfully validated using a gel hand sanitizer matrix containing a label claim of 70% ethanol, with glycerin, propylene glycol and aloe among the inactive ingredients. The correlation coefficient for linearity ($r^2$) was ≥ 0.9997, spike recovery values were from 99.1-100.3%, and %RSDs were < 1% for methanol, ethanol and isopropanol. The method has been used by the FDA Pacific Southwest Medical Products Laboratory to analyze 96 imported hand sanitizers, all but two of which were labeled with ethyl alcohol as the active ingredient. Of those, 29 hand sanitizers were found to have actionable levels of methanol (> 630 ppm), ranging from 1.6% to 79.3% v/v. All but two of the hand sanitizers containing methanol were subpotent in ethanol (< 90% of label claim amount), indicating an economically-motivated substitution of ethanol with methanol. The details of the method are described in an LIB that has been accepted for publication but not yet published.

## Introduction

Due to the COVID-19 outbreak, the CDC recommended the use of alcohol-based hand sanitizers that contain at least 60% alcohol, as a preventative measure in the spread of COVID-19 when soap and water are not available for proper hand hygiene. In response to the increased demand for these alcohol-based hand sanitizers, the FDA released a guidance communicating a temporary policy allowing for additional sources from industry to prepare certain alcohol-based hand sanitizer products for the duration of the COVID-19 public health emergency.[1] One of the main potential impurities of interest is methanol (MeOH), which can be used as an economically motivated adulterant in place of ethanol (EtOH) or isopropanol (IPA). Recently, a large number of hand sanitizer samples analyzed by Customs and Border Patrol (CBP) have tested positive for the presence of MeOH.[2,3] MeOH is toxic with many associated health hazards. The FDA guidance limits the amount of MeOH in hand sanitizer to 630 ppm.[1]

The USP <611> Alcohol Determination method IIB[4] uses Gas Chromatography with Flame Ionization Detection (GC-FID) for quantitation of EtOH in various drug products. This method can be used to quantify EtOH in alcohol-based hand sanitizer. However, to quantify IPA in hand sanitizers where that is the active ingredient, and to quantify MeOH if present as an adulterant, it is necessary to extend the method to add IPA and MeOH as analytes. Fortunately, the existing USP chromatographic method gives adequate peak separation between all three alcohols and acetonitrile (ACN) internal standard, such that no modification to chromatographic conditions is necessary.

Validation of USP <611> Alcohol Determination Chromatographic Method IIb for analysis of MeOH, EtOH and IPA was performed according to USP <1225>[5] and evaluates the performance characteristics accuracy, precision, specificity, detection limit, quantitation limit, linearity and range. The detection limit was evaluated to ensure that MeOH could be detected in hand sanitizer down to the 630 ppm limit specified in the FDA guidance.

Quantitation of MeOH, EtOH and IPA in hand sanitizers was performed by single point calibration using the peak area ratio of each alcohol to ACN internal standard. Overall sample dilution factor was 250×.

## Materials and Methods

**Equipment**

- Agilent Technologies GC 7890B Series with 7693A autosampler and FID (Flame Ionization Detector), or equivalent
- Restek Rtx-1301 Column, Catalog number: 16085, Nominal Dimensions: ID: 0.53 mm; Film Thickness: 3.0 microns; Length 30 m (USP phase G43)
- Positive Displacement Pipette – Eppendorf Repeater E3x, 1 µL – 50 mL, or equivalent
- Pipette tips – Eppendorf Combitips® Advanced, 1 mL, 5 mL, and 10 mL volumes
- Class A volumetric flasks

**Table 1.** GC-FID Parameters

| GC Parameters | |
|---|---|
| Oven initial | 50°C |
| Initial time | 5.0 min |
| Ramp rate | 10°C/min |
| Final temperature after ramp | 200°C |
| Final time after ramp | 4.0 min |
| Run time | 24 min |
| | |
| **Flow Rate** | |
| Average linear velocity | 34 cm/sec |
| Mode | Constant flow |

| Injection Parameters | |
|---|---|
| Mode | Split |
| Volume | 0.5 µL |
| Temperature | 210°C |
| Split ratio | 5:1 |
| | |
| **FID Parameters** | |
| Heater Temp | 280°C |
| $H_2$ Flow | 30 mL/min |
| Air Flow | 350 mL/min |
| | |

**Sample Matrix Used for Validation**

Hand sanitizer gel

- Active ingredient: ethyl alcohol, 70% v/v
- Inactive ingredients: water, glycerin, propylene glycol, isopropyl myristate, aloe barbadensis leaf juice, tocopheryl acetate, isopropyl alcohol, carbomer, triisopropanolamine

**Reagents and Standards**

- DI Water (NLT resistivity 18 MΩ·cm)
- Methanol (MeOH), USP reference standard, catalog number: 1424109
- Ethanol (EtOH), "Alcohol Determination—Alcohol" USP reference standard, catalog number 1012688 (approximately 2% v/v ethanol in water)
- Isopropanol (IPA), USP reference standard, catalog number: 1570428
- Acetonitrile (ACN), Fisher, catalog number: A955 (used as internal standard)

