

Article

Impact of Solvent-Mediated Phase Transitions by Artificial Gastrointestinal Buffers on Efavirenz Polymorphs

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Abstract: The implications of various pH solutions in the gastrointestinal fluid system as solvent-mediated phase transitions on concurrent polymorphism transformation, notably metastable polymorphic forms of Efavirenz (EFV), has never been investigated. The impact will be shifting in the solubility and crystallinity of EFV polymorphisms, particularly metastable Forms II and III. EFV's metastable form is generated by recrystallization with n-hexane and methanol, which were all immersed in artificial digestion buffer solutions for 10 and 100 h, respectively. Form II showed a 9–13.2% increase in solubility, whereas Form III increased by 2–7.3% over Form I. Interestingly, Form II revealed decreased crystallinity, but Form III tended to retain or slightly increase. In acidic solutions, all metastable polymorphs had the highest solubility and crystallinity. Form III appears to have a lower impact on phase transitions owing to pH variations than Form II. These findings indicate that variability in the pH of digestive secretions are essential steps in developing successful pharmaceutical formulations. Finally, our findings provide information on the complex interaction between solvents, pH variations, and EFV polymorphs. The findings identified the importance of these factors in the development of successful pharmaceutical formulations.

Keywords: efavirenz; metastable polymorphs; solvent-mediated transitions; solubility; crystallinity index; artificial gastrointestinal buffers



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1. Introduction

Studies on increasing the solubility of active pharmaceutical ingredients with poor soluble properties are primarily conducted through a formulation approach. Multi-component modification, in the form of salt, co-crystal, or co-amorphous, is often used to carry out molecular systems. However, polymorphic metastable forms, which theoretically tend to be more soluble, require further investigation. Although several studies have reported the preparation of pharmaceutically active ingredient polymorphs by solvent mediation [1–9], few studies have focused on such metastable forms.

Polymorphism can arise as a result of changes molecular packing in the crystal system, conformational flexibility, and supramolecular synthon competitions. They are characterized appropriately in terms of modifications called packing, conformational, and synthon polymorphism [1,10]. A conformational polymorph regain has been established for a variety of reasons as follows: (1) different conformational polymorphs of the same material can

display considerably different physical and chemical characteristics than one other; (2) the ability to use such polymorphs as ideal systems for comparing and studying structure-property relationships; (3) the enormous interest for the structural characterization and comparison of the polymorphs is a crucial step in determining the single crystal structure; (4) the acknowledgment of their function in pharmaceutical sectors and the high-profile patenting on polymorphism; (5) the ease with which these polymorphs with color and solubility changes may be published in mainstream scientific literature; (6) the crystallization of certain conformational polymorphs may be slightly harder due to the fact that their conformers are less available to experimentation [11–13].

Polymorphism can be contributed to the traditional nucleation hypothesis of crystal growth. Research shows that the growth rate of crystal nuclei may be altered by supersaturation circumstances, temperature variations, and ionic conditions under interfacial tension [3–5,11,14–16]. Because the nucleus can develop from the liquid–solid boundary under particular saturation circumstances, such as the ionic state and pH in an aqueous environment, phase transition events from the solid state influence the degree of crystallinity [3,7,8,11,15,16].

Numerous studies have observed polymorphic solvent-mediated phase transitions with many disparities in dielectric constants [1–3,7,8,11,15–18]. However, drug transitions under the influence of solutions of various pH, particularly in the gastrointestinal tract (GIT), have rarely been reported [10,12,13,15,19,20].

Few studies have focused on observing the effects of solvents on the phase transition phenomenon. For example, the development of pH crystallization has been studied using calcium salts and lysozymes [3,16]. However, this phase transition study did not reveal any properties such as solubility. Nevertheless, this phase alteration changed the degree of the crystallinity index and solubility. This transition phenomenon usually occurs by continuing in a state with more energy than the most stable state, which it cannot pass, called metastable state. In this study, polymorphic efavirenz (EFV) of Forms II and III were reported to have the best solubility [21–24]. Therefore, we aimed to study the impacts of pH on metastable EFV in the GIT solutions.

