Eco-friendly Manufacture of Ezetimibe: Impurity Control & Sustainability

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1. Introduction

Ezetimibe (**3**) approved by the USFDA, singly to lower elevated blood cholesterol levels and in combination with statins in select high-risk persons to whom low-density lipoprotein goals cannot be achieved by maximally tolerated statin alone.[1] The **Neuland** manufacturing process **(Scheme-1)** of **3** involves the cyclization of **2** using TBAF/ N-O-BSA, followed by the acid mediated de-silylation. The process results in the formation of an impurity, **oxazolidinone dimer** (**4**), which was traced due to the use of dichloromethane (DCM) as a solvent in the process. The control of **4** as per ICH guidelines in **3** has several challenges needing several purifications and lot of solvents.

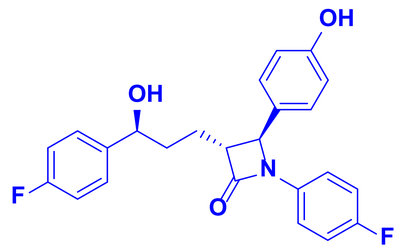


Fig 1 : Structure of Ezetimibe (3)

The **Neuland approach** presents a **"*greener and leaner*"** framework to the manufacturing of **3**. Replacement of DCM (**ICH: Class 2**) with Methyl-tert butyl Ether (MTBE, ICH: Class-3) solvent resulted in a environmentally sustainable process that eliminated the formation of **4**.

2. Route of Synthesis & Impurity Formation

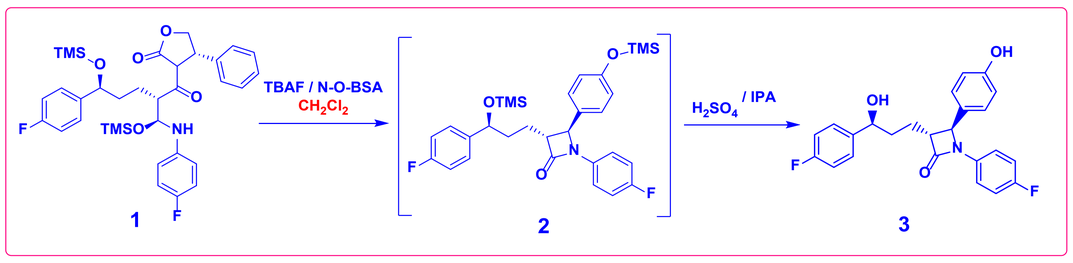


Fig 2: Synthesis of Ezetimibe

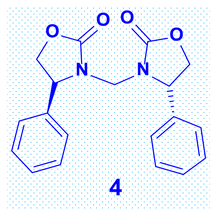


Fig 3: Impurity

CURRENT PROCESS CHALLENGES

- ***Dimeric impurity (HPLC RT 14.58)*** forms in the process, needed to control below *0.08%*
- ***DCM leaching & aq. alcohol purifications*** *required* to control this impurity below limit
- ***Huge yield losses*** observed due to repeated purifications

3. Impurity formation & HPLC trace

S-4-phenyloxazolidinone **(5)** obtained during the reaction, **dimerizes** in DCM to dimer impurity **4** (*S-4-phenyl oxazolidinone)*

