EG-002, a Novel Proprietary Abuse-Deterrent, Extended-Release Formulation of Oxycodone, Demonstrates Strong Abuse-Deterrent Potential Based on the Results From a Category 1 In Vitro Physical Manipulation Study

Edward J. Cone, PhD,[1] August R. Buchhalter, PhD,[1] Karsten Lindhardt, MSc, PhD, DBE,[2] Torben Elhauge, MS,[2] Jeffrey M. Dayno, MD[2]

[1]*Pinney*Associates, Bethesda, MD, USA; [2]Egalet Corporation, Wayne, PA, USA

Poster #31

For additional information, please contact:
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Phone: +X (XXX) XXX-XXXX
Fax: +X (XXX) XXX-XXXX
E-mail: xxxxxxx@xxxxxxxxx.com

Introduction

- Prescription opioid abuse is a significant public health problem in the United States (US). In 2013, 4.5 million people ≥12 years old reported nonmedical use of prescription pain relievers, including 492,000 using controlled-release (CR) oxycodone (OxyContin®; Purdue Pharma LP, Stamford, CT).[1]
  - Physical manipulation (eg, chewing, crushing, grinding) and chemical extraction of extended-release (ER) opioid formulations may accelerate the release of the opioid after ingestion, injection, nasal insufflation, or smoking.[2,3]
- In 2010, the introduction of an abuse-deterrent (AD) formulation of CR oxycodone was followed by marked reduction in its abuse[3] and overall overdose.[4]
  - However, recent data suggest that 1 in 3 recreational users of prescription opioids has learned how to thwart/defeat the AD technology of CR oxycodone.[5]
  - Consequently, more effective AD technologies are needed for effective abuse deterrence of ER opioids
- EG-002, an oxycodone ER formulation, incorporates a novel proprietary AD technology (Guardian™ Technology; Egalet Corporation, Wayne, PA) that combines an inert outer shell, polymer-based formulation, and unique process, plastic injection molding in the production of pharmaceutical tablets.
  - EG-002 is designed to resist chemical extraction, and the extreme hardness of its outer shell provides a barrier to physical manipulation that could prevent accidental misuse by legitimate pain patients especially by chewing.
- In April 2015, the US Food and Drug Administration (FDA) finalized guidance (Guidance for Industry Abuse-Deterrent Opioids – Evaluation and Labeling) on the evaluation and labeling of AD opioid formulations.
  - Included in the Guidance is the recommendation for in vitro manipulation studies (Category 1) to determine the difficulty of defeating potential AD properties of a formulation.[6]

Objective

- To evaluate the resistance of EG-002 to single-step physical manipulation in comparison with an approved AD CR oxycodone formulation using in vitro laboratory studies in accordance with the 2015 FDA Guidance for Category-1 AD testing.

Methods

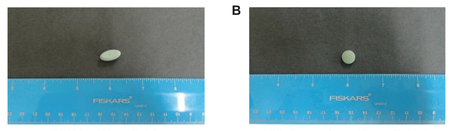
Study Design

- Single-step physical manipulation tests were conducted at an independent laboratory (DrugScan, Horsham, PA) without randomization.
- Trained, unblinded technicians followed standardized procedures using manual and electrical household tools commonly employed by recreational users of prescription opioids **(Table 1)**, to assess
  - Ability to crush the tablets (crushability)
  - Impact of heating and freezing on crushability
  - Results of these maneuvers on particle size reduction

Opioid Formulations Tested

- EG-002 80-mg tablets **(Figure 1A)** and CR oxycodone 80-mg tablets **(Figure 1B)**.

Figure 1. Study Formulations



CR=controlled release.

Assessments

- Comparative single-step crushability of EG-002 compared with CR oxycodone.
  - Endpoint 1: Physical condition of EG-002 tablets after attempted manipulation for an amount of time and effort equal to the time required for failure of CR oxycodone tablets **(Table 1)**.
  - Endpoint 2: Physical condition of EG-002 tablets after attempted manipulation for 5-fold the time and effort required for failure of CR oxycodone tablets **(Table 1)**.

Table 1. Household Tools Used for Tablet Manipulation

Tool	Procedure Applied to Tablet	Maximum Duration of Effort
Spoons	Manually crushed between 2 spoons	1 minute
Mortar/Pestle	Manually crushed with pestle	3 minutes
Hammer	Placed in plastic bag and beaten manually	1 minute
Food grater	Manually grated against surface	5 minutes
Foot file	Manually grated against surface	5 minutes
Razor blade	Manually cut into maximal number of pieces	5 minutes
Knife	Manually cut into maximal number of pieces	3 minutes
Pill crusher	Cap turned manually as far as possible	Limited by breakage of device
Pill splitter	Manually cut into maximal number of pieces	1 minute
Electric coffee grinder	Manually ground within permitted time	1 minute
Electric spice grinder	Manually ground within permitted time	1 minute

