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# Pharmacokinetic Study of Physically Manipulated Oxycodone Hydrochloride Products Following Nasal Insufflation in Recreational Opioid Users

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## PURPOSE.

In this study, we evaluated the pharmacokinetics (PK) of nasally insufflated milled oxycodone hydrochloride (HCl) extended-release (ER) abuse deterrent (AD) products characterized by different particle size and excipient [release-controlling polymer polyethylene oxide (PEO) + inactive material] amount and assessed the effect of these variables on the bioavailability of oxycodone. The objectives of this study were:

1. To assess the PK ($C_{max}$, $T_{max}$, $AUC_{0-t}$ and $pAUC_{0-3}$, $pAUC_{0-4}$ as supportive) and safety of oxycodone HCl ER AD product milled to two different sizes compared to milled oxycodone HCl immediate-release (IR) product following intranasal insufflation in recreational opioid users when administered under a naltrexone block.
2. To assess the excipient to drug (oxycodone HCl) ratio (EDR) on nasal bioavailability.

## METHODS.

A single center, randomized, open-label, single-dose, 4-sequence, 4-period, 4-treatment crossover, phase 1 study under a fasting stage (Table 1).

*Treatment.* Oxycodone ER and IR tablets (purchased through Purdue University Pharmacy) were finely or coarsely milled to a targeted particle size range of 106-500 µm or 500-1000 µm, respectively, using good manufacturing practices (GMP) (Table 2), Treatments A, B, and C contain PEO while D does not. Tablets were milled and packaged in the GMP facility then shipped to the clinical site for dosing.

*Subjects.* Healthy males and females aged between 18-55 with history of recreational opioid use defined by non-therapeutic usage on >10 occasions in their lifetime and at least one use in 12 weeks prior to screening, and with insufflation drug use experience (Table 3). Subjects were excluded if physically dependent on opioids demonstrated by failed naloxone challenge (Clinical Opiate Withdraw Scale >5).

*Assessment.* The subject-rated Ease of Snorting Visual Analogue Scale (ES-VAS) was conducted as a 100-point VAS answering the question, "Snorting this drug was", where 0 = "Very easy" and 100 = "Very difficult". Subject-Rated Assessment of Intranasal Irritation (SRAII) was administered through 8 hours post-dose on the 5-point scale (0 = No problem to 5 = Very Severe Problem). Ratings were based on 5 categories: Burning; Need to blow nose; Runny nose; Facial pain/pressure and Nasal congestion.

*Ethics.* This study was approved by the MidLands Independent Review Board (Overland Park, KS) and by the Research Involving Human Subjects Committee at the US FDA (Silver Spring, MD) and was conducted under an investigational new drug application.

*Bioanalytical.* Blood samples were collected in $K_2$ EDTA tubes, and were stored frozen until analysis. Plasma samples were assayed for oxycodone using a validated HPLC method with MS/MS detection. The lower limit of quantitation and upper limit of quantitation were 0.2 ng/mL and 100.0 ng/mL, respectively.

*Statistics*. Bioequivalence: two-sided 90% confidence interval of the ratio of geometric means (GM) for $C_{max}$, $AUC_{0-t}$ and supportive parameters $pAUC_{0-3}$, $pAUC_{0-4}$ based on ln-transformed data.

*EDR after milling.* $\frac{(recovered\ total\ milled\ tablet\ mass - recovered\ drug\ amount)}{Recovered\ drug\ amount}$

**Table 1. Study Design Summary**

| Period | | 1 | | 2 | | 3 | | 4 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Day | -28-1 | 1–2 | 3 | 4–5 | 6 | 7-8 | 9 | 10-11 | 12 | 14-15 |
| Activity | Screening | PK | Washout | PK | Washout | PK | Washout | PK | Discharge | Follow-up |

Blood Draw: Pre-dose, 0.08 (5 minutes), 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 hours post-dose (36 h shown in Figure 1).

