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EFAVIRENZ DISSOLUTION ENHANCEMENT II: AQUEOUS CO-SPRAY-DRYING

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Keywords:

Efavirenz, Dissolution, Spray-Drying, Sodium Lauryl Sulfate, Polyvinylpyrrolidone.

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ABSTRACT: Efavirenz is a crystalline lipophilic solid with a low aqueous solubility and intrinsic dissolution rate. It is classified in class II of the Biopharmaceutics Classification System, which means it is poorly water-soluble and highly permeable. Spray drying is a widely used manufacturing process wich uses the aerosol phase to dry particles. By modifying the spray drying operation parameters, it is possible to control the properties of spray dried particles towards enhancement of drug bioavailability and delivery. Most studies use organic solvents but some of them have already been prepared as water based systems. We propose the use of water as solvent, since the use of organic solvents is increasingly contraindicated in pharmaceutical industry. The use of water, normally do not generate amorphous systems for low soluble drugs, increasing wettability and drug dissolution, do not leading to stability concerns. The results obtained demonstrate that co-spray-drying of EFV:SLS and EFV:PVP samples is an effective technique in the enhancement of efavirenz dissolution, in a process industrially viable. Different from results previously obtained with co-micronization, PVP was more effective than SLS in the dissolution enhancement of efavirenz when used co-spray-drying process. The characterization proved that the dissolution enhancement was not derived from drug amorphization and that there was any dangerous interaction between the drug and the carrier. Dissolution enhancement is probably related to the formation a hydrophilic layer in drug particles, inducing the interaction with the dissolution medium. The samples demonstrated potential to provide a better bioavailability based on the systems formed.

INTRODUCTION: Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor [1], orally active and is specific for HIV type 1. EFV is a crystalline lipophilic solid with a low aqueous solubility and with a low intrinsic dissolution rate [2]. It is classified in class II of the Biopharmaceutics Classification System, which means it is poorly water-soluble and highly permeable. The low solubility of the EFV in aqueous medium hinders the absorption and biodistribution of the drug from the GI tract [3]. A spray-drying (SD) procedure converts a liquid feed into solid particles with specific characteristics modeled by the equipment design, the operating conditions and the process variables [4, 5]. Spray-drying is a widely used manufacturimg process based on the aerosol phase to dry particles, and this technology has been applied in many areas [6]. In the pharmaceutical industry it is used for different kind of substances,

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as well as for preparation of microparticles and slow-release formulations [7]. SD is commonly used in industrial process because the powders obtained meet the highest quality standards in terms of particle size distribution, homogeneity and shape. By modifying the spray-drying operation parameters, it is possible to control the properties of spray-dried particles towards enhancement of drug bioavailability and delivery [8 – 10]. One modification of the technique is co-spray-drying, in which different materials are solubilized or dispersed in a solvent and then sprayed. This procedure has been adopted for diverse proposes. The first one is stability enhancement, as demonstrated by Shen et al.[11], who prepared amorphous systems of ibuprofen, which were stable for 12 months. Other application is in inhalable systems, as Adi and collaborators[12] developed systems with higher antiinflamatory and osmotic effect based on ciprofloxacin and mannitol. It can also be generated samples with processability advantages, as demonstrated by Gonnissen et al.[13] by the preparation of paracetamol particles for direct compression.

In the case of release control, Al-Zoubi et al.[14] developed a sustained release formulation based on buspirone hydydrochloride. And, most important in the case of the present study, the dissolution/bioavailability enhancement systems have been described in the literature, as demonstrated by Pomázi et al.[15] with meloxicam, Sahoo and collegues[8] with artemisinin microparticles and Vogt and co-workers[16] with fenofibrate nanosizing, and many others [17–20, 9, 10].

Specifically in the case of efavirenz, Yang and co-workers[21] prepared amorphous solid dispersion of the active pharmaceutical ingredient (API) and PVP by spray-drying technology, where the purpose of work was understanding the factors governing the recrystallization of amorphous solid dispersion and develop a kinetic model capable of predicting the physical stability, nevertheless, any dissolution study was made. Furthermore, amorphous systems are inherently instable, and decrease of dissolution can occur with the time.

In the present study, PVP and SLS were elected as carriers because of its historical safety use in pharmaceutical formulations and also because of their use in recent works with the same aim [9, 10, 20].

Most studies cited in the literature use organic solvents but some of them have already been prepared as water based systems [12 – 15, 9, 10, 20]. We propose water as solvent, since the use of organic solvents is increasingly contraindicated in industry.

The water is a non-toxic, non-inflammable and low cost solvent. The samples prepared for solubilization generate often amorphous systems, which are unstable and tends to recrystallization. The use of water normally does not generate amorphous systems, increasing wettability and drug dissolution, but do not leading to stability concerns[22].

In previous studies, our research group have developed alternatives based on co-micronization to increase the dissolution rate of efavirenz. Based on the satisfactory results obtained, the same proportions of the carriers have been tested by a co-micronization technique, providing satisfactory results [23]. So, the objective of the present work was processing efavirenz by the co-spray-drying technique, with the same carriers tested by co-micronization, SLS and PVP, with the aim of enhancing the drug dissolution.

MATERIALS AND METHODS:

Spray Dried Powders:

The carrier (SLS, obtained from Vetec or PVP K30, purchased from Jlaozuo Meida Fine Chemicals) was dissolved in water and the drug (efavirenz) was dispersed in this solution, under magnetic agitation. The dispersions were homogeneized using an Ultraturrax (T18 IKA) for 30 min at 10000 rpm, and dried using a spray dryer (MSD 1.0, Labmaq) with 110 ± 5 ºC inlet and 60 ± 5 ºC outlet temperature. The other parameters were suspension feed rate of 0.4 L/h spray-dryer nozzle two-fluid (diameter of 1.2 mm), drying air flow rate 1,0 m³/min and air pressure 4 Kgf/cm². During the drying process the system was kept under magnetic stirring. The mass proportions drug:carrier tested were (1:0.50), (1:0.25) and (1:0.10), considering that the suspension should have a maximum of 20% (w/w) total solids. Samples with only carriers, without drug, were also processed, for comparison.

Scanning Electron Microscopy (SEM):
Scanning electron microscopy (SEM) was used to visualize the morphology of spray-dried particles and to determine particle size. The powder samples were mounted on aluminum stubs with double coated carbon conductive tape (Pelco Int.) and sputtered with gold in a Balzers apparatus, model FL-964. Observations and micrographies were made in a Jeol JSM-5310 scanning electron microscope [24].

Fourier Transformed Infrared (FTIR) Spectral Studies:
The FTIR analyses were done to confirm the occurrence of structural changes at molecular level due to co-processing of EFV with carriers SLS and PVP [25]. The FTIR spectrum was recorded in the transmission mode on Prestige FTIR 8000 Shimadzu spectrometer. The analyses were conducted applying Fourier transformed infrared (FTIR) spectroscopy where band positions are presented in wavenumbers (v) usually expressed in inverse centimeter (cm^{-1}), and band intensities expressed as transmittance (T). Approximately 3 mg of each sample was weighted and mixed with potassium bromide and compressed in hydraulic press under 10 T for 1 minute.

