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Overcoming the Challenges of Hand Sanitizer Analysis

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Introduction

The U.S. Food and Drug Administration (FDA) has placed methanol containing hand sanitizers on an import alert. These products do not list this ingredient and some are incorrectly labeled “FDA approved.” Nearly 100 hand sanitizers have been found to contain methanol. Methanol, known as wood alcohol, is commonly found in solvents, and windshield washer fluid. Ingestion of 10 mL can cause permanent blindness and 15 mL is considered a lethal dose. Transdermal methanol poisoning has been well documented and may result in optic nerve necrosis with permanent eye damage. Denatured alcohol is ethanol mixed with other alcohols and can contain 50% methanol, along with dozens of other possible contaminants.

The separation and analysis of these active and inactive compounds is challenging and finding the correct column and conditions to implement and validate a robust test method is difficult for any method development team. We started with computer software capable of modeling these compounds on a variety of stationary phases which allows us to adjust; flow, temperature, film thickness, column diameter and column length. Using the column recommendation, Santé Laboratories was able to transfer, qualify, optimize and validate a GC-MS published FDA method. The method parameters, chromatograms, and challenges encountered in developing this method, will be presented in addition to an introduction to novel modeling software.

Using Computer Modeling Software to Simulate Gas Chromatographic Separations

A free to use, web-based computer program has been employed to accelerate Gas Chromatography (GC) method development by direct simulation of the chromatographic process. The program makes use of a highly accurate time-summation modeling approach, coupled with large libraries of data to provide absolute retention time predictions.

The user is able to directly control every parameter of the chromatography being modeled including carrier gas, stationary phase, column dimensions, and temperature programs. The temperature program can be iteratively optimized to obtain the desired separation in the minimum run time. Pro EZGC is preloaded for modeling of more than 20 different stationary phases and thousands of compounds including; Solvents, Pesticides, PCB’s, PAH’s, semivolatiles, and volatile organics.

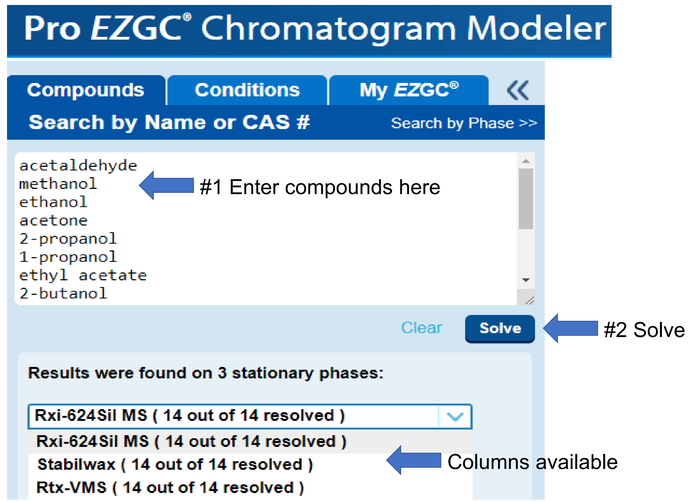
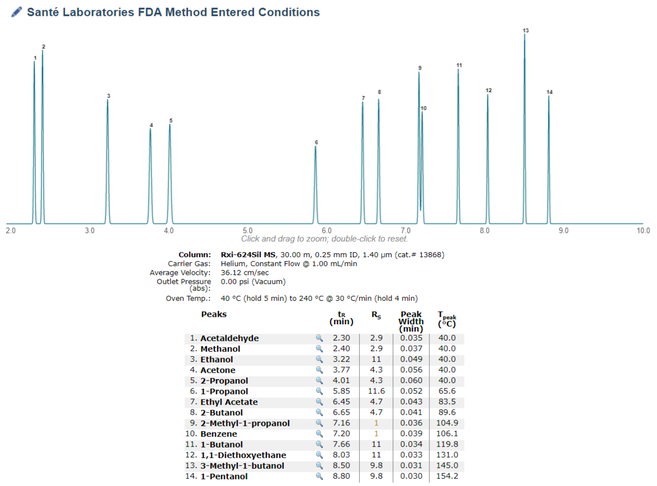


Figure 1: Using the FDA’s analytical procedure to assess finished hand sanitizers; Level 1 & Level II compounds were entered into Pro EZGC for modeling. Notice three columns were able to baseline resolve these compounds: Rxi-624Sil MS, Rtx-VMS and the Stabilwax.



