Drug Analysis:

Using HPLC to Identify Two Common Cutting Agents Often Found Illegal within Drugs

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Acceptance of Senior Honors Thesis

This Senior Honors Thesis is accepted in partial
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Abstract

Oftentimes, illegal drugs are cut with additional substances, known as cutting agents. These cutting agents fall into two categories: Diluents and adulterants. Diluents have no physiological effect on the user and simply allow the distributor to give the perception of "more product made." Common examples of diluents are usually everyday house-hold commodities (i.e., sugar or corn starch). On the other hand, adulterants are used to mimic or enhance the drugs physiological effects (i.e., caffeine in cocaine). As such, these do have drug-like properties (i.e., CNS stimulation or depression, etc.). This thesis seeks to use High-Performance Liquid Chromatography (HPLC) to efficiently detect and quantify mixtures of these cutting agents. It must be stated that this research did not examine any drug (over-the-counter or illegal). Instead this research focused on two legal cutting agents only. In summary, there are three goals for this project: (1) Research HPLC methods that can detect known concentrations of two common cutting agents, (2) identify these cutting agents as compared to the standards made in the laboratory, and (3) determine a method of analysis that can successfully detect these cutting agents in under ten minutes.

Drug Analysis:

Using HPLC to Identify Two Common Cutting Agents Often Found within Illegal Drugs

Introduction

Drug use is prevalent throughout the world and especially in America. According to *The National Survey on Drug Use Health*, there were 19.7 million adults in America that struggled with drug abuse in 2017 (Substance Abuse, 2018). Another survey, performed by the *National Institute on Drug Abuse*, showed that nearly half of all high schoolers at some point used marijuana (Kaliszewski, 2019). The use of illicit drugs is a common occurrence throughout the U.S., and with multiple states beginning to legalize the use of certain hard drugs, it is only to be expected that drug usage will increase. Therefore, being able to identify and locate the source of drug production is imperative. By identifying trends in drug distribution, prosecutors and law enforcement can use this information as a possible method of identifying clandestine sources. A way these original drug sources can be revealed is through the chemical makeup of the illicit drug: Specifically, through identifying their respective adulterant and diluent ratios.

Cutting Agents: Adulterants and Diluents

Illicit drugs, which at times can be sold in pure form, are often instead combined, or "cut," with an additional substance besides the drug itself. These additional substances are divided into two categories: Adulterants and diluents. While both are used to cut drug supplies, adulterants and diluents have different effects. However, before defining them, it is important to address a common misconception regarding cutting agents. Frequently, the public perceives drug dealers as angry, sneaky criminals that are always seeking to harm their customers by cutting their drugs with harmful, dangerous materials (for example, household cleaning products, brick

dust, ground glass, etc.) (Broséus et. al., 2016). Cutting is believed to harm consumers and to increase profit. While it is true that the use of cutting stems from a dealer's desire to increase profits, it is important to remember that drug dealing is a business at its core. Although certainly illegal, drug dealing still relies on repeat customers, just as in a business. As J. Broséus et. al. (2016) points out, "poisoning customers does not make good business sense regarding income supply or reputation" (p. 2). Some dealers, they state, even express concern over their customers' well-being (Broséus et. Al., 2016). Therefore, when speaking of cutting drugs, it is important to dispel the idea that drug dealers are seeking to harm their customers. As it was already pointed out, that would be bad for business.

According to the literature, there are two specific categories of cutting agents. An article from *Forensic Science International* defines diluents this way: "pharmacologically inactive and readily available substances" (Broséus et. al., 2015, p. 1). These inactive substances could be compounds like sucrose or cornstarch (the chemical structure of sucrose is shown below).

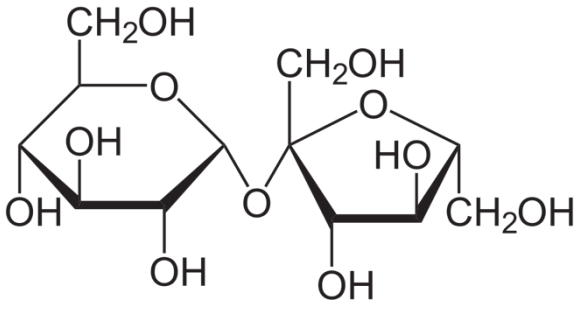


Figure 1. *Chemical structure of sucrose*.

These types of cutting agents are added to stretch the supply of the illicit compound and do not have any physiological effect. On the other hand, adulterants are defined in the following way: "They are used to enhance or mimic the effects of illicit drugs [and] to ease or make the

administration of the illicit drug more efficient" (Broséus et. Al., 2016, p. 4). Furthermore, adulterants are "pharmacologically active substances, usually more expensive and less available than diluents" (Broséus et. al., 2016, p. 4). For example, an adulterant for cocaine could be caffeine.