Differential Scanning Calorimetry (DSC):
This technique was used for evaluation of possible crystalline changes or drug degradation. DSC analysis was performed on spray-dried powders on Mettler Toledo differential scanning calorimeter model 822^e. Samples were analyzed using a heating rate of 10 ºC/min from 25 ºC to 250 ºC. The samples were weighted in open aluminum pans. An empty pan was used as reference.

Thermogravimetric Analysis (TGA):
A Mettler Toledo thermogravimetric analyzer model 851^e was utilized. Approximately 10 mg of each sample was weighted in aluminum pans. Sample mass was monitored and the temperature was increased from 25 °C to 300 °C at a rate of 10 ºC/min.

Hot-Stage Microscopy (HSM):
Hot-stage microscopy is a thermoanalytical technique in which optical property of the sample is monitored against the temperature or time, while the temperature of the sample, in specified atmosphere, is programmed. The information collected during visual analysis is valuable for the confirmation of physical changes detected in the DSC analysis. The heating rate should be the same used in DSC analysis, allowing direct comparison between results. HSM is required to confirm transitions such as melts and recrystallizations [26].

HSM was conducted using a heating cell FP 82 and a temperature controller SP 90 both Mettler Toledo, with an Olympus BX 50 optical light microscopy. The images were obtained at a heating rate of 10 ºC/min, in a temperature range of 30 ºC to 200 ºC.

Powder X-Ray Diffraction (XRD):
Powder X-ray diffraction (XRD) measurements were carried out in a Miniflex Rigaku diffractometer using the operation conditions as follows: Cuk_α radiation (λ = 1,5418 Å), voltage 30 Kv, current 15 mA and time constant 0,05 º/s.

Powder Dissolution Studies:
The powder dissolution method has been reported in the literature [22, 27, 28]. The 5th edition of the Brazilian Pharmacopea [29] indicates the use of aqueous solution containing 1% (m/v) SLS as dissolution medium for EFV tablets, while US Pharmacopea [30] preconizes 2% of SLS. Concentrations greater than 0.5% of SLS showed to not discriminate powder dissolution for EFV in previous studies (data not presented – internal results); Ad and coworkers [31] presented similar results). The dissolutor used was a Distek 6100.

Powder samples containing 600 mg of efavirenz (dosage presented in reference drug product) were put into dissolution vessels, stirred at 50.0 ± 0.1 rpm, using the paddle method (USP apparatus II). The media used was 900 mL of aqueous solution with 0.5% of sodium lauryl sulfate. The temperature was maintained at 37.0 ± 0.2 ºC. The dissolved solution samples of 10 mL were collected at 5, 10, 15, 30 and 45 minutes and filtered through 0.45 µm pore membrane. Samples were analyzed using an UV Shimadzu spectrophotometer and measured by absorption approach at 248 nm. For each sample the dissolution test was performed using 3 vessels.

The powder dissolution profiles were compared using a model independent method, based on calculation of similarity (*f*2) factor. Two dissolution profiles are considered to be similar if *f*2 has results between 50 and 100 [33].

RESULTS AND DISCUSSION:

Scanning Electron Microscopy (SEM):

From direct measurement by microscopy the unprocessed EFV particle presented sizes below 5.9 µm, the unprocessed excipients SLS and PVP, below 5.0 µm and 36.3 µm, respectively. The shape and surface morphology of spray dried microparticles are presented in **Fig. 1**. Those parameters are mainly determined by two factors, the rate of droplets evaporation and composition[34]. The SEM pictures show that these particles are, in general, spherical, especially the particles dried using PVP as carrier. These particles present higher homogeneity and are smaller than those obtained with SLS.

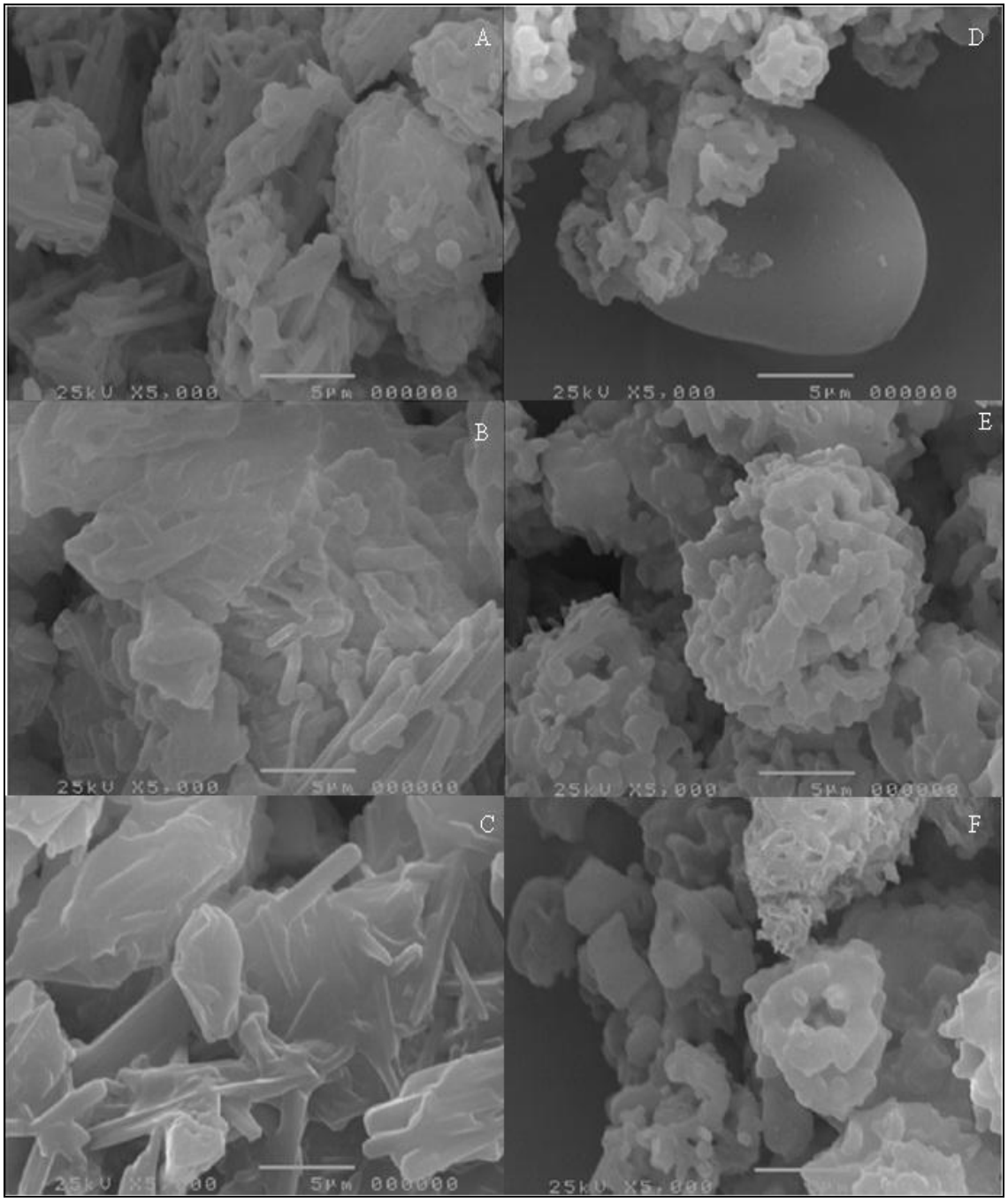

FIG. 1: CO-SPRAY-DRYING SAMPLES PHOTOMICROGRAPHS.

