

Pharmacokinetic Assessment of Attempts to Defeat the Rate–Controlling Mechanism of Remoxy, an Extended–Release Oxycodone Formulation

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Abstract

Introduction: Remoxy[®] is an encapsulated, highly–viscous formulation of micronized oxycodone extended release designed to maintain its extended–release characteristics following common forms of physical manipulation or chemical challenge. Here we describe the results of 2 *in vivo* studies that investigated attempts to defeat these characteristics and the effects this had on the pharmacokinetic profile of Remoxy.

Methods: These were single–center, phase I, 3–way crossover, active–controlled pharmacokinetic studies conducted in healthy volunteers aged 18–45 years (inclusive). Protocols were approved by an institutional review board and all subjects provided written informed consent. The individual studies assessed the effect of buccal dissolution (Study A) and chewing (Study B), respectively, on Remoxy 40 mg capsules (fed) compared with oral Remoxy whole (fed) and oxycodone immediate release (IR) solution (40 mg; fasted).

Results: Forty–two subjects were included in the analysis for Study A, and 44 were included in Study B. Although buccal dissolution and chewing resulted in an increase in the rate of absorption of oxycodone from Remoxy (compared with Remoxy whole), this increase was not consistent with dose–dumping. This was evidenced in both studies by the lower C_{max} and partial AUCs of Remoxy as well as a significantly longer T_{max} compared with the oxycodone IR solution ($P < 0.0001$).

Conclusions: Attempts to defeat the rate–controlling characteristics of Remoxy by chewing and buccal administration were not successful as they did not lead to rapid release and absorption of oxycodone (i.e., dose–dumping) demonstrating that Remoxy performed as designed.

Introduction

Chronic or persistent pain is a common and often debilitating condition estimated to affect 26% of the US population (ie, 76 million adults aged >20 years),^{1,2} with 9% of adults suffering from moderate to severe noncancer–related chronic pain.³

Chronic pain conditions, including fibromyalgia, osteoarthritis, back pain, and headache, can adversely impact emotional and psychological well–being, overall quality of life, and work productivity, and impart a substantial economic burden.^{4,6}

Opioids have been widely used for decades in the treatment of pain; however, the potential for unintended manipulation and abuse of opioids is a concern.⁷

These concerns regarding abuse or drug dependence may lead to undertreatment of patients with chronic pain.⁷

With the implementation of new pain management standards in the last decade,⁸ there has been a dramatic rise in the sales and use of opioid medications, particularly oxycodone (866% increase between 1997–2007), and a subsequent increase in reports of opioid misuse and abuse.⁹

Extended–release (ER) oxycodone presents a particular challenge because of the possibility of dose dumping through intentional or unintentional physical or chemical manipulation.¹⁰ Dose dumping has been defined by the FDA as “unintended, rapid drug release in a short period of time of the entire amount or a significant fraction of the drug contained in a modified release dosage form.”¹¹

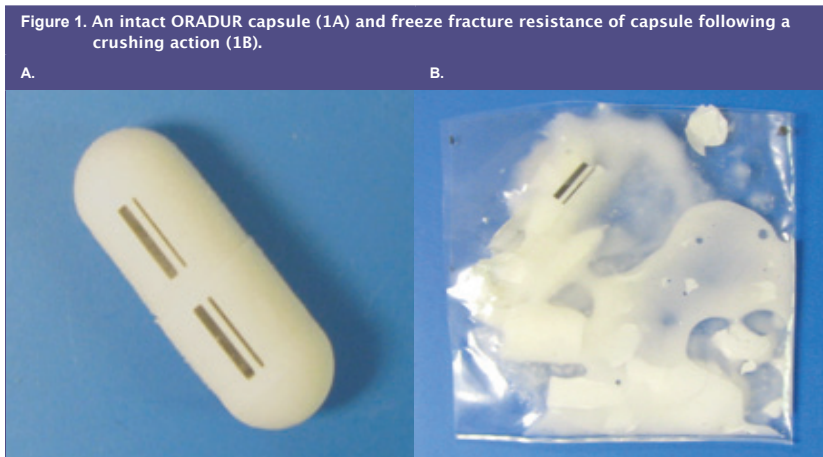
Remoxy[®] (King Pharmaceuticals, Inc., Bristol, TN) is a twice–daily (BID) ER oral capsule of oxycodone developed for the treatment of moderate to severe pain in patients requiring continuous around–the–clock opioid treatment for an extended period of time and is formulated with the ORADUR[®] (DURECT Corporation, Cupertino, CA) technology.

