

Nasal Pharmacokinetic Study of Abuse-Deterrent Oxycodone HCl ER Products Following Insufflation of Physically Manipulated Products

SBIA 2021: Advancing Generic Drug Development: Translating Science to Approval
Day 1, Session 2: (Considerations in Assessing Generic Drug Products of Oral Dosage Forms)

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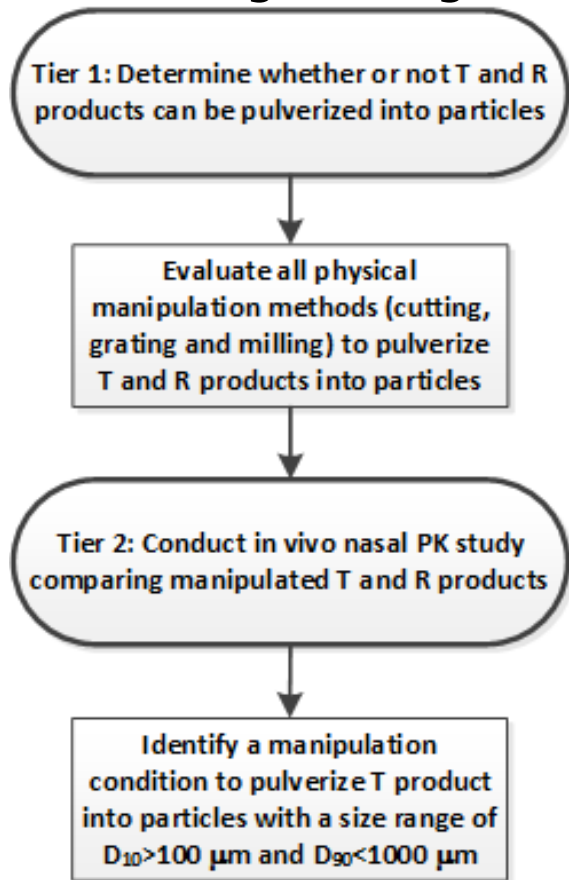
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Learning objectives

- Describe relevant concepts from general guidance on generic abuse deterrent (AD) opioids drug products as they relate to nasal pharmacokinetic (PK) studies
- Describe the study conducted to evaluate impact of particle size and polyethylene oxide to oxycodone ratio on nasal bioavailability
 - Describe clinical study design
 - Describe manipulation method development and dose preparation for the study
 - Describe study results

Generic AD general guidance and nasal AD PK studies



- Test product (T) and reference product (R) can be pulverized to a particle size range that is considered safe and tolerable for human insufflation (i.e., $D_{10} > 100 \mu\text{m}$ and $D_{90} < 1 \text{ mm}$)
- T is no less resistant to physical manipulation than R (i.e., R should be milled into the particle size range using the same milling conditions used for T or a lesser amount of energy input)
- Studies should be conducted in recreational opioid users