A. EFA:LSS 1:0.10, B. EFA:LSS 1:0.25, C. EFA:LSS 1:0.50, D. EFA:PVP 1:0.10, E. EFA:PVP 1:0.25 and F. EFA:PVP 1:0.50.

Using this technique, the higher the particle size, the greater the amount of carrier used. The average particle size measured directly is represented in **Table 1.**

TABLE 1: AVERAGE PARTICLE SIZE OF SAMPLES.

	Particle size (µm)	
	SLS	**PVP**
EFV:dispersant (1:0.10)	7.3 µm	4.7 µm
EFV:dispersant (1:0.25)	10.3 µm	9.3 µm
EFV:dispersant (1:50)	22.5 µm	8.7 µm

When SLS was used as carrier, the comicronized mixtures [23] resulted in smaller and more homogeneous particles than those obtained by co-spray drying, both in shape and size. In the case of PVP as carrier, otherwise, informations relative to particle size were not conclusive for a better comparison between both techniques, but co-spray-dried particles presented higher homogeneity then co-micronized ones. Informations about particle size are of great importance in the evaluation the dissolution enhancement of the processed systems in comparison with unprocessed drug. But other parameters, so as crystallinity and wettability, are also important and should be also evaluated in a product development plan.

Fourier Transform Infrared (FTIR):

The samples were analized in the range of 2500 – 500 cm^{-1}, where lies the most important peaks for the evaluation of EFV. FTIR spectra of unprocessed EFV showed characteristic bands, similarly to the spectra obtained by Shown and coworkers [35].

The spectra of the three proportions of EFV:SLS and EFV:PVP tested in spray drying technique are presented in figures 2 and 3, respectively, comparing to unprocessed EFV, SLS and PVP.

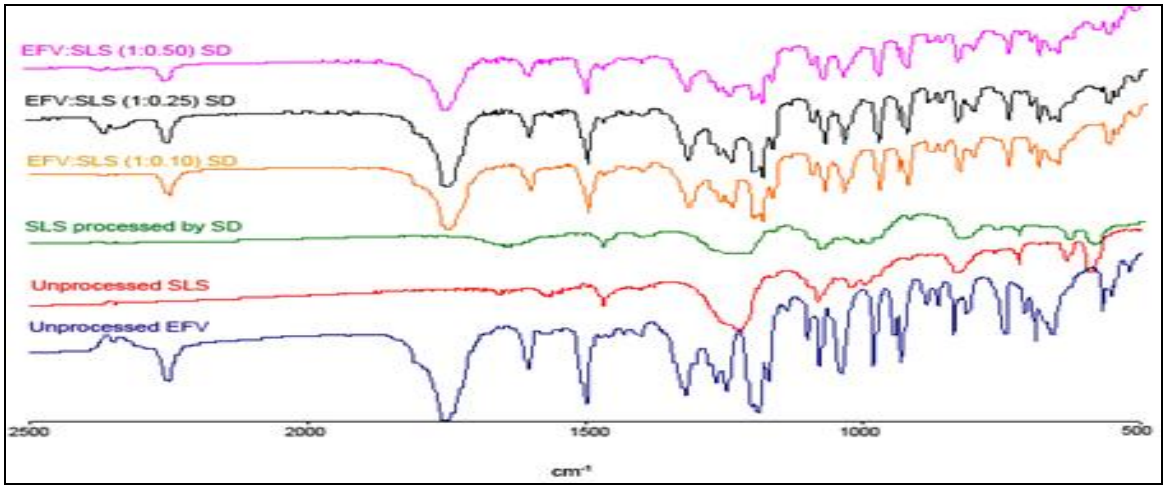

FIG.2: FTIR SPECTRA OF EFV:SLS SAMPLES.

Spectra of unprocessed efavirenz and SLS, spray-drying SLS and co-spray-drying mixtures of EFV:SLS 1:0.10, 1:0.25 and 1:0.50.

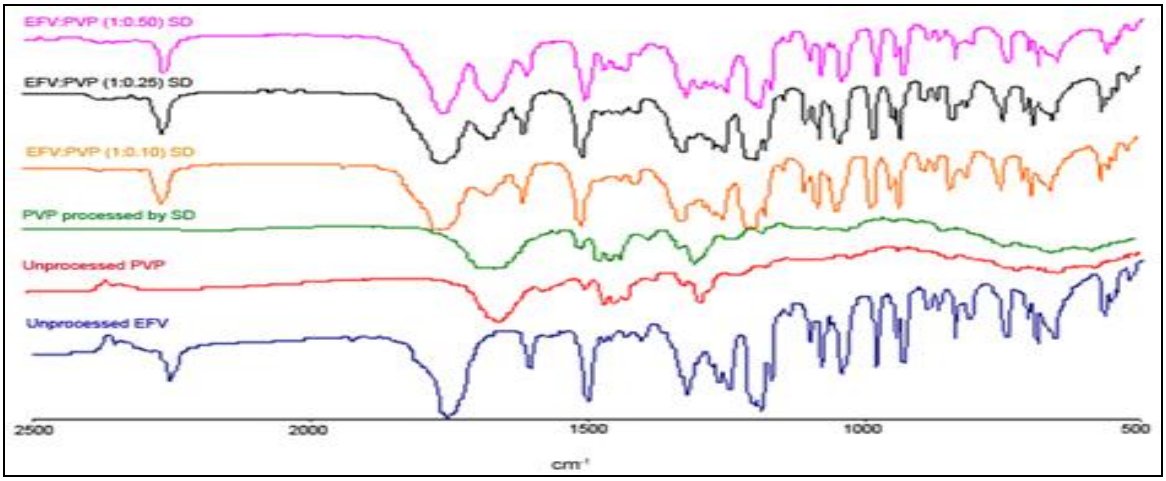

FIG.3: FTIR SPECTRA OF EFV:PVP SAMPLES.

Spectra of unprocessed efavirenz and PVP, spray-drying PVP and co-spray-drying mixtures of EFV: PVP 1:0.10, 1:0.25 and 1:0.50.

All systems obtained by spray drying showed similar spectra to those of hte corresponding physical mixture (data no showed), and there was not observed peak enlargement or displacement, with no indication of interaction in molecular or structural levels between the drug and the carrier. The same inference based on FTIR was used by other authors [15, 17, 20].

Differential Scanning Calorimetry (DSC):

The **Fig.4** shows DSC curves of unprocessed SLS and EFV and spray-dried EFV:SLS processed samples. The unprocessed EFV presented an endothermic peak at 137ºC, similar to the result obtained in literature, as Madhavi et al.[2] attributed the temperature range 135.27°C – 139.79°C to melting of EFV. SLS curve presented a first event, relative to water loss, and a second one attributed to melting point, as has been proved by hot-stage microscopy here and in the previous paper [23].