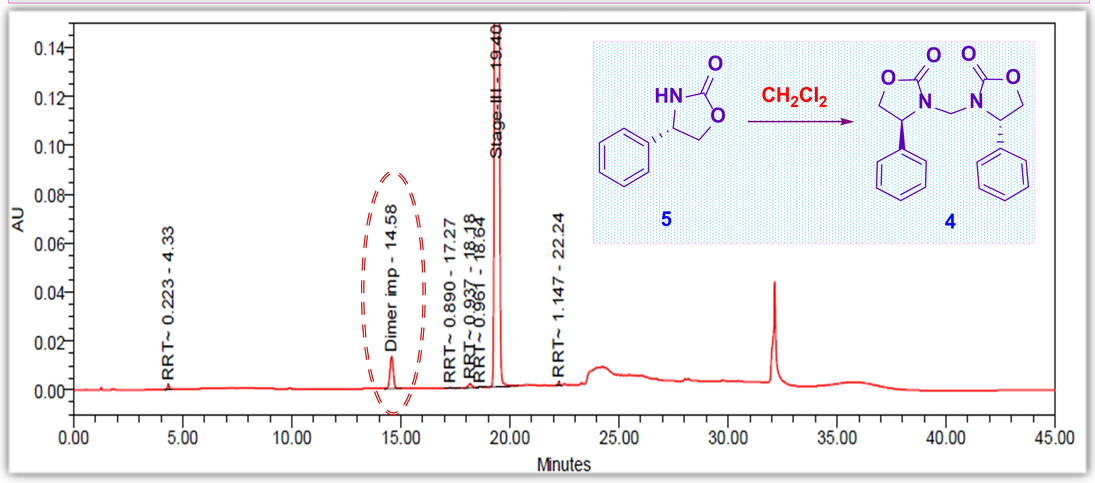


Fig 4 : Chromatogram of RS [Current Process]

4. Neuland Approach for a "Greener & Leaner" Process

4.1.Conceptual Diagram Of 8 Wastes [2]

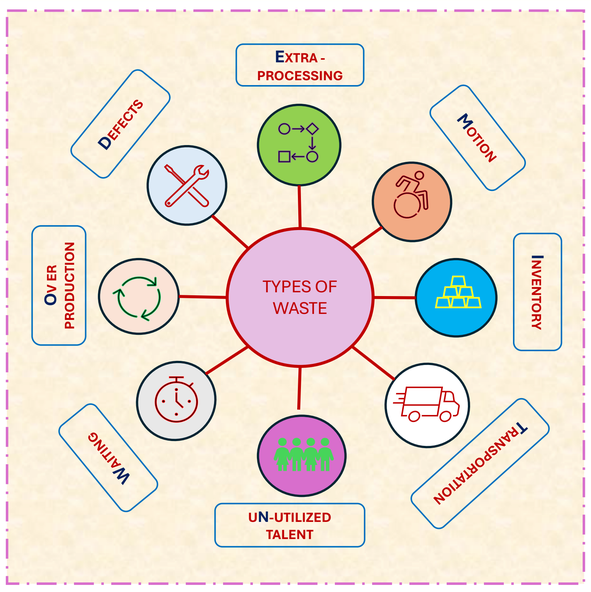


Fig 5. Types of Wastes (for a Lean Process)

