Siegfried

Oxycodone,
A 100-year old Synthesis:
Continuous Flow *vs.* Batch Process

RSC Symposium –
Continuous Flow Technology
Geneva, June 16, 2011
Beat Weber

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- **Introduction**
- **Chemical Background**
- **Proposed Approach**
- **CFT Application (Feasibility)**
- **CFT Optimization**
- **Achievements**

Overview
Profile

- Globally focused
- Independent
- Listed on the Swiss Stock Exchange (SIX)
- Concentration on the development and manufacturing of active pharmaceutical ingredients (API) and intermediates, as well as drug products
- Total work force: approx. 700
- Annual sales CHF: approx. 314 mio

Overview
Past to present

1873 Pharmacist Samuel Benoni Siegfried founds a company with 12 employees as a supplier to pharmacies

1904 Conversion into a joint stock corporation

1937 Founding of Ganes Chemical Works, Inc. (NJ, USA)

1973 Quotation on the Swiss Stock Exchange (SWX) in Basel

1991 Focus on development and custom manufacturing

2001 Building of two core divisions: Siegfried and Sidroga

Overview
Our Vision

To be a world-class service partner in developing and manufacturing drug substances and drug products that improve human life.

Introduction
The pain treatment landscape

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Severity of pain

Longevity of pain		Mild	Moderate	Severe
Acute	**Description**	• Soft tissue injuries and mild headaches	• Most post-traumatic and postoperative pain, most migraines	• Burn pain and severe post-operative pain
	Treatment	• Non-prescription drugs (*e.g.*, acetaminophen, OTC NSAIDs)	• Mild opioids (*e.g.*, Tramadol) or prescription NSAIDs	• Immediate-release, stronger opioids (*e.g.*, Fentanyl)
Chronic	**Description**	• Arthritis, back, and some chronic headache pain	• Arthritis, back, cancer, neurologic, and headache pain	• Severe arthritis, back, cancer, neurologic, and headache pain
	Treatment	• Non-prescription drugs (*e.g.*, acetaminophen and OTC NSAIDs)	• Opioid/nonopioid combinations and mild opioids (*e.g.*, Tramadol)	• Controlled-release, stronger opioids, or a pain management device

Opioids

SOURCE: Team analysis

Introduction

Differentiation of opioids by analgesic potency

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	Name	Relative Potency	Classification
Strong Opioids	Sufentanil	~1000	Agonist
	Fentanyl	120	Agonist
	Buprenorphine	~30	partial Agonist
	Hydromorphone	7,5	Agonist
	Oxymorphone	7	Agonist
	Oxycodone	1,5 – 2	Agonist
	Methadone	2	Agonist
	Hydrocodone	1,5	Agonist
	Morphine	1	Agonist
Mild Opioids	Pentazocine	0,3	mixed Agonist-Antagonist
	Codeine	0,2	Agonist
	Pethidine	0,1	Agonist
	Tramadol	0,1 – 0,2	Agonist
	Tilidine	0,1 – 0,2	Agonist

Introduction – The opiates family tree

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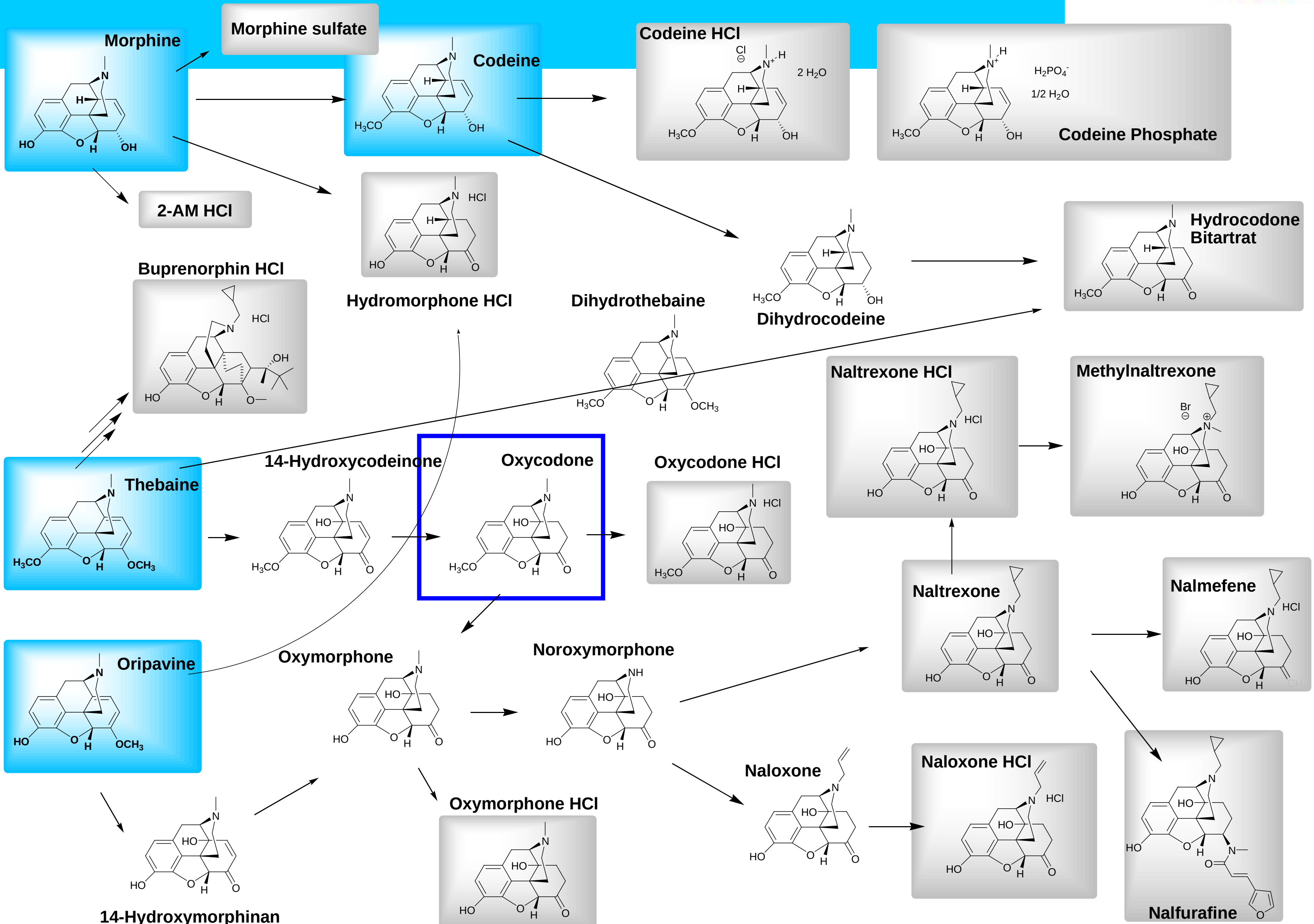
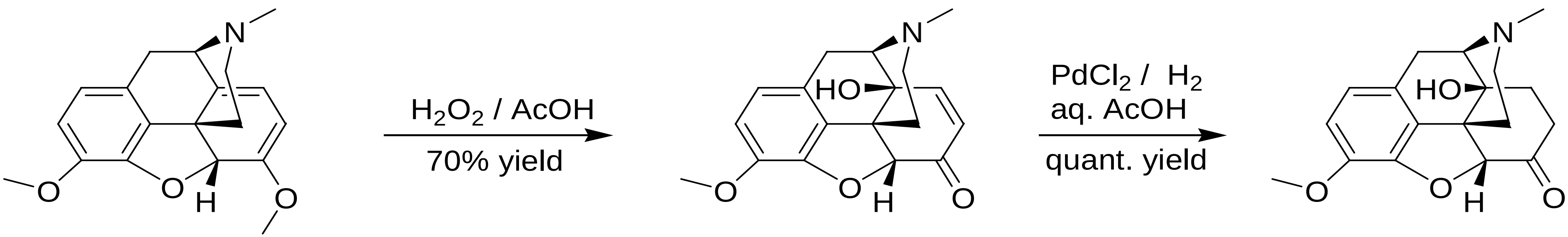


Introduction

Early Findings by Freund & Speyer



Thebaine

14-hydroxycodeinone

Oxycodone

Die neuen Verbindungen sollen als Arzneimittel Verwendung finden.

