FENTANYL TRANSDERMAL PATCHES: EXTRACTION OPTIMIZATION AND EVALUATION OF A NOVEL DISPOSAL METHOD USING NARCX®

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ABSTRACT

Travis Worst, Advisor

Currently, there is no known commercially available product for disposing of used fentanyl transdermal patches. In order to eliminate the potential for harm and abuse, a proper disposal method is needed - one that neutralizes the dangerous amount of residual fentanyl that often remains even after proper use. We propose creating a device, called "the patch catcher", which would lock the patch inside and subject it to NarcX®, a patent-pending liquid solution of activated carbon. In order to determine the amount of fentanyl remaining after a patch is treated with NarcX®, here a method has been optimized that uses hexanes to dissolve the patch adhesive followed by liquid-liquid extraction with methanol to recover the fentanyl. Using LC/MS, the extracts obtained with this method have shown between 85% and 117% recovery of fentanyl from new patches. This method optimization allowed for a quantitative evaluation of NarcX® treated fentanyl patches. 100 µg/h Apotex brand fentanyl patches were exposed to NarcX® for varying amounts of time (1, 24, 48, and 72 hours), and NarcX® was shown to adsorb fentanyl from the patches with varying degrees of success, demonstrating 67% fentanyl adsorption after 72 hours of NarcX® exposure. More work is needed to successfully neutralize the fentanyl patches in their entirety using NarcX®; however, this work demonstrates proof of concept.

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INTRODUCTION

Fentanyl, the structure for which can be seen in **Figure 1**, is a Schedule II synthetic opioid that was first synthesized in 1960. [1] As described by the United States Drug Enforcement Agency (DEA), a Schedule II drug is one that has a high abuse potential, but does have some accepted medical uses; currently there are five drug Schedules with I having the highest potential for abuse and dependency and V having the lowest potential. [7] Fentanyl affects the body by binding to and activating mu opioid receptors in the brain, which not only causes euphoria and analgesia, but also reinforces the addictive behavior due to the fact that the receptors are part of the reward pathway. [1, 5] When compared to another analgesic, morphine, fentanyl is understood to be 50-100 times more potent. [2] In addition, fentanyl's effects are seen quicker and last for a shorter time period than those of morphine. [1] These differences between morphine and fentanyl may be partially explained by the fact that fentanyl is very lipophilic, compared to morphine, which allows for fentanyl to more easily cross the blood brain barrier. [5,1,3] All of these factors contribute to fentanyl being a drug of abuse.

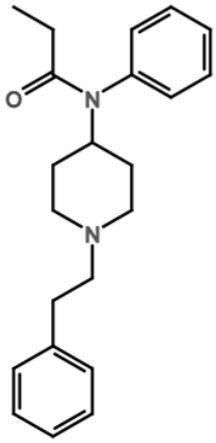

Figure 1: Chemical Structure of Fentanyl

The fact that fentanyl is lipophilic and has a relatively low molecular weight (336.5 g/mole), makes it a good candidate to be used in a transdermal delivery system, commonly referred to as a "patch". [2,3] Fentanyl transdermal patches are available in varying dosages ranging from 12.5 to 100 µg/h. [4] These transdermal drug delivery systems, or patches, come in two varieties: the reservoir type and the matrix type, as shown in **Figure 2**. The main difference between these two delivery systems being where the fentanyl is located. In the reservoir type, the fentanyl is maintained in a liquid-gel state within a reservoir, while in the matrix type, the fentanyl is located within in the patch's adhesive. [3] This research will focus on the matrix-type patch, as reservoir-type are being phased-out of production.

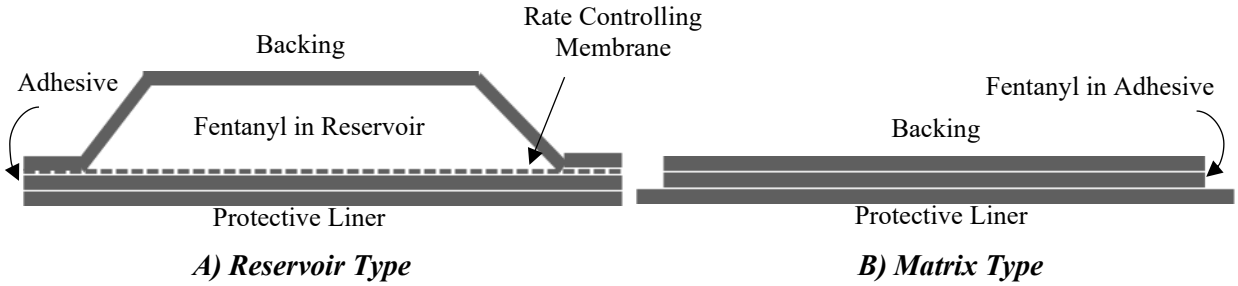

Figure 2: Types of Transdermal Fentanyl Patches: A) Reservoir and B) Matrix.
(figure modified from reference 3)

Regardless of the type of patch, the general method in which the fentanyl enters the body is the same. [3] Fentanyl moves from the patch into the skin due to the concentration gradient that is inherently created once the patch is applied. [5] Due to the lipophilic nature of fentanyl, it is promptly absorbed into the epidermal layer of skin. However, its dispersion is then drastically slowed due to the fact that the next layer of skin, the dermal layer, has a high water content. Because of this, the fentanyl accumulates, effectively forming a pouch in the epidermal layer. The fentanyl is then slowly released into the dermal layer where it can enter the blood stream. [3]

When these patches are applied to a patient, they release the average dosage per hour that is specified for that specific patch. However, in order to achieve that dosage, the patches are manufactured with more fentanyl than what will actually be released to the patient, meaning that following use, there is still a substantial amount of fentanyl remaining in each used patch. [6,8] Due to inter-patient differences, the amount of residual fentanyl is not consistent, having been reported as ranging from 28% to 84.4%, which translates to between 0.7 - 1.22 mg of fentanyl remaining in the 25 µg/h patches and between 4.46 - 8.44 mg of fentanyl in the 100 µg/h patches. [8] More recently, it has been reported that the amount of fentanyl in used patches (the dosages of the patches studied were 25, 50, 75, and 100 µg/h) ranges from 43% - 68%, or 1.8 - 2.4 mg, 4.8 - 5.3 mg, 6.9 - 7.5 mg, and 9.7 - 11.4 mg, respectively. [6] Alarmingly, the average lethal dose of fentanyl has been reported by the DEA as only 2 mg, although no data has been found to support that assertion, and especially in the opioid naïve, the acute toxicity is likely much lower. [9] As evidenced by the residual amounts reported from the literature above, even the lowest dosage patches tested, still contained a potentially lethal amount of fentanyl after prescribed use.

