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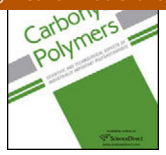

Multicomponent systems with cyclodextrins and hydrophilic polymers for the delivery of Efavirenz

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ABSTRACT

Efavirenz (EFZ) is one of the most used drugs in the treatment of AIDS and is the first antiretroviral choice. However, since it has low solubility, it does not exhibit suitable bioavailability, which interferes with its therapeutic action and is classified as a class II drug according Biopharmaceutical Classification System (low solubility and high permeability). Among several drug delivery systems, the multicomponent systems with cyclodextrins and hydrophilic polymers are a promising alternative for increasing the aqueous solubility of the drug. The present study aimed to develop and characterize in a ternary system of EFZ, MβCD and PVP K30. The results showed that the solid ternary system provided a large increase in the dissolution rate which was greater than 80% and was characterized by DSC, TG, XRD, FT-IR and SEM. The use of the ternary system (EFZ, MβCD and PVP K30 1%) proved to be a viable, effective and safe delivery of the drug. The addition of the hydrophilic polymer appeared to be suitable for the development of a solid oral pharmaceutical product, with possible industrial scale-up and with low concentration of CDs (cyclodextrins).

1. Introduction

Oral ingestion is the most convenient and commonly employed route of drug delivery due to its easy administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of the dosage form (Savjani, Gajjar, & Savjani, 2012).

However, the major challenge during the design of oral dosage forms lies in their poor bioavailability (Chaves, Vieira, Reis, Sarmento, & Ferriera, 2014). The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism, pre-systemic metabolism, and susceptibility to efflux mechanisms. However, the major issue that leads to low oral bioavailability is poor solubility and low permeability (Chouhan & Saini, 2014; Gundogdu, Koksal, & Karasulu, 2012; Savjani et al., 2012).

Low aqueous solubility is the major problem encountered with the formulation development of new chemical entities (Chaves et al., 2014). More than 40% of new chemical entities developed in the pharmaceutical industry are practically insoluble in water. Poorly water-soluble drugs present slow drug absorption, and lead to inadequate and variable bioavailability and gastrointestinal mucosal toxicity (Kumar et al., 2011; Miletic, Kyriakos, Graovac, & Ibric, 2013; Sharma, Soni, Kumar, & Gupta, 2009). This is a challenge especially for class II (low solubility and high permeability) substances according to the BCS. In these cases, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastrointestinal fluids (Krishnaiah, 2010; Kumar et al., 2011; Rong et al., 2014; Savjani et al., 2012).

Among all solubility enhancement techniques, the generation of inclusion complexes with cyclodextrins has been employed more precisely to improve the aqueous solubility, dissolution rate,

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and bioavailability of poorly water-soluble drugs (Pose-Vilarnovo, Rodríguez-Tenreiro Sánchez, Diéguez Moure, Vila-Jato, & Torres-Labandeira, 2003; Rong et al., 2014).

Cyclodextrins (CDs) are naturally available water-soluble cyclic oligosaccharides composed of α-1,4-linked D-glucopyranose units (Ribeiro, Carvalho, Ferreira, & Veiga, 2005) arranged in a donut-shaped ring having a hydrophobic cavity and hydrophilic outer surface (Savjani et al., 2012). This low polarity central cavity is able to encapsulate, either partially or entirely, a great variety of guest molecules of suitable size and shape resulting in a stable association without formation of covalent bonds, resulting in an entity known as a host–guest complex or inclusion complex (Miletic et al., 2013; Mora et al., 2003; Ribeiro et al., 2005; Saenger, 1980; Soares-Sobrinho et al., 2012), Unfortunately, the complexation efficiency of cyclodextrins is rather low and, therefore, a significant amount of cyclodextrins is needed to solubilize a small amount of water-insoluble compounds. However, enhanced complexation can be achieved by formation of ternary complexes (or co-complexes) between the drug molecule, cyclodextrin molecule and a third component. Moreover, recent works have shown that the addition of a suitable third component can often significantly improve both the solubilizing and complexing abilities of cyclodextrins with several drugs (Jug & Bećirević-Laćan, 2004; Mora et al., 2003).

For several reasons, including toxicology, dosage and cost, the amount of cyclodextrins used in most of the formulations must be limited. Therefore, it is important to develop strategies to increase the effectiveness of cyclodextrin complexation that could be reflected in a reduction in the amount of CD necessary in a particular drug formulation (Pose-Vilarnovo et al., 2003; Soares-Sobrinho et al., 2012). To this end the use of water-soluble polymers, the preparation of drug/CD/polymers (Du et al., 2012; Feng, Lu, Li, & Huang, 2013; Loftsson, Frikdriksdóttir, Sigurkdardóttir, & Ueda, 1994; Taupitz, Dressman, Buchanan, & Klein, 2013; Valero, Pérez-Revuelta, & Rodríguez, 2003), multicomponent systems, or the formation of CD complexes of salts of acidic drugs have been described. The use of polymers has been used, at great expense, in recent years but the exact nature of the polymer CD interaction is not known yet (Pose-Vilarnovo et al., 2003; Redenti, Szente, & Szejtli, 2001; Valero et al., 2003).