2. Materials and Methods

2.1. Materials

The EFV of pharma grade (Batch No. EZ1670711, Hetero Labs. Ltd., Nakkapally (Mandal), India) was obtained from PT Kimia Farma Tbk, Indonesia, and Efavirenz branded in market as a comparator. Analytical grade solvents for recrystallisation, such as acetonitrile, n-hexane, and methanol (Merck, USA), were used in this work. All solvents used were of analytical reagent grade without further purification. For solubility and crystallinity effect of the materials used were HCl, NaCl, KCl NaOH, Na₂HPO₄, NaH₂PO₄, KH₂PO₄, potassium hydrogen phthalate (KHP), and boric acid (H₃BO₃). J.T. Baker Chemicals provided all of the analytical-grade reagents that were used. Every buffer and reagent was prepared with water distillation (aquadest) and were CO₂-free.

2.2. Development of Polymorphs

The solid-state forms were made by the recrystallisation of crude EFV in analytical grade organic solvents, i.e., n-hexane, and methanol, and were named Forms II and III, respectively.

2.3. Characterization Methods

2.3.1. Differential Scanning Calorimetry (DSC)

The thermal behavior of polymorphs formed was recorded using NETZSCH DSC 214 Polymer on an aluminum crucible with about 1–3 mg of samples in a dynamic nitrogen environment and a heating rate of 10 °C/min in the temperature range of 30 to 250 °C. Before usage, the DSC instrument was calibrated using indium as a standard reference.

2.3.2. Powder X-Ray Diffraction (PXRD)

An X-ray diffractometer (XPERT-PRO, PANalytical, The Netherlands) using Cu-K α radiation as the tube anode was used to measure the crystallinity of the powders. The following conditions led to the recording of the diffractogram patterns in the following configuration: 2 θ range: 5 $\circ$ to 45 $\circ$, 0.02 step size, 0.8 s time per step, voltage 40 kV, 30 mA, and fixed divergence slit. Care was taken to prevent phase changes during sample preparation.

2.4. Solution-Mediated Polymorphic Transformation Experiments

2.4.1. Artificial GIT Medium Preparation

The preparation of artificial digestion buffers at pH between 1.2–4 was conducted using HCl, NaCl, and KHP with different compositions. At pH 5, KHP and NaOH were used, while at pH 6 and 7, KH₂PO₄ and NaOH were used. Meanwhile, at pH 8 and 9, H₃BO₃, KCl, and NaOH were used following the Indonesian Pharmacopeia Third Edition (39). Samples (10 mg) were dissolved in a methanol and buffer solution with a ratio of 4:6 up to 100 mL, and the pH was checked using a Mettler Toledo S20 pH meter.

2.4.2. Saturation In Vitro Solubility Studies

Approximately 10 mg of each sample was dissolved in 100 mL of each simulated gastrointestinal medium. The media were prepared at the pH of the GIT, i.e., pH 1.2, 4.6, and 6.8. The samples were agitated in the solutions using a mechanical agitator at 120 rpm for 24 h at room temperature. Before measurement, the sample solution was filtered through Millipore 0.45 μ m paper and suitably diluted. The sample solution was measured by UV spectroscopy at 248 nm.

2.4.3. Study of Crystal Transition Due to the Influence of Artificial GIT Medium Soaked

Each crystal form was weighed to around 100 mg and soaked in 5 mL of distilled water, 1.2 hydrochloric acid buffer solution, phosphate buffer pH 4.6, and phosphate buffer solution pH 6.8. After 10 h and 100 h, each solid sample undissolved was filtered and dried by heating at 40 °C. After that, the sample was observed by Powder X-Ray Diffraction (PXRD), and the results obtained were compared with the initial form.

3. Results and Discussion

3.1. Characterizations

Recrystallization was used to investigate the different EFV polymorphs. The process involved steeping and stirring the compound in various solvents produces variations in EFV polymorphisms. Figure 1 represents the characterization of the various EFV polymorphisms based on DSC thermal analysis findings and PXRD powder diffraction patterns, as reported by Wardhana et al. [22,23].

The resulting polymorphs exhibited varying solubility abilities in water and different GIT. As shown in Table 1 and Figure 2, Form II had the highest content among the selected polymorphic solubilities in each artificial GIT fluid. Additionally, the metastable form of EFV had more solubility, which was observed in Form II, with a better solubility increase of up to 13.24%. In contrast, Form III reached 9.18% in the same solvent (artificial gastric

fluid) at a pH of 4.6. For Form II, the increase in solubility was greater than for Form III, with an increase range of 9.37–13.24 % at various pH values.