Clearly, the amount of residual fentanyl in a patch after use creates a huge potential for harm. [10] For example, a published case study describes an incident where a 1 year old female was found deceased; her cause of death was determined to be fentanyl overdose due to ingestion of a used fentanyl patch. The child's caregiver was using 25 µg/h fentanyl patches; on the day of the child's death, the caregiver changed her patch, accidentally dropping her used patch on the floor. The child found the patch and ate it, ultimately killing her. [10] While these accidental contacts do happen, abuse of the used patches is more prevalently reported. [11] The use and abuse of discarded fentanyl patches in a number of imaginative ways has been documented,

including: ingestion, using more patches than prescribed, injection, and inhalation. [12] One case study, in particular, described the deaths of seven individuals (aged 20-51) due to 'oral abuse', which was defined as ingesting patches, sucking on/soaking the patch in the mouth, and chewing on patches. [13] In another review, the authors compiled case reports and publications found on PubMed describing fentanyl patch related deaths going back 26 years, which totaled 658 reported deaths; of these, the most commonly seen methods of abuse were transdermal, oral, and then intravenous. [11]

The currently prescribed method of disposal for used fentanyl patches is flushing them down the toilet. Janssen Pharmaceuticals, the manufacturer of the Duragesic® patches, suggests folding the used patches, prior to flushing them, so that the adhesive side is stuck on the inside. [14] Interestingly, this is also how the United States Food and Drug Administration (FDA) instructs people to dispose of used fentanyl patches, while admitting that this disposal method may present 'negligible' problems for the environment. [15] Although flushing eliminates the immediate threat of accidental contact or abuse, it does not completely remove the potential for abuse or harm because flushing does not degrade or sequester the residual fentanyl. ***A better disposal method is needed, one that destroys or irreversibly binds fentanyl, completely eliminating its potential for abuse.***

NarcX® is a patent-pending solution marketed for the disposal of unused medications and drugs. Although their formula is proprietary, in the manufacturer's patent application, it states that activated carbon is the main ingredient in NarcX®, and the patent application further explains that activated carbon works by permanently adsorbing the drugs. [16] Activated carbon would be useful for adsorption because it is highly porous and, therefore, has a large internal surface area [16] The manufacturer claims that NarcX® is effective in disposing of opiates;

although, it has not been used for disposing of transdermal patches. [17] However, Herwadkar et al. suggest that activated charcoal could work as a disposal method for fentanyl transdermal patches. [18] In the Herwadkar study, a sheet containing activated charcoal was used to deactivate the patches by adsorbing the fentanyl, and it was found that after 96 hours of the patch being in contact with the activated charcoal, they were only able to extract 9.34% of the amount of fentanyl extracted from a control, thus suggesting that over 90% of the fentanyl was adsorbed from the patch into the activated charcoal fabric. [18] Although this study did not use a liquid solution of activated charcoal, like NarcX®, it demonstrates a proof of concept for removal of fentanyl from patches using activated charcoal. In fact, the liquid solution may work better and require a shorter exposure duration because it may be able to access the drug better than the fabric.

In summary, to eliminate the abuse potential, a proper disposal method is needed for medicinal fentanyl transdermal patches. The best way to dispose of these patches would be in a manner that neutralizes the threat of abuse and harm, i.e. they should not simply be discarded with other household waste. Currently, there is no known commercially available product capable of either degrading or irreversibly binding the unused fentanyl within the patch, rendering it useless. Therefore, I propose using a liquid, activated charcoal product, NarcX®, as a fentanyl-eliminating solution.

METHODS

Materials

All chemicals used were purchased from Sigma-Aldrich (St. Louis, MO) or Thermo Fisher Scientific (Fair Lawn, NJ), unless otherwise specified. The fentanyl transdermal patches studied were as follows: Apotex (Apotex Corp., Weston, FL) 100, 87.5, 75, 62.5, 50, 25, 12.5 µg/h; Mylan® (Mylan Pharmaceuticals Inc., Morgantown, WV) 100 µg/h; Mallinckrodt™ (LTS Lohmann Therapy Systems Corporation, W. Caldwell, NJ) 100 µg/h; Alvogen® (3M Drug Delivery Systems, St. Paul, MN) 100 µg/h; Duragesic® (ALZA Corporation, Vacaville, CA) 100 µg/h. All dosages and brands of fentanyl transdermal patches were purchased from Ohio Pharmacy Services (Columbus, OH). The NarcX® used was obtained directly from NarcX® (SaltLake City, UT) The fentanyl standards for LC-MS were purchases from Cerilliant (Round Rock, TX).

Analysis

All instrumental analyses were performed on a Shimadzu LC/MS-8050 with a triple quadrupole detector, using a method that has been previously validated in our laboratory. The column used for separation was a Raptor biphenyl (2.7 µm, 50 x 2.1 mm) column with a force biphenyl EXP guard column both by Restek (Bellefonte, PA). The instrument run method used was in positive ion mode, with a mobile phase A of 0.1% acetic acid (4 mL 100% acetic acid LC/MS grade (EMD Millipore Corporation, Billerica, MA) into a 4 liter bottle of LC/MS grade water), and a mobile phase B of methanol (LC/MS grade). A mobile phase gradient starting at 1% methanol and gradually increasing to 100% methanol was utilized. The flow rate was consistently set to be 0.75 mL/min, with a 3 µL injection volume. The column oven temperature was set to 70°C and the ESI interface temperature set to 400°C. The precursor ion targeted had a

342.30 m/z, and the product ion targeted had a 188.20 m/z. Each run incorporated null injections, methanol blank injections, and fentanyl quality control checks to ensure that the instrument was working correctly. In addition, an eight point calibration curve ranging from 0.4 – 100 ng/mL prepared from fentanyl standards, using deuterated fentanyl as an internal standard, was run with every analysis. All fentanyl solutions were prepared by diluting a 1.0 mg/mL purchased fentanyl standard stock solution using methanol. Data analysis was performed using the LabSolutions Insight software (version 5.93). All statistical analyses were conducted in the freely available statistical software R (r-project.org, version 4.0.3)

Where necessary GC/MS analysis was done using the following parameters on an Intuvo 9000 GC/MS. The column used was an Agilent (Santa Clara, CA) DB-5MS UI 20m, 0.18mm, 0.18µm. A 1 µl injection was used. A gradient temperature program was used that started at 100°C held for one minute, the temperature was then ramped up 40°C per minute until a temperature of 300°C was reached. This was then held for one minute and then ramped up again 40°C per minute until the final temperature of 315°C was reached. This temperature was held for the remainder of the run. The software used for this analysis was MassHunter Workstation Software (version B.08.00) by Agilent.

Optimization of Extraction Method

All optimization was performed using Apotex 100 µg/h patches, which the manufacturer reports should contain 11.04 mg of fentanyl in its adhesive. [21] First, the method reported by Van Nimmen and Veulemans was attempted. [6] This involved cutting up a single patch into strips and placing the strips into 20 mL of freshly opened methanol (LC/MS grade). The patch and methanol were then shaken/vortexed for 15 minutes. Additionally, this method of fentanyl extraction was evaluated using a whole patch, rather than cutting the patch into strips. There

were two methods of agitation evaluated as well: 1) The patch was placed in a shallow glass container and allowed to shake on a Thermo Scientific LP Vortex Mixer set at a speed of 500 rpm. 2) The patch was placed in a 50 mL conical tube and a mix of hand shaking and vortexing on a Fisher Scientific Digital Vortex Mixer set at a speed of 2000 rpm was used. All extracts were diluted 10,000-fold and analyzed on the LC/MS, using the previously described method. When low fentanyl yields that were inconsistent with the published data were obtained from the Apotex patches, the Van Nimmen and Veulemans methanol extraction method was also attempted on Duragesic® patches (100 µg/h), as this was what was used in the original study.

As an alteration to the Van Nimmen and Veulemans methanol extraction method, a heating step was added to the extraction process. Due to instrumentation constraints, I was unable to shake and heat simultaneously. Therefore, the use of heat replaced the shaking in this extraction. This method was evaluated using both a whole patch and a patch cut into strips. In both cases, the patch (either whole or cut into strips) was placed into 20 mL of freshly opened methanol (LC/MS grade) and incubated at 37°C for 15 minutes. The methanol was then evaporated using nitrogen and the sample residue was reconstituted in 1 mL of methanol (LC/MS grade), which was then serially diluted down to 1:100,000 and analyzed on the LC/MS using the method previously described above.

