An Exploratory Study of Suboxone (Buprenorphine/ Naloxone) Film Splitting: Cutting Methods, Content Uniformity, and Stability

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Introduction
In 2016, an estimated 2.1 million individuals were reported to have substance-use disorder related to opioid pain medications.1 Currently, there are three treatment options for opioid use disorder: 1) methadone, 2) buprenorphine (with or without naloxone), and 3) naltrexone.2 Among these, buprenorphine represents a preferred treatment option due to its unique mechanism of action as a partial agonist at the mu opioid receptor with high affinity and slow dissociation.3 This partial agonist property increases the safety profile of buprenorphine because the ceiling effect limits the potential life-threatening side effects associated with overdose.

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Abstract
Suboxone films are U.S. Food and Drug Administration approved to treat opioid dependence. While the package insert states that films should not be cut, physicians often prescribe film fractions for treatment and tapering. There is no data to support this practice, and this study was initiated to evaluate cutting methods, content uniformity, and stability of split films. Suboxone 8-mg buprenorphine/2-mg naloxone films were split using four methods: 1) ruler/razor cut, 2) scissor cut, 3) fold/rip, and 4) fold/scissor cut. United States Pharmacopeia Chapter <905> was used to evaluate the weight variation and content uniformity of split films. The stability of split films stored in polybags was evaluated over 7 days. A stability-indicating high-performance liquid chromatography method was used for content uniformity and stability evaluation. The weight variation results were acceptable for the half films from all four cutting methods, but this was not true for the quarter films. The method of ruler/razor cut was determined most favorable and used for the content uniformity test. Based on the high-performance liquid chromatography results, the half films from the ruler/razor cut method met the passing criteria of United States Pharmacopeia Chapter <905> with acceptance values of 9.8 to 10.4 for buprenorphine and 8.4 to 11.5 for naloxone (<15 is considered passing). The stability results indicated that both actives retained >97.7% of initial strength. Four cutting methods were found to be acceptable for splitting Suboxone films into half but not quarter fractions. The half films from the ruler/razor cut method also passed United States Pharmacopeia Chapter <905> content uniformity test. Both actives remained stable for 7 days when the half films were stored in polybags at room temperature.

Editor's Note: A modification or alteration to a U.S. Food and Drug Administration-approved drug product is considered "compounding." Splitting and cutting manufactured films falls into the compounding category.
guidelines state that discontinuation of buprenorphine products may be a slow and prolonged process, possibly months to years. However, neither the guidelines nor the product labeling provide any recommendations on the tapering dose or schedule.

Among the buprenorphine/naloxone dosage forms, the Suboxone sublingual films are frequently prescribed for opioid dependence treatment and tapering. Despite clear product labeling that films should not be cut or torn, personal communications with community pharmacies indicate that patients are often prescribed to use partial films such as 1/2 or 1/4 films. Internet community discussion boards and pharmacy benefits management services have also discussed cutting the films as a means to save cost and/or allow for dose titration. Some websites focus on cutting the films to assist with dose tapering, with recommendations for cutting the film into as small as 1/16 of the original size. A literature search did not find any reliable published data to support such practices.

Current data does not indicate if the active ingredients in the film are uniformly distributed across the entire film, making the reliability of dose accuracy in split films unclear. Suboxone films do not contain any scoring or perforation to allow for accurate splitting, increasing the potential for dose variability among split-film fractions. Another potential source of dose variation is the stability of the split films. Suboxone films are packaged individually in polyester/foil laminated pouches intended for single use. Once opened, it is uncertain if the active ingredients remain stable over time. As shown in FIGURE 1, the chemical structures of buprenorphine and naloxone contain several functional groups which are prone to hydrolysis and oxidation.

The lack of data supporting the practice of film splitting lends itself for study. The purpose of this study is to evaluate the accuracy of common methods used to cut Suboxone films and to assess the cut fractions for content uniformity as well as stability outside the original packaging.

