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Solid dispersion of efavirenz in PVP K-30 by conventional solvent and kneading methods

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ABSTRACT

Efavirenz (EFV) used as a part of the treatment of first choice in antiretroviral therapy for AIDS has low aqueous solubility and presents problems of absorption. We thus initially present a phase solubility diagram with carriers of different classes. With a view to obtaining a solid dispersion (SD) with suitable consistency to that of a solid formulation, we chose to use PVP K-30, since polymers present some of the best results. The kneading (KN) and solvent evaporation (EV) methods were thus used at different rates. These were characterized by the way of DSC, FT-IR, SEM, DR-X and dissolution. SD EV proved unsatisfactory, resulting in a decreased dissolution rate, despite the amorphous state of the samples, while the SD KN 4:1 (EFV:polymer) and physical mixtures (PM) had a higher rate of dissolution. SD KN and PM 4:1 were also evaluated for stability after storage, with benefits being observed in relation to EFV.

1. Introduction

With the advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now poses one of the most frequent and greatest challenges for scientists in the pharmaceutical industry (Leuner & Dressman, 2000). These drugs have been shown to have an unpredictable dissolution rate and are absorbed slowly compared to drugs with higher solubility (Patel, Patel, Bhimani, & Patel, 2008). Antiretroviral EFV thus dissolves slowly because of its low water solubility, thereby giving rise to problems of bioavailability (Alves et al., 2010; Sathigari et al., 2009).

Among the techniques used to overcome this obstacle, there are several reports of the use of cyclodextrins and polymers alone or in the form of multicomponent systems (Soares-Sobrinho et al., 2012). The use of beta-cyclodextrin (β-CD), hydroxypropyl β-CD (HPβCD), and randomly methylated β-CD (RMβCD) in complexation of the EFV has been reported in the literature (Sathigari et al., 2009). Of the various approaches, SD in water soluble and water dispersible excipients is a simple, industrially useful approach to enhancing the solubility, dissolution rate and bioavailability of poorly soluble drugs (Alves, Lyra, Rolim, Presmich, & Rolim-Neto, 2012; Lima, Santos, Lyra, Santos, & Rolim-Neto, 2012). In the case of EFV, there are reports of SD using carrageenan polysaccharide (Vedha, Begum, & Ramya, 2012) and poloxamer 407 (Chowdary & Annamma, 2012).

Since hydrophilic synthetic polymers have been widely investigated as carrier substances for SD, polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP) are among the most frequently investigated hydrophilic polymer carriers (Lima et al., 2011; Shah, Vasanti, Anroop, & Vyas, 2009). For EFV, there are reports of the preparation of SD PEG 6000 (Kumar, Yunoos, Chandana, Habeeb, & Himaja, 2010; Madhavi et al., 2011) and PVP K-29/32 by spray drying (Yang, Grey, & Doney, 2010).

The present study thus aimed to evaluate the influence of PVP K-30, the most frequently used carrier (Kaewnopparat et al., 2009), on the solubility and dissolution of EFV with SD, obtained by two

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preparation methods and in distinct proportions of drug and carrier (1:1, 2:1 and 4:1, w/w). The dissolution and physicochemical characteristics were assessed using *in vitro* dissolution studies, X-ray powder diffraction (XRD), differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and Fourier transform infrared (FT-IR). Since storage might decrease the dissolution rate, the thermal stability of the SD that exhibited optimum dissolution was also examined.

2. Materials and methods

2.1. Materials

The EFV (Cristália®, Batch: 1289/07), provided by the Pharmaceutical Laboratory of Pernambuco State, of 98% purity, was assessed using liquid chromatography (USP, 34). To put together the solubility diagram, the following raw materials were used: polyvinylpyrrolidine K-30 (PVP K-30); polyethylene glycol 4000 (PEG 4000); PEG 6000; hydroxypropylmethylcellulose K100 (HPMC K100); polysorbate 80; urea; mannitol; sodium lauryl sulfate (SLS); polyoxyethylene-40-monostearate (Myrj 52); polyoxyethylene-50-monostearate (Myrj 53); Gelucire 44/14 and Solutol HS15. Subsequently, the PVP K-30 employed in this study was used to prepare PM and SD. Absolute ethyl alcohol and purified water obtained by a reverse osmosis system were also used for the preparation of samples for assay analysis.

2.2. Methodology

2.2.1. Phase solubility studies

An excess amount of EFV (~30 mg) was added to 10 mL of aqueous solution, each containing increasing concentrations of each carrier (i.e., 0.01%, 0.05%, 0.1%, 0.3%, 0.5%, 0.7% and 1%) (w/v), with the exception of HPMC, for which the concentrations tested were 0.01%, 0.05%, 0.1% and 0.3% (w/v), owing to its high viscosity (Ahuja, Katare, & Singh, 2007). The samples were sealed in triplicate and shaken in an oscillating water bath thermostatically controlled at 25 °C for 6 days, and then filtered through a 0.22 μm cellulose membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 247 nm (Alves et al., 2010). The values of Gibbs free energy (ΔG), relating to the spontaneity of the process of dissolution of the drug in aqueous solutions containing hydrophilic carriers, were calculated for each carrier for each concentration in accordance with Eq. (1):

$$\Delta G = -2.303RT \log\frac{Sc}{So} \quad (1)$$

where R is the universal gases constant (8.314472 J K^{-1} mol^{-1}), T is the temperature in Kelvin, Sc is the solubility of the drug EFV at a certain concentration of the carrier and So is the concentration of EFV in water in the absence of carrier, both in μg/mL.