An aqueous solution of trisodium phosphate was also attempted as the extraction solvent [27]. A whole patch was shaken, using shaking method 1 described above, in 20 mL of a 25% trisodium phosphate solution for 15 minutes. After removing the patch, the pH of the solution was adjusted to between pH 6.0 and pH 6.5 through dropwise addition of 36.5-38% HCl (VWR Analytical, Radnor, PA). To remove any potential adhesive residue and concentrate the fentanyl, the pH-adjusted trisodium phosphate solution was subjected to solid phase extraction, under

vacuum, using a Clean Screen® extraction column, following a published method from United Chemical Technologies. [19] Briefly, the column was conditioned using 3 mL of methanol (LC/MS grade), followed by 3 mL of deionized (DI) water, and finally 1 mL of a 100 mM phosphate buffer. The sample was then applied to the column and slowly passed through via vacuum pressure. The column was then washed with 3 mL of DI water, followed by 1 mL of 100 mM acetic acid (made from 17.4 M glacial acetic acid), followed by 3 mL of methanol (LC/MS grade). The column was then allowed to dry down by pulling ambient room air through the column via vacuum for 5 minutes. Finally, the column was eluted using 3 mL of a solution of dichloromethane (≥99.9%)/isopropyl alcohol (99.9%)/ammonium hydroxide (28-30%) (39:10:1). The eluant was then dried down using nitrogen and reconstituted in 1 mL of methanol (LC/MS grade), which was then diluted to 1:100,000 and run on the LC/MS using the previously described method.

Finally, hexanes (HPLC grade) were evaluated as the extraction solvent. A whole patch was soaked in 20 mL of hexanes, covered, for a minimum of 20 minutes. This volume of hexanes was then removed and set aside, and an additional 5 mL of fresh hexanes was added to the patch; any remaining adhesive was scraped from the patch using a spatula and added back to the solution. This 5 ml of hexanes and adhesive were then removed from the patch and combined with the first 20 mL of hexanes solution. A fresh 20 mL of hexanes was then added to the patch and allowed to sit, covered, for approximately 2 hours while the previously removed 25 mL hexanes/adhesive solution was subjected to a liquid-liquid extraction process using 9.5 mL of methanol (ACS grade) and 0.5 mL of DI water. The liquid-liquid extraction with methanol and water was repeated on the sample for a total of three washes. After soaking for approximately 2 hours, the hexanes from the final soak was removed and subjected to the same liquid-liquid

extraction procedure, for a total of one wash. Each of the four methanol washes were collected independently, diluted to 1:10,000 in methanol, and analyzed separately using the LC/MS method described above. This extraction method is further referred to as the hexane extraction method.

Evaluation of Extraction Method on Various Patches

The 100 µg/h dosage of all of the patch brands available to us were tested using the extraction method published by Van Nimmen and Veulemans (cut-up patch shaken in 20 mL methanol for 15 minutes) and also using the optimized hexane extraction method described above. This was done to determine if one extraction method would outperform the other, based on the specific adhesive type for each brand of patch. The Apotex patches use a polyisobutene adhesive, while the Mylan® and Mallinckrodt™ patches use a silicone adhesive, the Alvogen® patches use an acrylate copolymer adhesive, and the Duragesic® patches use a polyacrylate adhesive (**Table 1**) . [22-26] Owing to the different chemical properties of each adhesive, there was a concern that it may be necessary to use a different fentanyl extraction method to analyze each brand of patch. Specifically, from this, it was determined that the Apotex, Mylan®, and Mallinckrodt™ patches should be extracted using the hexane extraction method, and the Alvogen® and Duragesic® patches should be extracted using the Van Nimmen and Veulemans method.

Table 1: Differences Between Patches of Varying Brands (100 µg/h)

Brand	Adhesive	Amount of Fentanyl (mg)	Inactive Ingredients	Size (cm^2)
Apotex	Polyisobutene adhesive	11.04	Isopropyl myristate, octyldodecanol, polybutene	42.8
Mylan®	Silicone adhesive	10.20	Dimethicone NF	25
Mallinckrodt™	Silicone adhesive	11.0	Dipropylene glycol, hydroxypropyl cellulose, Ethylene vinyl-acetate coplymer	31.3
Alvogen®	Acrylate copolymer adhesive	10.65	Methyl laurate	37.76
Duragesic®	Polyacrylate adhesive	12.4	Isopropyl myristate	44

As a means of comparison, the optimized hexane extraction method was then tested on a range of dosages (12.5, 25, 50, 62.5, 75, 87.5, and 100 µg/h) of the Apotex patches and on the brands available to us (Apotex, Mylan®, Mallinckrodt™, and Alvogen®) at the 100 µg/h dosage. The amount of fentanyl extracted for each dosage and brand was compared to the corresponding manufacturer provided theoretical fentanyl amount per patch, using a single sample t-test. Further, one-way ANOVAs were used to compare the percent recovery among the different patch dosages and among the different brands. A Tukey's Honest Significant Difference (HSD) post hoc analysis was performed, where necessary.

Prior to laboratory testing, a power analysis had been performed in R to determine the number of patches needed for each analysis. For both the single sample t-test and ANOVA, the parameters used for the power analysis were: a large effect size of 0.8, power (1-β) of 0.8, and significance (α) of 0.05. For the single sample t-test, the result of the power analysis indicated that the sample size for each group should be 26 patches. For comparison of the seven Apotex patch dosages, the ANOVA power analysis determined that each of the groups should have a

sample size of 5 patches. The sample size needed for comparing between the different brands was determined to be 6. As can be seen, the single sample t-test analysis would require substantially more patches for analysis than the ANOVA analysis. However, due to constraints on resources, the large sample sizes needed for the t-test analysis was not feasible for this study. The actual sample size used for these studies was 8 patches per group. After laboratory testing, another power analysis was conducted with an n of 8, α of 0.05, and effect size of 0.8, in order to determine the statistical power of the analysis performed in this study; the result of this showed a power of 32%.

Evaluation of NarcX®

In evaluating NarcX®, the 100 µg/h Apotex patches were used. The volume of NarcX® used was 20 mL; this volume was chosen due to the fact that the "patch catcher" device being developed can only hold a maximum volume of 23 mL. The patches were soaked in the NarcX® solution for various periods of time, including: 1 hour, 24 hours, 48 hours, and 72 hours. After soaking the patches in NarcX® for the specified time period, the patches were then rinsed with deionized water, and the optimized hexane extraction method described above was used to extract the remaining fentanyl from the NarcX® treated patch. Those residual fentanyl extracts were then diluted 1:10,000 in methanol and analyzed using the same LC/MS method described previously.

Two sample t-tests were performed to compare the amount of residual fentanyl recovered from the NarcX® treated patch to the amount of fentanyl recovered from fresh untreated patches for each NarcX® exposure time. In addition, the average percentage of fentanyl neutralized by NarcX® treatment at each time period was compared using ANOVA and a Tukey's HSD post hoc analysis. The same power analysis described above applies here as well. The power analysis

for the two sample t-test indicated that 26 patches per time period should be tested. For comparing the four time periods, the power analysis for ANOVA determined that 6 patches would be needed per time period. Again, due to constraints in resources, it was not feasible to test 26 patches per time period; therefore, 8 patches per time period were analyzed. Again, after laboratory testing, another power analysis was conducted with an n of 8, α of 0.05, and effect size of 0.8, in order to determine the statistical power of the analysis performed in this study. The statistical power was determined to be 32%.