**Methods**

**MATERIALS**

Multiple lots of Suboxone (8 mg buprenorphine and 2 mg naloxone) sublingual films, manufactured by Indivior Inc. (NDC 12496-1208-1; Richmond, Virginia), were purchased between 2016 and 2018. For the high-performance liquid chromatography (HPLC) method, all solvents were purchased from Fisher Scientific (Fair Lawn, New Jersey); polytetrafluoroethylene (PTFE) syringe filters, 0.45-μm pore size, and 15-mm diameter, were purchased from Phenomenex (Torrance, California). For the stability study of split-film fractions, 3" x 5" and 2-mil low-density polyethylene bags (polybags) were purchased from Total Pharmacy Supply (Arlington, Texas).

**FILM SPLITTING**

Four splitting methods were evaluated in this study: 1) ruler/razor cut, 2) scissor cut, 3) fold/rip, and 4) fold/scissor cut. The specific details of each method are described in TABLE 1 and shown in FIGURE 2.

A total of 18 whole films (from three different lots) were used for each splitting method. Individuals completing the film splitting were provided with the written instructions shown in TABLE 1. All methods were performed on a clean, glass ointment slab while wearing gloves. Each film was cut midway of the long sides of the film into halves or quarters.

**WEIGHT VARIATION OF SPLIT FILMS**

The weight variation approach from *United States Pharmacopeia (USP)* Chapter <905> was used with modification to evaluate and

**FIGURE 1.**

**CHEMICAL STRUCTURES OF (A) BUPRENORPHINE HYDROCHLORIDE AND (B) NALOXONE HYDROCHLORIDE.**

**A**

**B**

---

**TABLE 1.**

**FILM-SPLITTING METHODS AND INSTRUCTIONS.**

<table>
<thead>
<tr>
<th>SPLITTING METHOD</th>
<th>INSTRUCTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruler/Razor Cut</td>
<td>1. Use the ruler to measure the longer sides of the film.</td>
</tr>
<tr>
<td></td>
<td>2. Mark the halfway points by scoring the film with the razor.</td>
</tr>
<tr>
<td></td>
<td>3. Line up the ruler across both marks scored in the film.</td>
</tr>
<tr>
<td></td>
<td>4. Use the razor to cut the film in half by connecting both halfway points</td>
</tr>
<tr>
<td></td>
<td>while applying pressure to the ruler to ensure the film does not move.</td>
</tr>
<tr>
<td>Scissor Cut</td>
<td>1. Visually estimate the halfway points of the longer sides of the film</td>
</tr>
<tr>
<td></td>
<td>without using any measuring devices.</td>
</tr>
<tr>
<td></td>
<td>2. Use the scissors to cut the film across the estimated halfway points.</td>
</tr>
<tr>
<td>Fold/Rip</td>
<td>1. Fold the film in half and apply pressure to form a crease.</td>
</tr>
<tr>
<td></td>
<td>2. Unfold the film.</td>
</tr>
<tr>
<td></td>
<td>3. Pinch both halves of the film on opposite sides of the crease.</td>
</tr>
<tr>
<td></td>
<td>4. Tear the film by pulling one side towards your body and the other side</td>
</tr>
<tr>
<td></td>
<td>away, rather than pulling both pieces to the side.</td>
</tr>
<tr>
<td>Fold/Scissor Cut</td>
<td>1. Fold the film in half and apply pressure to form a crease.</td>
</tr>
<tr>
<td></td>
<td>2. Unfold the film.</td>
</tr>
<tr>
<td></td>
<td>3. Use the scissors to cut the film along the crease.</td>
</tr>
</tbody>
</table>
compare the accuracy and variability of the four splitting methods. Each whole film was weighed prior to splitting, and this value was used to calculate the expected weight of the half and quarter films. After splitting, the half or quarter portions were immediately weighed. The weight of each split film was divided by the expected value and expressed as the percent expected weight. The standard deviation (SD) was calculated for each splitting method, and an SD of ≤6% was considered acceptable. For direct comparison across the splitting methods, the absolute value of the weight difference (observed weight – expected weight) was also calculated for each split film and used for student t-test analysis. Statistical significance was established if P was ≤0.05. As a control for potential moisture uptake/loss, a set of three films were removed from the foil packets and exposed to the same laboratory atmosphere for the typical duration of the experiments; no significant change in weight was observed.

