Outline

• Inherently Safer Process Design in the Pharmaceutical Industry (5 min)
• Case Study: Peptide Coupling Reagents (15 min)
• Conclusions and Future Work (5 min)
• Questions (5 min)
A study in 1989 by Barton and Nolan of incidents which occurred in batch reactors revealed “a lack of understanding of the process being carried out” as one of the main causes.

In 2001, the CSB concluded that inadequate knowledge of systems and inadequate hazard identification are still the main causes of reactive chemistry incidents.

A study in 1989 by Barton and Nolan of incidents which occurred in batch reactors revealed “a lack of understanding of the process being carried out” as one of the main causes.

In 2001, the CSB concluded that inadequate knowledge of systems and inadequate hazard identification are still the main causes of reactive chemistry incidents.

Since 2001…
Inherently Safer Process Design in the Pharmaceutical Industry

- December 19th, 2007 T2 Laboratories Explosion (Jacksonville, FL)

- Cooling failure led to thermal runaway reaction
- Thermal runaway not characterized during hazard analysis
- No evidence T2 performed required HAZOP before scale-up
- 4 deaths and 14 injuries

http://www.csb.gov/t2-laboratories-inc-reactive-chemical-explosion/
For the reaction: \( R1 + R2 \rightarrow P \)
For the reaction: \( R_1 + R_2 \rightarrow P \)

Hazards associated with \( R_1, R_2 \) and \( P \)

- Thermal stability
  - Onset temperature
  - Heat of decomposition
  - Adiabatic temperature rise
  - TMR, \( T_{D24} \)
- Impact and friction sensitivity
- Explosivity
- Combustible dust hazards (MEC, LOC, MIE, MIT, \( K_{ST} \), chargeability, etc.)
For the reaction: $R_1 + R_2 \rightarrow P$
For the reaction: \( R_1 + R_2 \rightarrow P \)

Reagent (R)
Solvent (S)
Temp (T)
Pressure (P)
Inherently Safer Process Design in the Pharmaceutical Industry

For the reaction: \[ R_1 + R_2 \rightarrow P \]

Hazards associated with \( R_1, R_2 \) and \( P \) AND \( R \) and \( S \)

- Thermal stability
  - Onset temperature
  - Heat of decomposition
  - Adiabatic temperature rise
  - TMR, \( T_{D24} \)
- Impact and friction sensitivity
- Explosivity
- Combustible dust hazards (MEC, LOC, MIE, MIT, \( K_{ST} \), chargeability, etc.)
- Heat of Reaction
- Associated pressure rise
- All credible maloperations
Inherently Safer Process Design in the Pharmaceutical Industry

For the reaction: $\text{R1} + \text{R2} \rightarrow \text{P}$

- Reagent (R)
- Solvent (S)
- Temp (T)
- Pressure (P)
For the reaction: \[ \text{R1} + \text{R2} \rightarrow \text{P} \]

What about byproducts?

\[ \text{Regent (R)} \rightarrow \text{X} \]
For the reaction: \( R_1 + R_2 \rightarrow P \)

What about byproducts?

\( \text{Regent (R)} \rightarrow X \)

What are the hazards associated with \( X \)?

- Thermal stability
- Explosivity
- Shock sensitivity
- Toxicity
Peptide Coupling:

\[ \text{R}_1 \text{COOH} + \text{R}_2 \text{NH}_2 \rightarrow \text{R}_1 \text{CONH}_2 + \text{H}_2\text{O} \]
Case Study: Peptide Coupling Reagents

Peptide Coupling:

$$R_1 \text{CO}_2 + H_2N\text{R}_2 \xrightarrow{>180 \, ^\circ \text{C}} R_1\text{NH}_2\text{R}_2 + \text{H}_2\text{O}$$
Peptide Coupling:

\[
R_1 \text{COOH} + H_2NR_2 \xrightarrow{>180 \degree C} R_1\text{CONH}R_2 + H_2O
\]

Lorlatinib
Peptide Coupling:

$$\text{R}_1\text{COH} + \text{H}_2\text{N}^\text{R}_2 \xrightarrow{>180 \degree \text{C}} \text{R}_1\text{N}^\text{R}_2 + \text{H}_2\text{O}$$

**Lorlatinib**
Peptide Coupling:

\[
R_1^{\text{COOH}} + H_2N^{R_2} \xrightarrow{>180^\circ C} R_1^{\text{CONH}}R_2 + H_2O
\]

