Complexometric Titration of Bismuth in Over-the-Counter Stomach Relief Products

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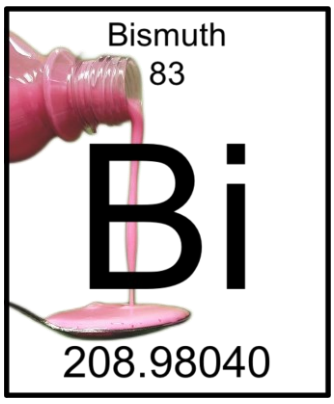
ABSTRACT: Three direct complexometric titration methods for bismuth subsalicylate determination in over-the-counter stomach relief caplets and liquids are presented, as well as a UV-Vis assay, for use in student laboratories. The main difference between titration methods is the choice of indicator; either xylenol orange (XO), pyrocatechol violet (PV), or potassium iodide (KI) is used. These methods are simple and safe, making this experiment desirable in a general chemistry or analytical laboratory to relate real-world sample analysis to theoretical titrimetric concepts. Learning outcomes, student feedback, and student data from Wichita State University (WSU) Chemistry II Honors lab, Bethel College Introduction to Chemistry lab, and University of Missouri (Mizzou) Quantitative Analysis lab are presented. The majority of students enjoyed this real-world sample analysis; however, titration results are more precise for more advanced students. The titration with EDTA using XO as indicator is the method of choice for caplet analysis by the authors, but methods utilizing PV or KI as indicator are also acceptable, albeit the KI method may generate large amounts of iodide waste depending on class size. All titration methods presented are selective at low pH (~1.5–1.6) and do not suffer interferences from commonly occurring ions such as magnesium and calcium. Using the titrimetric procedures presented in this work, all tested caplet and liquid brands appear to meet United States Pharmacopeia (USP) standards, where the allowable range of active ingredient is within 90–110% of label value.



KEYWORDS: High School/Introductory Chemistry, First-Year Undergraduate/General, Second-Year Undergraduate, Upper-Division Undergraduate, Quantitative Analysis, Titration/Volumetric Analysis, EDTA, Drugs/Pharmaceuticals, Consumer Chemistry

INTRODUCTION:

Titrations in high school and undergraduate chemistry laboratories remain ubiquitous, and the implementation of real-world sample analysis is desirable to help link theoretical concepts to the everyday experiences of students. Several applications of complexometric titrations to real-world samples have been published in this *Journal*. These include calcium and magnesium in milk[1], zinc in Cold-Eeze™ cold lozenges[2], EDTA content of consumer shower cleaner[3], aluminum and magnesium in commercial antacids[4], sulfate in water[5], mercury in water leached from improperly discarded batteries[6], copper and zinc in brass[7], calcium and magnesium in intravenous fluid bags[8], aluminum in various brands of deodorant[9], and zinc in pharmaceutical preparations.[10] Stomach relief caplets containing bismuth subsalicylate as the active ingredient are a great candidate for complexometric titration, yet a general lack of literature on the topic exists. While gravimetric[11] and electrochemical[12] determination of bismuth subsalicylate in stomach relief caplets and liquids have been reported in the chemical education literature, experiments incorporating volumetric techniques have not been published.

For this reason, the development and implementation of a simple and safe instructional laboratory experiment for the complexometric determination of bismuth in various brands of stomach relief caplets and liquids serves as a meaningful addition to the titrimetric education literature. Several methods for titrimetric bismuth determination appear in the older literature[13-17], and three of these methods were tested to determine their applicability to a range of over-the-counter stomach relief products. Two reports[14,15] recommend the use of pyrocatechol violet as the metal ion indicator, while others utilize xylenol orange[13], or potassium iodide (BiI_4^- has an intense yellow color) as indicators.[16] Upon titration with EDTA, the BiI_4^- complex is decomposed and the yellow color is lost. A method by Fritz[17], in which 0.6 grams of thiourea was used for each titration, was ruled out for application in the student chemistry laboratory due to the suspected carcinogenic nature of thiourea and anticipated large volume of thiourea-containing waste. Similar to the titration with KI as indicator, bismuth forms a yellow complex with thiourea that is subsequently lost when bismuth is chelated by EDTA. Herein, we report the practicality and limitations of three direct complexometric titration methods for the determination of bismuth in five caplet brands (Pepto-Bismol, Kroger, Equate, Kaopectate, and Soothe) and three liquid brands (Pepto-Bismol, Kroger, and Equate) of over-the-counter stomach relief products. Additionally, student titration results from Wichita State University (WSU) Chemistry II Honors lab, Bethel College Introductory Chemistry lab, and University of Missouri (Mizzou) Quantitative Analysis lab are presented, demonstrating the experiment's versatility for different student populations. To incorporate instrumentation, we have also adapted a previously reported colorimetric UV-Vis assay for bismuth in liquid stomach

relief[13] and include it here as an option for courses that may desire an experiment that compares accuracy/precision of different analytical techniques.