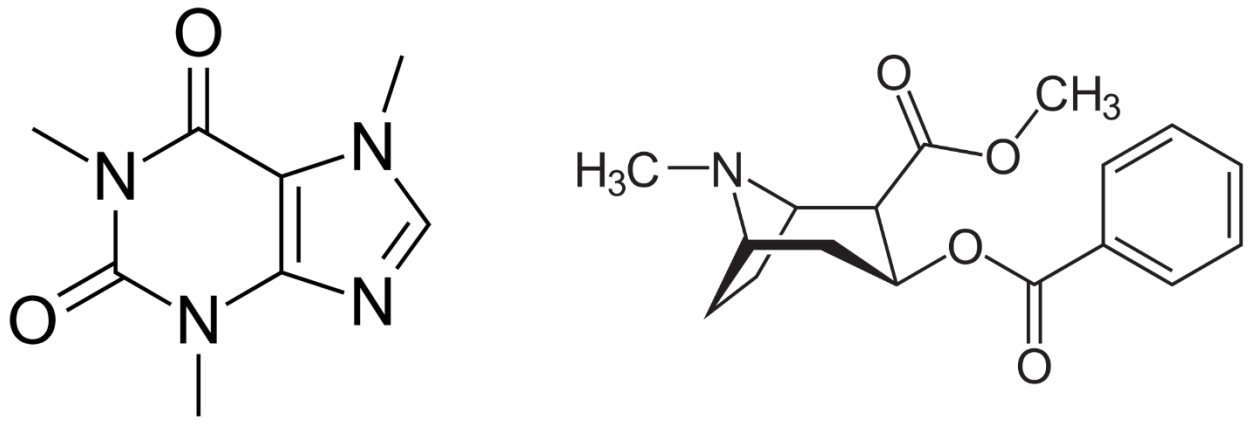
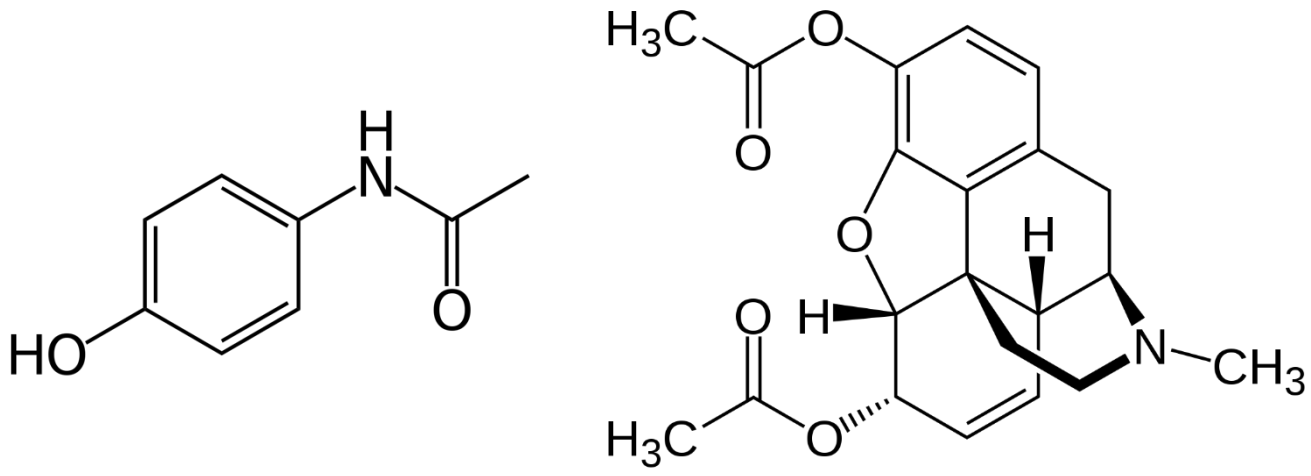


Figure 2. *Chemical structures of caffeine (left) and cocaine (right).*

Caffeine has psychoactive properties and mimics the effects of cocaine. Another example of an adulterant could be using paracetamol in heroin because of its analgesic properties.



Because these compounds' properties mimic the illicit drug's properties, adulterants are added strategically. Diluents have no physiological or psychoactive effects. As such, are added only to stretch supply.

Identification of adulterants and diluents in illicit drug samples may be able to help identify the distributor and distribution patterns. As mentioned already, adulterants are added strategically to the drug samples, both in type and amounts. This implies some consistency in the way that these drugs are produced. If cutting methods can be studied, as Broséus (2016) points out, at the production level, country of origin and country of consumption, then this information may be able to help incriminate dealers. For example, lidocaine and sugar were the two major cutting agents found in cocaine in the 1980s; this changed in the 1990s when lidocaine was no longer found in cocaine samples in Spain (Broséus et. al., 2016). If a drug sample was seized in Spain in the 1990s, but was found to contain lidocaine, this would indicate that the drug was produced in the 1980s. Therefore, this information would help investigators to potentially determine the time the illicit drugs were produced and narrow the list of suspects. Some countries also have specific adulterants that are used during drug production, which may also be able to reveal the geographical origin of the drug itself (Broséus, 2015). An efficient method of analysis for adulterant or diluent identification would be beneficial to investigators by helping locate sources of drug distribution.