* Different randomization sequences (ABDC, BCAD, CDBA, DACB) used for each period

**Table 2. Treatment Summary Study**

| | | Tablet Characteristics | | Milled Tablet Characteristics | | | |
|---|---|---|---|---|---|---|---|
| Treatment | Product Type | Tablet Strength (mg) | Tablet Weight (mg) | Milled Particle Size Range (µm) | Drug Administered (mg) | Amount of Milled Tablet Snorted (mg) | EDR |
| A | ER Oxycodone | 30 | 155 | 106-500 | 30 | 237 | 6.9 |
| B | ER Oxycodone | 30 | 155 | 500-1000 | 30 | 211 | 6.1 |
| C | ER Oxycodone | 80 | 260 | 106-500 | 30 | 177 | 4.9 |
| D | IR Oxycodone | 30 | 102 | 106-500 | 30 | 104 | 2.4 |

## RESULTS

**Table 3. Demographics**

41 Healthy Recreational Opioid Users Enrolled

| Characteristic | | PK Population | Safety Population |
|---|---|---|---|
| N | | 36 | 41 |
| Age, y | | | |
| | Mean | 30 (7) | 31(7) |
| | Range | 22-50 | 22-50 |
| Sex, n (%) | | | |
| | Male | 32 (88.9) | 36 (87.8) |
| | Female | 4 (11.1) | 5 (12.2) |
| Race, n (%) | | | |
| | White | 10 (27.8) | 15 (36.6) |
| | Black | 26 (72.2) | 26 (63.4) |
| Body Mass Index | | | |
| | Mean (SD), $Kg/m^3$ | 25.10 (3.65) | 25.38 (3.63) |

**Table 4. Treatment Summary**

| Parameter | Treatment-A | Treatment-B | Treatment-C | Treatment-D |
|---|---|---|---|---|
| Cmax(ng*h/mL) | | | | |
| Mean (C.V.%) | 68 (25) | 47 (28) | 61 (21) | 81 (27) |
| Tmax (h) | | | | |
| Median (range) | 1.5 (0.5-4) | 2.5 (0.75-8.0) | 2.0 (0.75-3.5) | 1.5 (0.5-1.5) |
| AUC0-t (ng/mL) | | | | |
| Mean (C.V.%) | 520 (104) | 441 (142) | 468 (118) | 415 (90) |

**Figure 1. Oxycodone Plasma Concentration Time Profiles (Mean ± SD)**

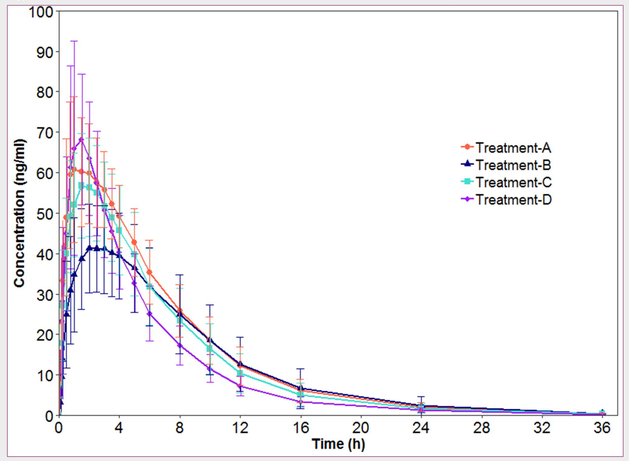
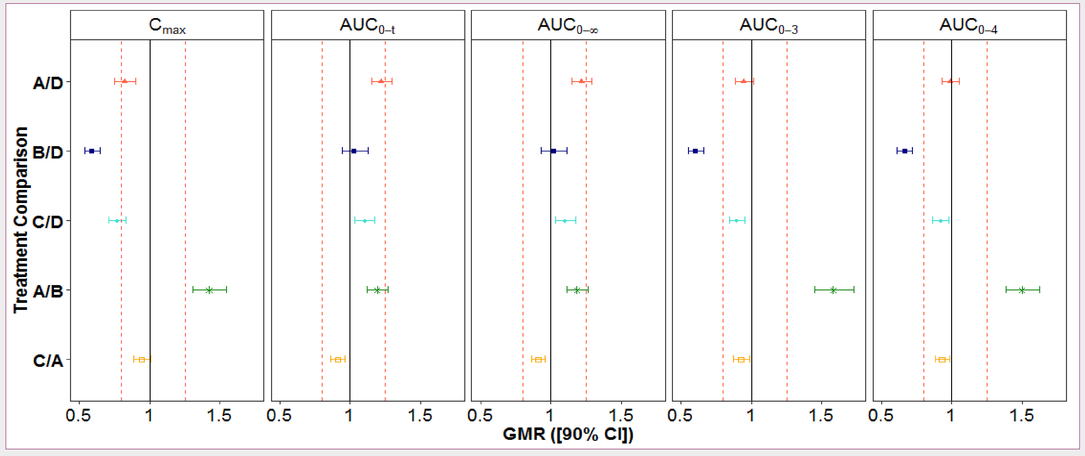



