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ARTICLE

Particle size affects pharmacokinetics of milled oxycodone hydrochloride tablet products following nasal insufflation in nondependent, recreational opioid users

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Abstract

This study assessed the impact of product particle sizes (fine: 106–500 μm; coarse: 500–1000 μm) on oxycodone pharmacokinetics (PK) following nasal insufflation of milled oxycodone extended-release (ER) abuse-deterrent (AD) tablets using immediate-release (IR) non-AD product as reference. Additionally, this study assessed the effects of different excipient to drug ratio (EDR) by comparing two products with fine particle size but different EDRs, again using IR non-AD as the control. Thirty milligrams of oxycodone were administered in each treatment. Coarsely milled 30 mg ER tablets demonstrated significantly lower maximum plasma concentration (C_{max}) and partial areas under the concentration-time curve (AUCs) than those of the finely milled IR tablets. Finely milled ER tablets demonstrated similar C_{max} and partial AUCs but higher total systemic exposures than those of finely milled IR tablets. Finely milled 80 mg ER tablets were bioequivalent to IR tablet on all parameters. The finely milled 30 mg ER tablet was not bioequivalent to the coarsely milled 30 mg ER tablet and had higher values for all parameters. The finely milled 30 mg ER tablets (EDR 6.9) showed no PK differences with finely milled 80 mg ER tablets (EDR 4.9). No serious adverse events were reported. The study demonstrated a significant effect of particle sizes (106–1000 μm) on PK of milled and insufflated oxycodone ER AD tablets. EDR difference did not have any significant effects on the PK of finely milled oxycodone ER AD tablets. Particle size distribution should be considered when nasal AD properties of opioid drug products are investigated during drug development.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Available literature suggests that product particle sizes of milled and insufflated polyethylene oxide (PEO)-based abuse deterrent (AD) oxycodone extended release (ER) tablet products could influence pharmacokinetic (PK) parameters of insufflated product. However, study designs in published literature are widely different and the

comminuted products have not been adequately characterized. Therefore, the reported results in literature are not consistent.

WHAT QUESTION DID THIS STUDY ADDRESS?

Does manipulation of a given tablet formulation to different particle sizes affect PK parameters of the insufflated comminuted product? If two different tablet's formulation with different PEO to oxycodone ratios are milled to the same particle size, does the difference in PEO to oxycodone affect PK parameters of the milled and insufflated product?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The study demonstrates a significant effect of particle sizes on PK of milled and insufflated oxycodone ER AD at the dose of 30 mg.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Particle size distribution should be considered in comparative PK studies to evaluate the nasal AD properties of opioid drug products.

INTRODUCTION

Prescription opioid analgesics play an important role in pain management. However, prescription opioid drug products can expose users to the risks of misuse, abuse, or addiction, potentially leading to overdose death. The National Survey on Drug Use and Health estimated that nearly 11.5 million adults misused prescription opioid drug products and 1.9 million of them developed a use disorder in 2015.[1] In addition, the Centers for Disease Control and Prevention reported over 17,000 prescription opioid drug products overdose-related deaths in the United States (US) in both 2016 and 2017.[2] Although overdose death from prescription opioids decreased by 13.4% in 2018 compared to 2017, the number of overdose deaths from prescription opioids is still high.[3] Whereas prescription opioid drug products can be commonly abused by oral ingestion (including chewing or taking more than the recommended dose), experienced abusers may progress to nasal insufflation or intravenous injection.[4] The US Food and Drug Administration (FDA), as part of its comprehensive action plan to reduce prescription opioid abuse, has encouraged the development of abuse deterrent (AD) formulations of opioids.[5] For example, the FDA has published several guidances for pharmaceutical industries and these cover new and abbreviated new drug applications for AD of solid oral opioid drug products.[6,7] To reduce or deter abuse of prescription opioid drug products, there are several potential AD technologies. These include having physical/chemical barriers, being formulated as agonist/antagonist combinations, having aversive properties, using special delivery systems to make abuse difficult, being a new molecular entity or prodrug, using a combination of the above AD technologies, and having other novel AD approaches.[6] As of April 2020, the FDA has approved 10 opioid analgesic products with physical, chemical, and/or pharmacological properties that are expected to deter nasal, intravenous, and/or oral abuse.[8] However, only four of these products are currently marketed.

One of the commonly used methods to deter abuse is the utilization of polyethylene oxide (PEO) matrices. They are widely used in manufacturing AD opioid tablet products, which are hard to crush for snorting, and if crushed and exposed to liquids for extraction, will form a gel that is hard to syringe.[9] Given that PEO is widely used as a physical barrier in AD drug development, a good understanding of the AD properties of opioid drug products including generic drugs containing PEO is important.