Student learning outcomes for the WSU Chemistry II Honors lab were gauged by a pre-lab assessment and post-lab assessment. These assessments quizzed students on proper burette readings, reporting standard deviation correctly, endpoint vs. equivalence point, identifying cations and anions, the concept of Lewis acids and bases, the chemical nature of chelating agents, and percent label values and USP standards. Introductory Chemistry students at Bethel were assessed on all of the same outcomes with the exception of Lewis acids and bases, and standard deviation, because these topics are not taught within the course.

EXPERIMENTAL PROCEDURE:[†]

† For information on chemicals and solution preparation details, see Supporting Information, pages S3-S5

Titration Using Metal Ion Indicator

Analysis of caplets: The mass of the caplet is recorded before crushing it using a mortar and pestle. A portion of the resulting powder (~0.15 g) is weighed on weighing paper and added into a 250 mL Erlenmeyer flask and 10.0 mL of 0.5 M nitric acid is added. Mild effervescence can occur at this point due to the presence of calcium carbonate. The mixture is swirled and diluted with 40 mL of deionized water and then gently boiled for 15 minutes. During this step, yellow coloration can develop from NO_2 (*g*) production. When this occurs, the heat is reduced for the duration of the digestion. Note that if PV is used for indicator, it is necessary to stop boiling *immediately* upon seeing yellow coloration and carry forward with the procedure. After boiling, the volume of the sample is increased to approximately 100 mL with the addition of 60 mL of deionized water, resulting in a mixture with a pH of ~1.5–1.6. If analyzing Pepto-Bismol or Soothe powder, the boiling step is unnecessary; after adding the 10.0 mL of nitric acid, simply dilute the mixture with an additional 90 mL of water. Three to five drops of PV or XO are then added, and the mixture is titrated with standardized 0.01 M EDTA from a 50 mL glass burette to the endpoint. Color changes that indicate the endpoint must be held for at least 5 minutes (blue to yellow for PV and red to yellow for XO). See Figures S1 and S2 in supporting information for a photo gallery of the color transitions and proper endpoint color identification for the caplets.

Analysis of liquid medicine: First shake the bottle to mix the contents, and, using a plastic disposable pipet, carefully add approximately 2.5 grams of liquid to a tared Erlenmeyer flask on an electronic balance. A procedure for density determination of stomach relief liquid is provided in the Supporting Information (page S5), so that volumetric transfers can also be used. Alternatively, a standard density of 1.02 g/mL is recommended.[13] Next, 10.0 mL of 0.5 M nitric acid is added and the flask must be immediately swirled to break up the pink liquid and help bring it into solution. After about 10-15 minutes, 90 mL of deionized water is added to the flask. For some liquid brands, noticeable "stringy goop" may be left undissolved, which could be xanthan gum. This undissolved substance does not appear to interfere with the bismuth determination and will sometimes completely break apart during titration with EDTA. Soap-like suds on the liquid surface are also common. The pH of this solution will be in the ~1.5–1.6 range. Three to five drops of PV or XO are then added and the mixture is titrated with standardized 0.01 M EDTA from a 50 mL glass burette to the endpoint. For either XO or PV indicator, make sure the endpoint color holds for at least five minutes. If residual pink color from D&C Red No 22 and/or D&C Red No 28 remains before adding indicator, the endpoint color may not be pure yellow; this however is not a major issue because the endpoint color change is still sharp. See Figures S3 and S4 in supporting information for a photo gallery of the color transitions and proper endpoint color identification for the liquids.

