# Pharmacokinetics of milled oxycodone hydrochloride tablet products following nasal insufflation in nondependent, recreational opioid users

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# Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

# Outline

- Background of study
- In vitro preparation of particles
- In vivo results
- Conclusions

# Study objectives

To obtain a better understanding of the abuse deterrent (AD) properties of extended release (ER) opioid products employing a polyethylene oxide (PEO) matrix:

Objective 1: evaluate the impact of particle size on the pharmacokinetics (PK) of comminuted oxycodone AD ER tablets relative to the PK of comminuted oxycodone immediate release (IR) tablets

Objective 2: evaluate the effect of excipient-to-drug ratio (EDR) on the PK of comminuted oxycodone ER AD tablets administered intranasally

# Nasal insufflation pharmacokinetic (PK) study

- The study is recommended in the FDA guidance for evaluating generic abuse deterrence opioid drug products[1]

- Oxycodone HCl ER tablet was the first opioid product with approved AD features

- Impact of formulation variables on PK study outcome:
  - Effect of milled tablet particle size on intranasal PK parameters
  - Impact of the EDR (including AD polymer, PEO)

- Learn how these variables impact generic product comparisons

1. General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. Nov 2017

# Research team

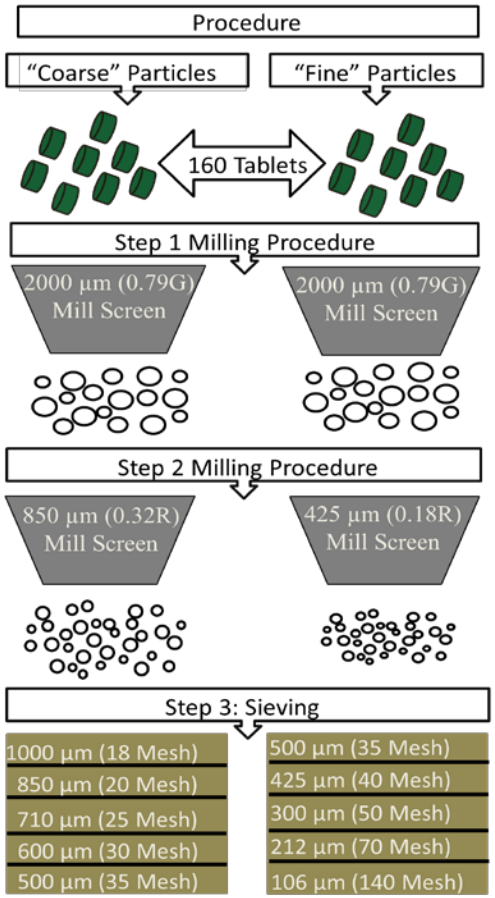
FDA
Research sponsor

- Contractor
- Contract Research Organization (CRO)
- In vivo human insufflation PK study

- Sub- Contractor
- In vitro physical manipulation method development
- In vitro evaluation of manipulated AD opioid products

- Good manufacturing practice (GMP) facility sub-contractor
- Clinical batch production