RESULTS

Optimization of Extraction Method

The amount of fentanyl able to be extracted from the 100 µg/h Apotex patches during the optimization is presented below in **Table 2**. With the methanol method by Van Nimmen and Veulemans, there was a 5.77% recovery of the fentanyl from the patch that was cut into strips and shaken. The addition of heat, rather than shaking, to the Van Nimmen and Veulemans methanol extraction method demonstrated a slightly better recovery (6.62%) than the cutting and shaking . Trisodium phosphate as the extraction solvent showed the lowest recovery at 0.36%. Ultimately, the optimized hexane method, which was used primarily throughout the course of the rest of this study, showed on average 96.34% recovery. After testing the method previously published by Van Nimmen and Veulemans on the Apotex patch, it was also tested on 100 µg/h Duragesic® patches, which have a different adhesive than Apotex. The results of this analysis can be seen in **Table 3**.

Table 2: Extraction Method Optimization using 100 µg/h Apotex Patches

Extraction Method	Fentanyl Extracted (mg)	Percent Recovery
Whole Patch Shaken	0.23	2.06
Cut Up Patch Shaken	0.64	5.77
Whole Patch Heated	0.42	3.83
Cut Up Patch Heated	0.73	6.62
Trisodium Phosphate	0.04	0.36
Hexanes	10.64	96.34

Whole Patch Shaken: whole patch shaken in 20 mL methanol using shaking method 1 for 15 minutes
Cut Up Patch Shaken: (Van Nimmen & Veulemans method) cut up patch shaken in 20 mL methanol using shaking method 1 for 15 minutes [6]
Whole Patch Heated: whole patch heated in 20 mL methanol at 37°C for 15 minutes
Cut Up Patch Heated: cut up patch heated in 20 mL methanol at 37°C for 15 minutes
Trisodium Phosphate: whole patch shaken in 20 mL 25% trisodium phosphate solution using shaking method 1 for 15 minutes
Hexanes: whole patch soaked in 20 mL hexanes followed by liquid-liquid extractions of the hexanes using methanol

Table 3: Analysis of the Van Nimmen and Veulemans Method on 100 µg/h Duragesic® Patches

Extraction Method	Fentanyl Extracted (mg)	Percent Recovery
Cut Up Patch Shaken – Method 1	9.81	79.14
Cut Up Patch Shaken – Method 2	11.56	93.20

Cut Up Patch Shaken: (Van Nimmen & Veulemans method) cut up patch shaken in 20 mL methanol for 15 minutes [6]
Shaking Method 1: gentler shaking using a Thermo Scientific LP Vortex Mixer in shallow glass container at speed of 500 rpm
Shaking Method 2: vigorous shaking using a mix of hand shaking and vortexing in a 50 mL conical tube on a Fisher Scientific Digital Vortex Mixer at speed of 2000 rpm

Evaluation of Extraction Method on Various Patches

The optimized hexane extraction method was tested on seven different dosages of Apotex brand patches. At each dosage, eight replicate extractions were performed. The results from each replicate for every dose tested can be seen in **Table 4**. The average percent recoveries obtained were all between 92% and 106%.

Table 4: Replicate Hexane Extractions of Varying Dosages of Apotex Patches

Replicate	100 µg/h		87.5 µg/h		75 µg/h		62.5 µg/h		50 µg/h		25 µg/h		12.5 µg/h	
	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery
1	11.44	103.64	8.95	92.62	7.88	95.22	7.19	104.19	5.18	93.90	3.08	111.61	1.37	99.09
2	10.21	92.49	8.98	93.02	8.02	96.83	6.25	90.55	4.79	86.84	2.46	89.20	1.39	100.91
3	10.57	95.72	9.09	94.13	7.50	90.58	6.46	93.70	5.14	93.21	3.10	112.23	1.41	101.89
4	10.07	91.19	8.94	92.54	8.10	97.8	6.68	96.80	5.52	100.08	2.50	90.58	1.24	89.96
5	9.97	90.32	9.14	94.63	8.27	99.84	7.81	113.21	5.34	96.74	2.96	107.41	1.29	93.37
6	11.58	104.87	9.04	93.61	8.58	103.68	7.39	107.07	4.97	89.98	3.24	117.23	1.42	103.11
7	9.73	88.10	9.08	94.01	8.45	102.08	6.63	96.13	4.97	90.00	2.96	107.37	1.46	105.93
8	11.52	104.37	9.10	94.25	7.04	85.04	6.57	95.28	5.05	91.43	2.91	105.56	1.36	98.35
Average	**10.64**	**96.34**	**9.04**	**93.60**	**7.98**	**96.39**	**6.87**	**99.62**	**5.12**	**92.77**	**2.90**	**105.15**	**1.37**	**99.08**
SEM	**0.27**	**2.45**	**0.03**	**0.28**	**0.18**	**2.17**	**0.19**	**2.73**	**0.08**	**1.48**	**0.28**	**3.57**	**0.02**	**1.84**

The average amount of fentanyl, in mg, extracted from each of the dosages of Apotex patch tested is displayed in **Table 5**. Single sample t-tests, with a significance of 0.05, were performed to determine if differences existed between the theoretical starting amount of fentanyl in each patch (e.g. 11.04 mg in the 100 µg/h dosage) and the amount of fentanyl that was able to be recovered using the optimized hexane extraction method. For all dosages, except 50 µg/h and 87.5 µg/h, there was no statistical difference between what was able to be extracted using the optimized hexane method and the amount declared by the manufacturer to be contained within the patches.

Table 5: Evaluation of the Optimized Hexane Extraction Method on Varying Dosages of Apotex Patches

Dosage (µg/h)	Manufacturer's Declared Amount of Fentanyl (mg)	Average Amount of Fentanyl Extracted (mg)	P-Value	Significant Difference Between Manufacturer's and Recovered Values
12.5	1.38	1.37 (0.02)	0.6369	N
25	2.76	2.90 (0.28)	0.1967	N
50	5.52	5.12 (0.08)	1.727×10^{-3}	Y
62.5	6.90	6.87 (0.19)	0.8882	N
75	8.28	7.98 (0.18)	0.1386	N
87.5	9.66	9.04 (0.03)	6.659×10^{-8}	Y
100	11.04	10.64 (0.27)	0.1788	N

Values given in parenthesis correspond to the standard errors of the mean (SEM). A significance of 0.05 was used.

Figure 3 compares the average percent recovery of fentanyl from each of the Apotex dosages tested, with the error bars representing the standard errors of the mean (SEM). No significant differences in fentanyl recovery were noted between the 12, 50, 62.5, 75, 87.5, or 100 µg/h patches. Similarly, no significant differences in fentanyl recovery were found between 12, 25, 62.5, 75, and 100 µg/h dosages. However, between these groups, there was a statistically significant difference in the fentanyl recovery between the 25 and 50 µg/h dosages and between the 25 and 87.5 µg/h dosages.

