OPTIMIZED USED OF SOLVENTS IN ACTIVE PHARMACEUTICAL INGREDIENTS PRODUCTION

Angelini Pharma

Iacoangeli T., Taffuri A., Scognamiglio F.

Global Industrial Operations, Angelini Fine Chemicals, Angelini Pharma S.p.A. - Via Guardapasso - Aprilia - Italy

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INTRODUCTION AND OBJECTIVE

As part of the Horizon Europe **ETERNAL** project, Angelini Pharma has investigated the possibility to **upgrade** in capability of the **distillation** used to achieve a challenging mixed solvent separation and recovery duty associated with a current commercial process, while studying the opportunity of substituting green, bio-based **solvent alternatives** for conventional solvents in Active Pharmaceutical Ingredients (APIs) manufacture whilst work continues.

Below, a summary of the main objectives:

OBJ 1: Investigating better use of solvents (purification):
A) Distillation through the revamping of the existing distillation column, by increasing quantity and quality of recycled solvents in API manufacture:

- Business drivers for applying this process & expected KPIs: to reduce the environmental impact (Energy, CO2, Cost,Toxicity);
- Increased amount of isobutyl alcohol recycled and reused in the analysed production process (from 50% to 65%);
- Increased amount of acetone recycled & reused in the production process of trazodone (from 90% to 95%).
- Increased amount of isobutyl alcohol recycled and acetone recycled corresponds to more than 200 tons/y at the end of the implementation.

B) Filtration.
Capture impurities and unreacted formulation components during production and in waste products.

OBJ 2: Future replacement of current fossil-based solvents (acetone and Isobutyl alcohol) **by greener bio-based solvents.**

METHODOLOGY

OBJ 1

GOAL — **Upgrading a distillation column**

WHAT — Increase the quantity and quality of recycled solvents with greater energy efficiency.

HOW

- Preliminary laboratory trials to characterize the solvent mixture to be purified
- In silico evaluation to create a thermodynamics model
- Laboratory trials to verify thermodynamics models
- Design of preliminary PFD (Process Flow Diagram) draft
- Verification of existing equipment (gap analysis)
- Detailed engineering
- Plant implementation & Plant qualification.

OBJ 2

Use of Bio-based Solvents for the drug substance manufacture

The future replacement of existing fossil-based solvents with more environmentally friendly bio-based alternatives: an attempt is made to synthesize intermediate and the final API, using more environmentally friendly solvents. The aim of the trials is to investigate the feasibility of using alternative bio-based solvents in the manufacturing process.

RESULTS

OBJ 1: Purification by filtration: The main objective is to capture impurities and unreacted formulation components generated during the production of the chemical, as well as those present in the waste products.

CONCLUSIONS

Greener solvents for API manufacture.
Regarding solvent pre-purification by filtration on chitosan, the analyses highlight two critical issues: mother liquor stability and water content.

Environmentally friendly solvent for API manufacture.
Bio-renewable acetone offers an alternative as solvent, giving the same results as standard acetone as expected, and could be a more environmentally friendly alternative.

Viability of 2-Me-THF as Solvent.
Good results are obtained using 2-Me-THF, although problems with its precipitation suggest that it is unlikely to be a viable alternative to the current standard process.

Challenges in Using Green Solvents.
However, the use of more environmentally friendly alternative solvents in the synthesis of the drug substance intermediate is more complicated than expected. Good results are only observed in terms of conversion when using 1-methoxy-2-propanol as a solvent, but difficulties are encountered in the work-up phase of the process. Ideally, several modifications will be required to replace the current isobutanol.

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