Interaction and compatibility studies of efavirenz with pharmaceutical excipients.

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Original Article

ABSTRACT

Although excipients have traditionally been thought of as being inert, experience has shown that there can be interactions between excipients and drugs. Thus, knowledge of potential physical and chemical interactions can be very useful. The compatibility of efavirenz with the excipients: sodium lauryl sulfate, spray dried lactose, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose and croscarmellose sodium was studied. X-ray powder diffraction (XRPD), Fourier Transform Infrared Spectroscopy (FT-IR), Raman spectroscopy (RS) and Differential scanning calorimetry (DSC) were used as screening techniques. DSC curves of binary mixtures were quite different from the efavirenz raw material, suggesting a strong interaction, including possible chemical reactions between efavirenz and excipients at increased temperatures. However, FT-IR, XRPD and RS showed that no chemical reaction occurred between efavirenz and excipients at room temperature. Efavirenz can exist in more than one crystalline form, which may have implications for its behavior during production, and also for its *in vivo* performance. XRPD, DSC, Scanning Electron Microscopy (SEM) and Intrinsic Dissolution Rate (IDR) were used for the solid-state characterization of efavirenz and showed that the raw material used corresponded to Form I and maintained its crystal structure during the study. Intrinsic dissolution studies indicated that bioavailability problems may arise because of the poor solubility of efavirenz.

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INTRODUCTION

In the solid state, both active pharmaceutical ingredients (APIs) and excipients can exist as

different crystalline forms and their physicochemical properties can vary (1-3). Different molecular arrangements in the crystal lattice may lead to remarkable changes in properties such as solubility, dissolution and bioavailability (2). Although, excipients have traditionally been thought of as being inert (4), experience has shown that they can interact with drugs (5-7). The selection of excipients can also influence solid-state reactions, including phase transitions, and may affect the pharmaceutical and biopharmaceutical properties of a formulation (5, 8). Incompatibilities may result in an accelerated loss of efficacy, complexation, acid-base interaction or the formation of a eutectic-mixture, resulting in lower bioavailability and/or poor stability (9). Therefore, when developing a pharmaceutical dosage form, it is essential to conduct compatibility studies between the drug and excipients.

Compatibility studies of efavirenz and the excipients magnesium stearate, microcrystalline cellulose and croscarmellose sodium using thermoanalytical techniques have been reported by Viana *et al.* (10). DSC is a useful technique for the evaluation of incompatibilities, because heat is one of the main factors that accelerate solid-state reactions. However, as the sample is submitted to higher temperatures to which the dosage form is not exposed, the results should be interpreted carefully to avoid misleading conclusions (11). Hence, it is necessary to support the conclusions using additional techniques. A compatibility study between efavirenz and excipients, some of them already reported using only DSC, as well as, with other excipients that have not been reported, was conducted. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for the treatment of human immunodeficiency virus type 1 infection (12, 13) (Figure 1). It is a lipophilic crystalline solid with a molecular weight of 315.68 g/mol (14), and an aqueous solubility of 9.0 μg/ml (13). It is a component of the High Activity Antiretroviral Therapy (HAART) in
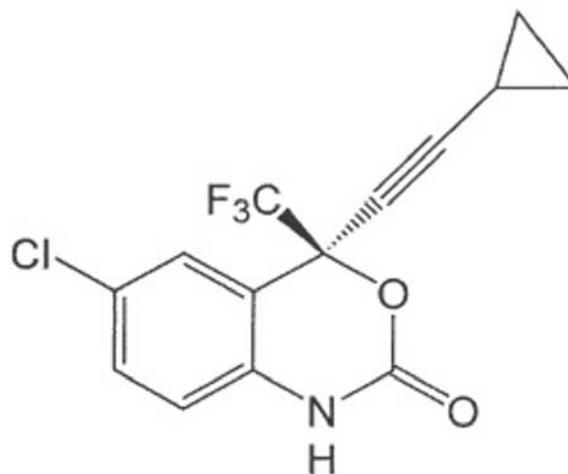
Figure 1 Chemical structure of efavirenz (adapted from Sathigari *et al.*, 2009)

combination with other drugs, and is considered a powerful choice in the treatment of adults and children (15). This API has more than one crystalline form and therefore it is also important to control phase transitions during the formulation.

The purpose of this study was to identify the crystal structure of the raw material used, and to evaluate the solid-state characteristics of efavirenz and its compatibility with sodium lauryl sulfate, spray dried lactose, hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose and croscarmellose sodium using a range of solid-state analytical techniques.

