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Laboratory Experiment

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# Purity Analysis of the Pharmaceuticals Naproxen and Propranolol: A Guided-Inquiry Laboratory Experiment in the Analytical Chemistry Laboratory

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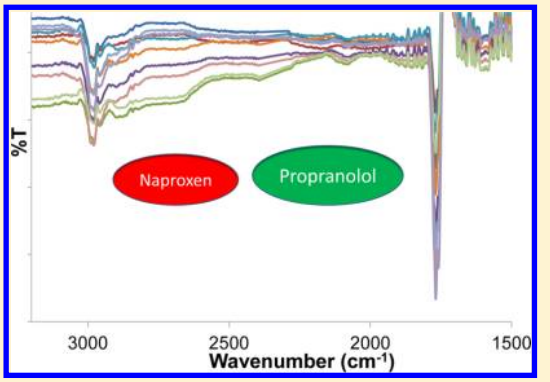
Supporting Information

**ABSTRACT:** Counterfeiting and adulteration of prescription drugs, herbal products, and food supplements are a global challenge, causing serious economic loss to drug marketers and health implications for humans. Accordingly, accurate determination of the purity of pharmaceuticals is critical for the quality assurance of prescription drugs. Herein, the first purity analysis of pharmaceuticals naproxen and propranolol in a guided-inquiry laboratory experiment (GILE) setting as part of an undergraduate instrumental analysis laboratory course is reported. The students were able to independently design analytical procedures to determine the purity and percentage composition of suspected adulterated naproxen samples with minimal supervision of the instructor. The results of the determined percentage compositions of naproxen by the students favorably compared with the known compositions of naproxen in their GILE samples provided by the instructor, with a root-mean-square percent relative error of 3.24%. The majority of the students were excited, motivated, and preferred the GILE to traditional laboratory experiments, in which students simply follow the lab manual. In addition, this GILE promoted the spirit of teamwork and challenged the students' critical thinking and problem-solving skills ability. The GILE also provided an opportunity for students to better understand the concepts and the practical utility of multiple analytical techniques for solving real-world problems and to experience typical challenges often encountered in the laboratory during chemical analysis and to determine strategies for resolving those challenges.




**KEYWORDS:** *Spectroscopy, Upper-Division Undergraduate, Analytical Chemistry, Hands-On Learning/Manipulatives, Inquiry-Based/Discovery Learning, Problem Solving/Decision Making, Applications of Chemistry, Drugs/Pharmaceuticals, Gas Chromatography*

## INTRODUCTION

Considerable efforts have been devoted to the development of pedagogical strategies to stimulate students' interest and to promote student learning in science, technology, engineering, and mathematics (STEM) in recent years. For instance, process-oriented guided-inquiry learning (POGIL) and guided inquiry laboratory experiments (GILEs) have been developed and strategically utilized in various laboratory curricular to promote student learning.[1−29] The distinct advantages of GILEs, including improved students' critical thinking and problem solving capability over traditional laboratory experiments where students simply follow a lab manual, have been widely reported.[1−29] In addition to the technical skills, GILEs are also known to promote the spirit of team-work and improve communication and leadership skills. These are essential skills that the students should possess in order to succeed in their future career endeavors.

Herein, the first purity analysis of pharmaceuticals naproxen and propranolol in a GILE setting in an undergraduate instrumental analysis laboratory course is reported. Naproxen chloride ((*S*)-2-(6-methoxy-2-naphthyl)propionyl chloride) is an anti-inflammatory and a pain killer, often prescribed for the treatment of arthritis, gout, and menstrual pain. However, propranolol hydrogen chloride ((*S*)-1-isopropylamino-3-(1-naphthyloxy)-2-propanol hydrogen chloride) is a beta-blocker, commonly used for the treatment of hypertension and panic attacks. Accurate determination of the purity of pharmaceuticals is critical in the pharmaceutical industry for the quality control and quality assurance of prescription drugs. The degree of global drug counterfeiting and adulteration of the prescription drugs, herbal products, and food supplements are problematic and alarming, with serious economic loss to pharmaceutical companies and drug marketers.[30−33] Approximately 10% of prescription drugs have been reported to be counterfeited or adulterated.[34,35] The adulteration of the prescription drugs often result in a reduced drug efficacy with serious adverse health





