

A New Formulation of
OxyContin[®] (oxycodone HCl controlled-release) Tablets

Presentation To
Joint Meeting of the
Anesthetic and Life Support Drugs Advisory Committee
and
Drug Safety and Risk Management Advisory Committee
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Speakers

J. David Haddox, DDS, MD

Vice President, Risk Management & Health Policy
Purdue Pharma L.P.

Jack E. Henningfield, PhD

Vice President, Research and Health Policy, Pinney Associates

Professor, Adjunct, Department of Psychiatry and Behavioral Sciences,
The Johns Hopkins University School of Medicine

Formerly Chief, Clinical Pharmacology,
National Institute on Drug Abuse

Richard Mannion, PhD

Senior Director, Pharmaceuticals
Purdue Pharma L.P.

Expert

Edward J. Cone, PhD

Scientific Consultant, Pinney Associates

Associate Professor, Adjunct, Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine

Formerly Chief, Chemistry and Drug Metabolism,
National Institute on Drug Abuse

Treatment of Persistent Pain

- Identify the underlying cause of pain and correct if possible
- Identify address co-morbidities (impaired ability to perform activities of daily living, mood disorder, etc.)
- Non-pharmacological approaches
 - Physical / Occupational therapy
 - Psychological therapies
- Pharmacological approaches
 - NSAIDs
 - Adjuvant analgesics (antidepressants, anticonvulsants)
 - Opioids

Opioid Analgesic Products

- Opioid analgesics are available in two subclasses:
 - Immediate-release
 - Combined with another non-opioid analgesic, such as aspirin, acetaminophen or ibuprofen
 - Single-entity
 - Long-acting opioid analgesics (single-entity)
 - Inherently long-acting
 - levorphanol, methadone
 - Pharmaceutically long-acting
 - fentanyl, oxycodone, oxymorphone, morphine

Recognition of the Importance of Long-Acting Opioid Analgesics in Persistent, Non-cancer Pain

- AMA – Dickinson BD, Altman RD, Nielsen NH, Williams MA, for the Council on Scientific Affairs. Use of opioids to treat chronic, noncancer pain. *West J Med* 2000;172:107-115.
- AGS Panel Persistent Pain in Older Persons. The management of persistent pain in older persons. *J Am Geriatr Soc* 2002;50(Suppl 6):S205-24.
- Veterans Health Administration, Department of Defense. VA/DoD clinical practice guideline for the management of opioid therapy for chronic pain. Washington (DC): Veterans Health Administration, Department of Defense; 2003 Mar.

Overview

Research Objectives – New Formulation

- The objectives of our research were to develop a new formulation of OxyContin that would:
 - Maintain the clinical benefits to patients, and
 - Reduce its desirability to abusers.

Overview

New Formulation

- Purdue has developed a formulation that:
 - Has met the statistical standards for bioequivalence to the original formulation, and
 - Through *in-vitro* testing, compared to the original formulation, introduces demonstrable barriers to
 - physical manipulation, and
 - extraction of oxycodone.

Overview

NDA Filing

- Purdue has submitted an NDA for the 10 - 40 mg tablet strengths of the new formulation.
- Purdue is completing an sNDA for the 60 and 80 mg tablets of the new formulation and will be prepared to submit it as soon as possible.
- Purdue intended to have all tablet strengths approved at the same time. However, development of 60mg and 80mg formulations with the required product attributes took longer.
- If approved, the potential public health benefits of the newly formulated lower tablet strengths (that comprise ~ 83% of current prescriptions for controlled-release oxycodone products), warrant their introduction prior to approval of the 60 and 80 mg tablets.

Overview

Abuse of OxyContin

- The 12-hour dose of oxycodone in each tablet that contributes to OxyContin being an effective pain reliever unfortunately also makes it a target of abusers.
- Abusers often crush, break or chew the tablets to destroy the controlled-release delivery system rendering a 12-hour controlled-release dose of oxycodone immediately available.
- Crushing the tablets results in a powder that can be readily swallowed, snorted or dissolved for injection.

Overview

Dangers of Tampering

- The dangers of tampering with the current controlled-release delivery system are great enough to warrant the following statement in the boxed warning for OxyContin:

“TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.”

Overview

Meaningful Incremental Improvement

- The new formulation provides an incremental and meaningful improvement in creating impediments to some forms of compromising OxyContin's controlled-release delivery system.
- The *in-vitro* studies demonstrate that the reformulated tablet would be substantially more difficult than the original formulation to crush or inject and suggest that it would be more difficult to chew or snort.
- An epidemiological study to assess the correlation between *in-vitro* tamper-testing results and any abuse resistance will be conducted following introduction of the new formulation.

