FY2018 GDUFA Science and Research Report: Abuse-deterrent Opioid Drug Products

This section contains only new information from FY2018. For background scientific information and outcomes from previous years on this research topic, please refer to:

- FY2013-2017 GDUFA Science and Research Report: Oral Abuse-deterrent Opioid Drug Products (https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm608671.htm)

Introduction

Several FY2018 extramural and intramural research projects continue FDA's efforts to advance and refine approaches towards evaluating abuse deterrence (AD) and regulatory standards for assessing generic abuse-deterrent formulation (ADF) opioid drug products. The key objectives include: (1) exploring quantitative metrics that reflect the degree of difficulty and success of manipulation methods; (2) refining nasal and oral in vivo study designs for evaluating AD; and (3) developing novel in vitro methods as alternatives to in vivo studies to predict bioavailability of ADF opioid drug products.

Research

Six internal research projects were conducted. These projects have focused on exploration of the applicability of the vertical cell diffusion/dissolution methods and in vitro chewing methods (see **Figure 1**) on evaluating opioid drug release of manipulated or chewed ADF opioid drug products in the nasal and oral routes, respectively. These in vitro studies may be used to develop quantitative metrics as comparative endpoints that reflect the extent to which each manipulation method succeeds in defeating ADFs and the resulting quality attributes.

FDA completed a FY2015 contract under which an in vivo nasal pharmacokinetic (PK) study on milled oxycodone hydrochloride (HCl) extended-release (ER) tablets was conducted to evaluate the effects of particle size and drug-to-polymer ratio on the resulting rate and extent of nasal absorption of opioids (HHSF223201510138C). One of the key findings is the heterogeneous distribution of drug content in each particle size fraction of the physically manipulated ADF tablets (see **Figure 2**), making it a factor that should be considered in the design of an in vivo nasal PK AD study. In addition, nasal in vivo studies on agonist/antagonist combination ADF products and an oral in vivo chewing study are in the research pipeline.

FDA has also been developing novel in vitro methods as alternatives to in vivo PK studies to predict nasal or oral bioavailability of ADF opioid drug products following nasal insufflation or chewing, respectively. We are developing a chewing in vitro-in vivo correlation (IVIVC) using the simulated mastication method and physiologically-based pharmacokinetic (PBPK) modeling (see **Figure 1**) as well as a PK absorption model to predict the nasal absorption of milled OxyContin tablets using computational fluid dynamic (CFD) models, vertical cell diffusion/dissolution, and regional deposition data. Furthermore, the in silico approach is an important tool guiding the design of in vivo studies used in generic drug research and development. FDA has investigated the use of quantitative clinical pharmacology to design in vivo PK studies to characterize the pharmacokinetics/pharmacodynamics (PK/PD) relationship of ADF opioid drug products. These in silico efforts provide justification for additional PK metrics (e.g., partial area-under-the-concentration-time curve, pAUC) to assist with evaluating in vivo PK AD studies. The suggested use of pAUC has been recommended in some of the product-specific guidances (PSGs) for ADF opioid drug products.

FDA laboratory-based studies included stability studies of ADF opioids to enhance assurance of AD properties during product shelf life. The aim of this research was to perform stability studies of ADF opioids under various

storage conditions to determine appropriate conditions for the stability evaluation of ADF products. Surrogate ADF tablets were prepared by direct compression followed by curing, using diltiazem hydrochloride as a model drug. Stability studies were conducted following the ICH Q1A (R2) guideline. While no change occurred in the tablet physical properties after three months of storage, a quicker release of drug from the tablets was noted at this timepoint. The study is still ongoing.