Despite being widely used in therapeutics, Efavirenz (EFZ) has very low oral bioavailability (40–45%) (Sathigari, Radhakrishnan, Davis, Parsons, & Babu, 2012). EFZ is crystalline, highly lipophilic and has been classified in the Biopharmaceutics Classification System as a class II compound with high permeability but low aqueous solubility (~3–9 μg/mL) with dissolution, rate-dependent absorption (Chiappetta, Hocht, Taira, & Sosnik, 2011; Lindenberg, Kopp, & Dressman, 2004; Madhavi et al., 2011; Sathigari et al., 2012).

Different techniques have been used to enhance the solubility and dissolution rate of poorly soluble drugs in water such as micronization, polymorphs, solid dispersions, complexation with cyclodextrins, polymeric and lipid nanoparticles, and salt formation (Alves et al., 2014; Chiappetta et al., 2011; Gaur, Mishra, Bajpai, & Mishra, 2014; Leuner & Dressman, 2000; Paudel, Worku, Meeus, Guns, & Van den Mooter, 2013; Soares-Sobrinho et al., 2012).

Therefore, the aim of this study was to evaluate the influence of the type of cyclodextrin on the properties of a poorly soluble model drug, EFZ, as well as to evaluate the effect of a drug–CD–polymer on the solubility of EFZ.

2. Materials and methods

Efavirenz (Cristália®, Batch: 1289/07) was provided by the *Laboratório Farmacêutico de Pernambuco* (LAFEPE). Methyl-β-cyclodextrin (MβCD) was provided by Roquette® (Spain), polyvinylpyrrolidone (PVP) K-30 by BASF®, Germany; and PVP K30 by ISO Brazil® (lot 05500138511V06/08), and sodium lauryl sulfate (SLS) by Vetec® (lot 0806072). The solutions were prepared using ultrapure water (MILLI Q) and filtered through a 0.22 μm Millipore® membrane (Millipore Corp, Billerica, MA). Other reagents and chemicals were of analytical reagent grade.

2.1. Phase-solubility diagram

The phase-solubility diagrams were performed similar to those performed by Soares-Sobrinho et al. (2012).

In order to select the best cyclodextrin, a phase-solubility diagram with different types of cyclodextrins (CDs) was constructed. Aqueous solutions of αCD, MβCD, HPβCD and RMβCD were prepared at the concentration range of between 1 and 20 mM, and between 1 and 15 mM for βCD due its low solubility (Loftsson & Brewster, 1996). An excess amount of EFZ (~30 mg) was added to each test tube containing 10 mL deionized water. The test tubes were sealed and shaken for 5 days in an oscillating water bath thermostatically controlled at 25 ± 0.5 °C and, then, the content of each test tube was filtered through a 0.22 μm cellulose membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically at 247 nm by a method previously developed and validated (Alves et al., 2010). The experiment was performed in triplicate.

Afterwards, in order to evaluate the interactions of cyclodextrins and a hydrophilic polymer in the increasing of EFZ solubility, another phase-solubility diagram was constructed. For this purpose, MβCD was used as a model at a fixed concentration (10 mM) in aqueous solutions while increasing concentrations (0.05–1%, w/w) of a hydrophilic polymer (PVP K30) were used.

2.2. Preparation of inclusion complexes in a solid state

For the obtainment of the solid inclusion complexes, EFZ/MβCD (mol/mol) was used with PVP-K30 in crescent concentrations (1%, 5%, 10% and 30%).

2.2.1. Preparation of physical mixtures (PMs)

EFZ and MβCD were precisely weighed in an equimolar ratio (10 mM) and PVP-K30 was used in different weight ratios (1, 5, 10 and 30%) in relation to the total amount of the binary systems EFZ:MβCD. Subsequently, the mixtures were pulverized with a mortar and a pestle and were sifted through a 250 μm mesh and stored in airtight glass desiccators under a vacuum.

2.2.2. Preparation of the kneading (KN) complexes

The KN system was prepared similarly to the physical mixture, supplemented by the slow addition of an ethanol/water solution (1:1, v/v) until homogeneous (Alves et al., 2014) in order to obtain a moist bulk, characteristic of the kneading process. The samples were dried at 50 °C for 60 min; the resulting solid inclusion complex was sifted through a 250 μm sieve and then the products were placed in vials and stored in an airtight glass desiccator under a vacuum. The kneading process has important advantages as simple obtention, high-yielding, and easy scale up. Nowadays, it is still the most commonly used method in the pharmaceutical industry (Pupe et al., 2011; Soares-Sobrinho et al., 2012).