# Oxycodone tablets were milled to either coarse or fine particle size

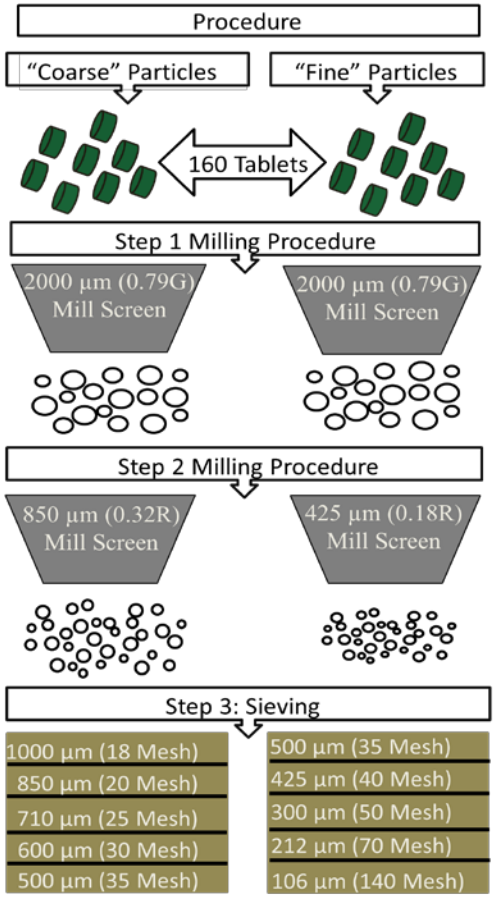


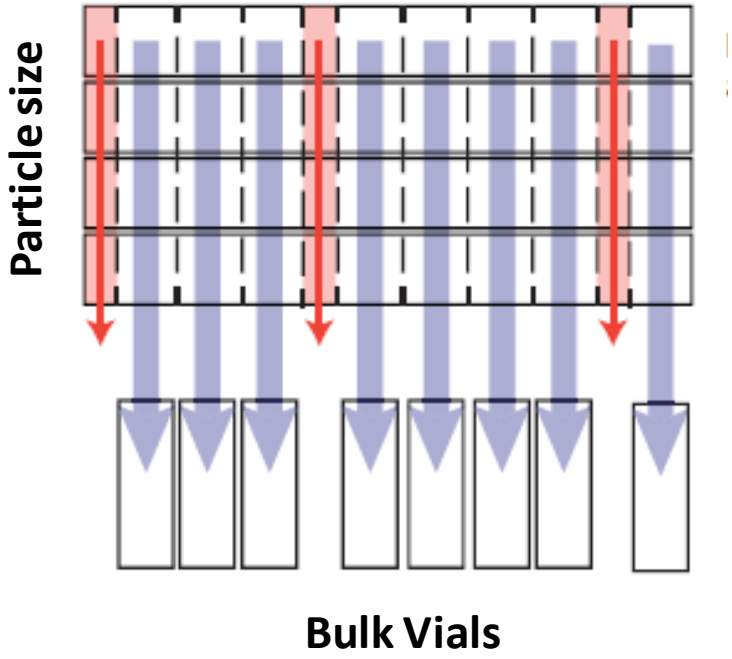

| | | |
|---|---|---|
| Coarse | = | 1000 – 500 µm |
| Fine | = | 500 µm – 106 µm |

- Ensure each bulk vial contains a similar particle size distribution
- Determine the drug concentration per formulation weight for each bulk vial
- Evenly distribute batch samples into individual vials for one cohort of subjects
- Demonstrate individual samples contain consistent drug content uniformity

# Proper sampling technique ensures each subject receives similar treatment

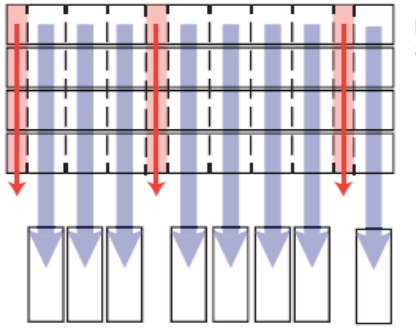
Step 1: Sieving of 160 milled tablets. Correct proportion of sample from each sieve added to each bulk vial