To date, there have been several nasal insufflation studies conducted with various comminuted AD opioid drug products.[9–14] However, there is significant variability across the literature with regard to comminution methods used and characterization of milled products (i.e., particle size distribution and drug content of the study treatment) making the interpretation of these clinical data challenging. Thus, to obtain a better understanding of the AD properties of opioid products using PEO matrix, the primary objective of this study was to evaluate the impact of particle size on bioavailability of comminuted oxycodone AD extended release (ER) tablets relative to bioavailability of comminuted oxycodone immediate release (IR) tablets as the reference. Earlier studies with PEO-based formulations generally indicated that particle sizes below 1 mm were suitable for snorting[9]; however, very small particles have the potential of bypassing the nasal cavity and being deposited in the lungs when snorted,[15,16] increasing subject risks. We selected particle sizes in the ranges of 106–500 μm and 500–1000 μm based on safety concerns and recommendations of the above-mentioned FDA guidances. In addition, effect of different excipient-to-drugs ratios (EDRs), as defined by the total weight of excipients divided by weight of the active ingredient in a drug product on nasal bioavailability of comminuted oxycodone ER AD tablets was

evaluated. The study drug products for this study had different EDRs for different strengths, which enabled us to evaluate this effect. Finally, this study assessed the adverse event (AE) profile and intranasal tolerability of milled oxycodone AD ER and non-AD IR drug products following insufflation when administered under naltrexone block in healthy, nondependent, recreational opioid users.

METHODS

Study approval and conducts

This study was approved by the MidLands Independent Review Board (Overland Park, KS) and the Research Involving Human Subject Research Committee at the FDA (Silver Spring, MD) following the Guidance for Industry, E6 Good Clinical Practice of FDA and the principles of the Declaration of Helsinki. The study was conducted by the Vince and Associates Clinical Research (Overland Park, KS). To protect the privacy of study participants, the certificate of confidentiality was obtained prior to the start of the study.

Study population

One hundred thirty-one subjects were screened and provided signed informed consents. Healthy subjects aged between 18 and 55 years were eligible to participate if they were recreational opioid user and not physically dependent on opioids and had nasal insufflation experience with recreational drugs on at least four occasions in 12 months prior to screening. A recreational opioid user was defined as at least 10 times of nontherapeutic uses of opioids in their lifetime and at least once in 12 weeks prior to screening. Subjects were excluded if they had moderate to severe substance use disorder based on the Diagnostic and Statistical Manual of Mental Disorders DSM-5[17] in the 12 months prior to screening or were physically dependent on opioids as demonstrated by a failed naloxone challenge. Female subjects of childbearing potential were asked to practice an acceptable method of contraception from the time of enrollment to at least 30 days after the last dose. Subjects abstained from alcohol and recreational drug use during the study.

Study design

This was an open-label, randomized, single-dose, four-sequence, four-period, four-treatment crossover study. After a screening visit, qualified subjects underwent a naloxone challenge test to confirm nondependence to opioids in the second visit.[18] Subjects who passed the naloxone challenge underwent a minimum of 72-h washout period and then entered the treatment phase. Subjects were randomly assigned to one of the four sequences and the order of drug administration was sequentially assigned from a computer-generated randomization list. Subjects received 4 intranasal treatments described in Table 1 following at least 8-h of overnight fasting before each treatment. Each treatment was a 30 mg of oxycodone dose from finely milled 30 mg oxycodone ER/AD tablet, coarsely milled 30 mg oxycodone ER/AD tablet, finely milled 80 mg oxycodone ER/AD tablet, or finely milled 30 mg oxycodone IR tablet. Subjects were allowed up to 3 minutes to snort the drug product. Any remaining drug was collected and carefully weighed. Approximately 1 h after each snorting, subjects' nostrils were examined, and investigational products were observed in 60% of the cases. Study medications were administered on days 1, 4, 7, and 10 during the treatment phase. Confinement period was from day 1 to day 12. Washout period between treatments was 72 h. Fifty (50) milligrams of naltrexone HCl were administered at 12 h and 30 min prior to each treatment and at 12 h after each treatment.

A follow-up telephone call was conducted 48–72 h following discharge from the treatment phase or after discontinuation from the study.

TABLE 1 Baseline demographics of study population

Characteristics	Safety population	PK population
N	41	36
Mean age (years, SD)	31 (7.0)	30 (7.0)
Mean weight (kg, SD)	79.3 (13.5)	79.0 (14.0)
Mean BMI (kg/m^2, SD)	25.38 (3.6)	25.10 (3.6)
Sex, *n* (%)		
Male	36 (87.8)	32 (88.9)
Female	5 (12.2)	4 (11.1)
Race, *n* (%)		
Black or African American	26 (63.4)	26 (72.2)
White	15 (36.6)	10 (27.8)
Ethnicity, *n* (%)		
Hispanic or Latino	3 (7.3)	1 (2.8)
Not Hispanic or Latino	38 (92.7)	35 (97.2)

Abbreviation: BMI, body mass index.

Comminution procedures and drug dispensing

All study drugs (powder from milled tablets) were prepared in a sterile facility under good manufacturing practices. Tablets were milled in bulk by a conical mill (Comil U5 Model #1033526; Quadro) before each clinical trial cohort, as

previously described.[19] Milled tablets were sieved to fine particles (106–500 μm) or coarse particles (500–1000 μm). Drug content was measured according to Bulk Powder Sampling Procedures <1097> in USP 41-NF 36 (2018) and using a validated high-performance liquid chromatography (HPLC) method. The milled tablets were then packaged in bulk vials at the manufacturing site and shipped to the clinical site.

At the clinical site, the pharmacist prepared individual treatment vials. In brief, the bulk container was rotated up and down for a total of 10 times to ensure bulk material was not segregated. The amount of milled product needed to dispense 30 mg of drugs was calculated based on the drug content in the bulk container and transferred to the individual treatment vial (Table S1).