ORADUR is a novel, oral, ER formulation comprised of a viscoelastic fluid matrix that was designed to deter most common methods of tampering (eg, crushing and swallowing, crushing and snorting, extraction, injecting, or volatilization) that would lead to a rapid release of the entire opioid content (ie, dose dumping).

ORADUR’s viscous properties are analogous to a thick honey that remain viscous even at subzero temperatures, thereby rendering freeze–fracture of the matrix virtually impossible (Figure 1).¹²

In vitro studies demonstrated the tamper–resistant properties of Remoxy when subjected to common methods of physical/mechanical and chemical challenges.¹²

Herein, we present results from 2 *in vivo* PK studies designed to assess the rate–controlling properties of Remoxy.



Objective

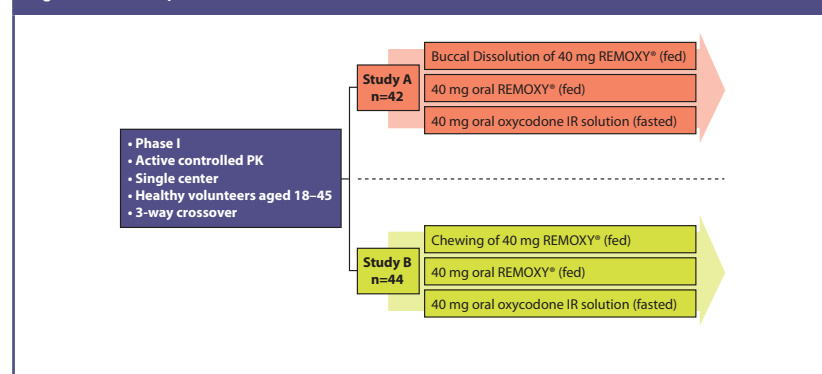
To evaluate the rate and extent of oxycodone absorption when Remoxy was dissolved in the buccal cavity (Study A) or rigorously chewed (Study B) compared with that of an oral dose of Remoxy administered whole and an oral dose of immediate release (IR) oxycodone oral solution

Methods

Study Design

Two phase I, single–center, randomized, open–label, active–controlled, 3–way crossover PK studies were conducted in healthy volunteers (Figure 2).

Figure 2. Summary of PK Studies



Subjects were randomized to 1 of 6 treatment groups in sequence (Table 1). During each 96–hour treatment period, subjects received a single oral dose of Remoxy 40 mg (fed state) or 2 mL (20 mg/mL) oxycodone IR oral solution (fasted state) as the active comparator.

Remoxy capsules were administered whole and either dissolved in the buccal cavity (Study A) or rigorously chewed (Study B). A 96–hour washout period separated each treatment sequence.

Unlike for oxycodone IR, the rate and extent of absorption is lower when Remoxy is administered under fasted conditions; therefore, Remoxy was administered in all studies in the fed state to achieve highest bioavailability.

To minimize the risk of opioid–related adverse events (AEs), naltrexone HCl 50 mg was given to subjects the evenings before and following each dose, and 30 minutes before study drug administration.

Protocols for both studies were approved by an Institutional Review Board and all study participants signed an informed consent form. Each study conformed to the International Conference on Harmonization and Good Clinical Practice guidelines.

Key Inclusion/Exclusion Criteria

Inclusion criteria were similar in both studies. Eligible subjects were men and non–pregnant women aged 18 to 45 years (inclusive) with a body mass index of 18 to 30 kg/m² who were non–smokers in good general health.

Subjects were not permitted to use other prescription drugs (except hormonal contraceptives) within 14 days or over–the–counter medications, alcohol, grapefruit, grapefruit juice, caffeine, or xanthine–containing products within 48 hours of study initiation.

Pharmacokinetic Assessments

Blood samples were collected at baseline and then at frequent intervals through 96 hours post–dose. Isolated plasma was analyzed at a separate laboratory (Worldwide Clinical Trials Drug Development Solutions, Austin TX) and oxycodone and metabolite concentrations measured using validated LC/MS/MS assays.

Among the PK parameters assessed were maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), the area under the curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{last}), partial AUCs, and observed terminal elimination half–life ($T_{1/2}$).

Safety Assessments

Safety assessments included a physical examination (ie, measurement of vital signs, evaluation of electrocardiograms (ECGs), and clinical laboratory tests) and review of AEs.