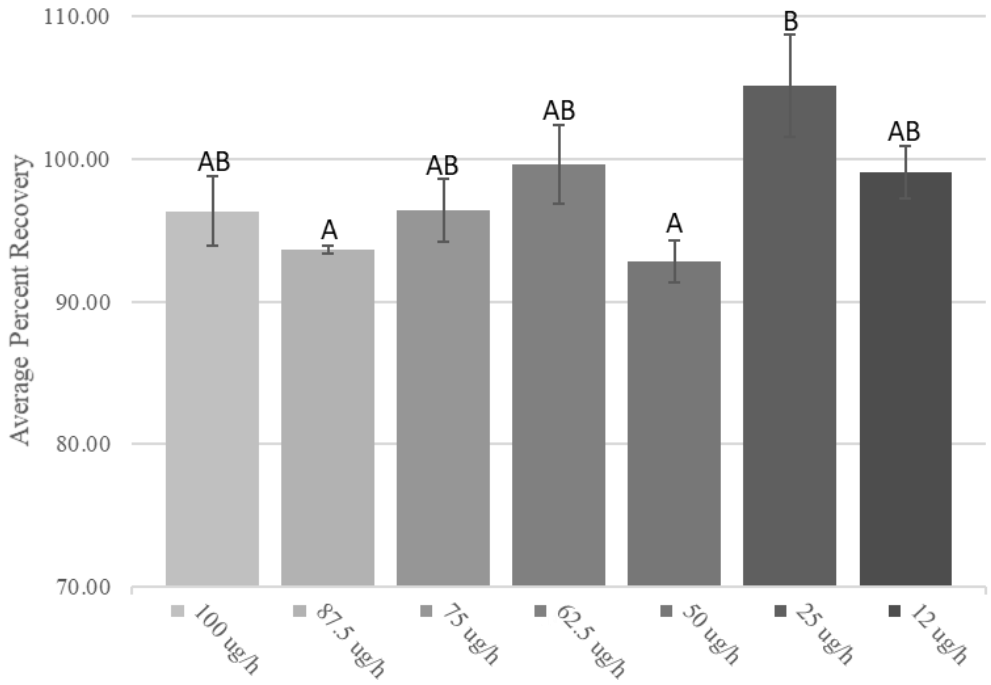

Figure 3: Average Percent Recovery of Fentanyl from Various Dosages of Apotex Patches. Results displayed represent the average of the eight trials +/- SEM. Letter designations represent Tukey's HSD comparisons: the same letter designation means results are not statistically different; when letter designations differ between groups, the p-value is less than 0.05.

The two extraction methods previously shown to be effective on either Apotex or Duragesic® patches were tested on the remaining brands in order to determine which extraction method would work best for each. Only one replicate was performed for each patch/extraction method. The results from the Van Nimmen & Veulemans methanol extraction method and the optimized hexane extraction method for each brand can be seen in **Table 6**. Apotex, Mylan®, and Mallickrodt™ patches all performed better with the optimized hexane extraction method, while Alvogen® and Duragesic® patches showed the best recoveries with the Van Nimmen & Veulemans methanol extraction method.

Table 6: Determination of the Best Extraction Method for Each Brand of Patch

Brand	Adhesive	Extraction Method	Percent Recovery
Apotex	Polyisobutene adhesive	Van Nimmen & Veulemans	5.77‡
		Hexane	82.87*
Mylan®	Silicone adhesive	Van Nimmen & Veulemans	56.27†
		Hexane	103.18
Mallinckrodt™	Silicone adhesives	Van Nimmen & Veulemans	10.46†
		Hexane	88.38
Alvogen®	Acrylate copolymer adhesive	Van Nimmen & Veulemans	92.55†
		Hexane	-
Duragesic®	Polyacrylate adhesive	Van Nimmen & Veulemans	93.20†
		Hexane	59.05*

*For the hexane method, the Apotex and Duragesic® analyses were done before it was discovered the patch should be covered while soaking in the hexanes.
† Shaking method 2.
‡ Shaking method 1.

The amount and percent recovery of fentanyl for the eight replicate extractions of the 100 µg/h dosages using the previously determined best extraction methods for each available brand can be seen in **Table 7**. The average percent recoveries ranged from 95.2% to 100.1%. It should be noted that while Duragesic® was originally tested, it was not included here in the extraction replicates due to a supplier shortage of those patches.

Table 7: Replicate Extractions of Varying Brands of 100 µg/h Patches

Replicate	Apotex*		Mylan®*		Mallinckrodt™*		Alvogen®†	
	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery	Fentanyl Extracted (mg)	Percent Recovery
1	11.44	103.64	10.17	99.70	11.18	101.62	11.74	110.24
2	10.21	92.49	9.95	97.52	10.33	93.87	11.60	108.90
3	10.57	95.72	11.66	114.33	10.61	96.47	9.37	88.03
4	10.07	91.19	10.24	100.44	9.79	89.01	10.68	100.28
5	9.97	90.32	10.49	102.85	11.01	100.09	9.64	90.54
6	11.58	104.87	10.16	99.62	10.18	92.60	10.57	99.25
7	9.73	88.10	10.26	100.62	10.09	91.74	9.15	85.89
8	11.52	104.37	9.39	92.08	10.58	96.22	9.90	92.98
Average	**10.64**	**96.34**	**10.21**	**100.12**	**10.47**	**95.20**	**10.33**	**97.01**
SEM	**0.27**	**2.45**	**0.07**	**0.71**	**0.16**	**1.50**	**0.35**	**3.26**

*Optimized hexane extraction method
†V & V methanol extraction method
The values highlighted in red were determined to be outliers using the Grubb's test, these were not included in the averaged values.

Similarly to the varying dosages, single sample t-tests were performed to compare the amount of fentanyl recovered in the lab to the amount of fentanyl the manufacturer states is present in the patch. **Table 8** lists the average amount of fentanyl extracted from each brand along with the p-values from the single sample t-tests that were performed. Only the recoveries from the Mallinckrodt™ patches were found to be statistically different from the manufacturer's value (p-value = 0.01526). **Figure 4** shows the average percent recovery of fentanyl for each brand. An ANOVA was performed comparing the percent recoveries of all four brands; even though there were two different extraction methods used, it was deemed acceptable to include all four in an ANOVA due to the fact that the values being compared were all normalized back to a manufacturer value to obtain a percent recovery. **Figure 4** shows that all four brands extracted were determined to have percent recoveries that were not statistically different.

Table 8: Evaluation of the Optimized Extraction Method on 100 µg/h Patches of Varying Brands

Brand	Manufacturer's Declared Amount of Fentanyl (mg)	Average Amount of Fentanyl Extracted (mg)	P-Value	Significant Difference Between Manufacturer's and Recovered Values
Apotex	11.04	10.64 (0.27)	0.1788	N
Mylan®	10.20	10.21 (0.07)	0.8768	N
Mallinckrodt™	11.0	10.47 (0.16)	0.01526	Y
Alvogen®	10.65	10.33 (0.35)	0.3893	N

Values given in parenthesis correspond to the standard errors of the mean (SEM). A significance of 0.05 was used.

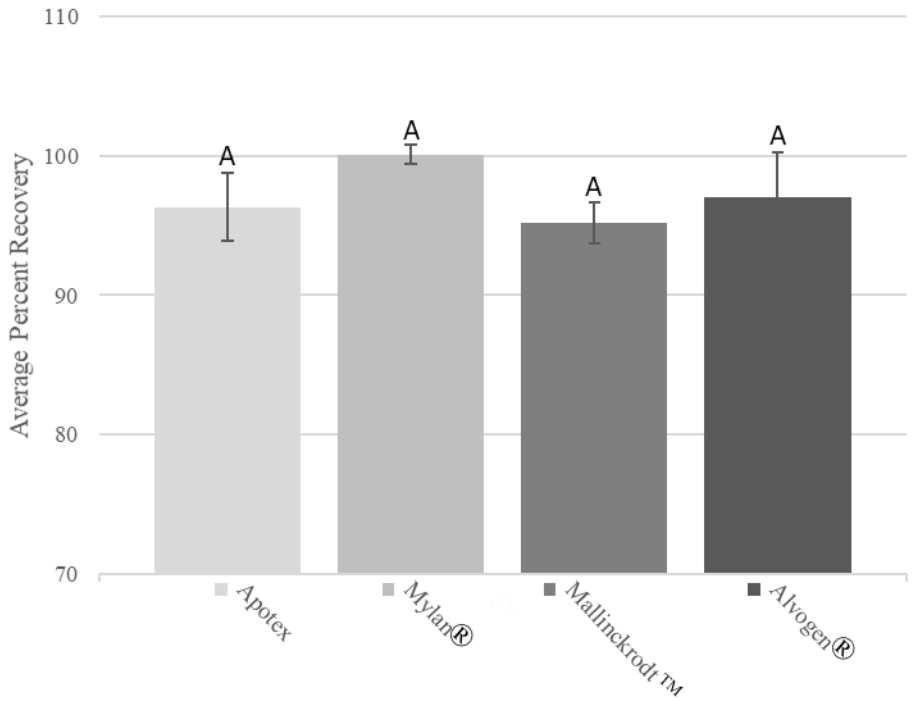

Figure 4: Average Percent Recovery of Fentanyl from 100 µg/h Dosages Across Four Patch Brands. Results displayed represent the average of the eight trials +/- SEM, with outliers excluded as appropriate. Letter designations represent Tukey's HSD comparisons: the same letter designation means results are not statistically different; when letter designations differ between groups, the p-value is less than 0.05.

