

DURECT CORPORATION

ORADUR™ Controlled Oral Delivery Technology



Overview

The 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. The abuse resistance is especially desirable for opioids, stimulants, sedatives and antidepressants. The 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.

DURECT welcomes your inquiries on product feasibility or development opportunities for your drug products that could benefit from our advanced drug delivery technologies.

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The photo below demonstrates the crush and freeze fracture resistance of ORADUR capsules.



ORADUR Crush and Freeze Fracture Resistant

The ORADUR technology has been deployed in the development of a number of opioids including oxycodone (Remoxy™: completed Phase III clinical trials for the treatment of patients with moderate to severe chronic pain) and a second undisclosed opioid that has successfully completed Phase I studies.

Shown below are anti-abuse results comparing Remoxy to OxyContin®, based on the cross-over clinical studies (n=10) performed with healthy human volunteers by Pain Therapeutics. 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.

Remoxy Clinical Data

	Remoxy™ AUC (hr*ng/ml)		OxyContin® AUC (hr*ng/ml)	
	Water	Alcohol	Water	Alcohol
60 Minutes	3.20	2.40	12.2	11.4
120 Minutes	8.00	8.40	29.5	26.3

The ORADUR technology can be used to develop formulations for both abused and non abused drugs in oral capsule forms. On ingestion, the ORADUR System controls the drug release kinetics and subsequently yields the desirable pharmacokinetic profiles. The figure below (Figure 1) illustrates zero-order drug release from an ORADUR controlled release system, in this case formulated for a water-soluble opioid salt.

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 figure below (Figure 2) illustrates controlled drug release kinetics from an ORADUR controlled release system, in this case formulated for the base form of an opioid.

Figure 1.

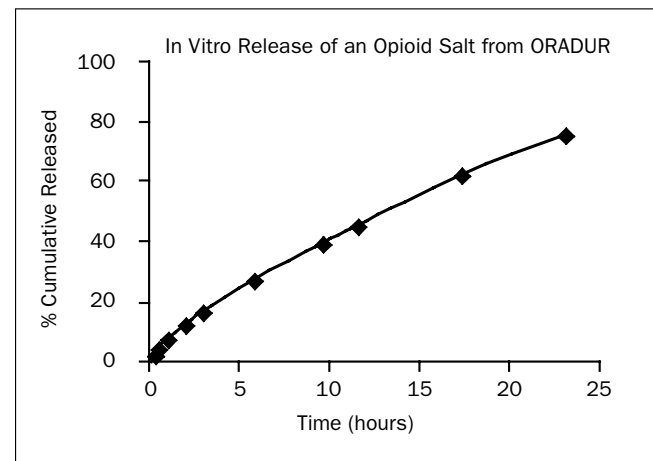
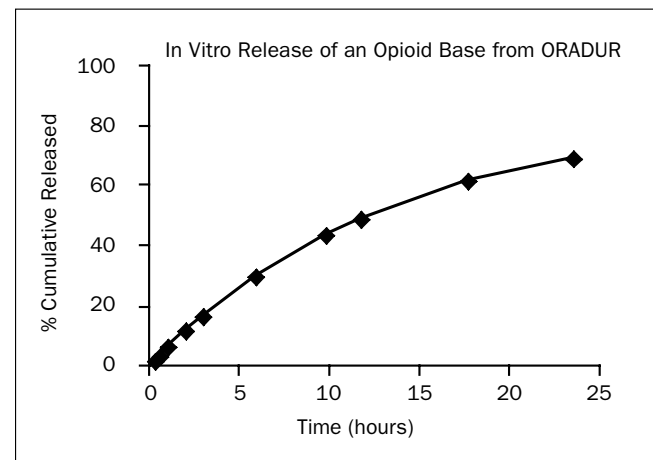
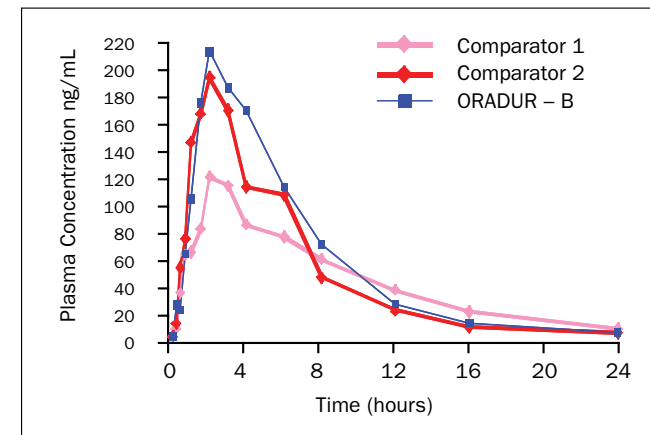
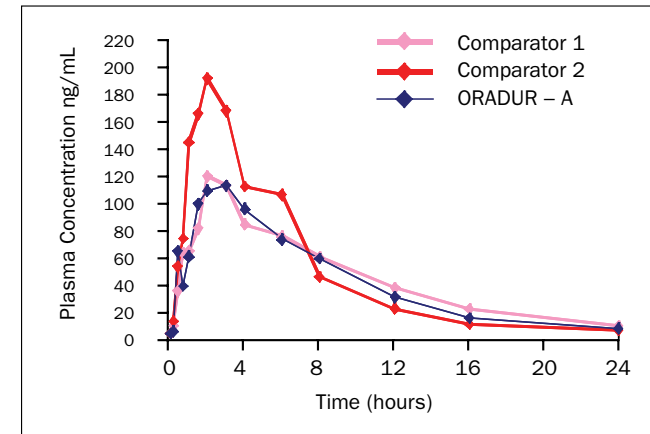


Figure 2.



The ORADUR platform is flexible, enabling a range of pharmacokinetic performance possibilities – from 1st order to near zero-order release. Figure 3 illustrates ORADUR's flexible release kinetics in comparison to two commercial products with the same active pharmaceutical ingredient.

Figure 3.



In December 2002, the Company entered into an exclusive agreement with Pain Therapeutics to develop and commercialize on a worldwide basis oral sustained release, abuse deterrent opioid products incorporating four specified opioid drugs, formulated using the ORADUR technology. In November 2005, Pain Therapeutics sublicensed their commercialization rights in the licensed ORADUR-based opioid products to King Pharmaceuticals. The first product being developed under the Durect/king/Pain Therapeutics collaboration is Remoxy, a novel long-acting oral formulation of the opioid oxycodone targeted to treat chronic pain while decreasing the potential for oxycodone abuse.

In December 2007, Pain Therapeutics and King Pharmaceuticals reported that the pivotal Phase III trial for Remoxy had successfully met its primary endpoint (p<0.01) that was prospectively defined by the FDA during the Special Protocol Assessment process. This pivotal Phase III randomized, double-blinded, placebo-controlled, multi-center study was designed to evaluate the analgesic efficacy of twice-daily Remoxy versus placebo over a 12-week treatment period. The study randomized 412 male and female patients, all of whom were diagnosed with osteoarthritis of the knee or hip. The primary endpoint was defined as mean decrease in pain intensity scores between Remoxy and placebo during the 12-week treatment period. Top-line data indicates that the study achieved a statistically significant result in its primary endpoint (p<0.01). In addition, the study achieved statistically significant results in secondary endpoints such as Quality of Analgesia (p<0.01) and Global Assessment (p<0.01). No drug-related safety issues were noted in this study.

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

- Tamper evident 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

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