Overview

Effective Communication Regarding the New Formulation

- We share FDA's concern that information about the new formulation be clear and accurate
- Already seeing misconceptions and confusion
- Our approach:
 - Add clear and accurate information about the *in vitro* tests to the Description section of the Full Prescribing Information (FPI)
 - Make no claims of abuse reduction until proven

Overview

Effective Communication Re: New Formulation

- Providing *in vitro* information in the FPI will:
 - Reduce misconceptions and confusion
 - Including, rather than excluding, accurate information provides clarity
 - Maintain FPI as the definitive source of product information for healthcare professionals
 - Provide uniform, approved language to facilitate clear, consistent communication about the medication

Overview

Claims of Abuse Resistance

- Purdue will make no claim that the new formulation reduces abuse until:
 - We submit results from an appropriately-designed study,
 - and
 - FDA approves the language of any claims based upon those results

Overview

10 - 40 mg Tablets

- The reformulated 10 - 40 mg tablets would be available before the reformulated 60 and 80 mg tablets.
- The sooner any tamper-resistant tablet strengths are available, the sooner there may be a significant public health benefit.

Overview

FPI for 10 - 40 mg Tablets

- FDA is concerned that the availability of the newly formulated 10 – 40 mg tablets before the 60 – 80 mg tablets are available could lead prescribers and patients to mistakenly assume that all strengths have the same features.
- Our approach:
 - Include in the FPI precise description of the *in vitro* tests, making clear that it applies to only the 10 - 40 mg tablets (until 60-80 mg formulations are approved)
 - Including precise information in the FPI is better than providing no information, which itself can lead to misconceptions and confusion.

Overview Summary

- Adding appropriate and precise language in the FPI regarding the *in-vitro* studies of the new formulation as each tablet strength is approved would provide health care professionals accurate information about the medicine and minimize misconceptions.

Proposed Label Addition

“During *in vitro* testing, tablets were manipulated to recover oxycodone by crushing, milling, heating, and crushing followed by boiling and filtering fragments, and crushing followed by extracting with various solvents, including ethanol. The tablets either did not break or broke into fragments that retained some of the controlled-release characteristics. When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass.”

Proposed Label Addition

- This wording is consistent with our understanding of the discussions with FDA and meets the dual goals of;
 - not making claims for abuse resistance,
 - nor providing clear instructions on how to tamper with the product.
- The proposed FPI for the new formulation also includes the same:
 - boxed warning,
 - other warnings,
 - precautions, and
 - information on drug abuse as the current OxyContin FPI.

Label Addition Is Necessary

- Health care professionals should know that there is a difference between the new and original formulations and make their prescribing decisions based on full information.
- As with any product safety concern, health care professionals should be warned about potential issues and advised of the product characteristics that may affect those issues.
- In this case, adding appropriate language in the FPI regarding the tamper-resistant qualities of the new formulation would provide health care professionals accurate information about the medicine and minimize misconceptions.

RiskMAP for OxyContin[®] (New Formulation)

Risk Management Plan

for OxyContin[®] (Original Formulation)

- OxyContin Risk Management Plan initially submitted to FDA January, 2004
- Two subsequent versions:
 - May, 2007
 - February, 2008
 - Revised to conform to FDA's RiskMAP Guidance

GOALS of RiskMAP

for OxyContin[®] (New Formulation)

1. To minimize abuse of OxyContin
2. To minimize diversion of OxyContin
3. To minimize exposure to OxyContin among those under age 18

Our new RiskMAP:

- Incorporates the new formulation as a key RM tool
- Ensures accurate and clear information about the appropriate use of product (education)
- Evaluates the impact of the new formulation on OxyContin abuse (epidemiological study)

Epidemiological Study

Compare the prevalence of OxyContin abuse, by site, among enrollees to opioid treatment programs (OTP) before and after availability of the new formulation.

OTP Study: Ongoing, cross-sectional assessment of drug abuse behaviors in adults (≥ 18 years old) seeking admission to one of 68 OTPs for addiction to opioids

A secondary data analysis of the RADARS[®] System's Opioid Treatment Program (OTP) study.

Epidemiological Study

Primary objective: Assess impact of the availability of OTR on the proportion of OTP study participants reporting past month use of OxyContin “to get high.”

