CONTROLLING THE POLYMORPHIC FORM OF INDOMETHACIN USING A SUPERCRITICAL CARBON-DIOXIDE METHODS

Fidel Mendez Canellas [1,2], Vivek Verma [1], Jacek Kujawski [4], Lidia Tajber [3], Robert Geertman [2], Luis Padrela [1]

[1] Chemical Sciences, University of Limerick, V94 T9PX, Ireland; [2] Janssen Pharmaceutica, 2340, Belgium; [3] Trinity College Dublin, D02 PN40, Ireland; [4] Wroclaw Medical University, 50-367, Poland

Background: The polymorphic control of active pharmaceutical ingredients (APIs) is vital in the manufacture of medicines within the pharmaceutical industry. Crystallisation methods based on supercritical carbon dioxide are capable of producing unique solid forms of APIs, nevertheless, the control over the polymorphic form remains a challenge. The work presented here shows that the gas antisolvent (GAS) method enables the control of the polymorphic form of indomethacin.

Methods: The GAS method based on supercritical carbon dioxide was explored to control the polymorphism of indomethacin. The effect of the pressure, stirring rate, temperature, solvent, and an additive were studied.

Results: The temperature parameter defined the predominance of the formation of the α form over the γ forms of indomethacin in some cases. However, the control over the production of the α metastable form of indomethacin was achieved when an addition of Poloxamer 407 (4:1 API and Poloxamer 407 ratio) was used in the experiments regardless of the other parameters. Therefore, a detailed molecular modelling study was also conducted and gave insight into the role of Poloxamer 407 in favouring the formation of the α polymorph.

Conclusions: Control over the polymorphic form of indomethacin was achieved with the GAS process using poloxamer 407 as an additive. The two experimental conditions that had an effect on the polymorphism of indomethacin were the temperature and the presence of Poloxamer 407. The α polymorph was consistently obtained from the experiments using this additive independently of all other conditions. Therefore, the GAS method together with the use of additives shows potential for controlling the polymorphism of APIs.