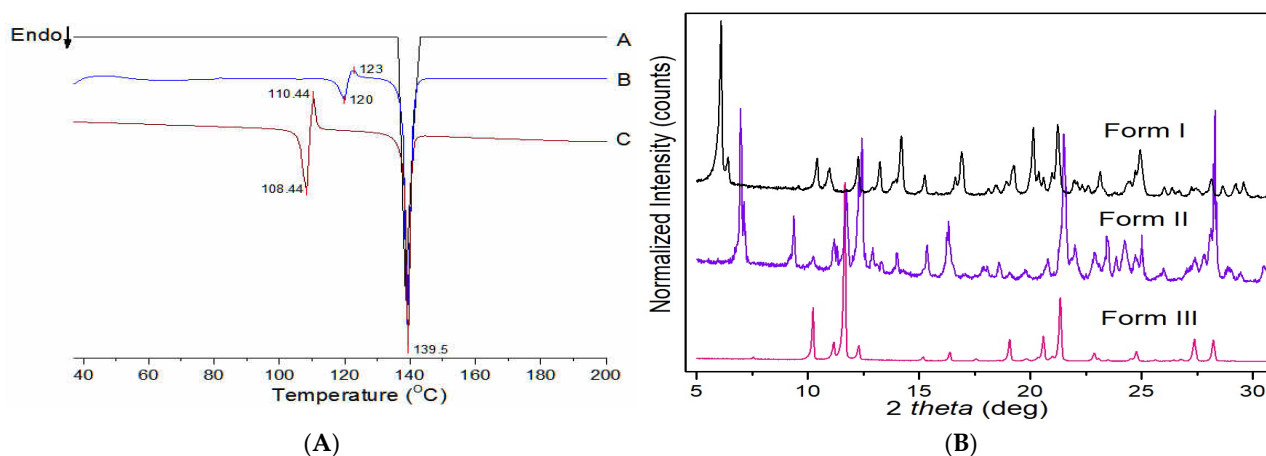


Figure 1. Characteristics of EFV polymorphs by (A) thermogram DSC and (B) diffractogram of PXRD [22].

Table 1. Solubility of EFV polymorphs in various artificial GIT fluids.

Medium	Solubility (µg/mL)			Improvement (%)	
	Form I (Market)	Form II	Form III	I to II	I to III
Water	6.40 ± 0.10	7.13 ± 0.13	6.87 ± 0.79	11.42	7.31
pH 6.8	6.69 ± 0.09	7.38 ± 1.23	7.13 ± 0.73	10.25	6.59
pH 4.6	8.12 ± 0.36	9.21 ± 0.14	8.86 ± 0.24	13.24	9.18
pH 1.2	9.16 ± 0.06	10.03 ± 0.02	9.39 ± 0.07	9.37	2.41

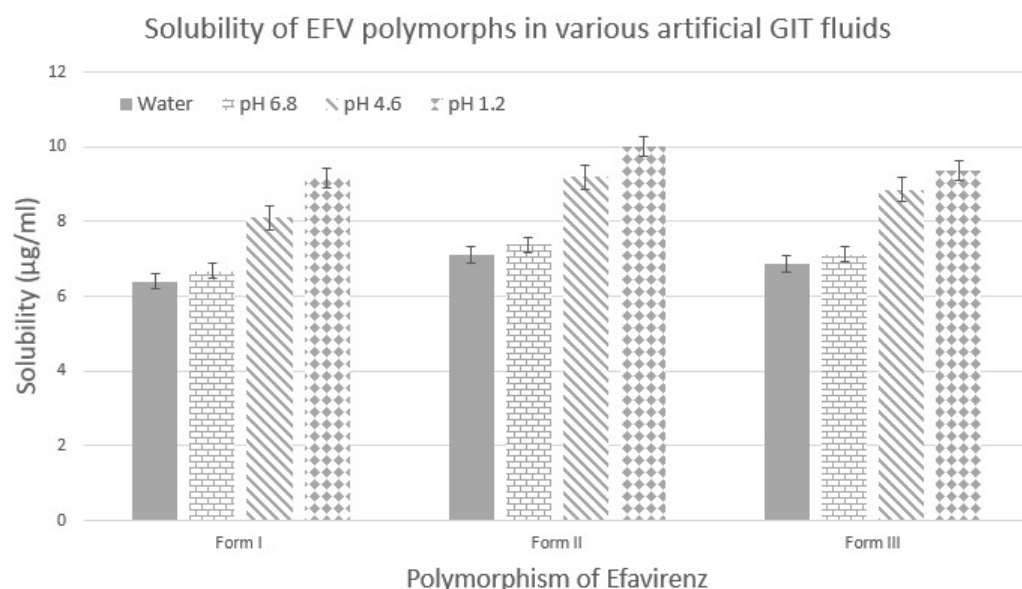


Figure 2. Solubility of EFV polymorphs in various artificial GIT fluids.