2.3. Characterization of the solid state complex

2.3.1. Dissolution profile

Studies of drug release were performed in quadruplicate 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 (Alves et al., 2014; Pinto, Cabral, & Sousa, 2014).

Capsules containing the equivalent of 30 mg of drug were used. Aliquots of 4 mL were withdrawn at 15, 30, 45, and 60 min, and the same volume of dissolution medium was replaced. The samples were filtered through a 0.45 μm porosity membrane and properly quantified.

2.3.2. 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.

2.3.3. Fourier transform infrared (FT-IR)

The infrared spectrum was obtained using a device equipped with a selenium attenuated total reflectance (ATR) crystal (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 10 scans. The micrographs were obtained for the range of 650–4000 cm^{-1} at a resolution of 4 cm^{-1}.

2.3.4. Differential scanning calorimetry (DSC)

DSC studies were carried out using differential scanning calorimeter (DSC 60, Shi-madzu, 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^{-1} at a temperature range of 25–200 °C. An inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 mL min^{-1}.

2.3.5. Thermogravimetry (TG)

Thermoanalytical characterization using TG was performed in triplicate by a, Shimadzu®TGA thermobalance, model Q60, in a nitrogen atmosphere with a flow of 50 mL min^{-1}. The sample mass was of about 4 mg (±0.4) of EFZ, packed in an aluminum oxide crucible at a temperature range of 25–500 °C at the heating rate of 10 °C min^{-1}.

2.3.6. Scanning electron microscopy (SEM)

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

3. Results and discussion

3.1. Phase-solubility diagram

Phase-solubility studies of binary systems (EFZ:CDs) (Fig. 1), were performed in order to observe the effect of the complexation ability of different types of cyclodextrin systems. In accordance with the results, it was observed that the cyclodextrin that increased EFZ solubility better was MβCD (from 9 μg/mL to 75,227 μg/mL) (Loh, Tan, & Peh, 2014).

Table 1
Complexation constants ($Kc_{1:1}$) for EFZ:CDs and EFZ:CDs:PVP K30 determined by solubility phase diagram.

Systems binary and ternary	Slope	Intercept	$Kc_{1:1}$ (M^{-1})
EFZ:βCD	0.00485	0.02613	184.7
EFZ:αCD	0.00630	0.02918	214.5
EFZ:RMβCD	0.00729	0.03032	238.7
EFZ:HPβCD	0.00956	0.02508	377.5
EFZ:MβCD	0.01060	0.02884	363.6
EFZ:HPβCD:PVP K30	0.03024	0.14246	218.9
EFZ:MβCD:PVP K30	0.05234	0.13256	416.6

In addition, it is well established that from these diagrams it is possible to estimate the stoichiometry involved (Jullian et al., 2008; Xu et al., 2014). The experimental results demonstrated that the obtainment of inclusion complexes with a typical profile and suggested an occurrence of soluble complexes with 1:1 stoichiometry (Sathigari et al., 2009).

The complexation constants (Kc) (Jug, Kosalec, Maestrelli, & Mura, 2011) are given in Table 1. $Kc_{1:1}$, calculated on the basis of the solubility phase diagram, shows that the formation of inclusion complexes and ternary complexes are stable with EFZ, since, according to Jun et al. (2007), the association constants for drugs with CDs appear in the 50–2000 M^{-1} band.

Regarding the ternary complexes, the choice of PVP K30 as a hydrophilic polymer to increase the solubility of EFZ had been already studied (Alves et al., 2014; Soares-Sobrinho et al., 2012). Besides, the effect of the hydrophilic polymer association with cyclodextrins to increase the solubility of insoluble drugs is well established in the literature (Cappello, Carmignani, Iervolino, Immacolata La Rotonda, & Fabrizio Saettone, 2001; de Melo et al., 2013; Soares-Sobrinho et al., 2012).

Increasing concentrations of MβCD have led to a proportional increase in EFZ solubility, as noted, from 9 μg/mL to 82.12 μg/mL. According to the results of the experiments, the use of PVP K30 at 1% promoted the best improvement in the solubility of EFZ.

This relationship could be explained by the electrostatic interaction, i.e., Van der Waals and hydrogen bonds, that may be formed due to the susceptible groups of EFZ and MβCD, favoring the stability of the complex (Ribeiro et al., 2005).

For subsequent studies, the MβCD at 10 mM was chosen as a model, as well as PVP K30 at 1%, for the characterization of the solid state.