# Proper sampling technique ensures each subject receives similar treatment

## Step 2: Determination of drug content from each bulk vial (Sample taken from each red partition in sieve)

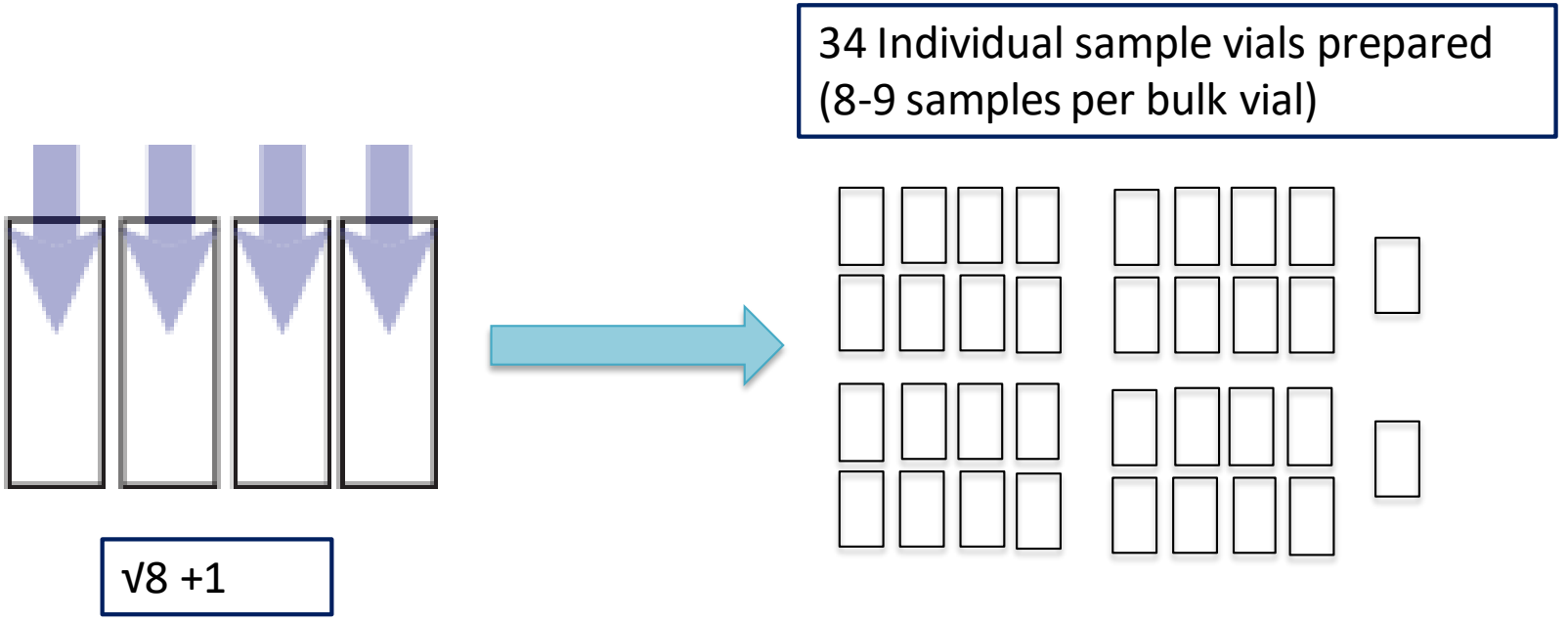


Bulk Vials

| | Bulk Vial Drug content (mg/100 mg) | | | |
|---|---|---|---|---|
| Sample ID | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
| OXF30 (A) | 12.58 (0.03) | 12.55 (0.05) | 12.65 (0.04) | 12.93 (0.09) |
| OXC30 (B) | 14.12 (0.05) | 13.99 (0.05) | 14.22 (0.13) | 14.35 (0.09) |
| OXF80 (C) | 16.79 (0.12) | 16.16 (0.03) | 17.94 (0.82) | 16.85 (0.10) |
| RXF30 (D) | 28.83 (0.14) | 28.75 (0.10) | 29.79 (0.81) | 28.99 (0.42) |

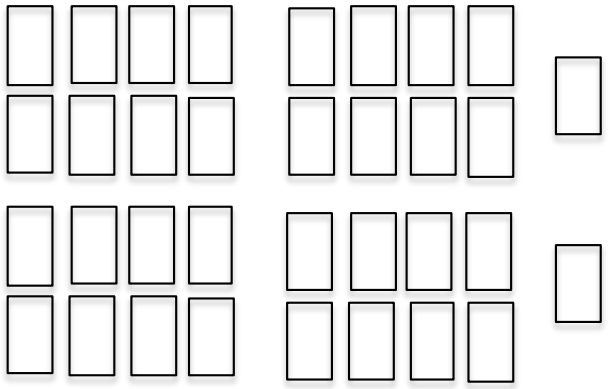
# Proper sampling technique ensures each subject receives similar treatment