Design: “pre”- “post”

“*Pre*” period = 4 quarters prior to availability of
10 - 40 mg OTR Tablets;

“*Post*” period = 4 quarters following availability of all
strengths of OTR Tablets.

Unit of analysis: Opioid Treatment Program site

Epidemiological Study

- 1-page, self-administered questionnaire
- Conducted at point of intake to OTP
- Data are reported anonymously
- Participants receive
- Items assess:
 - Demographics
 - OTP site
 - Checklist of drugs used “to get high” in past month (heroin, OxyContin, and 13 other opioid analgesic products)
 - Primary drug of abuse before seeking admission to this OTP

Epidemiological Study Analysis Plan

- 1) Two-sample z-test will be used to test the null hypothesis that the proportion of study participants at each OTP site who report use of OxyContin within the past month “to get high” has stayed the same or increased in the “post” period versus the alternative hypothesis that the proportion has decreased.
- 2) P-values from each of these two-sample tests will be pooled according to Fisher’s rule for combining significance probabilities.
- 3) Analysis results will be declared statistically significant if the overall p-value is less than 0.025.

Conclusion

- The introduction of the new OxyContin formulation has potential for meaningful public health benefits
- The new formulation of OxyContin is intended to be every bit as effective for patients as the original, with a potential to reduce abuse
- The new formulation resists crushing and other common methods of tampering

Conclusion

- We hope this will translate into reduced abuse but agree with FDA that post -approval study is required to determine if this goal is achieved
- The new formulation will not eliminate abuse
- The inclusion in labeling of descriptive information will help clarify understanding and minimize misconceptions

Jack E. Henningfield, PhD

Vice President, Research and Health Policy,
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Professor, Adjunct, Department of Psychiatry and Behavioral
Sciences, The Johns Hopkins University School of Medicine

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Definitions

- **Tamper Resistance:** The performance of a drug product in bench testing designed to simulate methods of formulation compromise commonly employed by drug abusers.
- **Abuse Resistance:** The ability of a tamper-resistant drug product to present sufficient barriers to formulation compromise such that a meaningful decrease in one or more methods of abuse can be scientifically demonstrated following its availability.
- **Abuse Proof:** A term to describe a therapeutic drug product that can not be abused in any manner; a theoretical ideal that is not achievable presently