Study design and objectives

Study objectives

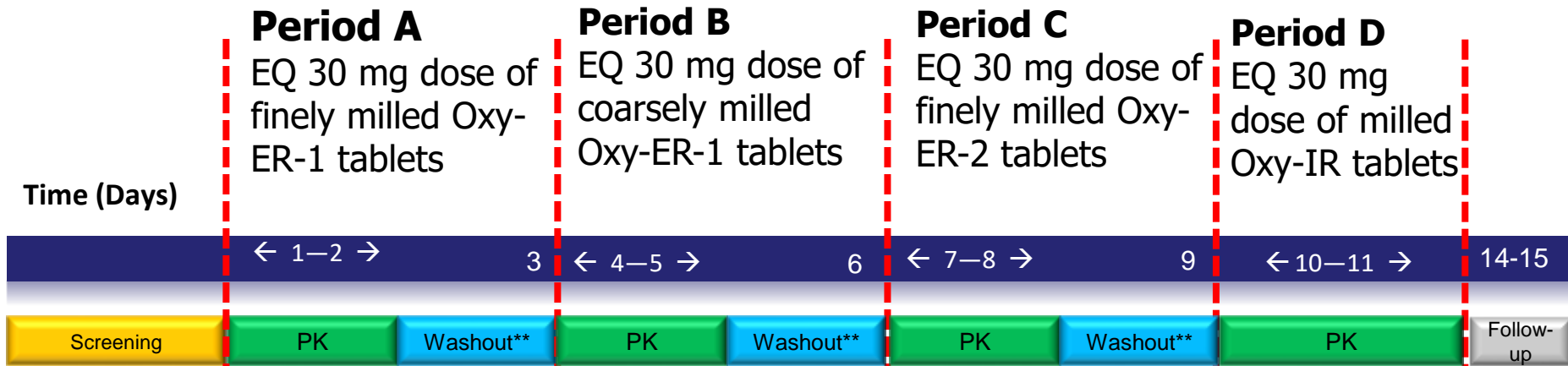
- To assess the pharmacokinetics of milled AD oxycodone extended release (ER) tablets compared to milled oxycodone immediate release (IR) tablets following intranasal insufflation in recreational opioid users
- To assess the effects of ratio of control releasing excipient, polyethylene oxide (PEO), to active pharmaceutical ingredient (API), oxycodone HCl, on nasal bioavailability of milled AD oxycodone ER tablets
- To assess the safety of milled AD oxycodone ER tablets compared to milled oxycodone IR tablets following intranasal insufflation in recreational opioid users, when administered under a naltrexone block

Opioid insufflation PK study



- 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)** – equivalent (EQ) 30 mg dose of manipulated Oxy-ER-1 tablet (AD oxycodone ER tablets with a polyethylene oxide to oxycodone ratio (PEO/API ratio) of 3.9)
 - B. Coarse particles (500-1000 μm)** – EQ 30 mg dose of manipulated Oxy-ER-1 tablets
 - C. Fine particles (106-500 μm)** – EQ 30 mg dose of manipulated Oxy-ER-2 tablets (AD oxycodone ER tablets with a PEO/API ration of 2.1)
 - D. Fine particles (106-500 μm)** – EQ 30 mg dose of manipulated Oxy-IR tablet (oxycodone IR Tablet) - non-ADF (control arm)
- A vs B → Effect of particle size
- A vs C → Effect of polymer-to-drug ratio

Example of subject dosing



- This is an example of the sequence period A → B → C → D
- Dosing interval: 72 hours

PK study – first question

What level of manipulation is required to defeat abuse deterrent properties of AD oxycodone ER tablets for nasal route?

- Oxy-ER-1 tablets were ground to two particle size ranges, 106 to 500 μm and 500 to 1000 μm , and were administered nasally as test products
- Oxy-IR tablets were ground to particle size range of 106 to 500 μm to be administered nasally as the control product
- Naltrexone block was used

PK study - second question

Does the ratio of polyethylene oxide to oxycodone affect the release properties of the manipulated AD oxycodone ER tablets?

- Oxy-ER-1 tablets (PEO/API ratio = 3.9) ground to particle size range of 106 to 500 μm
- Oxy-ER-2 tablets (PEO/API ratio = 2.1) ground to particle size range of 106 to 500 μm

Subject disposition and demographics

Category	Number
Subjects randomized	41
Safety Population	41
PK Population	36
Subjects completed	33

	Male (n=35)	Female (n=6)
Age	22-50	23-50
Race - Black or African American	24	2
Race - White	11	4

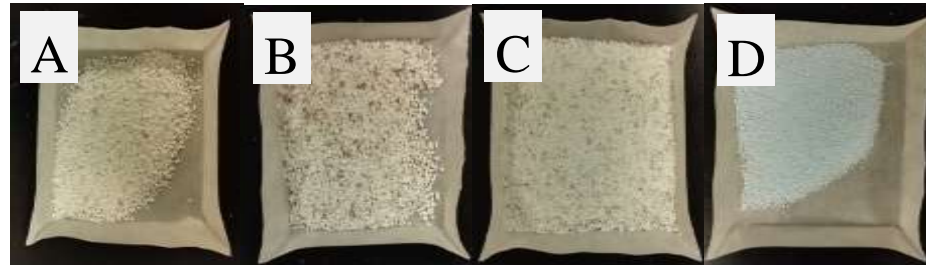
Tablet manipulation and study dose preparation

