Effect of Course Structure on the Accuracy of Nonsterile Compounded Preparations

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Objective. To investigate if students in the new course structure attained the same level of compounding competency as students in the legacy course structure.

Methods. Students compounded four nonsterile preparations common to both the legacy curriculum (PCL) and the transformed curriculum (TC). The preparations were compared using relative potency or weight variation as a measure of compounding competency. They represented the broad range of compounding complexities required in compounding courses at the school.

Results. The mean relative potencies of three nonsterile preparations were statistically different, with only the mean of the TC hydrocortisone medication stick being outside of the acceptable range of the laboratory’s criteria. However, the standard deviation (SD) was markedly different in each preparation pair suggesting that the number of students correctly compounding the preparation in the first attempt might be an important factor in the analysis. In contrast, the mean weight variation data of the phenolmenthol soft troches and enalapril tablet triturates were almost identical.

Conclusion. The relative potency results suggested that equivalent competency in the two student groups was possible for preparations that involved simple solutions or filled fixed volume molds. However, the hydrocortisone medication stick data indicated that understanding the science of a preparation may require more knowledge or time.

Keywords: relative potency, compounding, course structure, nonsterile preparations, analysis

INTRODUCTION

Pharmacy schools and colleges are transforming their Doctor of Pharmacy (PharmD) curricula to ensure their students are effective practitioners in today’s health care system. The University of North Carolina Eshelman School of Pharmacy began its curricular transformation in 2015 emphasizing the following three concepts: reengineered classroom instruction, early immersion of students in patient care, and creating leadership and innovation training and experiences.1-4 As with most of the curriculum, compounding education was modified in the curricular transformation.

In the legacy curriculum, compounding training was integrated into the five-semester Pharmaceutical Care Laboratory (PCL) experience. The PCL sequence was integrated in the two semesters of the P1 year, the two semesters of the P2 year, and the first semester of the P3 year. Compounding instruction occurred four to five times per semester in each of the five semesters of the PCL sequence, and involved a short pre-laboratory presentation (20 minutes) before each week that contained a compounding exercise. The instruction was supplemented with reading assignments in the required compounding textbook and video assignments from an open-source website (pharmlabs.unc.edu). Students would compound one preparation during each exercise and would complete the work as one of several tasks to accomplish during a 4-hour laboratory period. Over the course of the five-semester sequence, students would compound more than 20 nonsterile and sterile preparations. Students would compound simpler preparations in the P1 year before engaging in their first introductory pharmacy practice experience (IPPE) during the summer of that year. During the P2 year, students would compound more complicated preparations, or preparations that required specialized equipment or calculations before embarking on their second IPPE during the summer of that year. During the P3 year, the compounded preparations included mock chemotherapy agents, and nonsterile preparations that had unique properties or compounding requirements. Students also engaged in creating Formulation Records for new

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prescriptions, and had limited experience in selecting excipients for their proposed preparations before the proceeded to their advanced pharmacy practice experience (APPE) the summer of that year.

In the transformed curriculum, the required compounding course was taught during the second semester of the P1 year. It was a 12-week course in which students compounded nonsterile preparations in the first six weeks, and sterile preparations in the second six weeks. The course met weekly for an hour-long pre-laboratory class and then students had a 3-hour laboratory session for the compounding exercises. Students made two to three nonsterile preparations in each laboratory session. They also had required textbook readings and video assignments from the same pharmlabs.unc.edu website. Since this course was taught in the second semester of the P1 year, the TC students had not yet experienced any IPPE rotations (called immersion experiences in the transformed curriculum). The preparations used in the TC course were a subset of the compounds that had been used in the PCL sequence (Table 1).

Curricular transformation, which usually creates course structure changes, begins with the expectation that the student outcomes would be at least identical, and hopefully better, than the legacy curriculum. The objective of this study was to investigate if students in the transformed curriculum course structure attained the same level of compounding competency as students in the legacy curriculum course structure. Pharmacy schools and colleges have different types of curricular structures that include a mixture of didactic, laboratory, and experiential courses. Compounding instruction is exclusively a laboratory-taught skill. Factors such as GPA, course level, and course type have been found to have positive and negative effects on student ratings of didactic courses. However, additional factors can influence student learning in laboratory-based courses such as time spent in hands-on exercises, the ability to repeat learning activities, when the material was presented in the educational continuum, and student’s outside-of-class experiences (ie, immersions, IPPEs, APPEs, IPEs). This report investigated a novel aspect of the course type influence: Can a major change in course structure alter the level of achievement of a laboratory-learned skill such as compounding? The answer to this question will serve as an example of the extent of laboratory course structure changes possible at other pharmacy schools that provide the same learning outcomes.

