

Reductive Amination in a Pharmaceutical Process: Challenges from Catalyst Deactivation

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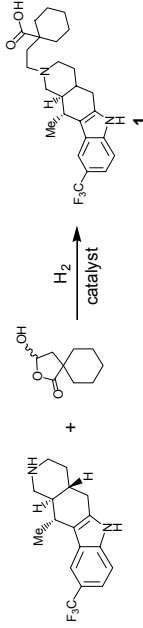
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Introduction

The synthesis of pharmaceutically active compounds is often dominated by methods, which are considered friendly to the synthetic organic chemist. As the syntheses move forward in the cycle of process development catalytic approaches are often employed displacing less process friendly alternatives. An often cited example [1] of such a process is the reductive amination of carbonyl compounds, where borohydride reductants are displaced by catalytic hydrogenation. Employment of the catalytic alternative offers some of the advantages enumerated in the Principles of Green Chemistry, namely: preventing waste, utilizing catalysts not stoichiometric reagents, maximizing atom economy and increasing energy efficiency [2]. Development of hydrogenation processes often reveals unique challenges compared to hydride reductions, however. These include the influence of mass transfer and the robustness of catalysts to deactivation. These parameters must be balanced with the required speed to production, which has great influence on the selection of process alternatives.

In the development of **1**, a potential biologically active molecule, a catalytic reductive amination process was developed to displace a stoichiometric hydride reductive amination. In the midst of scale-up and process development, catalyst deactivation



was identified as a significant challenge. This presentation will focus on characterization of the process and the catalyst employed, while highlighting process alternatives to overcome deactivation.

Materials and Methods

Hydrogenation experiments were conducted generally at 45°C and 4 barg H₂ with 30% acetic acid / isopropanol as solvent and 5% Pt/C (Johnson-Matthey B103032-5). Different reactors with overhead stirring capability and the ability to maintain a constant pressure in the reactor were employed in the study. These reactors had different mixing efficiencies as will be described. Catalyst samples before and after reaction were characterized by nitrogen adsorption, carbon monoxide chemisorption, ICP/MS and transmission electron microscopy. Reaction samples were analyzed by HPLC.

Results and Discussion

Catalyst deactivation during the production of **1** was shown to exhibit a strong dependence on mixing efficiency. Notably a reactor with poor mixing efficiency as measured by energy dissipation to the reaction mass (0.2 W/kg) showed marked deactivation, requiring additional catalyst charging (Figure 1). An efficiently stirred reactor (energy dissipation = 1.9 W/kg) provided smooth reaction to complete conversion and the data made a reasonable fit to first order kinetics ($k = 1.2 \text{ hr}^{-1}$ with 11% w/w catalyst loading). This presentation will describe the influence of gas to liquid mass transfer on kinetic models of this reaction. Characterization of the catalyst before and after deactivation shows only a 15% decrease in total surface area but a 72% decrease in active surface area. Mechanisms for these changes will be presented.

Significance

Development of this process precluded application of a stoichiometric hydride reduction with greater waste generation but also defined the important influence that physical/mechanical factors play in both the implementation of the catalytic process and the underlying kinetics.

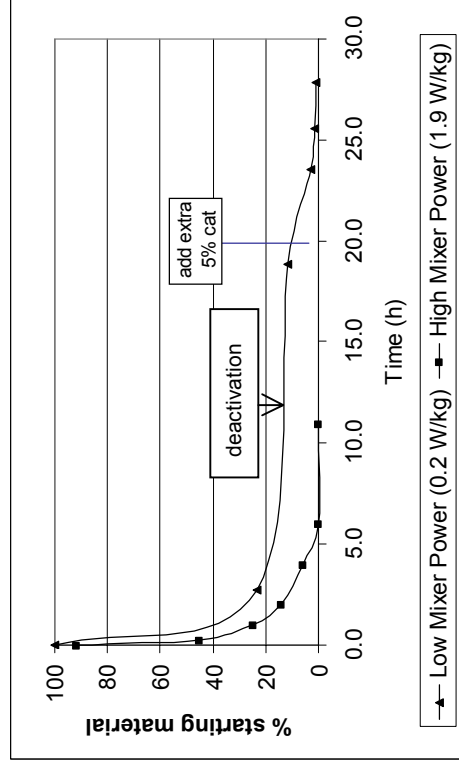


Figure 1. Kinetic profiles for two catalytic reductive amination reactions conducted at different mixer energies.

References

1. a) Chen, B. et al. *Appl. Catal. A: General* 280, 17-46 (2005). b) Tararov, V.I. et al. *Adv. Synth. Catal.* 344, 200-208, (2002).
2. Anastas, P. T. and Warner, J. C. in "Green Chemistry: Theory and Practice" p. 30. Oxford University Press: New York, 1998.