Characterization of manipulated dose

- Physiochemical properties of manipulated tablets
- Particle size characterization
- Drug loss during processing
- Drug load of administered dose

Producing targeted particle size

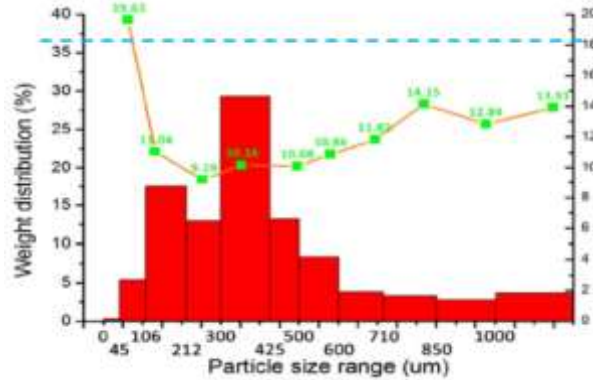
Treatment	Sample ID	Product Type	Particle Size Range	Amount milled tablet dispensed during Study (mg)
A	Oxy-ER-1	ER Oxycodone tablet	106 – 500 μm	266
B	Oxy-ER-1	ER Oxycodone tablet	500 – 1000 μm	252
C	Oxy-ER-2	ER Oxycodone tablet	106 – 500 μm	185
D	Oxy-IR	IR Oxycodone tablet	106 – 500 μm	116



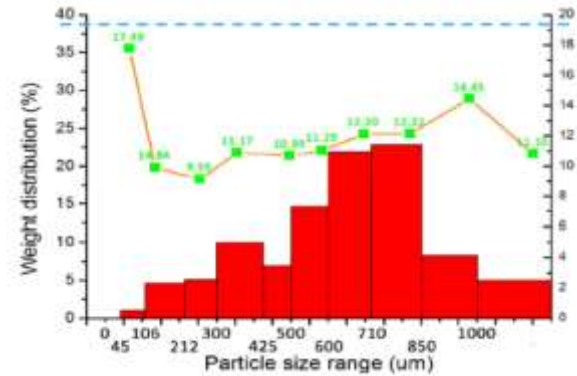
Content uniformity across particle size ranges