Statistical Analyses

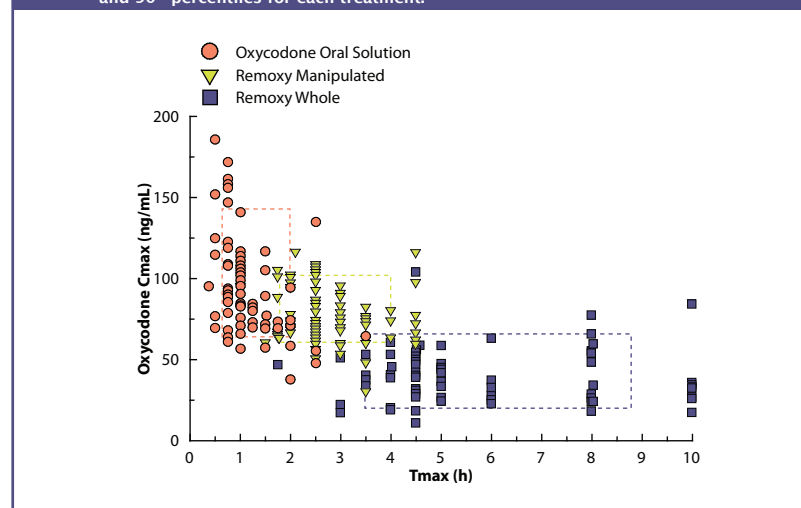
All subjects who received at least 1 dose of study drug were included in the safety analysis. All subjects who completed at least 2 of the 3 study periods in Studies A and B (must have included the Remoxy arms) were included in the PK analyses. All data were excluded for subjects who experienced emesis up to 12 hours post–dose. Plasma concentration–time data were analyzed using noncompartmental methods (WinNonlin). Partial AUCs for the time period at which most or all subjects had quantifiable plasma concentrations were determined using the linear trapezoidal rule with interpolation. Differences between treatments were analyzed using an analysis of variance model with factors for sequence, subject within sequence, period, and treatment.

Results

Combined Study Results

Combined C_{max} and T_{max} results from the 2 PK studies demonstrate that although the rate and extent of absorption of Remoxy when dissolved in the buccal cavity or chewed is increased compared with Remoxy taken whole, it remains below the rate and extent of absorption associated with an oral solution indicating that no dose dumping occurs (Figure 3).

Figure 3. Combined C_{max} and T_{max} results from studies A and B. Dashed lines indicate the 10th and 90th percentiles for each treatment.



Study A: Remoxy Dissolved in the Buccal Cavity

A total of 48 subjects were randomly assigned to a treatment sequence in Study A. 42 subjects were included in the PK analyses. 45 subjects completed the study and 3 subjects were excluded because they experienced emesis within 12 hours of receiving Remoxy whole. The majority of subjects were white (56.3%) and male (58.3%), and the mean age was 28.1 years (range 18–44 y).

Key PK parameters for oxycodone from Remoxy dissolved in the buccal cavity compared with the oral solution are summarized in Table 2.

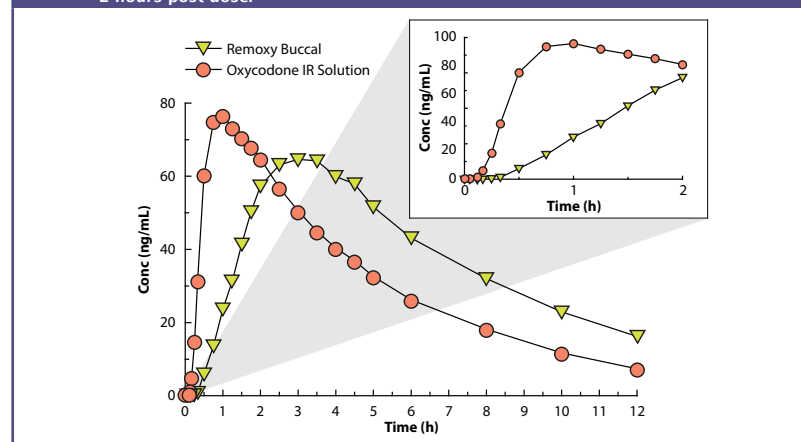
Mean estimates of C_{max} and early partial AUC values for Remoxy dissolved in the buccal cavity were lower compared with the oxycodone oral solution, while estimates of T_{max} were greater. Total exposure (AUC_{last}) was higher after dissolution in the buccal cavity.

The plasma concentration–time profile for Remoxy dissolved in the buccal cavity was associated with a broader peak that occurred at a significantly later time point compared with the oxycodone oral solution indicating no dose dumping occurred (Figure 4).