**Solutions:**

- Standard Solution: 0.4% v/v MeOH, EtOH and IPA in water with 0.4% ACN as IS
- Sample Stock Solution: 0.5 mL hand sanitizer gel sample diluted to 25 mL w/ water
- Sample Solution: 4 mL Sample Stock Solution + 4 mL 2% v/v ACN to 20 mL w/ water
- Spike Sample Solutions (spike levels 0.3%, 0.4% and 0.5% v/v MeOH, EtOH and IPA): 4 mL of Sample Stock Solution + 3, 4, or 5 mL of 2% EtOH in water + 3, 4, or 5 mL of 2% MeOH & IPA in water + 4 mL of 2% v/v ACN diluted to 20 mL w/ water
- Linearity Solutions: 0.001% - 1.0% v/v MeOH, EtOH and IPA with 0.4% v/v ACN
- LOD Solution: 0.00025% v/v MeOH, EtOH and IPA with 0.4% v/v ACN

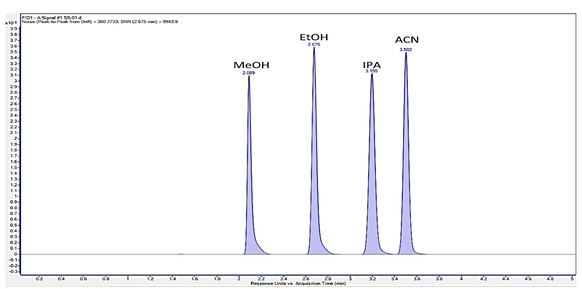


**Figure 1.** GC-FID Chromatogram of Standard Solution (0.4% v/v MeOH, EtOH & IPA with 0.4% v/v ACN Internal Standard)

## Results and Discussion

The method was validated using one hand sanitizer gel sample representative of commercially available products. System suitability criteria were taken from USP <611>. Linearity was determined by injecting standard solutions at seven concentration levels, from 0.001% to 1.0% v/v MeOH, EtOH and IPA. LOD and LOQ were determined by 3 injections each of 0.00025% and 0.001% v/v alcohol solutions, respectively. The LOD concentration was set sufficiently low to detect MeOH in hand sanitizer sample at the FDA guidance limit of 630 ppm, taking into account the dilution of the sample, and where signal-to-noise (S/N) values were consistently ≥ 3. LOQ was set at a level where the S/N values were consistently ≥ 10. Accuracy and precision were determined using 3 preparations of un-spiked hand sanitizer gel sample and 3 preparations each at 3 different spike concentrations. Results are in Table 2. All acceptance criteria were met.

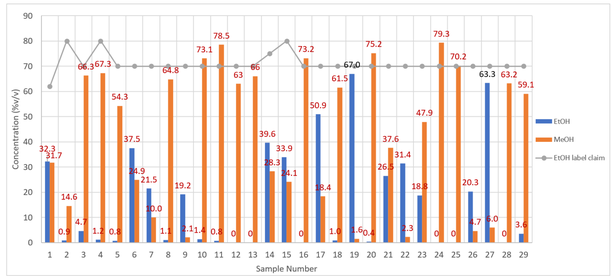


**Figure 2.** MeOH & EtOH Content in Hand Sanitizers #1-29, Previously Flagged Positive for MeOH by CBP (No IPA Detected in Any Samples)

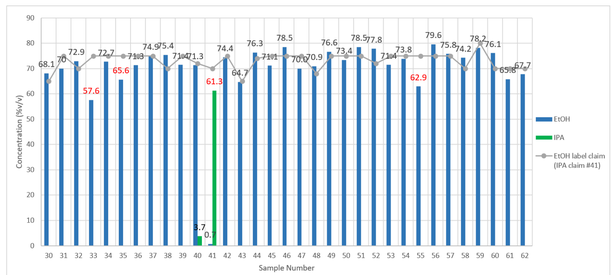


**Figure 3.** EtOH & IPA Content in Hand Sanitizers #30-62 (No MeOH Detected in Any Samples)

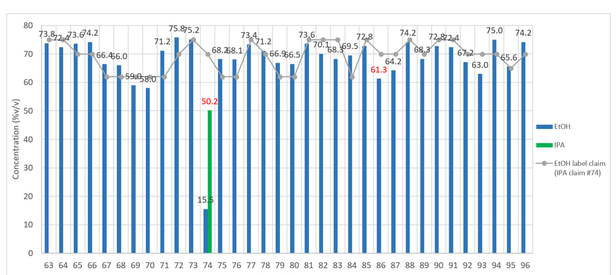


**Figure 4.** EtOH & IPA Content in Hand Sanitizers #63-96 (No MeOH Detected in Any Samples)

A variety of imported hand sanitizer gel samples (29 total) that tested positive for the presence of MeOH by CBP were sent to the Pacific Southwest Medical Products Laboratory to be tested for MeOH, EtOH and IPA content using the validated GC-FID method (Figure 2). The results from these samples are contrasted with imported hand sanitizer samples that did not test positive for the presence of MeOH (Figures 3-4). All samples except two claimed EtOH as the active ingredient, with label claim 62-80% v/v. Samples #41 and #73 claimed IPA as the active ingredient, with label claim 70% v/v. Each of the hand sanitizer gel samples were prepared twice, each preparation injected twice and the results of all injections averaged to produce the values reported in Figures 2-4. No interfering peaks were observed on the chromatograms for any of the samples.

