AURIGENE
PHARMACEUTICAL SERVICES
Aurigene Pharmaceutical services ltd

Case Study

Technology meets sustainability – How a complex API development process goes green

A Biotech customer approached Aurigene to develop a sustainable and scalable manufacturing process for a highly complex anti-inflammatory Phase II drug. By applying an eco-friendly approach, we have successfully developed a scalable manufacturing process for the API and increased the yield by 25 %. We have successfully controlled the impurities in the final stage of the production to below 0.2% while minimising the repeated time-consuming purification processes. We followed processes to ensure risk assessment and safety studies and evaluate alternate options to adopt green chemistry throughout our research process from development to manufacture. This helped in minimising the environmental impacts and enhanced the performance of the products.

26th July 2022

The challenges we faced:

Hazardous reactions:

The process involved multiple hazardous steps like cyanation followed by hydrolysis, use of sodium hydride in the primary step, carbonylation using carbon monoxide

Chiral purity requirements:

Nonavailability of purification protocol to eliminate impurities at the API synthesis final stage. Stereoselective installation of the methyl group by using chiral catalyst meeting the required quality and the quality of purified chiral phase transfer catalyst is crucial to obtaining desired chiral purity.

Stability issues of key intermediates:

Involves enamine formation and Chlorination using POCl 3 The Enamine intermediate is unstable and additional measures were required to avoid degradation during isolation, whereas chlorination using POCl 3 is highly sensitive and poses product stability concerns during the reaction. The synthesis of one of the fragments involved five linear stages and most of the intermediates are liquids that are highly unstable with poor yields

Complex chemistry and low yields:

Multiple challenges involved; nucleophilic substitution reaction, asymmetric installation of the methyl group, and amide coupling to form the final API. The yield was only 50%

How we addressed the challenges:

Hazardous reactions:

- Conducting and implementing adequate safety stability studies for handling sodium hydride in the primary stage
- Selection of an alternative method to avoid the usage of hazardous carbon monoxide gas by developing a safer Pd catalyzed cyanation using zinc cyanide followed by hydrolysis to eliminate safety risks

Chiral purity requirements:

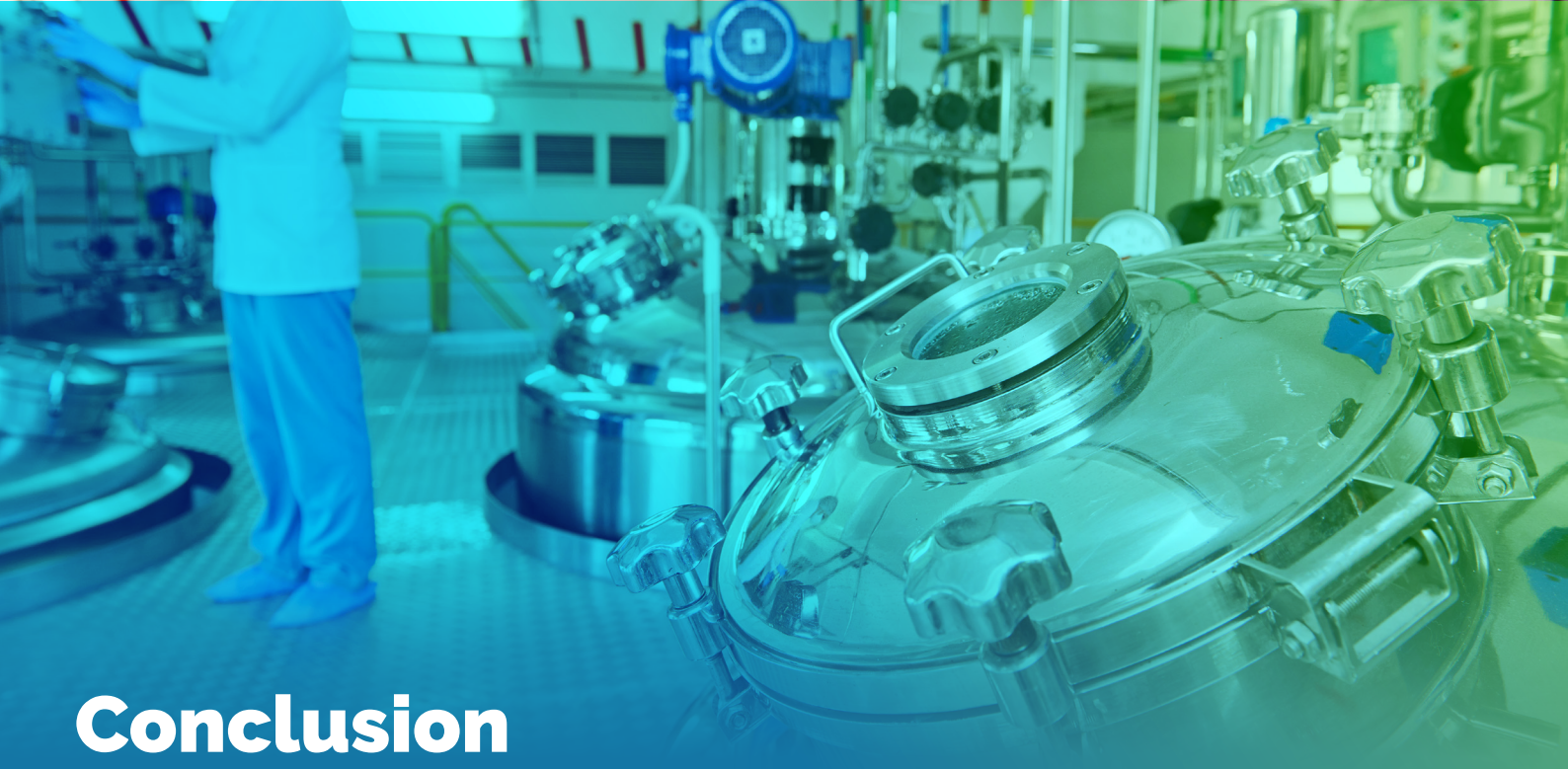
- We achieved ~99% enantio-selectivity by performing a more environmentally friendly organocatalytic asymmetric alkylation method using a cinchona-based phase transfer catalyst
- We implemented a rigorous control strategy for the impurities (> 0.2%), which helped meet the quality of the API without the need for further purification steps.

Addressing the issue of the unstable intermediate:

- We were able to minimize the stages, which involve the isolation of unstable intermediates
- An efficient telescopic process was developed to avoid the isolation of liquid intermediates

Challenges around yield and chemistry:

- We developed a more suitable filtration technique to prevent product loss and increase the yield from 50% to 75%.



Conclusion

The team has exhibited exemplary and outstanding performance in terms of development, execution, cross BU - CFT collaboration, quality and delivery commitment, and timely and transparent communication. Aurigene demonstrated unmatched expertise in addressing multiple challenges like instability of some intermediates, avoiding isolation of liquid intermediates, efficient installation of chirality in the molecule, and more importantly replacement of highly hazardous carbon monoxide gas with safety alternate reagents. Finally, a robust purification process reduced the purification steps and resulted in a more economical (+ 25% yield) and ecological process.

Thank You

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