Source: Chem. Zentralbl. 1915, 94, 156,157; DE296916 (1916); DE286431 (1914)

Introduction
Current Synthesis used by the Industry

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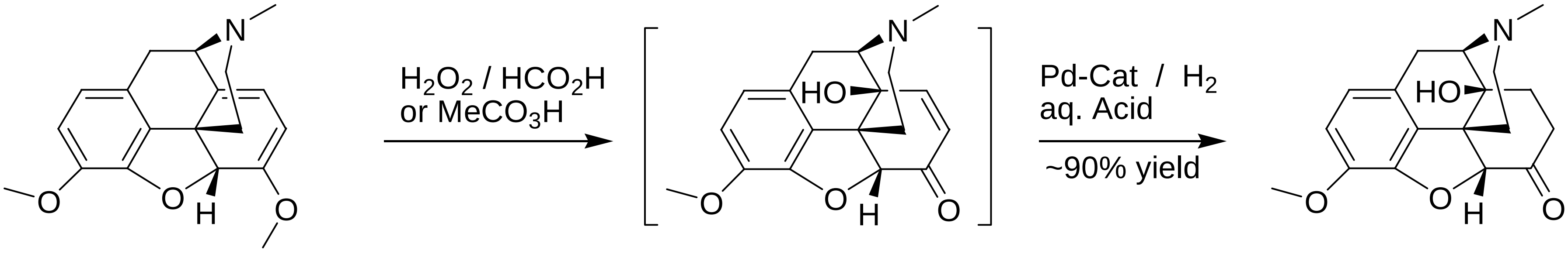

Thebaine

14-hydroxycodeinone
"14-HC"

Oxycodone

Still, more or less, the same route and conditions as Freund & Speyer

New challenge: **Regulatory authorities limit 14-hydroxycodeinone to not more than 10 ppm for pharmaceutical purposes**

Source: US 2008/0132703

Introduction
Adapt / Change the Current Process

Oxidation — Hydrogenation — Purification of oxycodone base — Oxycodone HCl (~1000 ppm 14-HC)

1? 2? 3? 4?

Modify the batch process to get product with 10 ppm level of 14-HC:

1 Apparently not relevant: oxidation product is 14-HC

2 Seems to be attractive as 14-HC is transformed into oxycodone

3 Typical up-grade / purification approach

4 Typical up-grade / purification approach

Introduction
Adapt / Change the Current Process

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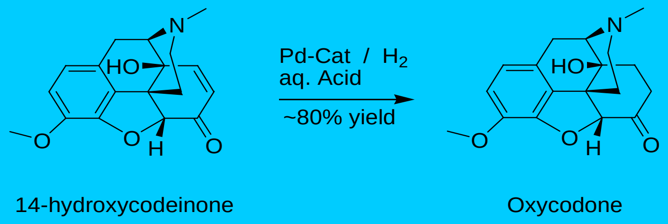
Oxidation — Hydrogenation — Purification of oxycodone base — Oxycodone HCl (~1000 ppm 14-HC)

1? **2?** **3?** **4?**

Purity up-grade approach was tested first with limited success:

14-HC can only be removed by processes associated with huge product losses



Chemical Background
Hydrogenation Step (2)

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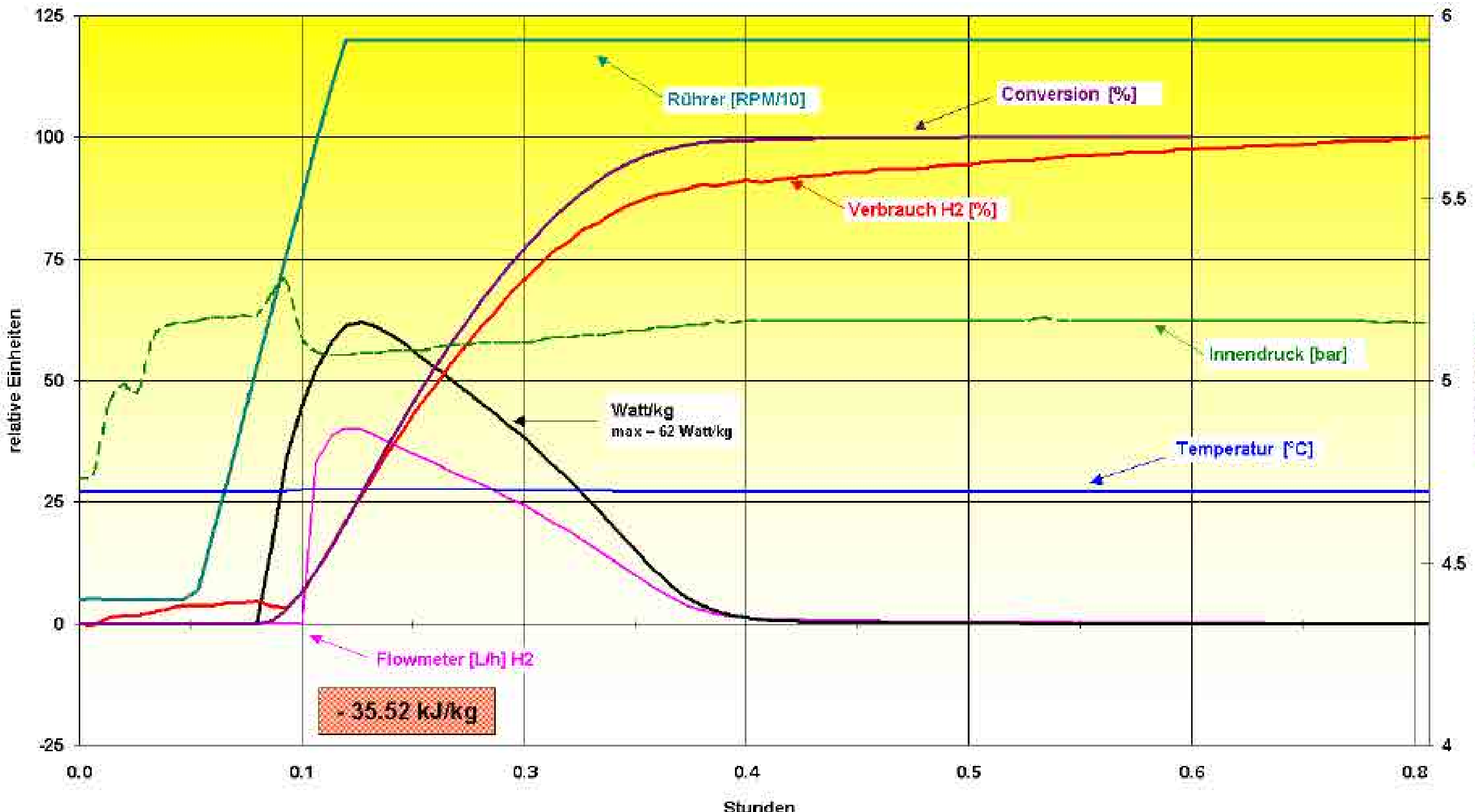
Oxidation — Hydrogenation — Purification of oxycodone base — Oxycodone HCl (~1000 ppm 14-HC)