Peaks	t_R (min)	R_S	Peak Width (min)	T_{peak} (°C)
1. Acetaldehyde	2.30	2.9	0.035	40.0
2. Methanol	2.40	2.9	0.037	40.0
3. Ethanol	3.22	11	0.049	40.0
4. Acetone	3.77	4.3	0.056	40.0
5. 2-Propanol	4.01	4.3	0.060	40.0
6. 1-Propanol	5.85	11.6	0.052	65.6
7. Ethyl Acetate	6.45	4.7	0.043	83.5
8. 2-Butanol	6.65	4.7	0.041	89.6
9. 2-Methyl-1-propanol	7.16	1	0.036	104.9
10. Benzene	7.20	1	0.039	106.1
11. 1-Butanol	7.66	11	0.034	119.8
12. 1,1-Diethoxyethane	8.03	11	0.033	131.0
13. 3-Methyl-1-butanol	8.50	9.8	0.031	145.0
14. 1-Pentanol	8.80	9.8	0.030	154.2

Figure 2: Pro EZGC Model solved for FDA’s Level I & Level II compounds where chromatographic conditions were entered, including; carrier gas flow rate, vacuum, and oven temperature gradient.

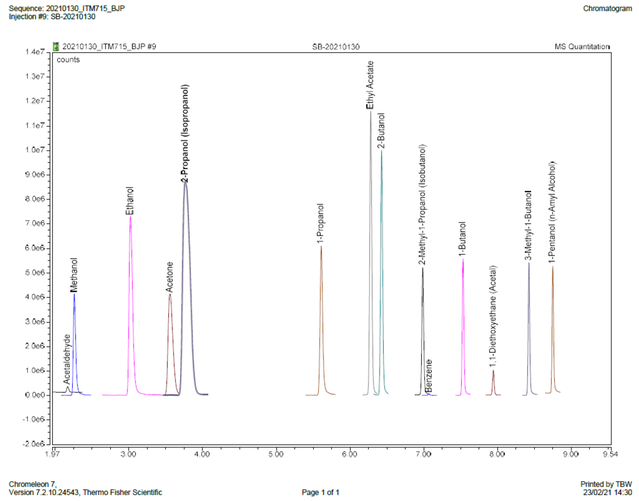


Figure 3: Chromatogram generated by Santé Laboratories using the FDA analytical procedure to assess finished hand sanitizers; Level 1 & Level II compounds closely match the Pro EZGC model (figure 2).

Conditions and Instrumentation

Instrument:	Thermo Scientific Trace 1310 GC, ISQ 7000 MS TriPlus RSH Autosampler
Column:	Rxi-624Sil MS, 30.00 m, 0.25 mm ID, 1.40 µm
Carrier Gas:	Helium, Constant Flow @ 1.00 mL/min, 36.12 cm/sec
Temperature Gradient:	40 °C (hold 5 min) to 240 °C @ 30 °C/min (hold 4 min)
Injection:	1uL, Split 50:1, 250°C
Liner:	Topaz Precision Split Liner with Wool

Direct Injection GC-MS Method for the Detection of Listed Impurities in Hand Sanitizers

The FDA’s analytical procedure can be used to evaluate products with either ethanol or isopropyl alcohol labeled as the active ingredient to asses percent alcohol as well as target impurities. This approach utilized MS, a departure from the USP <467> which allows detection by FID. In addition spike and recovery studies are conducted to evaluate matrix effects and standards are prepared using a stock standard working solution in acetonitrile.