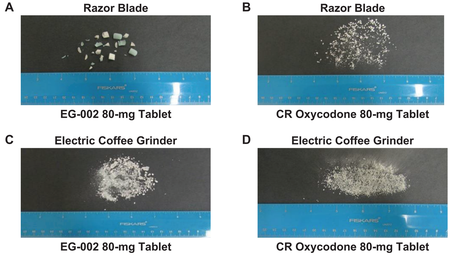
- Impact of heating and freezing of comparator formulations on crushability.
  - Comparator formulations were pretreated before crushability testing in 3 ways with comparison to untreated formulations:
    - Microwaved at 1200W for 1 minute
    - Heated in an oven for 30 minutes at 100°C
    - Cooled for 1 hour at –20°C
- Particle size analysis
  - A series of sieves were used to separate manipulated tablet fragments by particle size (<75, ≥75, ≥106, ≥212, ≥500, and ≥ 1000 µm).
  - The distribution of recovered particles by particle size was calculated from the mass of particles recovered on each sieve using the following formula: *% recovery of particle size X = (mass of particles retained on sieve size X / total weight of particles recovered from all sieves) × 100*

Results

Comparative Crushability

- Consistently across all tools used, attempted manipulation of EG-002 required up to 5-fold the time needed to manipulate CR oxycodone into a powder or small particles sizes.
  - Despite prolonged attempts at manipulation, the resulting particles of EG-002 were consistently larger than those obtained from manipulation of CR oxycodone.
  - For example, manipulation of CR oxycodone with a razor blade for 5 minutes produced substantial powdering, whereas no powdering of EG-002 was observed (**Figures 2A** and **2B**).
- Manipulation of EG-002 and CR oxycodone with an electric coffee grinder for 1 minute resulted in powdering of both tablets (**Figures 2C** and **2D**).
  - However, for the EG-002 tablets, both small and large chunks remained after grinding, whereas only small particles of CR oxycodone remained.

Figure 2. Physical Manipulation Results

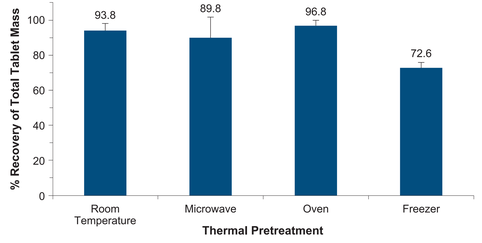


CR=controlled release.
Tablets were manipulated with the razor blade for 5 minutes and with the electric coffee grinder for 1 minute.

Impact of Heating and Freezing

- In general, the particle size distribution (content on 212, 500, or 100 µm sieve) for EG-002 did not change after thermal pretreatment.
- The recovery of particles of EG-002 tablets after grinding was 93.8% of the original tablet mass for tablets kept at room temperature, 96.8% for tablets preheated in an oven, and 89.8% for tablets preheated in a microwave **(Figure 3)**.
  - Freezing before grinding reduced the recovery of EG-002 to 72.6% of the original tablet mass.

Figure 3. Thermal Pretreatments Do Not Change the Recovery of EG-002 After Physical Manipulation

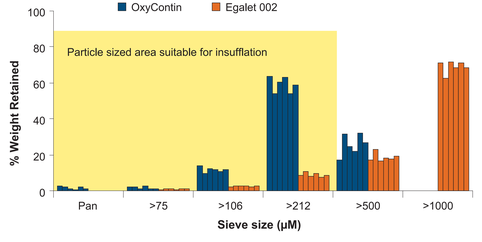


Values are the mean + standard deviation (SD) percentage of weight recovered of the ground core calculated from the total amount of core material (312 mg) in an EG-002 80-mg tablet.

Particle Size Analysis

- After manipulation (pounding and/or grinding), the percentage of particles suitable for insufflation (<500 µm) was substantially greater for CR oxycodone (72.5%) than for EG-002 tablets (12.6%; **Figure 4**).

Figure 4. Particle Size Distribution After Manipulation of Tablets



Values are the percentage of powder on each sieve calculated from the total retrieved weight. The shaded area represents particle sizes that can be insufflated.

Conclusions

- **In a series of physical manipulations attempting to defeat the AD technology of the comparator, EG-002 tablets resisted failure for up to 5-fold the duration of effort required for failure of CR oxycodone.**
  - **Physical manipulations attempted for an equivalent duration of effort yielded larger particles for EG-002 tablets (primarily too large for insufflation) compared with CR oxycodone tablets.**
- **The percentage of particles suitable for intranasal abuse that could be obtained from manipulation of EG-002 tablets was almost 6-fold lower versus CR oxycodone tablets.**
- **The difficulty and extreme effort needed to manipulate EG-002 tablets should offer substantial deterrence to methods of abuse requiring small particle size, such as nasal insufflation.**

References

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Conflict of Interest
Edward J. Cone and August R. Buchhalter are employees of **Pinney**Associates and provide consulting services to Egalet.
Karsten Lindhardt, Torben Elhauge, and Jeffrey M. Dayno are employees of Egalet and may own Egalet stock or stock options.

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