Drug Analysis Methods

There have been different methods of analysis put forth in the literature. The following are a few that will be briefly discussed: Capillary Electrophoresis, SPE/TLC, TLC, Gas Chromatography, and HPLC (spell out acronymns).

Capillary electrophoresis was put forth as a method of screening drugs for cutting agents. Barreto et al. (2020) performed experiments using Capillary Electrophoresis with capacity coupled contactless conductivity detection to quantify different drugs (some examples were cocaine, lidocaine, chloride, etc.). The researchers developed an expedient method of analysis, under two and a half minutes, and saw their method used in the field in 2018 (Barreto et al., 2020). Time is an important issue as forensic labs need to analyze a constant, heavy stream of drug samples quickly and accurately.

Another method mentioned in the literature is thin-layered chromatography (TLC). Kochana et al. used TLC to identify the active components in ecstasy tablets (10 March 2005). Ecstasy, or 3,4-methylenedioxy-methamphetamine (MDMA), is a psychoactive drug made synthetically to alter mood and perception. Very popular as a nightclub drug, ecstasy produces feelings of increased energy, warm feelings, and distorted sensory perception, among other effects (MDMA, 2020). Ecstasy is often laced with cutting agents. Using a methanol and phosphate buffer, Kochana and her team were able to isolate ecstasy from its adulterants and diluents (caffeine, glucose, and starch to name a few). Another research group used TLC along with solid phase extraction (SPE) to separate and profile the additional components of ecstasy (14 September 2005). Specifically, this group used SPE/TLC to separate the impurities in 3,4-methylenedioxy-methamphetamine, which is the main active component in ecstasy.

Gas chromatography was performed as an additional method of drug screening. Amphetamines (central nervous stimulants that can affect brain activity and induce higher energy, focus, and confidence) (Editorial Staff, 2021) have become the most popular illegal drug second only to cannabis (Aljohar et. al., 2019). Fenethylline, a type of amphetamine, typically

contains several adulterants and diluents. Aljohar et. al., (2019) experimented with fenethylline samples from Saudi Arabia. Aljohar et. al. used gas chromatography coupled with mass spectrometry and were able to separate the amphetamine from its diluents and adulterants.

The final analytical method to be discussed is High Performance Liquid Chromatography (HPLC). One technique put forth in the literature is micro-HPLC. Vinkovic et. al. (2018) analyzed the purity of cocaine seized by Austrian police from 2012 until 2017 using this method. Employing gradient elution and UV detection at four different wavelengths, the researchers developed a method to quantify 110 cocaine samples. They also analyzed the adulterants found in cocaine, among which were caffeine and lidocaine (Vinkovic et. al., 2018).

HPLC has also been used to analyze components of soft drinks, namely quinine (Samanidou et al., 2004). Samanidou et. al. used a simple and reverse-phase high performance liquid chromatography to quantify analytical standards of quinine and salicylic acid. This method will be examined in more depth than the other methods discussed later because of its relevance to this thesis.

High Performance Liquid Chromatography

Samanidou et. al. (2004) used the following instrumentation: An SSI 222D pump to pass their mobile phase to a Kromasil, C_{18}, 5μm, 250 x 4 mm^2, MZ analytical column. A Rheodyne 9125 injection valve with a 50 μL loop was used along with an RF-551 Shimadzu fluorescence detector. An HP3396A integrator quantitatively determined the eluted peaks. An Alltech Associates glass vacuum-filtration apparatus was used for the filtration of the buffer solution through Whatman 0.2-μm-membrane filters. Solvents were degassed by helium sparging prior to

use. A Transonic 460/H Ultrasonic bath sonicated the compounds to help with dissolution (Samanidou et. al., 2004).

As far as materials, the quinine that was used for this experiment was acquired from Sigma Aldrich. Methanol, acetonitrile, ammonium acetate, and salicylic acid were all acquired from Merck. Deionised water was used for all dilutions. Soft drinks were purchased that contained quinine: Ivi tonic water (Pepsico-Ivi, Athens, Greece), Britvic Indian tonic and Britvic bitter lemon drink (Britvic Soft Drinks LtD), Tuborg tonic water, Schweppes Indian tonic, Schweppes bitter lemon, and tonic water (DIA) (Samanidou et. al., 2004).

Analytical standards were prepared by the researchers from a stock standard solution of 100 ng/μL. The standards themselves ranged from 0.01-0.7 ng/μL in concentration and were all diluted from the stock solution (Samanidou et. al., 2004).

The seven drinks were analyzed over eight consecutive days. The data showed that HPLC was unaffected by food additives (sugar, glucose, artificial sweeteners, etc…) and that the concentration levels of quinine were able to be quantified. This method allowed for analysis to be completed within five minutes (Samanidou et. al., 2004).