All EFV polymorphs appeared to have higher solubility in alkaline than in acidic pH conditions. The optimum solubility for all forms is seen at pH 4.6, which may be a consideration in maintaining the level of solubility in the next step for developing of more the pharmaceutical dosage forms. Examining the outcomes that enhance the solubility

between the polymorphs could lead to the selection of Form II, but a thorough review of other factors is necessary before making a definitive choice. Another factor to examine is its stability, particularly its susceptibility to damage caused by pH changes that take a long time to transit through the gastrointestinal system. As it turns out, this study was done to give a more in-depth investigation of polymorph selection.

3.2. Solution-Mediated Polymorphic Transformation Experiments

Ease of alteration or phase transition in solvent medium with varying ionic strengths should also be considered. As the outcome, all metastable forms of EFV were soaked for 10 h and 100 h at different pH levels to determine their transformation capacity. The modifications in metastable crystals caused by this soaking are represented in the PXRD patterns (Figure 3) estimated for their crystallinity, as seen in Table 2.

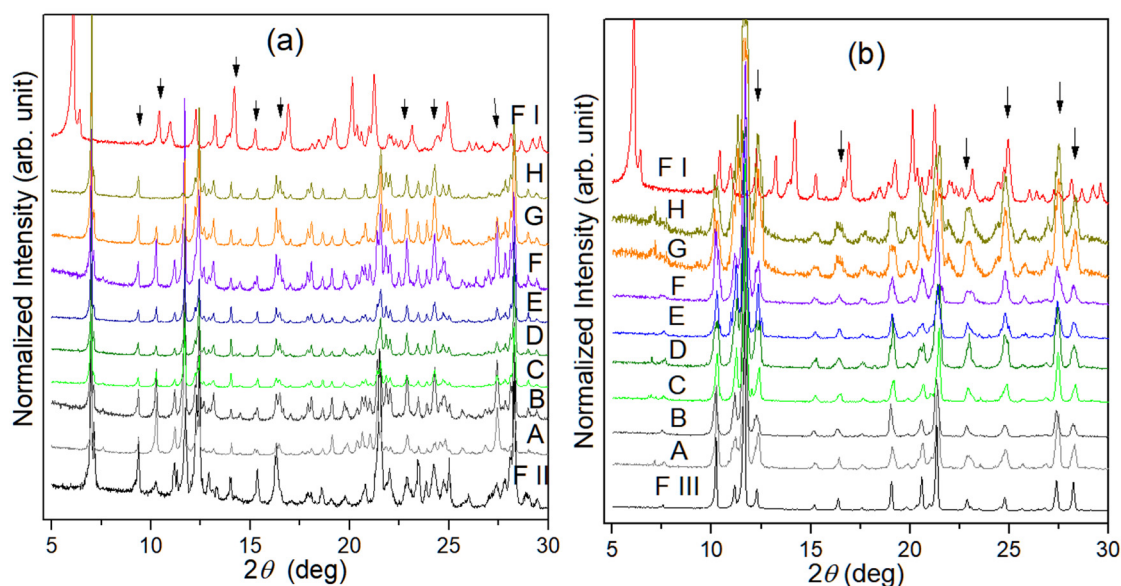


Figure 3. Changes (arrows indicate peak changes that occur) in the X-ray diffraction patterns of EFV metastable polymorphs (a) Form II, (b) Form III under soak at various artificial GIT fluids; A. Water in 10 h; B. Water in 100 h; C. Buffer pH 6.8 in 10 h; D. Buffer pH 6.8 in 100 h; E. Buffer pH 4.6 in 10 h; F. Buffer pH 4.6 in 100 h; G. Buffer pH 1.2 in 10 h; H. Buffer pH 1.2 in 100 h.

