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Observation of Polymorphic Transition of Efavirenz during Heating by Raman Spectroscopy

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Abstract: ***Efavirenz as an anti-HIV type 1 drughas a lot of polymorph forms. The references reported it had 23 different polymorph forms include amorphous. But the only form I used in pharmaceutical market widespread which known as a stable form with poor solubility properties. Common knowledge that besides a stable form there is a meta-stable form which has more benefit in solubility. One of themeta-stable forms aim to study in this research was the formβwhich result from methanol recrystallization. Characterization of form β was slightly different both in diffractogram patterns from XRPD (X-ray Powdered Diffractometry) and the thermogram from DSC(Differential Scanning Calorimetry)comparing with apatent. Others characterizations were carried out such as Infrared (IR) vibration spectrums with IR absorption (Fourier Transform IR) and IR scattering (Raman Spectroscopy) to described polymorph functional groups response. To re-examined the polymorphic transition information from DSC the in-situ temperature dependent of Raman spectroscopy was conducted. There has only a little temperature shifting, from the thermogram the polymorphic transition of formβtaken place in the range 108.4–110.4^{o}C, but from Raman spectral information happen in 100–115^{o}C.***

Keywords: Efavirenz, Polymorphic transition, Polymorph

1. Introduction

Determination of crystal forms properties among pharmaceutical development during the industrial process is therefore a crucial step in maintain product quality certainty [1]. Especially with substances which polymorphism phenomenon perform. Thermody-namically, only one form as stable under a specified condition. In practice, however, as long as the stability process meta-stable forms can exist or coexist in the presence of more stable forms. This can have very serious consequences on the life and effectiveness of a polymorphic product and the persistence over time of the desired properties [8].

One of the drugs with polymorphism phenomenon is efavirenz. Efavirenz (EFV) as the second generation for antiretroviral HIV–1 therapy has been reported having 23 different forms include amorphous [5, 6, 7, 9, 10, 12, 13, 14, 15, 16]. But only the stable one (Form I) with poorly soluble properties has been marketed widespread [8]. In addition, to optimal the goal of therapy others meta-stable forms which known having better solubility should be tried. But this strategy should be a careful consideration.

So, this investigation was monitored the polymorphic transition of selected meta-stable form due to heating with in situ temperature dependent in line with Raman spectroscopy. Information from this study has a valuable consideration among pharmaceutical product development.

2. Materials and Methods

2.1 Materials

A pharmaceutical grade of Efavirenz (EFV, Batch No. EZ1670711, Hetero Labs Ltd., India) was purchased from PT. Kimia Farma Tbk, Indonesia.

Figure 1: Molecular structure of Efavirenz

The analytical grade of solvents such as acetonitrile and methanol (ex-Merck, USA) was used in this work. All solvents used were of analytical reagent grade without further purification.

2.2 Methods

Polymorphs preparation
The polymorph forms were prepared following supersaturation solvents of acetonitrile and methanol according to Chadha, 2012.

Characterization

XRPD (X-ray Powdered Diffraction)
The Diffractogram patterns of crystalline polymorphs were analyzed under conditions: voltage 40 kV, 30 mA and fixed divergence slit using the configuration; 2θ range: 5^{o} to 45^{o},

0.02 step size, 0.8 s time per step using XPERT-PRO, PANalytical, Netherlands with Cu-Kα radiation as tube anode

DSC (Differential Scanning Calorimetry)
The thermogram of samples was obtained using NETZSCH DSC 214 Polyma on aluminum crucible under a dynamic nitrogen atmosphere and a heating rate of 10°C/min in the temperature range from 30 to 250°C.

FTIR (Fourier Transform Infrared)
The fingerprint patterns of samples were measured on a multi-scope spectrophotometer (IR Prestige-21 Shimadzu,Japan)by sealing thesample between two KBr plates by a hydraulic press under 200 kg/cm^2 for 15 seconds to form a disc. The range of analyzedwas recorded in 300–4500 cm^{-1}.

Raman Spectroscopy
The vibration spectrums of functional groups of polymorphs were analyzed in Raman dispersive spectroscopy (Bruker–Senterra Micro-Raman Spectrophotometer) uses diode laser system (785 nm, 100 mW) as the excitation source for spectrum recording at room temperature in the spectral regionat 50–3500 cm^{-1}.

PolymorphicTransition Evaluation on Heating Stage
The polymorphic transitions were observed in-situ temperature dependent using a heating/cooling stage (Linkam TM600E Tadworth UK) with in line on Raman dispersive spectroscopy (Bruker–Senterra Micro-Raman Spectrophotometer) and monitored in the range 30°–120°C.