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implications for humans.[36−38] Consequently, regulatory agencies, including the United States Foods and Drug Administration and the World Health Organization, have been proactive in the monitoring of the quality of pharmaceutical drugs to abate prescription drug counterfeiting.[39] Hence, analytical techniques such as high performance liquid chromatography, nuclear magnetic resonance, Raman, and infrared spectroscopy, electroanalytical techniques, and other methods have been strategically developed over the years for purity analysis and quality assurance of pharmaceuticals drugs and herbal products.[40−48] The GILE project was designed to allow students to utilize multiple analytical instruments and analytical techniques for their GILE with a minimum supervision by the instructor. The students were also allowed to work in groups to promote the spirit of teamwork.

## EXPERIMENT OVERVIEW

The total number of the students enrolled in this instrumental laboratory course is 13, of which 62% of the students are females and 38% are males. The majority of the students in the course plan to further their education in pharmacy or medical school. Others are interested in pursuing graduate study in chemistry. Consequently, a GILE that will expose the students to the real world analysis of pharmaceuticals using multiple analytical techniques was designed for the students. Suspected adulterated naproxen chloride samples, possibly with propranolol hydrogen chloride, were provided to the students on the first meeting day of the laboratory.

This GILE exercise was a semester-long project. However, the actual laboratory chemical analysis required only three to four scheduled laboratory meeting periods. The GILE project was assigned to the students at the beginning of the semester to allow the students to have enough time to discuss and conduct the library search and literature review related to their GILE project. This also allowed the student to fully master the concept and the use of the analytical instrument they would likely use for the GILE project. In addition, samples of published articles GILE describing the concepts and advantages of GILE over the traditional cook-book laboratory were also provided for the students to review.

The students were divided into groups (average of three students in a group) by the instructor to promote teamwork. Each group was advised to select a group leader to oversee the group's GILE exercise. Each group was required to design an effective method incorporating one or more suitable analytical techniques to evaluate whether the provided naproxen chloride samples were actually adulterated with propranolol hydrogen chloride. The students were also requested to design analytical protocol(s) to evaluate the purity and percent composition of naproxen chloride in each sample. Chosen analytical methods must, however, be justified and approved by the instructor before the commencement of the lab work. The students were expected to write a full ACS journal style article report of the GILE at proficiency or competency levels. The students were also requested to give a 30 min power point presentation of the results of their GILE work. Students were mandated to strictly observe all laboratory safety protocols and ethics during the laboratory analysis.

A list of available analytical instrumentation (FTIR, UV−visible, GC, GC−MS, and HPLC) that the students could choose from for the GILE purity drug analysis was provided. An average of three adulterated samples of varying naproxen chloride composition (prepared by the instructor) was provided for each group as the unknown GILE samples. The composition of naproxen chloride of the adulterated samples ranged from 93.0 to 99.54%. However, the percent composition of propranolol hydrogen chloride in the samples ranged between 0.46 and 6.7%. Pure naproxen chloride and propranolol hydrogen chloride were also provided for the students to use as standards and reference materials. A list of available materials and reagents including, spectroscopic grade methanol, ethyl acetate, acetone, ethanol, HPLC water, 1 cm path length quartz cells, Eppendorf pipettes and the tips, volumetric flasks, analytical balances, sample vials, weighing bottles, and so forth was provided to the students.