Titration Using Potassium Iodide Indicator

Sample preparation for this method is similar to that described above with two exceptions: (1) only 40 mL of deionized water is used to dilute the test solutions after nitric acid addition (50 mL total volume), and (2), the addition of indicator step. This procedure gave reliable results for all brands of liquids tested. However, it was found that the application of this indicator for all of the caplet brands is not possible; only the Pepto-Bismol brand gave reliable results, as the test solutions for the other brands could not be decolorized upon titration with EDTA. Once the samples are diluted, 1-2 mL of freshly prepared 0.5% (w/w) aqueous KI is added dropwise to the flask while swirling. This results in a yellow or yellow-orange solution. The flask is then titrated with standardized 0.01 M EDTA from a 50 mL glass burette to near the endpoint.[16] The yellow coloration (from BiI_4^- ion) will begin to fade, and when it does, an additional 8-9 mL of indicator is added slowly to re-intensify the color. Before the addition of extra indicator, it is

crucial that the endpoint is approached *slowly* to give the solution time to equilibrate and for the color to stabilize. The flask is then titrated until the yellow coloration completely disappears. If the sample had no coloration before indicator was added, the endpoint will be colorless; however, the sample may have some residual pink color before adding indicator, in which case the endpoint color will be faint pink with no yellow coloration. Color changes that indicate the endpoint must be held for at least 5 minutes. The presence of orange coloration during the titration may indicate the formation of an insoluble form of bismuth iodide, and Cheng[16] notes that this is undesirable. However, for this application, the orange coloration is completely eliminated during the course of the titration, evidence that EDTA successfully chelates all of the bismuth in the mixture, leading to a reliable endpoint. See Figures S5 and S6 in supporting information for a photo gallery of the color transitions and proper endpoint color identification for KI indicator.

Colorimetric Assay Using Spectronic 20

Spectrophotometric analysis offers an alternative method for quantifying bismuth, or it can be used as a supplement or analytical comparison.

Standard curve: Standard Bi^{3+} solutions are prepared by adding 0 (blank), 2.00 mL, 4.00 mL, 5.00 mL, 6.00 mL, 8.00 mL, and 10.00 mL of ~194 μM Bi^{3+} solution to different 50 mL volumetric flasks. Two (2.00) milliliters of 10% (w/w) aqueous ascorbic acid, 5.00 mL 20% (w/w) aqueous KI is added to each flask and then are diluted to the mark with 1.0 M nitric acid. For the results presented in Table S1, each flask was mixed thoroughly and absorbance was measured in triplicate of each solution in a 1.00 cm cuvette at 464 nm using a Spectronic 20 Genesys™ Spectrophotometer. When switching to a new solution we first used the blank to re-zero the instrument.

Caplet Analysis: the mass of a caplet is recorded followed by crushing with a mortar and pestle. Approximately 0.10 grams of powder is added to a 250 mL Erlenmeyer flask along with 10.0 mL of 0.5 M nitric acid. Note in Table S1 that ~0.13 grams of Kaopectate powder is used due to the higher caplet mass of that brand. After swirling the mixture, 40 mL of deionized water is added and the mixture boiled for 15 minutes. Pepto-Bismol and Soothe caplets need not be boiled. Quantitatively transfer the contents of the Erlenmeyer flask to a 1 liter volumetric flask using several rinses of 0.1 M nitric acid. Dilute the 1 liter flask to the mark using 0.1 M nitric acid and thoroughly mix. Allow any undissolved solid particles to settle toward the bottom, and, using a volumetric pipet, draw out three 10.00 mL aliquots of the caplet solution into three separate 50 mL volumetric flasks. To each of the three flasks, add 2.00 mL 10% w/w aqueous ascorbic acid, 5.00 mL 20% w/w aqueous KI, and then dilute each flask to the mark with 1.0 M nitric acid. Follow the same procedure as for the standard curve in obtaining measurements on the Spectronic 20.

RESULTS AND DISCUSSION:

Initial Testing of Lab Protocol

The formation constants (K_f values) of various metal ions of interest to this study with EDTA have been reported[18]. The log K_f values for the following expression, $M^{n+} + Y^{4-} \rightleftharpoons MY^{n-4}$, where Y^{4-} represents $EDTA^{4-}$, are as follows: K^+: 0.8, Na^+: 1.86, Mg^{2+}: 8.79, Ca^{2+}: 10.65, Al^{3+}: 16.4, Ti^{3+}: 21.3, Fe^{3+}: 25.1, and Bi^{3+}: 27.8. These K_f values are reported for 25°C and an ionic strength of 0.1 M, with the exception of bismuth, where the temperature was 20°C. The large K_f value for Bi^{3+} allows this metal to be titrated at low pH, and such a titration is relatively selective. Cheng[16] (KI indicator) and Fritz[17] (thiourea indicator) both found the optimal pH range for bismuth titration to be 1.5–2.0, while Cheng found that below a pH of 1, no sharp endpoint could be reached, and that above 2.5 bismuth hydroxide will precipitate. Cheng performed titrations with 0.01 M EDTA and 10–50 mg Bi per flask, Fritz with 0.05 M EDTA and 30–80 mg Bi per flask, and Schwarzenbach[14] (PV indicator) with 0.01 M EDTA and 20–30 mg Bi per flask. Fritz recommends 0.01 M EDTA when the bismuth per flask is less than 30 mg. The caplet procedure uses ~25–34 mg Bi per flask depending on the brand name, and the liquid medicine procedure ~25 mg Bi per flask. The pH changes very little during the course of caplet and liquid medicine analysis, and so all titrations using the above procedures take place within the 1.5–1.6 range.

Prior to deploying this new laboratory experiment in courses, the procedure was tested with a variety of products to demonstrate the ruggedness of the analysis. Results of titration and spectrophotometric analysis for caplets and liquid, under different experimental conditions, can be found in the supporting information, Tables S1-S3. In Table 1, the results for titrations of different stomach relief caplets are presented, using the procedure that was chosen for the piloted student laboratories. It was found that, except for Pepto-Bismol and Soothe, boiling the caplet powder

during digestion with 0.5 M nitric acid was necessary to release Bi^{3+} into solution for complexation with EDTA. For these two brands, Table S2 displays only marginal changes in percent label value found for the two digestion methods (boil vs. no boil). Boiling for more than 15 minutes leads to the production of NO_2 (from HNO_3 decomposition), resulting in darker yellow coloration in solution that interfered with endpoint identification when PV was used as the indicator, but had no effect with XO. Therefore, it is advised in the procedure to stop boiling immediately if yellow coloration begins to appear when using PV indicator.

Table 1. Investigator Results: Titration Results for Stomach Relief Caplets

Brand Name[a]	Milligrams of bismuth per caplet (based on label value)	Milligrams of bismuth per gram of caplet (based on caplet mass)	Amount Bi found (mg Bi per gram caplet)[b]	Percent relative standard deviation (rsd)	Percent of label value Bi found[c]
Pepto-Bismol	151	222	223 ± 4	1.9	101
Kroger	151	213	209 ± 2	0.85	98.1
Equate	151	221	213 ± 2	1.0	95.7
Kaopectate[d]	151	168	170 ± 2	1.3	101
Soothe	151	218	202 ± 5	2.5	92.5

a. Regardless of brand, approximately 0.15 grams of caplet powder was used for each titration. For each row in the table, two caplets of the respective brand were weighed together and crushed together to produce enough powder for six titrations. Solutions were boiled for 15 minutes, and xylenol orange (XO) indicator was used
b. Average value ± standard deviation for six titrations
c. Calculated by dividing the mass of bismuth found (column 4) by the stated label value (column 3), then multiplying by 100
d. Care was taken to exclude the hard shell coating when weighing the powder

During titrations carried out by the investigators, it was found that the bismuth content of the five caplet brands and three liquid brands meets United States Pharmacopeia (USP) standards,[19] in that the actual amount of active ingredient in the product is within 90–110% of label value. These results are consistent with a UV-Vis assay (Table S1) for three brands. One UV-Vis assay for Kaopectate came out below this standard (89.2%); the label dosage for the caplet brands is two caplets, and the average for Kaopectate for two separate assays (using one caplet each, respectively) does meet the standard (91.2%). Unlike the pink caplets (Pepto-Bismol, Equate, Kroger, Soothe), the larger white Kaopectate caplets contain a hard shell that perhaps does not contain bismuth subsalicylate. If some of this shell is naturally included in the sample mass during weighing and digestion, this will likely lead to systematic error, namely, artificially low calculated amounts of bismuth. The second and third Kaopectate entries in Table S2, and student results from WSU seem to give evidence for this hypothesis; when care is taken to exclude the hard shell coating during weighting, higher percent label values are found.