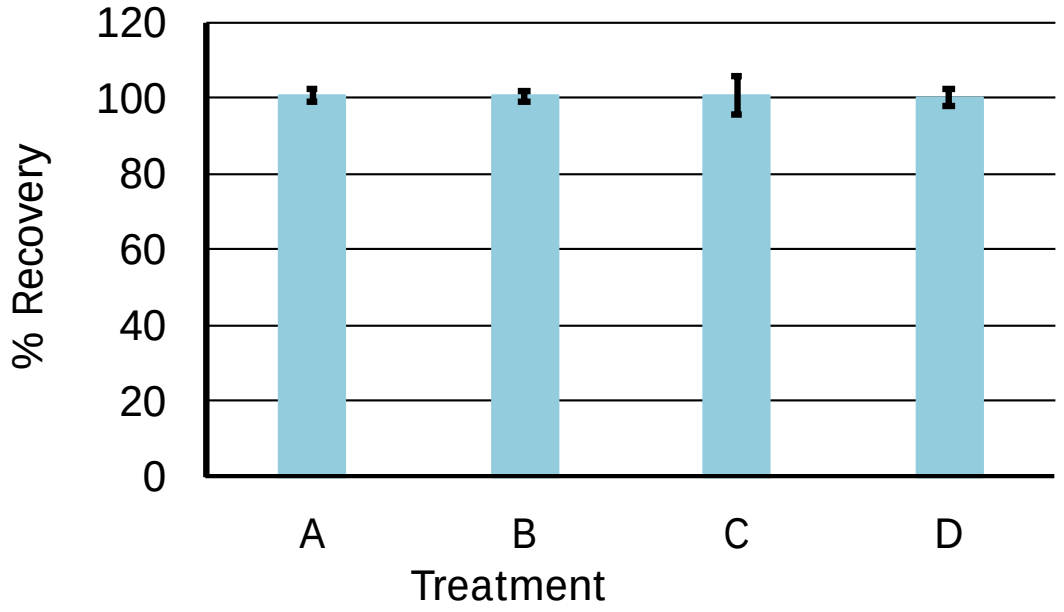
Step 3: 4 bulk vials randomly shipped to clinical site. The clinic dispenses individual samples from bulk vials using sampling protocol



# Proper sampling technique ensures each subject receives similar treatment

Step 4: Confirm individual samples have correct drug content after dispensing (n =34)