The students' initial responsibility during their group discussions was to obtain and examine the chemical structures of naproxen chloride and propranolol hydrogen chloride (Figure 1), which they can readily obtain from the Sigma-Aldrich Web

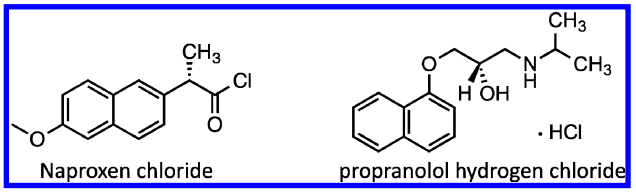


**Figure 1.** Chemical structure of pharmaceuticals: naproxen chloride and propranolol hydrogen chloride.

site. Most groups explored the possible use of Fourier transform infrared (FTIR) spectroscopy for qualitative drug sample analysis. Naproxen chloride has a carbonyl (C═O) group that should show the typical IR absorption at ∼1750 $cm^{-1}$. On the contrary, propranolol hydrogen chloride contains hydroxyl (OH) and amine (NH) group that will show broad FTIR absorption between 3300 and 2900 $cm^{-1}$. Because naproxen chloride has no OH or NH group, the absorption of these peaks were not expected in pure naproxen chloride. Therefore, IR absorption of OH and NH peaks in the drug sample may be indicative of naproxen chloride adulteration by propranolol hydrogen chloride.

Groups examined the use of UV−visible absorption spectroscopy for the analysis. UV−visible absorption spectra of pure naproxen chloride and propranolol hydrogen chloride standards were compared to those of drug samples. Students also deliberated on the possible utility of HPLC and GC−MS for their sample analysis. If the suspected drug samples were pure, the GC or HPLC chromatographic separation of the sample would only show one peak. The presence of the propranolol hydrogen chloride can be further confirmed using mass spectrometry analysis of the GC chromatographic peaks.

### Sample Preparation and Instrumental Analysis

The initial stock solutions ($1 \times 10^{-3}$ M) of naproxen chloride and propranolol hydrogen chloride standard were made by the students in spectroscopic grade mixed solvent consisting of 80% ethyl acetate and 20% methanol. Working range standard solutions ($1 \times 10^{-5}$ to $2 \times 10^{-4}$ M) used to construct the calibration curves for naproxen chloride and propranolol hydrogen chloride were subsequently made by serial dilution of the stock solutions. A known mass of the sample was dissolved in a mixed solvent consisting of 80% ethyl acetate and 20% methanol.

The FTIR spectral measurements were recorded in reflection mode using a FTIR spectrometer (Shimadzu 8400S). The spectrometer was equipped with a MiRacle ZnSe 3B crystal plate attenuated total reflectance device mounted on a Shimadzu platform. The MiRacle ZnSe 3B crystal plate permits the rapid


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and accurate measurement of solid samples with high sensitivity. The FTIR spectrum of each sample was scanned 50 times with a resolution of 4 $cm^{-1}$ over a 400 to 4000 $cm^{-1}$ wavenumber range. The FTIR spectrometer was always calibrated with a polystyrene standard before each use to ensure wavelength accuracy. The UV−visible spectra of the samples were scanned and recorded using a double beam UV−visible spectrometer (UV-2401PC, Shimadzu). Routine spectrometer checks and calibrations were performed before spectral measurements.

A 1 $\mu$L aliquot of the standard or sample solution was directly injected and separated using a GC instrument equipped with a mass-spectrometer detector (GCMS-QP5000, Shimadzu) . Both the standard and sample solutions were filtered before being subjected to GC−MS or HPLC analysis. The GC separation was performed on a Rtx-XLB column (inner diameter, 0.25 mm; film thickness, 0.25 $\mu$m; length, 30 m). The GC separation was performed using a column temperature gradient program, with an initial temperature of 160 °C, held for 2 min at 160 °C, and then increased at the rate of 20 °C/min to 300 °C. The temperature was then held for 1 min at 300 °C with total run time of 10 min. Helium (He) gas was used as the mobile phase, with a column injection pressure of 90.4 kPa, a total flow of 15.5 mL/min, column flow of 0.9 mL/min, linear velocity of 35.2 cm/s, and a split ratio of 15.1. The GC−MS interface temperature was set at 300 °C. The mass spectrometer detector was operated in a scan acquisition mode, scanning from 40 to 400 $m/z$. Each analyte peak in the sample GC chromatogram was identified and confirmed using the mass spectrometer. The HPLC separation was performed on a LC-2010C HT (Shimadzu) instrument using a UV−visible detector (254 nm) equipped with autosampler. The separation was performed on a C18 5 $\mu$m (100 × 2.1 mm) column in isocratic mode using a mixed solvent containing 10% methanol and 90% acetonitrile.