Completed preparations in this school’s compounding laboratory can be subjected to a multitude of assessments such as reviewing Compounding Records and the affixed preparation labels, observing the physical appearance of the finished preparation, measuring a physical property of the preparation (eg, osmotic pressure, density, weight), and evaluating the preparations’ relative potency by pharmaceutical analysis. All of these assessments

| Preparations             | Compounding Complexity                                                                 | Timeframe in Course |
|--------------------------|---------------------------------------------------------------------------------------|---------------------|
| Metronidazole Saturated Solution | Use prescription balance to weigh ingredients                                        | 1st semester        |
|                          | Use volumetric glassware to measure liquids                                           | Week 2              |
| Phenol and Menthol Soft Troches    | Use prescription balance to weigh ingredients                                        | 2nd semester        |
|                          | Use geometric dilution to mix powders                                                | Week 5              |
|                          | Melt solids and incorporate powders                                                   |                     |
|                          | Calibrate a troche mold                                                               |                     |
| Hydrocortisone Medication Stick | Use prescription balance to weigh ingredients                                        | 3rd semester        |
|                          | Use volumetric glassware to measure liquids                                           | Week 5              |
|                          | Melt solids in proper order and incorporate powders                                    |                     |
|                          | Transfer materials into packaging container – both at the proper congealing temperature and pour rate |                     |
| Enalapril Tablet Triturates   | Use prescription balance to weigh ingredients                                        | 4th semester        |
|                          | Use geometric dilution to mix powders                                                | Week 6              |
|                          | Calibrate a tablet triturate mold                                                    |                     |
|                          | Determine the correct wetting of powders                                              |                     |
|                          | Correctly pack a tablet triturate mold                                                |                     |
|                          | Use appropriate speed of packing                                                     |                     |
could have been used to compare differences in the students’ ability to compound preparations in the two curricular course structures. However, the comparisons of the potency analysis and physical properties were considered as the better direct indicators of the students’ compounding abilities since those were measurable objective parameters. The two course structures also had a high rate of consistency in that the same laboratory instructor was responsible for all instruction, the same reading and video assignments were assigned, the same preparations were compounded, the same analytical methods were used, and the same grade assessment methods were used.

METHODS

Four nonsterile preparations compounded by both the PCL and TC groups were selected for comparison in this study. Table 1 lists the preparations selected, the perceived complexity to compound the preparation, and when the preparation was made within the time frame of each course. The complexity of the preparation was thought to depend on the number of manipulations involved in the compounding process, the difficulty or skill necessary to carry out each manipulation, whether or not specialized equipment was needed, the skill level and technique of the compounder using the equipment, and the importance of timing and the order of mixing ingredients in the compounding process. The preparations were further chosen to demonstrate the range of complexities in the compounding exercises within the entire course structure.

Differences in the relative potency of the active pharmaceutical ingredient (API) or the weight variation of the preparations were used to assess the students’ skill level in the two course structures. Relative potency (percent of label) was measured as the API amount or concentration in the students’ preparation, which was determined using either HPLC or spectrophotometric analytical methods. To determine the percent of label, a linearity standard curve over 80% to 120% the expected percent of label was developed with a series of preparation standards that contained different API amounts or concentrations. The standards were compounded in triplicate by teaching assistants who had prior compounding experience in the laboratory. The standards were prepared within a week before the actual student laboratory exercise was conducted. The $R^2$ values of the standard curves were greater than 0.97. Appendix 1 provides the preparation formulations, the compounding procedures, and the methods used to analyze each preparation.