Study end points

Pharmacokinetic assessment

Blood samples were collected at predose and at 5, 10, 15, 30, and 45 min, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 h after initiation of dosing (subjects had up to 3 min to complete snorting). PK parameters including maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), abuse quotient (AQ; C_{max}/T_{max}), area under the concentration-time curve $(AUC)_{0-3}$, AUC_{0-4}, AUC_{0-T}, $AUC_{0-\infty}$, apparent elimination rate constant (λ_Z), and T_{half} were computed.

Ease of snorting visual analog scale

Subjects were asked about the ease of snorting the drug 5 min postdose on a 100-point visual analog scale (VAS), where 0 and 100 indicated "very easy" and "very difficult," respectively.[13]

Nasal tolerability assessment

The 6-point subject-rated assessment of intranasal irritation (SRAII; 0 = not observed/no problem, 5 = very severe problems) was used to rate the following items at scheduled time points up to 8 h after each treatment: nasal burning, need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion.[9]

Bioanalytical methods

The serial blood samples were collected and processed in K_2 EDTA tubes and stored frozen at −20°C until analysis (maximum of 122 days). Plasma oxycodone was measured at the bioanalytical facility of Algorithme Pharma. Liquid-liquid extraction was used to extract oxycodone from plasma. The compounds were identified and quantified using reversed-phase HPLC with tandem mass spectrometry detection over a theoretical concentration range of 0.200–100.000 ng/ml.

Safety evaluation

The safety analysis was performed on all 41 dosed subjects who received at least one dose of study drugs. Safety evaluations included physical examinations, pulse oximetry measurement, vital signs, clinical laboratory tests (including hematology, coagulations, chemistry, drug and alcohol screening, urinalysis, and pregnancy test), AEs (the type, incidence, severity, and causality assessment), electrocardiograms, and concomitant medication recording. In addition, symptom-directed physical examinations were performed throughout the study. A treatment emergent adverse event (TEAE) was defined as an AE that occurred after dosing or an existing AE worsened during the study. AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0, and severity was recorded and graded using the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03.

Statistical methods

SAS (version 9.4) was used to run an analysis of variance (ANOVA) model using the mixed procedure. The fixed factors included in this model were the group, treatment, period (nested within group), sequence, the group-by-sequence interaction, and the group-by-treatment interaction whenever statistically significant at the 2-sided 5% level. A random factor was added for the subject effect. The 90% confidence interval (C)I for the exponential of the difference in least square (LS) means between each comparison of interest were calculated for the ln-transformed parameters (treatment to treatment ratio of geometric LS means). The formula to estimate the root mean square error (MSE) was: $\sqrt{e^{MSE}-1}$, where MSE is obtained from the ANOVA model of the ln-transformed parameters. A supplementary analysis was performed using weight-adjusted dose pharmacokinetic (PK) parameter values.

The comparisons of interest were treatment-A, -B, and -C to treatment-D, and treatment-A to treatment-B and -C, which were conducted to inform the impact of particle sizes and EDRs on PKs of milled and insufflated oxycodone AD products.

TABLE 2 Characteristics of intact and milled oxycodone tablets used in each treatment

		Tablet			Milled tablet		
Treatment	Product type	Tablet strength (mg)	Tablet weight (mg)	Milled particle size range	Drug administered (mg)	Milled tablet dispensed (mg)	EDR
A	ER Oxycodone	30	155	106–500 μm	30	237 (3)	6.9
B	ER Oxycodone	30	155	500–1000 μm	30	212 (2)	6.1
C	ER Oxycodone	80	260	106–500 μm	30	177 (8)	4.9
D	IR Oxycodone	30	102	106–500 μm	30	103 (2)	2.4

Abbreviations: EDR, excipient to drug ratio; ER, extended release; IR, immediate release.

Milled tablet dispensed, pooled average (±SD) of batches across cohort.

RESULTS

Subject disposition, demographics, and treatments

Forty-one of the 131 subjects who were screened met the inclusion criteria of the study, were enrolled, and received at least one dose of the study medications (safety population). During the treatment phase, there were eight discontinued subjects, two voluntary withdrawals, one noncompliance, and five withdrawals due to TEAEs. Thirty-six subjects, including three of the eight discontinued subjects, provided sufficient data for PK analysis and were included in the PK analysis (PK population). Age range was 22–55 years and the body mass index (BMI) of the subjects ranged from 19 to 34 kg/m^2, and the mean BMI values were 25.38 and 25.10 for the PK and safety populations, respectively (Table 2). All subjects were nonsmokers.

Subjects were randomized into the four sequences (ABCD, BCAD, CDBA, or DACB) and received all treatments illustrated in Table 1. Milled product particle sizes after sieving in treatment-A (30 mg dose of finely milled ER oxycodone, 30 mg tablet), -C (30 mg dose of finely milled ER oxycodone, 80 mg tablet), and -D (30 mg dose of milled IR oxycodone, 30 mg tablet) were 106–500 μm and in treatment-B (30 mg dose of milled ER oxycodone, 30 mg tablet) were 500–1000 μm. Treatment-A and -C differed in the EDR (4.9 vs. 6.9). EDR of the manipulated drug product was calculated as the total weight of the excipient divided by the weight of oxycodone in 100 mg of powder. The milling procedure was reproducible and there was low variability between batches in the amount of powder required to deliver a 30 mg dose (Table S1). The amounts of milled products snorted by each subject in treatment-A, -B, -C, and -D ranged from 225.6 to 242.7 mg, 182.4 to 216.6 mg, 144.3 to 183.5 mg, and 82.8 to 105.6 mg, respectively (Figure 1). Except for a few outliers, these dosing ranges equated to ±10% of dispensed amounts equivalent to the desired dose of 30 mg without any statistically significant difference among treatments. Due to facility and space constraints, subjects were dosed in 4 groups ranging from 5 to 12 subjects per group.

