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

Francesco Tinazzi
Principal Scientist
API Manufacturing and Development
Aptuit Verona

Introduction

- A Design of Experiments applied to a chemical process is presented
- The synthesis of a chemical intermediate was studied in lab
- Some issues were encountered when the process was scaled up in the Pilot Plant
- DoE and computer modeling were used to understand the process and define new conditions
- New conditions were successfully applied to the following Pilot Plant campaign

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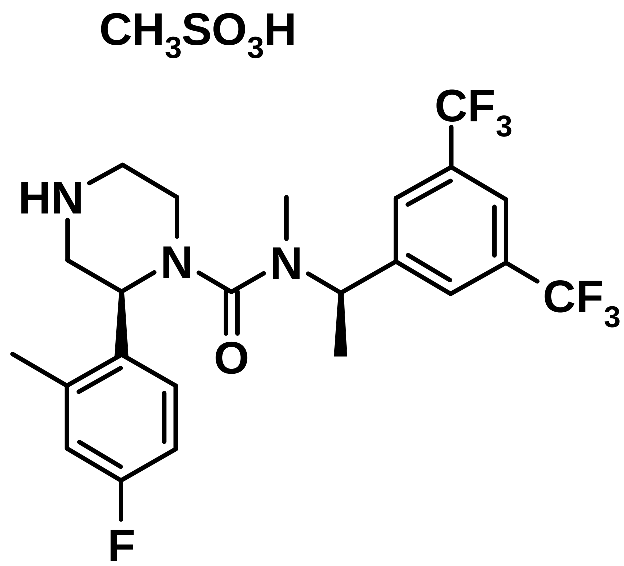
Vestipitant Mesylate

- NK-1 antagonist
- Total synthesis: 3 Stages, 9 Steps
- 2 chiral centers: 4 possible isomers
- Final product isolated as mesylate salt
- Dynamic Kinetic Resolution (DKR) is a key step in the synthesis of Vestipitant Mesylate



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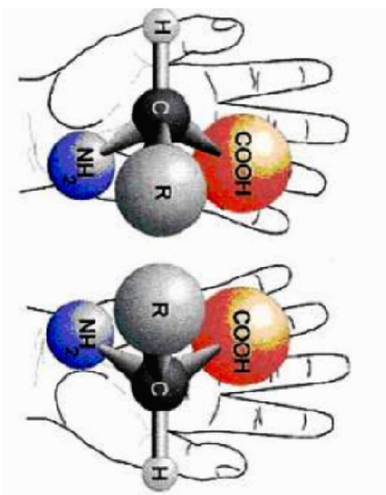
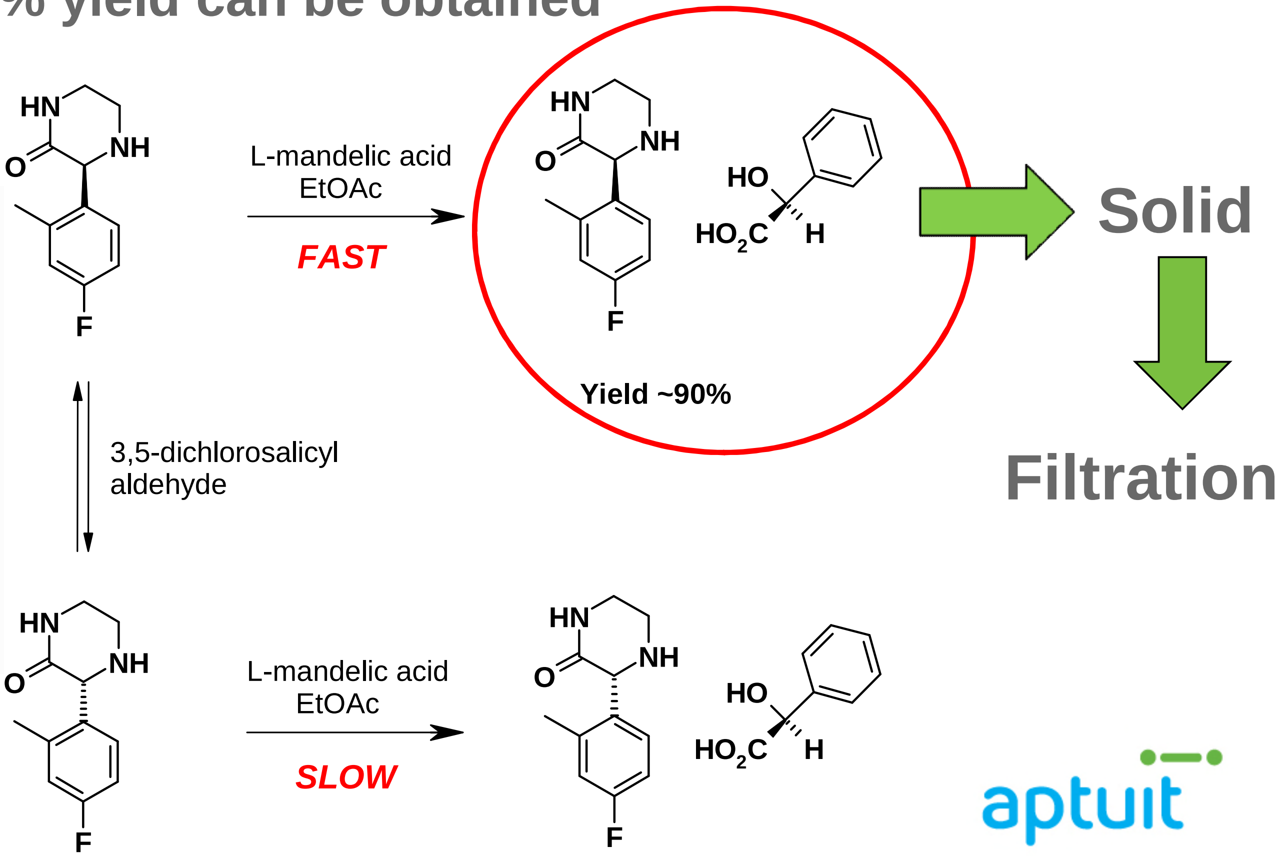
Dynamic Kinetic Resolution (DKR)