Lorlatinib
Case Study: Peptide Coupling Reagents

Peptide Coupling:

\[ \text{R}_1\text{COOH} + \text{H}_2\text{NR}_2 \rightarrow \text{R}_1\text{CONH}_2\text{R}_2 + \text{H}_2\text{O} \]
Peptide Coupling:

\[ \text{R}_1\text{COOH} + \text{H}_2\text{N}\text{R}_2 \xrightarrow{\text{Peptide Coupling Reagent}} \text{R}_1\text{CONH}\text{R}_2 + "Byproducts" \]
Peptide Coupling:

\[ \text{R}_1\text{CO}_2\text{H} + \text{H}_2\text{N}\text{R}_2 \xrightarrow{0 \text{ to } 60^\circ \text{C}} \text{R}_1\text{CO}\text{N}\text{R}_2 + \text{"Byproducts"} \]
Case Study: Peptide Coupling Reagents

Peptide Coupling:

\[
R_1\text{COOH} + H_2N^R_2 \rightarrow R_1\text{CONH}^R_2 + \text{"Byproducts"}
\]

0 to 60 °C

Mechanism:

\[
\text{Peptide Coupling Reagent} \rightarrow \text{Activated Ester} \rightarrow R_1\text{CONH}^R_2 + A^*
\]
Peptide Coupling:

\[
R_1\text{COOH} + H_2N\text{R}_2 \xrightarrow{0\text{ to }60^\circ C} R_1\text{CONH}\text{R}_2 + \text{"Byproducts"}
\]

Mechanism:

Peptide coupling reagent determines “A*”

\[
\text{Activated Ester}
\]

Peptide coupling reagent determines “A*”
Large-Scale Applications of Amide Coupling Reagents for the Synthesis of Pharmaceuticals

Joshua R. Dunetz,*† Javier Magano,*‡ and Gerald A. Weisenburger*‡

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‡Chemical Research & Development, Pfizer Worldwide Research & Development, Eastern Point Road, Groton, Connecticut 06340, United States

ABSTRACT: This review showcases various coupling reagents which have been implemented specifically for large-scale amide synthesis via the condensation of an acid and amine, while highlighting the benefits and drawbacks of each reagent on an industrial scale.

• In this presentation:
  – Studied 45 of the most common peptide coupling reagents used in the pharmaceutical industry
  • Differential Scanning Calorimetry
    – Left-limit onset temperature
    – Quantitative heat of decomposition
    – Yoshida Correlation (Shock sensitivity and explosivity)
  – Goal: Drive Inherently Safer Process Design
Case Study: Peptide Coupling Reagents

- Differential Scanning Calorimetry
Case Study: Peptide Coupling Reagents

- Differential Scanning Calorimetry

Advantages
- Small sample size (2-5 mg)
- Fast turnover (≈ 2 hours/sample)
- Quantitative heat of reaction/decomposition

Disadvantages
- Small sample size - unrepresentative
- Peaks shift with varying rate
- Onset temperatures can be ~100 °C lower than expected from DSC
- Isothermal, not adiabatic
Case Study: Peptide Coupling Reagents

Very High Thermal Potential

Integral: 1.082 x 10^3 mJ
Normalized: 2488.39 Jg^-1
Peak: 338.37 °C
Left Limit: 248.58 °C
Right Limit: 400.22 °C
Case Study: Peptide Coupling Reagents

Very High Thermal Potential
- Integral: 1.082e+03 mJ
- Normalized: 2488.39 Jg^-1
- Peak: 338.37 °C
- Left Limit: 248.58 °C
- Right Limit: 400.22 °C

Melt
Case Study: Peptide Coupling Reagents

![Graph showing thermal properties](image)

**Very High Thermal Potential**
- Integral: $1.082 \times 10^3$ mJ
- Normalized: 2488.39 Jg$^{-1}$
- Peak: 338.37 °C
- Left Limit: 248.58 °C
- Right Limit: 400.22 °C

Left limit onset temperature
Case Study: Peptide Coupling Reagents

Energy of decomposition

Very High Thermal Potential

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<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Integral</td>
<td>$10.82e+03$ mJ</td>
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<tr>
<td>Normalized</td>
<td>$2488.39$ J g$^{-1}$</td>
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<tr>
<td>Peak</td>
<td>$338.37$ °C</td>
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<tr>
<td>Left Limit</td>
<td>$248.58$ °C</td>
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<tr>
<td>Right Limit</td>
<td>$400.22$ °C</td>
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</table>

Lab: METTLER

STAR® SW 15.00
The Yoshida Correlations:

- Mathematical equations that correlate a material's onset temperature and energy from a DSC experiment to its ability to propagate an explosion and/or be shock sensitive.