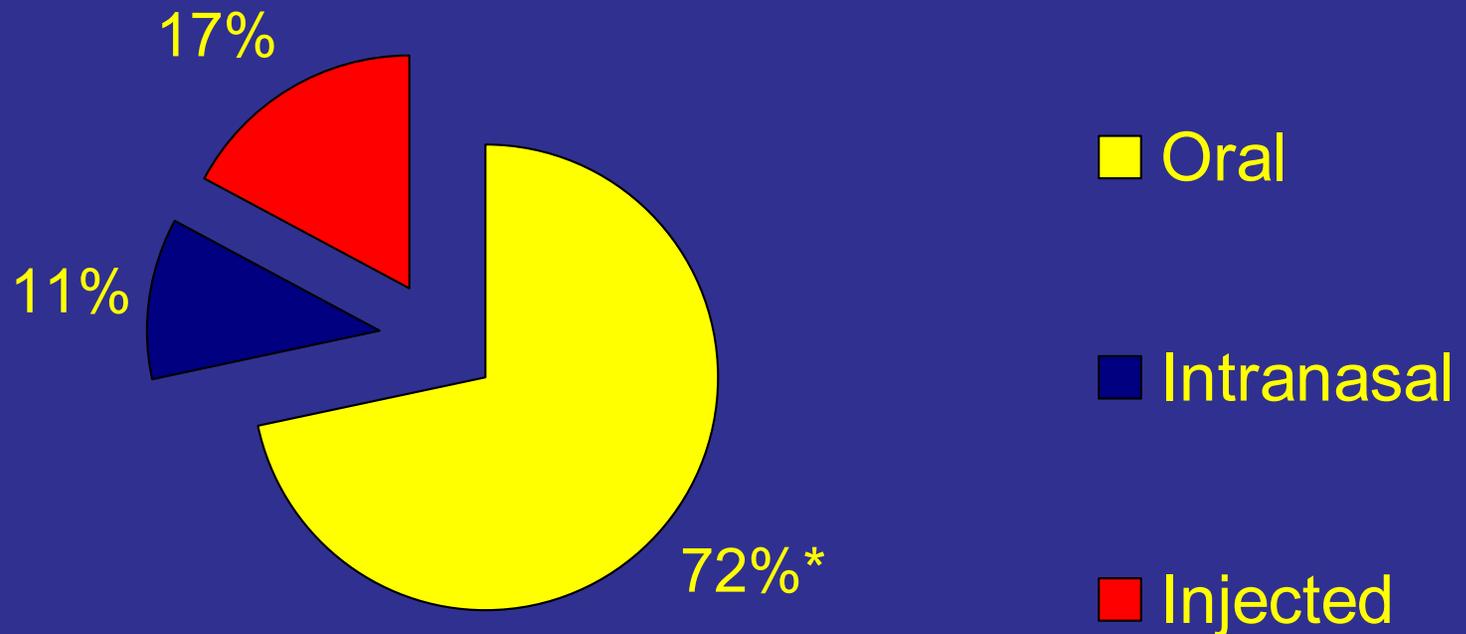
Past Month Nonmedical Use by Age

	Age Group (% Reporting Nonmedical Use)		
	12-17	18-25	26 or older
Pain Relievers	2.7	4.9	1.5
<i>OxyContin</i>	0.1	0.4	0.1
Tranquilizers	0.5	2.0	0.5
Stimulants	0.6	1.3	0.3
Sedatives	0.2	0.2	0.2

Routes of Abuse of OxyContin®

2001 – 2004

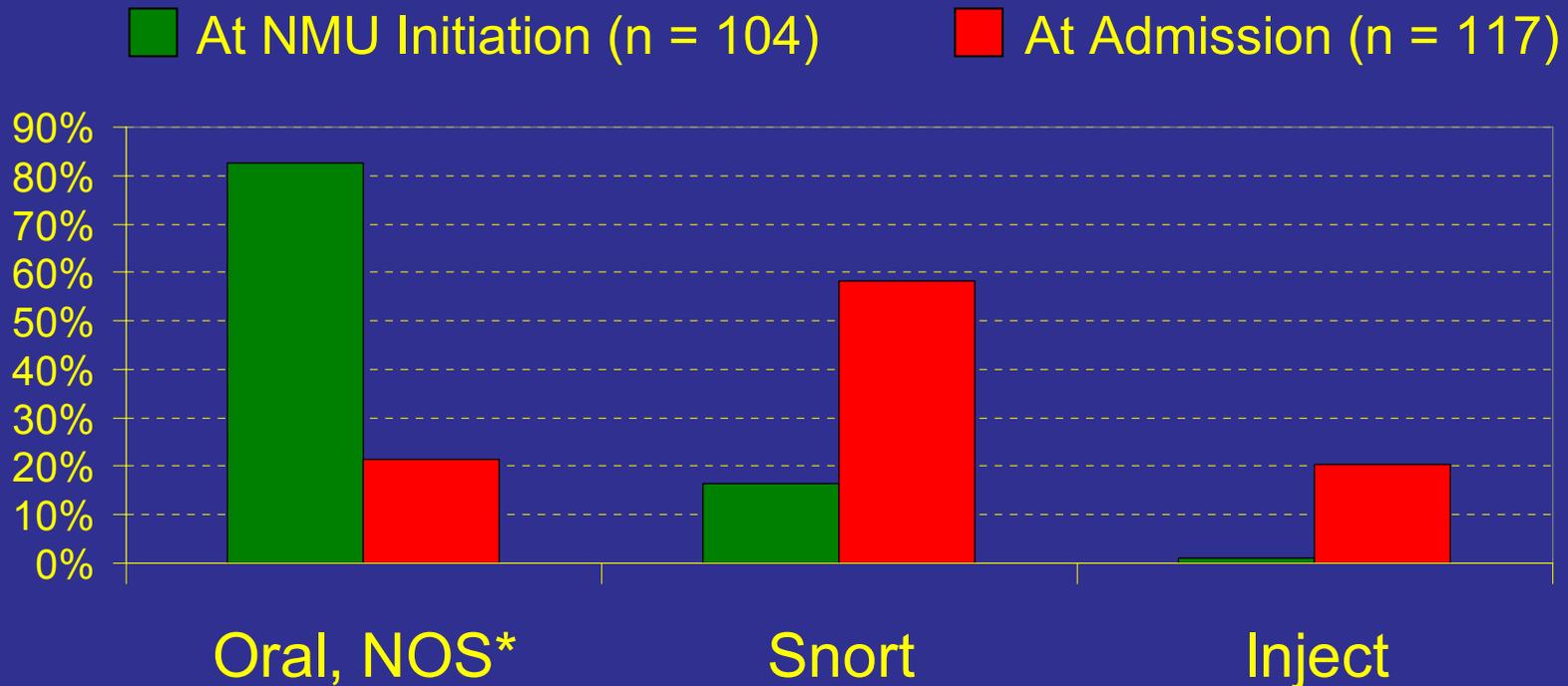
n = 1368 (of 27,816 total admissions)



*Unknown how many chewed or crushed.

