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OPIOIDS, SUBSTANCE ABUSE & ADDICTIONS SECTION

Original Research Article

Oral Abuse Potential, Pharmacokinetics, and Safety of Once-Daily, Single-Entity, Extended-Release Hydrocodone (HYD) in Recreational Opioid Users

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Abstract

Objectives. A once-daily, extended-release hydrocodone bitartrate tablet with abuse-deterrent properties (Hysingla ER [HYD]) is available for the treatment of chronic pain in appropriate patients. This study evaluated the oral abuse potential and pharmacokinetics (PK) of HYD intact, chewed, or milled to fine particles in comparison with hydrocodone solution or placebo.

Design. Single-center, double-blind, randomized, five-period, five-treatment crossover study.

Subjects. Healthy adult, nondependent, recreational opioid users.

Methods. Forty subjects received orally administered treatments of hydrocodone 60 mg solution, HYD 60 mg intact, HYD 60 mg chewed, HYD 60 mg milled to fine particles, or placebo, separated by a five- to seven-day washout. Assessments over 36 hours postdose included subjective measures of drug liking and willingness to take drug again (assessed using visual analog scales [VAS]), pupillometry, PK, and safety measures.

Results. Following oral administration, HYD intact, HYD chewed, and HYD fine particles led to significantly lower "at this moment" drug liking compared with hydrocodone solution. HYD intact and chewed were significantly different from hydrocodone solution on overall drug liking, take drug again, and good effects. Pupil constriction, as measured by pupillometry, occurred later with HYD intact and HYD chewed than with hydrocodone solution. Across treatments (hydrocodone solution, HYD fine particles, HYD chewed, and HYD intact, respectively), mean C_{max} and rate of absorption (C_{max}/T_{max}) values decreased, respectively, and median T_{max} values increased, respectively. Safety was consistent with the known effects of opioid agonists.

Conclusion. HYD demonstrated reduced oral abuse potential compared with hydrocodone solution in healthy adult, nondependent, recreational opioid users.*

Key Words. Hydrocodone; HYD; Abuse Potential; Abuse Deterrent; Pain

The order of author names and the author affiliations have been corrected since this article's original publication.

Introduction

Chronic pain is a prevalent medical condition, and several guidelines, including those of the American Academy of Pain Medicine and the American Pain Society, recommend the use of opioids for the management of chronic pain that is refractory to first-line therapies such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) [1–4]. The most commonly prescribed opioid treatment in the United States is immediate-release (IR) hydrocodone in combination with acetaminophen [5,6]. However, due to the risk of hepatic toxicity associated with acetaminophen when ingested in amounts exceeding the maximum recommended daily dose (4 g per day) [7], the maximum daily dose of hydrocodone attainable from this combination drug product is limited [6,8]. Hydrocodone combination products that include NSAIDs are available [6,9], but this nonopioid component is associated with gastrointestinal toxicity [9]. In recent years, single-entity, extended-release (ER) hydrocodone formulations have been developed in order to overcome the concerns associated with hydrocodone plus nonopioid combination products [6,10,11]. Other added advantages of these ER formulations are that they can provide stable analgesia over prolonged durations and allow for less frequent dosing, which may improve adherence to treatment in patients for whom around-the-clock analgesia is appropriate [8,12,13]. However, the higher opioid content in these formulations has led to concerns about potential abuse and misuse [6,8,14].

Prescription opioid abuse is a significant public health problem in the United States [15,16], and IR hydrocodone combination products are among the most commonly abused opioids [17,18]. Between 2004 and 2011, the rate of misuse of IR hydrocodone combination products increased by 107% [18]. Opioid abuse usually entails taking higher than the recommended dose of the intact prescribed medication. However, abusers may also tamper with opioid formulations (both IR and ER) and use crushing, chewing, dissolving, or extracting/separating opioid compound from other products or excipients in order to accelerate the release of the opioid via ingestion, injection, or inhalation (snorting and smoking) [19]. To minimize the abuse and misuse of prescription opioids, formulations of opioids with abuse-deterrent properties (ADFs) have been developed. ADFs may impede alternate or unintended routes of administration and reduce the public health burden of prescription opioid abuse [20,21]. A recent analysis of an opioid reformulated with abuse-deterrent properties demonstrated that rates of its abuse declined following reformulation [22].

A single-entity, once-daily, extended-release, hydrocodone bitartrate tablet with abuse-deterrent properties (Hysingla® ER [HYD], Purdue Pharma, Stamford, CT, USA) has been approved by the US Food and Drug Administration (FDA) for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment, and for which other treatment options are inadequate [11]. HYD tablets do not contain nonopioid components and are available in strengths of 20 to 120 mg, offering flexibility in meeting individual patient dosing needs [11]. HYD is formulated using Purdue Pharma's proprietary extended-release solid oral dosage formulation platform, RESISTEC.™ RESISTEC uses a unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions.

Abuse of prescription opioids and, in particular, hydrocodone-containing formulations, occurs most commonly via the oral route. Due to the relative ease of administration, intact and chewed oral administration is also the method of tampering most preferred by abusers [19,23]. This study evaluated the oral abuse potential of HYD compared with hydrocodone solution (positive control) and placebo in healthy, nondependent, recreational opioid users and assessed the safety and pharmacokinetic (PK) profile of intact, chewed, or milled-to-fine-particles of HYD when administered orally.

Methods

Study Population

This study included moderately experienced recreational opioid users who were healthy, between 18 and 55 years of age, and had a minimum weight of 50 kg and a body mass index (BMI) ranging from 18.0 to 29.9 kg/m^2. Moderate experience was defined as using opioids for nontherapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions within the previous year, with opioid use occurring three or more times in the 12 weeks prior to screening. Participating subjects were also required to have chewed an opioid on three or more occasions for the purpose of recreational oral abuse/misuse during the previous 12 months and to have reported using a 60 mg hydrocodone equivalent or higher opioid dose at least once during their lifetime. Negative urine drug screen results were required at screening and during each subsequent treatment visit, with the exception of cannabinoids and benzodiazepines (and their metabolites); subjects were required to test negative or demonstrate stable or decreasing concentrations of these substances due to their long half-life. Negative ethanol breath tests were required at screening and all treatment visits.

