

## Polymorphism of Efavirenz: Crystallization methods, Thermodynamic, and Dissolution Properties.

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### Introduction

Polymorphs, co-crystals, solvates and hydrates have been reported to Efavirenz (EFV) which composes the High Activity Antiretroviral Therapy (HAART) and it is considered the best choice in the treatment of adults and children<sup>1</sup>. However studies about thermodynamic stability and improvement of dissolution properties have been rarely reported to the anhydrous polymorphic forms. In addition, techniques such as X-ray Powder Diffraction (XRPD), Differential Scanning Calorimetry (DSC), Hot Stage Microscopy (HSM), Scanning Electron Microscopy (SEM) and different solvent and temperature conditions were used.

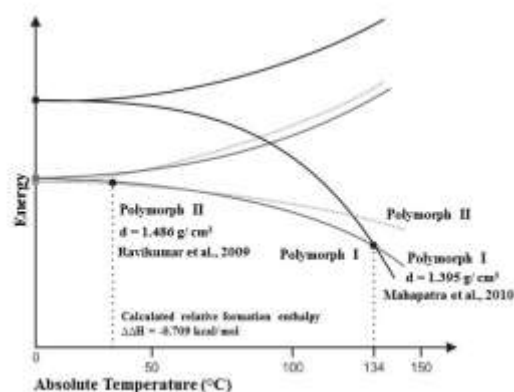
Therefore, the aim of this work was to characterize the solid state of anhydrous polymorph I and polymorph II<sup>2</sup>, to study the thermodynamic stability, strategies to improve the dissolution properties and crystallization conditions for pure forms preparations.

### Results e Discussion

EFV polymorphs I and II were completely characterized by solid state techniques, XRPD, DSC, HSM and SEM. Thermodynamic studies showed that these polymorphs are enantiotropically related and EFV polymorph II is more stable in comparison with polymorph I at room temperature since the isoenergetic point is between 35 °C and 40 °C (see Figure 1). However, the intrinsic dissolution rate of polymorph II is higher than polymorph I by more than tenfold. Therefore, EFV polymorph II is the most stable form (thermodynamic property) and the morphology modification allows the increasing of its dissolution rate (kinetic property).

Crystallization processes using different solvents such as methanol/water and acetone/hexane allowed to obtain different polymorphs in pure forms or mixture of both of them.

**Figure 1.** Schematic free energy versus temperature diagram of EFV polymorph I and II. The calculated relative formation enthalpy points to the polymorph II as the most stable.



### Conclusions

Thermodynamic studies showed that polymorphs I and II are enantiotropic. EFV polymorph II showed itself to be more stable and tenfold more soluble than polymorph I, due to morphology modifications. Solvents and temperature conditions of the nucleation process in the crystallization methods are critical to obtain pure polymorph I, II or mixture of them.

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