The mean and standard deviation (SD) of each preparation’s relative potency were calculated using Microsoft Excel (Redmond, WA), and a 2-tailed z-test was used to test for significant differences in the two curricular groups since the variance in each group was known, and the sample size was large (>30 samples). A $p<.05$ was taken as the level of significance.

RESULTS

Table 2 shows that the relative potencies were different in the preparations compounded in the two curriculum course structures. Of these three preparations (ie, metronidazole saturated solution, hydrocortisone medication stick, and enalapril tablet triturates), the mean percent of label for the hydrocortisone medication stick was lowest in the TC group, and was unacceptable by the criteria used in this school’s compounding laboratory for an acceptable compound (ie, less than ±10% of label). The SD was markedly different in each preparation pair suggesting that the number of students correctly compounding the preparation in the first attempt might be an important factor to consider.

The mean (SD) for each preparation and curricular group was based on the analysis of only one sample per student preparation and standard in the standard curve series. Only one sample was analyzed due to the time necessary to complete the analysis for approximately 170 samples for each preparation in each curricular group, the necessity to move to the next laboratory exercise, and the instructor’s desire to provide reasonable rapid turnaround results to the students. The limited sampling did not allow the opportunity to study the variation within a single preparation (eg, troche, tablet triturates, medication stick), which might have provided additional insight into the students’ competence to correctly compound the entire preparation instead of just the analyzed sample.

Table 2. Relative Potencies or Weight Variation of Compounded Nonsterile Preparations in Two Curricular Structures

| Preparations                        | PCL Group Potency (%) | TC Group Potency (%) | $p$ value |
|-------------------------------------|-----------------------|----------------------|-----------|
| Metronidazole Saturated Solution    | 100.9 (6.8) (n=160)    | 102.7 (15.8) (n=148) | <.001     |
| Hydrocortisone Medication Stick     | 103.9 (14.9) (n=155)   | 75.5 (32.0) (n=151)  | <.001     |
| Enalapril Tablet Triturates         | 93.5 (35.1) (n=156)    | 100.1 (12.1) (n=149) | <.001     |
| Phenol-Menthol Soft Troches (Weight in grams) | 1.13 (0.08) (n=159)   | 1.13 (0.08) (n=149)  | = .862    |
| Enalapril Tablet Triturates (Weight in grams) | 0.101 (0.008) (n=157) | 0.101 (0.009) (n=150) | = .983    |
DISCUSSION

The assessment of student compounded preparations by pharmaceutical analyses has been a major commitment of this compounding laboratory.8,9 For this study, the same compounding staff conducted the analyses for the metronidazole saturated solution, hydrocortisone medication stick, and enalapril tablet triturates with the same analytical procedures and equipment and precision volumetric glassware. They also created the linearity standard curves in each group. These variables were not directly measured in this study; however, the consistency of these parameters between the two groups support the conclusions that differences between the groups were due to other parameters outside of the analyses.

In terms of the metronidazole saturated solution and enalapril tablet triturate relative potencies, the differences between the two groups were significant but still within ±10% of label. One interesting observation was that the TC group’s relative potency average of the enalapril tablet triturates was 100% of label with a smaller variance compared in the PCL group. The enalapril tablet triturates were the last compound the TC group made in the non-sterile section of the course, and this was in their sixth consecutive week of compounding. The ability to match the compounding ability of the PCL group within six weeks suggested that the new compounding course structure was able to achieve at least a comparable level of performance when compounding tablet triturates. That result suggested that the continuous compounding laboratory structure of short duration was able to provide the same level of student performance as the intermittent laboratory structure of longer duration.

The hydrocortisone medication sticks might have been a more challenging preparation to compound than anticipated because of the criteria used to establish the complexity of the formulation. The sticks were the first semisolid preparation compounded in both groups. The most important step in the compounding process was to transfer the melted material into the packaging container; the mixture must be almost at the congealing temperature before being poured, and must be rapidly poured into the container once the correct temperature was attained. This step was crucial because of the speed at which beeswax congeals, which was within seconds of contacting a cooler surface. In the reaction vessel where the mixture was heated, beeswax’s rapid cooling has a negative effect because the rapid congealing can trap the API in the material that sticks to the side of the vessel. This would prevent a quantitative transfer of the API to the packaging container. On the other hand, the rapid cooling does have a positive benefit once the mixture was inside the packaging container since the rapidly cooling beeswax would prevent the API from settling. This would be particularly important if the API was insoluble in the base mixture and prone to settling.