Carise D, Dugosh KL, McLellan AT, et al. Prescription OxyContin Abuse Among Patients Entering Addiction Treatment. Am J Psychiatry 164: 1750 – 1756, 2007.

Routes of Abuse, OxyContin[®] KY Oct 2000 – Dec 2001



Hays L., Kirsh KL, Passik SD. Seeking drug treatment for Oxycontin abuse: A chart review of consecutive admissions to a substance abuse treatment facility in Kentucky. *J Natl Comp Cancer Network* 2003; 1(3):423-428.

*NOS = Not Otherwise Specified

Abuse of Opioid Analgesics

- Laboratory studies of animals and humans indicate that reinforcing effects are generally increased by:
 - Rapid onset of drug effects
 - High intensity of effects (~high brain levels)
 - Rapid offset of drug effects
- Intranasal and intravenous routes of self-administration of oxycodone, and many other drugs, meet these criteria.
- Additionally, intranasal and IV abuse are particularly dangerous methods of oxycodone administration because of the rapid achievement of high blood levels.

Implications for New OxyContin

- Laboratory studies of humans and animals indicate that intake and adverse effects can also be reduced when the effort or cost per dose is increased
 - The decreased intake is generally directly related to the increase in effort or cost
 - At high levels of effort requirement, self-administration efforts often cease (“break point”)
 - Animals and humans differ in the break points
- Taken together, these findings suggest that the impediments to tampering posed by the new formulation may reduce self-administration, however, real world experience will be necessary to confirm this

Proposed Label Addition

- FDA has discussed with Purdue its views concerning what the FPI should state concerning the tamper-resistant qualities of the new formulation.
- Based on these discussions, Purdue proposed an addition to the Description Section which has been provided in your background information from FDA.

Proposed Label Addition

“During *in vitro* testing, tablets were manipulated to recover oxycodone by crushing, milling, heating, and crushing followed by boiling and filtering fragments, and crushing followed by extracting with various solvents, including ethanol. The tablets either did not break or broke into fragments that retained some of the controlled-release characteristics. When in contact with aqueous media, the tablets or the fragments formed a gelatinous mass.”

New Formulation
OxyContin[®] Tablets
Development and Properties

Richard Mannion, PhD
Senior Director, Pharmaceuticals

May 5th, 2008

Challenges and Objectives in Developing a Tamper-Resistant Product

- Tamper-resistant characteristics
 - Resistant to physical crushing/milling
 - Resistant to chemical extraction
 - No accelerated dissolution in ethanol
- Characteristics for an effective product
 - Release the medication at the correct rate to be bioequivalent to original formulation
 - Robust process to enable commercial manufacture
 - Chemically and physically stable over time