2.2.2. Preparation of solid dispersions and physical mixtures

Taking into account the overall result obtained from the phase solubility studies, we selected PVP K-30 for the preparation of binary systems.

2.2.2.1. Physical mixtures (PM). The preparation of the PM of EFV and PVP K-30 in proportions of 1:1, 2:1 and 4:1 (w/w), respectively, was carried out using geometric dilution, to ensure a uniform product, with subsequent sieving through a 250 μm mesh and storage in airtight glass desiccators under a vacuum.

2.2.2.2. Solid dispersions: the kneading method (SD KN). The preparation of the SD of EFV with PVP K-30 by kneading, in due proportion, started out from the PM, with subsequent kneading with a solution 50% hydroalcoholic to a sufficient quantity to maintain a slightly moist consistency (about 10% of weight). After 20 min of kneading, the product was placed in an industrial oven at 50 °C for 16 h. The dried product was sieved through a 250 μm mesh and placed in a vial and stored in an airtight glass desiccator under a vacuum.

2.2.2.3. Solid dispersions: the solvent evaporation method (SD EV). The preparation of the SD in proportions of 1:1, 2:1 and 4:1 (w/w) was carried out by separate dissolution of the compounds, in minimum amounts of solvent, 10 mL methanol and 2 mL acetonitrile being required for EFV solubilization and 10 mL methanol for PVP K-30 solubilization (Kim et al., 2006). The solution containing the EFV was poured into the solution containing the polymer and the system was mixed using a rotary evaporator with fixed temperature (60 ± 5 °C) at reduced pressure (900 ± 20 mbar) and centrifuged at 90 ± 3 rpm, resulting in the EFV precipitating out with the polymer. After drying, the SDs were pulverized, mixed in a mortar with a porcelain pestle and sieved through a 250 μm mesh. Subsequently the products were placed in vials and stored in an airtight glass desiccator under a vacuum.

2.2.3. In vitro dissolution studies

Studies of drug release were performed in triplicate using dissolution test equipment, employing the apparatus paddle at 50 rpm in a dissolution medium of water with 0.5% sodium lauryl sulfate (SLS) (900 mL) at 37 ± 0.5 °C. The dissolution studies were performed for the pure drug, SD and PM containing an equivalent to 300 mg of drug. The EFV release was measured by withdrawing samples at regular time intervals, filtering them through a 0.28 μm membrane filter and replacing them with an equal volume of plain dissolution medium. The samples were analyzed spectrophotometrically at 247 nm (Alves et al., 2010).

2.2.4. Physicochemical characterization

2.2.4.1. Differential scanning calorimetry (DSC). DSC studies were carried out using differential scanning calorimeter (DSC 60, Shimadzu, Japan). The samples, with the equivalent of 2 mg of drug (±0.2 mg), were hermetically sealed in aluminum pans and heated at a constant rate of 10 °C/min over a temperature range of 25–200 °C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL/min.

2.2.4.2. Scanning electron microscopy (SEM). The samples were sputter-coated with gold using a vacuum evaporator (Metalizador Baltec® SCD 050) and examined using a scanning electron microscope (Jeol® JSM-5900) at 15 kV accelerating voltage.

2.2.4.3. X-ray powder diffraction (XRD). The diffraction patterns of samples were obtained using an X-ray diffractometer (Siemens®, D-5000), equipped with a copper anode. The samples were analyzed in the 2θ angle range of 2–60 at a scan speed of 0.02° 2θ/s. The samples were prepared in glass holders with a thin layer of powder material without solvent.

2.2.4.4. Fourier transform infrared (FT-IR). The infrared spectrum was obtained using a device equipped with selenium crystal attenuated total reflectance (ATR) (PerkinElmer®, Spectrum 400). The samples to be analyzed were transferred directly to the ATR compartment and the result was taken to be the average of four scans. The micrographs were obtained for the range of 650–4000 cm^{-1} at a resolution of 4 cm^{-1}.

2.2.4.5. Stability study. After characterization of the drug, SD and PM, the stability of the SD KN 4:1 and its PM were evaluated by storage in a climatic chamber at 40 ± 2 °C and 75 ± 5% RH. The samples

Table 1
Parameters of the solubility study of EFV obtained with the carriers 25 °C.