4.2. Process Flow [Existing vs. Improved Process]

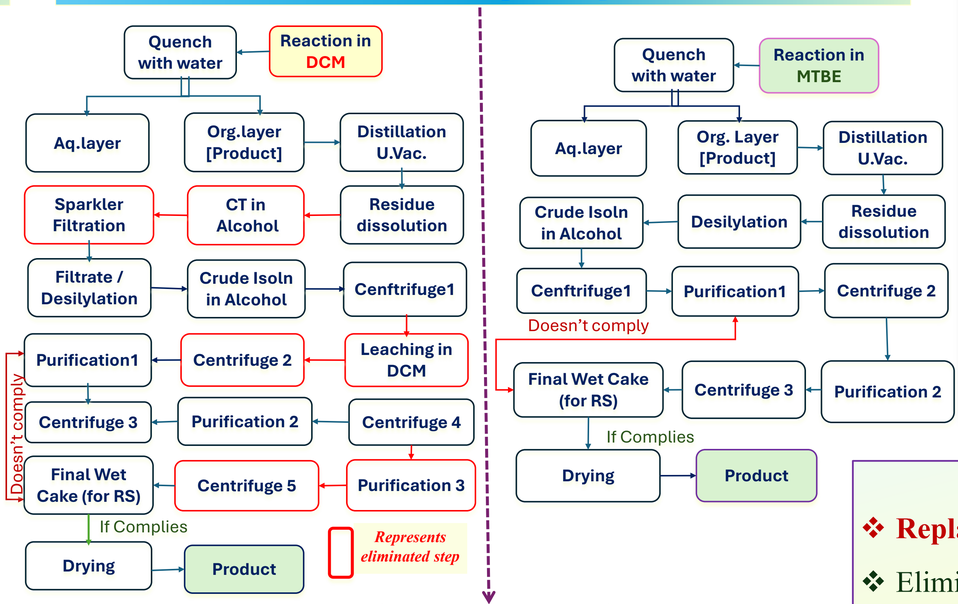


Fig 6. Process comparison

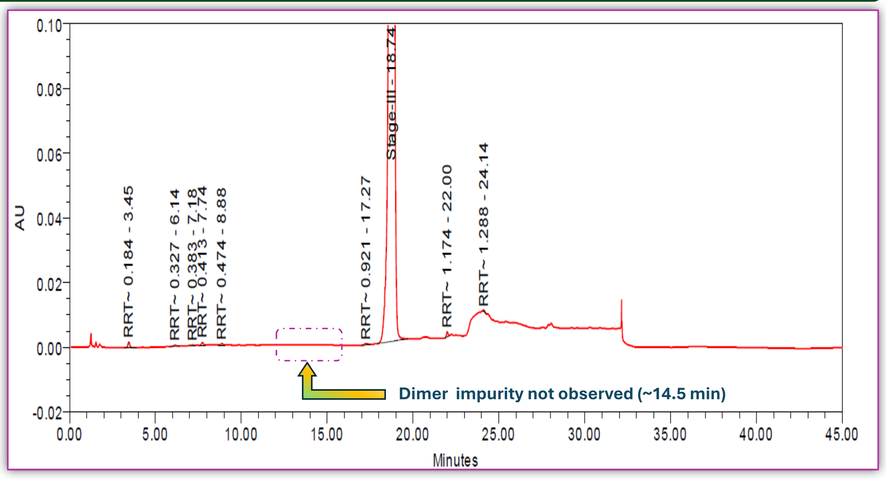
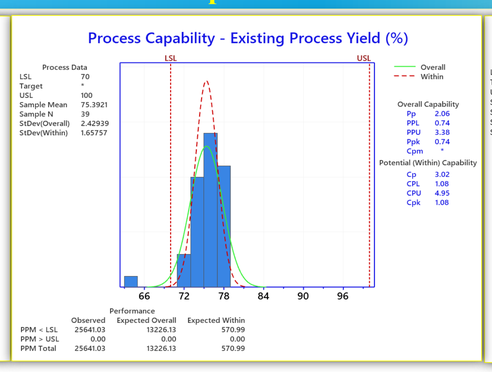
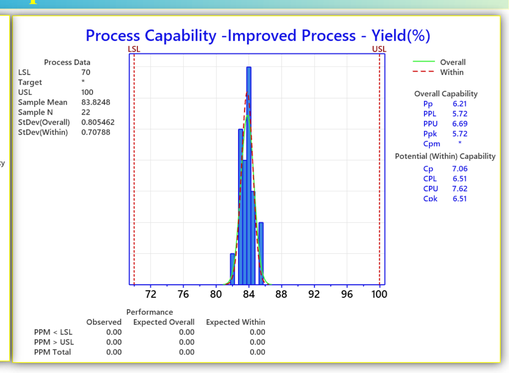


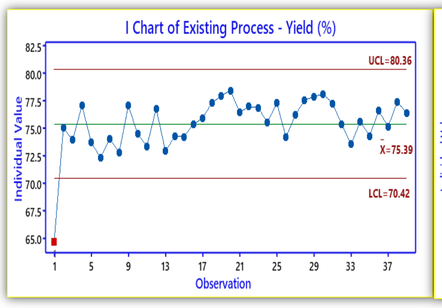
Fig 7 : Chromatogram of RS [Improved Process]

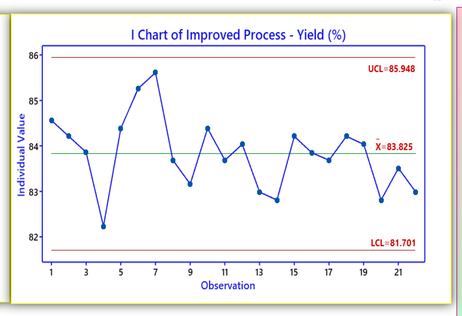
4.3. Statistical Representation Of Development