Subjects were excluded if they met any of the following criteria: demonstrated clinically relevant abnormalities on physical examination, medical history, 12-lead electrocardiogram, vital signs, or laboratory values; had a history or presence of any significant illness; or had clinically significant past or planned abdominal surgery, a history or presence of hypotension, acute asthma or other obstructive airway disease. Subjects with dental work or clinically relevant dental issues that would interfere with the study chewing procedures and subjects who consumed an average of 20 or more cigarettes per

day during the month prior to screening or were unable to refrain from smoking for a minimum of 10 hours were excluded. Subjects with previous (within the past two years) or current drug or alcohol dependence and subjects who had ever participated in a drug rehabilitation program were also excluded. Female subjects who were pregnant or lactating were excluded, as were subjects who exhibited withdrawal symptoms in response to the naloxone challenge test.

Study Design

This study was conducted in 2013, in accordance with the 2013 FDA draft guidance on the evaluation of abuse-deterrent opioids [24], and remains consistent with the final version of that guidance, issued in April 2015 (25). This was a single-center, double-blind, positive- and placebo-controlled, randomized, five-treatment crossover study. The study protocol was approved by the institutional review board of the participating center (Toronto, Ontario, Canada) and conducted in accordance with the principles of Good Clinical Practice and all applicable regulations. Subjects provided written informed consent prior to enrollment. The study consisted of four phases: screening, qualification, treatment, and follow-up (Figure 1). In the screening phase, eligible subjects underwent a naloxone challenge to exclude those with symptoms of opioid withdrawal.

Dose Selection

Hydrocodone 60 mg (immediate release) is within the range of oral doses previously evaluated in human abuse potential studies (unpublished data from the investigational site). Therefore, HYD 60 mg and hydrocodone 60 mg (solution) are considered suitable supratherapeutic doses for evaluation in this study.

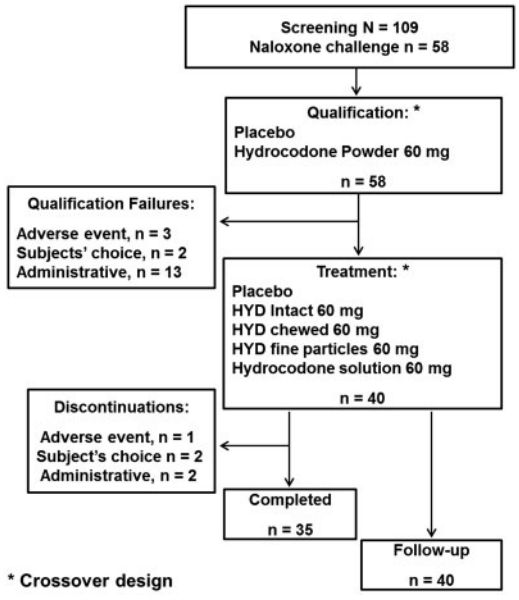

Figure 1 Study design and subject disposition. HYD = hydrocodone bitartrate once-daily tablet.

Qualification Phase

Eligible subjects entering the qualification phase were administered an oral solution of hydrocodone 60 mg and matching placebo solution in a double-blind crossover fashion. The treatments were separated by a 24-hour washout period. In order to be eligible for the treatment phase, subjects were required to show acceptable responses to hydrocodone solution and placebo on visual analog scales (VASs; 0–100) for subjective pharmacodynamic (PD) measures. Specifically, peak scores in response to hydrocodone solution were required to be greater than those of placebo in accordance with predefined criteria for the following measurements: 1) "at this moment" drug liking VAS (a difference of at least 15 points, or 30%); 2) overall drug liking VAS (a difference of at least 10 points, or 20%); 3) high VAS (a difference of at least 30 points, or 30%). Furthermore, in response to hydrocodone, a peak score of 75 or greater must have been indicated on the "at this moment" drug liking VAS, 70 or greater on the overall drug liking VAS, and 40 or greater on the high VAS. For the placebo, peak scores were considered acceptable if they ranged between 40 and 60 for "at this moment" drug liking VAS and overall drug liking VAS, and between 0 and 10 for high VAS. In addition, to be eligible for treatment, subjects had to tolerate hydrocodone and be capable of successfully completing the study, as evaluated by safety data and by the clinical staff, respectively.

Treatment Phase

Subjects fulfilling the qualification criteria entered the treatment phase and were randomized in a double-blind, five-period, five-treatment crossover fashion. There was a 72-or-more-hour washout between the qualification and treatment phases. The following treatments were administered orally: 1) HYD 60 mg tablet intact; 2) HYD 60 mg tablet chewed; 3) HYD 60 mg fine particles; 4) hydrocodone solution 60 mg; 5) placebo solution. To produce HYD fine particles, the HYD tablets were ground in an industrial mill to reach as near a minimum particle size as possible. For chewed HYD, subjects were directed to chew the tablets thoroughly (at least two to three minutes without swallowing). To maintain blinding across the five treatments, a quadruple-dummy procedure was used. At each treatment visit, subjects received an intact tablet, milled tablet, chewed tablet, and oral solution. All treatments were separated by a washout period of five to seven days. The follow-up visit occurred three to seven days after the last study drug administration.

Pharmacodynamic Assessments

PD measures were assessed during the qualification phase (up to 23 hours) and the treatment phase (up to 36 hours). During the qualification and treatment phases,

Table 1 Bipolar and unipolar visual analog scales

Category	Subjective measure	VAS type	0–100 VAS 0	50	100
Balance of effects	"At this moment" drug liking	Bipolar	At this moment, my liking for this drug is: Strong disliking	Neutral	Strong liking
	Overall drug liking		Overall, my liking for this drug is: Strong disliking	Neutral	Strong liking
	Take Drug Again	Unipolar	I would take this drug again: Definitely not		Definitely so
Positive effects	Feeling high		I am feeling high: Definitely		Definitely so
	Good effects		I can feel good drug effects: Definitely not		Definitely so
Negative effects	Bad effects		I can feel bad drug effects: Definitely not		Definitely so
	Feeling sick		I am feeling sick: Definitely not		Definitely so
Other subjective effects	Any effects		I can feel any drug effect: Definitely not		Definitely so
Sedative effects	Drowsiness/ alertness	Bipolar	My mental state is: Very drowsy	Neither drowsy nor alert	Very alert

VAS = visual analog score.

subjective VAS measures were assessed on either a 100-point bipolar (i.e., 50 = neutral response) or unipolar (i.e., 0 = no effect) scale (Table 1). "At this moment" drug liking, overall drug liking, and drowsiness/alertness were evaluated on a bipolar scale; whereas take drug again, feeling high, good effects, bad effects, feeling sick, and any effects were assessed on a unipolar scale. For this study, the "at this moment" drug liking VAS and feeling high VAS were the primary PD measures. Subjective drug value (SDV) was defined as the crossover point at which a subject was indifferent to choosing between the drug administered or money. Pupillometry was included as an objective measure of the effects of opioids, and pupil diameter was measured using an infrared digital pupillometer (NeurOptics Inc., Irvine, CA, USA).