Physical Appearance

New Formulation vs. Original Formulation 40 mg Tablets

New formulation



Original formulation

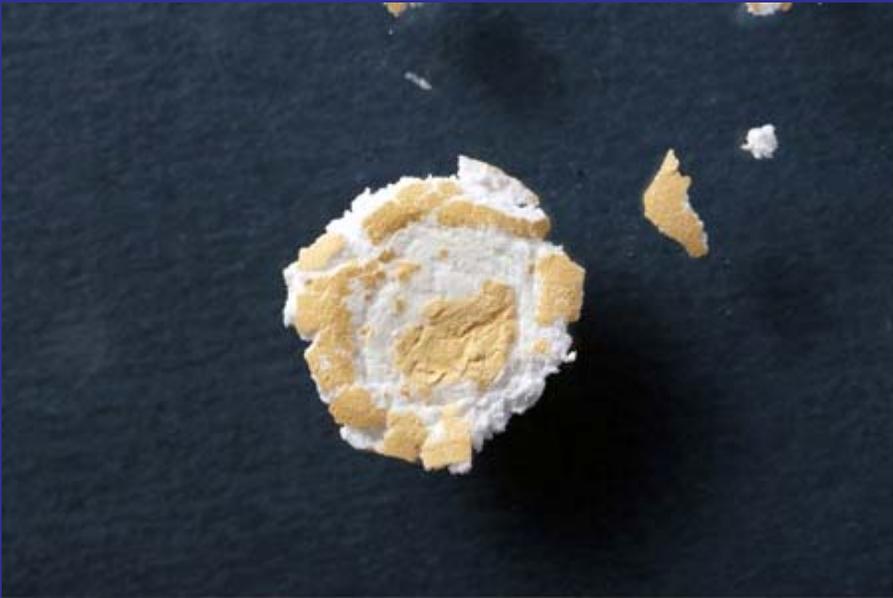


Development of Tamper-Resistant Properties

- Purdue developed and evaluated multiple technology platforms prior to selecting compositions containing a specific polymer
- This polymer, when subjected to novel manufacturing processing, makes the tablets difficult to break or crush
- If broken, tablet fragments retain some controlled-release properties
- On hydration of tablet fragments, the polymer becomes a viscous gel that inhibits extraction of the active ingredient for injection

Reformulated Tablets Resistant to Crushing

- Multiple strikes with a hammer deforms but does not crush reformulated tablets into powder



Crushing between Spoons

- Reformulation (left) cannot be crushed between spoons
- Original formulation (right) can be crushed between spoons

Reformulated (before)



Original (before)



Crushing between Spoons

- Reformulation (left) cannot be crushed between spoons
- Original formulation (right) can be crushed between spoons

Reformulated (after)



Original (after)



Background on Tamper-Testing Protocol

- No industry-wide standards for testing to assess tamper resistance properties
- Purdue has published and presented strategies for tamper testing
- The protocol used for the new formulation includes a series of internally-standardized tests
 - Submitted to FDA for review prior to NDA submission
 - Incorporated FDA input into protocol

Tamper –Testing Protocol

- Perform increasingly aggressive methods of tampering to simulate those used by abusers to defeat medications' controlled-release mechanism
- Physical Manipulation
 - Manual crushing or a mechanical mill followed by either a dissolution test or an extraction test
- Chemical Extraction
 - Simple – room temperature, readily available solvents
 - Moderate – room temperature, less readily available solvents
 - Advanced – higher temperature, longer duration, more toxic solvents (could need a secondary extraction)
- Simulated preparation for IV abuse

Manual Crushing Followed by Dissolution



Crushed New Formulation



Crushed Original Formulation

Product	% released
New Formulation 10-80mg	20 - 49%
Original 10-80mg	$\geq 91\%$

Simple Extraction

Manual crushing followed by short duration shaking extraction at room temperature

Product	% Released (range)				
	Simple solvent 1	Simple solvent 2	Simple solvent 3	Simple solvent 4	Simple solvent 5
New Formulation 10-80 mg (manually crushed)	8 - 51	5 - 40	11 - 54	0 - 6	6 - 50
Original Formulation 10-80 mg (manually crushed)	89 - 101	91 - 107	94 -102	12 - 79	89 - 99

Impact of Mechanical Mill – New Formulation Tablets

- Milling involves greater planning and effort.
 - Equipment and power source required