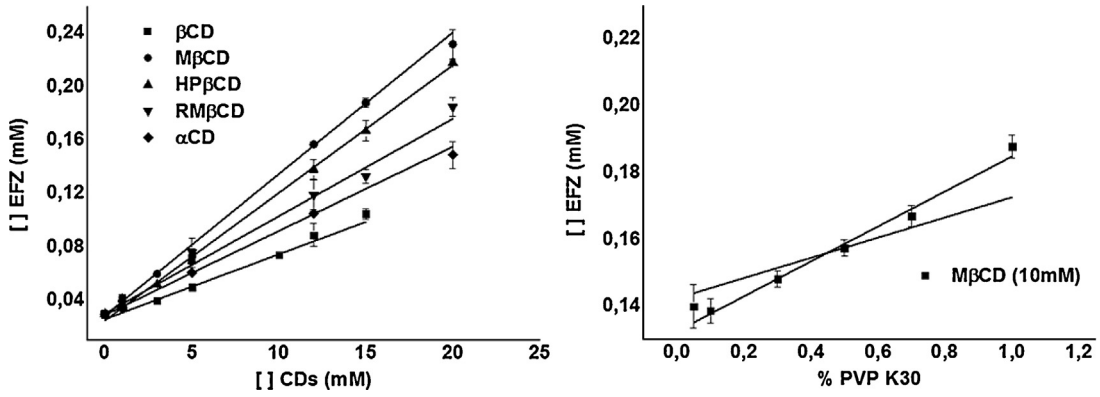

Fig. 1. Phase-solubility diagram with different types of cyclodextrins (a) and EFZ:MβCD with increasing concentration of PVP K30 (b).

3.2. Characterization of the solid state complex

3.2.1. In vitro dissolution studies

The dissolution profiles of EFZ, the kneading solid multicomponent (KN) with 1, 5, 10 and 30% and the respective physical mixtures are presented in Fig. 2. In accordance with the results, it is clear that the dissolved fractions of EFZ decrease with the increase of the amount of PVP K30, in the case of the kneaded compounds. What was not observed, in the case of physical mixtures, was exactly the opposite. It means that the kneading process promoted a higher interaction between the three compounds: drug–cyclodextrin–polymer, explained by the strong non-covalent interactions, already well described in the literature (Brewster & Loftsson, 2007; Jansook, Kurkov, & Loftsson, 2010). These behaviors of prolonged delivery of EFZ with 30% and 10% of PVP K30 is associated with the swelling phenomenon, a characteristic of hydrophilic polymers, in which larger amounts leads to the formation of a high viscosity gel layer around the powdered products which could control the diffusivity of the dissolved drug to the dissolution media (Nokhodchi, Raja, Patel, & Asare-Addo, 2012; Ribeiro et al., 2005). Although, in all cases, including PM, the solid complexes were able to improve the solubility of EFZ compared to the pure drug, which