Chemical Background
Hydrogenation Step (2)

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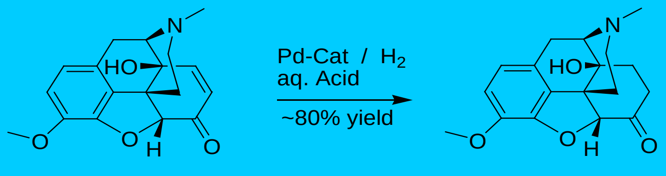
Hydrogenation runs smoothly

In-process monitoring shows complete consumption of 14-HC (~10 ppm)

Nevertheless, the product is contaminated with 500 to 1500 ppm 14-HC

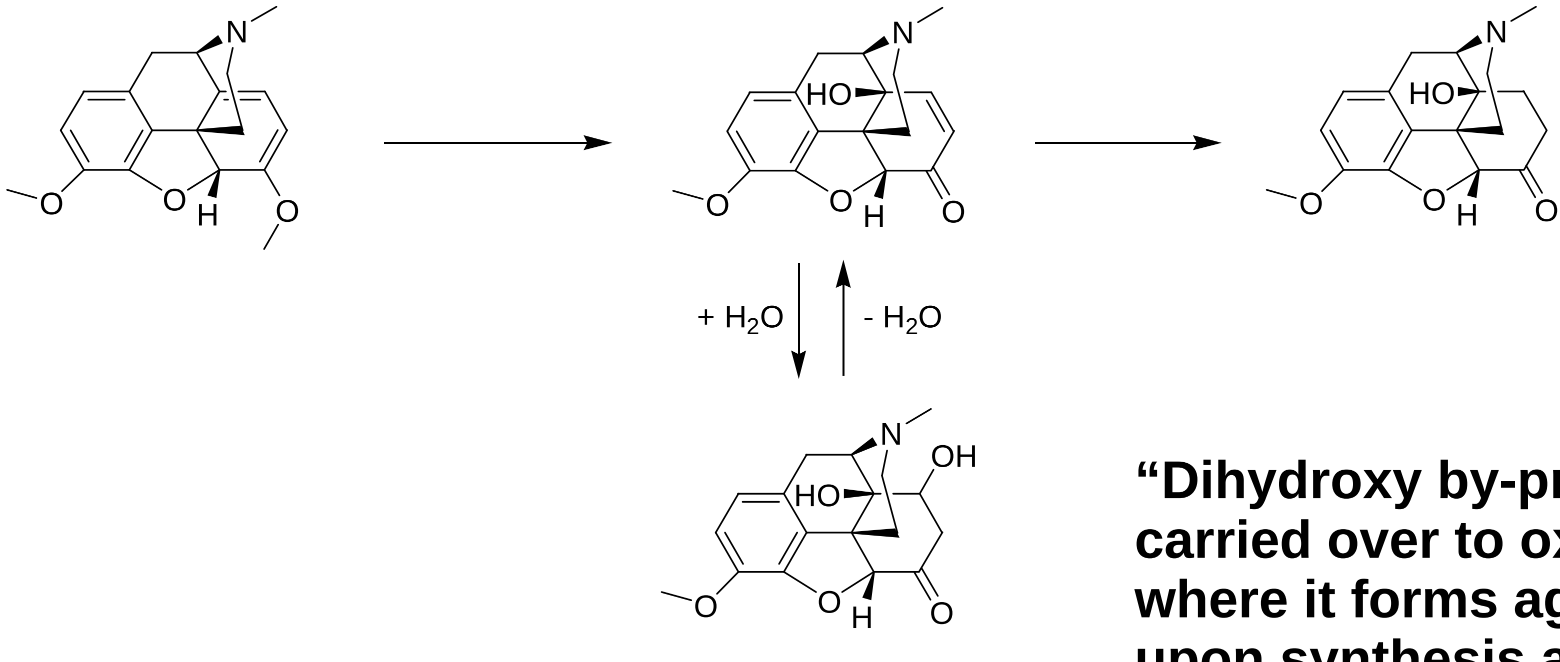
A second hydrogenation, with purification, removes the 14-HC to ≤ 10 ppm, but the trade off is product loss.



14-hydroxycodeinone

Oxycodone

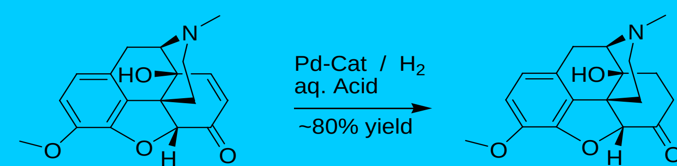
Chemical Background
Hydrogenation Step (2) – What's the Culprit?



6-Hydoxycodeinone

"Dihydroxy by-product" is carried over to oxycodone, where it forms again 14-HC upon synthesis and storage

ce: US2008/0132703



14-hydroxycodeinone

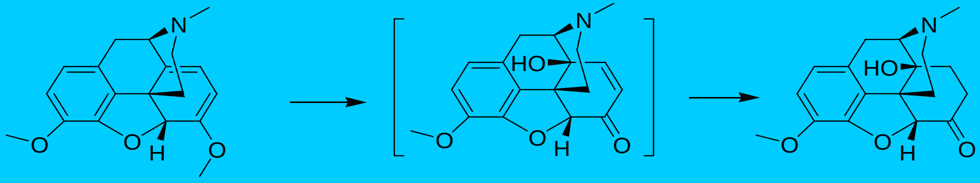
Oxycodone

Chemical Background

Challenges at the Hydrogenation Step (2)

- **A single hydrogenation step is desired –repeated hydrogenations are too expensive**
- **After hydrogenation, the level of 14-HC plus dihydroxy by-product must be < 50 ppm in the isolated base, to assure production of *USP* grade Oxycodone HCl**

- **Select an efficient hydrogenation catalyst – not sufficient**
- **Suppress formation of the dihydroxy by-product**