Carrier	Slope	R^2	% Increase of solubility (concentration carrier)	ΔG° (J/mol)
Organic acid				
Citric acid	4.24×10^0	0.9711	12.21 (1%)	−946.13
Hidrotopo				
Urea	-8.04×10^{-1}	0.5099	8.85 (0.5%)	−148.80
Polymers				
PVP K-30	1.50×10^1	0.9968	24.20 (1%)	−2642.03
PEG 4000	4.35×10^0	0.8859	14.64 (1%)	−1394.95
PEG 6000	7.13×10^{-1}	0.8899	9.05 (1%)	−205.15
HPMC K-100	2.91×10^0	0.7521	10.44 (0.3%)	−547.74
Polyol				
Mannitol	-4.80×10^{-1}	0.1863	11.17 (0.1%)	−725.46
Surfactants				
Polysorbate 80	9.01×10^2	0.9710	928.73 (1%)	−11,685.10
SLS	3.51×10^2	0.9522	318.18 (1%)	−9029.24
Myrj 52	2.52×10^2	0.9534	248.85 (1%)	−8419.83
Myrj 53	1.55×10^2	0.7542	216.66 (0.5%)	−7101.84
Solutol HS15	4.08×10^2	0.9826	429.63 (1%)	−9773.79
Gelucire 44/14	3.92×10^2	0.9028	378.87 (1%)	−9462.04

were analyzed after 1 month by FT-IR and thermogravimetry (TG). The methodology used for the FT-IR was the one described above. TG thermal analysis characterization was performed in duplicate (TG Q60, Shimadzu, Japan), with a nitrogen flow of 50 mL/min, and a sample mass of around 4 mg (±0.4) of EFV, placed in an aluminum crucible at temperatures rising from 25 to 500 °C at a heating rate of 10 °C/min.

3. Results and discussion

3.1. Phase solubility studies

The water solubility of EFV was 8.34 μg/mL, indicating that it is insoluble in water, as reported in the literature (Sathigari et al., 2009). Meanwhile, according to the results obtained for the different carriers used, these carriers influenced EFV water solubility in different ways.

Of the parameters evaluated, the linearity of the curves obtained for each carrier was analyzed in order to observe the tendency for drug solubility to increase in relation to the increase in carrier concentration, as well as the maximum solubilization percentage for the drug. These results were evaluated using the coefficient of determination (R^2) for each curve and the drug dissolved at the tested concentrations. This showed that not all carriers provided an increase in linear solubility (Table 1), with random variations for the different concentrations. In some cases, it was not possible to achieve solubility of EFV with increasing concentrations of carrier. The solutions that exhibited a more predictable and linear behavior were those with the following carriers: polysorbate 80, solutol HS15, SLS, Myrj 52, PVP K-30 and citric acid. These clearly demonstrate a positive influence of the carrier in an aqueous medium. The slopes of the linear curves further corroborate these results, as the higher the slope value, greater the increase in aqueous solubility.

The results obtained for Gibbs free energy demonstrate the spontaneity of the solubilization process. In general, the increase in solubility is directly associated with values of $\Delta G < 0$, which is usually proportional to the increase in concentration of carrier, in such a way that the higher the contribution to the negative value of ΔG, the better will be the solubilizing effect (Patel et al., 2008). In accordance with the results described above, the most negative value of ΔG was found for polysorbate, followed by solutol, gelucire, SLS, Myrj 52, Myrj 53, PVP K-30, PEG 4000, citric acid, HPMC, PEG 6000 and mannitol, with more negative values of ΔG for a concentration of carrier of 1%. For urea, at this same concentration, a positive ΔG value was observed, demonstrating the non-spontaneity of the solubilization process, as can be seen from the decrease in solubility of EFV in the presence of urea. The results show that surfactants provide a more significant increase in aqueous solubility. Previously, the SD had been prepared using surfactants, but it was observed that the system obtained by this method had a consistency unsuitable for placement in a solid dosage form, according to the methodology used to obtain the solid dispersion in the present study.

Given the above and the results obtained, it was decided to prepare the SD using PVP K-30, which provided the greatest increase in drug solubility of the polymers tested. This is also a polymer widely used in the pharmaceutical industry for various purposes and quoted extensively in descriptions of the preparation of SD.

3.2. In vitro dissolution studies

The dissolution profiles of EFV, SD and PM are shown in Fig. 1. EFV exhibited, within 60 min, a dissolution rate of 34.19% (±3.97).

The evaporated systems provided no increase in EFV dissolution. A negative effect was observed with decreasing proportions of polymer, reaching less than 5% in 60 min at 4:1 SD EV (3.74% ± 0.85). In the KN systems, an increasing proportion of polymer reduced release of the drug. SD KN 4:1 provided the highest percentage dissolution of EFV (58.83 ± 6.72%).

In both systems a polymer mesh was formed. In this case, the polymer took the form of a pseudo-gel layer, which swelled to control release of the drug. This also depends on its solubility. For drugs with solubility below 0.5 mg/mL, the drug is released from the polymer matrix primarily by way of erosion (Andreetta, 2003; Hardy et al., 2007). This same agglutination phenomenon has also been reported in other studies with different types of carriers, including different types of PEG and PVP (Akbuga, Gursoy, & Yetimoglu, 1988; Serajuddin, 1999).

The processes for obtaining the drug associated with the characteristics of PVP-K30 explain the behavior of the PMs. It was observed that PM had the highest dissolution rates, demonstrating that the mixture of the drug with PVP K-30 alone provides better dissolution. These results can be attributed mainly to the hydrophilic effect of the carrier, which reduces the interfacial tension to medium dissolution, contributing to drug wettability, through the formation of a microenvironment that facilitates solubilization around the particles. PM thus showed the negative influence of the methods used.