Table 2 shows the mean relative potency for the hydrocortisone medication sticks at 104% and 75% for the PCL and TC groups, respectively. Because this was the first semisolid preparation compounded in each group, the difference would not be from the number of prior exposures to semisolid preparations within either of the course structures. The reason the PCL group did significantly different than the TC group students was not known. However, the students in the PCL group were in their P2 year and completed an IPPE in the summer between the P1 and P2 years. Their additional experiences might have contributed to their successful compounding of this preparation.

Another measure of students’ compounding competency is the number of students who compounded acceptable preparations (ie, within 90% and 110% relative potency) in the first attempt. The means’ SD could be an indirect indication of this variance. The number of students who compounded an acceptable metronidazole saturated solution preparation was 146 vs 98; for the hydrocortisone medication stick, it was 82 vs 37; and for the enalapril tablet triturates, it was 48 vs 120 in the PCL and TC groups, respectively. The PCL group had more acceptable preparations from the initial semesters of their compounding course exercises compared to the TC group that had the same compounding course exercises only within weeks after beginning their compounding course. However, in the TC group, almost every student compounded an acceptable enalapril tablet triturate, which occurred at the end of the compounding course. This was not the result in the PCL group. An explanation for this result was not directly investigated as part of the study. One possible reason is that the TC group had been continuously engaged in weekly compounding exercises, which led to a more focused attempt to make a successful preparation. It is also possible that the continuous
exposure to compounding activities resulted in the TC group being better prepared.

The lack of significant differences in the weight variations of the phenol-menthol troches and enalapril tablet triturates suggested that using a calibrated mold with its fixed cavity size minimized the differences that might exist between the PCL and TC groups’ compounding competency. Since the mold cavities would only hold a defined amount of material, the weight of the individual units (ie, troches, tablets) should be almost identical if the cavities were completely filled (troches) or packed correctly (tablet triturates), and the preparations had the same densities. Therefore, the major source of any variation was the inability to completely pack each cavity in the mold, which would only occur if the student left the cavity partially filled or did not apply enough pressure on a spatula to completely pack every cavity.

CONCLUSION

The objective of this study was to determine if the TC course structure would provide at least a comparable level of compounding competency to its students compared to the PCL students in the legacy course structure. The enalapril tablet triturates data showed that the TC students demonstrated a competency equal to that of the PCL group for that preparation. The data regarding acceptable compounds on the first attempt suggested that the TC students might exceed the competency of the PCL group for that preparation. At the very least, the data indicated that students at the end of a continuous, short-term course structure had the same compounding competency as students who completed an intermittent multi-semester course structure.

The TC group was the first group of students to undertake the newly implemented curriculum. The curricular changes created new course structures, and these structures carried the expectations that student outcomes would be similar or better than the legacy curriculum course structures. This study indicated that the TC group competency outcomes were similar to the PCL group competency outcomes except for one preparation (ie, hydrocortisone medication stick). The curriculum has kept the TC course structure, and has become more focused on compounding science. Techniques and topics such as “errors and omissions” and “medication safety” have been placed in other courses of the curriculum.

One limitation of the study was the lack of follow-up student surveys or feedback to understand the reasons for the significant difference in the relative potency of the hydrocortisone medication stick and the larger variation of the PCL group’s enalapril tablet triturates relative potency. The opportunity to duplicate a similar study situation will not be available at this school, as the two course structures occurred only at one point in time, and that was when the two curricula were simultaneously taught.

Terry and colleagues and Krause reported on a course structure’s impact on student performance. The next important consideration for the new compounding course structure in the transformed curriculum will be the length of time students retain their compounding skills. If students take a compounding course in the first professional year but do not have other courses or opportunities to practice these skills, their preparedness for such activities in subsequent professional years will diminish. Ely and Birnie reported that students did not retain nonsterile compounding skills after a year. Mudit and Alfonso’s study showed that 25% of students had problems retaining nonsterile compounding skills for more than one semester. This lack of retention was also studied in compounded sterile preparations, and was addressed by having students complete additional training in their third professional year IPPE experiences.