In the treatment phase, PD measures were assessed predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 15, 24, and 36 hours postdose. Drug-specific measures, ie, drug liking, good effects, bad effects, and any effects were not administered predose. Global measures (overall drug liking VAS, take again VAS, and SDV) were assessed at 12 and 24 hours postdose.

Subjective PD measures (VAS assessments) were summarized by calculating mean maximum and/or minimum effect scores (E_{max} and E_{min}, respectively) as applicable. Furthermore, in compliance with the 2015 FDA guidance [25], the percent reduction in E_{max} of "at this moment" drug liking VAS for HYD in comparison with hydrocodone solution was determined for each subject. For the objective measure of pupillometry, maximum pupil constriction (MPC) was measured.

Pharmacokinetic Assessments

During the treatment phase, blood samples were collected at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 15, 24, and 36 hours postdose for PK assessments. Plasma concentrations of hydrocodone were determined using high-performance liquid chromatography with tandem mass spectrometry. The lower limit of quantification for hydrocodone was 0.1 ng/mL.

PK parameters were derived using a noncompartmental (model-independent) approach using WinNonlin (version 6.3). For the analysis, actual blood sampling times were used. PK parameters assessed included maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration time curve to last quantifiable concentration (AUC_{last}), area under the concentration time curve from time zero to infinity (AUC_{inf}), terminal phase half-life ($t_{1/2}$), and the average rate of increase in plasma hydrocodone concentration between dosing and T_{max}, defined as the ratio of C_{max}/T_{max}.

Safety Assessments

Safety evaluations included recording and monitoring adverse events (AEs), physical examinations, vital

signs measurements, and clinical laboratory assessments and performing 12-lead electrocardiogram. In addition, telemetry and pulse oximetry monitoring were conducted from predose to at least four hours postdose. All AEs occurring from the time of informed consent for study participation to the follow-up visit were reported by system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), version 16.0.

Statistical Analysis

Subjects who completed all visits of the treatment phase without major protocol deviations that would affect PD results were included in the PD analyses.

Most PD endpoints for the treatment phase were analyzed using a mixed-effect model for a crossover study. In this model, treatment, period, sequence, and first-order carryover effects were included as fixed effects, whereas baseline (predose) measurement was treated as covariate where appropriate and subject nested within treatment sequence was considered a random effect. Where applicable, nonparametric methods were employed for PD measurements. Tests for non-normality and homogeneity were conducted.

Statistical comparisons included hydrocodone solution vs placebo (study validity); HYD (intact, chewed, and fine particles) vs hydrocodone solution; HYD (intact, chewed, and fine particles) vs placebo; and pairwise treatment comparisons between HYD intact, chewed, and fine particles.

Consistent with previous reports [26], percent reduction of "at this moment" drug liking VAS E_{max} for HYD intact, chewed, or fine particles compared with hydrocodone solution was calculated using the following formula (where C = control, hydrocodone solution; T = test drugs, HYD intact, chewed, or fine particles; P = placebo):

$$\%\ reduction = \begin{cases} \dfrac{C-T}{C-50} \times \left(1 - \dfrac{P-50}{50}\right) \times 100\%, & if\ P > 55; \\ \dfrac{C-T}{C-50} \times 100\%, & if\ P \leq 55. \end{cases}$$

For the PK analyses, subjects who received at least 1 dose of active study drug during the treatment phase and had evaluable PK data were included. Hydrocodone plasma concentrations and PK parameters were summarized using descriptive statistics (mean, median, standard deviation [SD], range [min, max], and % coefficient of variation).

The safety population included all subjects who received one or more doses of study drug during the treatment phase and had evaluable safety data. Summaries of AEs presented the number and percentage of subjects experiencing one or more AEs. Demographics and baseline characteristics of the safety population were summarized using descriptive statistics.

Sample size determination was based on previous experience with oral hydrocodone 60 mg tablets. Data from 30 subjects completing all treatments were determined to be sufficient to detect a significant difference in "at this moment" drug liking VAS or feeling high VAS between hydrocodone oral solution and placebo with greater than 95% power. Statistical analyses were performed using SAS (version 9.3).

Results

Disposition and Subject Characteristics

In total, 109 subjects were screened during enrollment, of whom 58 were eligible for participation in the qualification phase. Among those completing the qualification phase, 40 subjects satisfied the qualification criteria and were randomized and dosed in the treatment phase. A total of 35 subjects completed all five treatment periods, and five subjects (12.5%) were discontinued (Figure 1). One subject discontinued the study due to a mild treatment-emergent AE (TEAE) of abnormal ECG P waves that occurred approximately six hours and 22 minutes following placebo administration in treatment period 2. This event was considered unlikely to be related to study drug and resolved approximately three minutes after onset without intervention. Two subjects chose to discontinue treatment due to personal reasons, and two others discontinued due to administrative reasons (e.g., noncompliance).

The majority of the safety population was male (82.5%) and white (72.5%) and had a mean body mass index (BMI) of 25.2 kg/m^2 (SD = 3.02, range = 18.8–29.7 kg/m^2). The mean age was 36.3 years (SD = 9.2, range = 21–54 years). All subjects had previous experience with recreational use of opioids and morphine derivatives. Additionally, subjects reported experience with cannabinoids (87.5%), stimulants (77.5%), hallucinogens (32.5%), depressants (32.5%), and dissociative anesthetics (20.0%).