(a) Spread of Yield data (b) Process Capability wrto Yield data





(c) Trend Yield

Fig 8. Statistical Analysis

Statistical Analysis

- ✓ **Increased CpK & PpK** shows the robust process capability **(1.08 to 6.51 & 0.74 to 5.72 respectively).**
- ✓ % Mean Yield shifted from **75.39 to 83.82**
- ✓ % Median Yield shifted from **~76 to ~ 84**
- ✓ Yield band shift is **81- 86% molar** from **70 -80%** molar

Section 4.3, 4.4 & 4.5 illustrates the optimization of the process steps, elimination of Class 2 solvent (Chlorinated), throughput increase (by ~20% on current), resulting in enhanced capacity. Statistical analysis confirms **process robustness,** showing a significant increase in **Process capability** (CpK / PpK values).

Highlights of Neuland's Improved Process

- ❖ **Replaced DCM** (Class 2) with ***MTBE*** (Class 3) as process solvent
- ❖ Eliminated the need for Leaching
- ❖ Aq. IPA (Class 3) utilized for better control on **impurities**
- ❖ Improved throughput with no dimer content & **Zero solid carbon**

4.4. Process Improvements & Category of Waste addressed

Existing Process	Improved Process	Type of waste
DCM: **09** Vols	Eliminated	✓ Defect & Inventory
DCM Leaching : **01**	Eliminated	✓ Extra Processing
Isolations / Purifications : **04**	Isolations / Purifications : **03**	✓ Extra Processing ✓ Waiting & Motion
Carbon Treatment: **01**	Eliminated	✓ Extra Processing
In process - Dimeric Impurity	Eliminated	✓ Defect, Waiting & Motion

Table 1

4.5. Process Levers

Summary of Improved Process

- ✓ Atom Economy : 48% ↑
- ✓ E-Factor : 22% ↑
- ✓ Avg. Yield : 20% ↑
- ✓ Time Cycle : 25% ↓
- ✓ Water Vol : 20% ↓
- ✓ Solvent Vol : 46% ↓

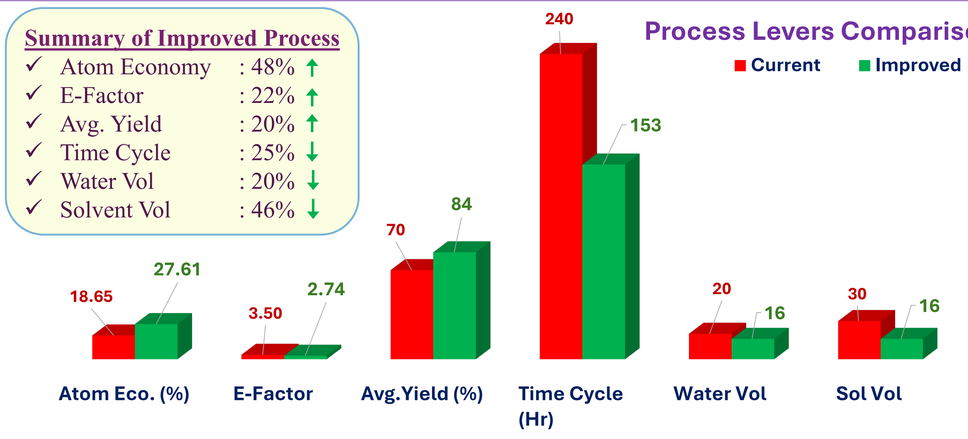


Fig 9. Graphical Representation for Process Levers

5. Results & Discussion

The introduction of **Methyl-tert butyl Ether (MTBE, ICH Class 3)** as a process solvent replacing the traditionally used **Dichloromethane (DCM, ICH Class 2)** prevents the formation of *oxazolidinone dimer* impurity at source, resulting in eliminating purifications, reduced water & solvent load on the process.

Neuland Laboratories' "**Green & Lean**" framework has significantly increased Atom economy, better E-Factor, eco-friendly and cost effective process.

6. Acknowledgement

Support of AR&D, CR&D, RA, IP, & QA teams of Neuland Laboratories Ltd. And its Management is acknowledged.

7. References

1. Vavlukis, M., Vavlukis A. *Drugs Context,* **2018,** Vol 7, Article No. 212534.
2. 8 Wastes of Lean Manufacturing | Machine Metrics