In DSC curve of EFV:SLS (**Fig. 4**) it is possible to observe the EFV melting point (3) in the sample with major concentration of EFV. Decreasing the drug concentration this peak gradually disappears. The peak referent to water loss (1) is present in all proportions and the peak referent to SLS melting (2) is displaced. These results can indicate some interaction between components.

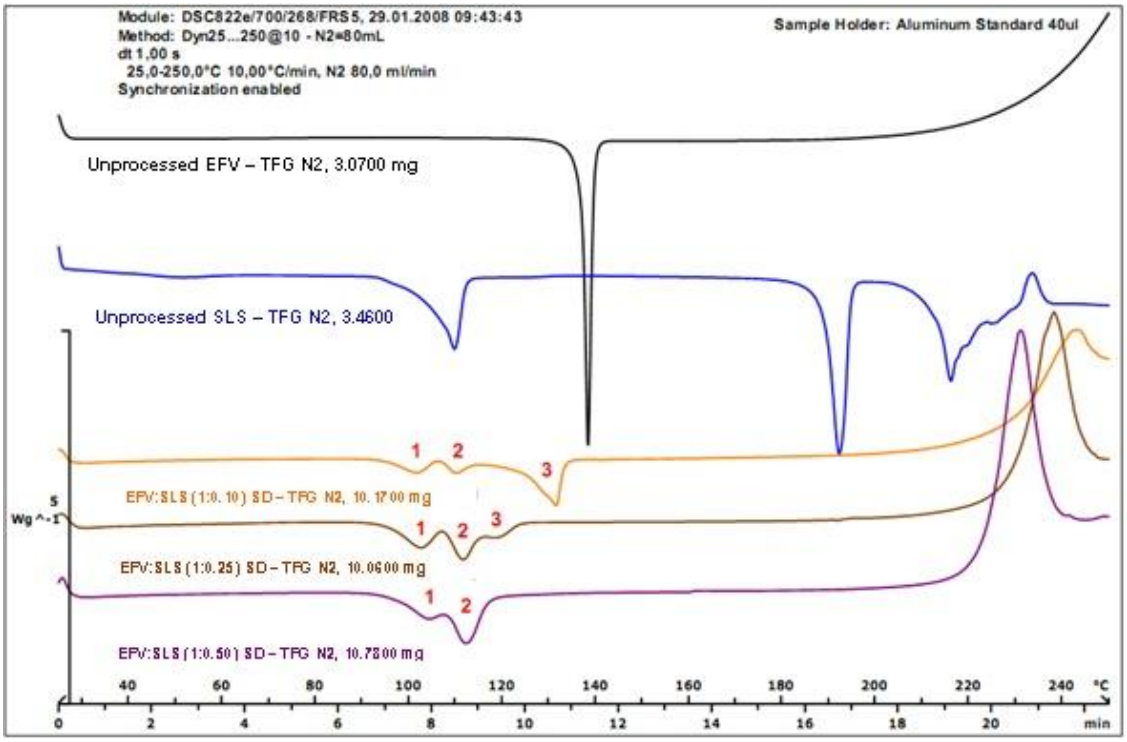

FIG.4: DSC CURVES OF EFV:SLS SAMPLES.

DSC curves of unprocessed efavirenz and SLS, compared to mixtures co-spray-drying at the proportions 1:0.10, 1:0.25 and 1:0.50.

Fig. 5 presents DSC curves of unprocessed EFV and PVP and spray dried EFV:PVP. Using PVP as the carrier, the peak of EFV melting decreased with decreasing drug concentration in the sample, and it could be observed the water loss of PVP only in spray dried EFV:PVP (1:0.50) sample.

Comparing DSC curves of EFV:SLS and EFV:PVP, in different proportions, it could be supported that there was an interaction between the drug and the carriers during heating, because of changes displayed on the peaks in relation to unprocessed drug. This possible interaction can happens from temperatures up to around 80ºC The possibilities of interaction are partial amorphization (in other words, a part of the drug loses cristallinity under analysis conditions) or the carrier is interacting with the drug, possibly solubilizing EFV with heating during analysis or the system suffers degradation.

Althoug it can be supposed some amorphization by DSC, X-ray diffraction and infrared spectroscopy, techniques that analyse the samples at room

temperature, do not lead to this conclusion. Hot-stage microscopy, as will be seen later in the paper, gives an additional information to this conclusion and this is also supported by the results and explanations from Pomázi et al[15] and Caron et al.[17].

Thermogravimetric Analysis (TGA):

Only The Sample Efv:Sls (1:0.25) Was Analysed to confirm water loss from SLS, due to the appearance of characteristic peak in DSC analisys. The TGA curve is represented in **Fig 6**.

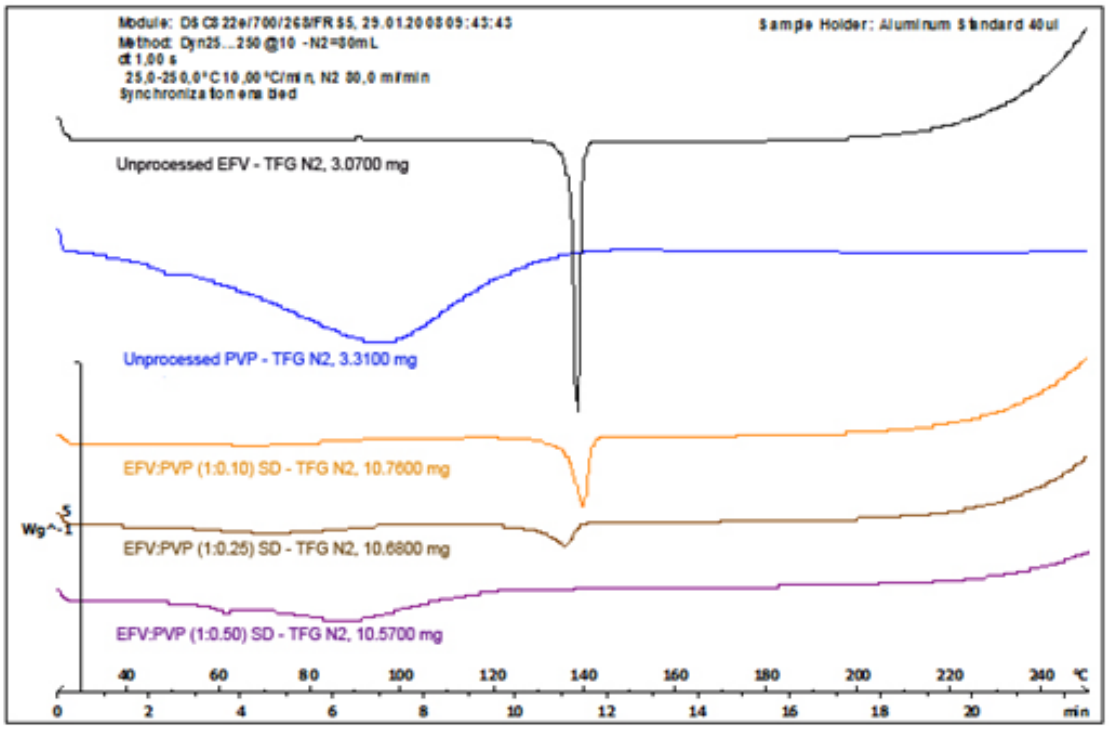

FIG.5: DSC CURVES OF EFV:PVP SAMPLES.