## HAZARDS

It was mandatory for all the students to wear the approved laboratory safety goggles and gloves in the laboratory. Flammable organic solvents were handled in the hood. Students were told to take precaution not to touch the GC−MS sample injection port because of the high injection port temperature.

## RESULTS AND DISCUSSION

The FTIR and UV−visible spectrometers, as well as GC−MS and HPLC instruments, required for the project were housed in the same laboratory, allowing different groups to work on their projects simultaneously in the same laboratory. For example, one group might be working using the FTIR instrument while the other is working on UV−visible spectrometer. The groups can later switch instruments. This working strategy allowed the instructor to attend to the needs of each group. A challenge students' encountered in the GILE was the selection of the appropriate solvent for sample preparation. Propranolol hydrogen chloride dissolves very well in methanol. However, naproxen chloride has poor solubility in methanol but dissolves in ethyl acetate. Consequently, the students had to determine the appropriate solvent mix (80% ethyl acetate + 20% methanol) to dissolve their drug samples. Other issues the students encountered include determining the appropriate analyte concentration range for HPLC and GC−MS analysis. This problem was resolved by initial preparation of 1 × $10^{-3}$ M naproxen chloride and 1 × $10^{-3}$ M propranolol hydrogen chloride stock solutions, followed by serial dilution of the stock solution by the students. The absorbance of the diluted solutions were recorded and monitored by the students using a UV−visible spectrometer until the absorbance of the solutions fell between 0.1 and 1.0. Another challenge the students' encountered involved determination of the sample size to be injected into the GC−MS. Initial sample injections were too large, leading to peak broadening.

Figure 2A shows the FTIR spectra of the pure naproxen chloride and propranolol hydrogen chloride standards. These

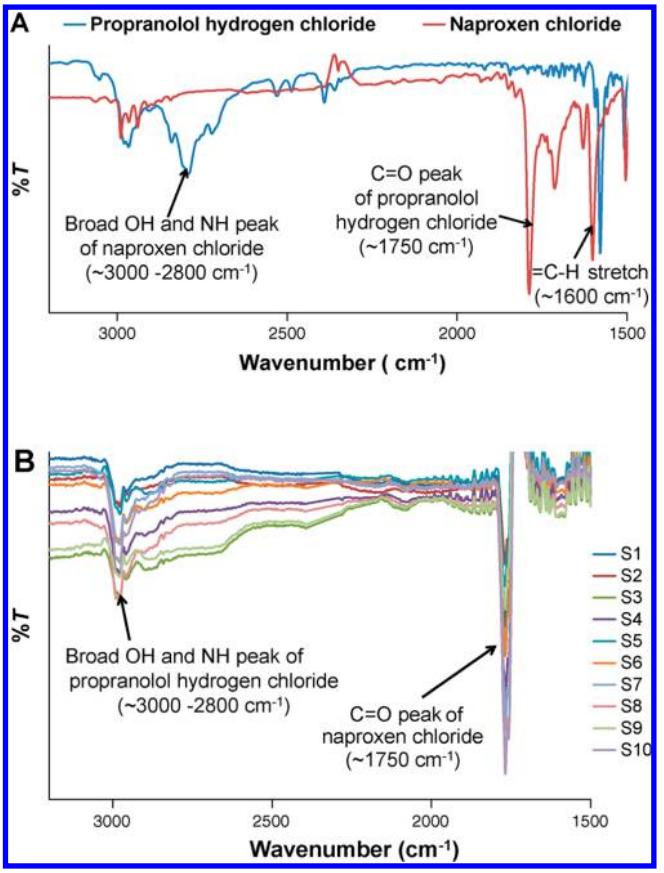


**Figure 2.** (A) FTIR spectra of pure naproxen chloride and propranolol hydrogen chloride standards. (B) FTIR spectra of adulterated drug samples of varying naproxen chloride and propranolol hydrogen chloride composition (S1 through S10 correspond to entries in Table 1).