All three indicators gave results with low relative standard deviation (rsd), with XO giving lower rsd than PV in all but two cases (Equate liquid, Pepto-Bismol caplet w/ 15 minute boil). Potassium iodide gave the lowest rsd for the Pepto-Bismol caplet analysis, but notably higher rsd for analysis of the three liquid brands. For the caplet brands, with the exception of Pepto-Bismol, the titrations using KI as indicator failed; for unknown reasons, these solutions could not be decolorized by addition of EDTA, and so no endpoint could be reached. Inactive ingredients listed on the stomach relief products tested in this study include: sodium starch glycolate, sodium lauryl sulfate, sodium salicylate, sodium benzoate, potassium hydroxide, potassium sorbate, magnesium stearate, magnesium aluminum silicate (Pepto-Bismol liquid), calcium carbonate, and titanium dioxide (Kaopectate caplets). Sodium and potassium do not form strong complexes with EDTA[18] and thus do not interfere in this titration. Calcium and magnesium do not interfere at the low pH of the bismuth titration (~1.5–1.6), nor does the aluminum ion.[14 (p. 184),16,17] The Ti(III) and Fe(III) ions do have the potential to interfere[16] even at such low pH, and perhaps the titanyl ion (TiO^{2+}) as well[14 (p. 199)], but it is assumed that only trace quantities of these ions exist in the test solutions and we do not consider them further. It is also possible that in test solutions containing titanium, the titanium is present as insoluble titanium (IV) oxide and does not interact with EDTA. Common anions such as chloride, sulfate, and nitrate do not interfere,[16,17] and it is expected that carbonate will react with the excess nitric acid to form carbon dioxide and water.

Application to Student Labs

Given that the particular focus for student chemistry lab was on caplet analysis, we decided to implement this laboratory using XO as indicator for the following reasons: 1.) It can be used effectively for a wide variety of caplet brands, 2.) It generally has a lower rsd than PV for this application, 3.) Slight yellow coloration from NO_2 production does not interfere with the XO endpoint, and 4.) We do not have to prepare and use large volumes of KI indicator solution. However, if XO is not readily available and PV or KI is in stock, the latter two are acceptable indicators to use, albeit KI appears to have applicability to a narrower range of products (as demonstrated in Tables S2 and S3). This lab may be effectively carried out by groups of two, or individually, within a 120-minute time frame.

Titration experiments are often used throughout the typical college chemistry curriculum. This experiment is broadly applicable to different groups of students, and the procedure and data analysis can be adapted easily to fit different learning objectives. For example, when this experiment was carried out in an Introductory Chemistry lab, there was no emphasis on metal ion chelation. The chemical reaction was discussed in more general terms: EDTA binds to bismuth ions in a 1:1 ratio more strongly than the indicator. When all bismuth is bound by EDTA, the indicator changes color and this is the endpoint. In addition, statistical analysis of results (standard deviation) was omitted because that is not taught in Introductory Chemistry. The topics of metal ion chelation, Lewis acid/base chemistry, and standard deviation are included in the general and analytical chemistry applications of this experiment. Indeed, the data generated in an Analytical Chemistry (Quantitative Analysis) setting could be applied to more advanced statistical analysis.

Although many bismuth quantification experiments can be performed by a broad range of student populations, there is an expected difference in accuracy and precision of the results obtained. Tables 2-4 show typical student results from Introductory Chemistry (Bethel College, Table 2), Honors Chemistry II (Wichita State University, Table 3), and Quantitative Analysis (University of Missouri, Table 4). As might be expected, students with more titration and/or basic laboratory experience performed better in terms of precision. However, on average, all three levels of students obtained results that meet USP standards. This demonstrates that this experiment can provide a useful learning experience throughout the chemistry curriculum.

STUDENT RESULTS AND LEARNING OUTCOMES:

Titration of Equate brand caplets was carried out by lab pairs in the Introductory Chemistry lab at Bethel College, using XO indicator. When comparing the cohorts of students included in this pilot, Introductory Chemistry students at Bethel College have the least experience in any sort of measurement. Indeed, they are in a one-semester, terminal, general education chemistry course and some of these students did not take chemistry in high school. This experiment represented the only exposure these students had to titration techniques. Results of their experiment are shown in Table 2, and not surprisingly the rsd for this group of students is the largest presented herein. However, this data set still demonstrates that the caplets meet USP specifications. Pharmaceutical analysis of a common household medicine provided an interesting context for a technique often found to be challenging for introductory students.