Table 2. The crystallinity of EFV after being soaked in various artificial GIT fluids.

Medium	The Crystallinity of EFV Polymorphs (%)	
	Form II	Form III
Baseline	92.06	75
Water	10 h	76.85
	100 h	77.53
pH 6.8	10 h	72.72
	100 h	67.93
pH 4.6	10 h	66.14
	100 h	77.78
pH 1.2	10 h	82.70
	100 h	72.72

The table shows that the degree of crystallinity of the polymorphs was affected by the ionic strength, which changed the crystal pattern. Form II decreased the crystalline quality in all pH mediums, while Form III showed steady or increased crystallinity in artificial GIT fluid (pH 1.2). Form II has the highest crystallinity, but is easily affected by the interaction of the ionic field, which can decrease its baseline crystallinity from 92.06% to 66.14% or 25.92%. In contrast, Form III, from a baseline of 75%, only declined to 61.64% or 13.36%, which had transformed. As shown in Figure 1, the significant peak changes of Form II in 2 theta angles are 9.37; 10.27; 11.2; 15.36; 16.32; 21.49; 22.87; 27.42, and Form III are 10.23; 11.17; 12.29; 21.33; 24.76; 27.37. Thus, the crystal lattice of Form III can better withstand the attack of ionic forces in the atmosphere of the digestive tract than that of Form II, indicating that the internal structural stability of Form III is better than that of Form II under various pH conditions.

According to CCDC data of EFV polymorphs for which Forms I, II, and III have pattern matches with the database at disposition numbers 767883, 758360, and 728655, the database being identified is termed AJEYAQ01, AJEYAQ, and AJEYAQ02, respectively. The polymorphic forms of alterations in molecular packing have only small modifications, with an orthorhombic shape overall but variations in the Z value, space group, and cell volume [21]. This is one of the building blocks that can account for polymorph solubility discrepancies. While supramolecular synthon bindings change amongst polymorphs, Form I exhibits the stiffest and tightest synthon bonds when compared to the polymorphic forms of Forms II and III. This situation appears to better explain the ability of EFV to dissolve in polymorphic modifications. Furthermore, the intermolecular conformation model shows that Form III has a little gaps as compared to Form II due to its resistance to ionic circumstances. Meanwhile, Form I is a stable form that is difficult to penetrate beneath both hydrogen bonding and ionic environments. Apart from the obvious information, the structural lattice is portrayed with tight gaps between molecules, which is further confirmed by the cell volume and Z value of each form, with Form III having the smallest cell volume and Z value.

The ionic strength of the solvent may impact conformational changes between polymorphs (as seen in Figure 4) when the crystal information above is analyzed using the Bravais–Friedel–Donnay–Harker law. The study of this image reveals that Form II is an intermediate form based on the ease of group mobility. Its role is to transition from a closed B synthon to an open C synthon. Aside from that, according to information on its solubility in water, Form II has a larger solubility capacity than Form III, indicating a lower Gibbs free energy; therefore, modifications are still feasible.

Figure 5, predicting of habit transition between polymorphs by ionic strength in water as solvent. The ease of dissolving in various ionic conditions appears to be correlated with disrupted molecular stability; basic conditions have a stronger tendency to affect conformation than acidic conditions. The alkaline environment causes a substantial decrease in crystallinity, and corresponds to a pKa value of EFV in the range of 10 [24], particularly for Form II as compared to Form III. This highlights the need for taking into consideration aspects other than dissolving ability. Looking at the metastable form of EFV, it has the capacity to remain present in many ionic conditions, whereas Form III is durable.