spectra show the characteristic sharp, intense C═O peak at ~1750 $cm^{-1}$ from naproxen chloride. The observed small broad absorption between 3000 and 2900 $cm^{-1}$ (which was not observed in pure naproxen chloride standard) was due to the OH or NH absorption from propranolol hydrogen chloride. The FTIR spectra of the adulterated GILE drug samples obtained by the groups is presented in Figure 2B. The UV−visible absorption spectra of naproxen chloride and propranolol hydrogen chloride standards are shown in Figure 3A. Naproxen chloride and propranolol hydrogen chloride are polycyclic aromatic compounds with two fused benzene rings so both contain highly conjugated $\pi$ systems. Consequently, absorption due to the $\pi \rightarrow \pi^*$ transition in the conjugated $\pi$ system are expected in the UV−visible spectra of the drug samples. The $n \rightarrow \pi^*$ transitions of lone pair electrons of the C═O in naproxen chloride and NH and OH groups from propranolol hydrogen chloride give rise to absorptions at relatively longer wavelengths in the UV−visible


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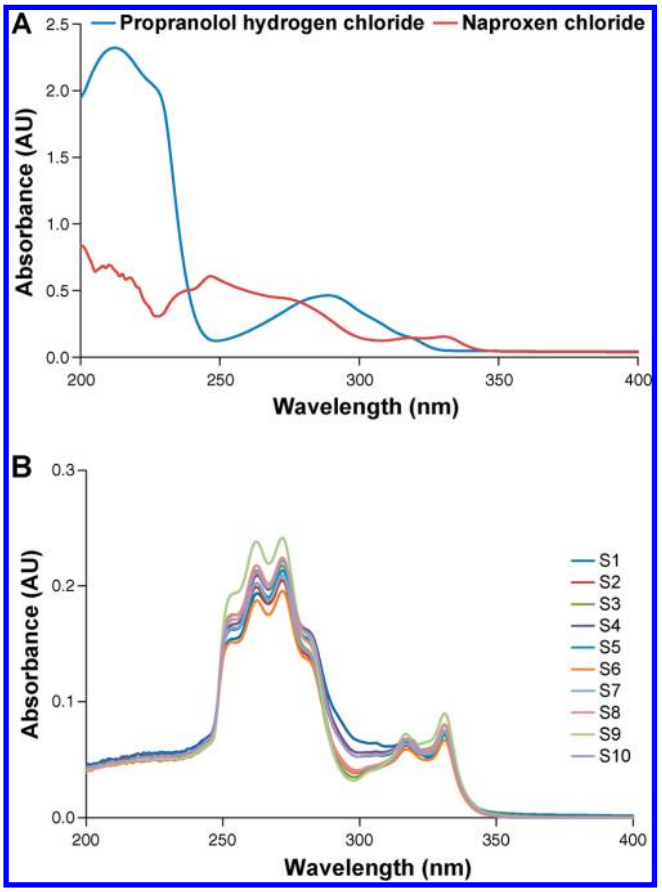


**Figure 3.** (A) UV−visible absorption spectra of the pure naproxen chloride and propranolol hydrogen standards. (B) UV−visible absorption spectra of the adulterated drug samples of varying naproxen chloride and propranolol hydrogen chloride (S1 through S10 correspond to entries in Table 1).