**DRUG CONTENT UNIFORMITY OF SPLIT FILMS**

Based on the weight variation results, splitting the films into halves was acceptable, and ruler/razor cut was the method of choice. The content uniformity test of USP Chapter <905> was then carried out using an HPLC method to quantitate the amount of the two active ingredients in the split films. Ten whole and ten half films were evaluated as per USP requirement. The ten half films were obtained by splitting five whole films using the ruler/razor cut method. Each whole or half film was dissolved in a sufficient amount of water to yield a theoretical concentration of 80 μg/mL buprenorphine and 20 μg/mL naloxone. About 1-mL aliquot from each sample was filtered through a PTFE syringe filter and collected in a vial for the HPLC assay. The content uniformity test was conducted on three separate lots of the films with each lot being evaluated on a different day. The percent label claim was calculated for each lot, and the mean and standard deviation values were used to calculate the acceptance value (AV) as described in USP <905>. An AV of ≤15 was considered passing.

**STABILITY OF SPLIT FILMS**

A 7-day stability study was conducted to evaluate the physical and chemical stability of the split films outside the original foil pouch. Films were removed from packaging and split in half. Each half film was placed into a polybag and stored at room temperature. On Day 0, 1, 3, and 7, three replicate samples were pulled for analysis by visual inspection and HPLC. Each half film was dissolved in a sufficient amount of water to yield a theoretical concentration of 80 μg/mL buprenorphine and 20 μg/mL naloxone. Standards were included for the HPLC assay on each day for calibration purpose. Samples were considered stable if there was less than 10% loss of each active.

**HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY ASSAY**

A stability-indicating HPLC method was developed to assay the content of buprenorphine and naloxone in the films and to monitor their stability when stored outside the original packaging. The analysis was performed using a Shimadzu LC-2010AHT system (Shimadzu Scientific Instruments, Marlborough, Massachusetts) with a Phenomenex C18 column (Kinetex, 150 x 4.6 mm, 5 μm, 100 A). The mobile phase consisted of two channels: A = water with 0.1% v/v TFA and B = acetonitrile with 0.1% v/v TFA. Due to the vastly different polarity of the two actives, a linear gradient was used from 15% to 55% of B over 10 minutes with a 5-minute re-equilibration period. The column oven temperature was maintained at 40°C, and the flow rate was 0.8 mL/min. All samples were passed through the PTFE 45-μm syringe filters prior to analysis, and the injection volume of each sample was 50 μL. The UV detection wavelength was set at 280 nm. Under these conditions the retention time for naloxone was around 9.8 minutes and buprenorphine around 8.8 minutes. A representative chromatogram is shown in FIGURE 3.

**FIGURE 3.**

**VISUAL REPRESENTATION OF THE FOUR FILM-CUTTING METHODS.**

A. Ruler/Razer Cut

B. Scissor Cut

C. Fold/Rip

D. Fold/Scissor Cut

Standard solutions of naloxone and buprenorphine were prepared for calibration purpose. Due to the regulatory barriers to obtain pure buprenorphine powder, calibration standards were prepared using Suboxone films (one from each corresponding lot) with the assumption that they contain 100% of the label claim quantity of each active. The concentrations of the standard solutions ranged from 64/16 μg/mL to 96/24 μg/mL buprenorphine/naloxone, covering 80% to 120% of the theoretical concentration of study samples. A calibration curve was constructed on each analysis day by linear regression of the peak area and drug concentration; separate curves were made for buprenorphine and naloxone. All calibration curves had a R² value of 0.99 or better, confirming linearity over the concentration range of interest. A forced degradation study was conducted to verify the ability of the above gradient HPLC method to separate the
potential degradation products from the two active ingredients. An 80/20 \( \mu \)g/mL buprenorphine/naloxone solution was prepared by dissolving a Suboxone film in water. The solution was divided into four different samples.

- Sample #1 was adjusted to a pH of 2 with 1 M hydrogen chloride and incubated in a 60°C oven.
- Sample #2 was adjusted to a pH of 12 with 1 M sodium hydroxide and incubated in a 60°C oven.
- Sample #3 was spiked with 3% (final concentration) hydrogen peroxide and incubated in a 60°C oven.
- Sample #4 was spiked with 3% (final concentration) hydrogen peroxide and was stored at room temperature and exposed to direct sunlight.