  - For **explosive propagation** (EP):
    \[
    EP = \log(Q_{DSC}) - 0.38 \times \log(T_{DSC} - 25) - 1.67
    \]
  
  - For **shock sensitivity** (SS):
    \[
    SS = \log(Q_{DSC}) - 0.72 \times \log(T_{DSC} - 25) - 0.98
    \]

  \(Q_{DSC}\) is the energy of the exotherm in cal/g.
  \(T_{DSC}\) is the onset temperature of the exotherm in °C.

  If EP or SS ≥ 0, the material is predicted to demonstrate the ability to propagate an explosion or be shock sensitive.

Case Study: Peptide Coupling Reagents

Yoshida and Pfizer-Modified Yoshida Correlations

- Yoshida Explosivity
- Yoshida Explosivity (Pfizer-Modified)
- Yoshida Shock
- Yoshida Shock (Pfizer-Modified)

DSC Average Total Energy (J/g)

DSC Onset Temperature (°C)
Case Study: Peptide Coupling Reagents

"Pfizer-Modified" = 25% conservation factor applied to Yoshida Correlation
## Case Study: Peptide Coupling Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Name</th>
<th>Abbrev.</th>
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<td>Bromo-tris-pyridinophosphonium hexafluorophosphate</td>
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<td>Chlorotripyridinophosphonium hexafluorophosphate</td>
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<td>(7-Azabenzotriazol-1-yl)oxy)tripyrrolidinophosphonium hexafluorophosphate</td>
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<td>O-(3,4-dihydro-4-oxo-1,2,3-benzotriazen-3-yl)-N,N,N',N'-tetramethyl-uronium tetrafluoroborate</td>
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<td>N,N,N',N'-Tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate</td>
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<td>O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate</td>
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<td><strong>Case Study: Peptide Coupling Reagents</strong></td>
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<td>Fluoro-N,N,N',N'-tetramethylformamidinium hexafluorophosphate</td>
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<td>1-[(Dimethylamino)morpholinomethylene]-1H-[1,2,3]triazolo[4,5-b]pyridine-1-im 3-oxide hexafluorophosphate</td>
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### Case Study: Peptide Coupling Reagents

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<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Average Major Left Limit Onset (°C)</th>
<th>Average Total Exothermic Energy (J/g)</th>
<th>Yoshida Shock(S) Explosive (E)</th>
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**Case Study: Peptide Coupling Reagents**

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<th>Entry</th>
<th>Reagent</th>
<th>Average Major Left Limit Onset (°C)</th>
<th>Average Total Exothermic Energy (J/g)</th>
<th>Yoshida Shock(S) Explosive (E)</th>
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Of the 45 peptide coupling reagents:
- 7 had at least 1 experiment that flagged as potentially shock sensitive
  NDSC, PyBOP, TDBTU, TBTU, TCTU, HATU, HDMA

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Case Study: Peptide Coupling Reagents

Of the 45 peptide coupling reagents:
- 7 had at least 1 experiment that flagged as potentially shock sensitive
  NDSC, PyBOP, TDBTU, TBTU, TCTU, HATU, HDMA

- 12 had at least 1 experiment that flagged as potentially explosive
  NDSC, PyBOP, TDBTU, TBTU, TCTU, HATU, HDMA, PyAOP, DMTMM, TNTU, TPTU, HBTU

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Case Study: Peptide Coupling Reagents
Case Study: Peptide Coupling Reagents

Yoshida Correlations for Explosivity

-2000.00
-1800.00
-1600.00
-1400.00
-1200.00
-1000.00
-800.00
-600.00
-400.00
-200.00

Average Onset Temperature, °C

0.00  50  100  150  200  250  300  350  400

-2000.00
-1800.00
-1600.00
-1400.00
-1200.00
-1000.00
-800.00
-600.00
-400.00
-200.00

Average Total Exothermic Energy, J/°C

Yoshida Correlation (Explosivity)
Pfizer Modified Yoshida (Explosivity)
Peptide Coupling Reagents
Reagents that flagged as potentially **shock sensitive**:  

- NDSC  
- PyBop  
- TBTU  
- TDBTU  
- TCTU  
- HATU  
- HDMA
Case Study: Peptide Coupling Reagents

