Drug Development and Industrial Pharmacy, 31:473–489, 2005

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500215958

Taylor & Francis
Taylor & Francis Group

Miscibility Behavior and Formation Mechanism of Stabilized Felodipine-Polyvinylpyrrolidone Amorphous Solid Dispersions

Evangelos Karavas
Department of Pharmaceutical Technology, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki, Greece
and
Institute of Biological Research and Biotechnology, National Hellenic Research Foundation, Athens, Greece

Georgios Ktistis
Department of Pharmaceutical Technology, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki, Greece

Aristotelis Xenakis
Institute of Biological Research and Biotechnology, National Hellenic Research Foundation, Athens, Greece

Emmanouel Georgarakis
Department of Pharmaceutical Technology, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki, Greece

ABSTRACT In the present study, solid dispersion systems of felodipine (FEL) with polyvinylpyrrolidone (PVP) were developed, in order to enhance solid state stability and release kinetics. The prepared systems were characterized by using Differential Scanning Calorimetry, X-Ray Diffraction, and Scanning Electron Microscopy techniques, while the interactions which take place were identified by using Fourier Transformation-Infrared Spectroscopy. Due to the formation of hydrogen bonds between the carbonyl group of PVP and the amino groups of FEL, transition of FEL from crystalline to amorphous state was achieved. The dispersion of FEL was found to be in nano-scale particle sizes and dependent on the FEL/PVP ratio. This modification leads to partial miscibility of the two components, as it was verified by DSC and optimal glass dispersion of FEL into the polymer matrix since no crystalline structure was detected with XRD. The above deformation has a significant effect on the dissolution enhancement and the release kinetics of FEL, as it causes the pattern to change from linear to logarithmic. An impressive optimization of the dissolution profile is observed corresponding to a rapid release of FEL in the system containing 10% w/w of FEL, releasing 100% in approximately 20 min. The particle size of dispersed FEL into PVP matrix could be classified as the main parameter affecting dissolution optimization. The mechanism of such enhancement consists of the lower energy required for the dissolution due to the amorphous transition and the fine dispersion, which leads to an optimal contact surface of the drug substance with the dissolution media. The prepared systems are stable during storage at 40±1°C and relative humidity of 75±5%. Addition of sodium docusate as surfactant does not affect the release kinetics, but only the initial burst due to its effect on the surface tension and wettability of the systems.

KEYWORDS Felodipine, Solid dispersions, Enhanced release, Miscibility behavior, Hydrogen bond, Formation mechanism

Address correspondence to Georgios Ktistis, Department of Pharmaceutical Technology, School of Pharmacy Aristotle University of Thessaloniki, Thessaloniki 54124, Greece; Fax: +30-2310-997652; E-mail: ktistis@pharm.auth.gr

INTRODUCTION

Felodipine (FEL) is a dihydropyridine derivative that is chemically described as ethylmethyl-4-(2, 3-dichlorophenyl)-1, 4-dihydro-2, 6-dimethyl-3, 5-pyridinedicarboxylate with a molecular weight of 384.26. In pharmaceutical science, it is widely accepted for its tolerant antihypertension and antianginal properties since it is a calcium antagonist compound (calcium channel blocker) (Edgar et al., 1987). Nevertheless, the formulation of FEL is generally problematic as its dissolution rate is limited by its physicochemical properties. Additionally, there are a lack of studies that describe fast release compositions, which are mandatory for the preparation of chronotherapeutical medications, as hypertension and angina are strongly correlated with circadian rhythmicity (Lemmer, 1991). Specifically, FEL is a compound with strong lipophilic character appearing as a crystalline powder practically insoluble in aqueous solutions (solubility less than 0.5 mg/l) (Abrahamsson et al., 1994). In contrast, FEL is rapidly absorbed by the gastrointestinal tract after dissolution, however, even though it has high permeability to biological membranes (Diez et al., 1991). The physicochemical characteristics of FEL indicate that its dissolution profile is the limiting factor for its bioavailability (Wingstrand et al., 1990).

In order to increase FEL dissolution rate, several attempts took place in the past. Since FEL is a crystalline compound, most of them deal with preparing a glassy state. Amorphous FEL prepared by cooling under room conditions or by quenching in liquid nitrogen has higher dissolution rates than the crystalline one (Kerč et al., 1991). Dissolution tests were performed in 30% ethanol in which the solubility of FEL is higher compared with pure water. Nevertheless, the solid state stability of the amorphous FEL prepared by the above method was found to be limited as recrystallization of the compound was taking place during the thermal analysis.

In a recent patent application, a method for preparing a dosage form of a stable FEL composition was invented. Granulated microparticles of FEL and cyclodextrin having a diameter ranging from 0.5 to 9 μm were prepared using the novel process known as microfluidization. For the dry granulate compositions, hydroxypropyl cellulose was used as binder while a swellable polymer such as hydroxyethyl cellulose was applied for control release. The dissolution properties of FEL were enhanced drastically by using such a formulation. However, to achieve 100% drug release, more than 25 h are required (Sharma et al., 2002).