After 48 hours, complete degradation of both actives was observed in Sample #3 (peroxide/60°C). A significant amount of degradation (32% to 65%) was also observed for Sample #2 (pH 12/60°C) and Sample #4 (peroxide/light). Both actives remained stable in Sample #1 (pH 2/60°C). All the degradation products were separated from the two active ingredients, and no interfering peaks were observed. The gradient HPLC method was considered to be stability indicating and suitable for the content uniformity and stability evaluation.

**Results and Discussion**

While multiple sources suggested that patients are splitting Suboxone sublingual films, no data are available to support this practice. Several studies conducted on traditional tablets provided context and discussed challenges associated with splitting dosage forms. Sublingual films are a relatively new class of dosage forms with unique properties. To the authors' knowledge, this is the first study to evaluate film-splitting methods and content uniformity of the resulting film fractions.

**EVALUATION OF FILM-SPLITTING METHODS**

All four splitting methods were carried out successfully without major handling issues. However, several limitations were observed. Due to the small size of the film, all methods required manual dexterity and visual acuity. The films also did not tear easily along a fold, so it was important to follow the exact directions included in Table 1 for the fold/rip method. Cutting accurately along the fold using scissors was also found to be more difficult than expected.

The weight variation results of the split films are summarized in Table 2. For the half films, the standard deviation of the four splitting methods ranged from 3.4% to 4.8%, which met the passing criteria of 6%. However, for the quarter films, the standard deviation increased for each splitting method, and only the ruler/razor cut method passed the test with a value of 5.2%. Similar trends were observed from the student t-test analysis of the absolute weight differences (actual – expected) among the four splitting methods as shown in Table 3. For half films, using scissors to split the films led to a significantly greater weight difference compared to the other three splitting methods combined (ruler/razor, fold/rip, fold/scissor); 0.85 vs. 0.60, \( P = 0.032 \). The quarter films indicated a similar trend with the two scissor methods yielding greater weight differences; however, only the results of the fold/scissor method were statistically significant (0.60 vs. 0.50, \( P = 0.013 \)). Additionally for the quarter films, the fold/rip method had a significantly smaller weight difference compared to the other three methods (0.48 vs. 0.55, \( P = 0.025 \)); this might be due to the fact that the other three methods included the two scissor methods.

Based on the overall weight results, splitting the Suboxone (8 mg buprenorphine/2 mg naloxone) films into halves was considered acceptable using all four cutting methods, with the scissor cut method being the least consistent. However, splitting the films into quarters or beyond was not acceptable due to significant weight variation.
TABLE 3. COMPARISON OF THE FOUR SPLITTING METHODS USING THE ABSOLUTE WEIGHT DIFFERENCE OF THE SPLIT FILMS.

<table>
<thead>
<tr>
<th>SPLITTING METHODS</th>
<th>HALF FILMS</th>
<th>QUARTER FILMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN (SD)</td>
<td>MEDIAN (IQR)</td>
</tr>
<tr>
<td>Ruler/Razor Cut</td>
<td>0.69 (0.49)</td>
<td>0.60 (0.35 to 0.90)</td>
</tr>
<tr>
<td>Other 3 Methods</td>
<td>0.84 (0.76)</td>
<td>0.65 (0.35 to 1.10)</td>
</tr>
<tr>
<td>Scissor Cut</td>
<td>0.93 (0.59)</td>
<td>0.85 (0.48 to 1.40)</td>
</tr>
<tr>
<td>Other 3 Methods</td>
<td>0.76 (0.73)</td>
<td>0.60 (0.30 to 0.95)</td>
</tr>
<tr>
<td>Fold/Rip</td>
<td>0.73 (0.82)</td>
<td>0.50 (0.25 to 0.85)</td>
</tr>
<tr>
<td>Other 3 Methods</td>
<td>0.83 (0.66)</td>
<td>0.75 (0.40 to 1.10)</td>
</tr>
<tr>
<td>Fold/Scissor Cut</td>
<td>0.86 (0.84)</td>
<td>0.68 (0.30 to 1.00)</td>
</tr>
<tr>
<td>Other 3 Methods</td>
<td>0.78 (0.65)</td>
<td>0.65 (0.35 to 1.00)</td>
</tr>
</tbody>
</table>

Absolute weight difference (mg) = | actual weight (mg) - expected weight (mg) | IQR = interquartile range; SD = standard deviation.