PK profiles of manipulated and insufflated oxycodone tablet products

The mean plasma oxycodone time-concentration profiles are presented in Figure 2, and the PK parameters for oxycodone are summarized by treatment in Table 3. Treatment-D and treatment-B had the highest and lowest mean C_{max} of oxycodone, respectively.

Descriptive statistics

Median values of T_{max} was 1.5 h in treatment-A and -D, although the range of T_{max} values of treatment-A was wider than those of treatment-D (0.5–4 h vs. 0.5–1.5 h). Mean values of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of treatment-A were higher than those of treatment-D. Early partial AUCs, including AUC from time zero to 3 h ($AUC_{0–3}$) and from time zero to 4 h ($AUC_{0–4}$), were similar between treatment-A and -D.

Mean values of $AUC_{0–t}$ and $AUC_{0–\infty}$ of treatment-B were similar to those of treatment-D. Early partial AUCs, including $AUC_{0–3}$ and $AUC_{0–4}$, were lower for treatment-B compared to treatment-D. Median T_{max} was delayed to 2.5 h for treatment-B compared to 1.5 h for treatment-D. Treatment-D and -B had the highest and lowest values of abuse quotient (AQ, C_{max}/T_{max}), respectively.

Mean values of AUC and C_{max} were lower for treatment-C compared to treatment-D. Median T_{max} was delayed to 2.0 h in treatment-C, compared to 1.5 h in treatment-D.

Dose-adjusted exposure (dose calculated based on the actual amount of powder snorted [predose vial weight minus postdose vial weight for each treatment]) parameters showed a similar pattern of results (data not shown). The T_{half} was comparable across the four treatments.

Bioequivalence between two treatments was assessed and defined as the geometric least square mean ratio (GMR) of

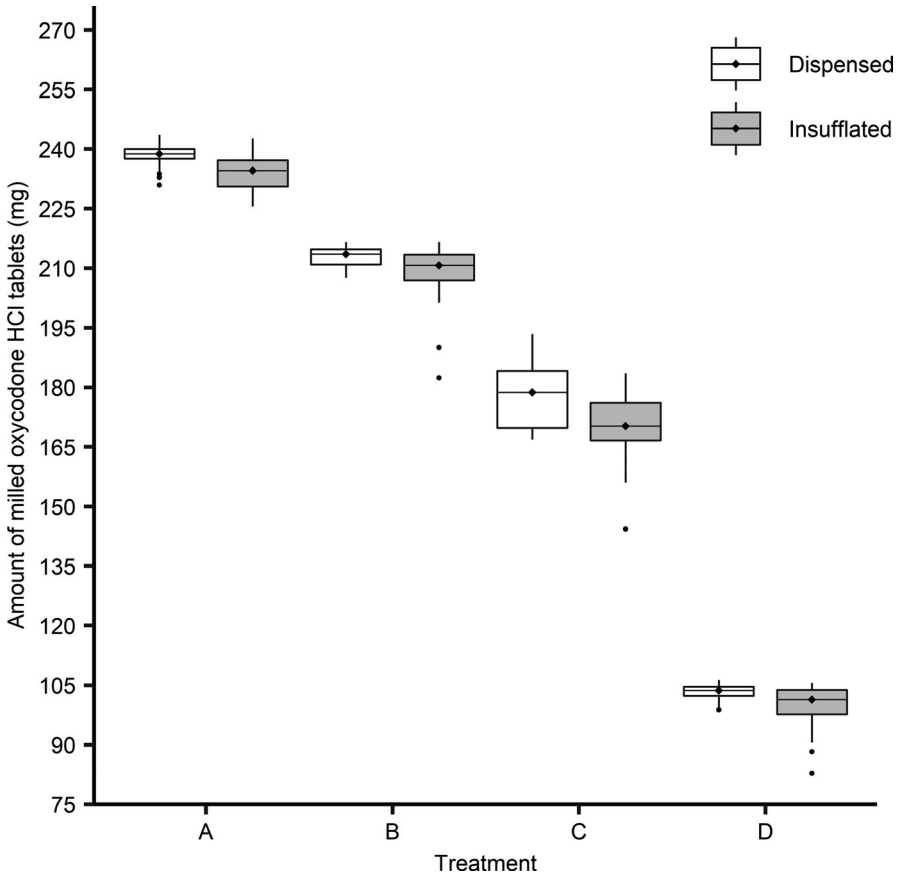

FIGURE 1 Amounts of milled oxycodone tablet products dispensed by the pharmacy and insufflated by subjects in each treatment. Treatment-A (30 mg dose of finely milled extended release [ER] oxycodone, 30 mg tablet), -B (30 mg dose of coarsely milled ER oxycodone, 30 mg tablet), -C (30 mg dose of milled ER oxycodone, 80 mg tablet), and -D (30 mg dose of milled IR oxycodone, 30 mg tablet)