Taking into account that poorly soluble drugs are often highly lipophilic, α-tocopherol, which is a very lipophilic compound, together with monoglycerides and free fatty acids, is used in order to enhance the solubility of such drugs, including FEL (Nielsen et al., 2001). α-Tocopherol is an excellent solvent for many poorly soluble drugs and thereby overcame the problem of limited uptake (Sonne, 1995). The addition of monoglycerides and free fatty acids increased the solubility of FEL in simulated intestinal fluids, but the presence of α-tocopherol had a negative effect. In all cases, the drug solubilization was measured after 24 h rotation of the formulations with simulated intestinal fluids in an incubator at 37°C. The data does not represent measurements of drug administration during time. Liphophilic excipients such as fatty alcohols, fatty acids, fatty acid esters, and polar waxes were also used to enhance the solubility of FEL (Savolainen et al., 2003). Micronization of FEL using supercritical carbon dioxide was also studied, since the use of supercritical fluids has gained increased importance in the pharmaceutical field (Kerč et al., 1999). In order to study the release characteristics of FEL from sustained release monolithic transparent films, Eudragit acrylic resins and different polyol adjuvants were used (Acartürk & Sencan, 1996). The addition of the adjuvants increases the water permeability of the prepared films, and, consequently, drug release was enhanced. A target release rate of FEL 0.729 mg/h was achieved from a film matrix prepared by using a combination of Eudragit RL 100 and RS 100 in molar ratios 1/1, containing also 10% w/w of glycerol, ethoxydiglycol, and propylene glycol. However, from another study, by using an asymmetric membrane-coated capsule the release of FEL was very low, less than 10% w/w after 5 h (Lin & Ho, 2003).

Most of the above studies focus on the preparation of sustained release medications as required by the pharmacokinetic properties of FEL (Weber et al., 1994), while the achievement of fast release compositions has not been extensively investigated. Nevertheless, during the last two decades, several studies have been performed concerning novel drug delivery systems aiming at covering the requirements of

chronobiology and chronopharmacology (Lemmer, 1991). Specifically, the long-standing pharmacokinetic concept, that a zero order release profile is the optimal way of drug delivery, has already been revised. Modern devices are focused on a profile corresponding to the release of the required quantity of the drug, within a definite time period, in order to eliminate the effect of circadian rhythms on the symptomatology of diseases. Pulsatile and bimodal release kinetics are characteristic examples for chronotherapeutics (Conte & Maggi, 1997; Streubel et al., 2000). The above complicated release kinetics require fast release periods for the drug substance. The achievement of the said fast release is sometimes limited by the physicochemical properties of the active pharmaceutical ingredients, such as lipophilic character and low solubility.

In the present study, a treatment of FEL with polyvinylpyrrolidone (PVP) is investigated, aiming at the formation of enhanced and fast release systems for their future use in chronotherapeutical formulations. PVP is widely used for the preparation of solid dispersion systems as it retards the crystallization of the drugs and enhances the dissolution rate (Ford, 1987; Sethia & Squillante, 2004; Valero et al., 2003) by forming molecular adducts (Horn & Ditter, 1982). Additionally, as FEL appears to have a degree of polymorphism (Srcic et al., 1992) an extended investigation of the solid state stability is performed as it is well known that amorphous materials appear to have several stability problems and polymorphic transitions. The solid state stability could be characterized as critical in a pharmaceutical formulation as different polymorphs appear to have different solubility and bioavailability. Finally, the formation mechanism and the exact characterization of FEL/PVP solid dispersion systems were investigated, as the above are the basic parameters for the predictability of solid dispersions. It is known that the lack of predictability is the main reason of the limited commercial use of solid dispersions although they have been developed since 1961 (Sekiguchi & Obi, 1961).

MATERIALS AND METHODS

Materials

Felodipine (FEL) with an assay of 99.9% was obtained from PCAS (Longjumeau, France). Polyvinylpyrrolidone (PVP) type Kollidon K30 with a molecular weight of 50,000 to 55,000 was obtained from Basf (Ludwigshafen, Germany). Dioctyl sodium sulfo-succinate (sodium docusate) was obtained from Cytec (Botlek RT, Holland), while Ethanol absolute was obtained from Merck. All the other materials and reagents were of analytical grade of purity.

Methods

Preparation of the Dispersion Systems

Solid dispersion systems of 10/90, 25/75, 50/50, and 75/25 w/w of FEL/PVP were prepared by dissolution of accurately weighed appropriate quantities of the drug substance and the polymer, in equal quantities of Ethanol absolute (Daniel Mwambete et al., 2004). The solutions were sonicated for 15 min. After dissolution, the samples were maintained at 40°C for 48 h in order to evaporate the ethanol slowly. The resulting films were pulverized and milled to a particle size of 109 μm to 250 μm. The final granules were assayed spectrophotometricaly (UV-VIS) for FEL content, at 362 nm by using a Shimadzu UV 1601 apparatus. Additionally, the content of the residual solvent, Ethanol, was determined by a prevalidated Head-space GC method. The above procedure was repeated for a system of 10/90 w/w of FEL/PVP containing 0.1, 0.5 and 1.0% w/w sodium docusate. The latter treatments were performed in order to study the effect of the surfactant on the dissolution profile of FEL. Furthermore, for comparison purposes, physical mixtures between FEL/PVP with the same compositions like solid dispersions were prepared, by conventional mixing of the components.

X-Ray Powder Diffraction (XRPD)

X-ray powder diffraction was used for the identification of the crystal properties of the pure materials and dispersion systems. Data for all samples were collected at room temperature (20°C) on an Image Plate RAXIS IV mounted on a Rigaku RU-H3R X-ray generator working at 50 KV and 100 mA (λ=1.5418 Å) equipped with an MSC/Yale double mirror focusing system. Data from FEL crystals were collected with an oscillation angle of 3°, 1.5 Å resolution, and raw data images were indexed using the program DENZO

(Otwinowski & Minor, 1997). For pure FEL, single crystal XRPD was used.

