



ORADUR™

Oral Delivery Technology

ORADUR technology is unique for its dual performance attributes of providing controlled drug delivery for both water soluble and water insoluble drugs and abuse resistance for those drugs that are abusable. Abuse resistance is especially desirable for opioids, stimulants, sedatives and antidepressants. ORADUR technology has a number of built-in mechanisms to resist abuse by crushing and drug extraction, which are usually the first steps that lead to drug abuse via snorting, ingestion and/or injection.

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ORADUR™ Oral Delivery Technology

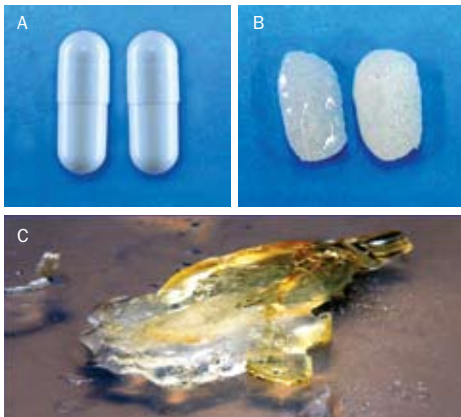
ORADUR technology has been deployed in the development of a number of opioids including oxycodone (Remoxy®: NDA filed for the treatment of patients with moderate to severe chronic pain), and two other undisclosed opioids as well as stimulants for the treatment of ADHD that are in development.

Shown below are anti-abuse results comparing Remoxy to OxyContin® based on cross-over clinical studies (n=10) performed with healthy human volunteers by Pain Therapeutics, Inc.. Both dosage forms were pulverized and consumed with either water or high proof alcohol, and blood levels of oxycodone were monitored. The AUC results for Remoxy (ORADUR-Oxycodone) were statistically significantly lower than those corresponding to OxyContin (p<0.05) at the time points when abusers expect to get high (Table 1).

TABLE 1

	Remoxy®		OxyContin®	
	AUC (hr*ng/ml)		AUC (hr*ng/ml)	
	Water	Alcohol	Water	Alcohol
60 Minutes	3.2	2.4	12.2	11.4
120 Minutes	8.0	8.4	29.5	26.3

The photos below demonstrate the dissolution of ORADUR capsules (A), yielding a rate-controlling matrix (B), and the crush and freeze fracture resistance of ORADUR capsules (C).

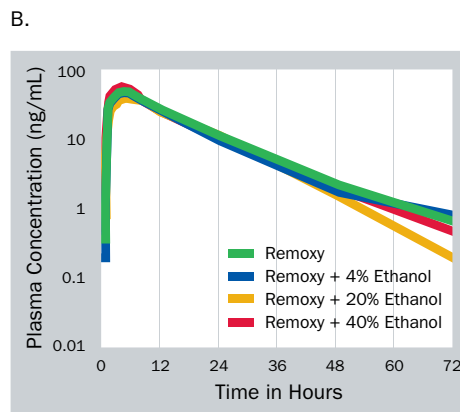
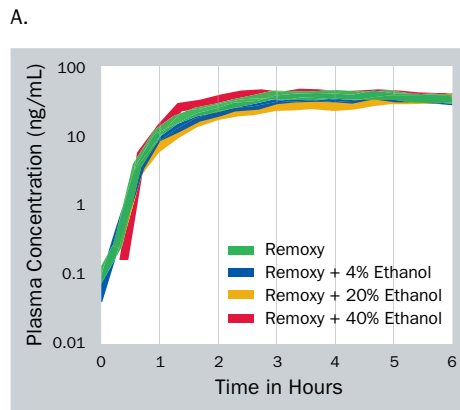


An additional robust clinical Phase I study in healthy volunteers (n = 37) assessed the effects of co-ingestion of alcohol on Remoxy. As can be seen in Figure 1, the shape of the plasma concentration time curve was not affected by the co-ingestion of Remoxy with ethanol and showed a typical controlled release profile for all treatments. Oxycodone C_{max} after Remoxy was

45.3 ng/ml with water alone, versus 45.0 ng/ml with 4% ethanol, 39.0 ng/ml with 20% ethanol, and 49.7 ng/ml with 40% ethanol.

The lack of dose-dumping prevents the quick, powerful euphoric high sought by recreational drug abusers. These data suggest Remoxy represents a safer alternative to current formulations of controlled-release oxycodone.

FIGURE 1. Mean Plasma Oxycodone Concentrations through 6 hr. Post-Dosing (A) and 72 hr. Post-Dosing (B)



ORADUR technology can be used to develop formulations for both abused and non-abused drugs in oral capsule forms. Upon ingestion, the capsule shell dissolves and the ORADUR drug gel in the gastric environment forms a rate controlling matrix. Desired drug release kinetics can be achieved via formulation engineering.

The ORADUR technology is capable of providing controlled delivery of water soluble and insoluble drugs as well as salt forms of drugs and non-ionizable drugs as well.

The ORADUR technology is flexible, enabling a range of pharmacokinetic performance possibilities – from first order to near zero-order release. Figures 2 and 3 illustrate flexible release kinetics from the ORADUR systems in comparison to commercial products containing an ADHD drug and an opioid, respectively.

FIGURE 2. ORADUR ADHD

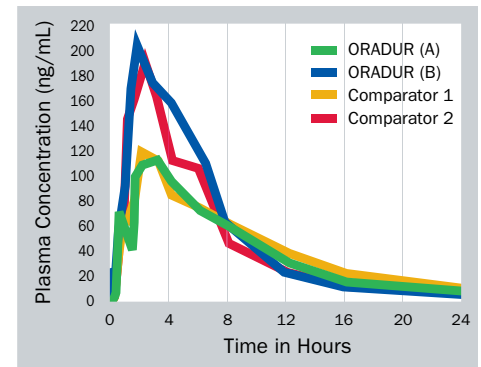
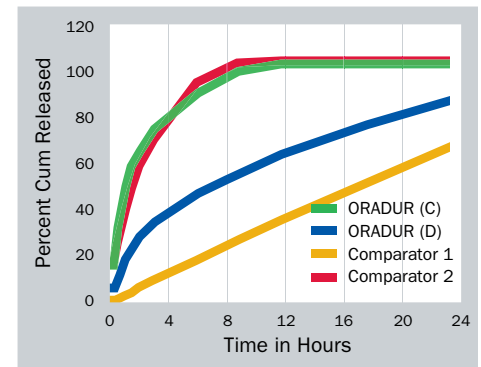


FIGURE 3. ORADUR Opioid



In addition to the performance attributes described earlier for the delivery of both water-soluble and poorly water-soluble drugs, ORADUR technology offers the following advantages over other oral drug delivery platforms:

- Tamper resistant capsule dosage form
- High drug loading
- Flexible formulation for drug solution or suspension
- Zero-order or near zero-order drug delivery kinetics
- Utilization of standard encapsulation process for oral capsule manufacturing
- Once-a-day or twice-a-day oral dosage form
- All inactive pharmaceutical ingredients are either compendial or GRAS listed or supported by long term preclinical toxicological data