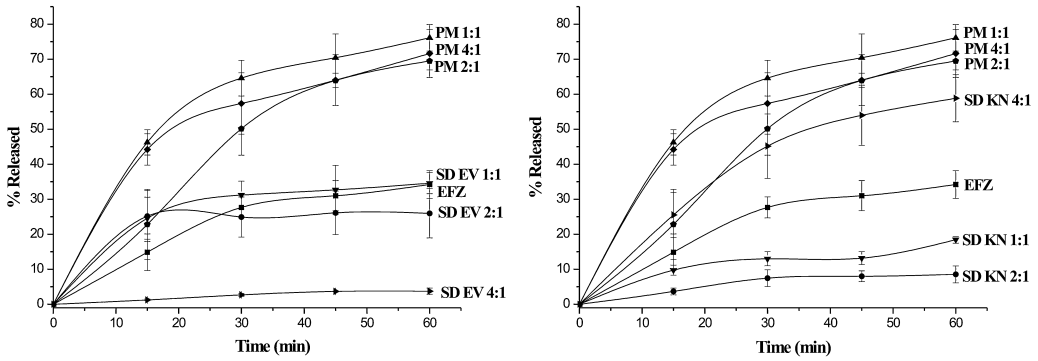

Fig. 1. Dissolution profiles of EFV, PVP K-30 and binary systems.

3.3. Physicochemical characterization

3.3.1. Differential scanning calorimetry (DSC)

Evidence of the thermal behavior of EFV may be provided by an endothermic peak corresponding to the temperature range from 136.86 to 141.75 °C, characteristic of the melting process of its crystalline structure (Fig. 2), confirmed by SEM (Fig. 3) and XRD (Fig. 4). The PVP K-30 can be observed as a slight endothermic curve, in the interval between 36.99 and 143.07 °C, 102.36 °C representing the evaporation of water from the material, confirmed by TG analysis. Such evaporation is responsible for a loss of 12.26% in weight of PVP K-30, occurring at the final temperature of the polymer-glass transition process.

The characteristic peak of EFV can be observed for all proportions of PM. A parallel shift was also observed in the melting peak of, on average, 3.21 °C, apart from the fact that the smaller the proportion of EFV in the system compared to PVP K-30, the less energy will be required for it to melt. This suggests that the PVP K-30 was able to provide mild solubilization of the EFV fraction in excess of the solid state during the heating process, as previously reported by Kaewnopparat et al. (2009). Despite this fact, use of this technique revealed that there was no evidence of chemical interactions and incompatibilities between the drug and the polymer in PM. Likewise, there was also evidence that EFV is present in crystalline form and this can be confirmed by the results of XRD studies. In addition, SD KN and SD EV in proportions of 1:1 and 2:1 showed similar behavior due to the absence of EFV peaks, from which it can be inferred that there may have been loss of the crystalline structure of the drug in these samples. However, this information can only be confirmed with the aid of other techniques such as XRD. The DSC curve of the SD EV 4:1 showed the presence of a melting peak with a shift of 14.44 °C, in addition to a slight variation in the energy required for this process, which probably indicates a decrease in drug crystallinity, owing to some interaction between the components. Likewise, in the curve of the SD KN 4:1, two displaced peaks were observed, corresponding to the formation of two phases, owing to an excess of drug and insufficient quantities of polymer being added for full drug solubilization. Despite this, there was a slight drop in the melting point of the drug, even in the crystalline form, for the system under evaluation.

3.3.2. Scanning electron microscopy (SEM)

SEM revealed the crystalline form of EFV, with irregular orthorhombic crystals, while PVP K-30 (Fig. 3) was shown to be composed of amorphous spherical particles. On the other hand, electron micrographs of SD KN and SD EV 1:1 and 2:1 did not show the original crystal morphology of EFV and there was a drastic change in the appearance of the polymer. These systems appeared as small aggregates of amorphous particles and it was not possible to visualize the drug and polymer separately. There was, however, a clear difference between the morphology of the dispersions obtained by the KN and EV methods. The drastic change in shape and appearance of the particles thus suggests the formation of a new solid phase, which can be attributed to changes in the crystalline state of these binary systems, leading to a single phase, or a real transition from crystalline to amorphous state, owing to possible chemical interactions occurring between the polymer and drug in the process of obtaining SD.

In the case of SD EV 4:1, it was possible to visualize some of the EFV particles inside larger dispersion particles, showing that, despite the observed changes in the original particles, some drug particles were still in crystalline form. This can be confirmed by the DSC curve of the SD, which showed peaks relating to the melting of EFV in the phases of the system under evaluation. Although it is not possible to see clear crystals of EFV in SD KN 4:1 using SEM, with small particles only visible with 8500 magnification, evidence of their presence can be provided by other techniques.

3.3.3. X-ray powder diffraction (XRD)

The XRD patterns for some dispersions of the drug indicate changes in its crystalline structure. The diffractogram revealed the presence of a very distinct peak around 2θ of 6.24°, along with others of lower intensity at 10.56°, 11.04°, 12.34°, 13.34°, 14.28°, 15.36°, 17.0°, 19.4°, 20.3°, 21.38° and 25.02°. PVP K-30 was characterized by a complete absence of peaks, as is characteristic of amorphous compounds (Fig. 4), in accordance with the data obtained using DSC and SEM.