Physical manipulation by milling is a commonly used test to evaluate the effectiveness of AD properties of a solid oral ADF opioid product. Different milling procedures could impact the outcome of the evaluation of the AD properties. Accordingly, the objective of an internal FDA study was to understand the effect of the milling process on milling efficiency (i.e., the mass percent of fine particles < 500 μm) and distribution of drug in various size fractions of the milled ADF with physical barrier design. The results showed that the milling process parameters, including milling time and number of tablets, could significantly affect the milling efficiency. Drug loss also occurred during the manipulation process. Drug distribution in the manipulated tablets varied significantly across different particle size fractions. Based on these results, the selected size fraction of particles should be assayed for actual drug content before being used for other studies.

Conventional dissolution methods, such as United States Pharmacopeia (USP) apparatuses 1 and 2, are designed for testing of finished drug products. However, for ADFs, particularly after manipulation, polymeric excipients within the sample matrix can greatly influence the dispersion process and may lead to problematic dissolution behavior. Internal FDA research in this area demonstrated that the dissolution characteristics of intact ADF tablets using USP apparatus 1 or 2 differed from those of manipulated ADF powder. An improved dissolution method based on USP apparatus 4 was developed, which minimized the variation and was found to be more suitable for dissolution of manipulated ADF powders under a wide range of experimental conditions.

Figure 1. Model-Guided In Vitro Chewing Method for Determining Opioid Availability of ADFs Following Chewing.