3. Results and Discussions

To given evidence that polymorphs were prepared in various forms, XRPD has been carried out. The diffractogram patterns showed that polymorphs preparation were achieved successfully. From the examined showed that original sample has asimilarpattern with polymorph from acetonitrile recrystallization

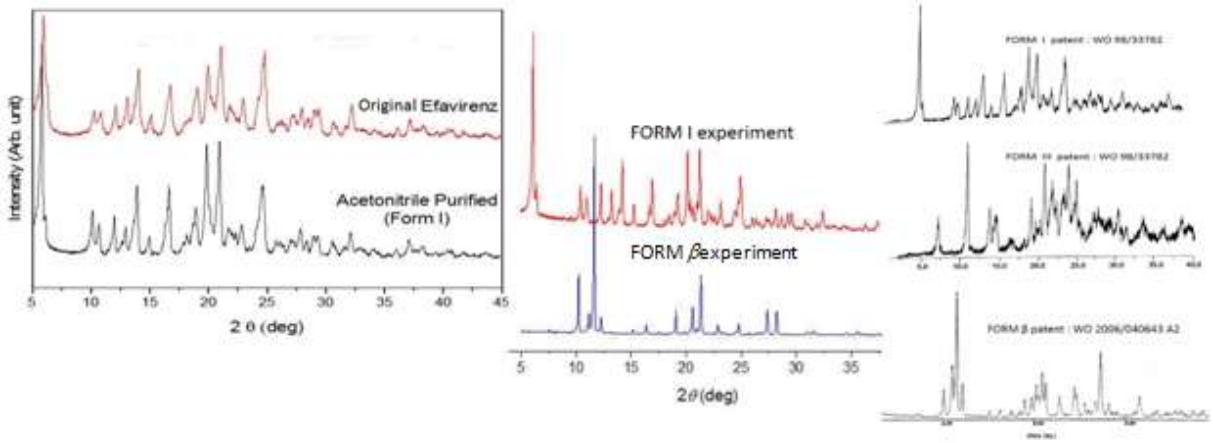

Figure 2: Comparative of diffratogram pattern between polymorphs and patent published

The polymorph was matching with Form I from the patent published no. WO 98/33782, but for the methanol preparation (Form III), there isdifference than those patent number. But if look more another polymorphs in another patent which is no. 2006/040643A2 showed that is likely Form *β*. The thermogram was proven that the polymorph resultfrom methanolrecrystallization has similar properties like Form *β* reported from 2006/040643A2.

It means that around 100–110°C, the polymorph was transformed to Form I. So, to known better the real transition temperature the in situ temperature dependent in line with Raman spectroscopy was conducted to monitored the polymorphic transition.

Before using Raman spectroscopy as a signal to monitored, FTIR was used for complementing the IR spectra. Vibration signals from functional groups in molecular bonding are informed from IR spectra. There are consist with symmetry and asymmetry vibrations. The symmetry vibration common

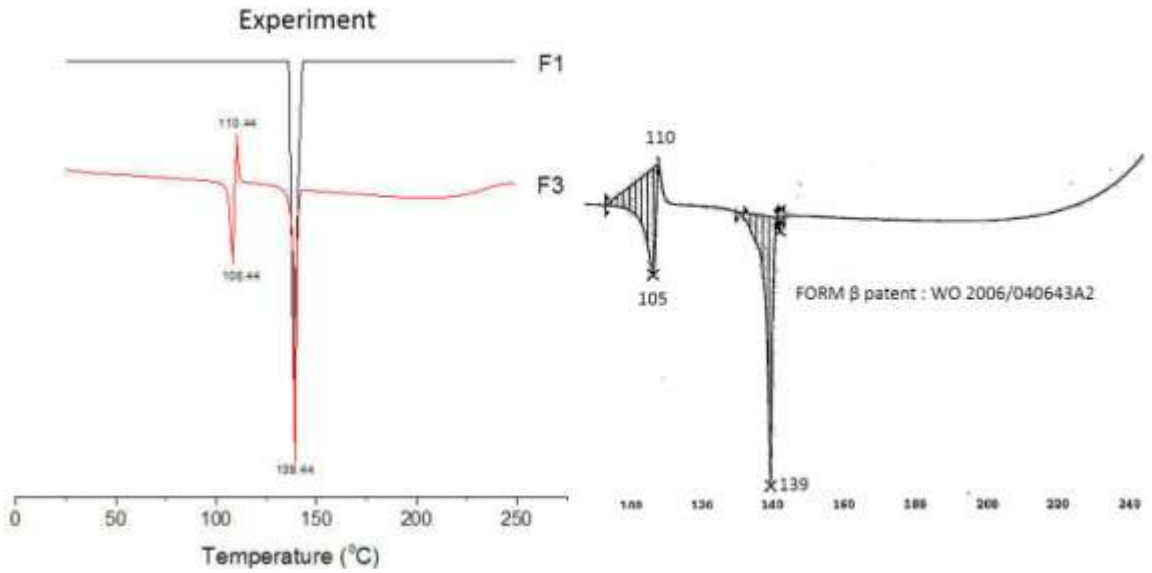

Figure 3: Comparative of thermogram profile of polymorph (especially Form *β*) with patent published

mention as IR active which observed by IR absorption from FTIR and the asymmetry vibration was said to be Raman active which observed by IR scattering from Raman spectroscopy. Examined result from the sample shown there have a little different spectrums from FTIR spectra fingerprints, but have a slightly differenced peaks spectra under Raman spectra scanned. On account of that, the Raman spectroscopy was selected for monitoring the polymorphic transition during direct heating in situ of the equipment. As information from DSC thermogram, heating scanned was conducted in range at 30–120°C. There was found that around 115°C the sample has been transformed completely become to Form I (stable). The shifting of Raman spectra was observed at band 867 cm^{-1} to 863 cm^{-1} and 885 cm^{-1} to vanished. According to Mishra, 2012 [11] this peak represent to the internal coordinate corresponding to the deformation of alkyl chains from the stretching mode*v*(C≡C).