Qualification Phase

During the qualification phase, peak mean (SD) "at this moment" drug liking VAS scores were 96.4 (6.3) for hydrocodone solution 60 mg compared with 50.6 (0.7) for placebo, where 100 was maximum liking, 50 was neutral, and 0 was maximum disliking. Mean (SD) feeling high VAS scores for hydrocodone solution and placebo were 98.9 (3.7) and 4.9 (14.3), respectively, where 100 was maximum high feeling and 0 was no high feeling. The 60 mg oral dose of hydrocodone solution (positive control) was well tolerated.

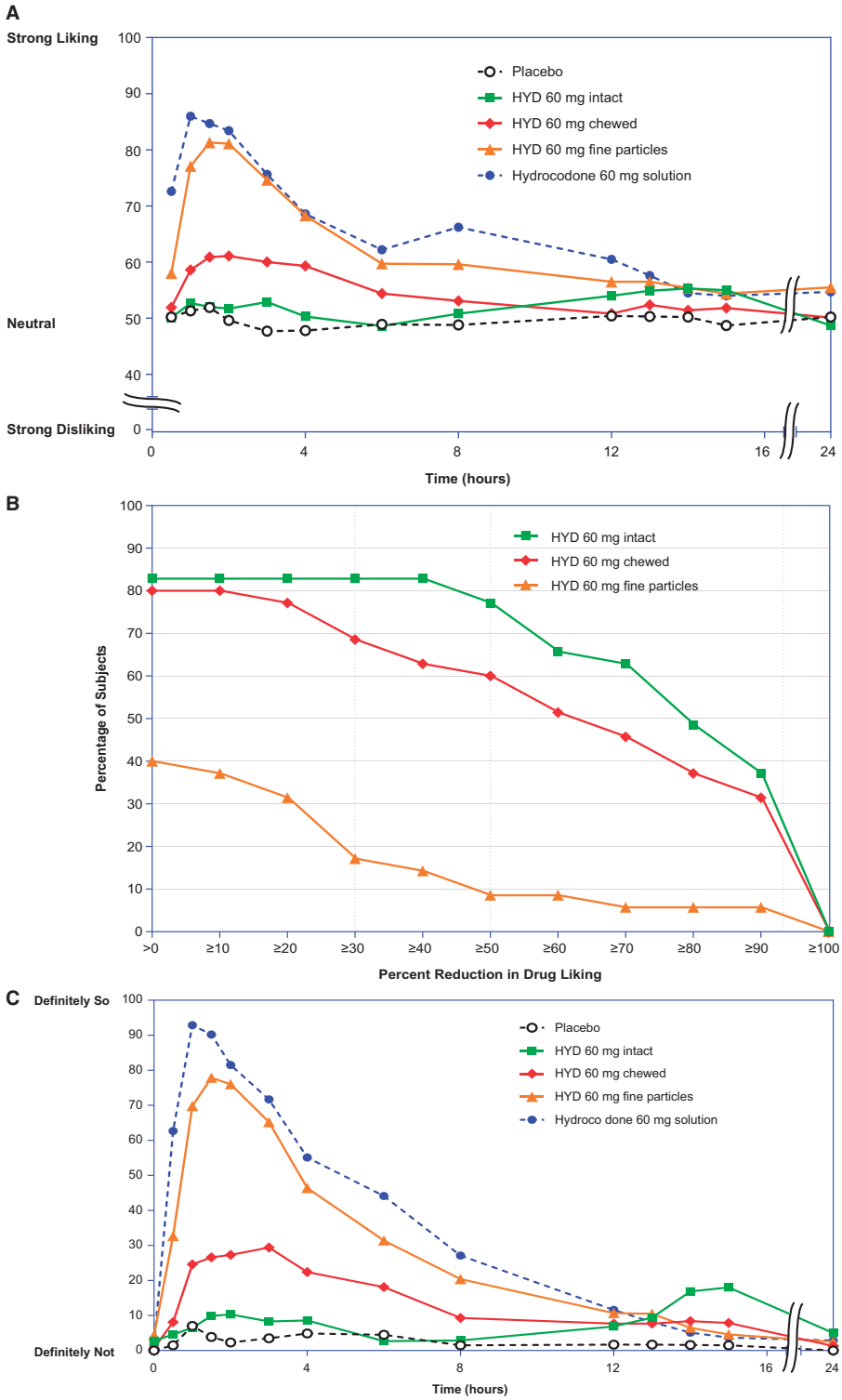

Figure 2 Subjective Measures. A) "At this moment" drug liking VAS. Drug liking was measured on a bipolar scale with values ranging from 0 to 100, where 0 represents maximum disliking, 100 represents maximum liking, and 50 represents a neutral response of neither like nor dislike. B) Percent reduction in drug liking VAS Emax compared with hydrocodone solution. C) Feeling high VAS. Subjects rated the statement "I am feeling high" on a unipolar scale of 0 to 100, where 0 represents definitely not and 100 represents definitely so. D) Mean (SD) Emax scores for overall drug liking VAS, take drug again VAS, and subjective drug value. Emax = maximum effect; HYD = hydrocodone bitartrate once-daily tablet; VAS = visual analog scale.