MATERIALS AND METHODS

Materials

Efavirenz was donated by the laboratory Farmanguinhos (FIOCRUZ-RJ) but for reasons of confidentiality the manufacturer's name cannot be stated. The excipients selected are commonly used in pharmaceutical formulations according to the European Drug Agency (16). Microcrystalline cellulose (Microcel MC-102, 100 microns average particle size, 0.28 - 0.33 g/cm³ bulk density range and maximum moisture of 7.0%) and

croscarmellose sodium (Solutab A, 60 microns average particle size) were provided by Blanver LTD. Magnesium stearate was supplied by AMC do Brasil, hydroxypropylcellulose (Klucel LF, 60 mesh average particle size, 0.5 g/cm³ bulk density and maximum moisture of 5.0%) was supplied by Ashland Aqualon Functional Ingredients (USA). Spray dried lactose monohydrate (SuperTab, 75 microns average particle size, 0.5 g/cm³ bulk density and max moisture of 0.5%) was provided by DMV Fonterra Excipients and sodium lauryl sulfate was donated by Stepan. All excipients were of USP-NF grade. To prepare the binary mixture (drug: excipient 1:1 w/w) equal quantities of drug and each excipient were weighed separately and then mixed on a glass plate.

X-ray powder diffraction (XRPD)

XRPD patterns were recorded on a XPERT PANalytical diffractometer, equipped with X' Celerator detector, using Ni filtered k_α radiation from a Cu tube operating with 40 kV and 45 mA, 2 Theta range from 5 - 60 degrees, scan step size of 0.033 degrees and scan step time of 45 seconds. The Soller, divergent and anti-scattering slits used were 0.04 rad and 0.25° respectively.

Fourier Transform Infrared Spectroscopy (DRIFTS)

FT-IR spectra of efavirenz, pure excipients and binary mixtures (drug: excipient at 1:1 w/w) were recorded using FTIR (Prestige-21 Shimadzu), in KBr (potassium bromide) discs over the range of 4000 - 600 cm⁻¹.

Raman spectroscopy (RS)

Raman spectra were collected in backscattering mode using a PeakSeeker 785 (RAM - PRO - 785) Raman system a 300 mW diode laser at 785 nm as the source. The collected Raman radiation was dispersed with a grating and focused on a Peltier-cooled charge-coupled device (CCD) detector having a spectral resolution of 6 cm⁻¹. The laser was focused on the sample by means of a 20x objective

microscope lens giving an irradiated area approximately 2 μm diameter. All spectra were recorded in the spectral window of 200 - 1800 cm⁻¹ with the same acquisition time (30 seconds). The powders were analyzed on glass slides at room temperature.

Differential Scanning Calorimetry (DSC)

DSC curves of efavirenz, pure excipients and binary mixtures (drug:excipient at 1:1 w/w) were obtained using a DSC-60 cell (Shimadzu) in aluminum pans containing about 2 mg of sample, under a dynamic nitrogen atmosphere (50 ml/min) at a heating rate of 10 K/min from 298 to 773 K. The DSC cell was calibrated using a standard reference, Indium.

Scanning Electron Microscopy (SEM)

The morphology of the efavirenz sample was investigated using SEM. The samples were mounted on metal stubs using double-sided adhesive tape, vacuum-coated with gold (350 Å) in a Polaron E-5000 sputtering chamber and analyzed using a scanning electron microscopy (Philips, Model XL 30) at an intensity of 10 kV, and a magnification of 3.000 x.

Intrinsic dissolution rate (IDR)

The IDR test consisted of preparing a non-disintegrating compact of the test material using a suitable compaction device consisting of a die, an upper punch, and a lower surface plate, fabricated out of hardened steel (17). 100 mg of the drug was compacted in disks using a hydraulic press fitted with a manometer (ASTA) to approximately 4KN. The surface area of the compact was 0.5 cm². Solid phase transition due to dissolution medium effects was investigated using XRPD, and the effect of pressure was investigated using DSC and XRPD. The compact was placed in a USP apparatus 2 dissolution test system (VARIAN VK 7000) in 200 ml of SLS 0.2 % (w/v) previously heated at 37°C ± 0.5°C. The analyses were carried out at a rotation speed of 75 RPM. The samples were withdrawn at 15,