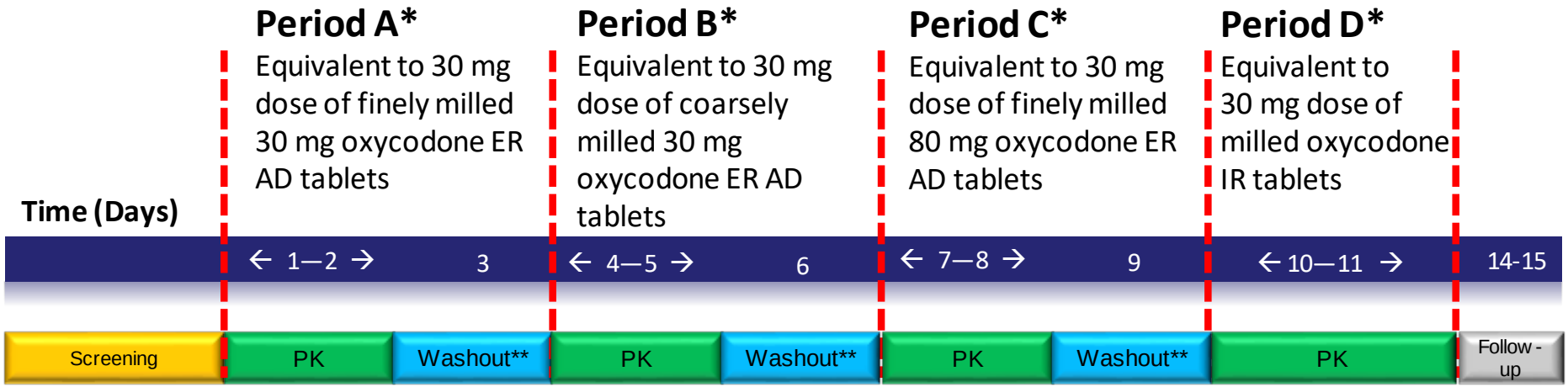


# Impact of dose normalization across treatment

| Ideal situation | | |
|---|---|---|
| | Drug (mg) | Formulation (mg) |
| Oxy 30 mg fine | 30 | 156 |
| Oxy 30 mg coarse | 30 | 156 |
| Oxy 80 mg fine | 30 | 97.5 |
| Roxi 30 mg fine | 30 | 100 |
| **Approach 1: Normalized by 30 mg drug** | | |
| Oxy 30 mg fine | 30 | 265.5 |
| Oxy 30 mg coarse | 30 | 252.1 |
| Oxy 80 mg fine | 30 | 185.2 |
| Roxi 30 mg fine | 30 | 115.8 |
| **Approach 2: Normalized by formulation** | | |
| Oxy 30 mg fine | 20 | 156 |
| Oxy 30 mg coarse | 21 | 156 |
| Oxy 80 mg fine | 41 | 260 |
| Roxi 30 mg fine | 29 | 100 |