The PM showed diffraction patterns similar to those of the drug, indicating that the crystallinity of the drug was not affected by the process of obtaining it. The result presented here concurs with those previously described. For SD EV, only at a ratio of 4:1, did the XRD pattern reveal the presence of the drug's main peak, although there was a decrease in intensity. This feature was also present for SD KN in proportions of 1:1 and 2:1, being more evident at a ratio of 2:1. However, it should be noted that there is a tendency for the samples to behave amorphously. On the other hand, SD KN 4:1 showed a more crystalline behavior, despite a decrease in the intensity of the peaks compared with EFV.

It can therefore be suggested that PVP K-30, during the process of obtaining SD, decreases the crystalline state of EFV in both systems, although the SD EV caused an increased reduction in crystallinity at the proportion analyzed. Although this helps to increase the solubility of the drug, since the non-crystalline forms are more easily solubilized than the crystalline ones, the dissolution study, along with this characterization, showed that, in this case, crystallinity is not the limiting factor for the rate of growth and percentage dissolution of the drug. On the other hand, preparation process used also has a direct influence on the results and needs to be carefully evaluated.

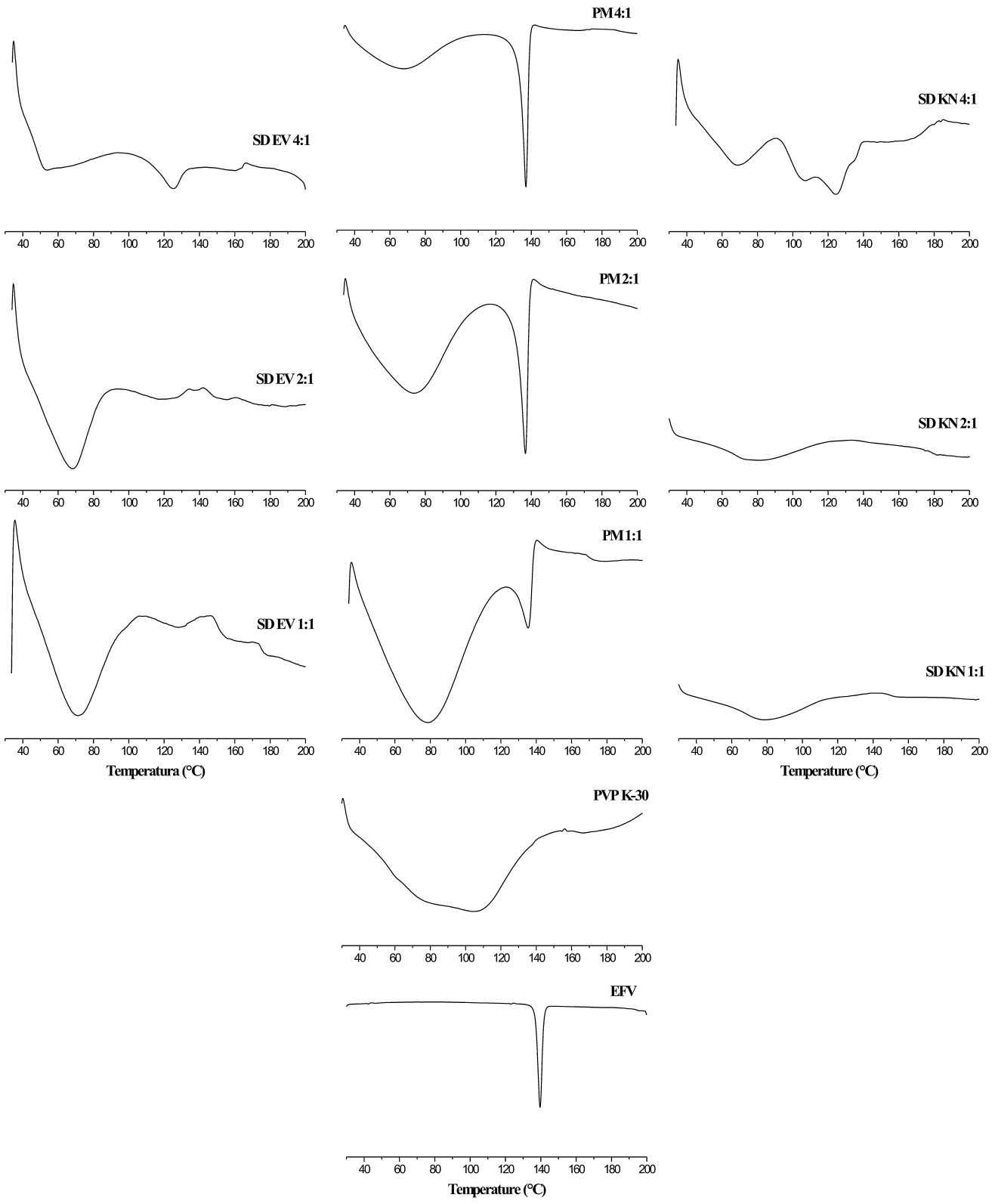

Fig. 2. DSC curves obtained at 10 °C/min in a nitrogen atmosphere at 50 mL/min.