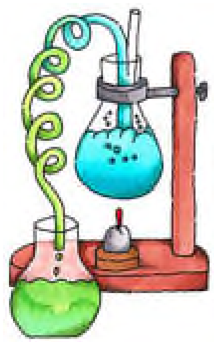
- Well known industrial method
- It combines the resolution step with an *in situ* racemisation
- In theory a 100% yield can be obtained





Lab Optimization

- The reaction was studied in laboratory using “conventional” methods (no statistical tools)



- Very viscous suspension at the beginning, more fluid after stirring
- Scaled on a 5 L scale
- No main issues encountered

- Yield= *ca.* 90% of the pure enantiomer

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Pilot Plant Issues

- **Very difficult azeotropical removal of the water to the target level**

- **Interaction of water with the reaction**

- **Slurry difficult to stir**

- **A considerable amount of product adhering to the reactor walls**

- **Yield decreased from 90% to *ca.* 50%!!!**

Chemical problem or Mechanical problem?

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Back to the lab

- Further understanding and optimization needed
- Brainstorming with different functions (chemists, engineers, analysts etc.)
- DoE required
- Parallel equipment used:
  - Able to mimic pilot plant conditions
  - Mechanical overhead stirring
  - Four reactions at the same time
- An initial screening with many parameters
- Identified three parameters as possible causes
  - Aldehyde amount
  - Water amount
  - Stirring rate

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Design of Experiment

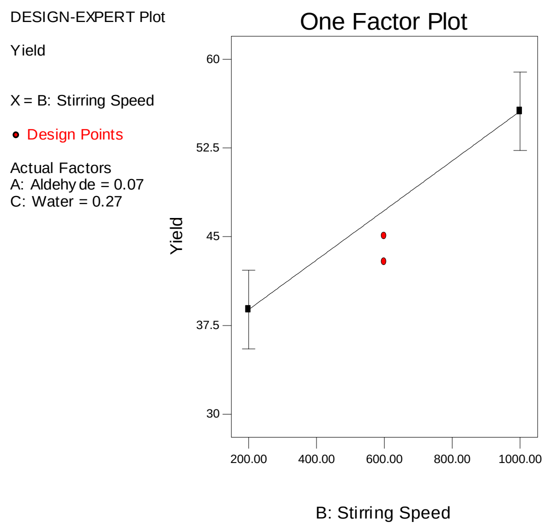
- Three parameters considered
- Three responses:
  - o Solid recovery (yield)
  - o Solid purity (enantiomeric excess)
  - o Total recovery (solid+solution)