The UNC Eshelman School of Pharmacy has started to address student learning retention of compounding skills after the completion of the required compounding course in the transformed curriculum by two methods. The first was the creation of a compounding elective course available to both P2 and P3 students. The Science of Pharmaceutical Compounding elective course was created as an exploration of the science and practice skills necessary for a pharmacist in contemporary compounding practice. A second method was to expand teaching assistant opportunities for students to assist in compounding activities throughout their entire professional program.

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Appendix 1: Formulation Records and Analytical Methodology for the Nonsterile Preparations

Metronidazole Saturated Solution

| Ingredient                  | Quantity   |
|-----------------------------|------------|
| Metronidazole               | 1.0 g      |
| HCl 10%                     | 1.5 mL     |
| Propylene Glycol            | 10.0 mL    |
| Methylparaben               | 100 mg     |
| Propylparaben               | 50 mg      |
| Purified Water              | qs 100 mL  |

Method of Preparation:
1. Calibrate a 4 oz. amber plastic prescription bottle to 100 mL.
2. Make the methylparaben and propylparaben trituration.
3. Add the methylparaben and propylparaben trituration to a scintillation vial and add 10 mL propylene glycol rinsing the weigh boat. Continue to shake the vial contents until powders are dissolved.
4. Add the metronidazole to about 50 mL of purified water in a 100 mL beaker and begin stirring with a stir bar.
5. Add the hydrochloric acid solution to the beaker.
6. Add the scintillation vial mixture to the beaker. Rinse the scintillation vial with a few portions of purified water.
7. Transfer the beaker contents to the prescription bottle.
8. Add sufficient purified water to bring the prescription bottle to volume rinsing through the beaker.

Process of Analysis:
A 50 µL sample of the preparation was added to 20 mL of deionized water. The sample was hand shaken and 25 µL was injected into the HPLC. An aqueous mobile phase of 60% methanol and 40% deionized water was used in a 4.0 × 250 mm C18 10µ column with a flow rate of 1.2 mL/min. The detector wavelength was 254 nm. The retention time of metronidazole, methylparaben, and propylparaben was 4 minutes, 6 minutes, and 11 minutes, respectively.

Standard Solutions:
Preparations of 0.8-1.0 g metronidazole per 100 mL were made in the same manner as the student preparations. A linearity standard curve was used to determine the concentration of metronidazole per 100 mL of solution.

Expected Concentration of API: 1 g of metronidazole per 100 mL.

Hydrocortisone Medication Stick

| Ingredient                  | Percentage |
|-----------------------------|------------|
| Hydrocortisone USP, micronized | 2.5%       |
| White Beeswax               | 20%        |
| Cetyl Esters Wax            | 20%        |
| Mineral Oil                 | 55%        |
| Acacia                      | 5%         |
Note: The medication stick will contain 2.5% of hydrocortisone. The remaining ingredients are the composition of the medication stick base, and their percentages are given.

Method of Preparation:
1. Accurately weigh the powders. Triturate the hydrocortisone and acacia in a mortar with a pestle, and sieve through a 40-mesh sieve onto glassine paper.
2. Heat to melt the beeswax (around 65°C) in the 100 ml beaker. Place the mineral oil in the 50 ml beaker, and set at the edge of the hotplate to warm (do not heat).
3. When the beeswax is melted, reduce the heat and melt the cetyl esters wax in the beaker. Use a stirring rod to mix, not a stirring bar. This will avoid getting the melted waxes of the side of the beaker where they will solidify and become difficult to add back to the melt.
4. When the cetyl esters wax is melted, add the mineral oil to the beaker and mix. Then add the hydrocortisone and acacia and mix.
5. When the hydrocortisone and acacia have dispersed in the waxes, remove from heat and cool the mixture until it is “just warm to the back of the hand.” Stir one final time just before filling the package.
6. Fill the application stick quickly in one pouring.

Process of Analysis:
A 250 mg sample was removed from the top of the stick, dissolved in 20 mL of tetrahydrofuran, and when dissolution was complete, the mixture was hand-shaken to mix well. The samples were left to stand overnight. One mL of the supernatant was further diluted with 10 mL of tetrahydrofuran and read at a wavelength of 242 nm using quartz cuvettes.