DSC curves of unprocessed efavirenz and PVP, compared to mixtures co-spray-drying at the proportions 1:0.10, 1:0.25 and 1:0.50.

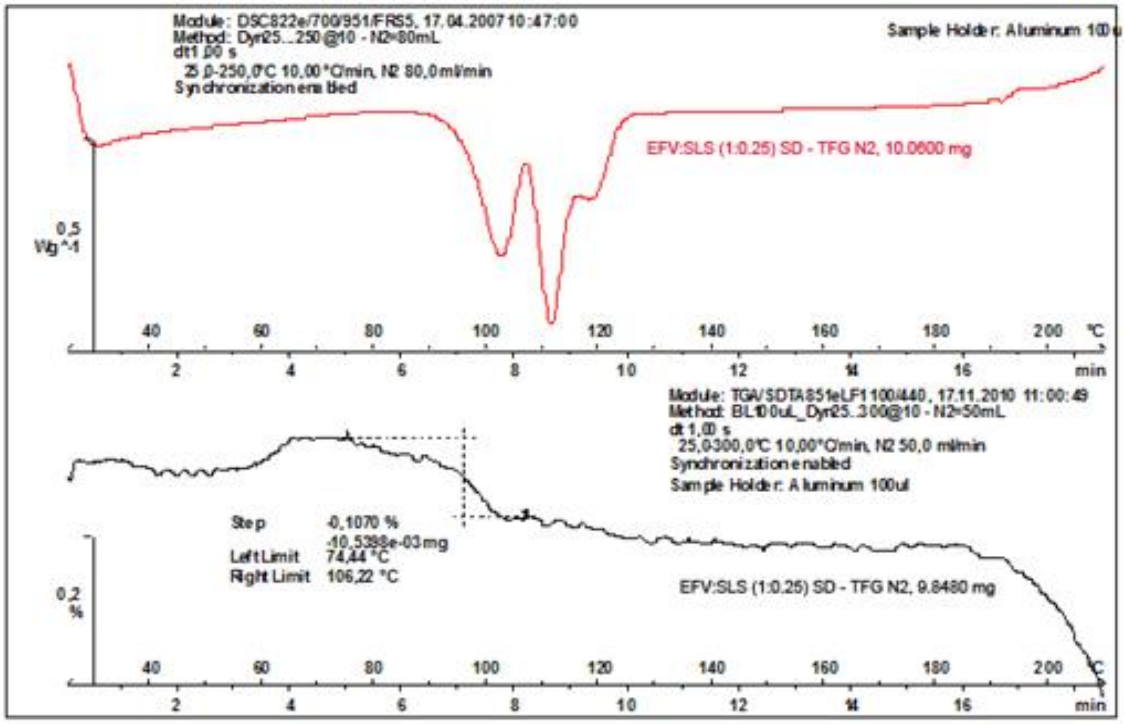

FIG.6: TGA CURVES OF EFV:SLS 1:0.25 SAMPLE.

Thermogravimetric analysis (TGA) curves of co-spray-drying mixture EFV:SLS proportion 1:0.25 compared to DSC curve.

It was possible to observe that the first endothermic peak in DSC corresponds to the weigth loss noted in TGA curve. This means that this peak is related to water loss, having no relation to material cristallinity. The amount of water incorporated is very small. The following two endothermic peaks are, therefore, related to structural transitions of the material, indicating a possible interaction between EFV and excipients, as previously discussed.

HOT-STAGE MICROSCOPY (HSM)

The **Fig.7** and **8** presented the results from spray dried samples (1:0.10) of EFV:SLS and EFV:PVP, respectively.

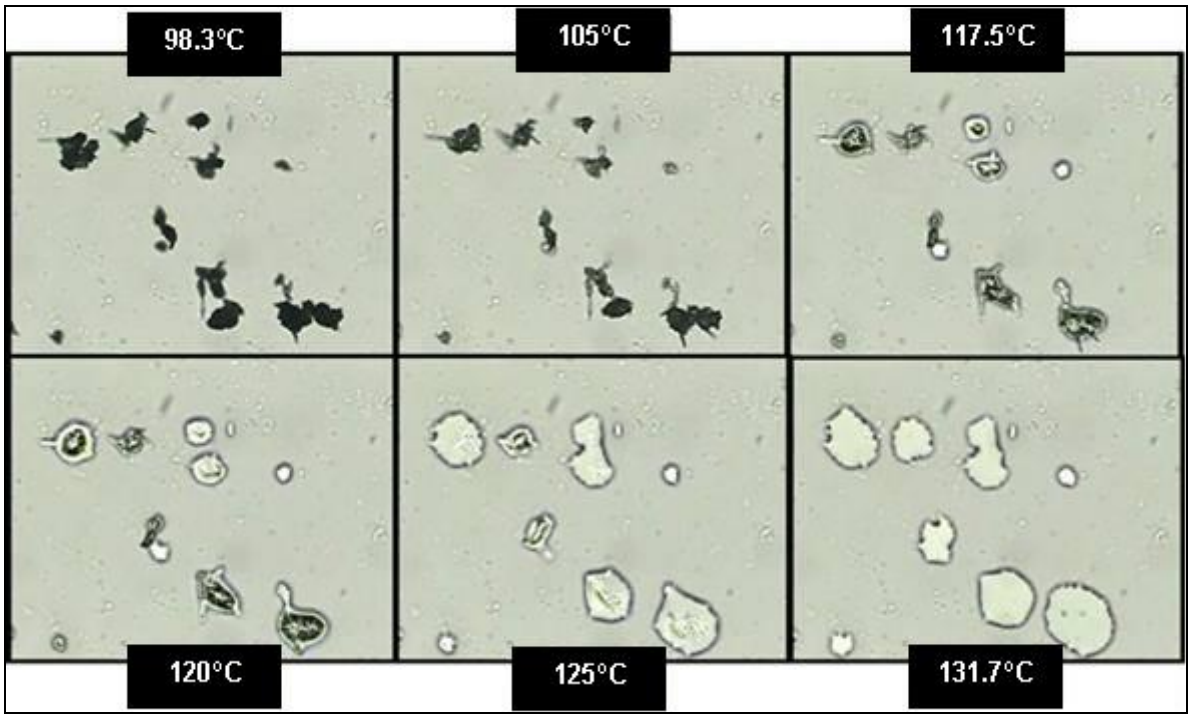

FIG.7: HSM OF EFV:SLS SAMPLE.
Hot-stage microscopy of co-spray-drying mixture EFV:SLS 1:0.10.

