JEEP 2023

October 4-6, 2023

Urea derivatives as transporter molecules in sublimation crystallization

K. Li[1,2], G. Gbabode[1], I.B. Rietveld[1,3]*

[1]Laboratoire SMS UR3233, Université Rouen Normandie, Rouen, France;
[2]Zhejiang Institute, Tianjin University, Tianjin, China
[3]Faculté de pharmacie, Université Paris Cité, Paris, France

*ivo.rietveld@univ-rouen.fr

Keywords: active pharmaceutical, crystal growth, intermolecular interaction

Interactions between pyrazinamide and urea derivatives (acetamide, urea and methyl and ethyl substituted urea molecules) in the vapor phase and in solution have been investigated. The presence of urea derivatives increases the crystallization rate and the crystal quality in sublimation crystallization. These effects depend on the vapor pressure of the urea derivatives and the possible interactions between pyrazinamide and the derivatives. No traces of solid solutions or co-crystals between pyrazinamide and the urea derivatives have been found, however.

NMR results in $CDCl_3$ demonstrate that the chemical shift of one hydrogen atom on the amide group (the one which is most removed from the pyrazine ring) of pyrazinamide changes with a change in concentration of pyrazinamide or with a change in concentration of the urea derivative (Figure 1). The chemical shift of the hydrogen atoms of the amide group of the urea derivative changes with a change in the concentration of pyrazinamide as well. Electrostatic potential distribution maps of pyrazinamide and the urea derivatives demonstrate that the highest electron density region is found on the carbonyl oxygen, and the lowest electron density region is found on the hydrogens of the amine group, which therefore clearly induces the interactions observed by NMR.

The interactions revealed in solution appear to be present in the gas phase too and this influences the crystallization of PZA by sublimation in the presence of urea derivatives in terms of a higher crystallisation rate and higher quality crystals. This may be used to obtain a better control over crystal quality of APIs in general.

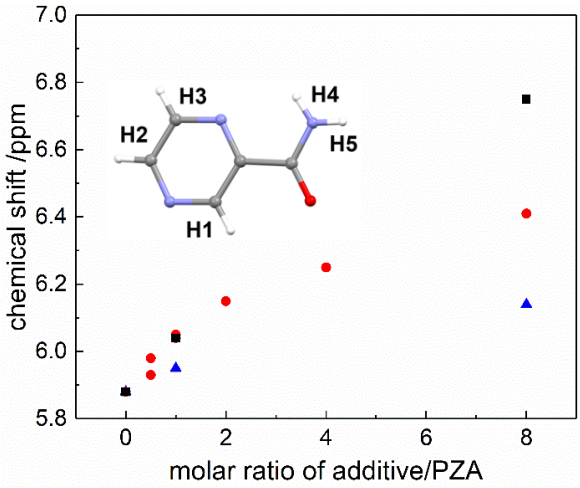

Figure 1. Interaction strength (in terms of chemical shift of the H5 hydrogen atom on the amide group of pyrazinamide) between pyrazinamide and acetamide (black square), 1,3-dimethylurea (red circle), and tetramethylurea (blue triangle). Inset: molecular structure of pyrazinamide.

JEEP 2023

October 4-6, 2023

Preferred type of contribution:

☒ **Poster**

☐ **Oral**

NB : The final decision belongs to the Scientific Committee