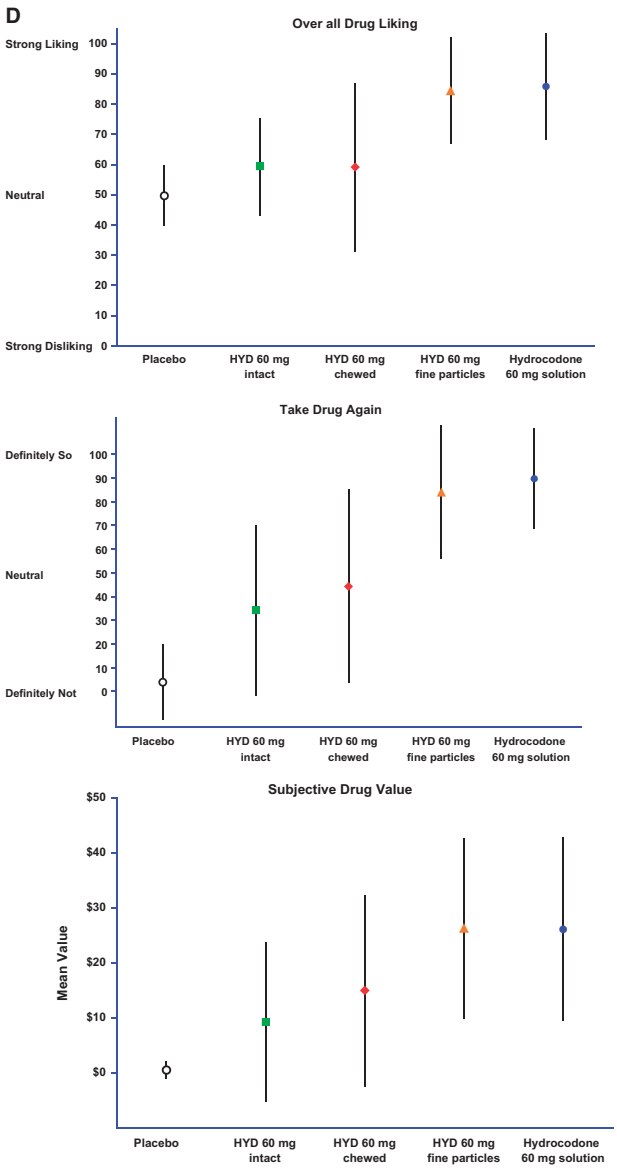

Figure 2 (Continued)

Treatment Phase

Pharmacodynamic Parameters

Subjective Measures. Hydrocodone solution was associated with significantly higher mean "at this moment" drug liking VAS E_{max} compared with placebo (94.0 vs 52.3, respectively; $P < 0.001$), thereby confirming study validity.

Mean scores following administration of placebo or HYD intact were similar over time for the bipolar "at this moment" drug liking VAS, whereas hydrocodone solution and HYD fine had values in the "liking" range (>50) between one-half and eight hours postdose, returning to just above neutral at approximately 12 hours postdose (Figure 2A). Peak "at this moment" drug liking VAS score for HYD chewed showed a relatively small increase (approximately 10 points) in drug liking VAS scores from approximately one to four hours postdose and then returned to neutral (Figure 2A). Relative to hydrocodone solution, the three HYD treatments (HYD intact, HYD chewed, and HYD milled) were associated with significantly lower peak "at this moment" drug liking VAS E_{max} scores (all $P \leq 0.015$) (Table 2), and time to reach the mean peak scores was slightly delayed for all three forms of HYD relative to hydrocodone solution (Figure 2A).

Table 2 Primary and secondary pharmacodynamic measures

	Placebo (n = 35)	HYD intact 60 mg (n = 35)	HYD chewed 60 mg (n = 35)	HYD fine particles 60 mg (n = 35)	Hydrocodone solution 60 mg (n = 35)	*P* values vs hydrocodone solution[a] HYD intact 60 mg	HYD chewed 60 mg	HYD fine particles 60 mg
"At this moment" drug liking VAS, E_{max}								
Mean (SD)	52.3 (7.14)	63.3 (16.0)	69.0 (17.5)	89.2 (14.0)	94.0 (10.2)	<0.001	<0.001	0.015
Median	51.0	58.0	66.0	93.0	100.0			
Feeling high VAS, E_{max}								
Mean (SD)	17.5 (28.5)	42.0 (37.6)	48.3 (36.2)	85.6 (26.4)	97.4 (5.76)	<0.001	<0.001	<0.001
Median	0.0	48.0	50.0	100.00	100.0			
Good effects VAS, E_{max}								
Mean (SD)	9.2 (25.6)	36.9 (37.2)	50.1 (39.3)	88.4 (27.2)	97.0 (5.97)	<0.001	<0.001	NS
Median	0.0	20.0	51.0	100.0	100.0			
Bad effects VAS, E_{max}								
Mean (SD)	4.6 (14.2)	18.1 (28.7)	27.1 (37.0)	24.7 (34.2)	31.4 (36.8)	0.034	NS	NS
Median	0.0	2.0	5.0	2.0	13.0			
Feeling sick VAS, E_{max}								
Mean (SD)	6.5 (21.0)	10.8 (23.6)	19.9 (34.6)	9.2 (21.3)	18.9 (32.0)	NS	NS	NS
Median	0.0	0.0	0.0	0.0	0.0			
Any effects VAS, E_{max}								
Mean (SD)	11.5 (26.0)	45.2 (41.0)	62.3 (39.0)	88.9 (24.2)	97.3 (5.4)	<0.001	<0.001	0.01
Median	0.0	32.0	74.0	100.0	100.0			
Drowsiness/alertness VAS, E_{min}								
Mean (SD)	35.7 (20.5)	25.9 (22.5)	27.3 (19.1)	22.2 (18.4)	18.5 (18.8)	NS	0.022	NS
Median	49.0	27.0	31.0	20.0	15.0			

E_{max} = maximum effect; E_{min} = minimum effect; HYD = hydrocodone bitartrate once-daily tablet; NS = not significant; VAS = visual analog scale.

[a]Pairwise comparison was only presented if the treatment effect *P* value was significant. For most measures, overall treatment effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. Drowsiness/alertness *P* values were estimated based on the least squares mean difference and corresponding 95% confidence intervals.

An analysis of the percent reduction of "at this moment" drug liking VAS E_{max} values for HYD intact, chewed, and fine particles relative to hydrocodone solution is shown in Figure 2B. Compared with hydrocodone solution, a 30% or greater reduction in "at this moment" drug liking VAS scores was seen among 83%, 69%, and 17% of subjects receiving HYD intact, HYD chewed, and HYD fine particles, respectively; a reduction of at least 50% was seen among 74%, 60%, and 9% of subjects receiving HYD intact, HYD chewed, and HYD fine particles, respectively; and a reduction of at least 90% was seen among 37%, 29%, and 6% of subjects receiving HYD intact, HYD chewed, and HYD fine particles, respectively.