Milled New formulation – larger pieces



Crushed Original formulation – fine powder



Impact of Mechanical Mill Followed by Dissolution

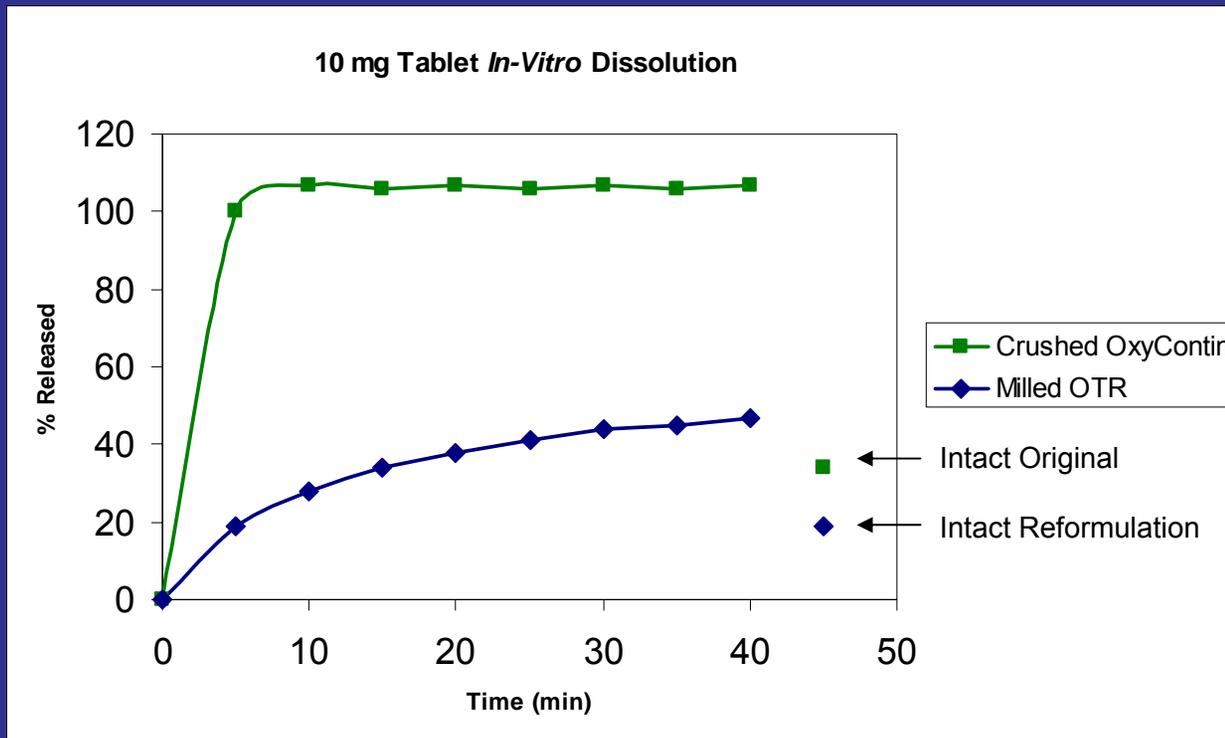
Product	% released after dissolution
New formulation 10-80mg (milled)	36 - 52%
Original formulation 10-80mg (crushed)	≥ 91%

Intact new formulation tablets released 18-20%

Intact original formulation released 31-43%

Physical Manipulation and Dissolution of New Formulation Tablets

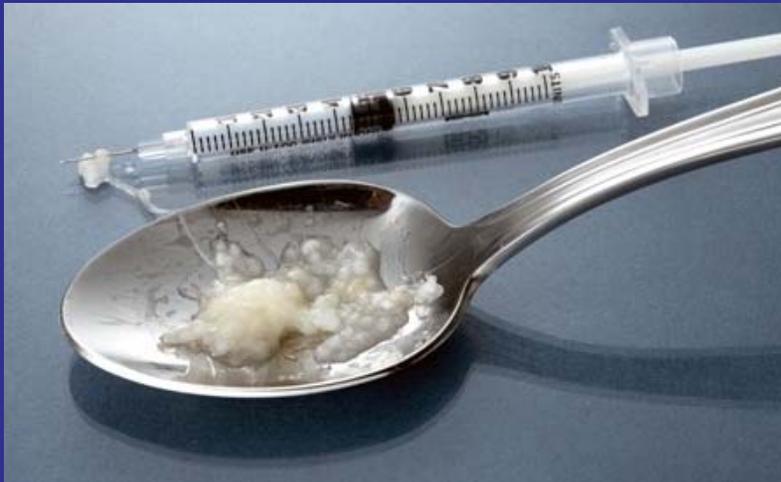
- Manually crushed original formulation releases 100% of active ingredient at 5 minutes
- Milled new formulation retains some controlled-release properties



Tampering for IV Abuse

- New formulation results in gelatinous material which cannot be drawn into a syringe for injection (the syringe is empty)

New formulation



Original formulation



Product	% recovered from insulin syringe
New formulation 10-80mg.	≤ 4%
Original formulation 10-80mg	49 - 58%

Thermal Extraction

- Milled new formulation and manually crushed original formulation added to solvent and boiled for a preset time.
- New formulation tablets released 21-48% less than corresponding strength of original formulation.

Moderate Extraction

Physically manipulated followed by short duration shaking extraction at room temperature

Product	% Released (range)		
	Medium Solvent 1	Medium Solvent 2	Medium Solvent 3
New formulation 10-80 mg (milled)	48-75	45 -71	14-27
Original formulation 10-80 mg (crushed)	96-101	94-98	16-53

Advanced Extraction

Physically manipulated followed by extended extraction time at room temperature

Product	% Released (range)				
	Simple Solvent 2	Medium Solvent 1	Medium Solvent 2	Complex Solvent 1	Complex Solvent 2
New formulation 10-80 mg (milled)	32 - 78	61 - 89	35 - 80	62 - 103	22 - 66
Original formulation 10-80 mg (crushed)	91 - 107	96 - 101	94 - 98	95 - 102	95 - 103