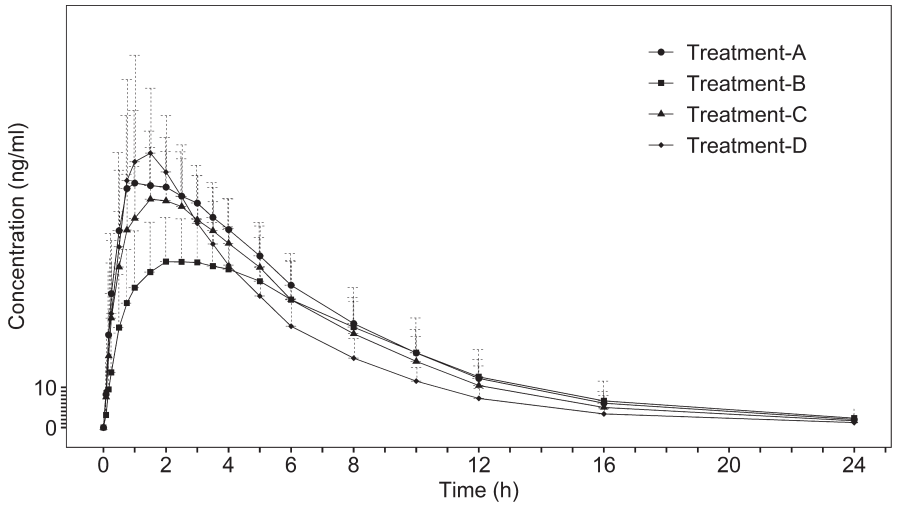

FIGURE 2 Pharmacokinetic profiles of oxycodone in recreational opioid users following nasal insufflation of milled oxycodone tablet products. Healthy recreational opioid users received 30 mg of milled oxycodone tablet products by nasal insufflation with naltrexone block. Plasma oxycodone concentrations were measured at the indicated time points. The number of subjects in each treatment were 36, 36, 34, and 34, respectively. Data were means with SD

PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) and the associated 90% CIs being fully contained within 0.80 to 1.25. Early partial AUCs (AUC_{0-3} and AUC_{0-4}) were analyzed as supportive data.

Assessment of particle size effect

PK parameters of milled oxycodone ER tablets (treatment-A and -B) were subject to bioequivalence analysis using finely milled oxycodone IR tablets (treatment-D) as the reference. As depicted in Figure 3, C_{max} was lower for both treatment-A and -B compared to finely milled oxycodone IR tablets; of note, the 90% CI for treatment-A overlapped with the 80%–125% bioequivalence limits. Treatment-B was bioequivalent to treatment-D with respect to systemic exposures (AUC_{0-t} and $AUC_{0-\infty}$); however, for both parameters, the upper bound of 90% CI was above 125% for treatment-A compared to treatment-D. Early partial AUCs (AUC_{0-3} and AUC_{0-4}) were bioequivalent between treatment-A and -D but they were not for treatment-B versus treatment-D. In direct comparison of treatment-A and -B, treatment-A had higher point

TABLE 3 Summary of oxycodone PK parameters

	Treatment-A		Treatment-B		Treatment-C		Treatment-D	
PK parameters	***N***	**Mean (CV %)**	***N***	**Mean (CV %)**	***N***	**Mean (CV %)**	***N***	**Mean (CV %)**
C_{max} (ng/ml)	36	68.61 (25.4)	36	47.40 (28.4)	34	61.31 (20.7)	34	80.95 (26.6)
$AUC_{0\text{-}t}$ (ng*h/ml)	36	518.15 (20.1)	35	433.79 (32.3)	33	465.41 (25.2)	34	415.08 (21.7)
$AUC_{0\text{-}\infty}$ (ng*h/ml)	36	521.84 (20.0)	34	438.44 (32.4)	33	468.15 (25.2)	34	418.61 (21.5)
$AUC_{0\text{–}3}$ (ng*h/ml)	36	160.64 (21.6)	36	101.06 (28.0)	34	145.20 (20.8)	34	165.91 (20.9)
$AUC_{0\text{–}4}$ (ng*h/ml)	36	213.14 (19.2)	36	141.21 (25.3)	34	194.02 (19.8)	34	211.49 (19.5)
T_{max} (h)[a]	36	1.5 (0.5, 4.0)	36	2.5 (0.75, 8.0)	34	2.0 (0.75, 3.5)	34	1.5 (0.5, 1.5)
AQ (ng/ml/h)	36	63.06 (73.7)	36	24.70 (84.9)	34	37.59 (56.2)	34	76.75 (57.5)
T_{half} (h)	36	4.84 (17.5)	34	4.78 (18.4)	33	4.83 (17.4)	34	5.07 (27.5)

Abbreviations: AQ, abuse quotient = C_{max}/T_{max}; $AUC_{0\text{–}\infty}$, area under the plasma concentration time curve extrapolated to infinity; $AUC_{0\text{–}x}$, area under the plasma concentration time curve calculated from time zero to x hours postdose; $AUC_{0\text{–}t}$, cumulative area under the plasma concentration time curve calculated from zero to the last measurable time point; C_{max}, maximum observed concentration; CV, coefficient of variation; PK, pharmacokinetic; T_{half}, terminal half-life; T_{max}, time to C_{max}.
Treatment-A (30 mg dose of finely milled extended release (ER) oxycodone, 30 mg tablet), -B (30 mg dose of coarsely milled ER oxycodone, 30 mg tablet), -C (30 mg dose of milled ER oxycodone, 80 mg tablet), and -D (30 mg dose of milled immediate release oxycodone, 30 mg tablet).