The article by Samanidou et. al. (2004) was examined in depth because our research sought to conduct similar experimentation using the laboratory equipment in Liberty University's Center for Natural Sciences. There are three goals for this project: (1) Research HPLC methods that can detect known concentrations of the cutting agent, (2) identify these cutting agents as compared to the standards made in the laboratory, and (3) determine a method of analysis that can be run successfully in under ten minutes.

Quinine and Salicylic Acid

Quinine is a naturally-occurring alkaloid derived from the bark of the Cinchonca tree that grows in South America. Quinine is a white crystalline solid that is made up of two major fused-ring systems. The following figure shows the chemical structure:

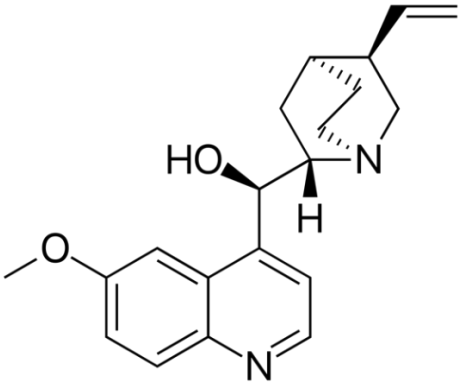


Figure 1. *Chemical structure of quinine*.

Quinine has multiple medicinal properties, among which are painkilling and anti-inflammatory properties. It is also used in bitter tasting drinks like soda and tonics (Dawidowicz et. al., 2018).

Salicylic acid is a naturally-occurring, corrosive compound that is derived from the bark of the white willow and wintergreen leaves. Salicyclic acid has many uses but is most popularly known as an ingredient in facial creams and acne medications due to its antibacterial properties. Salicyclic acid is a white to light tan, odorless solid (National Center, 2021) with a chemical structure that is simple, containing an aromatic ring, an alcohol group, and a carboxylic acid group:

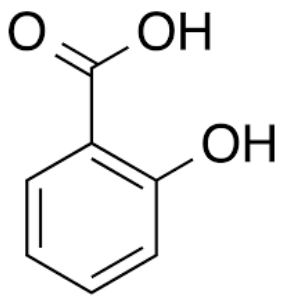


Figure 2. *Chemical structure of salicylic acid.*

Experimental

Instrumentation

Experimentation was carried out using an Agilent 1260 Infinity Quaternary pump, type ID G1311B, serial number DEADO 16907 (Agilent, Santa Clara, California). This pump was used to carry the mobile phase through the analytical column, Bondapak, C_{18}, 1 μm, 3.9 x 150 mm^2, Waters Corporation (Milford, Massachuesetts). Injection was carried out through the built-in injection valve and sample detection was achieved by an Agilent Diode Array Detector, Type ID G1315C, serial number DEAA 203238. Solvents were degassed through the built-in integrated vacuum degassing unit.

Reagents and Materials

The following reagents were used: Quinine (ACROS Organics, 99% anhydrous), salicylic acid (ACROS Organics, 99+%). The mobile phase was comprised of the following reagents: Acetic acid (RICCA Chemical, glacial ACS grade), Methanol (ACROS Organics, 100%), Deionized water, and 10 mM Na_2HPO_4 – 10 mM $Na_2B_4O_4$ (CAD prepared). All water was deionized through a Millipore Sigma Milli-Q® Direct 8 Water Purification System (Darmstadt, Germany).

Standardization

Standardization Definition

Standardization, as defined by the American Chemical Society's Committee on Environmental Improvement, is the process of determining the relationship between a signal and an amount of an analyte present in a sample (ACS Committee, 1980). A standard is divided into two categories: Primary standards and secondary standards. Harvey (2008) provides three requirements a standard must satisfy in order to be primary: It must have a known stoichiometry, have a known purity, and must be stable for long term storage. If a standard fails to meet these criteria, it is a secondary standard, and these are made relative to primary standards. Typically, standards are prepared using a pure compound with a known concentration in a suitable solvent. Oftentimes, multiple concentrations are needed for experimentation. Thus, the original standard is then serially diluted from a stock solution to obtain multiple, desired concentrations of standard. In our research, standards were made from using a stock solution of both quinine and salicylic acid. Both stock solutions were serially diluted with water to obtain 0.1 ppm, 0.3 ppm, 0.5 ppm, and 0.7 ppm of each (8 standards in total).