Scanning Electron Microscopy (SEM)

The morphology of the prepared blends of solid dispersions and physical mixtures as well as the initial materials were examined using a scanning electron microscope (SEM), type Jeol (JMS-840) equipped with an energy-dispersive X-ray (EDX) Oxford ISIS 300 micro-analytical system. For this examination, the fractured samples of solid dispersions prepared as described above were used. The films were fractured by using liquid nitrogen. All the studied surfaces were coated with carbon black to avoid charging under the electron beam.

Thermal Analysis

Thermal analysis of the samples was carried out using a Perkin-Elmer, Pyris 1 differential scanning calorimeter (DSC). The calorimeter was calibrated with Indium and Zinc standards. For each measurement a sample of approximately 6 mg was used, placed in aluminium seal and heated to 130°C at a heating rate of 10°C/min. The sample remained at that temperature for 15 min in order to remove the moisture traces of PVP. Afterwards, the samples were quenched to 0°C and scanned again up to 200°C using the heating rate of 20°C/min. From this second scan, the glass transition temperature (T_g), the melting temperature (T_m), and the heat of fusion (ΔH_m) were measured.

Fourier Transformation-Infrared Spectroscopy (FT-IR)

Fourier transformation-infrared spectra were acquired using a Biorad GTS-45A, FT-IR spectrometer. For each spectrum, 64 consecutive scans with 4 cm^{-1} resolution was co-added. Samples for FT-IR measurements were prepared by compression in KBr tablets.

In Vitro Release Profile

The release of FEL from the dispersion systems was measured by a modified dissolution apparatus II (paddles) USP (Wingstrand et al., 1990). A stationary disk was used in order to achieve hydrodynamic equilibration. The test was performed at 37±1°C with a rotation speed of 100 rpm using 500 ml of 0.1 M phosphate buffer pH 6.5 containing 2% w/w Polysorbate 20 as dissolution medium (Abrahamsson et al., 1994). Samples corresponding to 10 mg FEL into hard gelatine capsules were placed in each vessel. The disintegration time of the empty capsules was less than 5 min. Every 5 min samples of 5 ml were withdrawn and immediately replaced with an equal volume of the respective dissolution medium maintained at 37±1°C. The samples were filtered (0.20 μm) and assayed according to an RP-HPLC method at 237 nm using a C_{18} column in an analytical instrument, type Shimandzu LC-20-10A. The test was performed in triplicate. The instrumentation used for the dissolution test was an apparatus type DISTEK 2100B equipped with an auto sampler.

Physical and Chemical Stability

In order to investigate the compatibility between the drug substance and the used excipients, the single substances and the solid dispersion systems were stored for 6 months under accelerated conditions packed in PVC vials. Specifically, an Angelatoni stability oven was used set at a temperature of 40±1°C and a relative humidity (RH) of 75±5%. The samples were analyzed before and after storage for assay and chromatographic purity according to the HPLC method referred above. In order to investigate the solid state stability of the systems and the possibility of any recrystallization, the samples were stored for 7 days, in order to achieve moisture equilibration, at 25°C, under direct explosion in different values of relative humidity using the same oven. The experiment was performed in triplicate. After incubation, the water sorption curves were calculated while the solid state of the samples were re-evaluated after 6 months incubation at 25°C and 75% RH. The re-evaluation was performed by using the DSC method described above while X-ray diffraction measurements of the samples were performed by an automated powder diffractometer (PW 1050) with Bragg-Brentano geometry (θ–2θ), using Cuka radiation from 5 to 60 degrees.

RESULTS AND DISCUSSION

Preparation of the Dispersion Systems

Solid dispersion systems are widely used in Pharmaceutical Technology aiming at the optimization of the

dissolution rate of poorly soluble drugs (Karavas et al., 2001; Mura et al., 1999; Sumnu, 1986). The disadvantage of such systems is the use of toxic solvents and the thermal treatment, which corresponds to a risk of decomposition of sensitive drug substances. Additionally, specific techniques used for solvent evaporation, such as lyophilization, led to difficulties in scale up, and high production costs. Regarding the solid dispersion systems in the last years, there are two excellent reviews related to the methods of preparation, the physicochemical properties, the mechanism of drug release and enhancement of drug dissolution, the problems associated with large scale production, and the future prospects of such formulations (Craig, 2002; Serajuddin, 1999). In order to avoid such problems, the present study includes conventional materials and processes, which are widely used for the manufacturing of solid dosage forms. Specifically, all the materials used in the said treatment are common excipients, whilst the preparation process is suitable for scale up. Although rapid supersaturation achievement is a more appropriate method for preparation of amorphous state, in the present study an investigation of conventional solvent evaporation technique is performed, as this technique is easily scalable, while it does not require specific equipment.

Freely water soluble polymers like PEG and PVP are widely used drug carriers for solid dispersions (Tantishaiyakul et al., 1996). However PVP is one of the most successfully used polymers for solid dispersions where amorphous drugs can be produced (Paradkar et al., 2004). The amorphous state depends on the drug-PVP ratio and by increasing the polymer matrix also increases the percent of drug release. For this reason, PVP was chosen as an effective drug carrier for solid dispersion preparations of FEL. All the prepared films were transparent with a light brown color indicating a good miscibility and optimal dispersion between FEL and PVP. In the case of 50/50 w/w solid dispersion mixture the color takes a yellow hue also, since it has a high amount of FEL. Additionally, the thermal treatment of the samples used is identical to that for the drying step after a conventional wet granulation process using a dry oven technique. The assay of the samples after the preparation was found to be between 98% and 101% w/w of the theoretical amount of FEL. The results are acceptable for pharmaceutical preparations, which usually correspond to an assay value between 95% and 105% w/w of the theoretical amount according to the European Pharmacopoeia. The residual solvent (ethanol) was found to be between 0.1% and 0.3% w/w of the whole mass, indicating that the thermal treatment is capable of leading to a result within specifications. According to the European Pharmacopoeia, ethanol is classified as a Class C solvent with specification limit of 0.5% w/w of the whole mass.