Thebaine → [14-hydroxycodeinone] → Oxycodone

Chemical Background

Oxidation Step (1): Heat-Flow Regime

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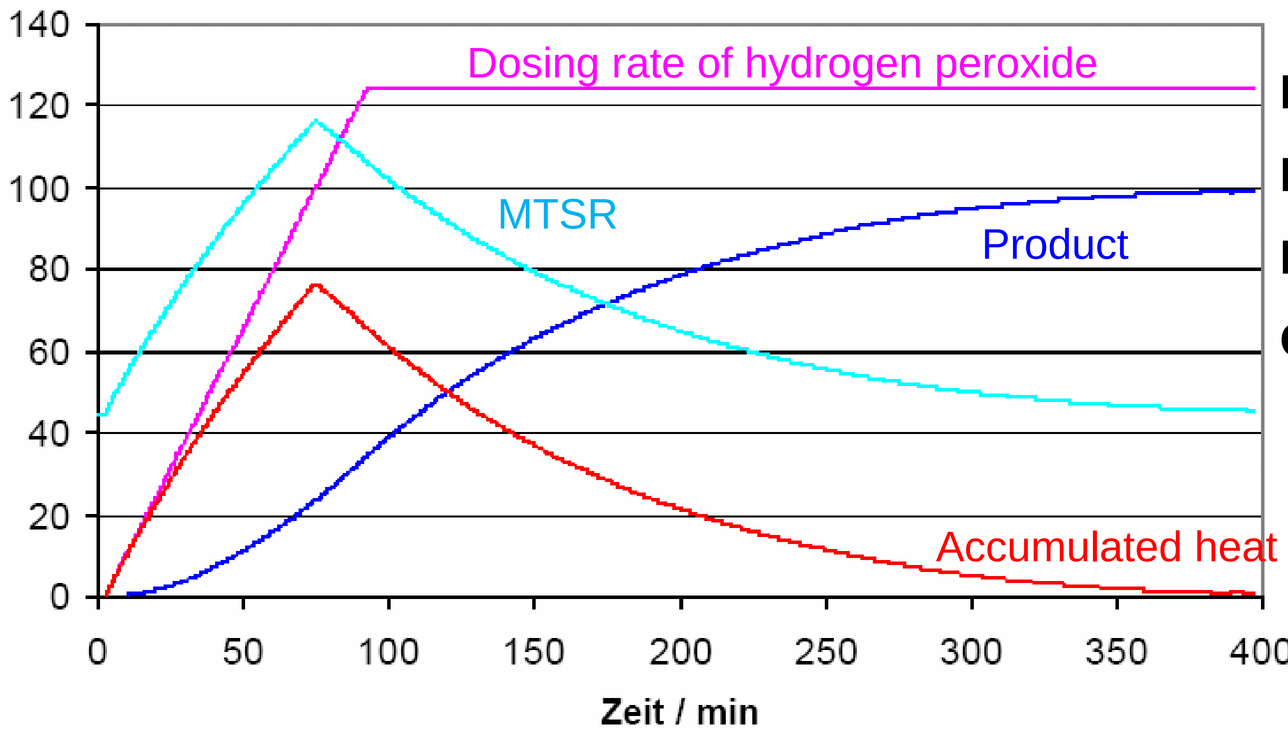
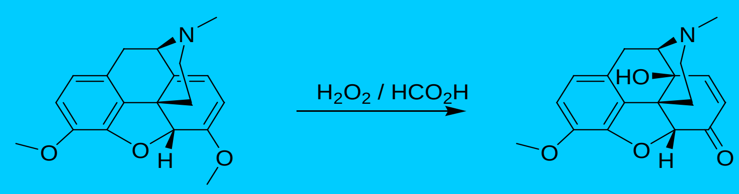


Reaction Enthalpy: 350 kJ/mol

Reaction Temperature: 45 °C

Dosing time needed: 8 h +

Onset of decomposition: ~65 °C

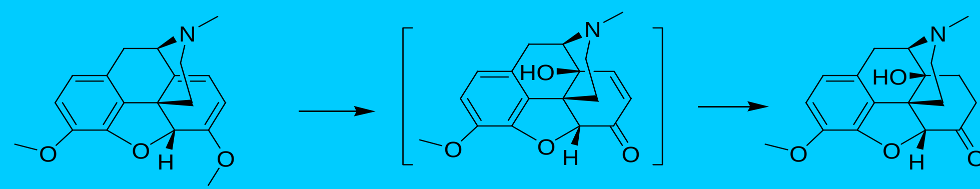


Thebaine

14-hydroxycodeinone

Chemical Background
Challenges at the Oxidation Step (1)

• **Desired reaction is slow**	• **Add a catalyst**
• **Reaction temperature is close to the decomposition temperature**	• **Tighten temperature control**
• **Reaction needs water (hydrolysis of ether)**	
• **Undesired side reaction needs water**	• **Need to compromise**
• **Formation of the dihydroxy by-product is faster in the presence of peroxides**	• **Control stoichiometry and quench quickly**
• **Unreacted thebaine will also form by-products; at most, 2% thebaine can be tolerated in 14-HC**	• **Push the reaction to not less than 98% conversion**
• **Suppress formation of the dihydroxy by-product**	• **?**



Thebaine — 14-hydroxycodeinone — Oxycodone

Proposed Approach

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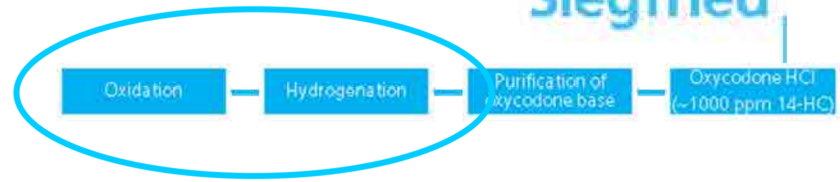
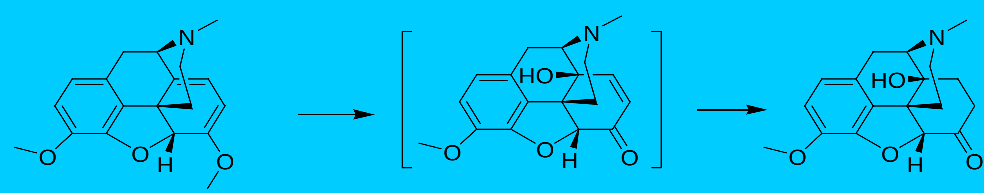


- **Add a catalyst during the oxidation to form the peracid faster – try phosphoric acid**
- **Run the oxidation in a well-defined temperature / time domain**
- **Start hydrogenation immediately after the oxidation step**

→ Continuous flow reaction for step 1

→ Develop PAT monitoring for oxidation step

→ Hydrogenate without delay



Thebaine → 14-hydroxycodeinone → Oxycodone

CFT Application (Feasibility)

Approach for Initial Tests

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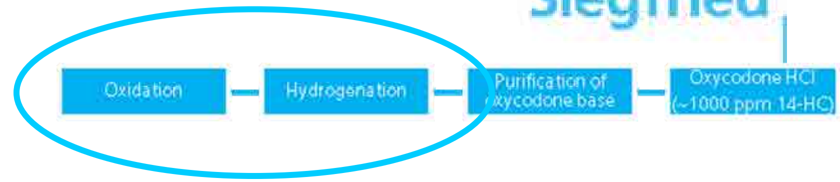
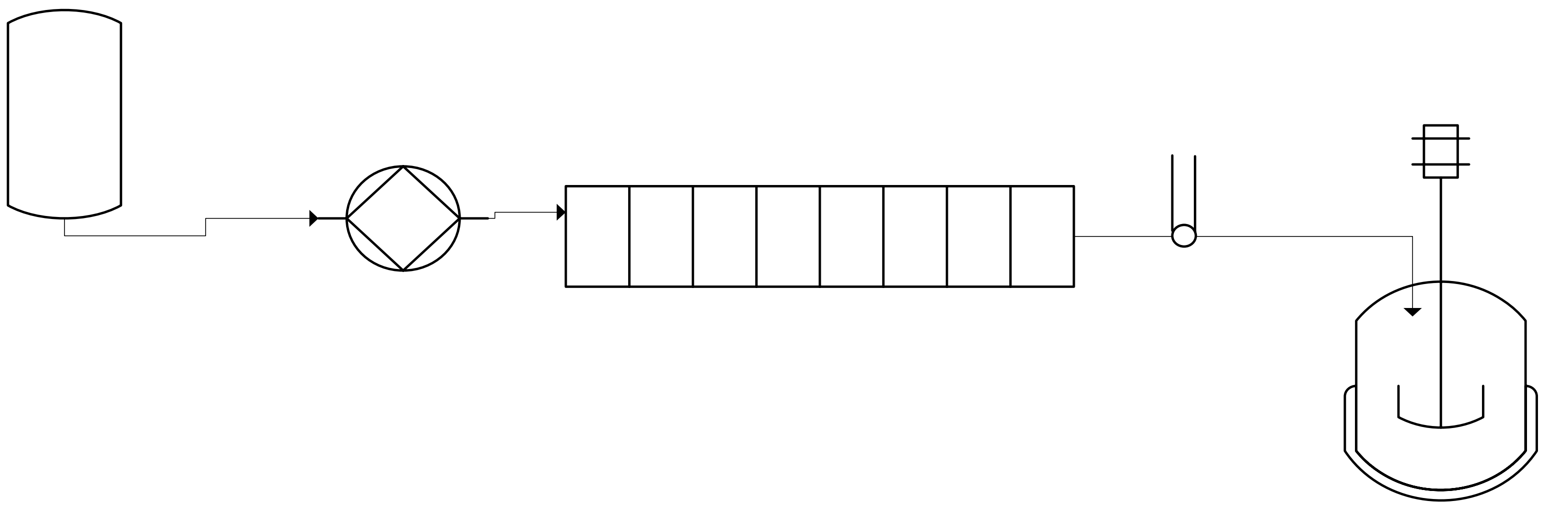
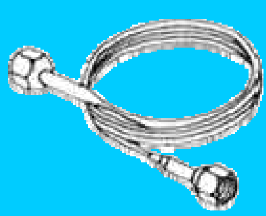
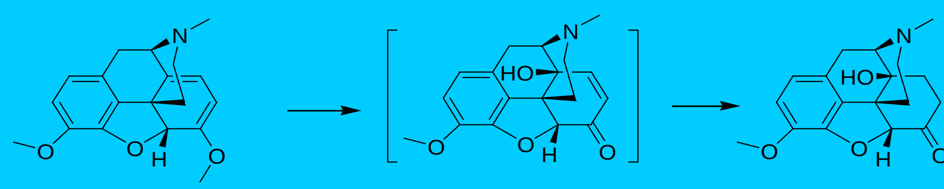






