The COVID-19 outbreak and pandemic resulted in an increase in the number of firms producing hand sanitizers and an increase in the number 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 (MeOH) in panel testing. ODSMPS determined that a single method was needed that could quantitate ethanolic or isopropyl active ingredient and quantitate methanolic adulterant if present. The analytical procedure described uses GC-FID for quantitation of ethanolic and isopropyl alcohol in hand sanitizer from levels as low as 2% v/v to above 99% v/v. The detection limit of methanol is 0.2 ppm v/v. The method is an extension of the USP (REF 1) Alcohol Determination method for ethanol, and new USP method for isopropanol and methanol in the analysis. This method was successfully validated using a gel hand sanitizer matrix containing a label claim of 70% ethanol, with glycerine, propylene glycol and ascorbic acid as the inactive ingredients. The method details are described in an LBI 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. In response to the increased demand for these alcohol-based hand sanitizers, the FDA released a guidance communicating a temporary policy allowing for the increased production of alcohol-based hand sanitizers. This policy was needed that could quantitate ethanol or isopropanol active ingredient and detect methanol 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 gel forms, while two of which were liquid hand sanitizers.

Validation of USP (REF 1) Alcohol Determination Chromatographic Method IIb for quantitation of ethanol and isopropanol in gel hand sanitizer. The validated GC-FID method was used to quantify the MeOH and EtOH content in a sample of gel hand sanitizer. The LOD level is approximately the same as the limit of MeOH in the FDA guidance, and the accuracy and precision were determined using 3 preparations of un-spiked hand sanitizer gel samples and 3 preparations each at 3 spike concentrations. Results are in Table 2. All acceptance criteria were met.

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 (REF 4). Linearity was determined by injecting standard solutions at seven concentration levels, from 0.0006% to 1.00% 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 samples at the FDA guidance level 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. The samples used to verify the MeOH and IPA in the hand sanitizer products were prepared as small aliquots from the same batch, which are commercially available products. System suitability criteria were taken from USP (REF 4). 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 samples at the FDA guidance level 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 samples and 3 preparations each at 3 different spike concentrations. Results are in Table 2. All acceptance criteria were met.

Materials and Methods

Equipment

Agilent Technologies GC-5890B Series with 5975A autosampler and FID (Flame Ionization Detector), or equivalent

Reagents

• Restek Rtx-520 Columns, Catalog number: 180556; Nominal Dimensions: ID: 0.53 mm; Film Thickness: 1.0 microns; Length 30 m (USP phase G43)

• Positive Displacement Pipette – Reagent Reservoir, 1 µL – 50 mL, or equivalent

• Pipette tips – Eppendorf Combiprep 1.5 mL, 5 mL, 50 mL, and 20 mL volumes

• Class A volumetric flask

Table 1. GC-FID Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P</th>
<th>Injection Parameters</th>
<th>Test MeOH</th>
<th>EtOH</th>
<th>IPA</th>
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</table>

Sample Matrix Used for Validation

Hand sanitizer gel

• Active ingredient: ethyl alcohol, 70% v/v

• Inactive ingredients: water, glycerin, propylene glycol, isopropyl myristate, isopropyl palmitate, isopropanol alcohol, ceramide, trisodiumphosphate

Reagents and Standards

• Methanol (MeOH), USP reference standard, catalog number: 1424109

• Ethanol (EtOH), “Alcohol Determination—Alcohol,” USP reference standard, catalog number: 1926268 (approximately 3% v/v ethanol in water)

• Isopropanol (IPA), USP reference standard, catalog number: 1172145

• Aesculetin (ACN), Fischer, catalog number: A055 (level as internal standard)

Solutions

• Standard solution: 0.4% v/v MeOH, EtOH and IPA in water ± 0.4% ACN in B

• Sample Stock Solution: 0.3 mL hand sanitizer gel diluted to 25 mL with water

• Sample solution: a.m. Sample Stock Solution + 4 mL of 2% v/v ACN to 20 mL with water

• Linearity Solutions: 0.0625% v/v of MeOH, EtOH and IPA in water ± 0.4% ACN

• Aesculetin (ACN) stock solution: 25 mg/mL

System Suitability

• Peak Tailing Factor ≤ 2.0%

• %RSD (n = 3) ≤ 20%

• Label claim (%v/v) N/A 70 N/A N/A N/A

• Average Concentration in Sample (%v/v, n = 3) 0.0 73.7 0.1 99.5

• Average %Recovery, 0.3% spike sample (n = 3) 99.5

• %RSD (n = 3) ≤ 20%

• LOD Conc. in solution (%v/v) 0.001 0.001 0.001 N/A

• LOQ Conc. in solution (%v/v) 0.001 0.001 0.001 N/A

Validation of USP (REF 1) Alcohol Determination Chromatographic Method IIb for quantitation of ethanol and isopropanol in gel hand sanitizer. The validated GC-FID method was used to quantify the MeOH and IPA in the hand sanitizer products. System suitability criteria were taken from USP (REF 4). 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 samples at the FDA guidance level 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 samples and 3 preparations each at 3 different spike concentrations. Results are in Table 2. All acceptance criteria were met.

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. The LOD established at 0.00025% v/v in solutions, corresponding to 0.63 ppm in test samples. The LOD level is sufficiently low to detect MeOH at the FDA guidance level of 630 ppm, ensuring that MeOH can be detected at levels just above the limit. LOQ was established at 0.0001% v/v in solutions, corresponding to 0.21 ppm in test samples. The validated GC-FID method was used to quantify the MeOH and IPA 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 or test positive for MeOH. The MeOH positive samples were found to have a wide range of MeOH content across samples, from 0.40%–14.0%, along with much lower Ethanol content than claimed, if detected at all. Most of the results for the MeOH positive samples were all contained within an 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 67 samples had less than 90% of the claimed EtOH (43, 45, 52 & 58). The two samples (41 & 73) that claimed IPA as active ingredient were both found to have less than 60% of the claimed active ingredient.