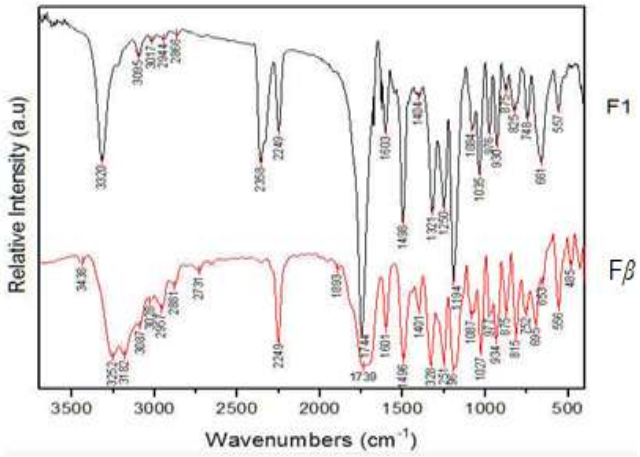

Figure 4: Infrared spectra of polymorphs from FTIR

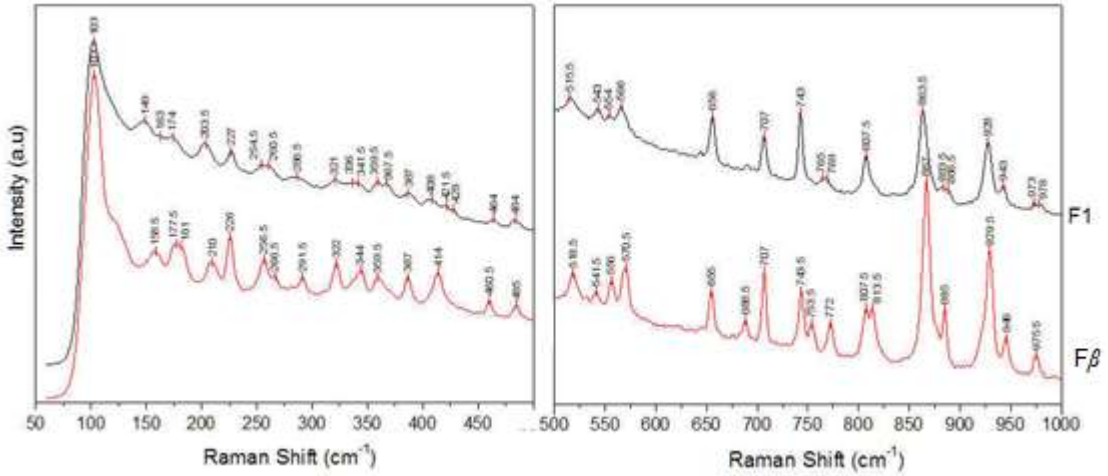

Figure 5: Raman scattering spectra of EFV polymorphs in the region 50–1000 cm^{-1}.

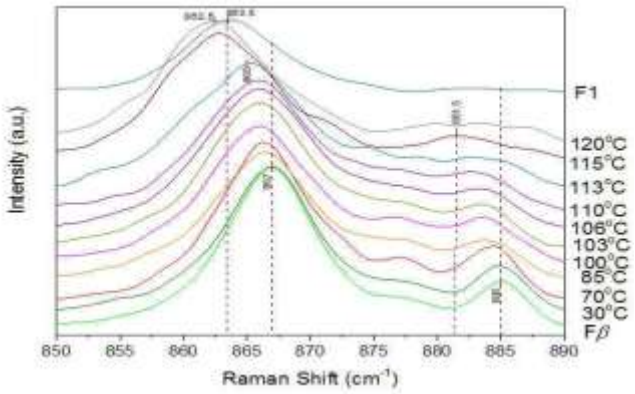

Figure 6: Monitored of Polymorphic Transition from Form β to Form I in Raman spectra around 850–890 cm^{-1}

4. Conclusion

Vibrational spectroscopy especially Raman spectroscopy has been succesfully proven the polymorphic transition of EFV under direct heating condition. The transition point have a little shifted with thermogram information, where the thermogram in the range 108.4–110.4^{o}C, but from Raman spectral information happen in 100–115^{o}C. It may happen cause differ in moment of the detector signal capturedbetween those equipment.

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