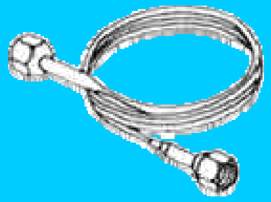
Thebaine,
HCOOH
Catalyst
Aq. H_2O_2 (30%)

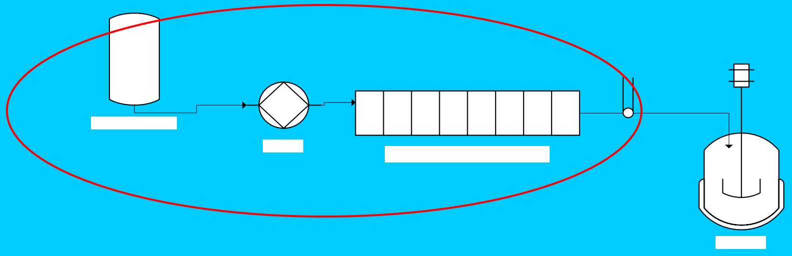


Thebaine 14-hydroxycodeinone Oxycodone

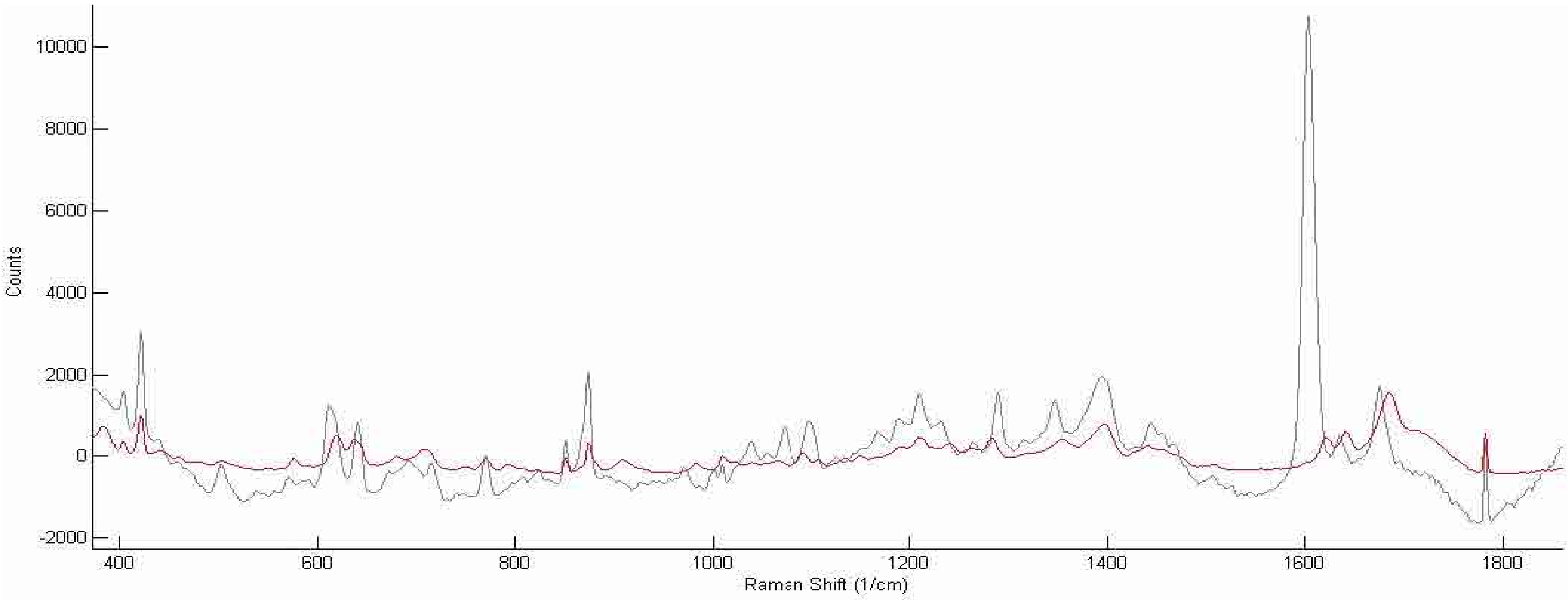
CFT Application (Feasibility)
Initial Results - Oxidation

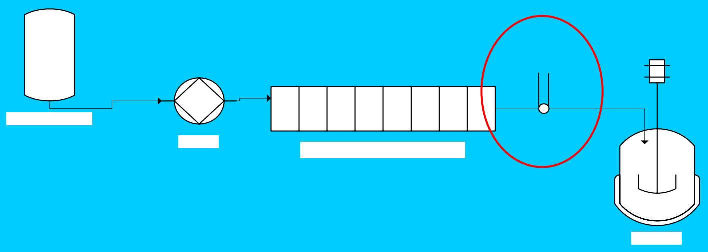
- **Phosphoric acid works as the catalyst**
- **Catalyst offers no advantage when the temperature exceeds ~60 °C**
- **Thermal reservoir (dilution) can be minimized within the CFT process**
- **At 100 °C, the reaction time is 2 - 3 minutes for > 98% conversion**
- **At 100 °C / 3 min, some unknown by-products can be tolerated (< 2%)**





CFT Application (Feasibility)
Oxidation Step – PAT Monitoring (Raman)





CFT Application (Feasibility)

Oxidation Step – PAT Calibration (Raman)