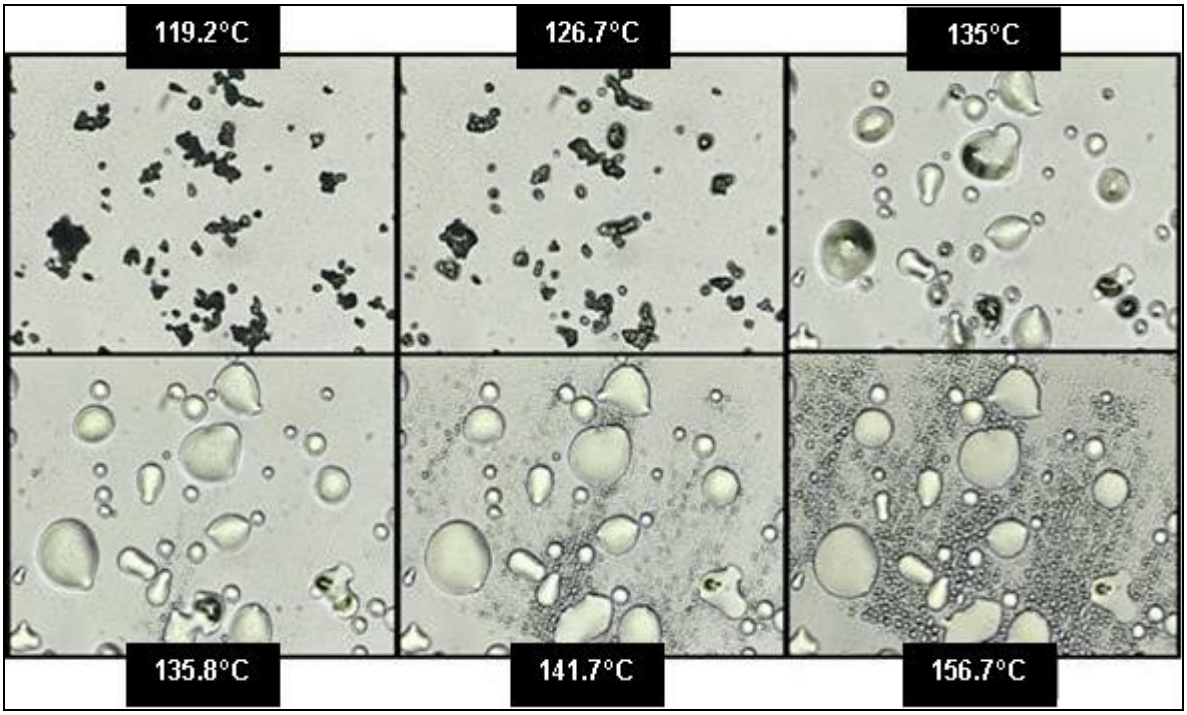

FIG.8: HSM OF EFV:PVP SAMPLE.
Hot-stage microscopy of co-spray-drying mixture EFV:PVP 1:0.10.

The profile obtained for spray dried EFV:SLS (1:0.10) powder presented a melting point slightly higher than other proportions, probably due to the smaller concentration of SLS.

For spray dried EFV:PVP powders it is possible to observe in HSM microcrystals of EFV in micelles of solubilized PVP during heating.

Hot-stage microscopy proved to be an useful tool in the elucidation of DSC results, allowing visual observation of the thermal behavior of the samples. This analytical tool has been used in the study and characterization of crystalline drug. In this study, it contributed significantly in the comparison of the samples, confirming the hypotesis made in the evaluation of data coming from DSC analysis. Similar results were cited by Pomázi et al[13].

Powder X-Ray Diffraction (DRX):

The diffraction patterns obtained of unprocessed EFV were similar to those presented in the literature[1]. The same peaks were observed for all spray dried powders, being the principal diffraction angles (2θ) under 6.20º, 20.20º, 21.35º and 25.00º (**Fig. 9** and **10**).

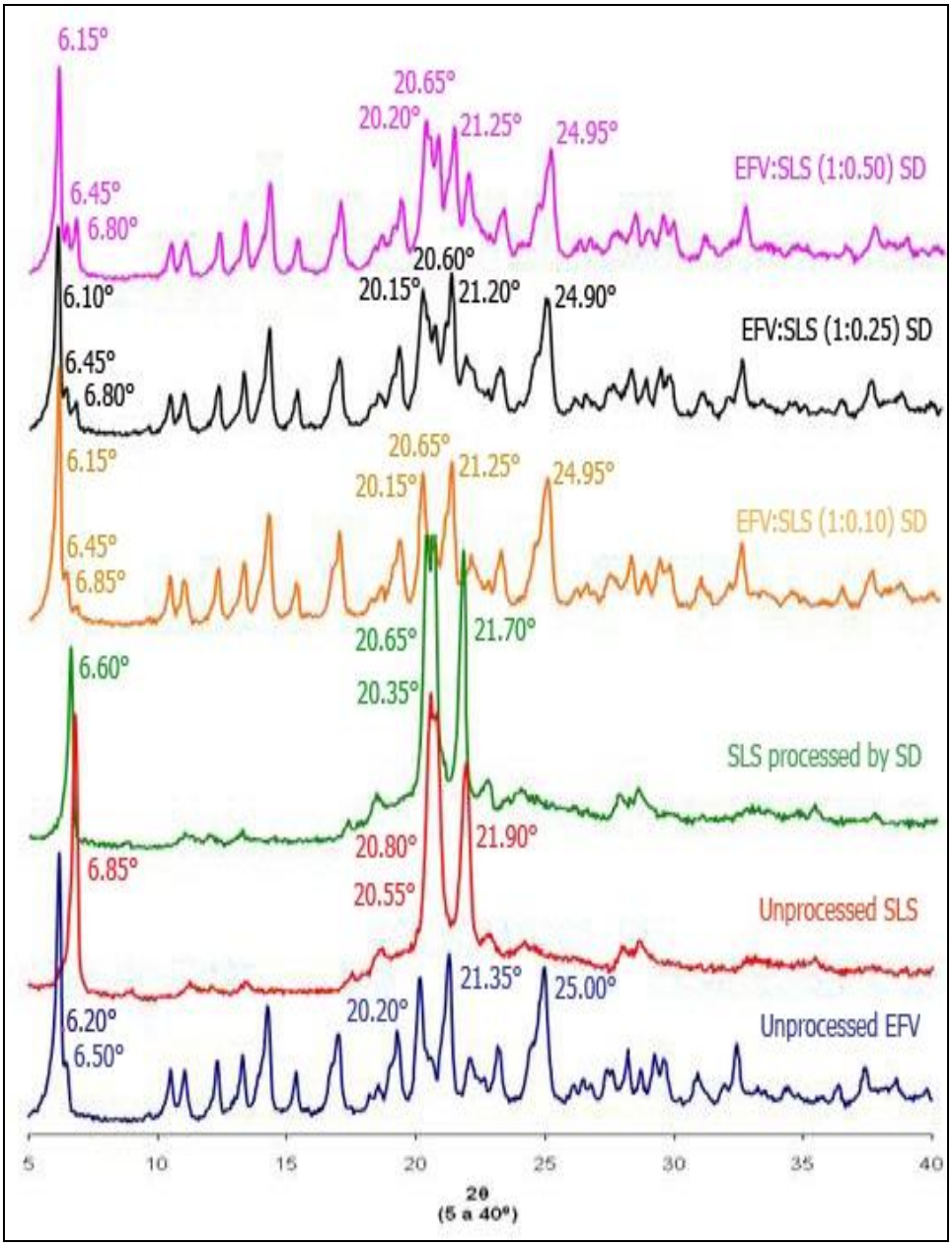

FIG.9: X-RAY DIFFRACTION PATTERNS OF EFV:SLS SAMPLES.