Evaluation of NarcX®

The results of the time trials for NarcX® exposure on the 100 µg/h Apotex patches can be seen in **Table 9**. The percent adsorbed was determined by comparison of the amount of fentanyl

extracted after treatment to the average amount of fentanyl able to be extracted from the fresh patches (**Table 7**), rather than the manufacturer's stated value. The highest percent of fentanyl that NarcX® was able to adsorb was 69.6%, seen at the 72 hour time point.

Table 9: Replicate Extractions of 100 µg/h Apotex Patches Soaked in NarcX® for Various Time Periods

	1 Hour		24 Hours		48 Hours		72 Hours	
Replicate	**Fentanyl Extracted (mg)**	**Percent Adsorbed into NarcX®**	**Fentanyl Extracted (mg)**	**Percent Adsorbed into NarcX®**	**Fentanyl Extracted (mg)**	**Percent Adsorbed into NarcX®**	**Fentanyl Extracted (mg)**	**Percent Adsorbed into NarcX®**
1	9.12	14.33	6.55	38.46	4.07	61.73	3.62	66.02
2	9.05	14.94	5.67	46.71	3.96	62.73	3.42	67.88
3	8.75	17.80	5.72	46.25	4.06	61.81	3.42	67.82
4	8.40	21.07	5.64	46.99	3.83	63.97	3.23	69.65
5	9.63	9.51	6.56	38.34	4.01	62.35	3.41	67.91
6	8.98	15.55	5.64	46.97	3.83	63.97	3.60	66.18
7	9.66	9.21	5.34	49.80	3.59	66.24	3.90	63.39
8	9.37	11.95	5.84	45.09	3.89	63.44	4.44	58.22
Average	**9.12**	**14.29**	**5.87**	**44.83**	**3.91**	**63.28**	**3.51**	**66.98**
SEM	**0.15**	**1.43**	**0.16**	**1.48**	**0.06**	**0.53**	**0.08**	**0.75**

The values highlighted in red were determined to be outliers using the Grubb's test, these were not included in the averaged values.

Table 10 lists the averages from each time point, along with the results of two sample t-tests that were conducted to compare the amount of fentanyl extracted from NarcX® treated and untreated patches. Every time point tested showed a significant decrease in the amount of fentanyl able to be extracted after treatment with NarcX®. A graphical depiction of these results can be seen in **Figure 5**, along with the results of the ANOVA and Tukey's HSD analyses. The 1 and 24 hour time points were statistically different from each other and from the 48 and 72 hour time points. However, the 48 and 72 hour time points were not found to be statistically different. From the figure, it appears that saturation of the NarcX® may occur after 48 hours of exposure, suggesting it may be that no additional fentanyl would be absorbed, no matter how long NarcX® exposure would be extended.

Table 10: Evaluation of the Effect of NarcX® Exposure for Various Amounts of Time on 100 µg/h Apotex Patches

Time Point	Average Percent Fentanyl Adsorbed Into NarcX®	Average Fentanyl Extracted From Untreated Patches (mg)	Average Fentanyl Extracted From Patch After Treatment (mg)	P-Value	Significant Difference Between Fentanyl Recovered From Treated and Untreated Patches
1 hour	14.29 (1.43)	10.64 (0.27)	9.12 (0.15)	4.757×10^{-4}	Y
24 hours	44.83 (1.48)		5.87 (0.16)	7.22×10^{-9}	Y
48 hours	63.28 (0.53)		3.91 (0.06)	1.705×10^{-8}	Y
72 hours	66.98 (0.75)		3.51 (0.08)	4.255×10^{-9}	Y

Values given in parenthesis correspond to the standard errors of the mean (SEM). The p-value represents the results of two sample t-tests comparing the amount of fentanyl recovered from the treated patches to the amount of fentanyl recovered from new patches. A significance of 0.05 was used.

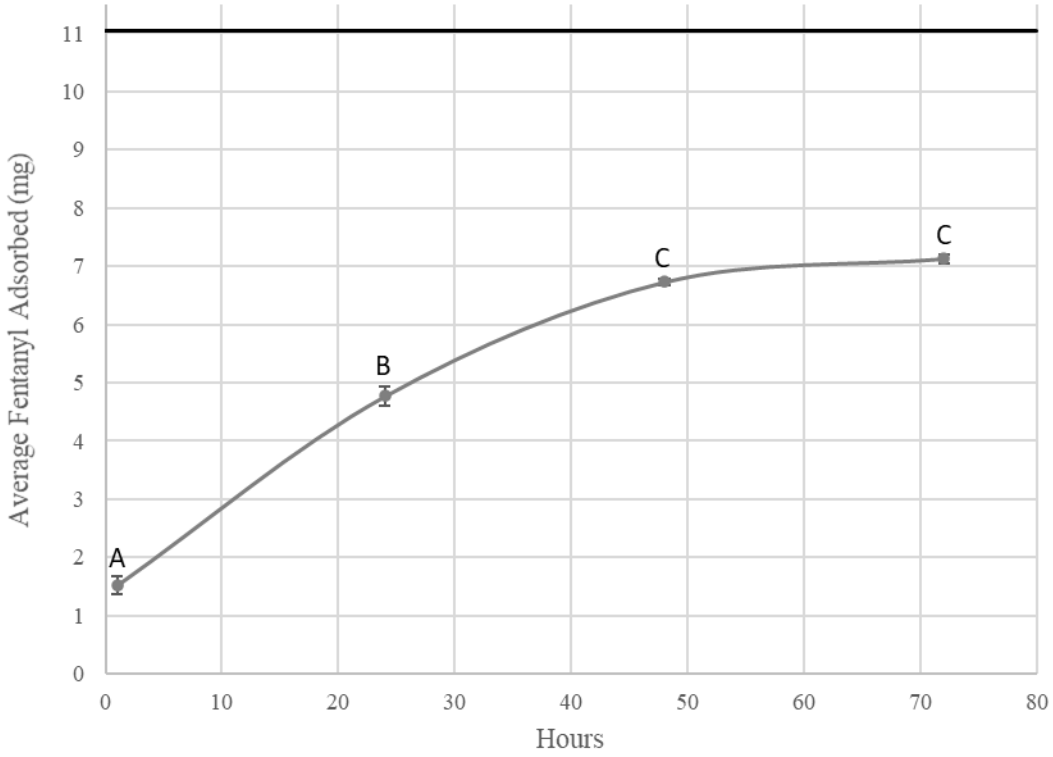

Figure 5: Average Percent Fentanyl Adsorbed by NarcX® from 100 µg/h Apotex Patches Over Time. The solid black line represents the amount of starting fentanyl the manufacturer states is in the patch. Results displayed represent the average of the eight trials +/- SEM, with outliers excluded as appropriate. Letter designations represent Tukey's HSD comparisons: the same letter designation means results are not statistically different; when letter designations differ between groups, the p-value is less than 0.05.