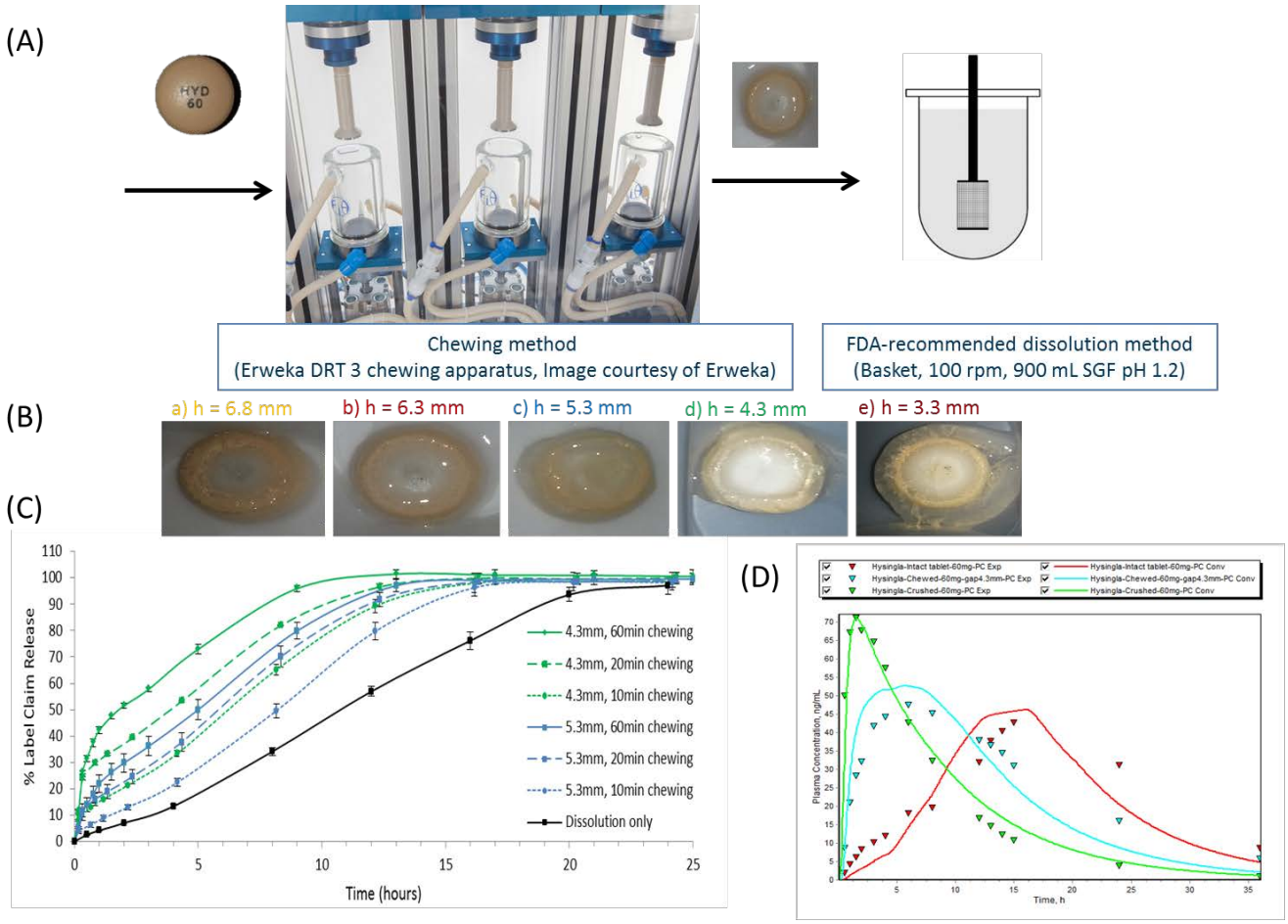
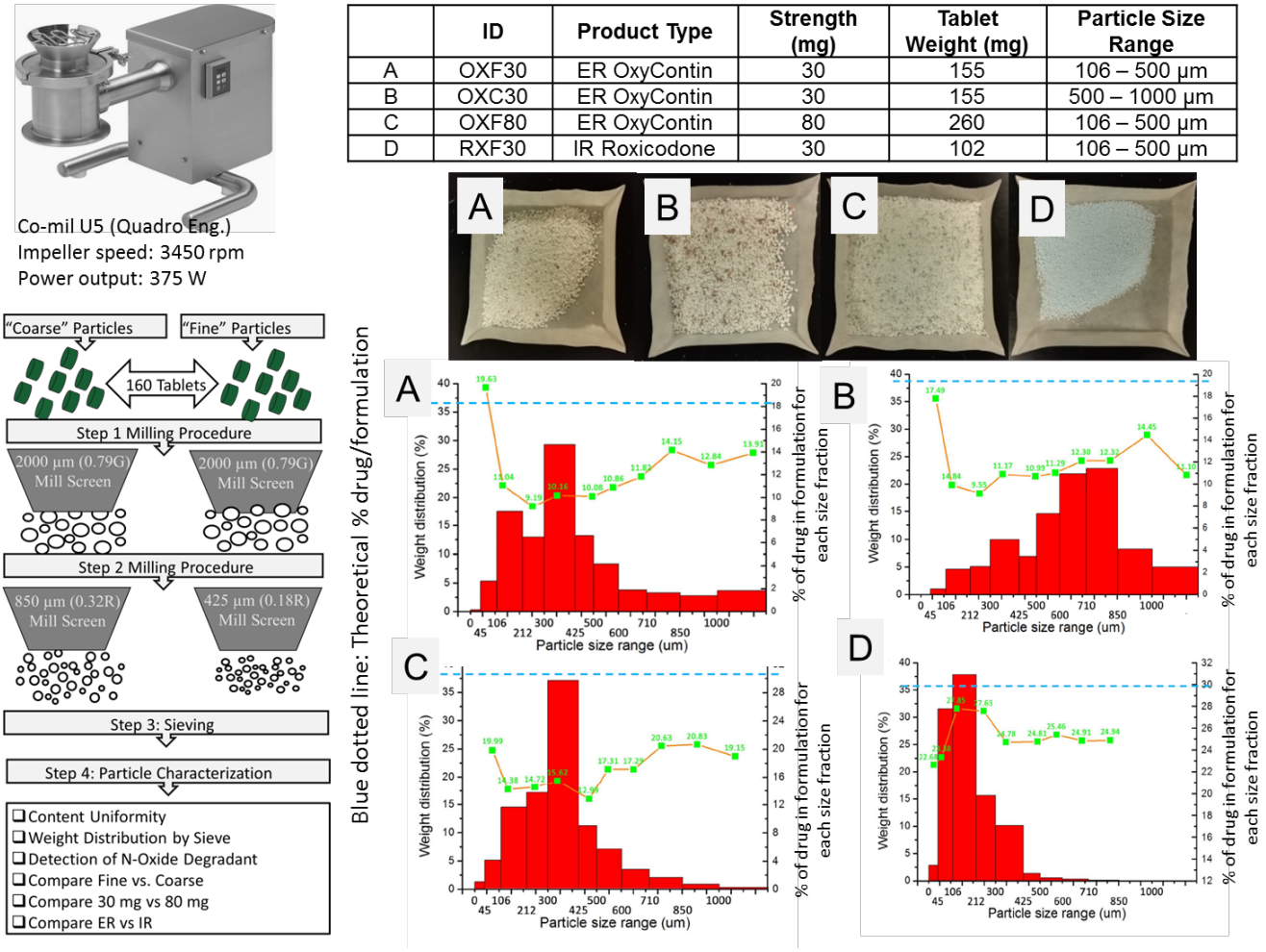