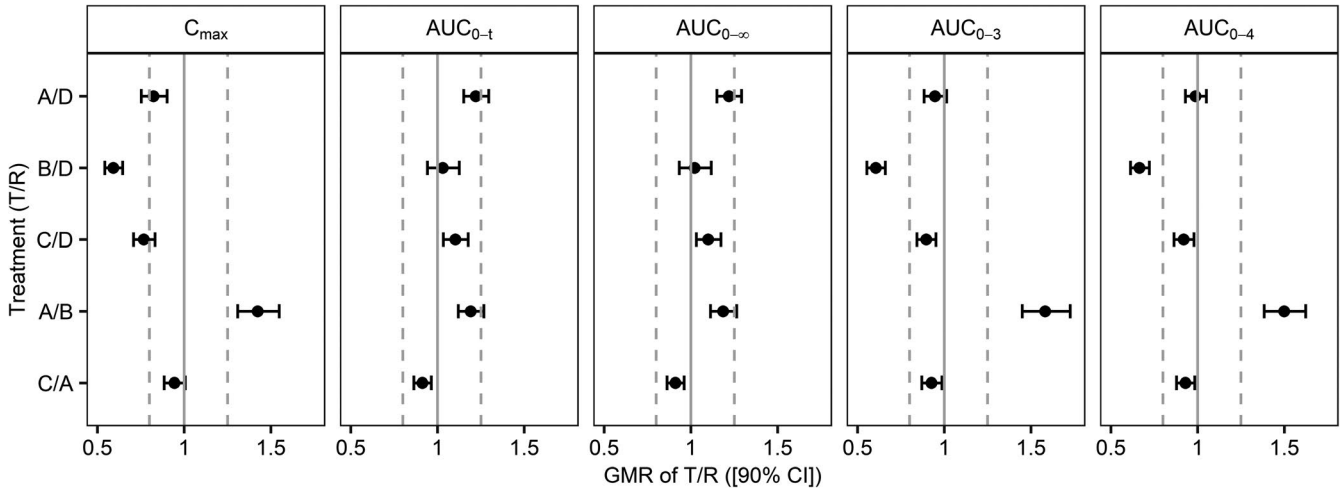

FIGURE 3 Comparison of PK parameters across treatments. Solid circles indicate GMR; horizontal error bars represent 90% CIs; dotted grey lines indicate bioequivalence limits of 0.80 and 1.25. AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic; T/R, comparison of treatments T and R using R as the reference

estimates for C_{max} and all AUCs and the two treatments were not bioequivalent on any of the parameters. Fixed effects for period (nested within group) were significant for $AUC_{0\text{-}t}$ in comparison of treatment-A and -D (p value = 0.0312).

Assessment of EDR

PK parameters of milled oxycodone ER tablets (treatment-A, and -C) were subject to bioequivalence analysis using finely milled oxycodone IR tablets (treatment-D) as the reference. As depicted in Figure 3, the C_{max} for both treatment-A and -C, when compared to treatment-D, had a lower point estimate than 1 but the 90% CI overlapped with 80%–125% bioequivalence limits for both treatments. Treatment-C was bioequivalent to treatment-D with respect to systemic exposures ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$). The upper bounds of 90% CI for $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were above 125% for treatment-A. Early partial AUCs ($AUC_{0\text{–}3}$ and $AUC_{0\text{–}4}$) for treatment-A and -C were bioequivalent with treatment-D. In direct comparison of treatment-A and -C, the two treatments were bioequivalent with respect to C_{max} and all AUCs, although treatment-C consistently had a lower point estimate for all parameters. Fixed effects for period (nested within group) in comparison of treatment-A and -C were significant for AUCs (p value range = 0.0084 to 0.0371). The group by treatment

interaction was also significant for this comparison (p value = 0.0366).

Dose-adjusted exposure (dose calculated based on the actual amount of powder snorted [predose vial weight minus post-dose vial weight for each treatment]) parameters showed a similar pattern of results (data not shown). The T_{half} was comparable across the four treatments. Of note, double peaks of PK profiles were seen in many subjects received either finely or coarsely milled oxycodone ER tablets (Figure S1).

Comparison of PK parameters across treatments

Bioequivalence between two treatments was assessed and defined as the LS GMR of PK parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) and the associated 90% CIs being fully contained within 0.80 to 1.25. Early partial AUCs ($AUC_{0\text{–}3}$ and $AUC_{0\text{–}4}$) were analyzed as supportive data. First, PK parameters of milled oxycodone ER tablets (treatment-A, -B, and -C) were subject to bioequivalence analysis using finely milled oxycodone IR tablets (treatment-D) as the reference. As depicted in Figure 3, C_{max} was lower with all milled oxycodone ER tablets treatments compared to finely milled oxycodone IR tablets (all GMRs < 0.83, all lower bounds of 90% CI < 0.8). Treatment-B and -C were bioequivalent to treatment-D with respect to systemic exposures ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$). Early partial AUCs ($AUC_{0\text{–}3}$ and $AUC_{0\text{–}4}$) were bioequivalent between finely milled oxycodone ER tablets (treatment-A or -C) and finely milled oxycodone IR tablets (treatment-D). Second, treatment-A had a higher C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{–}3}$, and $AUC_{0\text{–}4}$ compared with treatment-B. Third, comparison of treatment-C and -A (as the reference) showed that the C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{–}3}$, and $AUC_{0\text{–}4}$ met bioequivalence criteria, even though the majority of GMRs and upper bounds of the 90% CIs were close to or less than 1.00. Comparison results across treatments were similar with the analysis results using the dose-adjusted PK parameter values (Figure S2).