30, 60, 90, 120, 180 and 240 minutes and were replaced with an equal volume of preheated fresh medium to maintain a constant total volume. The sample aliquots were filtered and analyzed using high performance liquid chromatography (HPLC). The HPLC analyses were performed using a Shimadzu LC10AT equipped with a vacuum degasser (DGU-10AL), UV-VIS detector (Shimadzu SPD-10Av) and auto-injector (Rheodyne 7125). The chromatograms were recorded using CLASS-VP software (version RV 6.14). A PerkinElmer® C18 (150 mm x 4.6 mm, 5 µm) column was used. The chromatographic conditions were as follows: mobile phase - acetonitrile: ammonium acetate buffer pH 7.5 (50:50 v/v), flow rate of 1 ml/min, injection volume of 20 µl, detection at 272 nm and retention time of 27 minutes for efavirenz. The parameters used were according to USP (18) for efavirenz. Sink conditions during the IDR assays were assured for this polymorphic form of efavirenz in 200 ml of SLS 0.25% according to USP (19). The addition of SLS 0.25% (w/v), almost at the limit of Critical Micellar Concentration (CMC), was necessary to improve the wetabillity and solubility of efavirenz. The IDR tests were carried out in triplicate, and the standard deviation of the three IDR values was determined using GraphPad Prism® software.

RESULTS AND DISCUSSION

Characterization of efavirenz raw material

The efavirenz raw material was characterized before and monitored during the compatibility studies. The results obtained by DSC were in agreement with the literature, for Form I, which cites a melting point of about 411 - 413 K (20). Figure 2 shows the XRPD diffraction patterns of the calculated structure determined for efavirenz and identified as a Form I by Mahapatra *et al.* (20), and for the raw material used in this study. The XRPD pattern of efavirenz characterized in this work is identical to Form I. Figure 2 shows the same peak positions as the calculated pattern. It is,
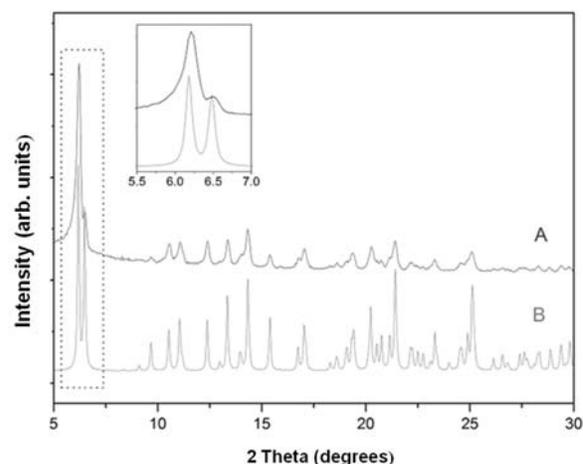
Figure 2 XRPD patterns for efavirenz: (A) experimental and (B) calculated

however, clear from the differences in the intensities that the raw material sample has a preferred crystalline orientation. Using SEM it was possible to make a topographic analysis to examine the morphology and porosity of this efavirenz. Literature reports indicate that efavirenz Form I presents as a predominently layered morphology (21). An example SEM of the efavirenz used in these studies is shown in Figure 3. The shape of the crystals could be visualized at 3000x magnification. Defined and regular forms were observed as for the majority of drugs (18) as does this efavirenz sample showing columnar crystals. According to the Biopharmaceutical Classification System (BCS),
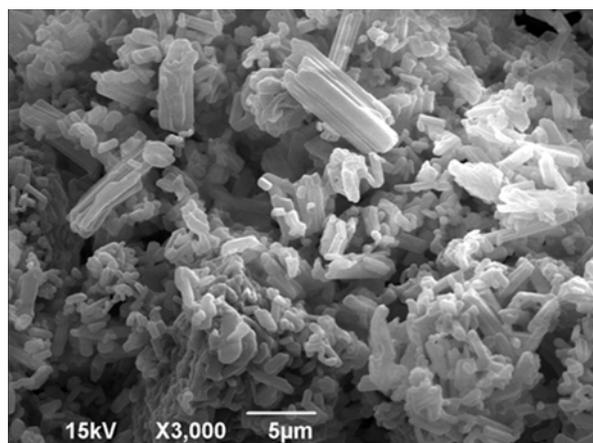
Figure 3 Scanning electron photomicrograph of efavirenz
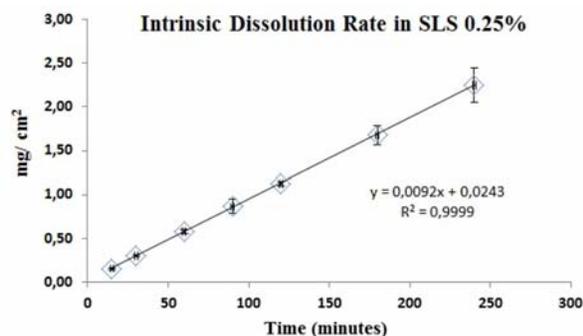
Figure 4 Intrinsic dissolution profile for efavirenz raw material