Thermal Analysis

The thermal behavior of the prepared solid dispersions was studied by DSC in comparison with physical mixtures. Characteristic DSC thermograms for pure FEL, PVP, and solid dispersion systems containing 10, 25, and 50% w/w of FEL are shown in Fig. 1. Since PVP is very hydrophilic, in order to avoid the effect of moisture traces into DSC thermograms, all mixtures were dried in a vacuum oven at 130°C for 6 h. Furthermore, all mixtures were first run on DSC until 130°C and remained at that temperature for 15 min. Preliminary studies showed that PVP moisture gives a broad endothermic peak with a maximum at 110–120°C, which corresponds to water evaporation and takes the maximum rate at this temperature. With such heating treatment, it was ensured by termogravimetric analysis (TGA) that all moisture traces are removed from samples. In order to obtain the glass transition temperatures of the prepared samples a second run until 200°C was necessary. This second run was performed after quenching the temperature at

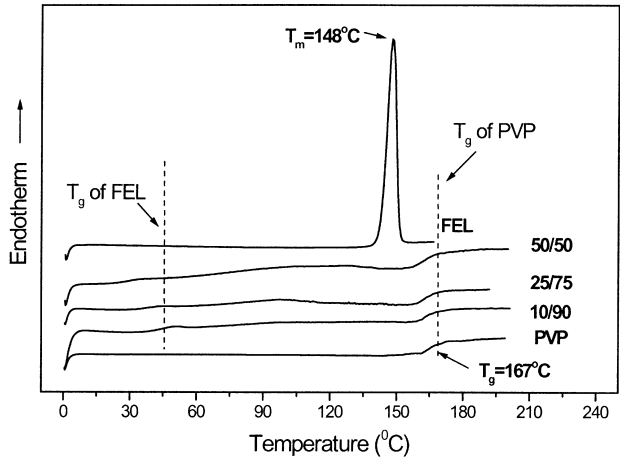


FIGURE 1 **DSC Thermograms of Felodipine, PVP, and their FEL/PVP Solid Dispersion Systems, Containing Different Weight Ratios.**

0°C. The thermal treatment at 130°C, 6 h was necessary as the preliminary TGA studies showed that this was the only way to remove the moisture included in the system in order to record the thermal behavior. This process was very risky as there was a high possibility of recrystallization of amorphous FEL during such treatment. Specifically, FEL could be crystallized at temperatures closed to 100°C (Kerč et al., 1991). However, such crystallization was not observed in our case and FEL remained in amorphous state due to the interactions that take place between FEL and PVP. In amorphous materials (polymers or compounds), thermal treatment does not eliminate the Tg and the only affect is for the relaxation to become more evident.

FEL shows the characteristic endothermic peak at 148°C which corresponds to the melting point (T_m) of the drug substance. PVP appears as an amorphous thermoplastic polymer with a glass transition temperature (T_g) at 167°C. The absence of any endothermic peak in the thermograms of the solid dispersion mixtures, corresponding to the melting point of FEL, indicates that these are amorphous systems. Furthermore, the glass transition temperature of PVP in these mixtures shows a slight shift at lower temperatures (3–4°C) depending on the weight ratio between FEL and PVP (Table 1). Such shifts in T_g of a binary system is evidence that molecular interactions between the two components are taking place or, the component with the minor amount, in our case FEL, acts as a plasticizer for PVP. However, examining more carefully these thermograms, one more glass transition can be found at lower temperatures, attributed to T_g of FEL. This is an indication that the prepared solid dispersions do not constitute a miscible system, since two individual phases are present. From these thermograms, it can be seen that the T_g of FEL is also shifted to lower temperatures by increasing its amount into PVP matrix (Table 1).

It is well known that FEL can be prepared fully amorphous from its melt by slow cooling rate or by quenching in liquid nitrogen. Also, it was reported that the glass transition of FEL depends on its treatment and, with a very slow cooling rate (1°C/min) appears at 45.37°C (Kerč et al., 1991). This temperature is very close to that found by us with the same cooling rate at 45.2°C, while after immediate cooling at 0°C the T_g is recorded at 42.5°C. However, in our solid dispersion samples, the T_g is shifted at an even lower temperature, especially in the sample with 50/50 w/w the T_g is more than 12°C lower than pure FEL. The above shifts in both compounds are evidence that some interactions take place between the two components. However, these are not strong enough to ensure the miscibility of the system and it can be said that they are at the boundaries of miscibility. In this case, we can characterize the prepared solid dispersions as compatible or better as partially miscible mixtures and the evolved interactions are appropriate to maintain FEL into amorphous state.