Table 2. Bethel College Student Titration Results for Equate Caplets

Brand Name[a]	Group number	Milligrams of bismuth per caplet (based on label value)	Milligrams of bismuth per gram of caplet (based on caplet mass)	Amount Bi found (mg Bi per gram caplet)[b]	Percent rsd	Percent of label value Bi found
Equate	1	151	222	223 ± 5	2.3	100.
Equate	2	151	233	217 ± 7	3.1	93.2
Equate	3	151	226	244 ± 47	19	108
Equate	4	151	222	194 ± 21	11	87.0
Equate	5	151	219	221 ± 8	3.7	101
Equate	6	151	226	189 ± 9	4.6	83.9
Equate	7	151	226	315 ± 41	13	140.
Equate	8	151	226	214 ± 5	2.4	94.8
Equate	9	151	225	230 ± 19	8.3	102
Equate	10	151	222	275 ± 20	7.2	123
Equate	11	151	221	263 ± 30	12	119
Equate	12	151	233	254 ± 40	16	109
Equate	13	151	229	228 ± 36	16	99.3
Equate	14	151	219	326 ± 26	7.9	149
				Average:	**9 ± 6[c]**	**105 ± 18[d]**

a. Approximately 0.15 grams of caplet powder was used for each titration. For each row in the table, one Equate caplet was crushed to use for analysis. Note: Group number 14 used approximately 0.05 grams of powder for each titration.
b. Average value ± standard deviation for three titrations
c. Average value ± standard deviation for n=14 (14 groups)
d. Average value ± standard deviation for n=42 (42 total titrations)

Results for WSU Chemistry II Honors lab students are presented in Table 3. The students found an average value of 95% label value bismuth, and had an average value of percent relative standard deviation (rsd) of 6. As a point of comparison, a lab commonly performed by WSU General Chemistry II students is the standardization of NaOH (*aq*) using potassium hydrogen phthalate (KHP) with phenolphthalein as indicator. In terms of endpoint detection, phenolphthalein is a relatively easy indicator for beginning students; if the solution holds even a very faint pink color, the endpoint has been reached. Student data for this standardization lab from the past was collected. A comparison of percent rsd values for phenolphthalein and XO was as follows: (5 ± 7)% (*n*=142) for phenolphthalein, and (6 ± 4)% (*n*=14) for the Kaopectate caplet analysis seen in Table 3. Each data point *n* used in this analysis is a percent rsd value from three titrations. Potential outliers were not excluded in this rsd comparison. The similarity of the rsd values between the two indicators gives evidence that the XO endpoint is sharp enough for General Chemistry II students with limited titration experience.

Table 3. WSU Chemistry II Honors Lab Student Titration Results for Kaopectate Caplets

Brand Name[a]	Student number	Milligrams of bismuth per caplet (based on label value)	Milligrams of bismuth per gram of caplet (based on caplet mass)	Amount Bi found (mg Bi per gram caplet)[b]	Percent rsd	Percent of label value Bi found
Kaopectate	1	151	171	179 ± 3	1.9	105
Kaopectate	2	151	169	161 ± 4	2.6	95.3
Kaopectate	3	151	168	167 ± 20	12	99.2
Kaopectate	4	151	170.	159 ± 6	3.7	93.4
Kaopectate	5	151	163	168 ± 11	6.6	103
Kaopectate	6	151	171	154 ± 17	11	89.6
Kaopectate	7	151	172	173 ± 9	5.3	100.
Kaopectate	8	151	172	148 ± 8	5.5	85.9
Kaopectate	9	151	169	177 ± 9	5.3	105
Kaopectate	10	151	172	171 ± 19	11	99.7
Kaopectate	11	151	172	152 ± 6	4.0	88.1
Kaopectate	12	151	168	171 ± 8	4.9	102
Kaopectate	13	151	180.	145 ± 6	4.3	80.4
Kaopectate	14	151	176	149 ± 20	13	84.6
				Average:	**6 ± 4[c]**	**95 ± 10[d]**

a. Approximately 0.15 grams of caplet powder was used for each titration. For each row in the table, one Kaopectate caplet was crushed to use for analysis. These caplets were from the same bottle of Kaopectate as used in Table 1, and students were told to exclude the hard shell coating when weighing the powder
b. Average value ± standard deviation for three titrations
c. Average value ± standard deviation for *n*=14 (14 students)
d. Average value ± standard deviation for *n*=42 (42 total titrations)

Meanwhile, students in Quantitative Analysis at Mizzou demonstrated the ability to achieve considerable precision with bismuth titrations using XO indicator. This group of students had performed one previous titration for Quantitative Analysis lab, namely, the iodometric determination of vitamin C. Some students reported having titration experience from previous classes, however, roughly half had never performed a titration prior to Quantitative Analysis lab. The rsd values (Table 4) show most students achieved precision values near those reached in investigator results (Table 1), demonstrating both achievement of laboratory skills for the quantitative analysis students and the ease of use of XO indicator with these systems. The Quantitative Analysis students conducted titrations of a variety of different bismuth-containing stomach relief caplets. Results indicate bismuth quantities within the USP standard for all class averages, and most individual experiments.