3.3.4. Fourier transform infrared (FT-IR)

The EFV spectrum was obtained using this technique. The presence of the following characteristic bands was observed: 3314 cm^{-1} (NH stretch vibration), 2249 cm^{-1} (C≡C stretching vibration), 1742 cm^{-1} (C═O stretching vibration), 1601 and 1494 cm^{-1} (C═C of benzene ring stretching vibration), 1240 cm^{-1} (CN stretch) and 1165 cm^{-1} (CO stretching vibration). In the region of lower frequency bands at 1073 and 1037 cm^{-1} assigned to CH deformation vibrations on the plane and at 976 and 926 cm^{-1} on the CH out of plane deformation. Finally, the CF stretching vibration was observed at a frequency of 689 and 652 cm^{-1}. Likewise, the PVP K-30 spectrum revealed significant bands at 2952 cm^{-1} (C—H stretch)

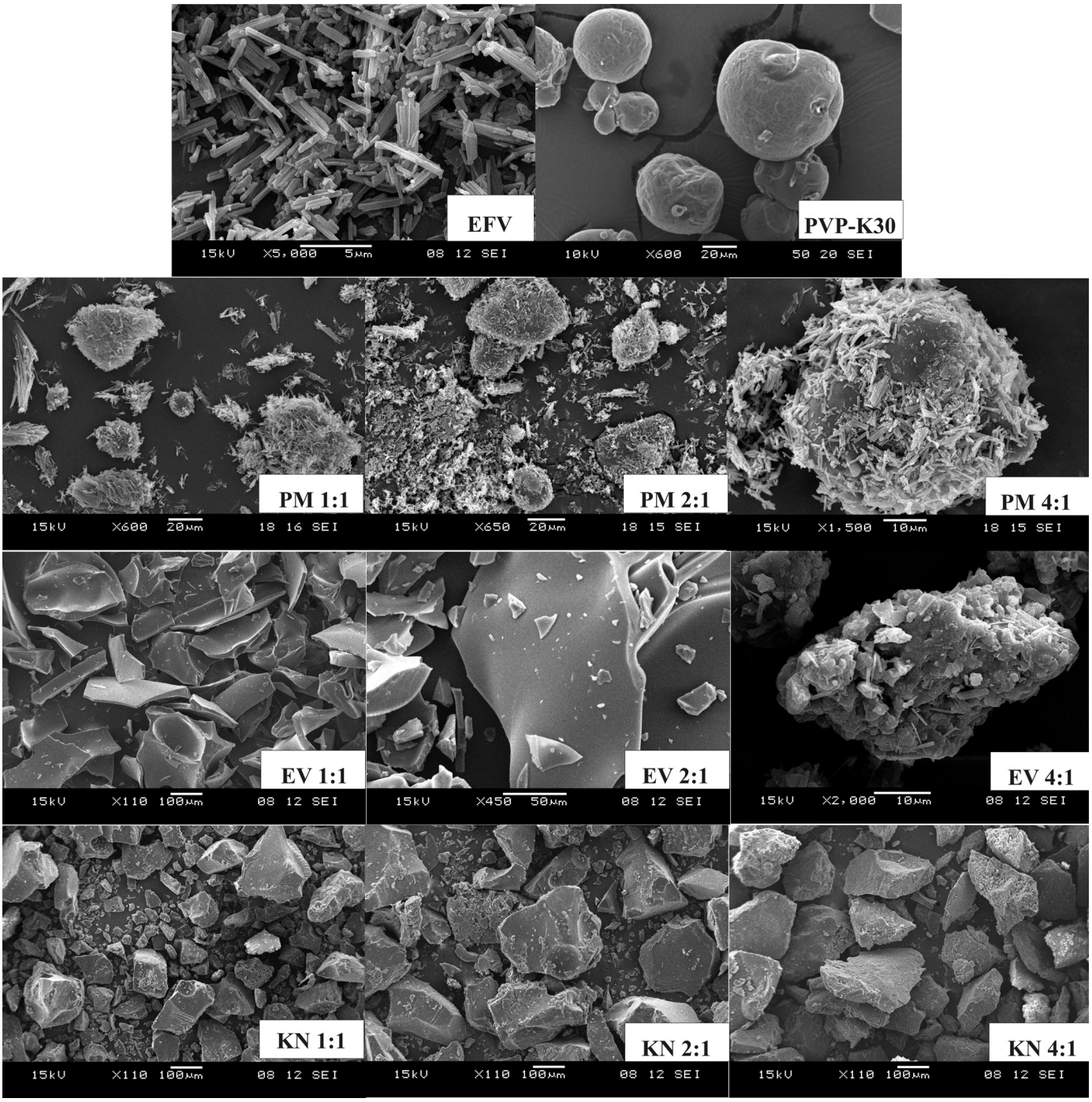

Fig. 3. Electron micrographs of SEM of EFV, PVP K-30 and binary systems.

and 1647 cm^{-1} (C=O stretch) (Fig. 5). A broad band can also be seen at 3419 cm^{-1} and this is associated with the presence of water, as confirmed by DSC analysis.

The PM IR spectra were generally similar in terms of overlapping bands of EFV and PVP K-30, with a predominance of EFV, indicating no interaction between these. For all the SDs, neither the OH band at 3419 cm^{-1} of PVP K-30 nor NH band at 3314 cm^{-1} of EFV were present, with the exception of the proportion of 4:1, where this band was found to a lesser extent. However, all SD spectra showed bands for the stretching of the C—H and C=O of PVP K-30 and the C=O of EFV, which are always present to a lesser degree and with a slight shift. This behavior can also be seen in the bands at 689 and 652 cm^{-1}. The results therefore show that, for all SDs, regardless of the process by which they were obtained, there were intermolecular interactions between PVP K-30 and EFV, mainly on hydrogen bonds.