Note: The bolded results represent a statistically significant difference for the splitting method when compared to the other methods.

CONTENT UNIFORMITY OF SPLIT FILMS

While the weight variation results provided useful information, direct measurement of the active ingredients by HPLC was necessary to confirm the actual drug contents in the split films. To this end, the content uniformity test procedure of USP <905> was applied to analyze the half films prepared by the ruler/razor cut method.13 Three different lots were tested in case there was any significant lot-to-lot variability. The whole films were also analyzed for comparison purpose. The content uniformity analysis was performed for both buprenorphine and naloxone, and the acceptance value (AV) was calculated using the formula in USP <905>. As shown in TABLE 4, the AV results of buprenorphine ranged from 7.2 to 12.1 for the whole films and 9.8 to 10.4 for the half films. Similarly in Table 5, the AV results of naloxone ranged from 8.2 to 11.1 for the whole films and 8.4 to 11.5 for the half films. According to USP <905>, an AV of ≤15 is considered passing.11 Based on this criterion, the content uniformity of buprenorphine and naloxone was considered acceptable in the half films from all three lots. Additionally, the AV values of the half films were comparable to those of the whole films.

STABILITY OF SPLIT FILMS

Based on the chemical structures (Figure 1) and the forced stability study results (Methods section), there was a potential concern for the stability of buprenorphine and naloxone once the films are removed from the original packaging. The physical stability of the films was also unknown. A 7-day stability study of the split films was conducted to address these concerns. The half films were stored in polybags at room temperature. Based on visual inspection, the films appeared to lose some flexibility over seven days, but they did not become too fragile for normal handling. The chemical stability was monitored by the stability-indicating HPLC assay, and the results are shown in TABLE 6. Both buprenorphine and naloxone retained >97.7% of their initial strengths over the study period.
TABLE 6.
CHEMICAL STABILITY OF THE TWO ACTIVE INGREDIENTS IN THE HALF FILMS STORED IN POLYBAGS OVER 7 DAYS AT ROOM TEMPERATURE (n=3 FOR EACH TIME POINT).

<table>
<thead>
<tr>
<th>ACTIVE INGREDIENT</th>
<th>INITIAL DRUG CONTENT (MG), MEAN ± SD</th>
<th>% INITIAL DRUG CONTENT REMAINING, MEAN ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAY 1</td>
<td>DAY 3</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>4.28 ± 0.09</td>
<td>100.8 ± 0.8</td>
</tr>
<tr>
<td>Naloxone</td>
<td>1.08 ± 0.01</td>
<td>99.6 ± 1.3</td>
</tr>
</tbody>
</table>

SD = standard deviation

STUDY LIMITATIONS
First, this study only evaluated one strength (8 mg buprenorphine and 2 mg naloxone) of Suboxone films. It is unknown if these findings also apply to the other strengths, since the package insert states that there is some variation in film composition between strengths. Secondly, due to regulatory challenges to obtain the pure buprenorphine powder, this study used a single Suboxone film to prepare the HPLC calibration standards on each analysis day. This may explain why the average drug content was >100% of the label claim in all samples (TABLES 4 AND 5). Nevertheless, this was taken into account for the calculation of the acceptance values, and the overall conclusions remained the same. In future studies, standards should be prepared using pure drug if attainable or a pooled solution of multiple films to improve accuracy of the standards.

Conclusion
Four cutting methods were found to be acceptable to split the Suboxone film (8 mg/2 mg strength) into half fractions based on weight variation data. Additionally, the content uniformity of the actives in the half films was confirmed for the ruler/razor cut method. The half films were stable for at least seven days when stored in polybags at room temperature. The data did not support cutting the films into pieces smaller than halves due to considerable weight variation between pieces.

It should be emphasized that this is an exploratory feasibility study. According to the package insert, the size and excipient composition of Suboxone films differ between the strengths, which in turn may affect the rate and extent of buprenorphine absorption. Prescribing film fractions represents an off-label use, and patients should be closely monitored for symptoms related to over- or under-dosing. Due to the lack of available data to support the use of Suboxone film fractions to treat or taper opioid dependence, this practice should be approached carefully, and more clinical studies are needed. A call for scientific publication of relevant clinical practice is highly recommended.

References

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