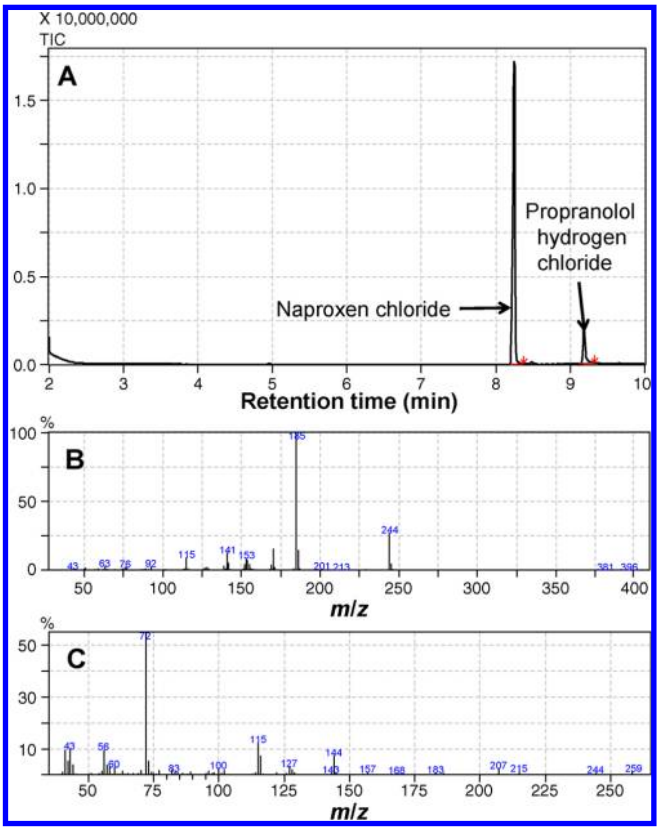


**Figure 4.** Typical GC−MS separation of a selected drug sample. (A) GC chromatogram separation of a selected sample. (B) Mass spectra of naproxen chloride. (C) Mass spectra of propranolol hydrogen chloride using electron impact ionization method.

spectra. The UV−visible absorption spectra of drug samples obtained by the students are shown in Figure 3b. Overlap of the UV−visible absorption spectra of naproxen chloride and propranolol hydrogen chloride in Figure 3a prevents the use of UV−visible spectroscopy for quantitative determination of naproxen chloride composition of the samples without tedious spectral deconvolution.

The students performed the HPLC separations of the compounds; however, GC−MS was utilized for quantitative analysis. Accordingly, GC−MS was utilized for the quantitative analysis of the percentage naproxen chloride in the drug samples.

Figure 4A is a typical GC chromatogram of the separation of a drug sample obtained by one of the groups. The students were able to accurately identify and confirm the peaks in the chromatogram using a mass spectrometry and spectral database searching. The mass spectra of naproxen chloride and propranolol hydrogen chloride obtained from the GC separation are shown in Figure 4B and C, respectively. The retention times of naproxen chloride and propranolol hydrogen chloride were 8.23 and 9.25 min, respectively. The most significant $m/z$ peaks in the mass spectra were the base peak ($m/z$, 185), observed in naproxen chloride due to $[\text{M-COCl}]^+$, whereas the base peak ($m/z$, 72) in propranolol hydrogen chloride was due to the $[CH_2NHCH(CH_3)_2]^+$ ion.

The percent composition of naproxen in drug samples was calculated from the ratio of the naproxen chloride GC chromatogram peak area to the total GC chromatogram peak area of naproxen chloride and proporanolol multiplied by 100 using eq 1

$$\%\ \text{naproxen in each drug sample} = \frac{\text{naproxen peak area}}{(\text{naproxen peak area} + \text{propranolol peak area})} \times 100 \quad (1)$$

However, the percent composition of the naproxen in the drug samples can also be calculated using an internal standard analysis protocol if there is no time constraint. Table 1 compares the students results from the GC analysis to the actual percentage of