Preparation of Experimental Standard Solutions

Standards were prepared using a 1 L stock solution of each salicylic acid and quinine (each with a concentration of 100 ppm in DI water). Working standards were prepared using these stock solutions by appropriate dilution to yield an individual standard of each at 0.1 ppm, 0.3 ppm, 0.5 ppm, and 0.7 ppm respectively. An additional standard was made that was 0.3 ppm quinine and 0.3 ppm salicylic acid combined. Each standard was 100 mL and stored in a Pyrex, A grade, 100 ± .08 mL volumetric flask. Standards were stoppered, covered with parafilm, and refrigerated for storage. The following table shows the equation and conversions that were used:

Table 1. *Equations for deriving standard solutions*

$$\frac{\text{ng}}{\mu\text{L}} = 1 \text{ ppm} = \frac{\text{mg}}{\text{L}}$$

$$M_1V_1 = M_2V_2$$

The following table shows the individual calculations for each standard:

Quinine

0.1 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.1 \text{ ppm})(100 \text{ mL})$ | **V_1 = 1 mL**

0.3 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.3 \text{ ppm})(100 \text{ mL})$ | **V_1 = 3 mL**

0.5 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.5 \text{ ppm})(100 \text{ mL})$ | **V_1 = 5 mL**

0.7 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.7 \text{ ppm})(100 \text{ mL})$ | **V_1 = 7 mL**

Salicylic Acid

0.1 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.1 \text{ ppm})(100 \text{ mL})$ | **V_1 = 1 mL**

0.3 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.3 \text{ ppm})(100 \text{ mL})$ | **V_1 = 3 mL**

0.5 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.5 \text{ ppm})(100 \text{ mL})$ | **V_1 = 5 mL**

0.7 ppm standard – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.7 \text{ ppm})(100 \text{ mL})$ | **V_1 = 7 mL**

Quinine and Salicylic Acid

0.3 ppm of quinine – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.3 \text{ ppm})(100 \text{ mL})$ | **V_1 = 3 mL**

0.3 ppm of salicylic acid – $|M_{stock}V_1 = M_2V_2$ | $(10ppm)V_1 = (0.3 \text{ ppm})(100 \text{ mL})$ | **V_1 = 3 mL**

For the combined standard of both quinine and salicylic acid, 0.3 ppm salicylic acid were combined with 0.3 ppm quinine to produce a combined total of 0.6 ppm of solution in DI water. Then, 6 mL of this solution was combined with 94-mL of DI water to produce a stock that was a combined 0.3 ppm of quinine and 0.3 ppm of salicylic acid.

Chromatographic Conditions

The analytical column was a Bondapak, C_{18}, 1 μm, 3.9 x 150 mm^2 column. The mobile phase consisted of acetic acid, methanol, CAD prepared Na_2HPO_4 – $Na_2B_4O_4$, and deionized water. The method was varied in order to find the optimal ratio of the mobile phase for the fastest procedural time.

Results and Discussion

Trial 1

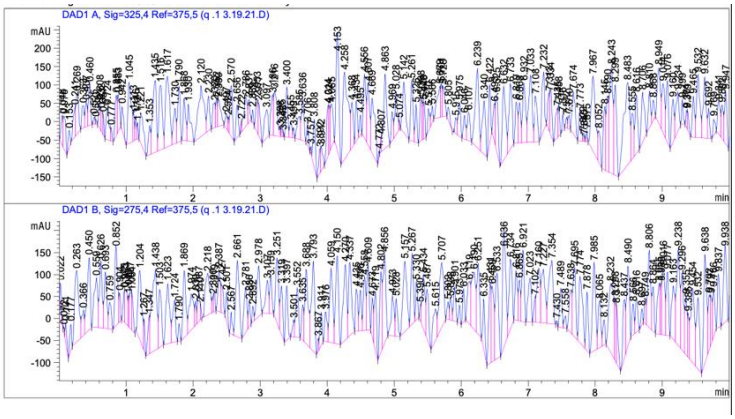
Experimentation

Experimentation was carried out using an Agilent 1260 Infinity Quaternary pump, type ID G1311B, serial number DEADO 16907 (Agilent, Santa Clara, California). This pump was used to carry the mobile phase through the analytical column, Bondapak, C_{18}, 1 μm, 3.9 x 150 mm^2, Waters Corporation (Milford, Massachusetts). Injection was carried out through the built-in injection valve and sample detection was achieved by an Agilent Diode Array Detector, Type ID G1315C, serial number DEAA 203238. Solvents were degassed through the built-in integrated vacuum degassing unit. The method used was 70% DiH_2O (.1% TFA), 20% Methanol (100% BASILE), 9% acetonitrile (.1% TFA), and 1.0% glacial acetic acid (100% RICA), with a run time of 10 minutes per sample. Standard HPLC vials were used and 200 μL samples of the standards were pipetted into the vials using a Poseidon, Genesee Scientific, 20-200 μL transfer

