Use of the Design of Experiments to Develop a Scalable Route to a Key Chirally Pure Arylpiperazine

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The dynamic kinetic resolution (DKR) of an Arylpiperazine in the presence of 3,5-dichlorosalicyl aldehyde as racemizing agent and (L)-mandelic acid as precipitating agent is a key step in the synthesis of a final API selected as novel NK-1 antagonist. The reaction was optimised on a laboratory scale and no problems were encountered. However, some problems were encountered in the pilot plant, with a considerable amount of product adhering to the reactor walls. Moreover, a very difficult azeotropical removal of the water to the target level led to a further decrease of the yield. In fact while the yield achieved on a 5 L scale was about 70%, the overall yield in plant was only about 50%.
Hence, it was evident that the DKR needed further optimization. This was accomplished by means of a full factorial Design of Experiment (DoE) study, implying 12 reactions and two center points to evaluate the curvature, which looked into reaction conditions and stirring rates. As a result of the DoE study, stirring rate was the most significant factor influencing the primary yield of the reaction. Moreover, a strong interaction between water and dichlorosalicyl aldehyde was observed; thank to this, the larger amount of water obtained in the pilot plant scale, was buffered by a larger amount of aldehyde.

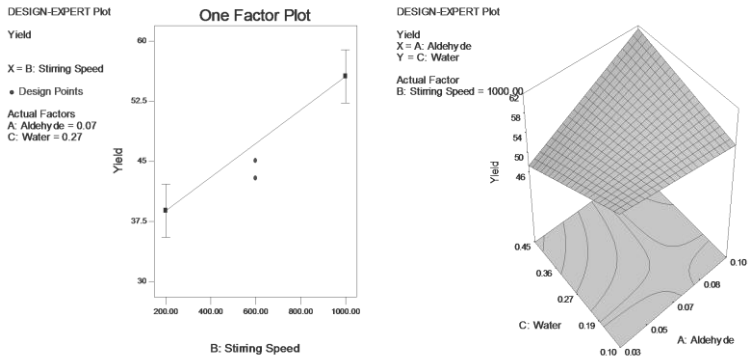

Figure 1. DoE on parameters affecting the DKR

Further to the DoE, a computer modelling study was carried out, enabling us to design an appropriate reactor configuration to ensure efficient mixing. The initially employed round bottomed vessel with baffles led to the tendency to form dead mixing zones, which subsequently turned into encrustation. The computer modelling suggested using a conical vessel without baffles, as this would be ideal for thick suspensions and would avoid the dead mixing zones issue.

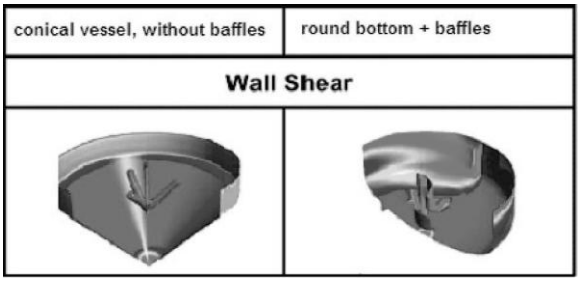

Figure 2. Computer modelling

When the process was repeated on pilot-plant scale with the new conditions (more aldehyde and the suggested vessel configuration) it was possible to reproduce the yield and purity achieved on the lab scale.

Bibliography

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