In partial miscible systems, which appear to have two-shifted glass transition at different temperatures than the initial components, the amount of each one component diffused at the other phase, can be calculated (Bikiaris et al., 2004). This investigation was based on the evaluation of T_g shifts according to the empirical equation of Wood:

$$T_g = W_1 T_{g1} + W_2 T_{g2} \quad (1)$$

where T_g is the observed T_g of each component (FEL and PVP in this work), W_1 is the weight fraction of the component 1 having T_{g1} and W_2 is the weight fraction

TABLE 1 **Glass Transparent Temperature (T_g) and Apparent Weight Fraction (W_1') of Felodipine (FEL) and Polyvinylpyrrolidone (PVP) in the Rich Phase of Each Component for FEL/PVP Systems**

			FEL rich phase		PVP rich phase	
FEL/PVP [w/w]	T_g of FEL [°C]	T_g of PVP [°C]	W_1' of FEL	W_2' of PVP	W_1' of FEL	W_2' of PVP
100/0	45.2	—	—	—	—	—
50/50	30.1	162.6	0.876	0.124	0.036	0.964
25/75	37.6	163.8	0.938	0.062	0.026	0.974
10/90	44.7	164.9	0.996	0.004	0.017	0.983
0/100	—	167.0	—	—	—	—

of the component 2 having T_{g2}. This equation was rearranged by Fox (1956) as following

$$W_1' = (T_{g1b} - T_{g2})/(T_{g1} - T_{g2}) \quad (2)$$

where W_1' is the apparent weight fraction of the substance 1 in the substances rich phase and T_{g1b} is the observed T_g of the substance 1 in the blend. The same equation can be applied to calculate the apparent weight fraction of the second component W_2' into the other rich phase.

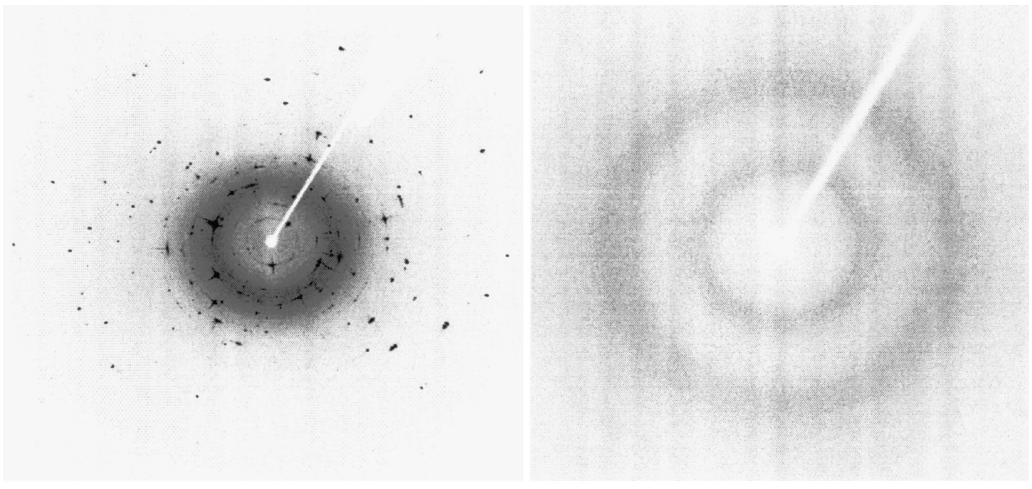
After application of T_g values, measured with the above DSC method, in Eq. 2, the results presented in Table 1 were calculated regarding the apparent volumes for each component in the different rich phases of FEL and PVP.

As shown in Table 1, by increasing the amount of the polymer in the systems, the weight fraction of PVP in FEL rich phase and the weight fraction of FEL in PVP rich phase are decreased. Nevertheless, the absolute quantity of FEL, present in PVP rich phase, is increased by increasing the polymer concentration, reaching up to a percentage of 15.30% w/w for the system 10/90 w/w of FEL:PVP. Furthermore, from this analysis it can be concluded that the two separate phases shown by the two different T_g are not composed by pure components but a quantity of PVP is dissolved in the FEL rich phase, while a quantity of FEL is dissolved in PVP rich phase. This behavior leads to partial miscibility between PVP and FEL in glass state. The presence of the macromolecules in FEL phase could be explained with the interactions which take place. Additionally, this phenomenon could explain the formation mechanism of amorphous state of FEL. Specifically, the presence of the polymer chains into FEL mass on synergy with the possible interaction does not allow the formation of a crystal lattice leading to amorphous material. Nevertheless, the small amount of PVP in FEL rich phase indicates that this is not the only responsible mechanism for the formation of an amorphous state. For this reason, possible synergies with the particle size of the dispersions were evaluated during SEM analysis.

X-Ray Powder Diffraction (XRPD)

In order to verify the DSC results and to exclude the possibility of the existence of crystalline material into solid dispersions, these systems were studied with XR-diffraction. A characteristic X-Ray Diffraction of pure FEL (a) and another of a solid dispersion system 25/75 w/w of FEL/PVP (b) is shown in Fig. 2.

The XRPD examination of the drug substance FEL shows that it is a crystalline compound whilst the systematic absences and symmetry are consistent with the space group P_{21} (monoclinic) with unit cell dimensions a=13.2 Å, b=12.2 Å, c=13.4 Å, and α=90°, β=111.6°, γ=90°. The polymer PVP was found to be amorphous. The same was also found in all solid dispersion systems indicating that PVP, during the stage of solvent evaporation, acts as a limiting factor for the recrystallization of FEL. All solid



a. b.

FIGURE 2 X-ray Diffraction of: (a) Pure FEL Crystals, Collected with an Oscillation Angle of 3°, 1.5 Å Resolution, and (b) Dispersion System 25/75 w/w of FEL/PVP.