Blue dotted line: Theoretical %
drug/formulation

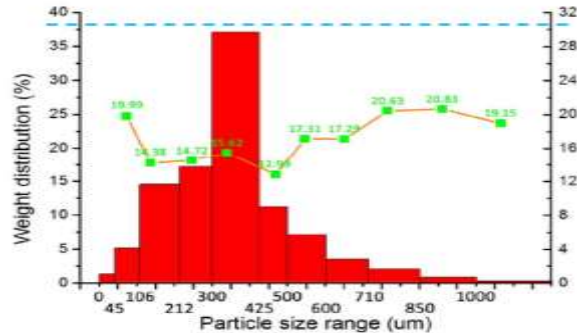
Oxy-ER-1 fine particles



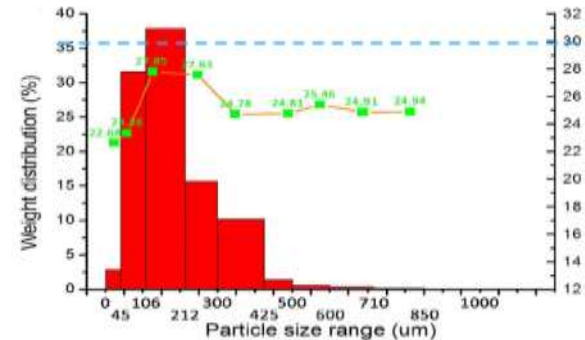
Oxy-ER-1 coarse particles



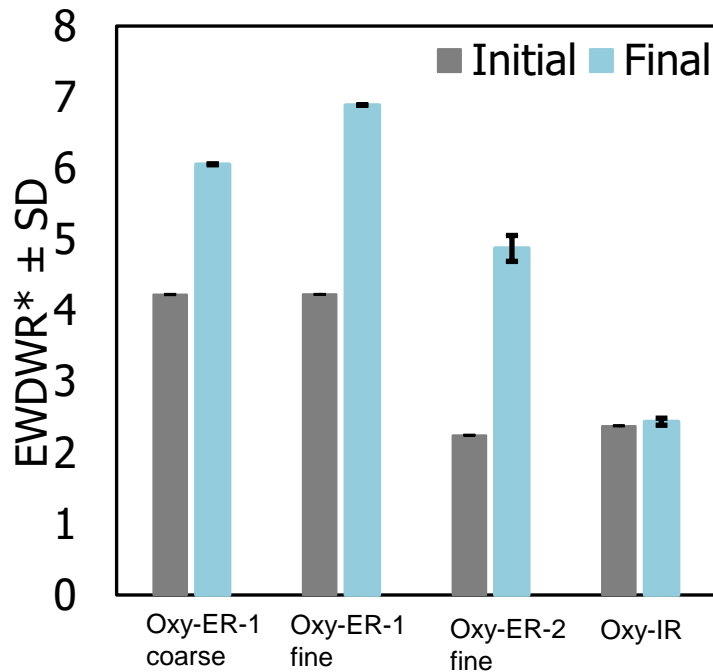
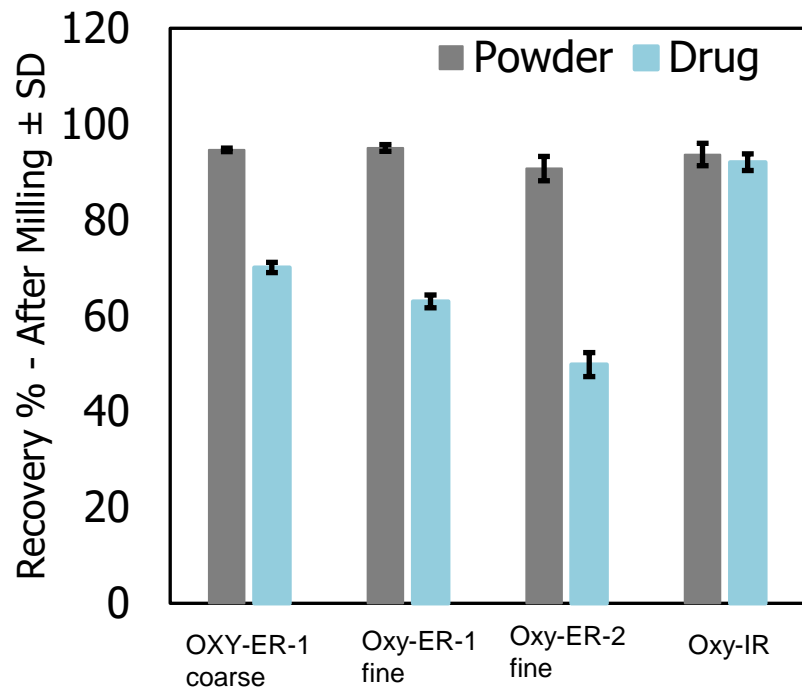
Oxy-ER-2 fine particles



Oxy-IR fine particles



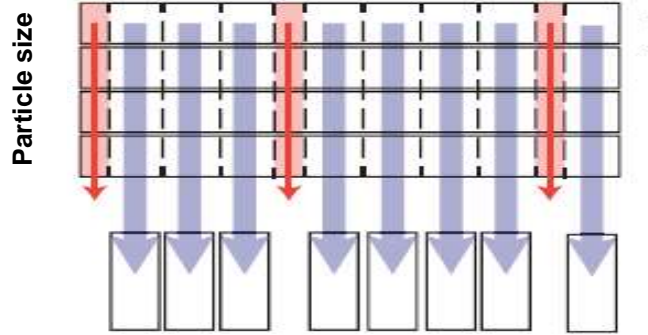
Physical manipulation and preferential drug loss



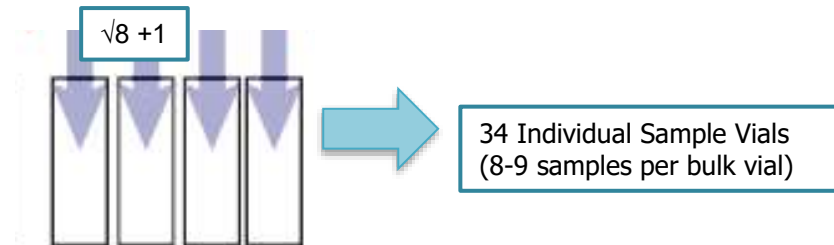
*Excipient weight-to-drug weight-ratio (EWDWR)