Differences in T_{max} between Remoxy whole and dissolved in the buccal cavity and between Remoxy dissolved in the buccal cavity and oxycodone oral solution were statistically significant ($P < 0.0001$).

The rate and extent of oxycodone absorption was increased after Remoxy was dissolved in the buccal cavity relative to Remoxy taken whole.

Figure 4. Study A: Mean plasma concentration–time profiles. The inset graph represents the first 2 hours post dose.



Sequence	Treatment Period 1	Treatment Period 2	Treatment Period 3
A (n=8 per study)	Remoxy 40 mg capsule (whole), fed	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed	2 mL oxycodone IR oral solution,* fasted
B (n=8 per study)	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed	2 mL oxycodone IR oral solution,* fasted	Remoxy 40 mg capsule (whole), fed
C (n=8 per study)	2 mL oxycodone IR oral solution,* fasted	Remoxy 40 mg capsule (whole), fed	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed
D (n=8 per study)	Remoxy 40 mg capsule (whole), fed	2 mL oxycodone IR oral solution,* fasted	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed
E (n=8 per study)	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed	Remoxy 40 mg capsule (whole), fed	2 mL oxycodone IR oral solution,* fasted
F (n=8 per study)	2 mL oxycodone IR oral solution,* fasted	Remoxy 40 mg capsule, fed Study A: dissolved in buccal cavity Study B: chewed	Remoxy 40 mg capsule (whole), fed

Table 2. Summary of Key Oxycodone PK Parameters

Study Description	Treatment	C_{max}^{\dagger} ng/mL	AUC_{0-2}^{\dagger} h·ng/mL	Parameter, Mean (SD)				
				AUC_{0-4}^{\dagger} h·ng/mL	AUC_{0-8}^{\dagger} h·ng/mL	AUC_{last}^{\dagger} h·ng/mL	T_{max} h	$T_{1/2}^{\ddagger}$ h
Study A: Effects of buccal absorption	Remoxy buccal	71.1 (14.2)	48.44 (22.49)	173.7 (44.46)	277.9 (56.78)	596.2 (177.2)	2.89 (0.79)	7.47 (1.42)
	Oxycodone oral solution	86.7 (30.8)	116.8 (31.32)	219.2 (52.46)	434.1 (148.4)	434.1 (148.4)	1.15 (0.62)	7.00 (0.85)
	<i>P</i> -value [§]	<0.0001	<0.0001	<0.0001	0.5171	<0.0001	<0.0001	n/a [¶]
Study B: Effects of rigorous chewing	Remoxy chewed	82.3 (16.7)	64.09 (27.94)	211.5 (50.92)	325.9 (65.08)	596.8 (134.4)	2.67 (0.78)	7.00 (1.11)
	Oxycodone oral solution	102 (33.4)	138.8 (40.12)	250.3 (60.09)	317.8 (73.71)	455.8 (113.6)	1.07 (0.46)	7.05 [¶]
	<i>P</i> -value [§]	<0.0001	<0.0001	<0.0001	0.1861	<0.0001	<0.0001	n/a [¶]

[†]*P*-value for the difference in the treatment estimates based on the natural log-transformed systemic exposure parameters.

[‡] $T_{1/2}$ could not be calculated for all subjects.

[¶]Data were available for 1 evaluable subject.

Study B: Effects Following Rigorous Chewing

A total of 48 subjects were randomly assigned to a treatment sequence in Study B.

44 subjects completed all 3 treatment sequences and were included in the PK analysis; 4 subjects withdrew prematurely from the study due to AEs (vomiting, 2; nausea and vomiting, 1; dizziness, 1). Most of the subjects were white (58.3%) and male (60.4%), and the mean age was 28.5 years (range 18–45 y).

Key PK parameters for oxycodone from Remoxy chewed compared with the oral solution are summarized in Table 2.