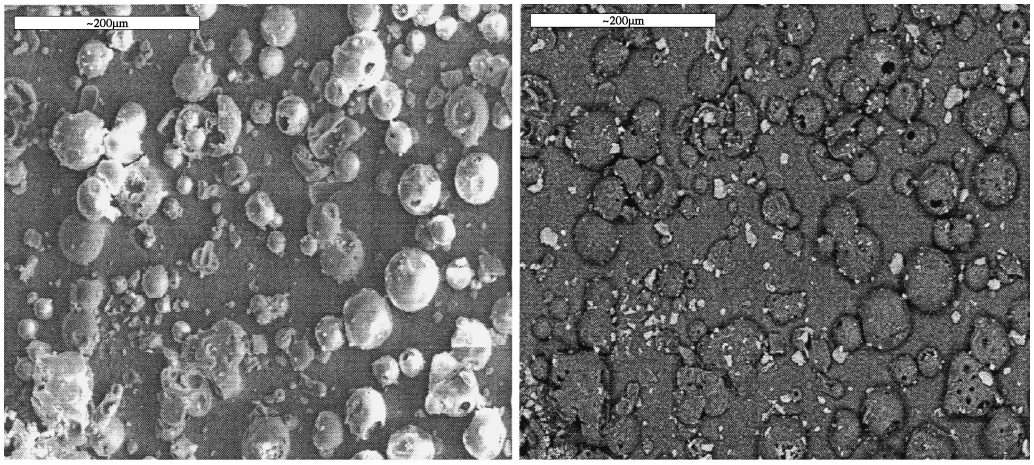
dispersion formulations are fully amorphous material. Only the dispersion system containing 75/25 w/w of FEL/PVP showed a degree of crystallinity possibly due to the high amount of FEL that lead to accumulation and recrystallization of the drug substance. The crystallinity of the system was verified by DSC while the crystals were visible in naked eye. No modification of the XRPD results was observed for the systems containing sodium docusate.

This result implies that the crystalline structure of FEL was destroyed during the solid dispersion procedure and is in agreement with the corresponding observation from DSC data. The partial miscibility of the two components and the presence of possible interactions are the most possible mechanisms for the formation of the glassy state. Nevertheless, it is reported that sometimes, if the material exists in a microcrystalline state, the small crystals could pass the detection of XRPD (Yu, 2001). DSC is used to distinguish amorphous and microcrystalline states based on the presence or absence of glass transition when XRPD failed (Bikiaris et al., 2004). Comparing the results of DSC and XRPD, in our study, the presence of glass transition corresponding to FEL in the systems, in relation to the absence of endothermic peaks corresponding to the melting point and the absence of diffraction spots, lead to the conclusion that the dispersion systems are for sure amorphous.

SEM Observations

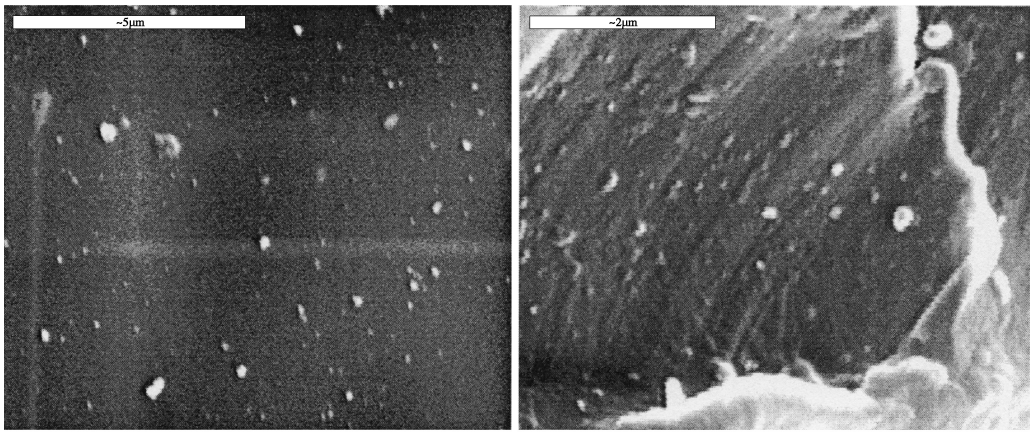
Since in almost all solid dispersion systems with improved drug solubility the drug is in the amorphous state, most of the researchers claim that the drug is in molecular dispersion preventing the formation of crystalline structure. However, as far as it is known, there are no available data to verify such a finding. In the present study, even though FEL is in an amorphous state, from DSC thermograms it was found that all solid dispersions consisted from a binary, but partially miscible mixture. This means that FEL is in separate phase dispersion into PVP matrix with particle sizes larger than 10 nm. In order to investigate the morphology of the materials and to identify these particle sizes, Scanning Electron Microscopy (SEM) was used. The SEM analysis of pure FEL revealed that it consists of large cubic crystals with sizes about 100 μm as well as smaller particles. It can be said that the main particle sizes lies between 20–30 μm. In physical mixtures between FEL/PVP, these particles can be detected without doubt since PVP is in the form of spherical particles with sizes ranging from 10–60 μm (Fig. 3a). However, FEL particles are detected with higher accuracy in the SEM micrographs taken with back scattered electrons (Fig. 3b) instead of using the secondary electrons. In this case, FEL particles have lighter color than PVP particles due to the existence of the heavy chloride molecules on its structure.