Product	% Released (range)				
	Simple Solvent 4	Medium Solvent 3	Complex Solvent 3	Complex Solvent 4	Complex Solvent 5
New formulation 10-80 mg (milled)	2 - 9	27 - 39	12 - 60	5 - 25	2 - 11
Original formulation 10-80 mg (crushed)	14 - 42	30 - 53	40 - 82	10 - 30	4 - 26

Advanced Extraction

Physically manipulated followed by extended extraction time at elevated temperature

Product	% Released (range)						
	Simple Solvent 2	Medium Solvent 1	Simple Solvent 4	Medium Solvent 2	Complex Solvent 2	Complex Solvent 1	Complex Solvent 4
New formulation 10-80 mg (milled)	34 - 68	53 - 78	0 - 7	57 - 70	21 - 74	51 - 78	9 - 39
Original formulation 10-80 mg (crushed)	91 - 107	96 - 101	19 - 38	94 - 98	95 - 103	95 - 102	16 - 37

Summary

- The *in vitro* testing was rigorous and extensive
 - simulated increasingly aggressive methods for defeating the controlled release mechanism

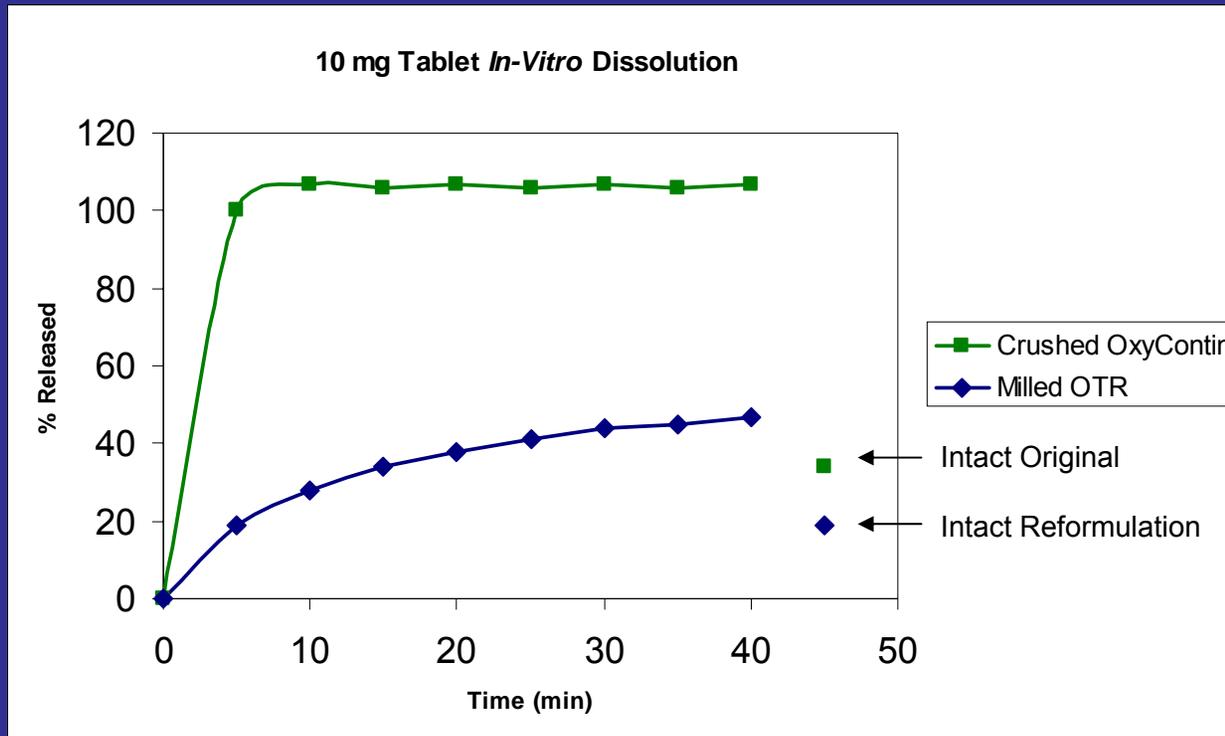
Summary

- The tablets are difficult to break



Summary

- If they break, they break into fragments which retain controlled-release characteristics.



Summary

- Gelatinous mass forms when tablets or fragments are in contact with aqueous media
- Active ingredient is difficult to extract