DISCUSSION

Optimization of Extraction Method

Optimizing an extraction method for fentanyl from transdermal patches was imperative to this study, so that any disposal system could be evaluated, meaning that a method was needed to be able to make a comparison of patches before and after treatment with the NarcX® to show whether NarcX® was actually able to adsorb the fentanyl from the patches. From the literature, an extraction method by Van Nimmen and Veulemans was found to have been able to extract between 95% and 110% of the fentanyl from Duragesic® patches. [6] Because of the success previously shown with this extraction method, this was the first method attempted on the Apotex 100 µg/h patch. This extraction method involves cutting the patch into strips and shaking it in methanol; however, this method was also attempted on a whole patch, rather than cutting it up, as the change in surface area was not expected to make a difference in the amount of fentanyl that could be extracted. After testing the method on a whole patch and a cut-up patch, I was able to demonstrate that cutting the patch into strips resulted in over 3.5% increase in the amount of fentanyl able to be extracted. However, as can be seen in **Table 2**, I was unable to obtain the same extraction recoveries as what had previously been published, with either the intact patch or the cut patch. The only apparent difference between what was done by Van Nimmen and Veulemans and what I had done was the brand of patch being used; therefore, this method was attempted on a Duragesic® patch as well to see if this could account for the drastic difference in recovery, as shown in **Table 3**. First, a Duragesic® patch was analyzed using shaking method 1, as this was what was previously used on the Apotex patches. After seeing a lower percent recovery of fentanyl than what had been reported by Van Nimmen and Veulemans, 79.14%, shaking method 2 was implemented in order to determine if a more vigorous shaking would

increase the percent recovery. With shaking method 2, I was able to show a recovery that was more in line with what Van Nimmen and Veulemans reported using the Duragesic® patch (93.20%). From this, I hypothesized that the type of adhesive used on different brands of patches may make a difference in the amount of fentanyl that can be extracted with the Van Nimmen and Veulemans method.

Since a method had already been shown to extract the fentanyl from the Duragesic® adhesive, the rest of the optimization studies focused on the Apotex patches. The next aspect that was tested was the addition of heat to the Van Nimmen and Veulemans method. Heat was attempted because the patches come with a warning for patients to avoid applying heat to the patch, as this can cause too much fentanyl to be released. [21] However, because of instrumental limitations, heating and shaking could not be conducted simultaneously; therefore, methanol heated to 37°C for 15 minutes was attempted on both intact patches and patches cut into strips. As seen with the shaking, the better extraction was seen with the cut up patch over the whole patch. Ultimately though, the addition of heat did not dramatically increase the amount of fentanyl able to be extracted from the patch, as can be seen in **Table 2**.

Next, trisodium phosphate was tried as the extraction solvent. This was attempted due to a conversation with a representative from NarcX®; it was suggested that trisodium phosphate may be able to punch holes through the adhesive matrix. [27] Because of this, extraction of a whole patch was tested by shaking it in a 25% trisodium phosphate solution. However, as can be seen from **Table 2**, complete extraction of the patch was not achieved. In fact, the trisodium phosphate actually performed worse than methanol.

As the previous attempts to extract fentanyl from the Apotex patch had failed, the specific adhesive was taken into account for the next extraction attempt. The adhesive used in the

Apotex patches is a polyisobutene adhesive, which was found to be soluble in hydrocarbon solutions. [22,20] Because of this, the next extraction solvent tested was hexanes. It was determined that the Apotex adhesive could be fully dissolved in the hexanes in approximately 20 minutes. After dissolving the adhesive in hexanes, and so as to not add the adhesive matrix to the LC/MS column, a liquid-liquid extraction with methanol was utilized to pull the fentanyl into the methanol layer. Methanol was chosen due to its immiscibility with hexane and due to the fact that fentanyl is soluble in methanol. Three methanol washes were determined to be sufficient to extract the fentanyl from the hexane layer; after three methanol washes, the hexane layer was analyzed using GC/MS, and no fentanyl peak was observed. The initial results seen from this extraction method were very promising (82.87%). This recovery was improved upon by ensuring that while the patch was soaking in the hexanes, it remained covered. This small change in methodology resulted in an average fentanyl recovery of 96.34% from the 100 μg/h Apotex patches. This extraction method was ultimately determined to be the optimized extraction method for the Apotex patch.

Evaluation of Extraction Method on Various Patches

In order to evaluate this optimized hexane extraction method, it needed to be tested on a variety of fentanyl dosages and brands, as different dosages could result in saturation of the solvent and each brand potentially has a different adhesive composition. The optimized hexane extraction method was tested on seven different dosages of the Apotex brand, including 12.5, 25, 50, 62.5, 75, 87.5, and 100 μg/h. This was done because each dose has a different amount of fentanyl in the adhesive, as shown in **Table 5** [21]. Testing each dose allowed me to determine if the differing amounts of fentanyl could each be completely extracted using this new method; in addition, at the higher dosages, it was important to show that the extraction solvent and washes

would not become saturated. As can be seen in **Table 4**, eight replicate extractions were performed on each of the Apotex dosages available. Of all of the replicates, over all of the dosages, the lowest percent recovery seen was 85.0% from a 75 µg/h patch; the highest percent recovery seen was 117.2% from a 25 µg/h patch. It is postulated that the percent recoveries above 100% may, in part, be due to some variance in the LC/MS analysis, the pipettes used to create the dilutions, and the amount of fentanyl actually in each patch, i.e. there is most likely some sort of tolerance allowed when manufacturing these patches. Using Grubbs' tests, it was determined that there were no outliers in this data set.

Table 5 lists the average amount of fentanyl extracted from each dosage of Apotex patch. Using single sample t-tests, those values were compared to the manufacturer declared amount of fentanyl contained within each patch; the resultant p-values can also be seen in **Table 5**. Of the dosages tested, the recoveries from the 12.5, 25, 62.5, 75, and 100 µg/h patches were all found to be statistically the same as the values given by the manufacturer, meaning that the optimized hexane extraction was able to fully extract the fentanyl from those patch dosages. For the 50 and 87.5 µg/h dosages, the p-values suggest a statistical difference between the amount of fentanyl extracted via the hexane extractions and the amount the manufacturer has declared to be in the patch. This may be due to variation observed in the small number of replicates tested. With more replicates, the average amount of fentanyl extracted may shift to better represent the true mean.

In order to compare the percent recovery among the different dosages analyzed, an ANOVA was performed. The ANOVA suggested statistical differences did exist in the percent of fentanyl recovered between the dosages (p-value = 0.00742). A Tukey's HSD analysis indicated that significant differences existed between the percent recoveries of the 25 and 87.5 µg/h patches (p-value = 0.01328) and also between the recoveries of the 25 and 50 µg/h patches

(p-value = 0.00656), with the rest of the comparisons having found no statistical differences (**Figure 3**).

In addition to testing the hexane extraction on the varying dosages, the optimized method was also evaluated on different brands of fentanyl patches, aside from Apotex. This was done because of the fact that the adhesive used and its composition vary between the brands, with Apotex using a polyisobutene adhesive, Mylan® and Mallinckrodt™ using silicone adhesives, Alvogen® using acrylate copolymer adhesive, and Duragesic® using a polyacrylate adhesive (**Table 6**). [22-26] In this portion of the study, only the 100 µg/h patch was analyzed because 1) the highest concentration, theoretically, should be the most challenging to extract in its entirety, and 2) the adhesive does not differ among the patch dosages within a single brand. Each brand was first tested using both the Van Nimmen and Veulemans methanol extraction method and the optimized hexane extraction method to determine the best extraction method for each type of adhesive (**Table 6**). Of the brands tested, it was found that the Van Nimmen and Veulemans methanol extraction method was ideal for the Duragesic® and Alvogen® patches. This is not surprising as both of these brands use a type of acrylate adhesive [25,26]. However, the hexane method was found to be preferable for the Apotex, Mylan®, and Mallinckrodt™ patches. The Apotex pach uses a polyisobutene adhesive, while the Mylan® and Mallinckrodt™ patches both use a silicone adhesive [22-24]. Note, the Alvogen® patch was not taken completely through the hexane extraction as there was incomplete separation at the liquid-liquid extraction step. Since the layers were not clear, and to avoid potentially damaging the LC/MS instrument, the Alvogen® patches extracted with hexane were not analyzed.