Table 4. Mizzou Quantitative Analysis Lab Student Titration Results for Pepto-Bismol (PB) Ultra, Soothe, and Equate Caplets

Brand Name[a]	Student number	Milligrams of bismuth per caplet (based on label value)	Milligrams of bismuth per gram of caplet (based on caplet mass)	Amount Bi found (mg Bi per gram caplet)[b]	Percent rsd	Percent of label value Bi found
PB Ultra	1	303	227	229 ± 3	1.1	101
PB Ultra	2	303	226	220.9 ± 0.2	0.11	97.9
PB Ultra	3	303	224	204.4 ± 0.2	0.099	91.4
PB Ultra	4	303	228	206 ± 4	2.0	90.0
PB Ultra	5	303	224	219 ± 2	1.1	98.0
PB Ultra	6	303	229	212 ± 4	1.8	92.4
PB Ultra	7	303	226	222.0 ± 0.7	0.34	98.3
PB Ultra	8	303	227	215.8 ± 0.7	0.33	95.1
PB Ultra	9	303	227	214 ± 8	3.9	94.4
PB Ultra	10	303	224	226 ± 7	3.1	101
PB Ultra	11	303	227	217 ± 3	1.5	95.6
PB Ultra	12	303	224	207 ± 2	0.93	92.3
PB Ultra	13	303	224	224 ± 3	1.5	100.
PB Ultra	14	303	225	217 ± 10	4.7	96.8
PB Ultra	15	303	226	212.9 ± 0.7	0.35	94.3
				Average:	**2 ± 1[c]**	**96 ± 4[d]**
Soothe	1	151	212	212 ± 7	3.3	99.7
Soothe	2	151	218	188 ± 2	0.81	86.2
Soothe	3	151	216	209 ± 5	2.6	96.7
Soothe	4	151	216	192.38 ± .04	0.022	89.0
Soothe	5	151	216	207 ± 3	1.5	95.9
Soothe	6	151	215	194 ± 5	2.6	90.5
Soothe	7	151	212	217 ± 10	4.6	102
Soothe	8	151	206	192 ± 3	1.4	93.5
Soothe	9	151	212	210.1 ± 0.8	0.37	98.9
Soothe	10	151	214	195 ± 1	0.59	91.0
Soothe	11	151	213	192.3 ± 0.8	0.42	90.2
Soothe	12	151	213	190.2 ± 0.1	0.071	89.5
				Average:	**2 ± 1[e]**	**94 ± 5[f]**
Equate	1	151	158	178 ± 5	2.8	112
Equate	2	151	156	164 ± 4	2.5	105
Equate	3	151	157	149 ± 3	2.2	95.1
Equate	4	151	155	162 ± 3	1.5	105
Equate	5	151	154	153.7 ± 0.5	0.34	99.9
Equate	6	151	156	160 ± 3	1.9	102
Equate	7	151	157	157 ± 3	2.1	99.6
Equate	8	151	158	151 ± 1	0.98	95.4
Equate	9	151	157	156 ± 4	2.8	98.9
Equate	10	151	156	156.1 ± 0.4	0.23	100.
Equate	11	151	154	154 ± 4	2.8	99.9
Equate	12	151	159	154 ± 3	1.7	97.3
Equate	13	151	157	161 ± 3	2.0	102
Equate	14	151	160.	171 ± 7	4.3	107
Equate	15	151	157	150.9 ± 0.9	0.58	96.1
Equate	16	151	155	154 ± 3	2.2	99.5
Equate	17	151	156	159 ± 9	5.7	102
Equate	18	151	155	162.6 ± 0.8	0.51	105
Equate	19	151	156	155 ± 2	1.0	99.4
Equate	20	151	170.	166.6 ± 0.2	0.12	98.1
Equate	21	151	156	143 ± 6	4.4	92.0
Equate	22	151	156	161.3 ± 0.5	0.32	103
Equate	23	151	157	161 ± 2	1.3	103
Equate	24	151	156	165.4 ± 0.2	0.097	106
				Average:	**2 ± 1[g]**	**101 ± 5[h]**