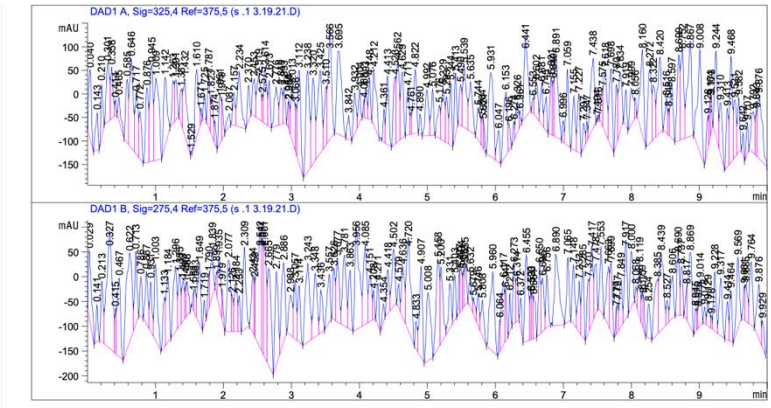
pipette. Nine samples in total were run, which were one of each of the following: 0.1 ppm salicylic acid, 0.3 ppm salicylic acid, 0.5 ppm salicylic acid, 0.7 ppm salicylic acid, 0.1 ppm quinine, 0.3 ppm quinine, 0.5 ppm quinine, 0.7 ppm quinine, and a .03 ppm salicylic acid/quinine mix.

Results

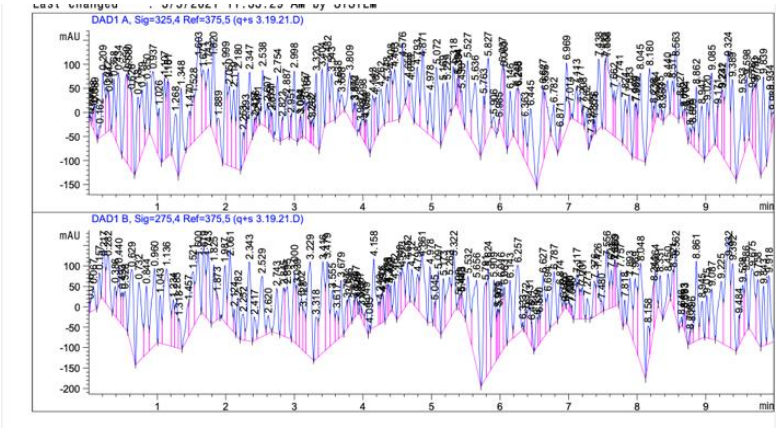
The following figures show the results of the first trial:



(a)



(b)



(c)

Figure 6. *The HPLC results of (a) 0.1 ppm quinine standard (b) 0.1 ppm salicylic acid standard and (c) the combined 0.3 ppm quinine, 0.3 ppm salicylic acid standard.*

Rather than listing all nine trials, three were chosen to represent the overall results due to errors that were made in experimentation. While it is not immediately apparent (unless the reader is familiar with HPLC), the error can be seen when juxtaposed with a traditional HPLC graph:

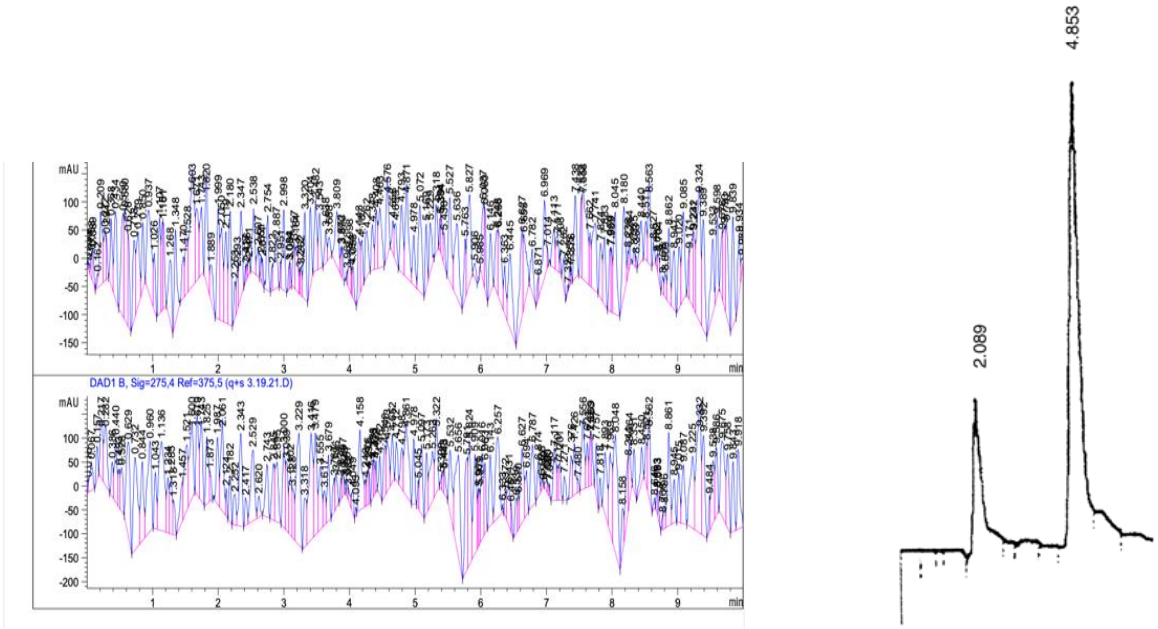


Figure 7. *On left, experimental results are shown and on right, HPLC graph taken from quinine research performed by Samanidou et al. (2004).*