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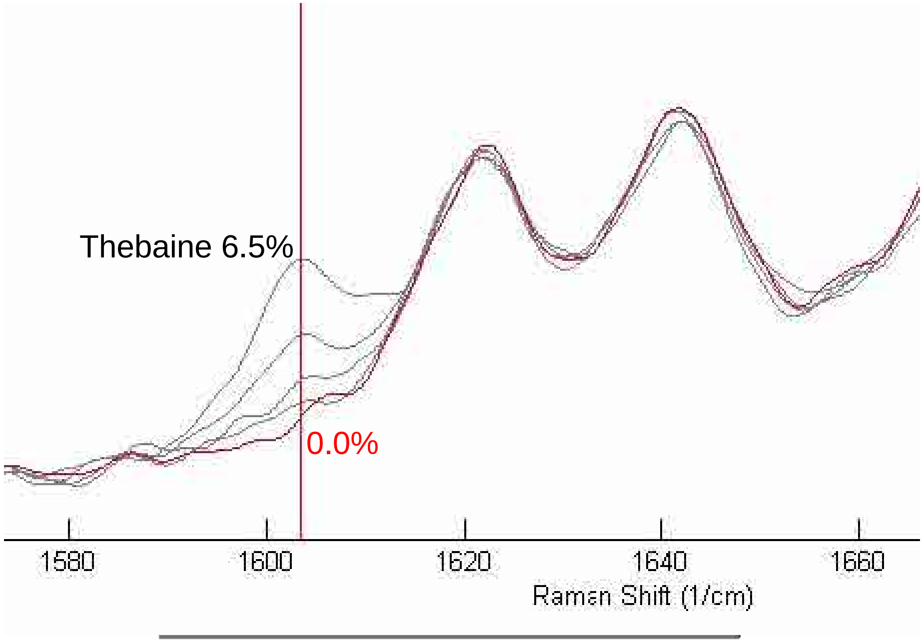
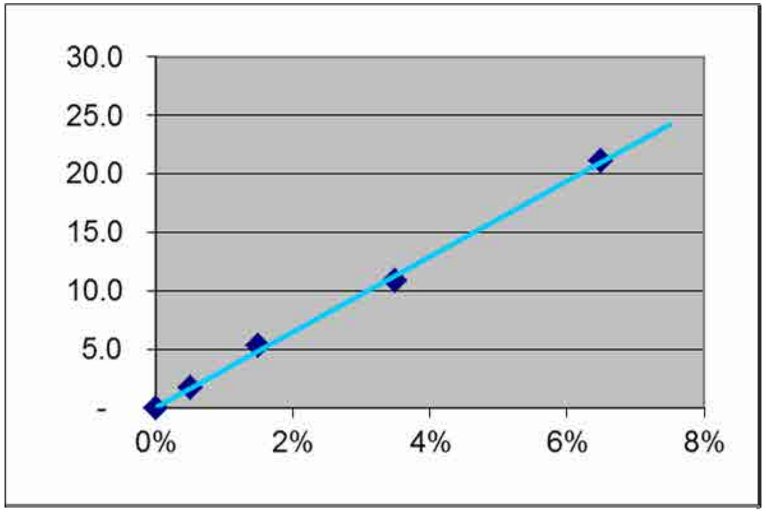
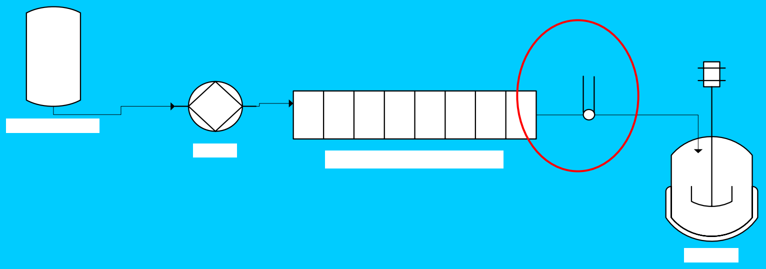


Signal *vs*. Unreacted Thebaine



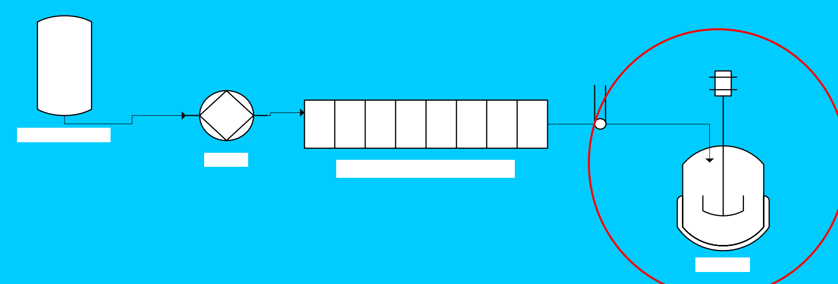


CFT Application (Feasibility)
Hydrogenation – Safety Concerns

- **The reactor contains hydrogen gas and a precious-metal catalyst**
- **Excess peroxide may form oxygen, and create an explosive mixture**

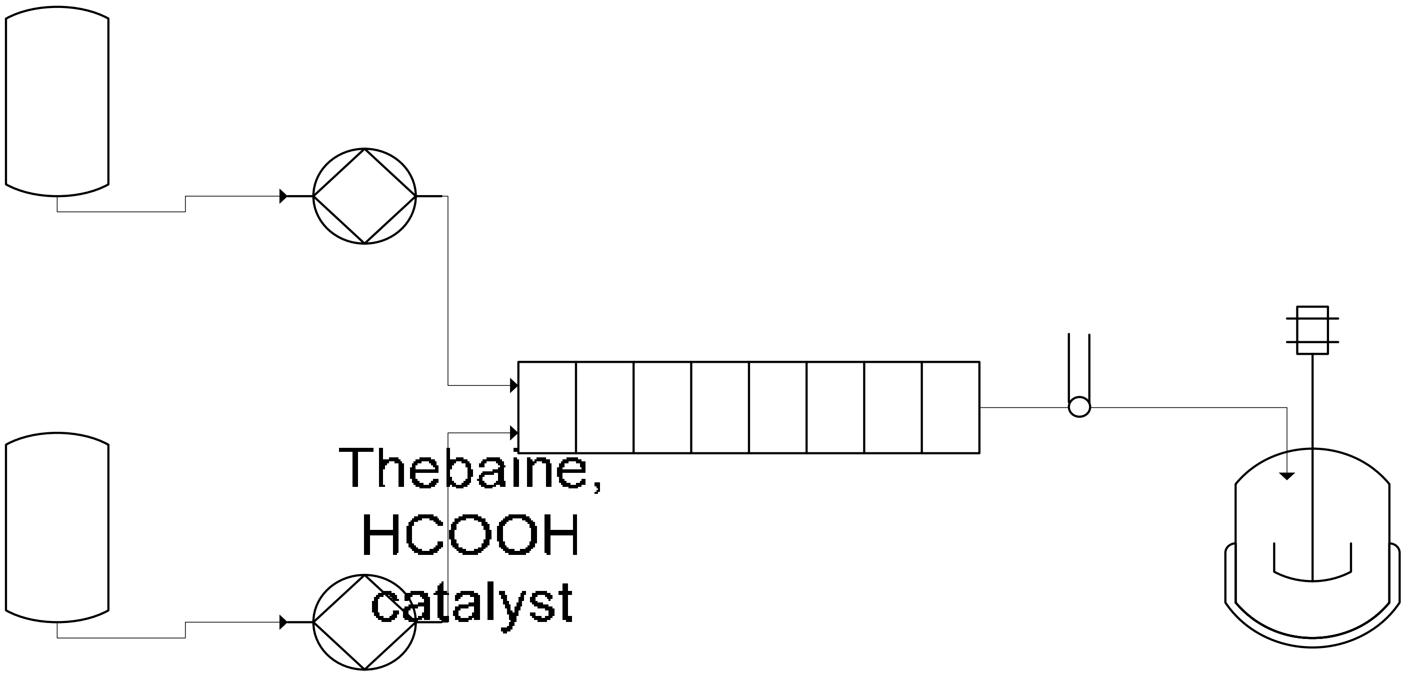
→ **Absence of peroxide confirmed at the outlet of the CFT unit**