Mean E_{max} scores for feeling high VAS followed a pattern similar to that of the "at this moment" drug liking VAS scores (Figure 2C and Table 2). Feeling high VAS (mean E_{max}) scores for hydrocodone solution (97.4) and HYD fine particles (85.6) were markedly higher than for placebo (17.5) (Table 2). E_{max} for HYD fine particles was not significantly different from hydrocodone solution, while HYD chewed and HYD intact were associated with significantly lower E_{max} values compared with hydrocodone solution ($P < 0.001$ for both comparisons) and significantly higher E_{max} values than placebo ($P < 0.001$ and $P = 0.003$, respectively). Significant differences in peak score between hydrocodone solution and both HYD chewed and HYD intact were also seen for good effects

Table 3 Overall subjective drug effects at 12 and 24 hours

Pharmacodynamic measure	N	12 hours Mean (SD)	24 hours Mean (SD)
Overall drug liking VAS			
Placebo	35	48.2 (13.1)	48.1 (13.0)
HYD intact 60 mg	35	53.3 (16.8)	54.9 (22.2)
HYD chewed 60 mg	35	57.6 (28.3)	56.8 (28.1)
HYD fine particles 60 mg	35	83.7 (18.0)	80.1 (22.4)
Hydrocodone solution 60 mg	35	83.0 (19.2)	84.1 (19.7)
Take drug again VAS			
Placebo	35	3.9 (15.9)	2.2 (12.8)
HYD intact 60 mg	35	19.5 (33.7)	32.6 (35.5)
HYD chewed 60 mg	35	41.3 (40.7)	43.0 (41.2)
HYD fine particles 60 mg	35	82.6 (29.7)	77.0 (31.5)
Hydrocodone solution 60 mg	35	84.6 (25.7)	86.7 (22.8)
Subjective drug value ($)			
Placebo	35	0.5 (1.4)	0.5 (1.6)
HYD intact 60 mg	35	6.8 (14.6)	8.8 (14.5)
HYD chewed 60 mg	35	11.4 (14.8)	13.7 (16.5)
HYD fine particles 60 mg	35	24.2 (17.0)	25.9 (16.5)
Hydrocodone solution 60 mg	35	22.9 (17.1)	25.8 (16.8)

HYD = hydrocodone bitartrate once-daily tablet; VAS = 100 mm visual analog scale.

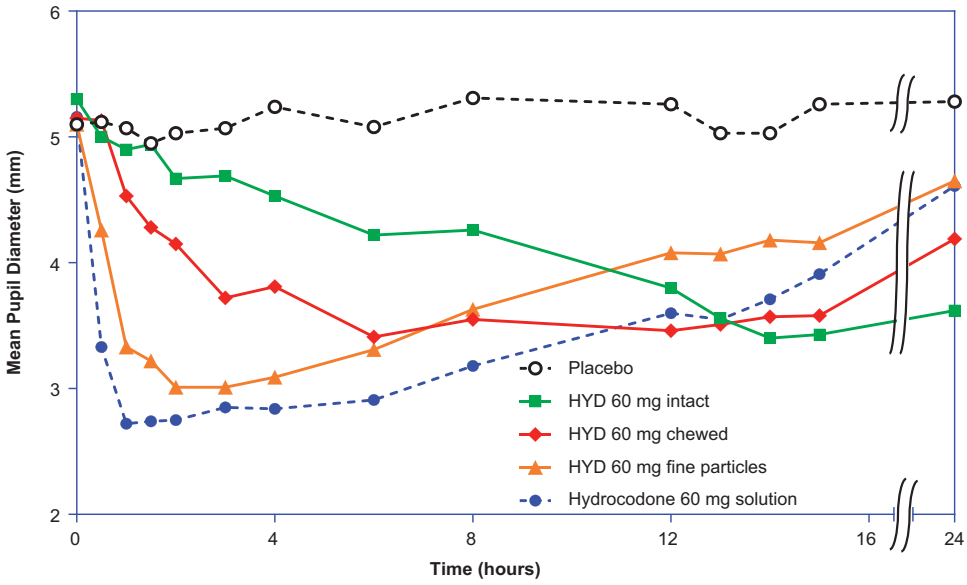

Figure 3 Pupillometry. HYD = hydrocodone bitartrate once-daily tablet.

VAS and any effects VAS ($P < 0.001$) (Table 2). Of the three forms of HYD, bad effects VAS E_{max} scores were significantly lower than hydrocodone solution for HYD intact only ($P = 0.034$). The drowsiness/alertness VAS minimum score was significantly higher for HYD chewed ($P = 0.022$) than for hydrocodone solution, indicating less drowsiness. Differences between all HYD treatments and placebo were significant for all VAS scores examined ($P < 0.05$).

Mean overall drug liking VAS, take drug again VAS, and SDV scores for each treatment at 12 and 24 hours are shown in Table 3. Hydrocodone solution and HYD fine particles had the highest mean scores for E_{max} compared with all other treatments for all three global measures. Compared with hydrocodone solution, both the HYD chewed and HYD intact were associated with significantly lower mean E_{max} scores on overall drug liking VAS, take drug again VAS, and SDV ($P \leq 0.001$ for all

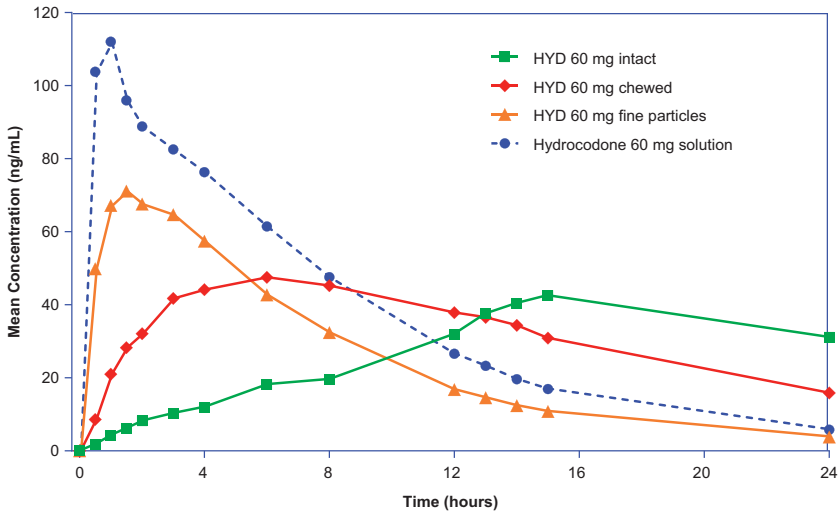

Figure 4 Mean hydrocodone plasma concentration vs time. HYD = hydrocodone bitartrate once-daily tablet.

