

## Computer Simulations to Study the Efficiency of Solvents in the Synthesis of Benzilidenethiazolidinedione in Micro-reactor

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Abstract: In the synthesis of pharmacological substances, batch process is largely used due to its capacity of high increment of size production. However, this method requires analysis of the system before its enlargement (called "scale-up") that can be complex and longstanding. An alternative way of production is by continuous flow, when the reagents are put together with a solvent in small tubes (usually in micro-reactors) and submitted to high temperatures and pressures. This environment enhances the rate production due to high heat and mass transfer, due to a large surface area through a long extension of the tubes. The continuous flow method does not require scale-up process and results in high quality products (homogeneous mixtures, small reaction time etc.) with ease size production choice [1].

In this context, thiazolidinedione (TZD) derivatives that are used in diabetes treatment can be produced via continuous flow method with benzaldehyde and TZD as reagents. To evaluate the best efficiency production, different configurations of productions were analyzed. Three different solvents were used (Methanol, Ethanol and Propanol) in three temperatures: 98, 120 and 140°C [1]. The experimental data shows that, as temperature rises, ethanol becomes the solvent with best profit, followed by methanol and propanol.

In this work we performed theoretical studies using molecular simulation to try to understand the interactions between the reactants and the solvent in specific thermodynamic conditions used in the micro-reactors. Initially we performed quantum mechanical calculation of the reagents properties (geometry, dipole moment, hydrogen bonds formation; all calculated with the Gaussian09 software[2]). Electronic structure is also calculated separately for the different solvents.

As a first insight, it was found two configurations with hydrogen bond that could enable the reaction between the TZD and benzaldehyde. These two configurations were then used in the initial configuration to simulate the system in solution using Monte Carlo method (with the DICE software [3]), in the correspondent pressure and temperature used in the experimental arrangement. Then, we analyzed the binding energy and the radial distribution functions between the reagents in the presence of the solvent. Our results indicate a small interaction between the reagents. They were separated most of the configurations generated in the simulation. Our result is still not conclusive because we have few configurations to analyze the interactions. Now, we are



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performing longer simulations to perform the analysis and try to understand the reactants interactions in the different solvents and the specific thermodynamic conditions.

Key-words: Synthesis, Continuous flow, Computational Simulation, Monte Carlo, Solvents, Efficiency.

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