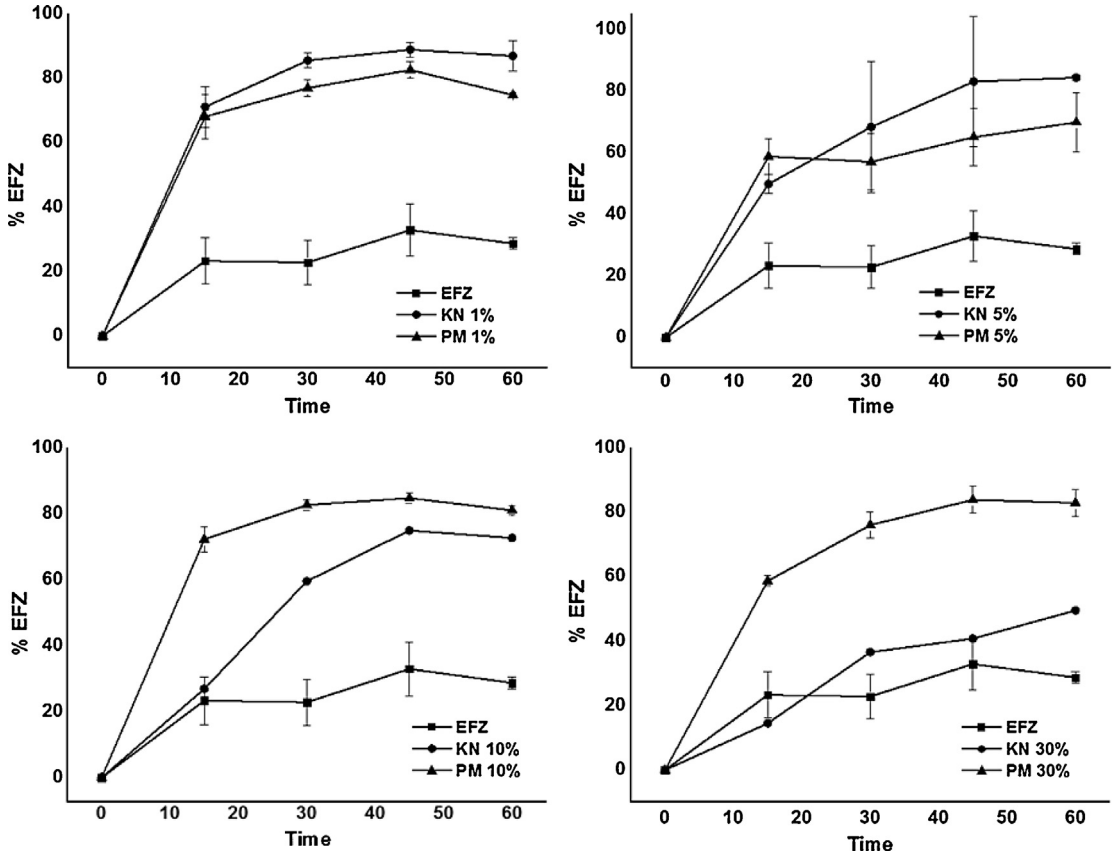

Fig. 2. In vitro dissolution studies: EFZ, physical mixtures and kneading at different concentrations of PVP K30 (1%, 5%, 10% and 30%).

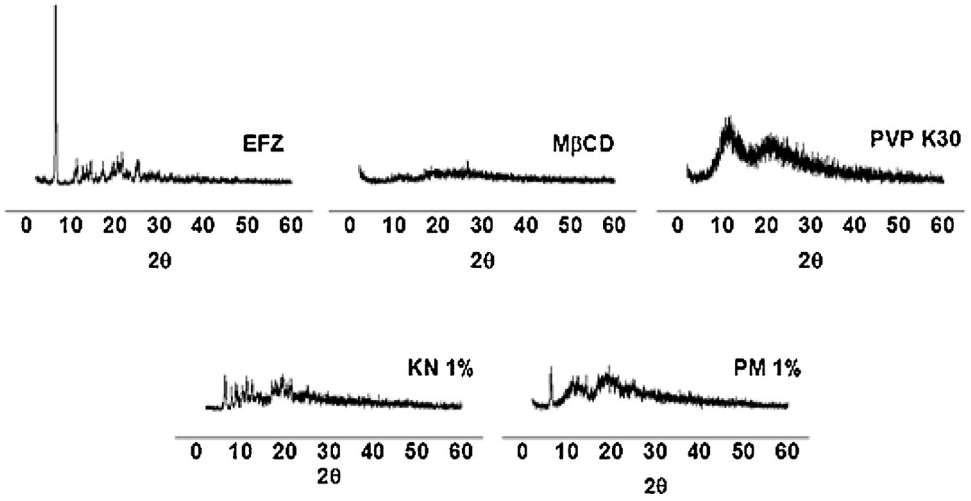

Fig. 3. Diffractogram of the separate excipients EFZ, MβCD, PVP K30 and the KN 1% and PM 1% ternary systems.

may be explained by the decrease in the crystallinity of the final compounds due to the presence of PVP K30.

On the other hand, the KN complex with 1% PVP K30 promoted the best increase in the solubility and delivery of EFZ. In 30 min, more than 80% of the total drug was delivered, against less than 25% compared with EFZ alone. In this case, the PVP K30 acted as a co-complexing agent, increasing the hydrophilic potential of MβCD (de Melo et al., 2013; Ghosh, Biswas, & Ghosh, 2011).

3.2.2. X-ray diffraction (XRD)

For the further characterization of the complexes obtained, the best system was chosen as a model: EFZ:MβCD:PVP K30 1%.

XRD patterns for solid compounds are mainly used for evaluating changes in crystalline structure of the drug (Fig. 3). The EFZ diffractogram, according to the literature (Alves et al., 2014), presented a very distinct peak at 2θ of 6.24°, and others of lower intensity between the range of 10° and 30°. Regarding the XRD patterns of PVP K30 and MβCD, both were characterized by a complete absence of peaks, due to their amorphous compound characteristic (Ghosh et al., 2011).

Regarding the ternary systems, it was observed that physical mixtures were basically an overlap of the EFZ, PVP K30 pattern profiles and MβCD, with a decrease in the intensity of the main peak of EFZ at 6.24°. In the case of KN compounds, a slight increase in the secondary crystalline peaks, between 10° and 30°, was observed, which did not, necessarily, have to do with the crystallinity of EFZ, but with the new shapes that the solid complexes exhibited, as seen in the microscopies. This fact reinforces the results obtained in the dissolution profile which indicates a strong interaction between the constituents of the ternary system, revealing that, although KN is not completely amorphous, it does not affect the increased solubility of EFZ. This behavior of a