→ **Palladium catalyst selected does not decompose peroxide to oxygen**



CFT Application

Plant Simulation – Initial CFT Set-Up

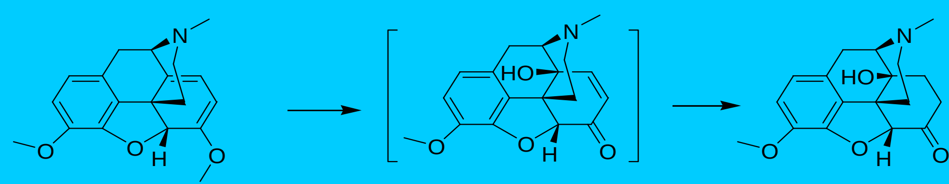


Conversion < 98%

More by-products

Changing stoichiometry failed to optimize the reaction

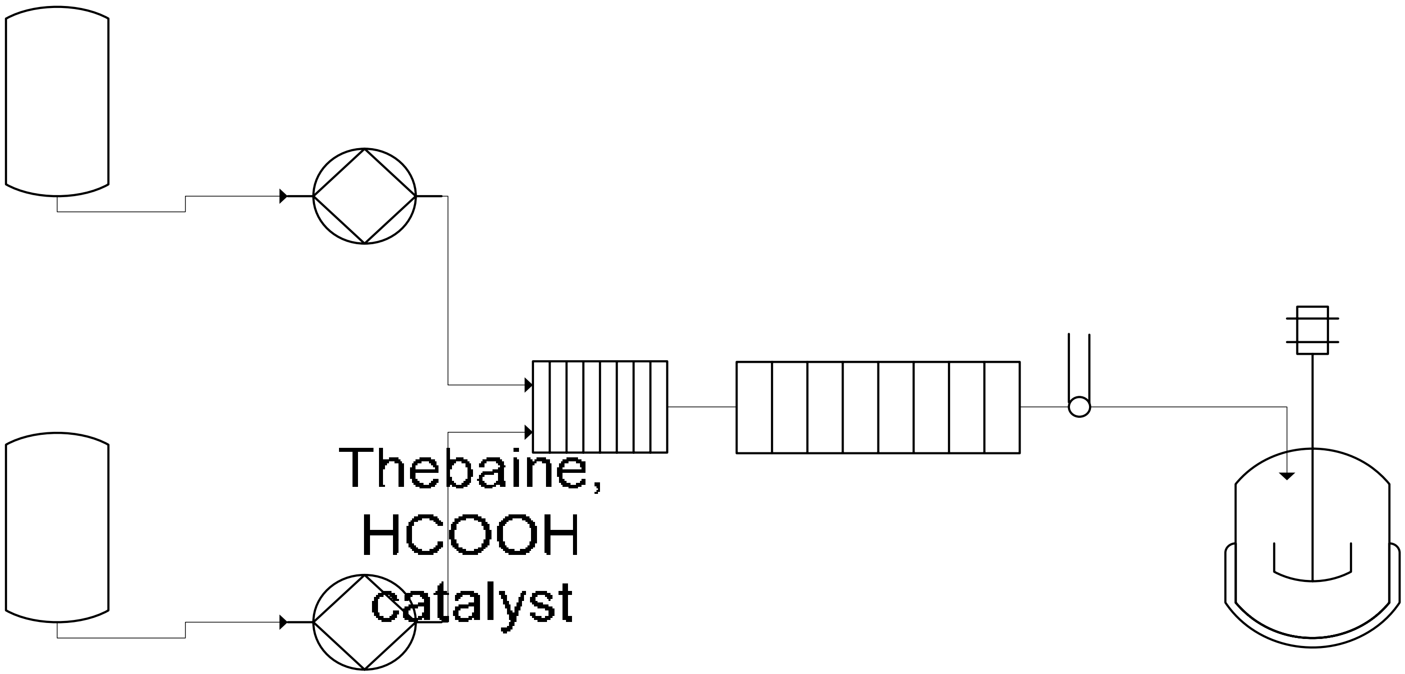
Pump 2



Thebaine 14-hydroxycodeinone Oxycodone

CFT Optimization

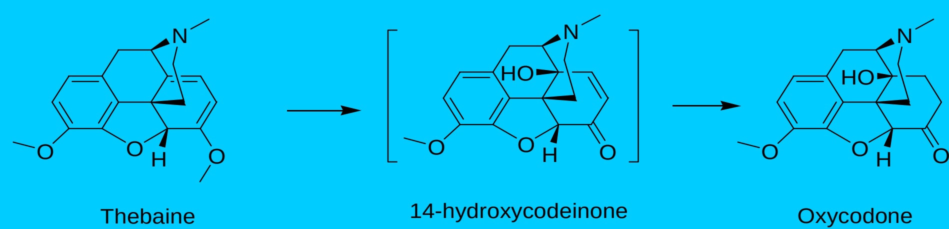
Plant Simulation – Modified CFT Set-Up



Conversion > 98%

Quality criteria achieved

Pump 2



CFT Optimization

Design Space for Oxidation Step (1)

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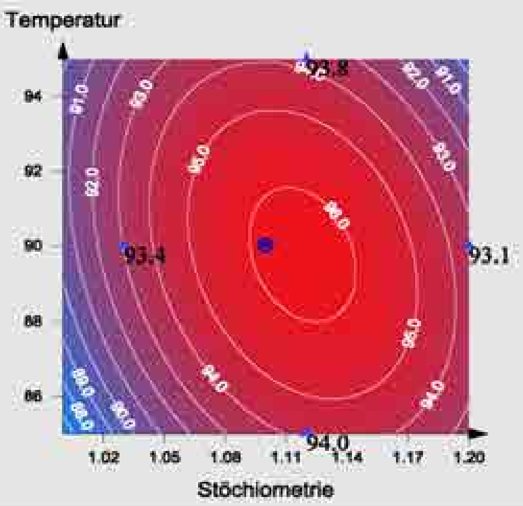
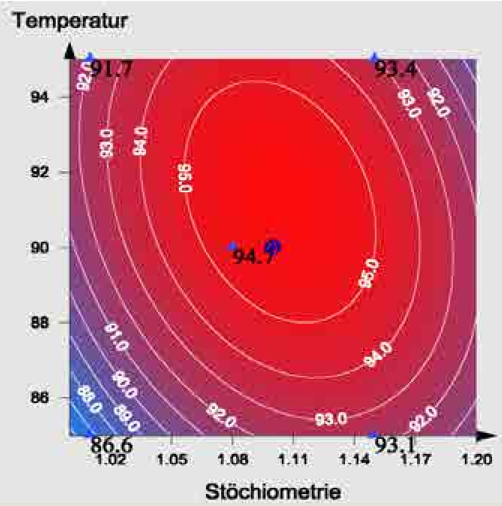
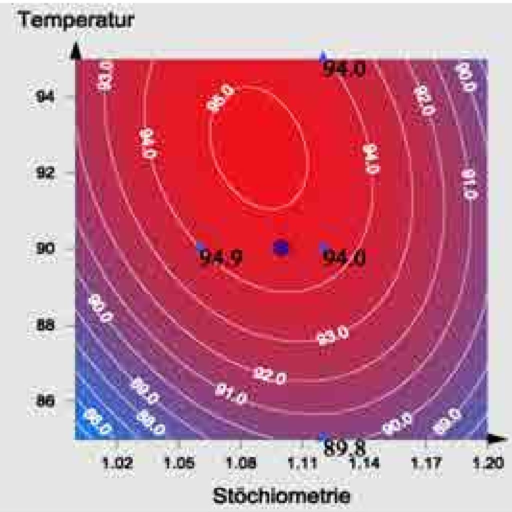
3.0 min



