ORGANIC

UNDERGRADUATE EXPERIMENT

Quantification of Pseudoephedrine in OTC Medications

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INTRODUCTION

The use of over the counter (OTC) medications is quite popular for countering cold- or flu-like symptoms. Common active pharmaceutical ingredients (APIs) such as ibuprofen and pseudoephedrine (**Figure 1**) are essential parts of many of these medications. However, the chemical modifications of these APIs can result in a drug with adverse effects. For example, pseudoephedrine, a regularly used decongestant, is a precursor for a more potent drug, methamphetamine (more commonly known as crystal meth).

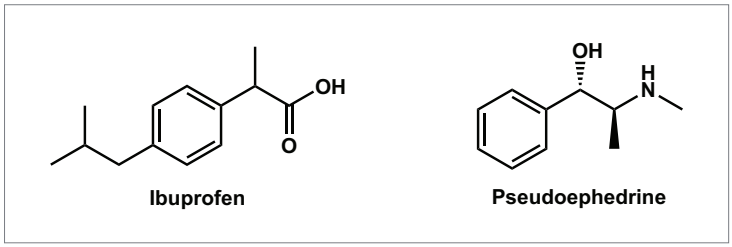

Figure 1. *Chemical structures of ibuprofen and pseudoephedrine.*

Methamphetamine, a common illicit drug, is often sought after due to the feelings of euphoria that it gives its user. As such, the demand for this product has increased over the years. A common method for synthesizing methamphetamine is by using cold medications containing pseudoephedrine. The reasoning behind the use of pseudoephedrine as a precursor is simply because a single transformation is needed to synthesize methamphetamine (*N*-methyl-1-phenylpropan-2-amine). This reduction reaction is shown in **Figure 2**.

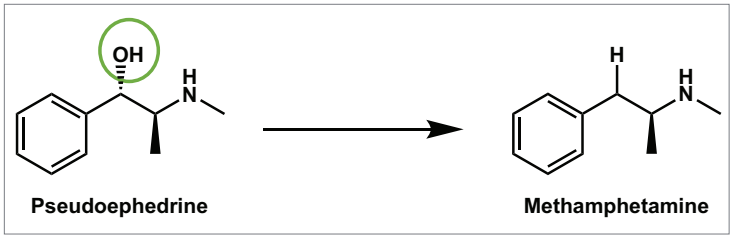

Figure 2. *Chemical conversion of pseudoephedrine to methamphetamine. The green circle represents the hydroxyl group that is being changed.*

With such easy access to these common OTC medications, the quality and control of these pharmaceutical products is important. Owing to this, the analysis of these drugs should be conducted with an analytical technique to ensure specific quantities of these APIs are present in medicines. A large array of analytical methods are available to perform such analyses, with nuclear magnetic resonance (NMR) spectroscopy being one of the more popular options.

NMR spectroscopy is typically introduced to undergraduate students in the organic chemistry curriculum with an emphasis on structural elucidation. Although this approach is great for qualitative analysis, students are not introduced to the quantitative capabilities of NMR, an approach termed quantitative NMR (qNMR). This technique represents a powerful aspect of NMR spectroscopy, especially for pharmaceutical applications. Despite the wealth of information that can be obtained from an NMR spectrum, the analysis of NMR data is often complex, and some valuable information can sometimes be left behind or overlooked. To circumvent this issue, quantitative global spectral deconvolution (qGSD) can be used to extract the information we need. qGSD, a deconvolution tool developed by Mestrelab, is a method that can be implemented to deconvolute the experimental data obtained. This tool allows the user to extract specific signals of interest and plot these signals into a new spectrum; this is done by using a generalized Lorentzian function to model the experimental lineshape.[2] In this sample experiment, the quantification of pseudoephedrine in common OTC medication is conducted using qGSD and qNMR.

