Exploratory In-vitro Mastication to Assess the Potential Accelerated Release of Fentanyl from a Transdermal Patch

Christopher J. Altomare, Paul Fort, Eric R. Kinzler PhD, Anthony G. Costantino PhD

Introduction

- Illicit use of fentanyl, a synthetic opioid analgesic used for treatment of chronic pain, has increased significantly since 2012 as toxicology data from New York City shows fentanyl was identified in 2% of drug overdose deaths from 2000 to 2012, then in 2017, fentanyl was linked to 57% of drug related overdose deaths.[1]
- Access to fentanyl by abusers comes in a variety of forms, and while the largest illegal sources of fentanyl come from China and Mexico[1] ; acquiring fentanyl from prescription drugs (CPDs) is commonly achieved through diversion of fentanyl-containing transdermal patches.
- Fentanyl transdermal patches are designed to deliver the drug at a slow rate: a single 25 mcg-h fentanyl transdermal patch is intended to deliver 1.8 mg of fentanyl over 72 hours at a rate of 0.025 mg per hour.
- Due to absorption and pharmacokinetics, the same patch contains 4.2 mg of fentanyl, two times the intended deliverable dose. Thus, excess fentanyl is added to patches and remains in exhausted patches which may subject patches to intentional abuse.
- Oral abuse of fentanyl transdermal patches by sucking or chewing may release high concentrations of fentanyl that are quickly absorbed into the buccal mucosa.[2]

Methods

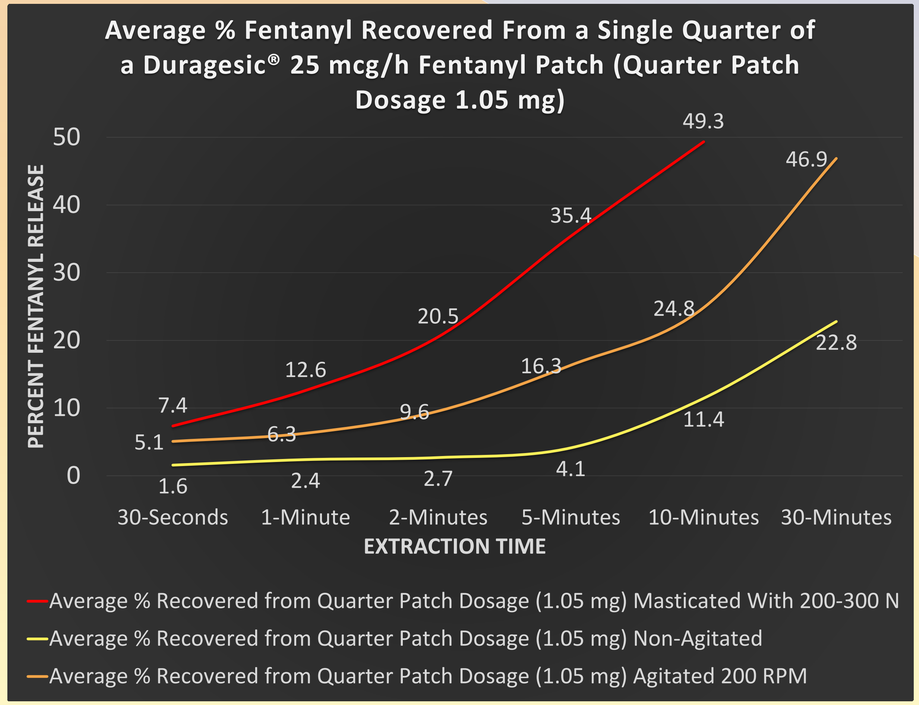
- Utilizing investigative methods similar to those recommended in the FDA's Guidance documents to simulate mastication (chewing) in vitro of abuse deterrent opioids, a mastication apparatus (ERWEKA DRT™) manufactured by ERWEKA GmBH Heusenstamm Germany was used to evaluate the rate and total release of fentanyl from a transdermal patch when abused by chewing.
- All experiments were performed in duplicate in 10 mL of pre heated (37°C) synthetic negative oral fluid media with extraction buffer, and for each experiment, one quarter of a 25 mcg-h fentanyl transdermal patch was used.
- Control experiments were performed in a water bath shaker with agitation at 200 RPM and without agitation.
- Mastication experiments utilized the ERWEKA DRT™ which can tightly regulate temperature, compression force and distance, torsion, and mastication frequency and duration.[3]
- Human bite forces can vary greatly, and the compression force (bite force) for these experiments was set to not exceed 250 N which is lower than the maximum human bite force for persons between 12 to 60 years old, and characteristic human mastication parameters were used. [4,5,6,7]
- The compression gap distance between the mastication jaws and mesh was set to zero, a torsion angle of 20°, and mastication frequency of approximately 40 strokes/min 1.57 Hz) were used for all experiments. [5,6,7]