Figure 1: (A) in vitro chewing method coupling Erweka DRT 3 chewing apparatus with USP dissolution apparatus, (B) images of tablet residues after 60 min of chewing with different setting for the size of the gap between the upper and lower jaws, (C) drug release during simulated chewing experiments with different chewing times (10, 20 and 60 min) for a gap size of 4.3 and 5.3 mm followed by 24 hours of USP dissolution testing using the FDA recommended dissolution method, (D) comparison between observed PK data and IVIVC model convoluted plasma concentration of hydrocodone for intact, chewed and crushed forms.

Figure 2. Summary of Bulk Milling of Oxycodone HCl Tablets.



	ID	Product Type	Strength (mg)	Tablet Weight (mg)	Particle Size Range
A	OXF30	ER OxyContin	30	155	106 – 500 µm
B	OXC30	ER OxyContin	30	155	500 – 1000 µm
C	OXF80	ER OxyContin	80	260	106 – 500 µm
D	RXF30	IR Roxicodone	30	102	106 – 500 µm

Figure 2: Process of physical manipulation milling oxycodone HCl ER and immediate-release (IR) tablets into coarse and fine particles (*left*), identification and images of milled tablets (*upper right*) and particle size distribution and drug recovery in each size fraction of the resulting particles (*lower right*) – (A) fine particles (106-500 µm) of OxyContin ER tablets at 30 mg strength (B) coarse particles (500-1000 µm) of OxyContin ER tablets at 30 mg strength, (C) fine particles (106-500 µm) of OxyContin ER tablets at 80 mg strength, (D) fine particles (106-500 µm) of Roxicodone IR tablets at 30 mg strength.

Research Projects and Collaborations

Continuing Grants and Contracts

- Active Contract (HHSF223201510138C) *Pharmacokinetics Study of Opioid Drug Product Following Insufflation of Milled Drug Products* with Bradley Vince at Vince & Associates Clinical Research
- NIPTE Grant (U01FD004275): 1) Effect of Excipient Variability on the Critical Quality Attributes of Opioid Drugs Based on Polyethylene Oxide Matrix; and 2) Methods for Evaluation of Abuse Deterrence via

Smoking and Vaping, with NIPTE (University of Texas at Austin, University of Maryland, Purdue University, and Texas A&M)

Active FDA Research

- *Development of an In Vivo Predictive Method for Determining Opioid Availability Following Chewing of Solid Oral Opioids*
- *Development of In Vitro Methods for Nasal ADF Opioids* with
- *Stability Study of ADF Opioids to Enhance Assurance of AD Properties During Product Shelf Life*
- *Impact of Milling Process on the Evaluation of Abuse-Deterrent Formulations*
- *A Flow-through Dissolution Method for Evaluation of Drug Release from Manipulated ADFs*
- *Standardization of Syringeability and Injectability Assessment for Abuse Deterrent Formulations using a Time-dependent Force-distance Profile*
- *Quantitative Analysis of PKPD Relationship of Abuse Deterrent Opioid Products*
- *Development of CFD-PBPK Models for Nasal Delivery of Abuse Deterrent Opioid Formulations*

Outcomes

General Guidance

- *Final Guidance on "General principles for evaluating the abuse deterrence of generic solid oral opioid drug products"* FDA Guidance Posting. November 2017. Link to Posting.