Procedure

A medicinal tablet containing pseudoephedrine was dissolved in 3 mL of DMSO-d_6 with 80-90 mg of high purity maleic acid (internal calibrant). The mixture was warmed and sonicated to ensure the formation of a homogenous mixture. An aliquot of the sample was then transferred into an NMR tube and analyzed via ^{1}H NMR spectroscopy using the Nanalysis 60 MHz instrument. The ^{1}H NMR spectra were subsequently collected in triplicates using the following acquisition parameters:

Spectral Width: 40 ppm	Interscan Delay: 30 sec
Spectral Centre: 10 ppm	Number of Points: 16384
Number of Scans: 16	Dummy Scans: 0
Receiver Gain: Auto	Pulse Angle: 90°

The mass of pseudoephedrine was then determined using the qNMR formula described in **Equation 1**. For information on how to analyze spectral data using qGSD, refer to the official Mestrelab website:

https://resources.mestrelab.com/qgsd-quantitative-global-spectral-deconvolution/

Note:
**Depending on the brand of medication obtained, the coating of the capsule may interfere with signals of interest in the NMR spectrum when dissolved. If this is the case, try to remove as much of the fluid from the capsule as possible rather than dissolving the capsule.*

Results and Discussion

^{1}H NMR spectroscopy was used to qualify and quantify pseudoephedrine present in OTC medication. A stacked plot of maleic acid, pseudoephedrine, ibuprofen, and a mixture of OTC medication and maleic acid is presented in **Figure 3**. By comparing the spectra of the pure compounds to the spectrum of the OTC medication, the contents of the mixture can be easily identified. **Figure 3** confirms that ibuprofen and pseudoephedrine are present in the medication, and by using the stacked plot, the representative signals of each component can be identified. Ibuprofen can be easily recognized via the aromatic signal at 7 ppm and the aliphatic signals present between 0.5 – 2.5 ppm. Pseudoephedrine has a characteristic signal at 7.30 ppm that makes it simple to detect in this mixture. Although maleic acid is not present in the medicinal tablet, a small amount was added into the mixture and can be distinguished as a sharp singlet at 6.10 ppm.

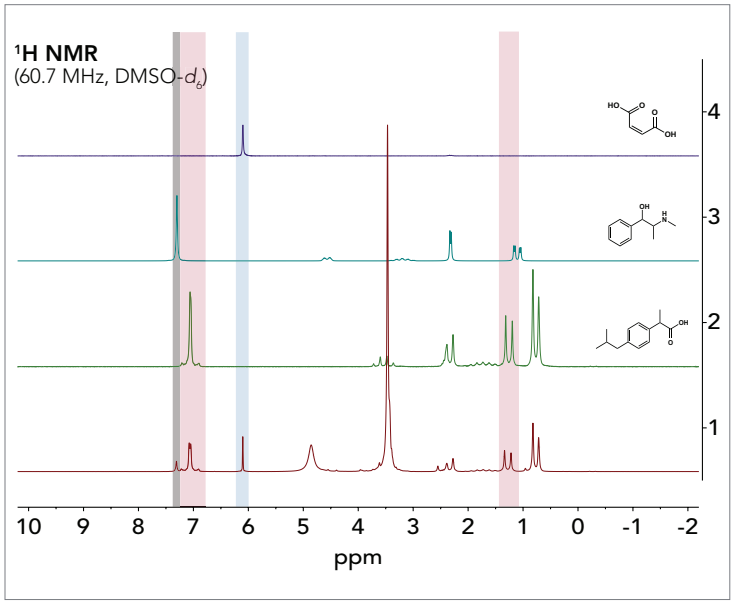

***Figure 3**. Stacked plot of ^{1}H (60.7 MHz) NMR spectra representing OTC medication with added maleic acid internal calibrant (1), ibuprofen (2), pseudoephedrine (3), and maleic acid (4). Spectral data of pseudoephedrine was simulated using the NMR Predict plugin developed by Mestrelab.*

The APIs present in OTC medications can be easily quantified using the equation below:

$$m_{API} = \frac{I_{API} * N_{IC} * M_{API} * m_{IC} * m_T}{I_{IC} * N_{API} * M_{IC} * m_s} \qquad (1)$$

Where *I* represents the integral of the signal of interest, *N* represents the number of protons associated with a signal, *m* represents the mass, *M* represents the molar mass, *API* represent the active pharmaceutical ingredient, *IC* represents the internal calibrant, *T* represents the tablet, and *s* represents the sample, where the sample is an accurately weighed portion of the tablet.