Methods (cont'd)

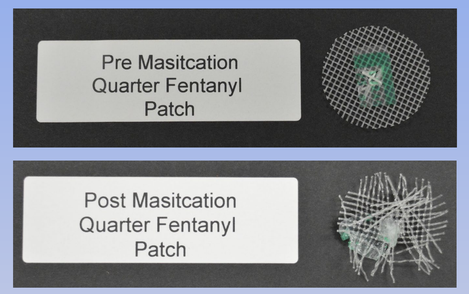
- The mastication experiments were conducted for a total of 10-minutes and controls were run for 30 -minutes with aliquots taken at 30-seconds, 1, 2, 5, 10 and 30-minutes.
- All aliquots were diluted and analyzed by LC-MS/MS for fentanyl content.

Results

- Mastication increases Fentanyl release relative to unchewed samples.
- The average percent recovery of fentanyl after 10-minutes of in vitro mastication was 49.34%.
- In contrast, at 10-minutes the average percent recoveries from the water bath extractions was 24.83% and 11.44% with and without agitation, respectively.
- Additionally, the average percent recovery of fentanyl after 10-minutes of in vitro mastication was higher than the average percent recoveries after 30-minutes of extraction in the water bath with and without agitation which were 46.88% and 22.79%



Results (cont'd)



Conclusion

- Based on these results, chewing a quarter 25 mcg-h fentanyl transdermal patch could result in the release of nearly 50% of the drug content in 10-minutes. This potentially provides an abuser with approximately 0.5 mg of fentanyl. This is nearly one third of the 72-hour dose of the entire patch.
- Additional experiments are needed to determine the maximum recovery of fentanyl achieved from repeated chewing of a single quarter 25 mcg-h fentanyl transdermal patch as the data trend of drug release was increasing to the end for all experiments.
- Overall, these data suggest that transdermal fentanyl patches are highly subject to abuse via mastication, potentially releasing dangerous amounts of fentanyl to multiple abusers using a single patch.

References

1. United States. Drug Enforcement Administration (DEA). "2018 National Drug threat Assessment". U.S. Dept. of Justice, Drug Enforcement Administration, October 2018: dea-dct-dir-032-18.
2. Grissinger M. "Fentanyl Patch Fatalities: We all have a role in prevention". Pharmacy and Therapeutics. 2016; 41(7): Pages 405-406.
3. Kvist, C., Andersson, S. B., Fors, S., Wennergren, B., & Berglund, J. Apparatus for studying in vitro drug release from medicated chewing gums. International Journal of Pharmaceutics,189(1), 57-65. 1999.
4. Takaki, Patricia, MarilenaVieira, and Silvana Bommarito. "Maximum Bite Force Analysis in Different Age Groups." International Archives of Otorhinolaryngology 18.3 (2014): 272–276. PMC. Web. 13 June 2017.
5. Gajendran J, Kraemer J, Langguth P. In vivo predictive release methods for medicated chewing gums. Biopharm Drug Dispos . 2012 Oct;33(7):417 24. doi : 10.1002/bdd.1796. Epub 2012 Jul 11.
6. European Pharmacopoeia 9th Edition 2017, General Monograph 2.9.25: Dissolution Test for Medicated Chewing Gums. pp 340 343, Directorate for the Quality of Medicines of the Council of Europe, Strasbourg, France, 2017.
7. JM, P. Time frequency analysis of chewing activity in the natural environment. Journal ofDental Research, 1206 10. 2011.

DRUGSCAN CAT.ONE™