Table 4 Hydrocodone pharmacokinetic parameters

Parameter	HYD intact 60 mg (n = 36*)	HYD chewed 60 mg (n = 36†)	HYD fine particles 60 mg (n = 37)	Hydrocodone solution 60 mg (n = 39‡)
AUC_{last} (h*ng/mL) Mean (SD)	886 (208)	913 (218)	648 (201)	951 (238)
AUC_{inf} (h*ng/mL) Mean (SD)	1,059 (266)	943 (244)	656 (206)	971 (244)
C_{max} (ng/mL) Mean (SD)	48.4 (14.3)	67.3 (24.6)	81.0 (23.7)	127.1 (36.4)
T_{max} (h) Median (range)	15.1 (13.0–24.1)	8.0 (1.1–36.0)	1.6 (0.5–4.1)	1.1 (0.5–6.1)
$t_{1/2}$ (h) Median (range)	7.1 (4.6–9.2)	5.6 (4.4–7.6)	5.4 (4.2–7.6)	5.4 (3.7–7.1)
C_{max}/T_{max} (ng/mL/h) Mean (SD)	3.1 (1.3)	14.7 (16.8)	70.4 (57.1)	153.9 (92.5)

AUC_{inf} = area under the plasma concentration vs time curve extrapolated to infinity; AUC_{last} = area under the plasma concentration vs time curve from 0 to the last quantifiable concentration; C_{max} = maximum plasma concentration; HYD = hydrocodone bitartrate once-daily tablet; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.
*n = 11 for $t_{1/2}$ and AUC_{inf}.
†n = 27 for $t_{1/2}$ and AUC_{inf}.
‡n = 38 for $t_{1/2}$ and AUC_{inf}.

three measures), while HYD fine particles was not significantly different from hydrocodone solution (Figure 2D).

Pupillometry

Maximum pupil constriction was the highest for hydrocodone solution, followed by HYD fine particles, chewed, and intact (Figure 3). The mean (SD) MPC values were 0.65 (0.41), 2.19 (0.68), 2.23 (0.59), 2.29 (0.73), and 2.62 (0.66) mm for placebo, HYD intact, HYD chewed, HYD fine particles, and hydrocodone solution, respectively ($P < 0.001$ comparing HYD intact and chewed vs hydrocodone solution, $P = 0.002$ comparing HYD fine particles vs hydrocodone solution).

Pharmacokinetic Parameters

Mean hydrocodone plasma concentrations vs time profiles for the four active oral treatments are shown in Figure 4. Administration of hydrocodone solution resulted in the highest mean C_{max} (127.1 ng/mL), followed by HYD fine particles (81.0 ng/mL), HYD chewed (67.3 ng/mL), and HYD intact (48.4 ng/mL) (Table 4). The median T_{max} was shortest for hydrocodone solution (1.1 hours) compared with HYD fine particles (1.6 hours), HYD chewed (8.0 hours), and HYD intact (15.1 hours). Accordingly, the mean ratio of C_{max}/T_{max} of hydrocodone was highest for hydrocodone solution (153.9 ng/mL/h), followed by HYD fine particles (70.4 ng/mL/h) and HYD chewed (14.7 ng/mL/h), and lowest for HYD intact (3.1 ng/mL/h). Systemic hydrocodone exposure, as evaluated by mean AUC_{last} and AUC_{inf}, was similar following administration of hydrocodone solution (951 h•ng/mL and 971 h•ng/mL, respectively), HYD chewed (913 h•ng/mL and 943 h•ng/mL, respectively), and HYD intact (886 h•ng/mL/mL and 1059 h•ng/mL, respectively); treatment with HYD fine particles resulted

Table 5 Treatment-emergent adverse events reported by ≥5% of subjects for any treatment, safety population

Preferred term*	Placebo (n = 38) N (%)	HYD 60 mg intact (n = 36) N (%)	HYD 60 mg chewed (n = 36) N (%)	HYD 60 mg fine particles (n = 37) N (%)	Hydrocodone 60 mg solution (n = 39) N (%)
Any event	13 (34.2)	25 (69.4)	27 (75.0)	35 (94.6)	38 (97.4)
Euphoric mood	2 (5.3)	12 (33.3)	14 (38.9)	25 (67.6)	31 (79.5)
Pruritus, localized	0 (0.0)	15 (41.7)	15 (41.7)	24 (64.9)	25 (64.1)
Somnolence	2 (5.3)	10 (27.8)	8 (22.2)	11 (29.7)	15 (38.5)
Headache	4 (10.5)	6 (16.7)	6 (16.7)	3 (8.1)	2 (5.1)
Feeling hot	0 (0.0)	2 (5.6)	1 (2.8)	5 (13.5)	8 (20.5)
Nausea	1 (2.6)	2 (5.6)	3 (8.3)	2 (5.4)	7 (17.9)
Dizziness	1 (2.6)	2 (5.6)	2 (5.6)	5 (13.5)	2 (5.1)
Pruritus, generalized	0 (0.0)	2 (5.6)	1 (2.8)	2 (5.4)	3 (7.7)
Dry mouth	0 (0.0)	2 (5.6)	1 (2.8)	2 (5.4)	2 (5.1)
Fatigue	0 (0.0)	2 (5.6)	1 (2.8)	1 (2.7)	2 (5.1)
Vomiting	0 (0.0)	0 (0.0)	2 (5.6)	0 (0.0)	3 (7.7)
Agitation	1 (2.6)	0 (0.0)	0 (0.0)	1 (2.7)	2 (5.1)
Disturbance in sexual arousal	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)	1 (2.6)

*Preferred terms of the Medical Dictionary for Regulatory Activities, version 16.0.

in lower AUC_{last} and AUC_{inf} values (648 h•ng/mL and 656 h•ng/mL, respectively) (Table 4). It should be noted that AUC_{inf} could only be estimated for 11 subjects following administration of HYD intact because of nonestimable $t_{1/2}$ due to insufficient sampling points after T_{max}.

Safety

A summary of AEs that occurred during the treatment phase of the study and were reported by 5% or more of the population is presented in Table 5. The incidence of TEAEs was the highest following administration of hydrocodone solution (97.4%) and HYD fine particles (94.6%) (Table 5). Treatment with HYD chewed (75.0%) and HYD intact (69.4%) resulted in fewer TEAEs, while placebo administration was associated with the lowest TEAE incidence (34.2%).