As Figure 7 shows, our results should have resembled the results from Samanidou et al.'s (2004). The error in experimentation may be explained by a few reasons. First, a time limit was set on the control panel to 90 minutes because it was expected for each trial to run a maximum of 10 minutes until finish. However, the trials ran longer than expected. As a result, the machine cut off at 90 minutes and the vial containing 0.5 ppm of quinine was not run by the HPLC. Additionally, because the time limit was only set for 10 minutes, the instrument did not have had enough time to analyze the vials completely. This may account for the lack of signal. Secondly, the acetonitrile in our mobile phase was not marked as HPLC grade. Because of the precision of the HPLC instrument, there may have been impurities within the acetonitrile which produced incoherent spikes on the graphs. Thirdly, the standard solutions may have become contaminated during the transfer (through pipetting) of our standard solutions from the flasks to the HPLC vials. The vials may not have been cleaned properly or the tip that was used for the pipette may not have been contaminated. This would have resulted additional compounds in the solution and as such, the HPLC would have picked these up in addition to the standards. This would have produced additional peaks and interference, resulting in a chromatogram that only showed its signal-to-noise.

Trial 2

Experimental

Like the first trial, experimentation was carried out using an Agilent 1260 Infinity Quaternary pump, type ID G1311B, serial number DEADO 16907 (Agilent, Santa Clara, California). This pump was used to carry the mobile phase through the same analytical column, Bondapak, C_{18}, 1 μm, 3.9 x 150 mm^2, Waters Corporation (Milford, Massachusetts). Injection

was carried out through the built-in injection valve and sample detection was achieved by an Agilent Diode Array Detector, Type ID G1315C, serial number DEAA 203238. Solvents were degassed through the built-in integrated vacuum degassing unit. The same method was used as the previous trial (70% DiH_2O, 0.1% TFA, 20% Methanol, 100% BASILE, 9% acetonitrile, and 1.0% glacial acetic acid, 100% RICA) except this time the acetonitrile that was used was HPLC grade pure acetonitrile supplied by Eastman Kodak Company. The run time was extended in this trial to 15 minutes per sample instead of 10 minutes. The same standard HPLC vials were used and 200 μL samples of the standards were pipetted into the vials using a Poseidon, Genesee Scientific, 20-200 μL transfer pipette. The same nine trials were run.

Results

Despite changing the acetonitrile and adjusting the run time, Trial 2 produced similar results to trial 1. The chromatograms should only sign-to-noise without any direct signals from the cutting agent. When considering potential error, two possibilities were thought of, and then a third realized later. Firstly, the run time again may have been too short. While the overall experiment itself took 125 minutes total to run, 15 minutes for each test still may have not been enough time to produce results. It is possible that given more time the experiment would have produced clearer results.

Secondly, the precision of the diode array detector was not considered. HPLC machines are known for precise analysis, exceptionally more so than something like a simple TLC (thin layer chromatography). One article measured the precision of HPLC and found the repeatability of an HPLC experiment to be within 0.8% for solutions (Ermer et. al., 2005). The precision of

detection for fluorescent detectors/diode array detectors may account for the disruptions in the chromatograms.

The third possibility was discovered soon after the other two. The machine must be flushed with water prior to experimentation to eliminate any bubbles in the analytical column. It was also discovered the bulb in the diode array detector was not functioning, which as such would not allow for detection. All these issues were considered and adjusted for in trial 3.

Trial 3

Experimental

Experimentation in this trial was carried out using an Agilent 1260 Infinity Quaternary pump, type ID G1311B, serial number DEADO 16907 (Agilent, Santa Clara, California) just like before. This pump was used to carry the mobile phase through the analytical column, Bondapak, C_{18}, 1 μm, 3.9 x 150 mm^2, Waters Corporation (Milford, Massachusetts). Injection was carried out through the built-in injection valve, sample detection was achieved by an Agilent Diode Array Detector, Type ID G1315C, serial number DEAA 203238, and the bulb in the detector was replaced. Solvents were degassed through the built-in integrated vacuum degassing unit. The method this time was a simple 60% DiH_2O (.1% TFA) and 40% Methanol (100% BASILE) with a run time of 30 minutes per sample. Standard HPLC vials were used and 200 μL samples of the standards were pipetted into the vials using a Poseidon, Genesee Scientific, 20-200 μL transfer pipette. Two samples in total were run: 0.7 ppm of salicylic acid and 0.7 ppm of quinine, and the analytical column was flushed prior to the trial.