class II drugs such as efavirenz have low solubility and high permeability, and the correlation between *in vivo* results and dissolution tests is likely to be good because dissolution rate is the primary limiting aspect to absorption (22, 23). Intrinsic dissolution rate has been used to characterize solid drugs, and can be correlated with *in vivo* drug dissolution better than equilibrium solubility because it is a rate phenomenon. Such data can be better correlated with the dynamics of dissolution in the gastrointestinal tract (24). This evaluation can be carried out by measuring the intrinsic dissolution rate such that the surface area is kept constant. The speed at which a solid dissolves in a dissolution medium or a biological fluid is a function of its surface area, solubility, its dissolution rate constant, and of the solute concentration in the medium (9). SLS 0.25% is a suitable concentration for an anionic surfactant. The CMC of pharmaceutically acceptable anionic surfactants is reached at concentrations of the order of 1 - 10 mM, that is, approximately between 0.03 and 0.25% (25). The maintenance of sink conditions during the IDR assays was confirmed as the solubility after an equilibration period of 96 hours was 239.75 ± 0.01 μg/ ml of efavirenz and the concentration of the drug after 240 minutes in the IDR analysis was 4.49 μg/ml. Therefore, the maximum solubility of the drug was more than 50 times the drug concentration in the dissolution medium. This confirms that sink conditions were maintained during the IDR test (20). The IDR of efavirenz raw material is

shown in Figure 4. The IDR was 0.0092 mg min^{-1} cm^{-2} obtained via linear regression. The IDR value is below 0.1 mg min^{-1} cm^{-2}, therefore bioavailability problems may arise due to poor dissolution. The linear regression obtained y = 0.0092x + 0.0243 (R^2 = 0.9999). Standard deviation showed that the triplicate results obtained for the IDR were not significantly different (α = 0.05, p < 0.1).

Analysis of compatibility between efavirenz and excipients

The heat of fusion of pure efavirenz was 40.10 ± 0.98 J/g. Chadha *et al.* (2012) reported 15.22 KJ/mol or 48.21 J/g (26) and Viana *et al.* (2008) reported 49.4 J/g (10) for the enthalpy of fusion for this drug. The DSC curves of efavirenz and the binary mixtures (1:1 w/w) are shown in Figure 5. The results suggest that at increased temperatures, there are no interactions between the drug and spray dried lactose or croscarmellose sodium. For lactose the endothermic peak of efavirenz (411.66 K) shifted slightly. The first endothermic peak (410.53 K) is close to that observed for the pure drug, and the second endothermic peak is characteristic of the melting point of lactose. The physical mixture of efavirenz and croscarmellose sodium showed that an endothermic peak shifted to a lower temperature (411.66 K to 407.70 K). However, interactions with efavirenz at elevated temperature were observed for the other
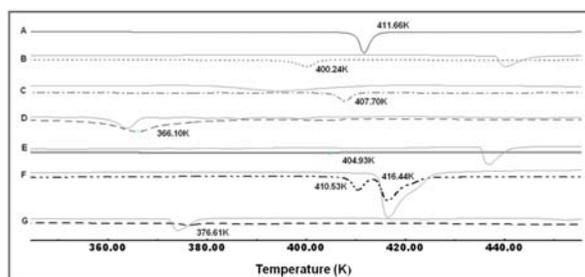
Figure 5 DSC curves for: (A) efavirenz, (B) efavirenz: microcrystalline cellulose, (C) efavirenz:croscarmellose sodium, (D) efavirenz:magnesium stearate, (E) efavirenz: hydroxypropylcellulose, (F) efavirenz:spray dried lactose and (G) efavirenz:sodium lauryl sulfate. The excipients are represented by gray lines above each physical mixture (efavirenz:excipient physical mixtures are 1:1 w/w)
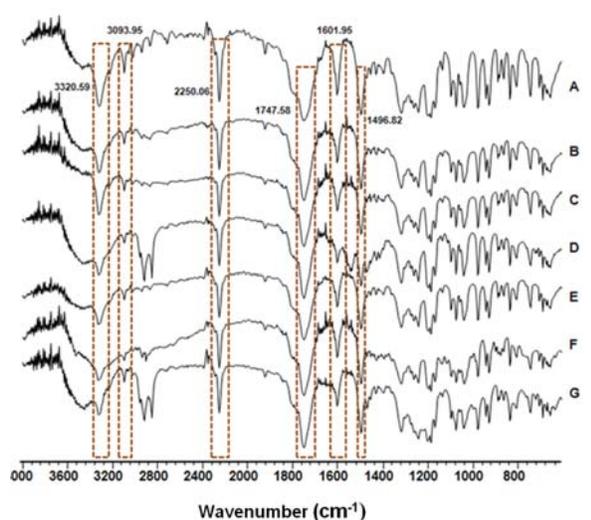
Figure 6 FT-IR spectra for: (A) efavirenz, (B) efavirenz: microcrystalline cellulose, (C) efavirenz:croscarmellose sodium, (D) efavirenz: magnesium stearate, (E) efavirenz: hydroxypropylcellulose, (F) efavirenz: spray dried lactose and (G) efavirenz: sodium lauryl sulfate