Product-Specific Guidances

- *Revised Draft Guidance for Hydrocodone Bitartrate Oral Tablet, Extended Release*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *Revised Draft Guidance for Morphine Sulfate; Naltrexone Hydrochloride Oral Capsule, Extended Release.* FDA Guidance Posting. July 20, 2018. Link to Posting.
- *Revised Draft Guidance for Oxycodone Hydrochloride Oral Tablet, Extended Release*. FDA Guidance Posting. July 20, 2018. Link to Posting.
- *Revised Draft Guidance for Morphine Sulfate Oral Tablet, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *Revised Draft Guidance for Oxycodone Oral Capsule, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Morphine Sulfate Oral Tablet, Extended Release*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.
- *New Draft Guidance for Oxycodone Hydrochloride Oral Tablet*. FDA Guidance Posting. Sept. 13, 2018. Link to Posting.

Publication

- Boyce, H., Smith, D., Byrn, S., Saluja, B., Qu, W., Gurvich, V. J., and Hoag, S. W. *In Vitro Assessment of Nasal Insufflation of Comminuted Drug Products Designed As Abuse Deterrent Using the Vertical Diffusion Cell*. AAPS PharmSciTech. (2018) **19**(4):1744–1757. doi: 10.1208/ s12249-017-0947-2. PMID: 29582347.
- Boyce, H. J., Ibrahim, A., and Hoag, S. W. *Physical Barrier Type Abuse-Deterrent Formulations: Monitoring Sintering-Induced Microstructural Changes in Polyethylene Oxide Placebo Tablets by Near Infrared*

Spectroscopy (NIRS). Drug Development and Industrial Pharmacy. (2018) **44**(11):1885–1894. doi: 10.1080/03639045.2018.1504965. PMID:30070152.

Posters

- Externbrink, A. *Application of an In Vitro Chewing Method to Assess the Effect of Shelf-Life and Storage Conditions on the Chewing Resistance and Drug Release Properties of Abuse-Deterrent Hysingla*. Poster Presentation at Controlled Release Society Annual Meeting. New York City, NY, July 23, 2018.
- Externbrink, A., Sun, D., Sharan, S., Saluja, B., Gao, Z., Keire, D., and Jiang, W. *Development of an In-Vitro Chewing Method for Determining Opioid Availability Following Chewing of Solid Oral Extended-Release Opioids*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.
- Feng, X., Balajee, V., Leissa, J., Ashraf, M., Cruz, C.N., and Xu, X. *Standardization of Syringeability and Injectability Assessment for Abuse Deterrent Formulations using a Time-dependent Force-distance Profile*. Poster Presentation at 2018 CRS annual meeting. New York, NY, July 22, 2018.
- Sharan, S., Externbrink, A., Sun, D., Zhang, X., Fan, J., Jiang, W., Gao, Z., Keire, D., Lionberger, R., and Zhao, L. *Development of Mechanistic In Vitro In Vivo Correlation (IVIVC) of Abuse-Deterrent Hydrocodone Bitartrate Extended Release Tablets*. Poster Presentation at AAPS Annual Meeting. San Diego, CA, Nov. 14, 2017.

Presentation

- Xu, X., and Sun, D. *In Vitro and In Vivo Abuse Deterrence (AD) Evaluation of Generic Opioid Products*. Presentation at CDER SBIA Complex Generic Drug Product Development Workshop, Silver Spring, MD, September 12-13, 2018.