Results

The following figures show the results of trial 3:

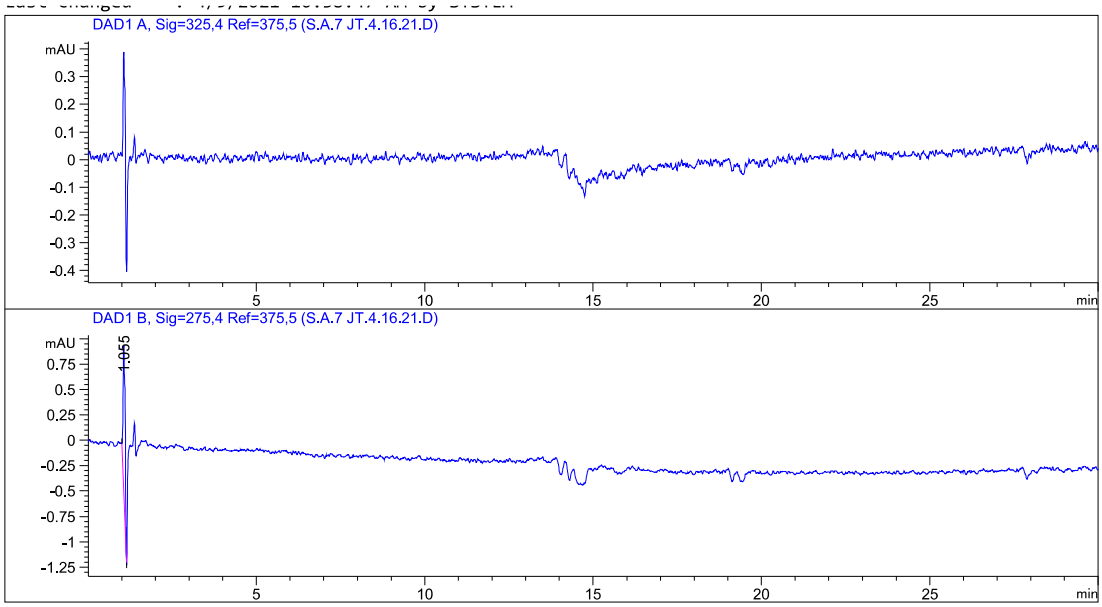


Figure 8. *HPLC graph of 0.7 ppm salicylic acid solution.*

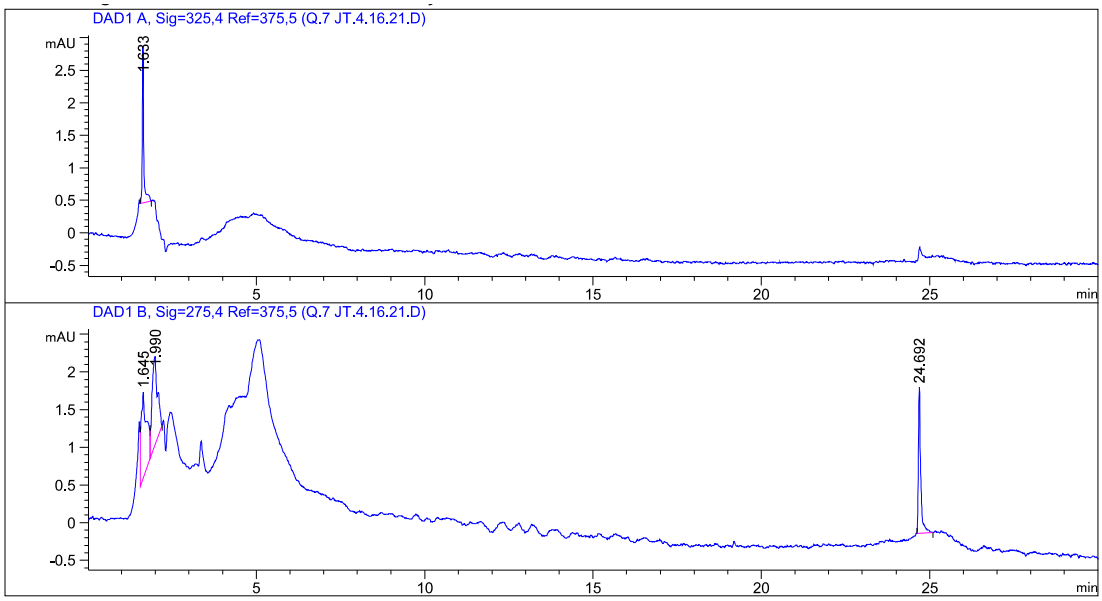


Figure 9. *HPLC graph of 0.7 ppm quinine solution.*

Peaks were achieved in both runs. In figure 8, salicylic acid was detected within 2 minutes and in figure 9, quinine was detected in less than 5 minutes. The peaks are clear, readable, and are similar to the peak from Samanidou's research shown in figure 7.

Conclusion

The goal of experimentation was to establish a method of analysis that could detect cutting agents within 10 minutes. The method used in this final trial (60% water/40% methanol mobile phase) and flushing the analytical column prior to use presented a quick and effective way to analyze known and unknown solutions. While the combined solution of quinine and salicylic acid was not run, the method was successful for these separately. Further research should be performed with the same method to attempt to analyze mixtures of solutions to see if these solutions could be identified from one another. This could be extremely beneficial in profiling illicit drugs and cutting agents, especially because the method was able to be performed in less than 5 minutes.

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