3.3.5. Stability study

The TG curves of the samples before storage under certain conditions showed that the EFV has two decomposition stages, the first between 230.38 and 276.58 °C and the second for carbonization (Δm = 75.91%). Analysis of the PVP K-30 TG curve shows that relative water loss (Δm = 12.55%) occurred between 42.28 and 102 °C and the main decomposition process, to the order of 58.20%, subsequently occurs from 405 to 458 °C, followed by carbonization.

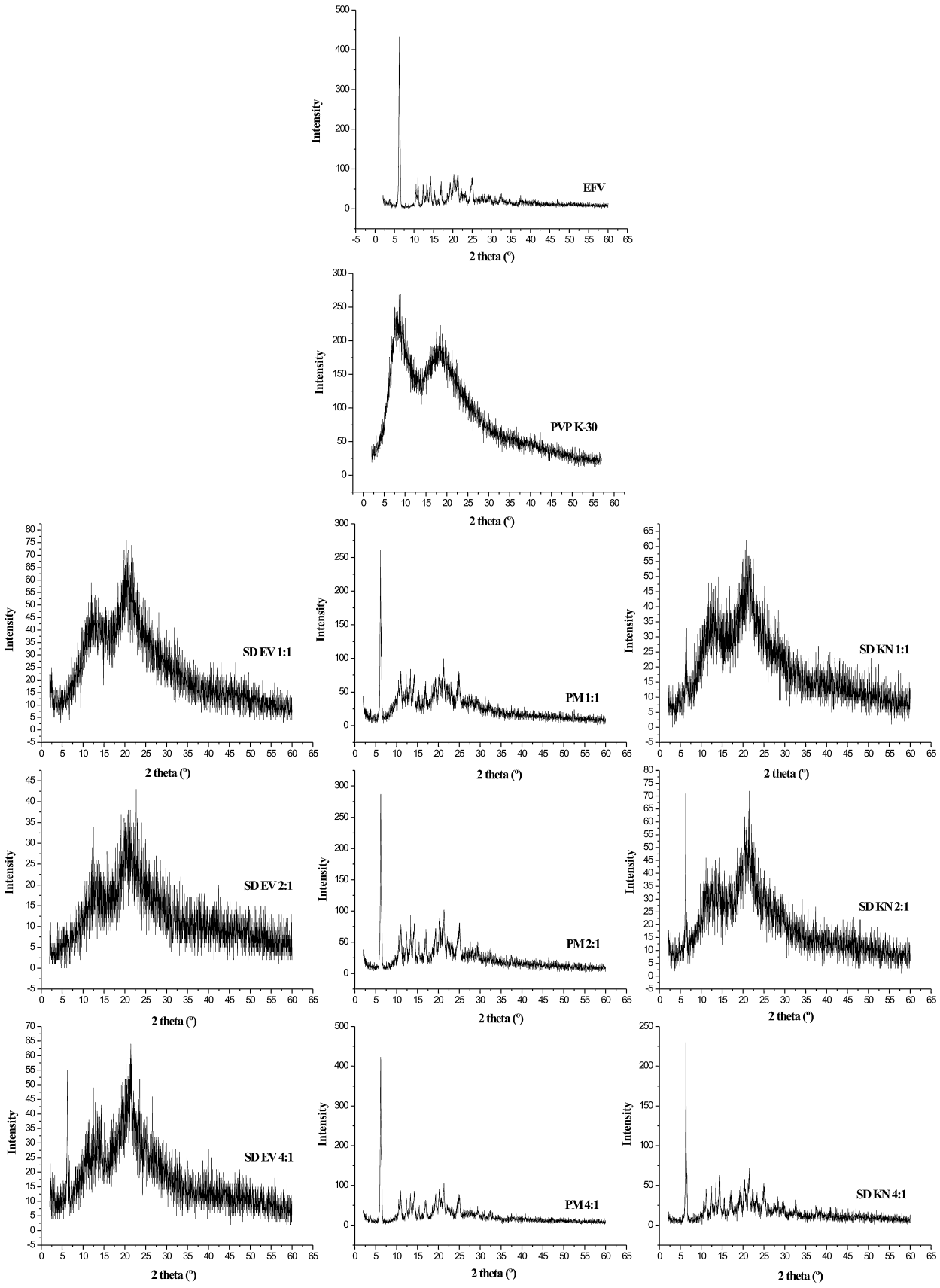

Fig. 4. XRD patterns of EFV, PVP K-30 and binary systems.