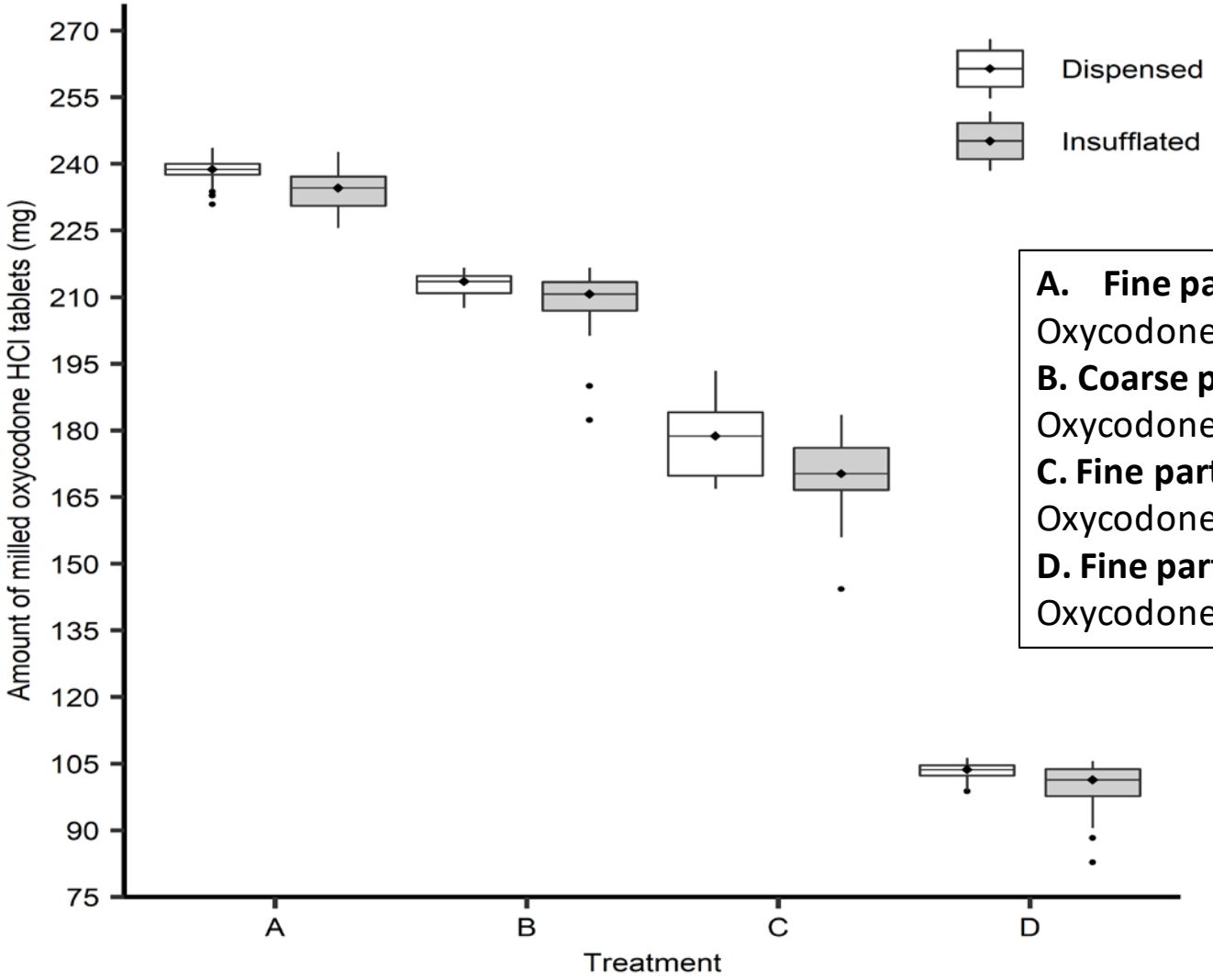
# Nasal insufflation PK study design

- Single center, randomized, open-label, single-dose, 4-sequence, 4-period, 4-treatment crossover design under fasting conditions in 41 healthy recreational opioid users
- Treatment arms:
  - **A. Fine particles (106-500 µm)** – oxycodone ER AD 30 mg (EDR = 6.9)
  - **B. Coarse particles (500-1000 µm)** – oxycodone ER AD 30 mg (EDR = 6.1)
  - **C. Fine particles (106-500 µm)** – oxycodone ER AD 80 mg (EDR = 4.9)
  - **D. Fine particles (106-500 µm)** – oxycodone IR 30 mg (non-ADF control, EDR = 2.4)
- A vs B → Effect of particle size
- A vs C → Effect of polymer-to-drug ratio