After making the determination of the best extraction method for each patch brand, eight replicates of each brand were extracted using the appropriate method. These results (**Table 7**)

were compared to the manufacturer stated starting fentanyl amount in each patch (**Table 8**). The fentanyl extracted from Apotex, Mylan®, and Alvogen® patches were all found to be statistically the same as the amount declared to be in the patches. This suggests that the optimized hexane extraction method is able to extract the fentanyl in totality, or very near, from these brands. However, it was found that the Mallinckrodt™ patches did show a significant difference (p-value = 0.01526) between the manufacturer's value and the extraction values. Again, this may be resolved if more replicates were conducted, or this could be due to the difference in adhesive, i.e. the hexane extraction method may not work as efficiently for the Mallinckrodt™ patch/adhesive. However, two Mallinckrodt™ extraction replicates resulted in over 100% fentanyl recovery (100.09 % and 101.62%) (**Table 7**), which suggests that it is possible for the hexane method to fully extract the fentanyl from the patch.

An ANOVA was performed on the percent recoveries of the four brands tested. These results are shown in Figure 4; as can be seen, the recoveries of Apotex, Mylan®, Mallinckrodt™, and Alovgen® were found to have no statistical differences among them (p-value = 0.554). Although Mallinckrodt™ was previously found to have a statistical difference between the amount of fentanyl recovered and the manufacturer's amount, this ANOVA proposes that the true difference in means among the percent recoveries of these four groups is zero. This further suggests that the extraction method works equally well for all brands tested.

Evaluation of NarcX®

With an optimized extraction method having been developed and evaluated, assessment of NarcX® as a patch disposal method was possible. More specifically, an optimized extraction method allowed for the comparison between the amount of fentanyl extracted from fresh patches and the amount of fentanyl extracted from patches treated with NarcX® to discover the ability of

NarcX® to adsorb the fentanyl from the patch. In order to test this, 100 µg/h Apotex patches were soaked in NarcX® for varying amounts of time, and then, the remaining fentanyl was extracted via the optimized hexane method. 100 µg/h Apotex patches were chosen, as they had been previously shown to perform well with the hexane extraction method. In addition, the highest available dosage was used since this contains the most fentanyl, which could saturate the NarcX®.

The full results of the NarcX® time point study can be seen in **Table 9**. The amount of fentanyl extracted from the patches after NarcX® treatment decreases as the amount of time the patches were exposed to NarcX® increases, suggesting that more fentanyl is being adsorbed by the NarcX® over time. The lowest percentage adsorbed was seen at the 1 hour time point (9.2%), and the highest percentage adsorbed was seen at the 72 hour time point (69.6%), as would be expected. However, it did appear from the data that saturation of the NarcX® may occur after 48 hours of exposure. (**Figure 5**) One confounding factor to keep in mind though is that NarcX® is a liquid solution where the activated carbon is suspended in the liquid. Over these time points tested, the patches were just soaked in a static solution of NarcX®, because of this, settling of the particulates in the solution was seen. This could mean that the entire NarcX® solution was not saturated, but the unsaturated particulates were settled at the bottom and not in contact with the patch. One way to avoid settling and separation of the solution would be to add shaking during the various time periods of exposure; this would keep the particulates suspended in the solution and would constantly subject the patch to the activated carbon. While this may result in an increase in the amount of fentanyl the NarcX® is able to adsorb, it is also important to keep in mind the goal of this research is a disposal method. It is not necessarily feasible to implement a disposal method where one must shake the disposal device for an extended period of time to get

neutralization of the patch. An ideal disposal method would be one where a person could just insert the patch and walk away and be confident that the remaining fentanyl would be neutralized in its entirety.

As can be seen in **Table 10**, the amount of fentanyl extracted after NarcX® treatment was compared to the average amount of fentanyl able to be extracted from untreated patches of the same dosage and brand. Every time point tested was found to be statistically different between the amount of fentanyl extracted from NarcX®-treated and untreated patches, meaning that soaking the patches in the NarcX® solution for just 1 hour has a statistically significant effect. Although extended exposure to NarcX® significantly decreased the amount of fentanyl able to be extracted from a patch, it is important to be aware of just how much fentanyl was still able to be extracted after NarcX® treatment. For instance, at the 72 hour time point, soaking the patch in NarcX® resulted in a 67% decrease in the available fentanyl, yet on average, at least 3.5 mg of fentanyl, an amount well over the lethal dose threshold, was still able to be extracted from the patch. The potential for harm and abuse from these fentanyl patches has not been eliminated with these conditions.

Of the time points tested, the largest jump in percent adsorbed was seen in the first 24 hours; from 1 hour to 24 hours there was on average a 30% increase in the amount of fentanyl able to be adsorbed. However, adding an additional 24 hours of NarcX® exposure did not make the same jump; from 24 to 48 hours there was a less than 20% increase seen. The increase goes down even further with the third 24 hours; from 48 to 72 hours the increase seen in amount of fentanyl adsorbed was less than 5%. It is clear that there is a leveling off that is occurring over time; it is thought that this may be happening due to the NarcX® solution becoming saturated (**Figure 5**). As only 20 mL of the NarcX® solution was used for soaking the patches, there is only

a finite amount of activated carbon in that solution. Currently, this data seems to support saturation; however, further research would be needed to better show this. For example, if the NarcX® exposure were extended long enough, or if shaking were added, then the fentanyl may be able to be neutralized fully. Although, because the NarcX® seems to be trending toward saturation, it has been realized that, with the current specifications, NarcX® may not be a suitable disposal method, as it could leave a dangerous amount of fentanyl behind in a patch. However, it is important to keep in mind that this has only been tested on Apotex 100 µg/h patches; more testing would be needed to determine if these parameters could successfully neutralize the lower dosage patches as they contain less fentanyl to begin with. In addition, this testing was done on new patches; if this were to be implemented as a disposal method it would theoretically not need to be able to neutralize the full amount of fentanyl in a new patch. These current specifications may be sufficient for used patches; however, more research would need to be done on actual used patches as the amount of residual fentanyl varies.

CONCLUSION

Due to the fact that after transdermal fentanyl patches are used, they still have a dangerous amount of residual fentanyl left behind in the adhesive, a proper disposal method is of utmost importance. [6,8] Not only does the amount of fentanyl left behind in these patches have the potential to harm innocent children or animals, there is also a huge potential for abuse. [10,13,11] Currently, these used patches are simply disposed of by flushing them down the toilet; however, this disposal method does not deal with the real problem at hand, as it does not address the residual fentanyl. [15] It is clear that a better disposal method is needed that will either degrade or irreversibly bind the fentanyl in these transdermal patches, rendering them harmless. In this current work, NarcX®, a liquid solution of activated carbon that could adsorb the fentanyl from the used patches, was analyzed as a possible disposal solution. While it was shown that NarcX® could adsorb some of the fentanyl from the patches, with the current parameters NarcX® was not able to remove the fentanyl in its entirety, still leaving potentially lethal amounts behind in the patch adhesive. This means that if NarcX® were to be used as a disposal method, more work would first need to be put in to this area.

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