Calibration Stocks		*Mixed Stock*	*Working Standard (Nominal)*	Spiked Blank (Nominal)	Working Standard (Measured)								
	mg	mL	*ug/mL*	*ug/mL*	*ug/mL*	WS1	WS2	WS3	WS4	WS5	WS6	AVG	STDEV	RSD
1,1-Diethoxyethane (Acetal)	10.91	100	109.1	10.9	1.1	11.3	10.9	10.5	10.8	10.8	9.4	**10.6**	**0.6**	**5.4**
1-Butanol	152.63	100	1526.3	152.6	15.3	158.3	151.3	148.1	149.9	151.0	132.5	**148.5**	**7.8**	**5.3**
1-Pentanol (n-Amyl Alcohol)	147.02	100	1470.2	147.0	14.7	155.0	141.7	138.0	146.6	146.9	129.9	**143.0**	**7.9**	**5.5**
1-Propanol	155.15	100	1551.5	155.2	15.5	160.3	155.0	151.0	154.7	154.3	137.5	**152.1**	**7.1**	**4.6**
2-Butanol	144.80	100	1448.0	144.8	14.5	151.3	144.7	140.8	143.0	142.4	122.7	**140.8**	**8.7**	**6.2**
2-Methyl-1-Propanol (Isobutanol)	146.10	100	1461.0	146.1	14.6	152.6	144.0	141.9	144.5	143.2	125.4	**141.9**	**8.2**	**5.8**
2-Propanol (Isopropanol)	380.54	100	3805.4	380.5	38.1	398.8	376.1	366.7	373.9	368.0	321.7	**367.5**	**23.1**	**6.3**
3-Methyl-1-Butanol	158.69	100	1586.9	158.7	15.9	164.2	157.4	154.5	157.4	154.7	137.1	**154.2**	**8.3**	**5.4**
Acetaldehyde	10.49	100	104.9	10.5	1.0	11.0	10.2	10.1	10.4	10.1	8.4	**10.1**	**0.8**	**8.0**
Acetone	154.89	100	1548.9	154.9	15.5	163.8	153.2	149.1	151.1	149.0	128.0	**149.0**	**10.7**	**7.2**
Benzene, ~1000 ug/mL in ACN	392.58	100	3.4114	0.3	0.0	0.4	0.3	0.3	0.3	0.3	0.3	**0.3**	**0.0**	**5.5**
Ethanol	388.27	100	3882.7	388.3	38.8	402.7	383.2	379.7	387.7	385.1	336.8	**379.2**	**20.3**	**5.4**
Ethyl Acetate	173.77	100	1737.7	173.8	17.4	182.4	172.5	168.9	170.6	169.7	148.1	**168.7**	**10.3**	**6.1**
Methanol	152.51	100	1525.1	152.5	15.3	159.3	151.7	147.8	152.4	150.4	130.9	**148.8**	**8.7**	**5.9**

Figure 4: Quantitation of the impurities is based on peak area of impurity in sample chromatogram compared to an external calibration standard containing the reference standards. These working standards were analyzed for standard deviation and relative standard deviations (%RSD) where the replicates may not exceed 10% RSD.

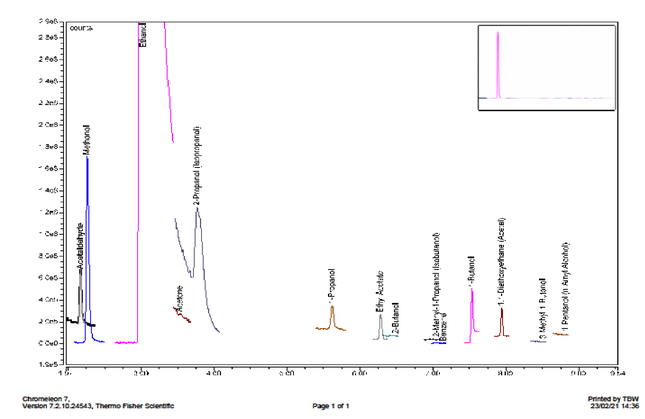


Figure 5: Client sample of finished product exceeding acceptable levels of acetaldehyde (86.6 ug/g) and below limit concentrations of methanol (less than 316.4 ug/ml). Other impurities match retention times and spectra but fall well below FDA limit guidelines.

Conclusions

The compliance testing team at Santé Laboratories; a contract development and manufacturing organization (CDMO) headquartered in Austin, Texas, performs raw materials and finished product lot release testing for a variety of industries. The testing includes active ingredients and excipients frequently used to manufacture effective and safe hand sanitizers. Restek’s Pro EZGC software enables laboratories to quickly determine GC conditions for targeted methods and specific resolution requirements. This software was successfully used to predict retention times using FDA’s GC conditions and Santé Laboratories was able to develop and validate this analytical procedure.