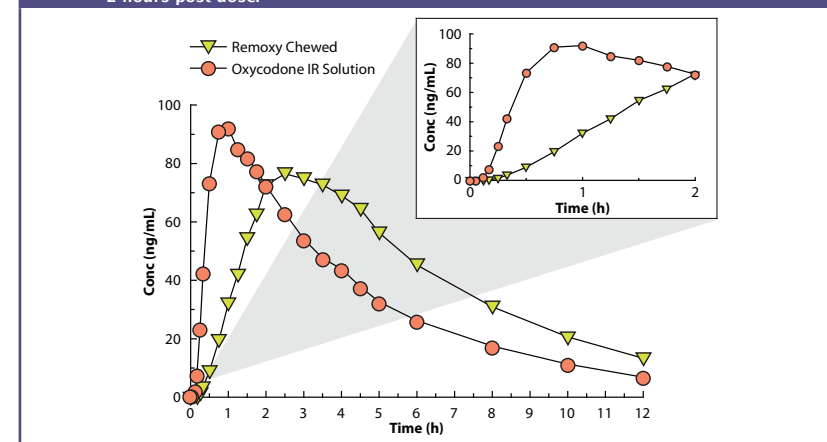
Mean estimates of C_{max} and early partial AUC values for Remoxy chewed were lower compared with oxycodone oral solution, while estimates of T_{max} were greater. Total exposure (AUC_{last}) was higher after rigorous chewing.

The plasma concentration–time profile for Remoxy chewed was associated with a broader peak that occurred at a significantly later time point compared with oxycodone oral solution indicating no dose dumping (Figure 5).

Differences in T_{max} were significant between Remoxy whole and chewed and between Remoxy chewed and oxycodone oral solution ($P < 0.0001$).

The rate and extent of absorption of oxycodone increased after Remoxy was chewed compared with Remoxy taken whole.

Figure 5. Study B: Mean plasma concentration–time profiles. The inset graph represents the first 2 hours post dose.



Safety

There were no deaths or serious AEs reported in either study. No clinically meaningful changes were observed for any laboratory values, vital signs, physical examination findings, or ECG readings.

In Study A, treatment–emergent AEs were reported by 34.0%, 26.7%, and 28.9% of subjects receiving Remoxy whole, Remoxy dissolved in the buccal cavity, and oxycodone oral solution.

The most common treatment–emergent AEs (reported in >5% of subjects during any treatment period) included headache, abdominal pain, nausea, dizziness, diarrhea, and vomiting.

In Study B, treatment–emergent AEs were reported by 37.8%, 34.8%, and 32.6% of subjects receiving Remoxy whole, Remoxy chewed, and oxycodone oral solution.

Frequently reported (>5% of subjects during any treatment period) treatment–emergent AEs were dizziness, headache, constipation, and nausea.

Conclusions

Data from 2 phase I single dose studies indicate that common forms of physical manipulation to defeat the rate–controlling characteristics of the Remoxy formulation were not successful.

Administration of Remoxy dissolved in the buccal cavity or rigorously chewed did not result in dose dumping, as evidenced by the lack of immediate sharp peaks in oxycodone plasma concentrations.

Although these methods of physical manipulation led to an increase in the rate of oxycodone absorption relative to Remoxy administered whole, there was still a significant delay in T_{max} , lower C_{max} , and lower early partial AUCs relative to the oral oxycodone solution.

References

- National Center for Health Statistics. Health, United States, 2006 with chartbook on trends in the health of Americans. NCHS. Available at: www.cdc.gov/nchs/data/atus/atus06.pdf.
- Gallagher RM and Rosenthal LJ. *Arch Phys Med Rehabil*. 2008;89(3 Suppl 1):S77–82.
- American Pain Society and Janssen Pharmaceutica. Chronic Pain in America: Roadblocks To Relief: a study conducted by Roper Starch Worldwide for American Academy of Pain Medicine. Available at: http://www.ampainoc.org/links/roadblocks_conclude_road.htm. Accessed November 8, 2010.
- Brennan MJ and Stanos S. *PM R*. 2010;2(6):544–558.
- Kroenke K, et al. *Gen Hosp Psychiatry*. 2009;31(3):206–219.
- Zorba Paster R. *Expert Opin Pharmacother*. 2010;11(11):1823–1833.
- Chou R, et al. *J Pain*. 2009;10(2):113–130.
- Phillips DM. *JAMA*. 2000;284(4):428–429.
- Manchikanti L, et al. *Pain Physician*. 2010;13(5):401–435.
- Martins SS, et al. *Drug Alcohol Depend*. 2009;99(1–3):58–67.
- Meyer RJ and Hussain AS. Awareness Topic: Mitigating the risks of ethanol induced dose dumping from oral sustained/controlled release dosage forms. Available at: http://www.fda.gov/ohrtm/dockets/ac/05/briefing/2005-418781_01_08-Alcohol-Induced.pdf. Accessed February 25, 2011.
- Zamlot M, et al. *J Appl Res*. 2010;10(3):88–96.

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