pharmaceutical excipients, i.e., microcrystalline cellulose, magnesium stearate, hydroxy-propylcellulose and sodium lauryl sulfate. This interaction in the physical mixture is not necessarily an incompatibility as has been previously discussed by Mura *et al.* (27) and Cides *et al.* (6). Representative DSC curves of efavirenz and microcrystalline cellulose showed some broadening of the endothermic peak accompanied by decreasing temperature. The decrease in efavirenz melting point in the physical mixture with magnesium stearate indicated a strong interaction, since the efavirenz endotherm peak shifted from 411.66 K to 366.10 K. In general, lubricants are present in pharmaceutical formulations at low concentrations, which is different from the mixture investigated here (1:1 w/w), suggesting a solid-solid interaction, but not necessarily an incompatibility (7, 28). For the binary mixture of efavirenz and hydroxypropylcellulose the endothermic peak of efavirenz disappeared in all the samples, indicating a strong interaction. For sodium lauryl sulfate the melting point characteristic of this excipient (gray line) and the absence of a peak corresponding to efavirenz, indicated a strong interaction

between efavirenz and this excipient. It is suggested that the liquid phase of sodium lauryl sulfate solubilized the efavirenz and the peak observed is related to the fusion peak of SLS (29).

FT-IR spectra, XRPD diffraction spectra and Raman spectra of efavirenz and binary mixtures of the drug and excipients (1:1 w/w) were carried out in order to confirm any possible chemical interactions between them. The results obtained are shown in Figures 6-8 indicating the absence of any chemical interaction or change in the crystalline structure when the binary mixtures were evaluated at room temperature. Figure 6 shows the characteristics bands corresponding to efavirenz and physical mixtures of drug and excipient (1:1 w/w). Efavirenz main absorption bands were observed in spectrum at 3093 (-NH), 3320 ($\equiv$CH), 2250 (C$\equiv$C), 1747 (C=O), 1601 (C=C), 1496 (aromatic ring stretching) cm^{-1}, and these values were in agreement with existing literature (30). From the FT-IR spectra for efavirenz and the excipients, the efavirenz characteristic bands were clearly identified in all physical mixtures analyzed without the appearance of any new bands in the IR spectra, no shift and, most importantly, the efavirenz characteristic bands were maintained in all physical mixtures, confirming that no chemical incompatibility occurred. These results were confirmed by XRPD patterns of the characterized raw material, excipients and binary mixture which showed no pattern alteration or modification. In addition, the raman spectra of efavirenz and those of the binary mixtures showed no differences (Figure 7). The results obtained using XRPD and RS showed that there had been no change in the efavirenz crystalline structure when the binary mixtures were prepared. A comparison between XRPD patterns of the raw material and the binary mixture of drug and excipient, showed that a solid solution of crystalline efavirenz in the usually amorphous or poorly crystalline excipients can be seen. The diffraction peaks and/or halos of the excipients (gray patterns in Figure 8) can easily viewed in the diffraction
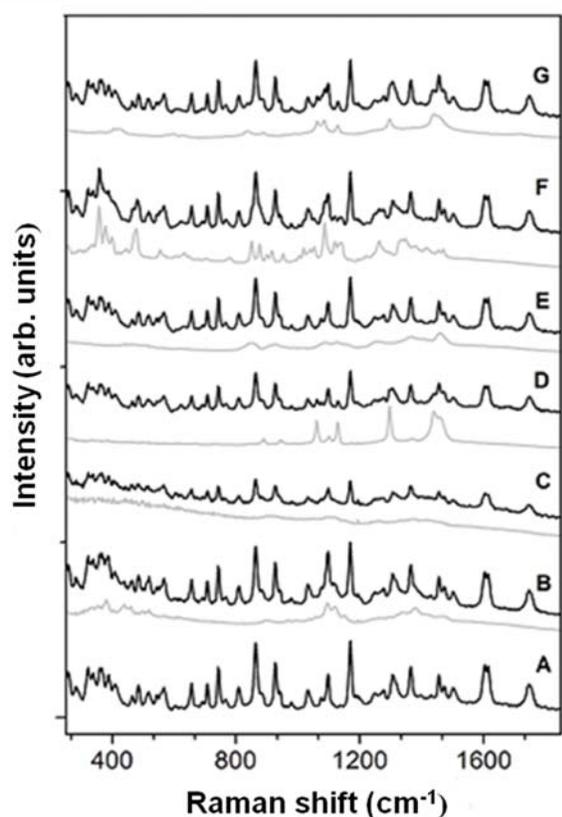
Figure 7 Raman spectra for: (A) efavirenz, (B) efavirenz: microcrystalline cellulose, (C) efavirenz: croscarmellose sodium, (D) efavirenz: magnesium stearate, (E) efavirenz: hydroxypropylcellulose, (F) efavirenz: spray dried lactose and (G) efavirenz: sodium lauryl sulfate. Pure excipients (gray lines) and binary mixture (dark lines)