Most subjects experienced TEAEs that were mild in severity. The majority of TEAEs were deemed possibly or probably related to study treatments. Three subjects experienced TEAEs of moderate severity: one episode of presyncope following administration of HYD fine particles, one episode of sinus bradycardia following administration of hydrocodone solution, and one episode of headache following administration of HYD intact. Euphoric mood was the most common TEAE, with its incidence highest after administration of hydrocodone solution (79.5%), followed by HYD fine particles (67.6%), HYD chewed (38.9%), HYD intact (33.3%), and placebo (5.3%). Pruritus and somnolence were the second and third most common TEAEs. There were no deaths or serious AEs during this study.

Discussion

Opioid analgesics represent an important component of modern pain management, but their abuse and misuse has created a serious and growing public health problem [27–31]. Among the most common reasons for drug-related emergency room visits in the United States in 2011 was abuse or misuse of narcotic pain relievers [32], and IR hydrocodone-containing products are among the most commonly abused drugs [23,31,33].

To help reduce this problem, opioid formulations with abuse-deterrent properties have been developed. HYD is formulated to resist the manipulations used to facilitate the rapid uptake of hydrocodone [11]. In this study, oral abuse potential was compared among hydrocodone solution, HYD fine particles (milled), HYD chewed, and HYD intact. The manipulation methods chosen for evaluation were in accordance with guidelines issued by the FDA [25]. The HYD fine particle size was included as a study treatment to represent the manipulation allowing for the highest release of the opioid. Because of the difficulties encountered when milling HYD in this fashion (including mills that regularly broke because of the hardness of the tablets), it is not expected that

milling would be a feasible method of tampering in the real world [34].

Oral administration of hydrocodone solution (the positive control) showed statistically significant differences from placebo on the peak scores for the primary measures of "at this moment" drug liking and feeling high, thus confirming the sensitivity of the measures and validity of the study.

Compared with hydrocodone solution, the abuse potential of HYD was reduced when administered orally in its intact form or when tampered with by chewing or milling. This effect was most pronounced for HYD intact and chewed, as demonstrated by significantly lower E_{max} for the primary PD measures of "at this moment" drug liking VAS and feeling high VAS compared with hydrocodone solution. In addition, relative to hydrocodone solution, HYD intact and chewed demonstrated lower E_{max} scores for PD measures including overall drug liking VAS, take drug again VAS, SDV, good effects VAS, and any effects VAS. Furthermore, drowsiness/alertness VAS E_{min} values were higher for HYD chewed relative to hydrocodone solution, indicating less sedation. Consistent with these observations, opioid-induced pupil constriction following administration of HYD chewed or HYD intact was significantly lower compared with hydrocodone solution. The differences in abuse potential were less apparent with HYD fine particles, although statistically significant decreases were observed on the primary measures of "at this moment" drug liking VAS and any effects VAS relative to hydrocodone solution.

The PK profiles for HYD fine particles, chewed, and intact showed varying degrees in reduction of C_{max} and delay in T_{max} compared with hydrocodone solution. Compared with hydrocodone solution, orally administered HYD fine particles demonstrated lower C_{max}, whereas T_{max} was slightly delayed (1.6 hours vs 1.1 hours postdose), suggesting partial maintenance of the ER properties. Chewed and intact HYD achieved a more pronounced reduction in peak hydrocodone concentrations relative to hydrocodone solution and much more prolonged T_{max} (8.0 hours and 15.1 hours, respectively). Overall, the results of the PK analysis indicate that the rate of hydrocodone absorption, illustrated by the calculation C_{max}/T_{max}, decreased in parallel with the PD measures of abuse potential. These differences may be associated with lower abuse potential because the rate of increase in concentration of opioid in plasma (C_{max}/T_{max}) is suggested to be positively correlated with the likelihood of abuse [35].

Similar to the subjective effects profile, the incidences of potential abuse-related TEAEs were highest after oral administration of hydrocodone solution, followed by HYD fine particles. A lower incidence of TEAEs was noted for HYD chewed, HYD intact, and placebo. Consistent with known opioid-related AEs [36,37], euphoric mood, pruritus, somnolence, and nausea were among the most commonly reported AEs in this study. Most TEAEs were mild in severity and likely to be related to study drug.

As with all studies evaluating the abuse-deterrent properties of opioids, this study has several limitations [38]. Briefly, this study was conducted in a controlled, clinical environment, hence the abuse-deterrent potential of HYD in "real-world" settings could not be determined. Furthermore, the only subjects included in this study were recreational opioid users; pain patients addicted to or progressing to opioid addiction have not been considered. Other factors not incorporated in the study design include the likelihood that opioid abusers will find new ways to sidestep the abuse-deterrent properties of the HYD tablet. Although blinding of study treatments constituted an important part of study design, it was not always possible to completely prevent subjects from making comparisons between study treatments and thus introducing bias. Additionally, testing a broad range of doses may provide useful information for drug liking; however, it is generally acceptable in these types of studies to include one strength of the positive control that satisfies both the high levels of drug liking and validates the study [25].

This study was conducted in accordance with the FDA's 2015 guidance for industry on the development and assessment of abuse-deterrent technologies [25]. Based on premarketing data, the abuse-deterrent properties of HYD are expected to reduce potential for oral and intranasal abuse [34,39]. Results from category 1 studies investigating in vitro manipulation and extraction methods indicate that physical and chemical properties of HYD are a deterrent to intravenous and intranasal abuse [34]. Category 3 studies (including the present study) examining the clinical abuse potential of formulations also indicate that the HYD formulation is a barrier to intranasal abuse [39] and to oral abuse via chewing [34]. Despite these findings, abuse of HYD by the intravenous, intranasal, and oral routes is still possible. The full abuse-deterrent potential of HYD should be assessed by long-term postmarketing epidemiologic studies.

Conclusions

In summary, HYD demonstrated significantly lower subjective and physiologic effects compared with hydrocodone solution when administered by the oral route as intact, chewed, or industrially milled tablets. The most substantial reductions in abuse potential were observed with intact and chewed HYD. The differences in abuse potential were less pronounced when HYD was subjected to a rigorous particle size reduction using an industrial mill. Thus, based on these results, the physicochemical properties of HYD tablets are expected to reduce the potential for oral abuse when taken intact or chewed. The real-world abuse-deterrence properties of HYD remain to be evaluated by postmarketing studies.

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