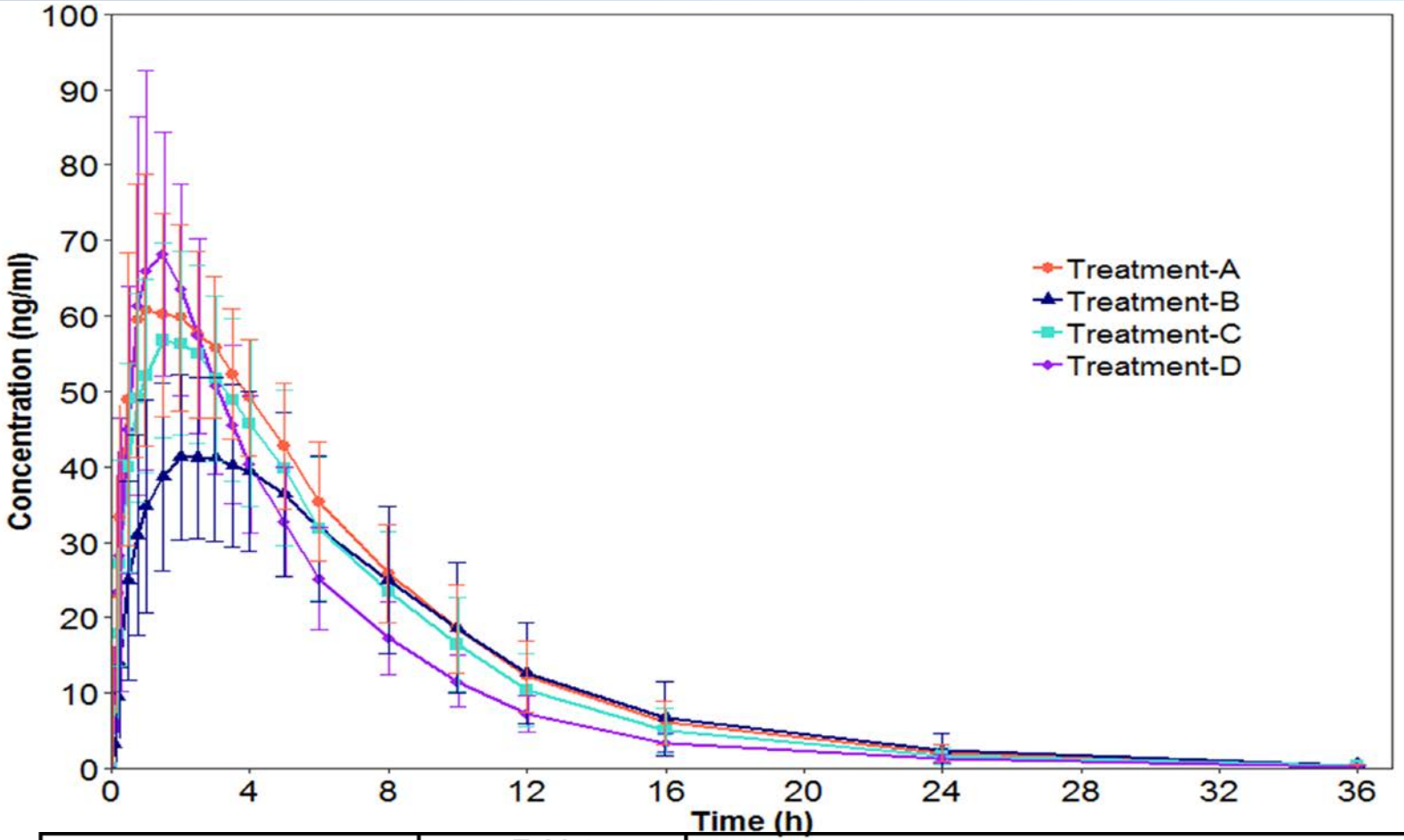

* This is an example of the sequence Period A → B → C → D
**Dosing intervals of approximately 72 hr

# Insufflated product equated to ±10% of dispensed amounts equivalent to the desired dose of 30 mg



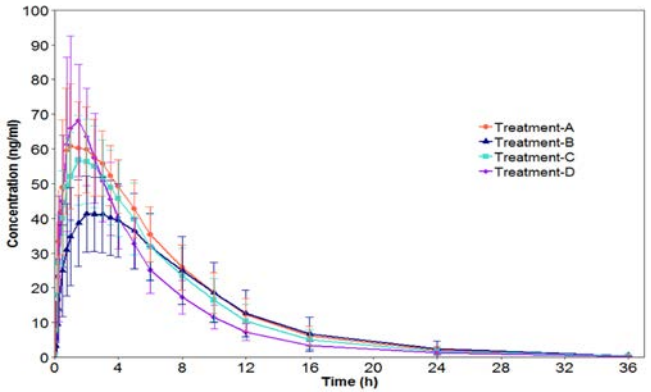

**A. Fine particles (106-500 µm)**
Oxycodone ER AD 30 mg
**B. Coarse particles (500-1000 µm)**
Oxycodone ER AD 30 mg
**C. Fine particles (106-500 µm)**
Oxycodone ER AD 80 mg
**D. Fine particles (106-500 µm)**
Oxycodone IR 30 mg (non-ADF control)