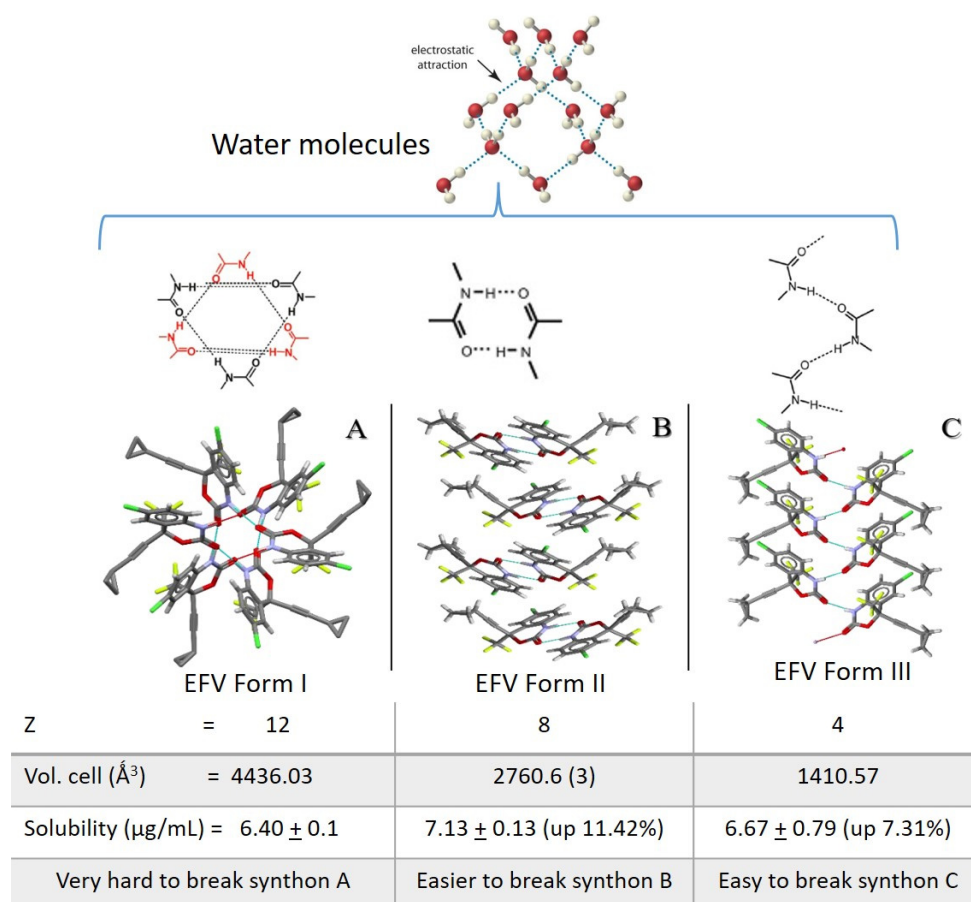


Figure 4. Predicting the defensive mechanism of the crystal structural lattice of polymorphic modifications of EFV against hydrogen bonds using molecular model analysis (A) is molecule model for Form I, (B) is Form II, and (C) is Form III with different synthon from CCDC (Cambridge Crystallographic Data Centre).

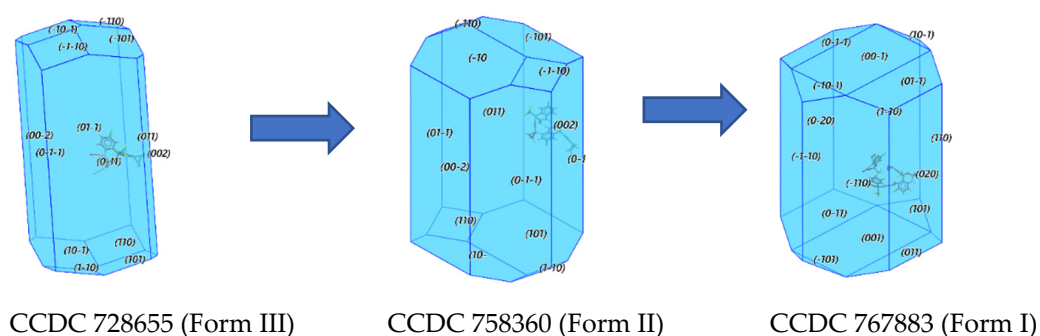


Figure 5. Predicting of habit transition between polymorphs by ionic strength in water as solvent.

4. Conclusions

The decision to choose a polymorphic form for usage in a dosage form demands thorough evaluation, not only of the superiority of one characteristic, such as solubility. In this study, we further demonstrate that the chosen metastable forms can alter in vitro in response to ionic stimuli in the gastrointestinal tract using artificial gastrointestinal fluids. According to the facts from the findings of soaking in the digestive system for varied durations of 10 h and 100 h, the alterations tend to remain, indicating that the metastable form with its highest solubility, Form II, but easily modified by ionic environments especially in basic environment. For EFV, the ionic conditions that impact crystallinity transition are

alkaline, demonstrating that the metastable Form III can endure better with a sufficient amount of solubility.

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Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

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