In the case of solid dispersions, FEL is the minor component and for this reason it is expected to find separate FEL particles well dispersed into PVP matrix. The molecular dispersion is excluded taking into account the DSC thermograms. Examining the micrographs of solid dispersions containing 10/90 and 25/75 w/w of FEL/PVP taken with secondary electrons



a. b.

FIGURE 3 Scanning Electron Micrographs of FEL/PVP 10/90 w/w Physical Mixture with a) Secondary Electrons and b) Back Scattered.

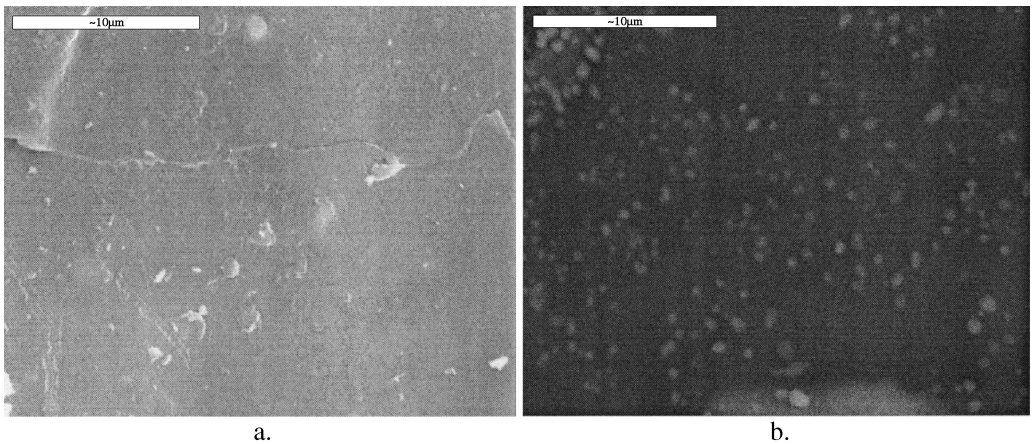


a. b.

FIGURE 4 **Scanning Electron Micrographs of FEL/PVP Solid Dispersions Mixtures with Secondary Electrons a) 10/90 w/w and b) 25/75 w/w.**

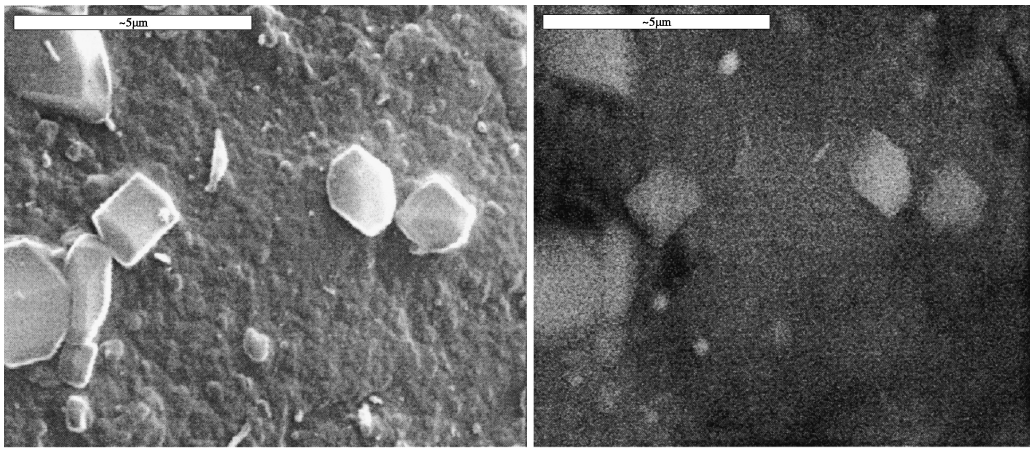
and in high magnification (×10,000) such spherical particles can be observed (Fig. 4). At such magnification, particles of 25 nm should be visible. Furthermore, it is realized that their size depends on the amount of FEL in the mixture. In the case of FEL/PVP of 10/90 w/w, the particle sizes of FEL are ranging from 30 to100 nm while of 25/75 w/w solid dispersion these particle sizes are higher, ranging from 50 to 130 nm. However in 50/50 w/w of FEL/PVP solid dispersions, there are some difficulties to identify these particles, while some particles with diameter higher than 1 μm are visible (Fig. 5a). This is unexpected because the particular system is also amorphous as was verified with XRPD and DSC studies. In this case, the back scattered micrographs can give more information about the real state of FEL dispersion. So, as can be seen in Fig. 5b particles of FEL are not higher than 500 nm and seem to be well in dispersion into PVP matrix.

From SEM image analysis, it was proved that the FEL/PVP solid dispersions concluded from fine dispersion of FEL. However the main question remains if some of the drug amount is also in molecular dispersion. This possibility shall not be rejected, since the DSC data analysis revealed that small amounts of FEL dissolved into PVP rich phase. These molecules may be at molecular dispersion and their exact amount depends on the FEL/PVP ratio. However, the prepared system is more close to the described system by Savolainen et al. (2002), where FEL exists as a partial solid solution in a similar system. His suggestion was based on hot stage microscopy observations. In our prepared solid dispersions, it was found by SEM micrographs that the particle sizes are not higher than 500 nm. These particles seem to be small enough to hinder the crystal formation and FEL remains in amorphous state, which is the case in order to enhance its dissolution properties. Additionally, the presence of



a. b.

FIGURE 5 **Scanning Electron Micrographs of FEL/PVP 50/50 w/w Solid Dispersion with a) Secondary Electrons and b) Back Scattered.**



a. b.