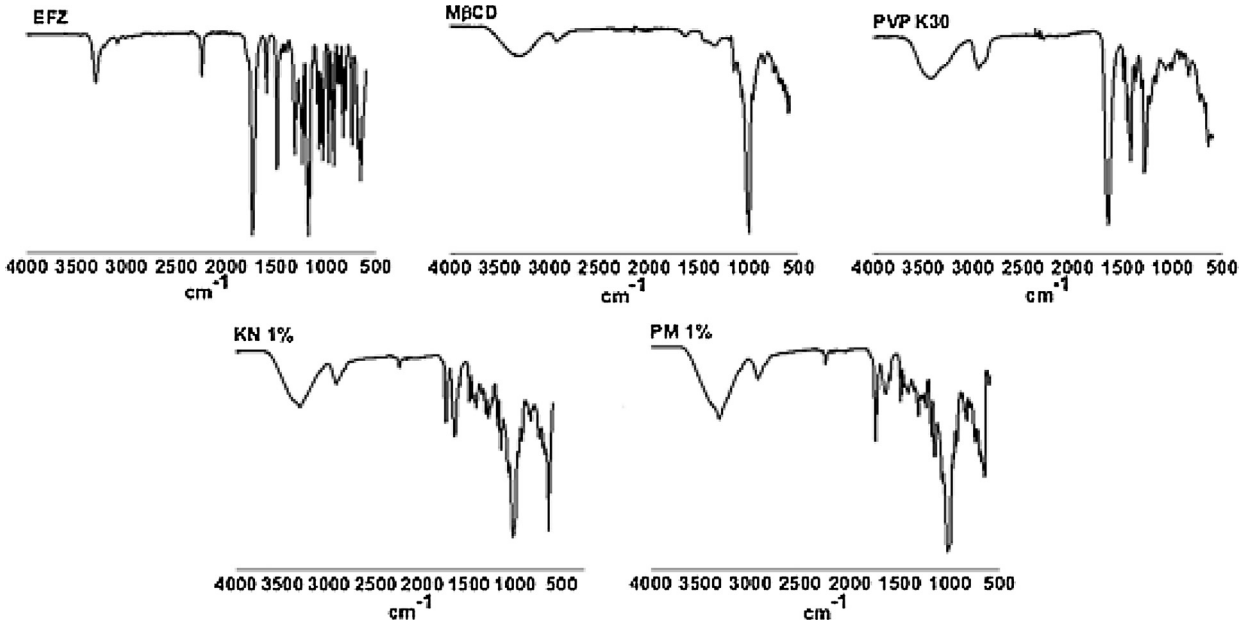

Fig. 4. Infrared spectra of the separate excipients EFZ, MβCD, PVP K30 and the ternary KN 1% and PM 1% systems.

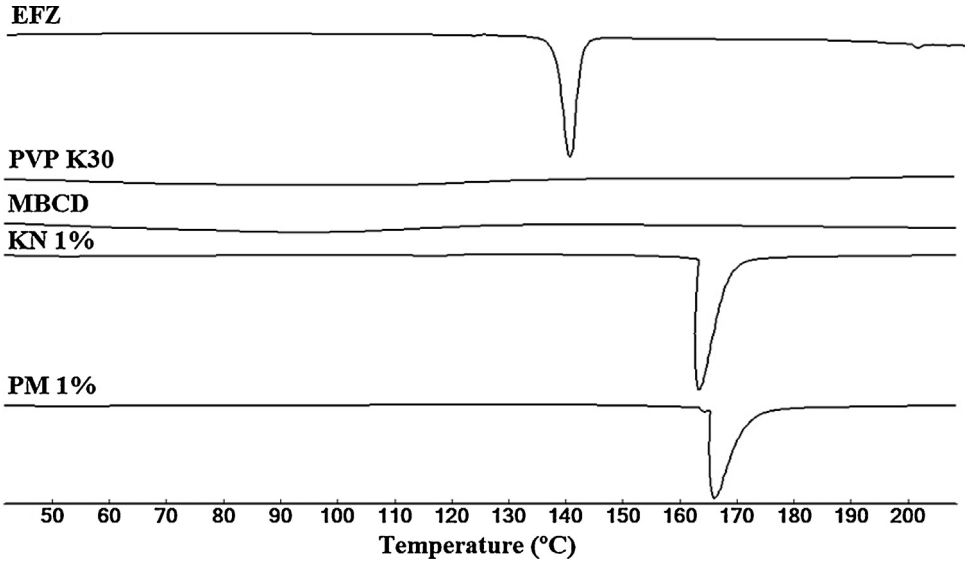

Fig. 5. DSC thermograms of the separate excipients EFZ, MβCD, PVP K30 and the KN1% and PM 1% ternary systems.