**Table 2.** Validation Results

| Parameter | Test | MeOH | EtOH | IPA | Criteria |
|---|---|---|---|---|---|
| System Suitability | %RSD Peak Area Ratio, 0.4% standard (n = 6) | 0.10 | 0.06 | 0.03 | ≤ 2.0% |
| | Peak Tailing Factor | 1.4 | 1.2 | 1.1 | ≤ 2.0 |
| | Peak Resolution with ACN, 0.4% standard | N/A | N/A | 3.3 | ≥ 1.5 |
| Sample Matrix Analysis | Average Concentration in Sample (%v/v, n = 3) | 0.0 | 73.7 | 0.1 | 63-77 |
| | %RSD (n = 3) | N/A | 0.2 | 3.3 | ≤ 10 |
| | Label claim (%v/v) | N/A | 70 | N/A | N/A |
| Linearity | Standard Solution Range (%v/v) | 0.001-1.0 | 0.001-1.0 | 0.001-1.0 | N/A |
| | $r^2$ | 0.9997 | 0.9997 | 0.9998 | ≥ 0.995 |
| Accuracy | Average %Recovery, 0.3% spike sample (n = 3) | 99.5 | 100.1 | 99.7 | 90-110 |
| | Average %Recovery, 0.4% spike sample (n = 3) | 99.5 | 100.0 | 99.5 | |
| | Average %Recovery, 0.5% spike sample (n = 3) | 99.3 | 99.3 | 99.4 | |
| Precision | %RSD, 0.3% spike sample (n = 3) | 0.11 | 0.21 | 0.12 | ≤ 10 |
| | %RSD, 0.4% spike sample (n = 3) | 0.18 | 0.36 | 0.18 | |
| | %RSD, 0.5% spike sample (n = 3) | 0.27 | 0.16 | 0.22 | |
| LOQ | LOQ Conc. in solution (%v/v) | 0.001 | 0.001 | 0.001 | N/A |
| | LOQ Conc. in sample (%v/v) | 0.25 | 0.25 | 0.25 | N/A |
| | Average S/N (n = 3) | 12.4 | 13.1 | 12.9 | ≥ 10 |
| | Average %Recovery (n = 3) | 108.1 | 99.5 | 109.1 | 80-120 |
| | %RSD (n = 3) | 8.8 | 2.4 | 1.3 | ≤ 20% |
| LOD | LOD Conc. in solution (%v/v) | 0.00025 | 0.00025 | 0.00025 | N/A |
| | LOD Conc. in sample (ppm) | 625 | 625 | 625 | N/A |
| | Average S/N (n = 3) | 3.8 | 3.7 | 3.7 | ≥ 3 |

## Conclusion

The method validation study showed that the GC-FID method is specific, accurate, precise, and linear for the analysis of MeOH, EtOH and IPA in gel hand sanitizer. LOD was established at 0.00025% v/v in solution, corresponding to 625 ppm in test sample. This LOD level is approximately the same as the limit of MeOH in the FDA guidance, ensuring that MeOH can be detected at levels just above the limit. LOQ was established at 0.001% v/v concentration in solution, corresponding to 0.25% v/v in test sample.

The validated GC-FID method was used to quantify the MeOH and EtOH content in a variety of imported hand sanitizer gel samples that previously tested positive for the presence of MeOH by CBP, as well as other imported samples that did not previously test positive for MeOH. The MeOH positive samples were found to have a wide range of MeOH content across samples, from 1.6%-79.3% v/v, along with much lower EtOH content than claimed, if detected at all. Most of the results for the MeOH positive samples were consistent with economically motivated partial or complete substitution of EtOH with MeOH in the product. The non-MeOH positive samples, on the other hand, did not show any MeOH in the product by GC-FID, and generally gave EtOH results consistent with the product label claim. Only 4 out of the 65 such samples had less than 90% of the claimed EtOH (#33, 35, 55 & 86). The two samples (#41 & 74) that claimed IPA as active ingredient were both found to have less than 90% of the claimed amount.

REFERENCES

1. "Temporary Policy for Preparation of Certain Alcohol-Based Hand Sanitizer Products During the Public Health Emergency (COVID-19) Guidance for Industry" published March 2020; updated February 10, 2020; U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER).
2. Hand sanitizer samples were tested by Customs and Border Protection using a Gemini hand-held FTIR/Raman spectrometer.
3. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use
4. USP43-NF38 <611> "ALCOHOL DETERMINATION" method IIB
5. USP43-NF38 <1225> "VALIDATION OF COMPENDIAL PROCEDURES"