Standard Solutions:
Preparations of 2.0% to 3.0% of hydrocortisone medication sticks were prepared in the same manner as the student preparations, and preparations were used as a linear standard curve to determine the student preparation percentage. Expected Concentration of API: 2.5% hydrocortisone per stick.

Enalapril Tablet Triturates

| Ingredient                | Amount |
|---------------------------|--------|
| Enalapril Maleate USP      | 500 mg |
| Sucrose FCC               | qs*    |
| Lactose, monohydrate      | qs*    |

Method of Preparation:
1. Accurately weigh the ingredients using the prescription balance.
2. Mix the powders using the geometric dilution technique in the mortar using the pestle.
3. Pass the powder mixture through a 40-mesh sieve onto a glassine sheet.
4. Add powder mixture back into the mortar. Using the wetting solution, wet the powder mixture scrapping with a rubber kitchen spatula until the wetted mixture all “sticks” to the pestle. Add three more drops.
5. Transfer the wet powder to the cavity plate of the tablet trituration mold. Ensure that every cavity is completely filled to its capacity. Use sufficient pressure with the hard rubber spatula to ensure that each cavity is tightly packed.
6. Slowly and carefully lower the cavity plate onto the peg plate until the tablets are removed from the cavity plate.
7. Allow the tablets to air dry on the peg plate without removing the cavity plate.
8. When the tablets have dried, remove them from the peg plate and package.
9. Wash and dry the tablet trituration mold.

Note: The tablet triturate mold capacity is approximately 100 mg per cavity.

Process of Analysis:
A tablet was selected at random from the compounded tablets and dissolved in 20 mL of 25% methanol in distilled water. When dissolution was affected, 1 mL of the solution was added to 19 mL of distilled water, the solution was hand shaken, and 20 µL was injected into the HPLC. A mobile phase (pH 2.0) of 65% acetonitrile and 35% 20 mM monobasic potassium phosphate was used in a 4.6 × 150 mm C8 5µ column with a flow rate of 1.8 mL/min. The detector wavelength was 215 nm. The retention time of enalapril was 5.8 minutes.

Standard Solutions:
Preparations of 8-12 mg/tablet of enalapril were prepared in the same manner as the student preparations, and preparations were used as a linear standard curve to determine the student amount of API in the tablet.

Expected Amount of API: 10 mg enalapril per tablet.
Phenol and Menthol Soft Troches

| Ingredient                           | Amount   |
|--------------------------------------|----------|
| Phenol                               | 0.36 g   |
| Menthol                              | 0.24 g   |
| Aspartame                            | 0.55 g   |
| Silica Gel                           | 0.24 g   |
| Acacia                               | 0.5 g    |
| Citric Acid Monohydrate              | 0.7 g    |
| Polyethylene Glycol (PEG) 1450       | qs* (determined after mold calibration) |

Method of Preparation:
1. Turn on the low temperature hotplate to about 60 °C.
2. While the hotplate heats, accurately weigh ingredients using the prescription balance.
3. Place the PEG 1450 into a small beaker (50 mL) and begin heating. Do not add a stir bar at this time.
4. Mix the remaining powders using the geometric dilution technique in the mortar using the pestle.
5. Pass the powder mixture through a 40-mesh sieve onto a glassine sheet.
6. Once the PEG 1450 has melted, reduce the heat, add a stir bar and set at the lowest spin rate.
7. Sprinkle the powders into the melted PEG 1450 ensuring each addition is wetted before adding more powder.
8. Once the powders have been added to the PEG 1450, remove the beaker from the hotplate, allow to cool until it is “just warm to the back of the hand.” If liquefied phenol is used, add at this point.
9. Mix again with a glass stirring rod, and pour the mixture quickly into the mold beginning at the B2 position, overfilling each cavity.
10. After pouring, move a stainless-steel spatula over the mold just touching the melted powder mixture (let the mixture “wick” up to the spatula). Do not touch the mold with the spatula. This will spread the mixture evenly over the mold, and still allow each cavity to be overfilled.

Note: The troche mold capacity is approximately 27 grams of PEG 1450.