X-ray diffraction patterns of unprocessed EFV, unprocessed and spray-drying SLS, compared to co-spray-drying mixtures EFV:SLS in the proportions 1:0.10, 1:0.25 and 1:0.50.

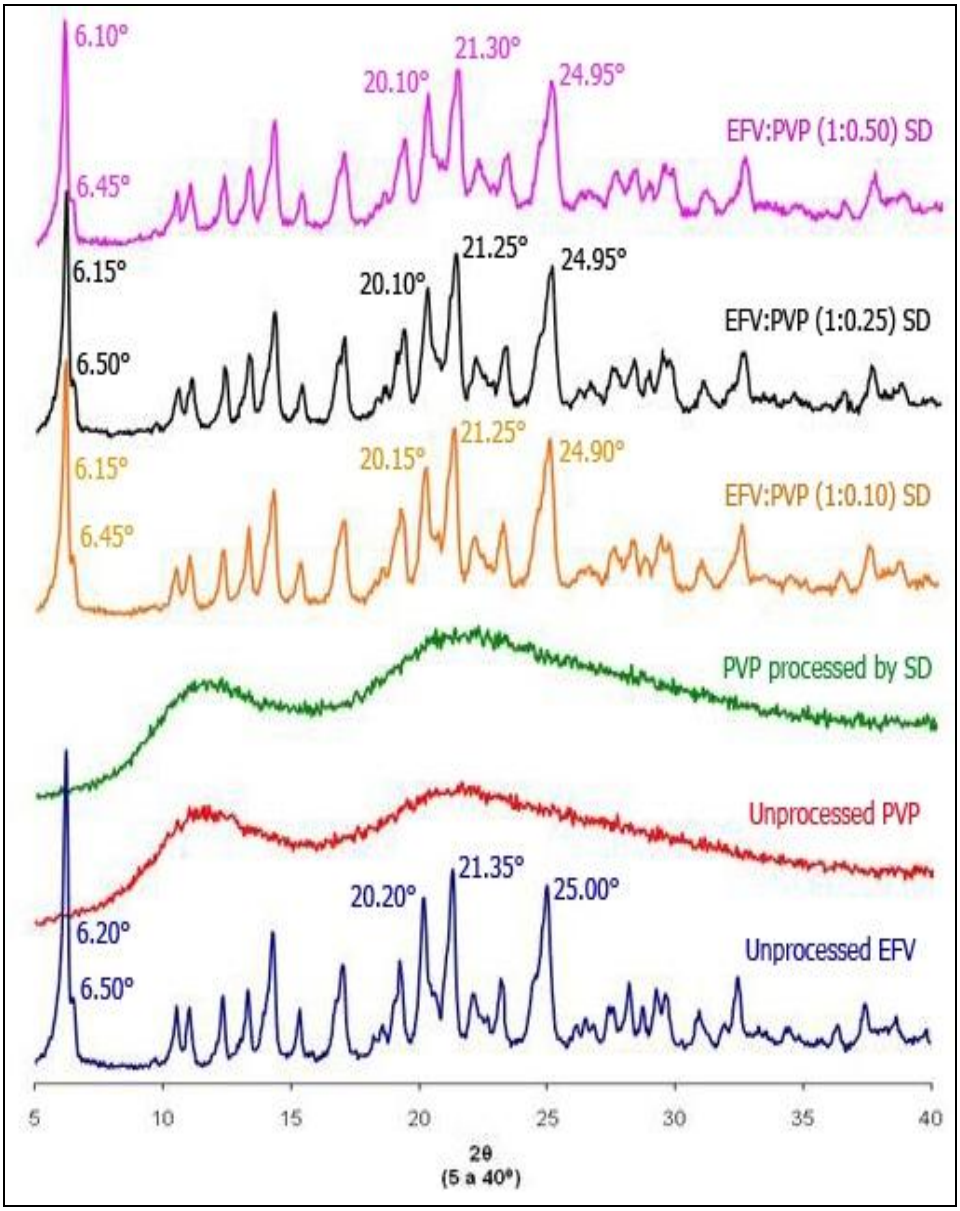

FIG.10: X-RAY DIFFRACTION PATTERNS OF EFV:PVP SAMPLES.

X-ray diffraction patterns of unprocessed EFV, unprocessed and spray-drying PVP, compared to co-spray-drying mixtures EFV:PVP in the proportions 1:0.10, 1:0.25 and 1:0.50.

Differently of previous studies [36, 37, 38] that used spray drying to generate dissolution enhanced systems we observed no crystallinity loss using XRD. It is important to mention that in those cases an organic solvent was used and the drug was solubilized before spraying. Although drug amorphization can provide prompt bennefities in terms of drug dissolution, it can also result in drug instability during time, considering that the substance can recrystallize and, so, result in a dissolution even lower than that observed before processing [39, 40]. Other papers obtained the same results as us for other drugs but using similar methodologies [9, 15, 20].

Caron et al[17] compared spray-drying and milling and, in their case, spray-drying derived systems with some amorphization, particularly in comparison with milling process.

In our studies, both of comicronization [23] as this, which uses spray drying technique, crystallinity is maintained after processing. However, their methodology is different from ours, where the drug was not previously solubilized. According to our search, there was not found a result comparing these processes with any disperse system.

Powder Dissolution Studies: The dissolution profiles obtained for all spray dried powders, both processed with SLS (**Fig. 11**) as with PVP (**Fig. 12)**, were enhanced when compared with that of unprocessed EFV. This system is aqueous and EFV has very low hydrossolubility, becaming technically unfeasible to process the drug without a carrier.

