OraGuard™ Abuse Deterrent Alcohol Resistant Technology

Protect your extended release formulations with OraGuard™ Abuse Deterrent and Alcohol Resistant drug delivery technology from CIMA

Dose dumping is a well known concern for opioid products. However, the FDA is now considering ethanol dose dumping to be a "critical failure mode" for extended release products.[1] Ethanol dose dumping is an issue for all extended release products, not just opiates. Unintentional dose dumping can occur if a patient consumes alcohol while taking a medication. This could cause the entire dose to be released resulting in increased toxicity / side effects or in loss of extended therapeutic benefit. CIMA's OraGuard Abuse Deterrent and Alcohol Resistant drug delivery technology reduces the risk of both intentional and unintentional dose dumping.

Proof of Concept: OraGuard™ Abuse Deterrent and Alcohol Resistant Opioid Products

Extended release opioid products have faced two major challenges in the past decade:
1) The rampant and escalating abuse of drugs
2) The susceptibility to alcohol induced dose dumping.

According to the US Drug Abuse Warning Network (DAWN) report, the number of emergency visits related to non-medical use of opioids nearly tripled between 1995 and 2002 (The DAWN Report: Narcotic Analgesics, 2002 Update, 2004). Extended release opioid products are more attractive targets for abuse owing to their increased drug loads and the potential for higher euphoric effect if the release extension components are compromised. In 2005, the FDA requested and Purdue Pharma agreed to the voluntary withdrawal of Palladone® (hydromorphone hydrochloride extended release capsules) from the US market citing potentially fatal adverse reactions when the product is taken together with alcohol.[2] Other extended release opioid products' labels have included a special warning about increased plasma levels if the product is co-ingested with alcohol.

Accordingly, it is essential for drug manufacturers to develop tamper deterrent extended release technology that can also provide protection against alcohol induced dose dumping.

CIMA OraGuard™ Abuse Deterrent and Alcohol Resistant Technology

CIMA has developed the OraGuard technology an abuse deterrent and alcohol resistant extended release formulation platform that is applicable to opioids as well as other drugs. The formulation design is primarily focused on maximizing the following:

1. Resistance against mechanical crushing (a typical abuser's approach for I.V. injection, snorting or oral ingestion)
2. Resistance against small volume extraction with aqueous or organic solvent
3. Protection against unintentional dose dumping with alcohol

As part of product optimization, the developed prototypes are subjected to a battery of tests designed to simulate several extraction techniques used by abusers.

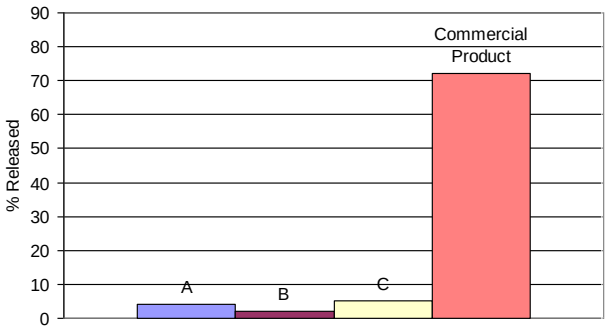
[1] AAPS Workshop on the Role of Dissolution in QbD and Drug Product Life Cycle. Date and Location: April 28-30, 2008, in Arlington, VA. Presentation Eric Duffy, Ph.D.
U.S. Food and Drug Administration Alcohol Effect on Extended Release Solid Oral Dosage Forms

[2] FDA News P05-42 July 13, 2005

CIMA
Your drug, delivered

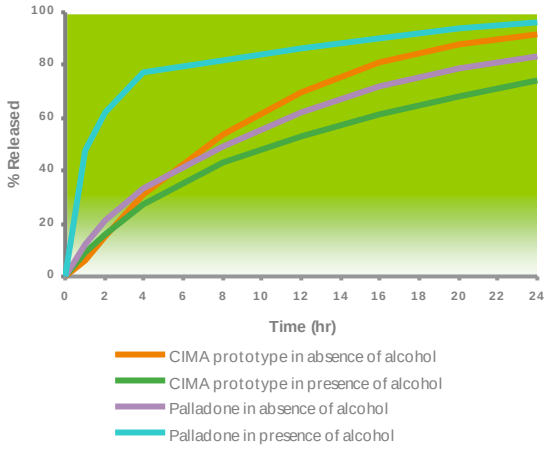
The Figure below presents the % oxycodone HCl released from three of CIMA's OraGuard Abuse Deterrent prototypes (designated as A, B and C) compared to a commercially available extended release oxycodone product after a "simulated I.V. tampering" test. In this test, the prototypes were crushed with a pill crusher/splitter followed by extraction by boiling in water. All the tested prototypes released 5% or less of their oxycodone content compared to more than 70% from the commercial product.

Simulated IV Tampering



The following figure illustrates hydromorphone HCl release from CIMA's OraGuard Abuse Deterrent and Alcohol Resistant prototype using "simulated alcohol dose dumping" testing. In this test, drug release is measured in the presence and absence of 40% alcohol using USP dissolution test methodology. As seen in the figure alcohol has no effect on the amount of drug released from the CIMA prototypes after up to 6 hours of exposure, which is longer than the expected alcohol exposure *in vivo*. The Palladone data was interpolated and added to the graph from the reference.[3]

Simulated Alcohol Dose Dumping



CIMA 's patent pending OraGuard Abuse Deterrent and Alcohol Resistant Technology provides the following benefits:

- Universally adaptable to varieties of molecules
- Use compendial excipients
- Uses common solid dosage forms manufacturing processes that have already been successfully scaled up to commercial equipment
- Provide resistance against different abusers' tampering methods including crushing, chewing, small volume aqueous or organic extraction as well as protection against alcohol induced dose dumping
- Provides resistance to inadvertent alcohol induced dose dumping

If you are interested in learning more about our Technology, please contact John C. Nagel, MBA, Senior Director of Business Development at 763-488-4975 john.nagel@cimalabs.com, or Jeremy G. Webber, M.S., Alliance & Business Development Manager at 763-488-4784 jeremy.webber@cimalabs.com

[3] Gupta, S.K. Development and Regulatory Challenges in Osmotic Technology. Presented in the CRS and AAPS Workshop titled: Development and Regulatory Challenges for Controlled Release Formulations, San Diego, CA, Nov 9-10, 2007.

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