Sampling/dispensing technique

Step 1: Sieving of 160 Milled Tablets
Correct proportion of sample from each sieve added to bulk vial



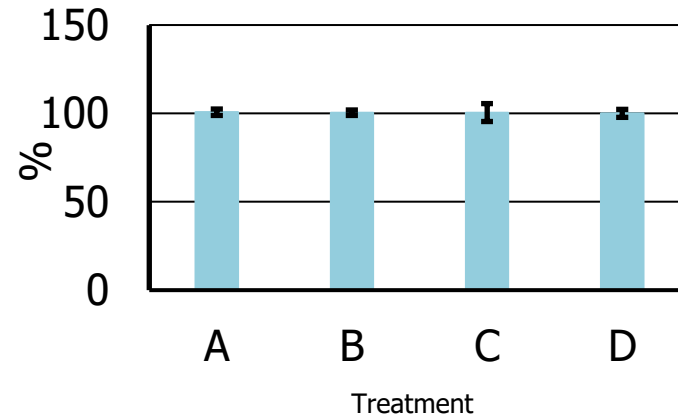
Step 3: Clinic dispenses individual samples from bulk vials using protocol



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

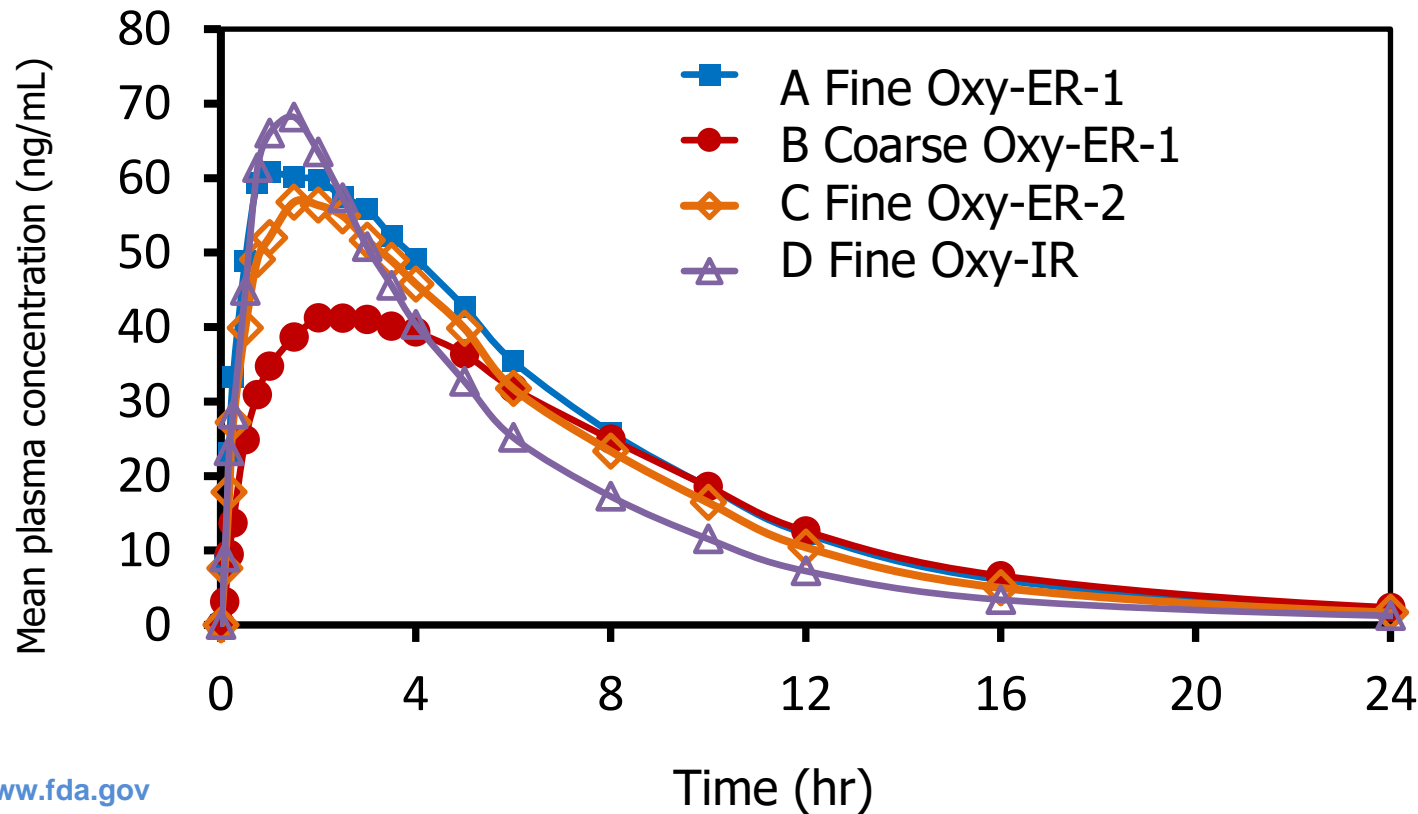
	Drug content (mg/100 mg)			
Sample ID	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Oxy-ER-1 (A)	12.6	12.6	12.7	12.9
Oxy-ER-1 (B)	14.1	14.0	14.2	14.4
Oxy-ER-2 (C)	16.8	16.2	17.9	16.8
Oxy-IR (D)	28.8	28.7	29.8	29.0