Figure 4 depicts the ^{1}H NMR spectrum of the OTC medication that was purchased at a local pharmacy. The capsule was dissolved in DMSO-d_6 and the internal calibrant, maleic acid, was added before data acquisition. Based on the label of the medication, the capsule should contain 200 mg of ibuprofen and 30 mg pseudoephedrine.

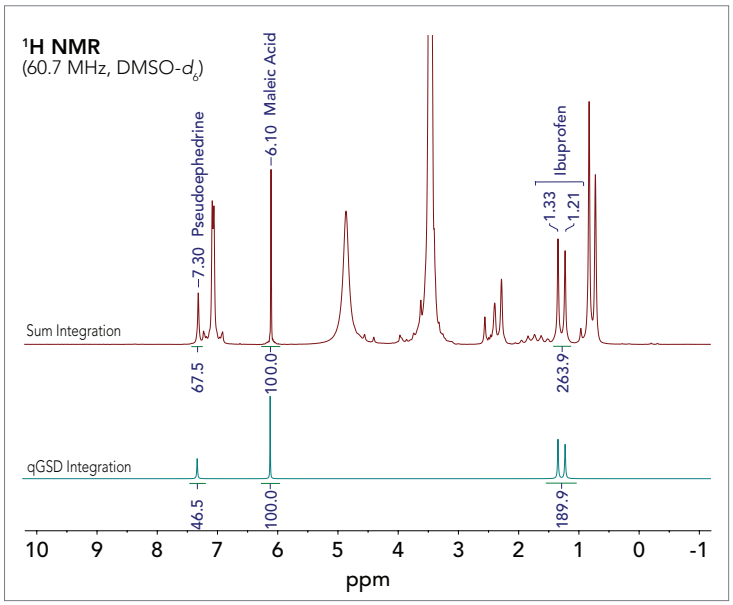

Figure 4. *^{1}H (60.7 MHz) NMR spectrum of an OTC medication and maleic acid dissolved in DMSO-d_6. Signals of interest for ibuprofen, maleic acid, and pseudoephedrine are annotated, peak picked, and integrated using sum integration (bottom) and qGSD (top).*

Table 1 summarizes the results of analysis of pseudoephedrine and ibuprofen with and without the use of qGSD. As shown, the relative amounts of ibuprofen and pseudoephedrine are 198.9 mg and 28.5 mg, respectively, when the deconvoluted data was analyzed. When analyses are conducted without deconvolution, the relative amounts of ibuprofen and pseudoephedrine are 227.6 mg and 33.9 mg, respectively. As evidenced, the use of qGSD analysis allowed for the extraction of more accurate and precise values when compared with the more convoluted data analysis and the use of sum integration. Sum integration is expected to yield overestimated values due to overlapping signals of both pseudoephedrine and ibuprofen as shown in Figure 3.

Table 1. *Comparison between masses obtained via ^{1}H NMR spectroscopy using qGSD analysis, without qGSD analysis (sum integration), and those listed on the manufacturer's label.*

	Maleic Acid (mg)	Ibuprofen (mg)	Pseudoephedrine (mg)
Capsule NMR (qGSD)	**88.08**	**198.9 (1.1)**	**28.5 (1.1)**
Capsule NMR (sum integration)	**88.08**	**227.6 (1.2)**	**33.9 (2.9)**
Capsule Label	**-**	**200**	**30**

**Relative standard deviation (RSD) values shown in parentheses*

Conclusion

In this experiment, the amounts of ibuprofen and pseudoephedrine in common OTC cold medication were determined using the Nanalysis 60 MHz instrument. The values obtained correlated well with the pharmaceutical labels when qGSD was used during processing. The experiment is simple to perform in undergraduate laboratories and highlights the use of NMR spectroscopy as both a qualitative and quantitative analytical technique.

References

[1] Blough, E.R.; Wu, M. *Front. Pharmacol* **2011**, *2*, 72.
[2] Mestrelab. qGSD – quantitative Global Spectral Deconvolution. *https://resources.mestrelab.com/qgsd-quantitative-global-spectral-deconvolution/*

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