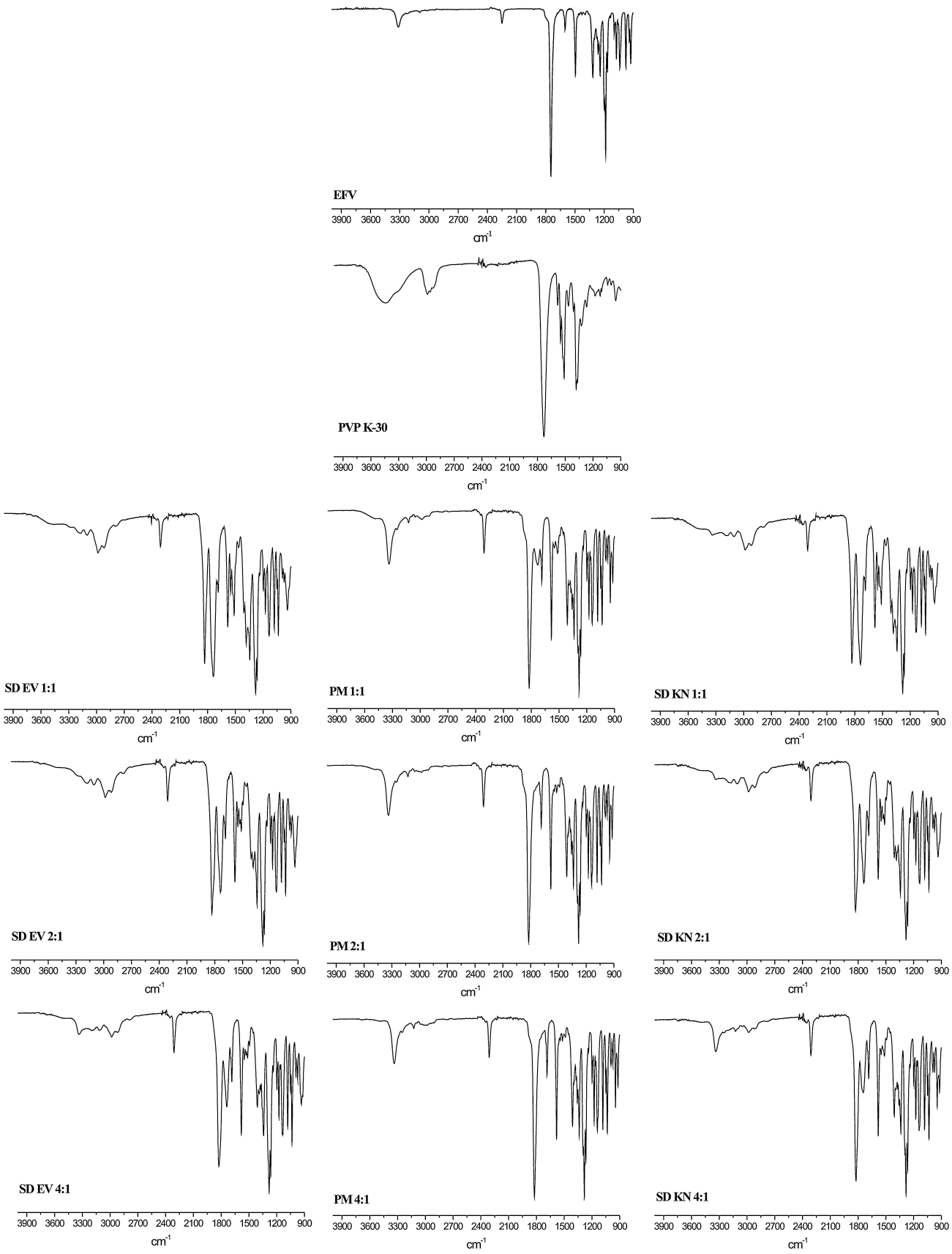

Fig. 5. Infrared spectra of EFV, PVP K-30 and binary systems.

The decomposition of 4:1 PM and 4:1 SD KN 4:1 can be seen to be divided into three stages, two of which are the main processes. The present study will use the first stage of decomposition to assess drug stability. This is the first step in the range of 231.76–283.13 °C for PM and 237.15–278.76 °C for SD. For this latter, it was observed that the onset of decomposition was slowed more significantly, with mass loss of 53.99%. While for PM, it was observed that the final decomposition has been extended to higher temperatures compared to the drug alone (Δm = 54.18%). For both systems, the smaller weight loss drug, expressed greater stability (Freitas et al., 2012; Soares et al., 2011). It can be easily seen that PVP K-30 provided greater stability in the binary drug-polymer system, since there was a statistically significant decrease in the quantity of drug degraded in the same temperature range (One-way ANOVA).

For samples subjected to controlled storage conditions, temperature and humidity, it was concluded that there were no changes in the initial behavior. For systems noted that there is only a more pronounced loss of water mass (Δm = 56.69% to PM and Δm = 58.47% to SD), owing to its hygroscopic nature of PVP K-30 and humid atmosphere. The FT-IV analysis performed also confirmed the absence of modifications of the initial bands in the samples, demonstrating that the samples remain stable even under adverse storage conditions.

4. Conclusion

It has been observed here that the methodologies employed for preparation and the proportions of the carrier used had a significant influence on the physicochemical characteristics of the drug. In high proportions, PVP K-30 was inadequate in these systems, as it inhibited the release of the drug and broke down the crystalline structure of EFV. Given these results, SD KN 4:1 was also evaluated with respect to density and compressibility, showing a significant increase in bulk density and compaction in comparison with the drug. This system has also proved advantageous in terms of stability, after TG evaluation, since the reduced drug degraded somewhat even after being subjected to adverse storage conditions.

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