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



Pharmacokinetic results and evaluation

Summary of PK results



Bioavailability of finely milled AD oxycodone ER tablets compared to IR tablet

- For finely milled Oxy-ER-1 (PEO/API ratio = 3.9) tablets and finely milled Oxy-ER-2 tablets (PEO/API ratio = 2.1) compared to oxycodone IR tablets
 - Point estimates for C_{max} , Partial AUCs, AUC_{0-T} , and $AUC_{0-\infty}$ were all within the 80-120% bioequivalence limits.
 - Upper limit of confidence interval for all measured parameters was above 80%.

Bioavailability of coarsely milled AD oxycodone ER tablets compared to oxycodone IR tablet



- For coarsely milled Oxy-ER-1 compared to oxycodone IR tablets, point estimates for C_{\max} , $AUC_{0-0.5}$, and AUC_{0-4} , were below 80%.
- Upper limit of confidence interval for all three parameters was also below 80%.
- Point estimate and 90% confidence intervals of AUC_{0-T} and $AUC_{0-\infty}$ were within 80-125% limits.

Oxy-ER-1 Tablets, Coarse (B) vs. Oxy-IR Tablets, Fine (D)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans ^a		Ratio (%)	90% Confidence Limits (%)	
		Treatment-B	Treatment-D		Lower	Upper
C _{max}	20.5	46.021	77.802	59.15	54.25	64.50
AUC _{0-0.5}	39.4	5.512	11.019	50.02	42.55	58.80
AUC ₀₋₄	19.4	136.239	204.807	66.52	61.30	72.19
AUC _{0-T}	21.0	408.795	397.037	102.96	94.23	112.51
AUC _{0-∞}	21.0	411.890	403.374	102.11	93.29	111.77

^a units are ng/mL for C_{max} and ng·h/mL for AUC_{0-0.5}, AUC₀₋₄, AUC_{0-T} and AUC_{0-∞}

- The clearly lower C_{max}, AUC_{0-0.5}, and AUC₀₋₄ of coarsely milled Oxy-ER-1 Tablets show that it retains extended release properties at least up to four hours.
- Based on AUC_{0-∞} ratio and confidence intervals, the coarsely milled oxycodone ER tablets have the same overall bioavailability as the milled oxycodone IR tablets.