**Table 5. Summary of ES-VAS**

| Statistics | Treatment-A | Treatment-B | Treatment-C | Treatment-D |
|---|---|---|---|---|
| Mean (SD) | 28.1 (26.0) | 24.7 (27.1) | 20.7 (23.8) | 8.1 (11.8) |
| Median | 26.00 | 16.00 | 11.00 | 3.00 |
| Range | 0.0 – 82.0 | 0.0-94.0 | 0.0-74.0 | 0.0-51.0 |

**Figure 2. GM Ratio Comparisons of Primary and Supportive PK Parameters (red dotted line = bioequivalence bound, symbols = GM ratio point estimate, error line = 90% confidence interval)**




## RESULTS

### Summary of Particle Size and EDR Effect

- EDR did not have an effect on PK at 106 – 500 µm (Figure 2, C/A) when ranged from 4.9 to 6.9. Treatment A and C were BE.
- Particle size had an effect on how fast and the extent to which drug was absorbed (Figure 2, A/B).

1. Product milled to 500-1000 µm (Treatment B) delayed $T_{max}$ and lowered $C_{max}$ in comparison to finely milled product (Treatment A, C) (Figure 1 & Table 4).
2. Although A & C include control release polymer PEO, when finely milled to 106 to 500 µm the GM ratios were similar to milled IR product with respect to key PK parameters ($C_{max}$, $AUC_{0-t}$) and supportive PK parameters ($pAUC_{0-3}$, $pAUC_{0-4}$) (Figure 2, A/D & C/D). This indicates particle size was more significant than EDR in affecting nasal bioavailability.

- Although Treatment A and C were BE, Treatment C appeared to exhibit lower $C_{max}$, longer $T_{max}$, lower overall exposure ($AUC_{0-t}$) as well as lower exposure after snorting ($pAUC_{0-3}$, $pAUC_{0-4}$) than Treatment A (Figure 2 & Table 4).The amount of material snorted may have influenced this trend (Table 2). For instance, Treatment A had the highest exposure, most likely a combination of high EDR, 25% more material snorted and fine particle size which may have allowed for longer residence time in the nasal mucosa with increased nasal bioavailability.

### Summary of SRAII and ES-VAS

- Treatment A was associated with the highest mean and median ES-VAS scores which indicates snorting was more difficult for this treatment.
- ES-VAS increased with increased amount of powder snorted (Table 2 & Table 5).
- The most number of irritations were reported at 0.25 h post-dose; 2/3 of subjects reported no issues over the entire time course.
- The least number of irritations were reported with Treatment-D (most by Treatment-C) and were mostly resolved by 2 h.
- Of the 113 Treatment emergent adverse events reported by 32 subjects, 5 were moderate in severity, and no serious adverse events were reported.

## CONCLUSIONS.

This study demonstrated that when AD oxycodone ER tablets (30 mg and 80 mg) were milled to a particle size between 106-500 µm, the PK exhibited similar $C_{max}$ and median $t_{max}$ to that of an IR product with similar particle size range. However, milling to a range of 500-1000 µm delayed $t_{max}$ and lowered the $C_{max}$ when compared to the IR product. The EDR of ER oxycodone product did not have an impact on intranasal PK when finely milled to a size between 106-500 µm, however, it is unknown if EDR has an effect on PK at 500 – 1000 µm. The treatment emergent adverse events reported were mostly mild and directly related to local irritation from insufflation. There were no serious adverse events reported.

## Disclaimer & Acknowledgements..

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