# Tablets milled to larger particle size delayed $T_{max}$ and lowered $C_{max}$

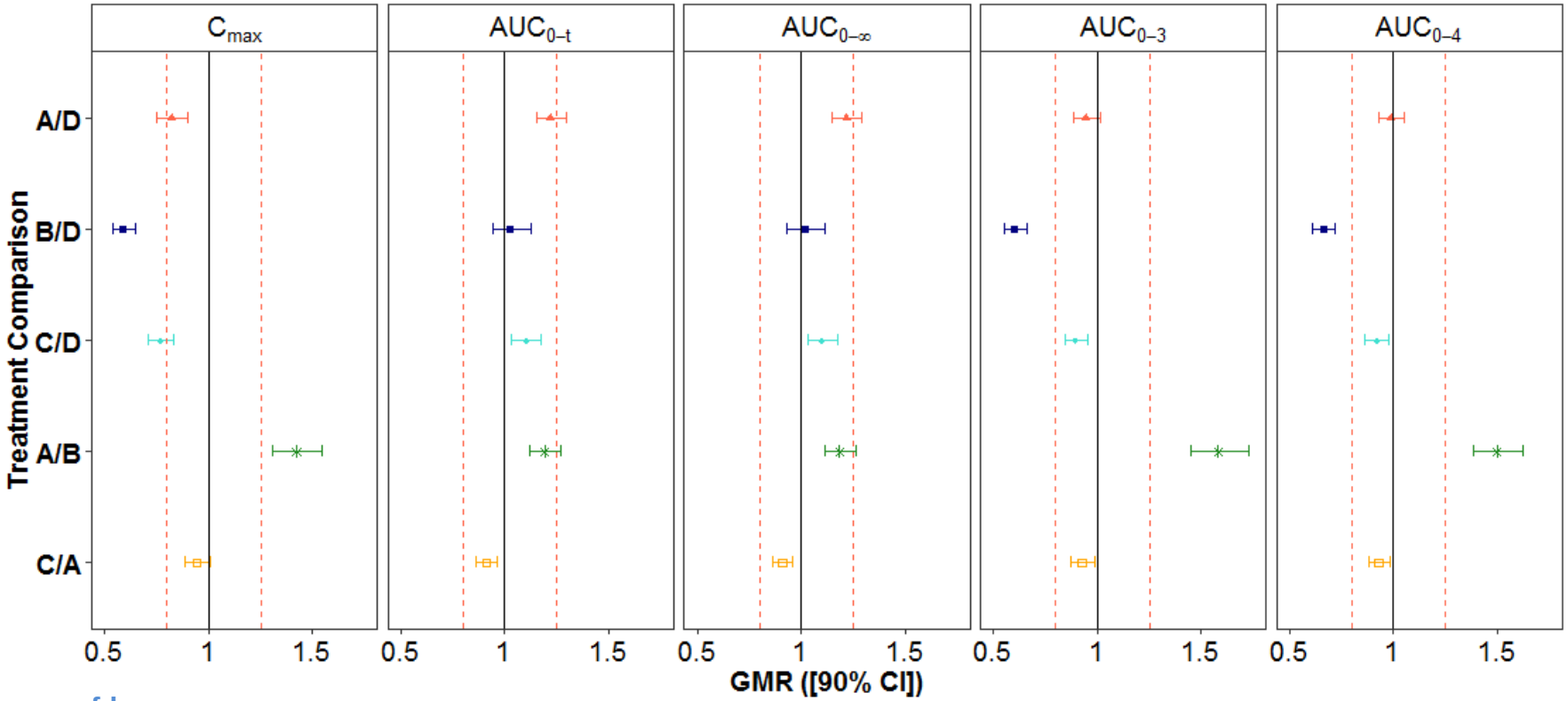



| Treatment | Product Type | Tablet Characteristics: Tablet Strength (mg) | Tablet Characteristics: Tablet Weight (mg) | Milled Tablet Characteristics: Milled Particle Size Range | Milled Tablet Characteristics: Drug Administered (mg) | Milled Tablet Characteristics: Amount of Milled Tablet Snorted (mg)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

# EDR impact on PK was not significant




- Particle size affected how fast and the extent to which drug was absorbed intranasally
- PEO to drug ratio did not have an effect on PK when the drug was milled to 106 – 500 µm



# Conclusions

- Preferential drug loss occurs after tablet is milled to specified particle size distribution
- Milling and dispensing methods were suitable for preparing reproducible sample for nasal insufflation clinical PK studies
- Subjects were able to snort ±10% of sample dispensed to them
- Finely milled oxycodone ER exhibited higher $C_{max}$, AUCs, and early partial AUCs in comparison with coarsely milled oxycodone ER
- There was no significant effect of EDR on the PK of finely milled oxycodone within the ranges studied

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