2.4 min



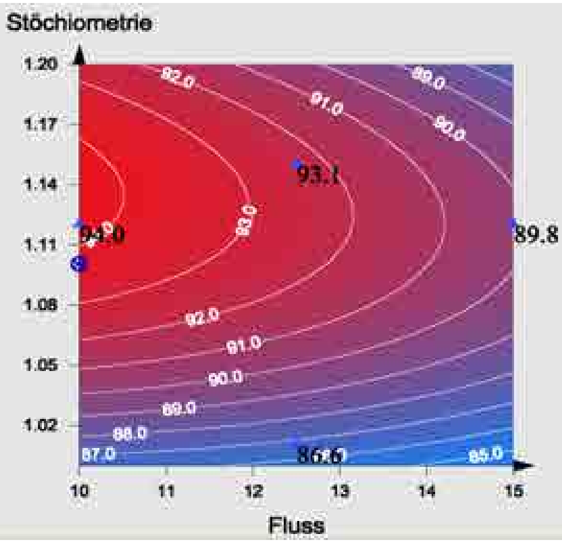
2.0 min



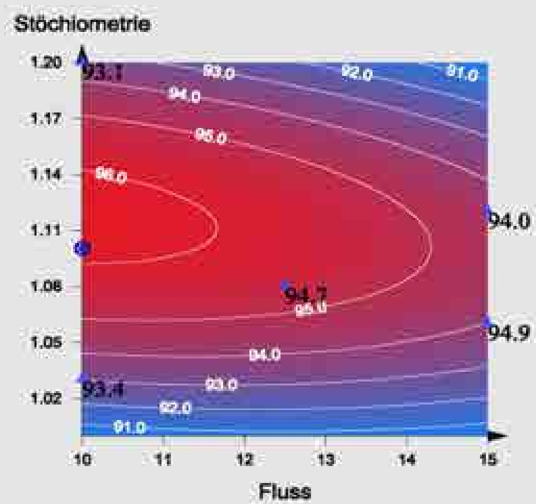
➢ **Optimum residence time is 2.4 min**

CFT Optimization
Design Space for Oxidation Step (1)

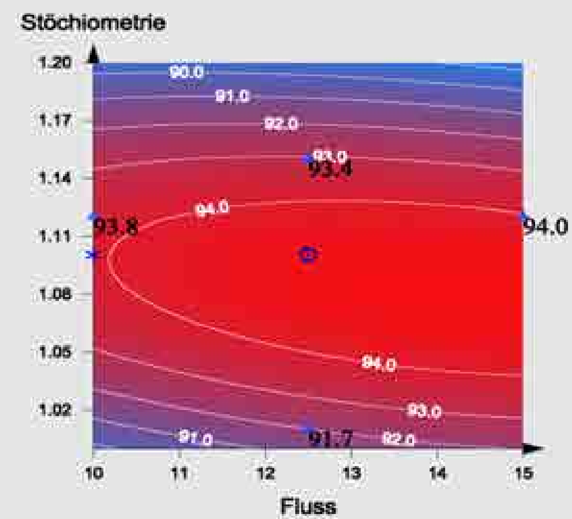
85 °C



90 °C

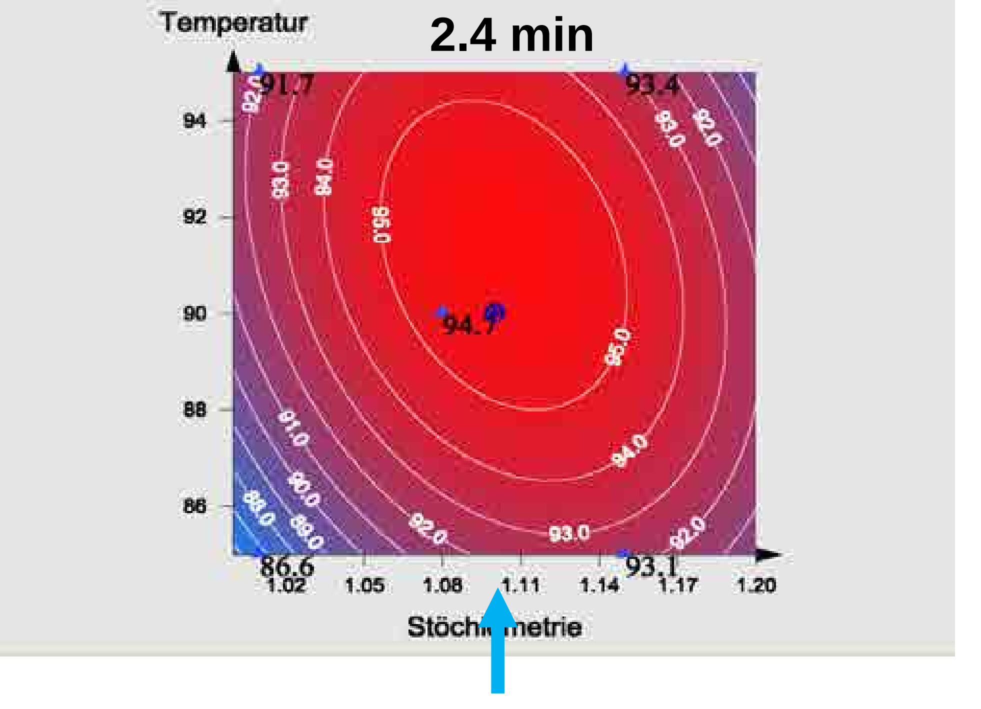


95 °C



- **Optimum reaction temperature is 92 °C (with a residence time of 2.4 min)**

CFT Optimization
Design Space for Oxidation Step (1)



➢ **Optimum stoichiometry is 1.1 equivalent of hydrogen peroxide**

Achievements
Adapt / Change the Current Process

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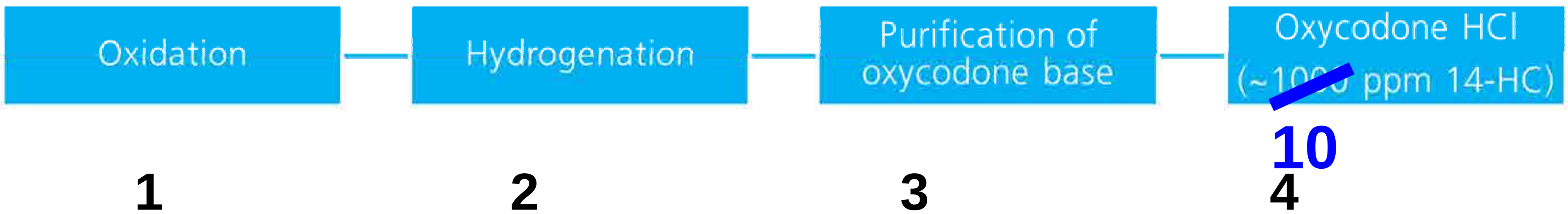

1 → do the oxidation step continuously

2 → run the hydrogenation more concentrated

3 → simplify the existing purification protocol

4 → use the existing salt formation process

Achievements

Comparison of CFT with Batch Processes

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	Original batch process	Modified batch process	CFT process
Stages	1. Oxidation 2. Reduction – isolation of oxycodone base 3. Purification of oxycodone base 4. Formation of Oxycodone HCl	1. Oxidation 2. Reduction – isolation of oxycodone base 3. Purification of oxycodone base 4. Re-hydrogenation – isolation of oxycodone base 5. Formation of Oxycodone HCl	1. CFT process– isolation of oxycodone base 2. Formation of Oxycodone HCl
Batch cycle time	--	+ 33%	- 33%
Level of 14-HC	1000 ppm	10 ppm	10 ppm

Achievements
Commercial Aspects

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- Cycle time shortened → shorter lead time → less net working capital
- Stringent quality attribute achieved without extra purification steps
- Inherent process safety is built in, and PAT capability easily installed

  → minimization of failed batches

- Siegfried plans installation of a 3-liter reactor, with a capacity of 20 MT/year

Thank you

• Stefan Sahli	CFT
• Vinzenz Blum	CFT
• Etienne Trachsel	CFT
• Roland Eberli	Analytics
• Bernhard Berger	Analytics
• Alexander Franz	Chemistry
• Orrin Viele III	Chemistry
• Michael Levis	Chemistry