a. Regardless of brand, approximately 0.15 grams of caplet powder was used for each titration. For each row in the table, one caplet of the respective brand was crushed to use for analysis

b. Average value ± standard deviation for three titrations

c. Average value ± standard deviation for *n*=15 (15 students), d. Average value ± standard deviation for *n*=45 (45 total titrations)

e. Average value ± standard deviation for *n*=12 (12 students), f. Average value ± standard deviation for *n*=36 (36 total titrations)

g. Average value ± standard deviation for *n*=24 (24 students), h. Average value ± standard deviation for *n*=72 (72 total titrations)

While student lab reports at WSU generally indicated an understanding of the concepts and calculations, student pre and post-lab assessment results at WSU and Bethel indicated that students continued to have difficulty with some key concepts. For Bethel students, the average score on both the pre-lab and post-lab quizzes was 48%, with students

showing improvement on items quizzing the ability to properly read burette values (from 27% to 45% correct) and determining sig figs in calculation of averages (from 42% to 70% of students correct). This is what we would expect because the experiment represented the first experience in titration for many of these students. Because quantitative analysis lab is focused on developing skill in high-precision titrations, pre- and post-lab quizzes were not used at Mizzou as they were at WSU and Bethel. For WSU Chemistry II Honors students, an average score of 70% was achieved on the pre-lab assessment, and a 77% on the post-lab assessment (S10-S15). Figures S9 and S10 display full assessment results for each question at Bethel and WSU, respectively. WSU students were asked two reflection questions on the post-lab assessment: one question asked their thoughts on working with household products and the other question inquired about the ease of working with XO indicator. Students indicated that they enjoyed working with household products, especially because they were able to verify the active ingredient in an over-the-counter medication, and nine students found their respective caplet to meet USP standards. As to the question regarding XO indicator, most students found the endpoint easy to observe. Four students were not overly pleased with the five-minute wait time at the endpoint. In fairness, there were moments during instructor data gathering (Tables 1, S2 and S3) when we grew somewhat annoyed with the wait time! However, we found the five-minute wait to be a reasonable balance between minimizing titration error and maximizing procedural efficiency in a student lab setting when time is of the essence. Full responses to reflection questions were recorded in Table S8.

CONCLUSION:

Lab procedures for the quantification of bismuth in over-the-counter stomach relief caplets and liquids are presented. Investigator results for EDTA titrations using three different indicators: xylenol orange (XO), pyrocatechol violet (PV), and potassium iodide; and UV/Vis spectrophotometric assays all indicate that accurate results can be obtained, with bismuth amounts in medications within United States Pharmacopeia (USP) standards. Student labs were carried out in three different levels of college chemistry courses, at three different locations. Although class precision varied by student experience level, in all cases, many of the students were able to find bismuth dosages in line with the stated amounts on medication labels. The relative standard deviation values in student titration experiments with bismuth were statistically equivalent to those achieved by similar student populations carrying out titrations with phenolphthalein indicator, demonstrating that this lab using xylenol orange indicator can give a similar introductory experience to titrations. Students expressed in post-lab assessments that they enjoyed working with household products, finding quantification of active ingredients in medicine to be relevant to quality control and community health.

HAZARDS AND WASTE DISPOSAL:

Concentrated nitric acid is an oxidizer that may intensify a fire, is corrosive, toxic if inhaled, and will cause severe skin burns and eye damage. If used to dissolve bismuth metal, NO_2 gas will be generated and is extremely toxic. Therefore, it should only be manipulated in the fume hood. 0.5 M nitric acid can cause severe tissue and eye damage. Safety goggles and disposable lab gloves should be worn when manipulating both concentrated and 0.5 M nitric acid. Within the 15 minute sample digestion window, a small amount of NO_2 gas may be generated, and so boiling in a fume hood or in a well ventilated area is advised. Each student or group should combine titrated samples in a large beaker and, in the sink, neutralize the contents with sodium bicarbonate before flushing down the drain.

SUPPORTING INFORMATION: Product and chemical information, solution preparation details, liquid medicine density determination, photo gallery of caplet and liquid medicine titrations using PV, XO, and KI indicators, UV-Vis assay results, and student pre and post-lab assessments with results (DOC). Student laboratory handout (DOC).

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