**Table 1. Results of Actual and Determined Percentage Composition of Naproxen in Drug Samples**

| Sample | Actual % Naproxen Chloride | Determined % Naproxen Chloride | Absolute Error | % Relative Error[a] |
|---|---|---|---|---|
| S1 | 96.46 | 98.93 | −2.47 | −2.56 |
| S2 | 99.51 | 100.00 | −0.49 | −0.49 |
| S3 | 93.30 | 98.96 | −5.66 | −6.07 |
| S4 | 99.54 | 98.79 | 0.75 | 0.75 |
| S5 | 92.35 | 98.87 | −6.52 | −7.06 |
| S6 | 98.82 | 100.00 | −1.18 | −1.19 |
| S7 | 97.54 | 98.80 | −1.26 | −1.29 |
| S8 | 96.23 | 95.84 | 0.39 | 0.41 |
| S9 | 96.30 | 98.94 | −2.64 | −2.74 |
| S10 | 98.90 | 98.80 | 0.10 | 0.10 |

[a]The root-mean-square percentage of relative error was 3.24%


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naproxen chloride in the drug samples. The root-mean-square percent relative error (RMS%RE) was utilized to evaluate the accuracy of the students analysis of percent composition of naproxen is given by eq 2

$$\text{RMS\%RE} = \sqrt{\frac{\sum (\%\text{RE}_i)^2}{n}} \quad (2)$$

where $\%\text{RE}_i$ is the percent relative error determined from the actual and determined percent composition of naproxen values for the $i$th sample, and $n$ is the number of total GILE samples. The overall RMS%RE of the analysis was 3.24%. Obviously, the determined percent compositions of naproxen chloride in the samples were very close to the actual naproxen chloride in the unknown GILE sample, as demonstrated by the low absolute errors and percent relative errors. The observed small RMS%RE of drug analysis may be due to the unavoidable error during the sample preparation or chromatographic sample injection. Overall, the results of the analysis demonstrated that students were proficient in sample preparation and in the use of the GC for the purity analysis of naproxen chloride compositions in pharmaceutical samples.

### Evaluation of the Student Experience in GILE

Student rating of laboratory instruction as well as personal pre- and post-experiment discussions with students were utilized to evaluate the students' experience in this GILE. To further assess the student experience, a set of voluntary and anonymous survey questionnaires was administered to the students at the end of the semester. The result of the survey analysis revealed that all of the students (100%) found the GILE beneficial to their future professional development. Approximately 70% of the students also preferred the GILE format to a traditional lab format where they follow lab manual procedures. It is of considerable interest to note that an overwhelming number of the student (92%) also expressed an interest in participating in future GILEs in other laboratory courses. Most importantly, a majority of the students found the GILE very interesting and felt it promoted their critical thinking and problem solving abilities. Also, the students found GILE useful in enhancing their spirit of team-work. Some of the direct comments of students' experience in the GILE are provided below:

*This GI lab experiment was very informational. I enjoy every part of it. I feel more comfortable with performing different instruments.*

*I really enjoyed this experiment. Overall, it enhanced my ability to work well with others on a group project. In addition, it allowed me to work somewhat independently and use problem solving and collaboration to complete the analysis. Great experience.*

*I enjoyed this lab because it was a practical point of view, plus I got to enjoy getting to know my group better outside of lab.*

## CONCLUSION

A purity analysis of pharmaceuticals naproxen and propranolol in a GILE setting to promote students' learning and students' problem solving ability in an Instrumental Analysis Laboratory curriculum was reported. The students were able to independently design analytical protocols for accurate determination of the purity and percent composition of naproxen, with RMS%RE of less than 4%. The majority of the students were excited and motivated by their GILE experiment. The majority of the students also preferred the GILE to traditional laboratory experiments and expressed interest to participate in GILEs in future courses. This GILE provided the opportunity for students to better understand the concept and the practical utility of multiple analytical techniques for solving real world problems of pharmaceutical interest. The GILE also provided the opportunity for students to experience common challenges often encountered in the laboratory during chemical analysis and to determine strategies for resolving those challenges. In addition to the technical skills, critical thinking, and problem solving skills, this GILE also promoted the spirit of team-work and the students' leadership skills in the laboratory.

## ASSOCIATED CONTENT

### Supporting Information

The text describing instructions to the students and instructors, hazards, required analytical instrument and equipment, chemical required, safety, preparation of the unknown samples and reference standard, the group size, and the time requirement for this GILE project. This material is available via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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