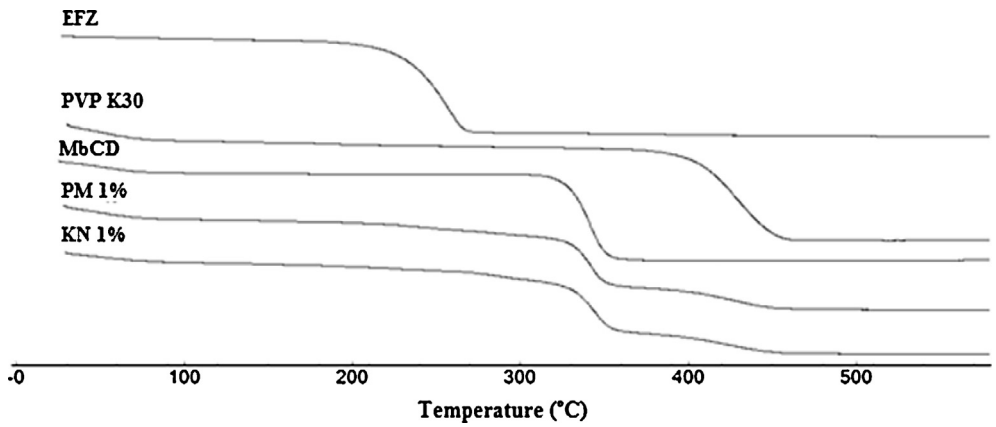

Fig. 6. TG curves of the separate excipients EFZ, MβCD, PVP K30 and the KN1% and PM1% ternary systems.

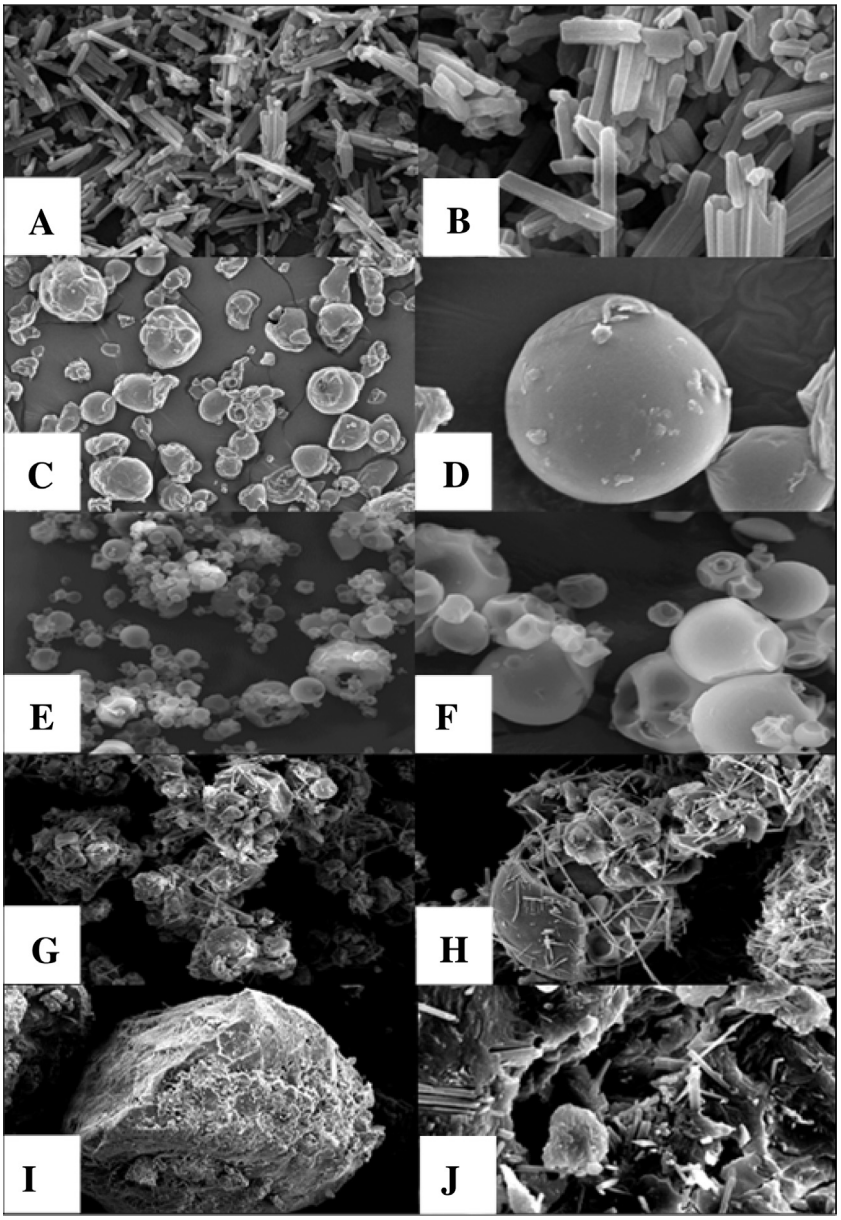

Fig. 7. SEM micrographs in two dimensions of separate excipients: EFV (A and B), PVP K30 (C and D), MβCD (E and F) and KN1% (I and J) and PM1% (G and H) ternary systems.

slight increase in the crystallinity of KN complexes was already described.