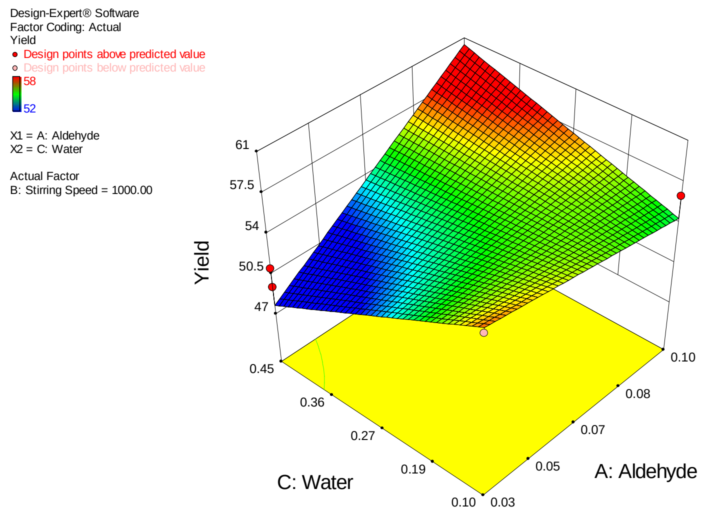
Number of Factors

Experiments	2	3	4	5	6	7	8	9	10	11	12	13
4	Full	1/2 Fract.										
8		Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.						
16			Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.	1/32 Fract.	1/64 Fract.	1/128 Fract.	1/256 Fract.	1/512 Fract.
32				Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.	1/32 Fract.	1/64 Fract.	1/128 Fract.	1/256 Fract.
64					Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.	1/32 Fract.	1/64 Fract.	1/128 Fract.
128						Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.	1/32 Fract.	1/64 Fract.
256							Full	1/2 Fract.	1/4 Fract.	1/8 Fract.	1/16 Fract.	1/32 Fract.

- Fractional Factorial Design (Full) with three Blocks
- Block 2:
  - o Two center points, to evaluate the curvature
  - o Two repeated points (factorial), to estimate the block effect and the pure error
- Twelve reactions

Result output 1: Solid Recovery





B) Stirring rate:

- the most significant factor
- high yields were obtained with high stirring speeds

AC) Interaction Aldehyde/Water

- a larger amount of water was buffered by a larger amount of aldehyde

•Curvature not significant

•Mechanical and Chemical effects

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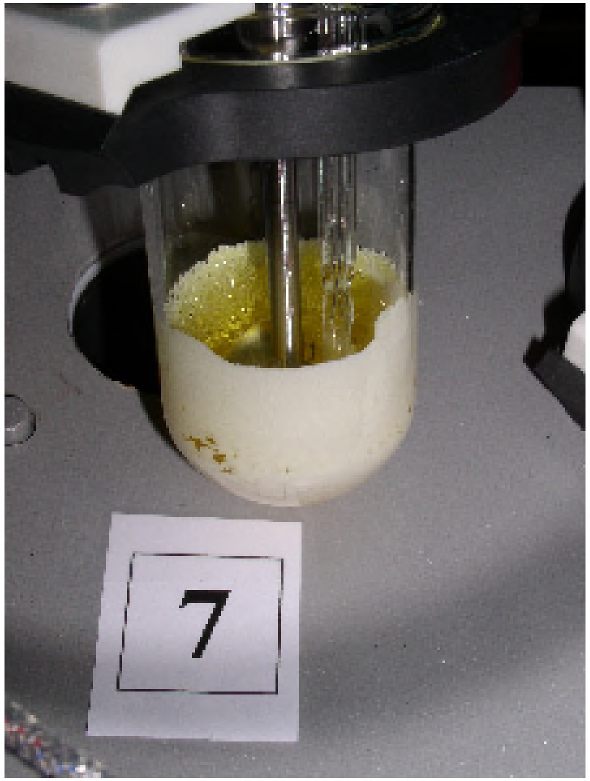
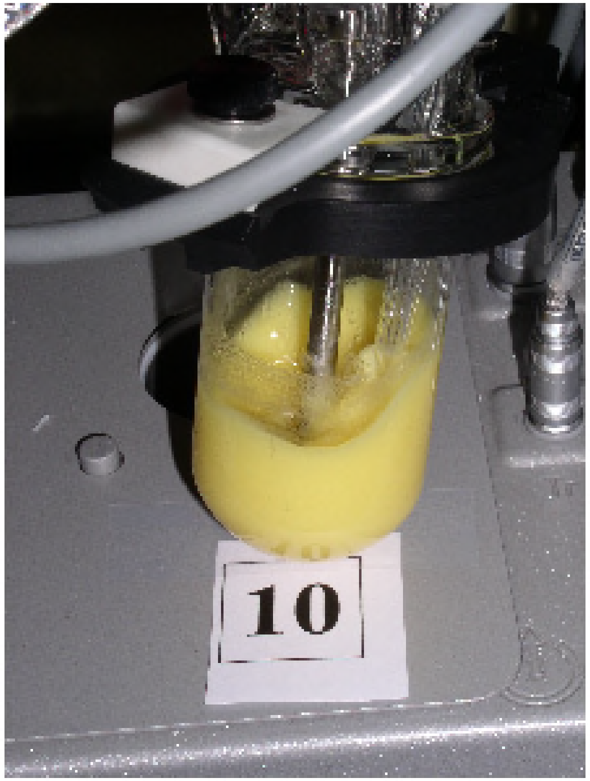
Effect of Aldehyde on the solid