Oxy-ER-1 Tablets, Fine (A) vs. Oxy-ER-1 Tablets, Coarse (B)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans ^a		Ratio (%)	90% Confidence Limits (%)	
		Treatment-A	Treatment-B		Lower	Upper
C _{max}	20.4	64.848	45.565	142.32	130.87	154.77
AUC _{0-0.5}	41.5	12.939	5.451	237.37	201.20	280.05
AUC ₀₋₄	19.4	204.387	136.386	149.86	138.37	162.30
AUC _{0-T}	14.8	487.998	409.592	119.14	111.99	126.75
AUC _{0-∞}	14.8	492.236	415.069	118.59	111.24	126.43

^a units are ng/mL for C_{max} and ng·h/mL for AUC_{0-0.5}, AUC₀₋₄, AUC_{0-T} and AUC_{0-∞}

- As evident from C_{max} ratio, AUC_{0-0.5}, and AUC₀₋₄, finely milled oxycodone ER tablets have higher bioavailability than coarsely milled oxycodone ER tablets up to four hours.

Oxy-ER-2 Tablets, Fine (C) vs. Oxy-ER-1 Tablets, Fine (A)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans ^a		Ratio (%)	90% Confidence Limits (%)	
		Treatment-C	Treatment-A		Lower	Upper
C _{max}	14.4	60.465	64.068	94.38	88.49	100.65
AUC _{0-0.5}	30.2	10.886	13.091	83.16	73.33	94.30
AUC ₀₋₄	13.2	190.071	204.492	92.95	87.87	98.32
AUC _{0-T}	12.6	443.276	485.766	91.25	86.39	96.39
AUC _{0-∞}	12.4	446.186	489.882	91.08	86.29	96.14

Formulation	PEO/API Ratio	
	Intact Tablet	Powder
Oxy fine 30 mg	3.9	7.9
Oxy fine 80 mg	2.1	5.9

^a units are ng/mL for C_{max} and ng·h/mL for AUC_{0-0.5}, AUC₀₋₄, AUC_{0-T} and AUC_{0-∞}

- The point estimate for all measured PK parameters fall within the 80-125% bioequivalence limits.
- At the particle size range of 106-500 μm, the difference in polymer to oxycodone ratio does not affect bioavailability.

PK Conclusions

- Coarsely milled AD oxycodone ER tablets had lower nasal bioavailability than immediate release oxycodone tablets
- Finely milled AD oxycodone ER tablets did not demonstrate lower nasal bioavailability than oxycodone IR tablets
- At particle size range of 106-500 μm , differences in polyethylene oxide to oxycodone ratio do not seem to affect nasal bioavailability

Adverse Events (AE)

Total AEs reported

- Total of 122 AEs reported for 32 subjects (78%)
 - 114 Treatment-Emergent AEs (TEAE)
 - 102 AEs Possibly and/or Related to Oxycodone

Most frequently reported AE

Adverse event	Occurance
Headache	12
Euphoric mood	11
Rhinorrhea	11
Nasal discomfort	6
Drowsiness	7
Nausea	5
Dizziness	5
Nasal congestion	5

Adverse Events (AE)

- Five subjects (12.2%) withdrew from the study due to mild TEAEs that were considered expected and at least possibly related to study drug
- Five subjects required concomitant medications (ibuprofen or acetaminophen) to treat TEAEs during the study, the majority of which were expected and considered at least possibly related to study drug

Challenge Question #1

What is the objective of nasal PK studies in the context of ANDAs:

- A. To establish that the test product is abuse deterrent
- B. To establish that the reference product is abuse deterrent
- C. To establish that the test product is no less abuse deterrent than the reference product
- D. To establish that the reference product is no less abuse deterrent than the test product

Challenge Question #2

Which of the following statements is NOT true?

- A. The study showed that PEO/API ratio influences nasal bioavailability of oxycodone.
- B. No significant differences were observed in $AUC_{0-\infty}$ of coarsely milled oxycodone AD tablets and $AUC_{0-\infty}$ of milled oxycodone IR tablets.
- C. Coarsely milled oxycodone AD tablets have lower AUC_{0-4} than finely milled oxycodone AD tablets.
- D. No significant differences were observed in the bioavailability of finely milled oxycodone AD tablets and milled oxycodone IR tablets.

Overall take home message

- Oxycodone ER tablets milled to particle size range of 500-1000 μm retain ER property while milling the tablets to particle size range of 106-500 μm results in loss of ER property.
- Polymer to oxycodone ratio at particle size range of 106-500 μm does not affect PK parameters.
- Manipulation of Oxycodone ER tablets results in considerable oxycodone loss.



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