3.2.3. Fourier transform infrared (FT-IR)

The KN and PM spectra (Fig. 4) were similar in relation to the decrease in the intensity of the EFZ main bands, especially the ones related to the C=O stretching (1742 cm^{-1}) besides highlighting the presence of the bands concerning the stretch O—H of the PVP K30 (3419 cm^{-1}) and MβCD (3297 cm^{-1}) which overlaps the N—H band of EFZ (3314 cm^{-1}. Simultaneously, all the bands of the spectra related to the C—H stretching (2952 cm^{-1}) and C=O (1647 cm^{-1}) of PVP K30 were always present at a lower intensity. Additionally, we noted that the stretch vibration of the C≡C (2249 cm^{-1}) of EFZ is practically absent in the KN system, suggesting a possible complexation with the MβCD within the cyclopropane group of EFZ. The stretch vibration C≡C in the PM (2249 cm^{-1}) was still present, but at a lower intensity, due to the proportionally lower amount of drug in the system. This suggests that the kneading process may induce the formation of a complex between EFZ:MβCD, since during the preparation of the PM no addition of water occurred, which is essential to obtain a complex. In addition, with the spectra obtained, it is clear that in both ternary systems (PM and KN) intermolecular interactions between PVP K30, and the MβCD EFZ, especially hydrogen bonding, are strongly present (Mura, Faucci, & Bettinetti, 2001; Soares-Sobrinho et al., 2012).

3.2.4. Differential scanning calorimetry (DSC)

The EFZ thermograms, obtained by DSC, showed an endothermic event in the range between 123.31 and 145.20 °C (DH = 41.7 J/g) corresponding to the melting of the drug. On the other hand, the PVP K30 thermograms showed a discrete endothermic event in a broad range between 50 and 120 °C (peaking at 104.21 °C) corresponding to the evaporation of water as can be seen in Fig. 5. The same event can be observed for MβCD in the range between 40° and 130 °C.

The DSC curve of the PM showed an endothermic event between 163.3 °C and 171.5 °C (226.1 J/g), which melting point was shifted and extended to a higher temperature comparing to the pure drug. A similar event can be observed in the KN curve, which showed an endothermic event between 160.6 °C and 168.7 °C (116.69 J/g).

Hence, it is suggested that the presence of MβCD and PVP K30 hinder the EFZ melting process, leading to both its shift to a higher temperature and enlargement of the peak, with consequent increased energy involved. Thus, it is suggested that the system gives stability to the drug, which can be confirmed by TG analysis.

3.2.5. Thermogravimetry (TG)

It can be seen that in the PM as in the KN the degradation steps are the sum of the individual degradation of EFV, MβCD and PVP K30 (Fig. 6). In the PM decomposition event of EFZ (T_{onset} = 224.0 °C) it occurred at lower temperatures when compared to isolated EFZ (T_{onset} = 231.9 °C). The same does not occur in KN, when the decomposition process was shifted to higher temperatures (T_{onset} = 272.6 °C) compared with EFZ.

Furthermore, the percentage of EFZ weight loss was lower for KN (78%) when compared to the PM (81%), demonstrating that the product obtained by the kneading technique provided greater stability to EFZ (Freitas et al., 2012).

3.2.6. Scanning electron microscopy (SEM)

Through the SEM images, the crystalline form of EFZ can be observed with orthorhombic crystals of an irregular shape (Fig. 7A and B), while PVP K30 (Fig. 7C and D) and MβCD (Fig. 7E and F) are spherical particles.

In electron micrographs of the PM (Fig. 7G and H), we could see the permanence of EFZ in its crystalline form, despite being only superficially adhered to PVP K30 and MβCD, which continued with the same morphology. This adherence does not occur with KN (Fig. 7I and J), where uniform particles were observed, demonstrating changes in both the original forms of EFZ as the other constituents of the ternary system. Regarding KN, it can also be observed that crystals of the drug are sometimes partially, hereby fully inserted, in the matrix, maintaining the system with some crystalline character, as detected in the XRD and DSC characterization (Ghosh et al., 2011).

4. Conclusion

The results demonstrate a superior water solubility of the multicomponent system EFZ:MβCD:PVP K30 in the concentration of 1% against the inclusion complex EFZ:MβCD at the same molar ratio. The use of the KN technique to obtain the ternary solid state system, permitted the formation of a uniform, substantially non-crystalline particle, which increased the dissolution rate of EFV, and provided an increase in the stability of the drug as demonstrated by thermal analysis, with strong electrostatic interactions between the PVP K30 and MβCD, as seen by FT-IR.

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