Run7
Aldehyde=0.033wt
Stirring=250rpm
Yield=0%

Run10
Aldehyde=0.1wt
Stirring=1000rpm
Yield=56%

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Result output 2: Solid purity

- Required≥99%
- Response range between 99.0 and 99.75%
- Considered robust!

nse 1 ld	Response 2 e.e.	Re R
.4496	99.51	
.4375	99.24	
.4553	99.37	
.9699	99.49	
.7322	99.4	
.1337	99.27	
.0499	99	
.8612	99.39	
.6679	99.13	
.8361	99.47	
.6173	99.75	
.7023	99.31	

Lowest value

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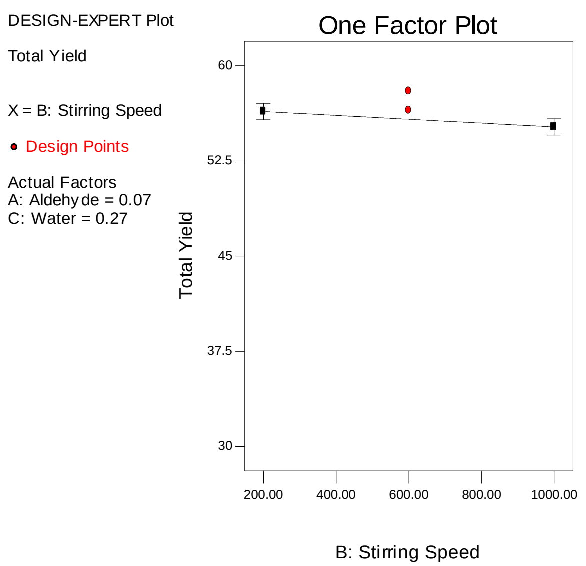
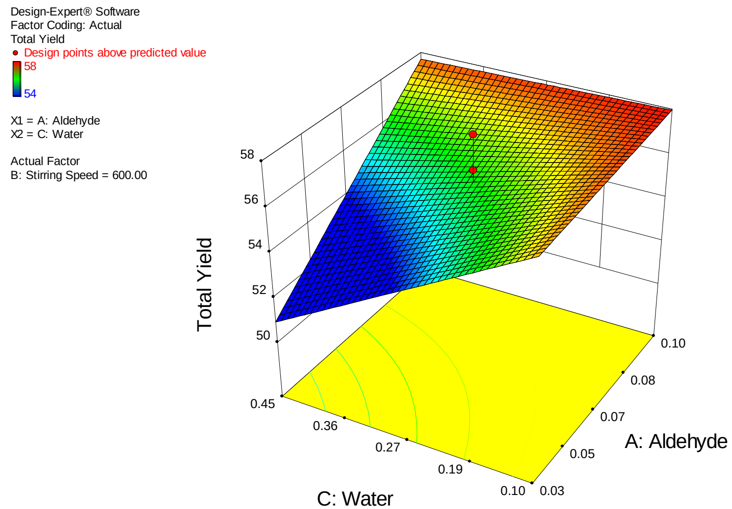
Result output 3: Total Recovery (Solid+Solution)





B) stirring rate:

- **Not significant**

AC) interaction Aldehyde/Water

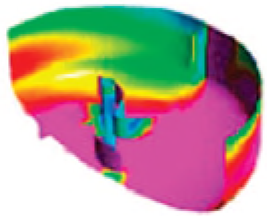
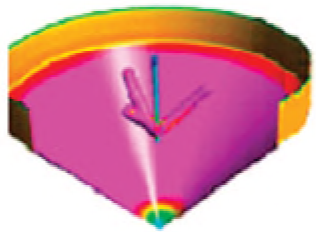
- **The negative effect of higher water amount was balanced by a higher quantity of aldehyde**

- **Curvature not significant**
- **Only Chemical effects**

Computer Modeling

•Design an appropriate reactor configuration

•Ensure efficient mixing.

round bottom + baffles	conical vessel, without baffles
Wall Shear	
	

- **Round bottomed vessel with baffles** (initially employed)
  - Dead mixing zones
  - Encrustation
- **Conical vessel without baffles**
  - No dead mixing zone
  - Ideal for thick suspensions

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Test on the Pilot Plant

- The new process was repeated in the pilot plant using:
    - Suggested vessel configuration
    - More aldehyde
    - Proper stirring rate

- Yield and Purity reproduced

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Conclusions

- Pilot Plant issues

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- Brainstorming to decide how to approach the problem

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- DoE to understand the problem encountered in the Pilot Plant
- Parallel equipment used to mimic on a small scale the problems

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- Identified parameters affecting the final yield
- Computer modeling to identify proper vessel configuration

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- New condition successfully applied on the Pilot Plant

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Synthesis of the NK1 Receptor Antagonist GW597599. Part 1: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine

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