Reagents that flagged as potentially **explosive**:

- NDSC
- PyBop
- TBTU
- HBTU
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- TCTU
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- **TCTU**
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- **HDMA**
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- **PyAOP**
- **TNTU**

These reagents contain known **High-Energy Functional Groups (HEFGs)**
Case Study: Peptide Coupling Reagents

1-hydroxybenzotriazole (HOBT)  1-hydroxy-7-aza-benzotriazole (HOAt)
Case Study: Peptide Coupling Reagents

1-hydroxybenzotriazole (HOBt)

1-hydroxy-7-aza-benzotriazole (HOAt)

HOBt, dry, Koenen test at 10mm
HOBt, dry, detonation test (UN test A.1)
HOBt with 50% water, Koenen test at 2.0 mm

Peptide Coupling:

\[ \text{R}_1\text{COH} + \text{H}_2\text{N}^-\text{R}_2 \xrightarrow{\text{Peptide Coupling Reagent}} \text{R}_1\text{N}^-\text{R}_2 + \text{"Byproducts"} \]
Peptide Coupling:

\[
\text{R}_1\text{COH} + \text{H}_2\text{N}_-\text{R}_2 \xrightarrow{\text{HBTU}} \text{R}_1\text{NH}_-\text{R}_2 + \text{"Byproducts"}
\]
Peptide Coupling:

\[
\text{R}_1\text{COOH} + \text{H}_2\text{N-R}_2 \xrightarrow{\text{HBTU}} \text{R}_1\text{NH-CO-R}_2 + \text{Inorganic Salts}
\]
Peptide Coupling:

For a 10 g reaction (based on LR): 9.9 g of HOBt will be produced (Laboratory Scale)
For a 1 kg reaction (based on LR): 991 g of HOBt will be produced (Kilo-lab Scale)
For a 10 kg reaction (based on LR): 9.91 kg of HOBt will be produced (Pilot Plant Scale)
For a 100 kg reaction (based on LR): 99.1 kg of HOBt will be produced (Commercial Scale)
Peptide Coupling:

For a 10 g reaction (based on LR): 9.9 g of HOBt will be produced (Laboratory Scale)
For a 1 kg reaction (based on LR): 991 g of HOBt will be produced (Kilo-lab Scale)
For a 10 kg reaction (based on LR): 9.91 kg of HOBt will be produced (Pilot Plant Scale)
For a 100 kg reaction (based on LR): 99.1 kg of HOBt will be produced (Commercial Scale)

Unless reaction is quenched with an aqueous solution, HOBt will be generated as an anhydrous solution in an organic solvent.

Carboxylic Acid
MW 250 g/mol
1.1 equiv.

Amine
MW 150 g/mol
1.0 equiv. (LR)

HBTU
MW 379.25 g/mol
1.1 equiv.

Desired Product
MW 382 g/mol
1.0 equiv.

Inorganic Salts

HOBt
MW 135.13 g/mol
1.1 equiv.
Peptide Coupling:

\[
\begin{align*}
\text{Carboxylic Acid} &\quad \text{MW 250 g/mol} &\quad 1.1 \text{ equiv.} \\
\text{Amine} &\quad \text{MW 150 g/mol} &\quad 1.0 \text{ equiv. (LR)} \\
\text{HBTU} &\quad \text{MW 379.25 g/mol} &\quad 1.1 \text{ equiv.} \\
\text{Desired Product} &\quad \text{MW 382 g/mol} &\quad 1.0 \text{ equiv.}
\end{align*}
\]

The generation of anhydrous HOBt must be thoroughly assessed during the Process Safety Review.
Case Study: Peptide Coupling Reagents

Or better yet…Can we develop processes that **AVOID** the use of HOBt and HOAt-based coupling reagents??
Or better yet…Can we develop processes that **AVOID** the use of HOBt and HOAt-based coupling reagents??

Answer: We **can** and we **should**!
### Case Study: Peptide Coupling Reagents

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<th>Use with Caution</th>
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* Based on thermal stability data of the peptide coupling reagent and generation of hazardous by-products. Every process should be thoroughly assessed by professionally trained Process Safety scientists.
Future Work

- All shock sensitivity testing has been completed
- All explosivity testing has been completed
- All adiabatic testing has been completed

- Get manuscript published!!
Acknowledgements

Process Safety Labs (Groton, CT)
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Iain Gladwell
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