Safety, ease of snorting, and intranasal tolerability

Safety

No serious or life-threatening AE was reported during the study. Five subjects (12.2%) withdrew from the study due to mild TEAEs that were considered expected and at least possibly related to the study drugs. All AEs were reported to be mild in severity except for five moderate cases (3 headaches, 1 dizziness, and 1 toothache). Of the 113 TEAEs reported by 32 subjects, 101 were reported to be related or possibly related to the study medications. The incidence of TEAEs was slightly higher for treatment-A and -C than for treatment-B and -D (Table S2).

Ease of snorting

Treatment-A had the highest mean (28.1) and median (26.0) ease of snorting VAS scores indicating that snorting was more difficult relative to other treatments (Table S3). Treatment-D had the lowest mean (8.1) and median (3.0) VAS scores. Difficulty of snorting appears to be proportional to the amount of powder snorted (Figure 1).

Intranasal tolerability

Thirty-five subjects who finished SRAII evaluation during all four treatments were included in the intranasal tolerability analysis. There were 9, 13, 7, and 19 subjects who reported no issues for all SRAII categories in treatment-A, -B, -C, and -D, respectively. Among all time points scored, most intranasal irritations occurred within the first 2 h after dosing, and the subjects received milled ER tablets (treatment-A, -B, and -C) reported more intranasal irritations than those received milled IR tablets (treatment-D; Figure 4). Treatment-C had the highest and treatment-D had the lowest mean score for irritation. There was no difference in the SRAII scores between finely and coarsely milled ER tablets.

DISCUSSION

This study investigated the effects of product particle size and EDR on oxycodone PK profile following nasal insufflation of milled oxycodone AD ER and IR tablet products in healthy, nondependent, recreational opioid users.

The study design was based on the FDA guidances on AD opioid formulations.[6,7] Subjects were selected from a population of healthy nondependent recreational opioid users with a history of intranasal drug use. The subject population was selected to minimize ethical and safety concerns and reduce insufflation and PK variabilities. As the study involved an unapproved route of administration and dosage form, in vitro studies, including comminution procedure, storage stability, moisture control, and particle sizes of milled oxycodone powder, were conducted to characterize the study drugs.[19] Due to a preferential drug loss after bulk milling and sieving, dosing amount of milled oxycodone product was normalized to 30 mg of oxycodone HCl per dose. Subjects were instructed not to spit for at least 5 min after snorting the milled product and not to blow their nose for 1 h. The predose and postdose weights of the dosing vial were measured to determine the actual dose

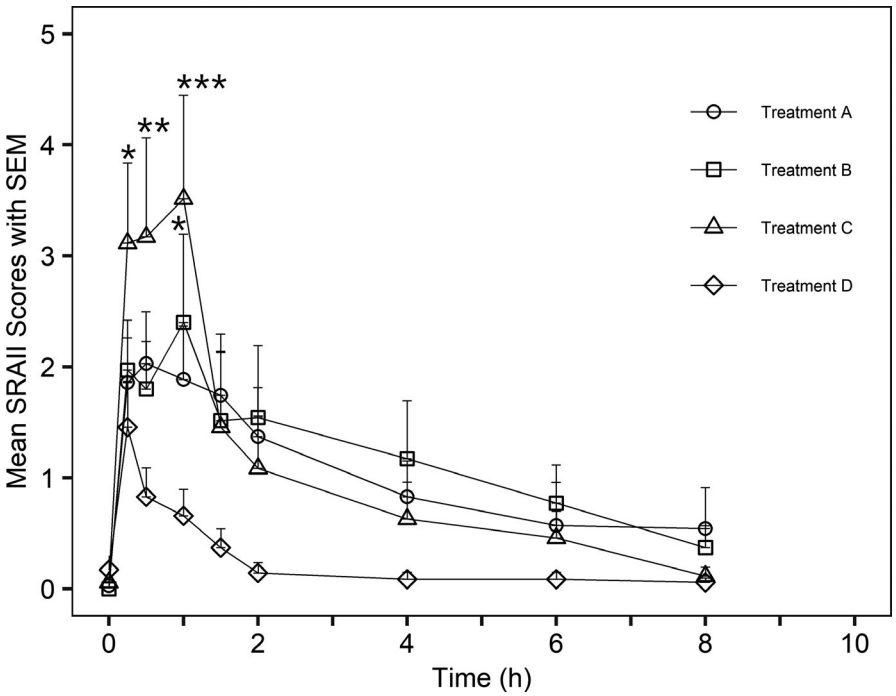

FIGURE 4 Intranasal tolerability assessment using SRAII. The 6-point SRAII was used to assess subject intranasal tolerability at predose (0) and at 0.25, 0.5, 1, 1.5, 2, 4, 6, and 8 h postdose. Data were presented as mean with SEM. The embedded small columns were the sums of SRAII scores of the 8 assessed time points post-dose, and data were presented as median with 95% CI. $n = 35$; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ versus treatment-D. CI, confidence interval; SRAII, subject-rated assessment of intranasal irritation

for each subject in each treatment (Figure 1). Most subjects completely insufflated the dispensed milled product with a small variation of within ±10% of the planned drug dose of 30 mg. Overall, these special considerations helped reduce the variability of PK parameters (root MSE < 25%) and minimize the impact of potential confounding variables on the study results.