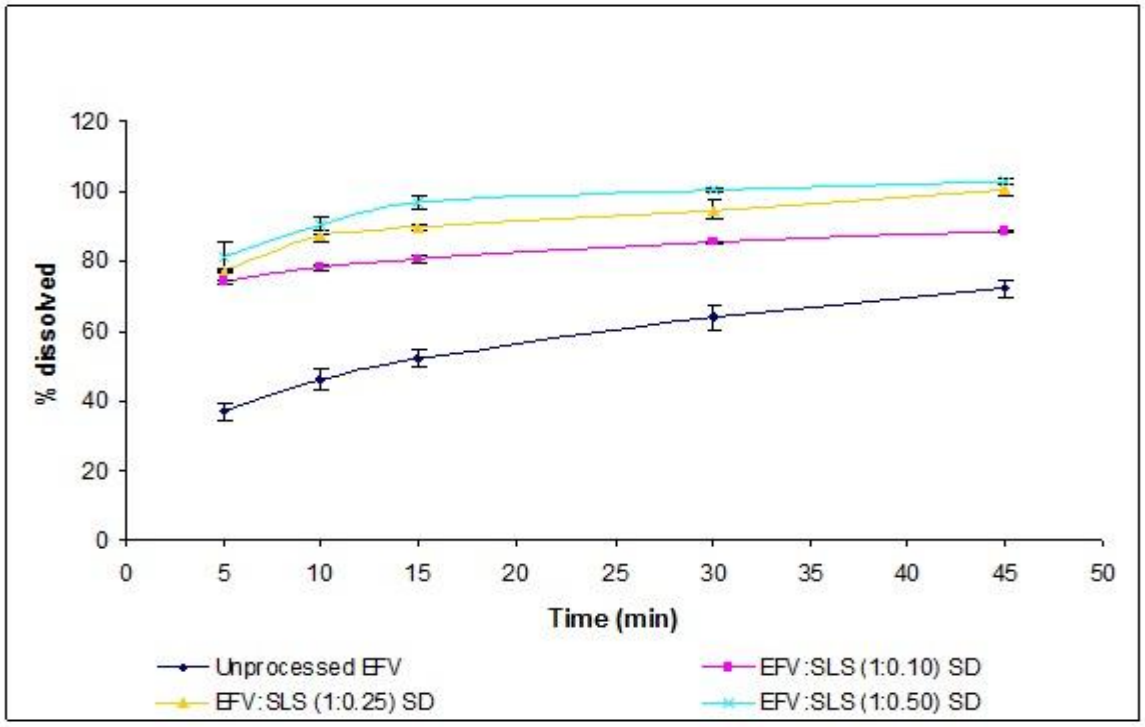

FIG.11: POWDER DISSOLUTION PROFILES OF EFV:PVP SAMPLES.

Powder dissolution profile of unprocessed EFV in SLS 0.5% (n = 3) compared to co-spray-drying mixtures EFV: SLS at the proportions 1:0.10, 1:0.25 and 1:0.50.

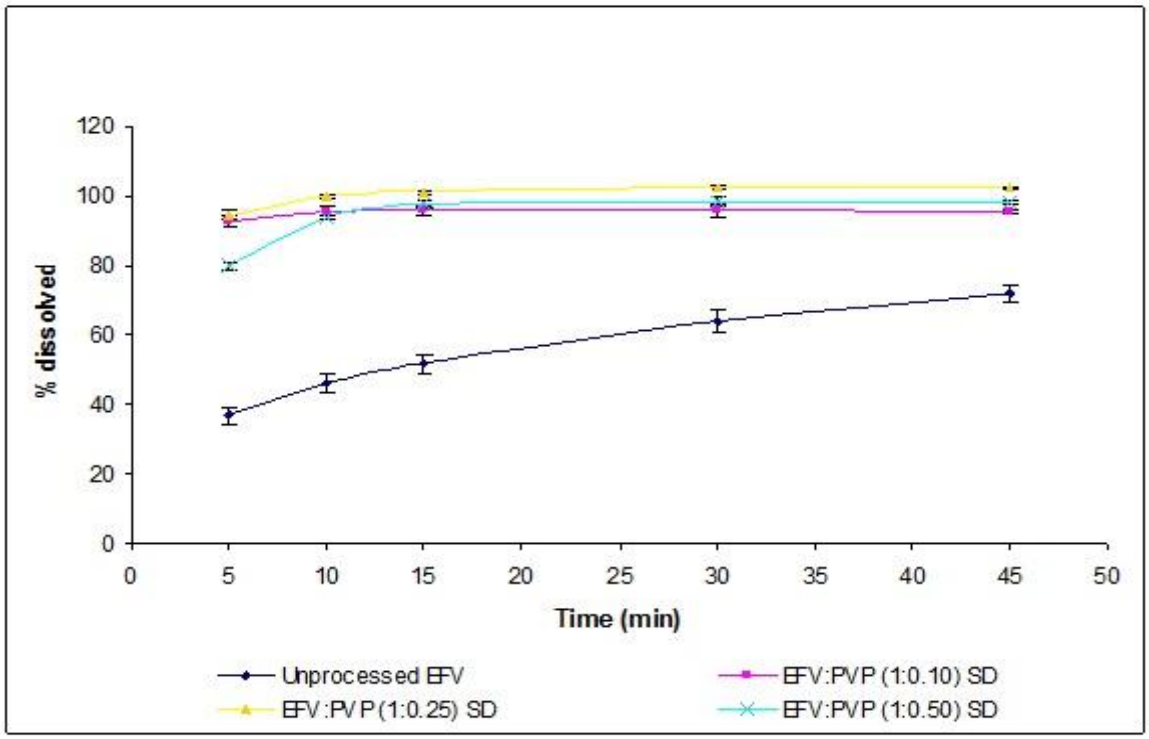

FIG.12: POWDER DISSOLUTION PROFILES OF EFV:PVP SAMPLES.

Powder dissolution profile of unprocessed EFV in SLS 0.5% (n = 3) compared to co-spray-drying mixtures EFV:PVP at the proportions 1:0.10, 1:0.25 and 1:0.50.

According to difference and similarity factors (*f1* and *f2*, respectively) the spray-dried powders using SLS in proportion (1:0.25) showed dissolution profile similar to those of the other two proportions, (1:0.10) and (1:0.50). However, these proportions had dissolution profiles significantly different between them.

Using PVP as carrier, the obtained dissolution profiles were significantly similar in all tested proportions.

The carrier proportions used in this study are different from those suggested for co-micronized systems [23] because it was expected that being the drug dispersed in a hydrophilic carrier solution, obtaining more spherical particles, it would result in more satisfactory dissolution profiles with a lower carrier concentration.

The dissolution profiles obtained in this study were not so higher compared with those obtained with co-micronization technique when using SLS. In the case of formulations based on PVP, it has happened the opposite, with the results from co-spray-dried samples higher than those of co-micronization ones. It can be related to particle characteristics as co-micronized samples with SLS were more homogeneous and presented lower particle size in relation to those co-spray-dried, the opposite of the results obtained for the PVP co-spray-dried systems[23].

The enhancement in wettability, the carrier solubilization effect, the dissolution of the drug in the hydrophilic carrier and/or the combination of all these mechanisms are hypothesis that can explain the enhancement in the powder dissolution profile by both co-processing approaches, but additional tests are necessary [9, 15, 17, 20].

It is very important to enfasize that the proportions of carriers used in this study are quite below other cases cited in the literature. Yan and collaborators [9] used a proportion of drug:carrier of 1:1,3, Tran et al[10] of 1:4 and Park et al[20] as high as 1:9. It turns our experiments even more interesting in terms of industrial applicability and reduces the cost of the final system.

CONCLUSION: The results obtained demonstrate that co-spray-drying is an effective technique in the enhancement of efavirenz dissolution. The formulation was obtained by a water-based process, bringing a good perspective in terms of environmental and regulatory concerns. Moreover, the process is industrially viable, considering that spray-drying is an effective pharmaceutical operation and is being each time more applicable.
Different from results previously obtained with co-micronization[23], PVP was more effective than SLS in the dissolution enhancement of efavirenz when used as water-based carrier for co-spray-drying process.

The characterization proved that the dissolution enhancement was not derived from drug amorphization and that there was no harmful interaction between the drug and the carrier. As suggested in other works, dissolution enhancement is related to the formation of a hydrophilic layer surrounding the drug particles, enhancing the interaction with the dissolution medium, however, wetting tests should be performed.

The samples must still be submmitted to processability evaluation as well as stability studies.

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