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Short communication

Detection of adulteration in acetonitrile

Guoxiang Chen, Kiyoshi Fujimori, Hans Lee, Yasser Nashed-Samuel*, Joseph Phillips, Gary Rogers, Hong Shen, Chanel Yee

Process & Product Development, Amgen Inc., 1 Amgen Center Dr, Thousand Oaks, CA 91320, USA

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ABSTRACT

To address the increasing concern that acetonitrile may be intentionally adulterated to meet the shortfall in global supplies resulting from a downturn in its manufacturing, three analytical techniques were examined in this study. Gas Chromatography with Thermal Conductivity Detection (GC–TCD), Near Infrared (NIR) spectroscopy and Fourier Transform Infrared (FT-IR) spectroscopy were assessed for their ability to detect and quantify potential adulterants including water, alternative organic solvents, and by-products associated with the production of acetonitrile. The results of the assessment of the three techniques for acetonitrile adulteration testing are discussed.

1. Introduction

Acetonitrile is an organic solvent that is widely used in the pharmaceutical industry. Recently a global shortage in the supply of acetonitrile has driven its price up and raised great concern over the opportunity for intentional economic adulteration of this popular solvent.

The quality of raw materials used in the manufacturing of pharmaceutical drugs is critical to patient safety. Adulterated raw materials can lead to failure of a drug manufacturing process or, more dangerously, threaten the lives of patients. Recently the U.S. FDA reported that 146 deaths were linked to contaminated Heparin, a blood thinner, in the first 5 months of 2008 [1]. The Heparin API contained 5–20% of an identified contaminant, oversulfated chondroitin sulfate (OSCS), which was the cause of severe adverse reactions following intravenous administration of Heparin [2–4]. The contaminated Heparin material was imported from China, raising the concern about adulteration of raw materials from countries where current Good Manufacturing Practice (cGMP) is not strictly enforced. While acetonitrile is not typically used in the manufacture of biological therapeutics it is a very common reagent in the testing and release of product where economic adulteration could result in failed assays and a fairly significant cost in the quality environment.

For the purpose of this study, we define "economic adulteration" as the presence of 5% (v/v) or more of either single or multiple known or foreign substances that have purposely been added to or not removed from a raw material. Much of the commercial acetonitrile is obtained as a by-product of the manufacture of acrylonitrile [5]. We chose to evaluate acrylonitrile and propanenitrile (propanenitrile can be produced by the reduction of acrylonitrile during its manufacture) as examples of compounds not removed during the manufacture. We also included methanol, ethanol, isopropyl alcohol and water which are miscible with acetonitrile, relatively inexpensive, readily available and are used in similar applications as examples of compounds that might be added to acetonitrile as adulterants. Each of these was individually spiked into acetonitrile at the 5% (v/v) level generating 6 separate samples for comparison. Another spiked sample containing all six adulterants at 5% (v/v) each in acetonitrile was also examined. It is important to note that this study is not intended to detect minor impurities. Although 5% adulteration is considered here to be a minimum level of adulteration that would be economically viable, we have not ruled out lower levels of purposeful dilution for economic gains.

For Quality Control (QC) testing, it is highly desirable to have analytical techniques that provide fast, sensitive, and effective means of detecting adulteration in commercially available raw materials. Gas Chromatography (GC) is readily available in QC laboratories and is commonly used for the analysis of volatile compounds [6]. GC is both a qualitative and quantitative technique that is widely used for detecting adulteration in food, especially

* Corresponding author. Tel.: +1 805 447 5483.
E-mail address: snashed@amgen.com (Y. Nashed-Samuel).

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Table 1
Adulteration chemicals.

1	Water, Millipore
2	Methanol, HPLC grade, JT Baker
3	Ethanol, 190 proof, EMD
4	Isopropyl Alcohol, Mallinckrodt
5	Acrylonitrile, 99+%, Aldrich
6	Propanenitrile, 99% Aldrich

oils and drinks [7–12]. GC with thermal conductivity detection (TCD) was selected in this study due to its ability to detect water as well as a broad range of organic solvents. Near-infrared (NIR) spectroscopy has been widely used for both qualitative and quantitative analysis in the pharmaceutical industry [13–16]. As a non-destructive technique, NIR offers the advantages of speed, ease of use, automatable data analysis, and the ability to analyze samples with little or no sample preparation. A typical modern NIR instrument can generate a spectrum in a few seconds. NIR is becoming increasingly popular for routine use in QC labs, where inexpensive high-throughput methods are desired. NIR spectra are usually analyzed with aid of chemometric software. The Conformity Test method is one chemometric tool often used to confirm identity of raw materials. This method determines whether a sample falls within the normal variability of the raw material under test by checking the variation at each wavelength within the spectral range. A positive confirmatory result is given when the variation at each wavelength is within the pre-defined threshold. The method has been used successfully to detect sulfanilic acid contamination in sulfamethoxazole at or greater than 2% (w/w) [17]. Fourier transform infrared (FTIR) spectroscopy is another technique used for raw material identification. Although it is mostly used in the identification of pure chemicals, the technique has recently been employed as a useful tool in the authentication [18,19] and quantification of adulteration of food products [20]. The technique has proven useful in detecting the adulteration of hazelnut oil [21] and extra-virgin olive oil [22]. The FT-IR method takes only a few minutes per sample once the analytical procedure had been developed.