spectra of binary mixtures.

CONCLUSIONS

The results obtained in this study showed that the efavirenz raw material used here was Form I, as its crystalline structure was maintained throughout the investigation. The intrinsic dissolution rate test showed that bioavailability problems may arise because of poor dissolution. This is typical of BCS class II drugs. In addition, DSC alone was shown to be an inconclusive technique, and suggested considerable interaction and/or solid-state reaction between efavirenz and sodium lauryl sulfate, hydroxypropylcellulose, magnesium stearate and microcrystalline cellulose when the temperature is increased. This indicates that

precautions should be taken, for example, during storage of products containing efavirenz and the above excipients. Finally, the additional techniques of XRPD, FT-IR and RS showed that at room temperature there was no chemical incompatibility, and there were no changes in the crystalline structure of the mixtures studied.
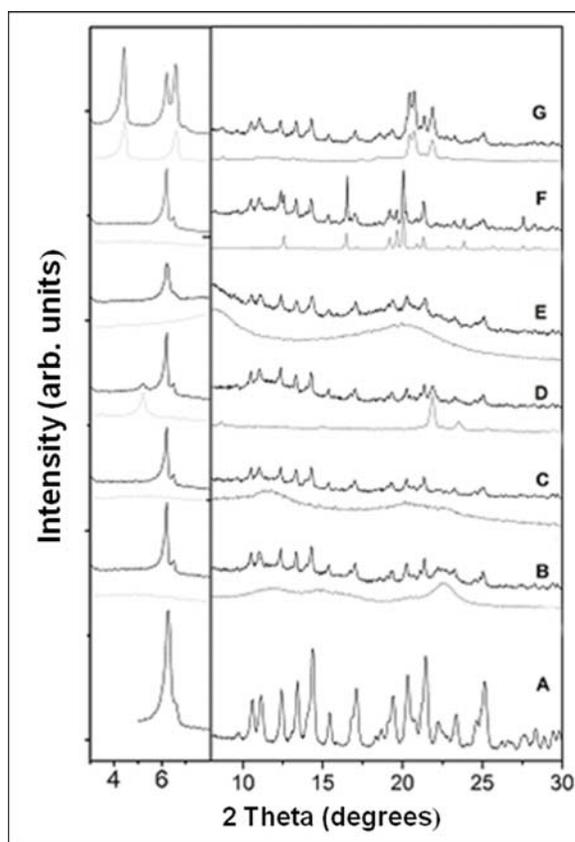
Figure 8 XRPD diffraction spectra for: (A) efavirenz, (B) efavirenz: microcrystalline cellulose, (C) efavirenz: croscarmellose sodium, (D) efavirenz: magnesium stearate, (E) efavirenz: hydroxypropylcellulose, (F) efavirenz: spray dried lactose and (G) efavirenz: sodium lauryl sulfate. Pure excipients (gray lines) and binary mixture (dark lines)

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