This study showed significant differences in the PK profiles of milled oxycodone ER tablets (treatment-A, -B, and -C) compared to finely milled IR tablets (treatment-D), with treatment-B showing the largest difference. As shown in Figure 2 and Table 3, all treatments with milled ER tablets had lower values of mean C_{max} and AQ compared with milled IR tablets, suggesting that the comminution procedure did not completely defeat the controlled release properties of the oxycodone ER. Treatment-B had the lowest C_{max} among treatments, and only in treatment-B the upper bounds of CI for C_{max} and both partial AUCs were below 80% using treatment-D as the reference, indicating that coarse particles retained more controlled release properties. The total systemic exposures ($AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$) of finely milled ER (treatment-A) were higher than those of finely milled IR (GMR around 1.2; upper 90% confidence bound over 1.25; Figure 3). One possible explanation is that some excipients in ER AD may improve nasal membrane permeation and/or prolong drug retention time in nasal cavity, resulting in an enhanced nasal bioavailability.[20,21] Because drugs absorbed by the nasal route are not subject to hepatic first-pass metabolism, enhanced nasal bioavailability could result in higher overall drug exposure.[22] Nevertheless, based on the finding that the upper 90% CIs of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were above 1.25, finely milled ER tablets failed to demonstrate less bioavailability than finely milled IR tablets. It is interesting to mention that finely crushed oxycodone ER and oxycodone powder were reported to have comparable $AUC_{0\text{-}\infty}$.[9] However, that study also reported incomplete dosing in 34% and 0% of subjects receiving finely crushed oxycodone ER and oxycodone powder, respectively, without adjusting for incomplete dosing in PK analysis.

The study showed that milled product particle sizes had a significant effect on the PK of insufflated oxycodone. Finely milled oxycodone ER exhibited higher C_{max}, AUCs, and early partial AUCs in comparison with coarsely milled oxycodone ER (Figure 2 and Table 3). The particle size of milled oxycodone products may affect drug deposition in the nose, lungs, and/or gastrointestinal tract, and may also affect drug dissolution rate in the nasal cavity and/or absorption across the nasal mucosa, which can ultimately affect PK profiles. Of note double peaks of PK profiles were seen in some subjects received either finely or coarsely milled oxycodone ER tablets (Figure S1). It should be noted that the impact of product particle size on the nasal PK of opioid ER AD is inconsistent in the literature.[9,10,14] Specifically, in one study, "finely" crushed oxycodone ER showed a slightly higher mean C_{max} (~ 10% increase), but smaller mean AUCs (about 7% reduction) compared to "coarsely" crushed oxycodone ER.[14] In contrast, in another study, the mean C_{max} was similar between "finely" and "coarsely" crushed oxycodone ER, whereas mean $AUC_{0\text{-}\infty}$ was slightly less for "finely" crushed oxycodone ER (about 90%).[9] In a PK study of milled and insufflated hydrocodone bitartrate ER, the C_{max} and $AUC_{0\text{-}\infty}$ were higher following insufflation of "fine" particles compared with "coarse" particles.[10] The inconsistent effect of "particle size" on PK of insufflated opioid ADs in these

studies could in part be due to the differences in comminution methods, variations in defined particle size ranges for "fine" and "coarse," and whether dosing amount and insufflation amounts of milled products were quantified.

In addition, after comparing the PK profiles of treatment-C (EDR: 4.9) with treatment-A (EDR: 6.9), there was no significant effect of EDR on the PK of finely milled oxycodone ER). However, the effect of EDR on PK of coarsely milled oxycodone ER was not assessed in this study. Furthermore, it remains unknown whether a wider range of EDR would result in different PK profiles of milled and insufflated oxycodone ER tablets. One limitation of this study is that the sieve procedure to obtain defined particle size resulted in partial removal of drug and excipient. Therefore, the PK comparison results between treatment-A and -D may only apply to the fine particles separated from the milled ER and IR products, but not the entire particles from the milled products.

Overall, the study demonstrated significant effects of particle size on the PK of milled and insufflated oxycodone ER tablets in healthy, nondependent, recreational opioid users, and the evaluated EDR ratios had no effect on PK of finely milled and insufflated oxycodone ER tablets. More importantly, the comparative PK study demonstrated that finely milled oxycodone ER tablets were no less bioavailable than finely milled oxycodone IR tablets following intranasally administered at a dose of 30 mg. These findings suggest that particle size distribution should be considered in comparative PK studies to evaluate the AD properties of milled and insufflated opioid drug products.

DISCLAIMER

The opinions expressed in this paper are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

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CONFLICT OF INTEREST

All authors declared no competing interest for this work.

AUTHOR CONTRIBUTIONS

Z.L., M.K., H.B., S.R., K.N., and M.-J. K. wrote the manuscript. M.-J.K., D.K., R.L., M.L., D.S., M.K., Z.L., S.R., M.F., L.Z., and H.B. designed the research. Z.L., M.K., D.S., H.B., S.R., R.L., M.L., M.F., L.Z., K.K., and M.-J. K. performed the research. Z.L., M.K., D.S., H.B., S.R., R.L., M.L., K.N., and M.-J. K. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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