In this manuscript, the three analytical techniques, GC–TCD, NIR, and FTIR, have been evaluated and compared for their ability to detect economic adulteration in acetonitrile.

2. Materials and methods

2.1. Materials

Five lots of neat acetonitrile, three from J. T. Baker, one from B & J and one from Sigma, were used as received in this study. Detailed information regarding the six chemicals used as adulterants in this study is listed in Table 1.

2.2. Methods

Adulterated acetonitrile samples, each containing one adulterant, were prepared by adding 5% (v/v) of each of the six adulterants into neat acetonitrile. Another adulterated acetonitrile sample, containing all six adulterants, was prepared by spiking 5% (v/v) of each adulterant into neat acetonitrile.

2.3. GC–TCD

An Agilent 6890 GC equipped with a liquid autosampler (Agilent Technologies, Santa Clara, CA), split/splitless inlet, HP-1 column (J&W, 30 m length × 530 μm ID × 3 μm film), and TCD detector was used to analyze the acetonitrile samples. The samples were injected at 0.2 μL with a split ratio of 1:50 and the inlet temperature set to 240 °C. The flow rate was held constant at 10 mL/min He. The initial column temperature was held at 40 °C for 0.5 min, then ramped to 210 °C at a rate of 25 °C/min, and held at 210 °C for an additional 3 min. The detector temperature, reference flow, and make up flow were set to 250 °C, 48 mL/min, and 2 mL/min He, respectively. The GC–TCD method was used to test neat acetonitrile and adulterated samples. Results for the adulterated samples were compared with those for neat acetonitrile to determine the resolution of the adulterants. For precision and accuracy, acetonitrile was spiked at levels in the range of 1–25% of each adulterant.

Table 2
Precision of retention time and peak area of 1% water, methanol, ethanol, isopropyl alcohol, acrylonitrile and propanenitrile in acetonitrile by GC–TCD.

Adulteration chemicals	Retention time (n = 6)		Peak area (n = 6)	
	Time (min)	RSD	Area	RSD
Water	1.06	<0.1%	25.5	1.7%
Methanol	1.19	<0.1%	15.9	2.0%
Ethanol	1.42	<0.1%	16.4	0.6%
Isopropyl alcohol	1.62	01%	26.4	4.9%
Acrylonitrile	1.69	<0.1%	24.0	2.6%
Propanenitrile	1.98	<0.1%	16.4	2.5%

2.4. NIR

Neat and adulterated acetonitrile samples were measured using a Bruker MPA NIR Spectrometer (Bruker Optics, Billerica, MA). Three replicate spectra were collected for each sample in transmission mode. The vials were repositioned between measurements. Each NIR spectrum represents an average of 16 scans with 8 cm^{-1} spectral resolution from 12,000 to 3500 cm^{-1}. The Conformity Test function in Bruker OPUS 6.5 software was used to analyze the NIR data.

2.5. FTIR

All samples were injected in an IR liquid cell comprising two CaF_2 discs with a 15 μm Teflon spacer. FTIR analysis was performed using a Bruker Vertex 70 with the IR source in transmission mode (Bruker Optics, Billerica, MA). Each FTIR spectrum represents the average of 128 scans with 4 cm^{-1} spectral resolution. Bruker OPUS 6.5 software was used to analyze the data.

3. Results and discussion

3.1. GC–TCD

The six individual adulterated acetonitrile samples and the sample containing all of the adulterants were analyzed by GC–TCD. Peaks corresponding to each adulterant were well resolved (Fig. 1). Data were obtained for samples containing the adulterants in the range 1–25% (v/v). Peak retention time and area with relative standard deviation "RSD" (n = 6) values of <1% and <5%, respectively, for each adulterant at the 1% (v/v) spiked level are shown in Table 2. Five point calibration curves ranging from 1 to 25% (v/v) for each adulterant exhibited linear regression "R^2" values ≥0.999. The recovery of each adulterant spiked at the 2% and 20% levels in acetonitrile was between 93 and 105% of the actual concentration (Table 3). The method was applied to 19 lots of acetonitrile samples from six regular suppliers and no adulteration in these samples was observed.