FIGURE 6 Scanning Electron Micrographs of FEL/PVP 75/25 w/w Solid Dispersion with a) Secondary Electrons and b) Back Scattered.

PVP chains in FEL rich phase could also be a reason for crystallization inhibition. The most possible mechanism for the formation of amorphous state is the partial miscibility shown by DSC studies on a synergy with the small particle size which correspond to an extended contact surface between two phases allowing the development of interactions between the two compounds. Crystallization can take place only when higher amounts of FEL are used as it happens in FEL/PVP solid dispersion containing 75/25 w/w (Fig. 6). In such systems, well formed crystals are observed in both micrographs taken with secondary and back scattered electrons. The extremely higher amount of used FEL was appropriate to form these crystals after solvent evaporation. In this case, PVP was not available, due to its low amount, to restrict the recrystallization of FEL.

Fourier Transformation Infrared Spectroscopy (FT-IR)

All of the above experiments show that the investigated systems are amorphous dispersions of polymer concentrations more than 50% w/w. FEL was not crystallized in the examined solid dispersion systems, possibly due to the optimum dispersion of its particles into the matrix of polymer and the partial miscibility of the systems. This optimal dispersion can be caused by the presence of heteromolecular interactions between FEL and PVP, which should be stronger than the homomolecular interactions. Fourier transformation infrared spectroscopy (FTIR) is a versatile technique for studying such specific interactions between reactive groups in polymer blends as well as between polymer and other compounds like FEL that were used in the present study. There are several characteristics like the position, the form, and the intensity of spectral bands that provide useful information about the kind and extent of these intermolecular forces. PVP is a water soluble tertiary amide polymer. As its polar group is a strong proton acceptor, it can easily create hydrogen bonds with other polymers or small molecules, whereas the late are proton donors like FEL. This effect enhances compatibility or miscibility between the used materials since hydrogen bonding induces a negative, favorable enthalpic contribution to the Gibbs free energy of mixing. When such bonds are formed, the spectral changes are subtle because of conjugated contributions and new spectral signal unfolding. To investigate the types of these interactions that take place between FEL and PVP, solid dispersions were studied with FT-IR.

As can be seen from the molecular structure of FEL, there are a lot of polar or negative charged groups like >C=O, >N–H, and –Cl which are able to interact with other appropriate reactive groups to form mainly hydrogen bonds. Since PVP has only carbonyl groups, the only possibility is the interaction of these groups with the secondary amino groups of FEL. To verify this, the FT-IR spectra of all compounds and solid dispersions were studied. In Fig. 7, the FT-IR spectra of PVP, FEL, and their solid dispersion containing equal amounts of each one are presented. The most characteristic peaks of PVP are at 1668 cm^{-1} and 1280 cm^{-1}, attributed to the stretching of amide >C=O and >N–C groups, respectively. At the same area, FEL also has the strong absorbance of carbonyl

ester stretching, while other characteristic peaks are those of >N–H at 3370 cm^{-1}, at 1698 cm^{-1} attributed to the ester groups, and at 1495 cm^{-1} assigned to N=C stretch peak. The FT-IR spectrum of solid dispersion confirms the presence of molecular interactions. Specifically, the peak corresponding to amino group was recorded at 3370 cm^{-1} in pure FEL. However, the appearance of new peaks at 3294 cm^{-1}, which were observed in the spectra of dispersion systems, is an indication that the amino-group of FEL is under strong interactions in the dispersion systems. Additionally, a shift in the absorbance of unsaturated methylene groups (from 3100 cm^{-1} to 3092 cm^{-1}) is observed. According to the structural formula of FEL presented above, these groups are the 2, 6 groups, directly bonded with the amino group. The characteristic shift of this peak indicates that the chemical environment of the unsaturated methylene groups has been modified. According to the molecular structures of FEL and PVP, these interactions could be caused by the formation of a hydrogen bond between the amino group of FEL and carbonyl group of PVP.

This case usually causes a modification to the characteristic peak of the carbonyl group at 1668 cm^{-1}. However, due to the broad absorption of PVP at this area, this shift is not clear. In this case the subtracted spectrum is ideal to give information about the interactions that take place, which is presented in Fig. 8. This spectrum was formed after removal of PVP and FEL absorbencies from the spectrum corresponded to FEL/PVP solid dispersion. As can be seen, the secondary amine group has a negative value which means that this peak is moved to a lower wavelength. Such shifts of the main absorbance of

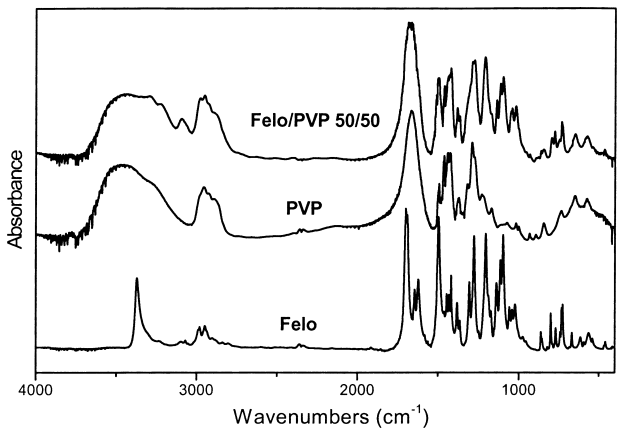


FIGURE 7 **FTIR Spectra of FEL, PVP, and their Solid Dispersion System with 50/50 w/w.**

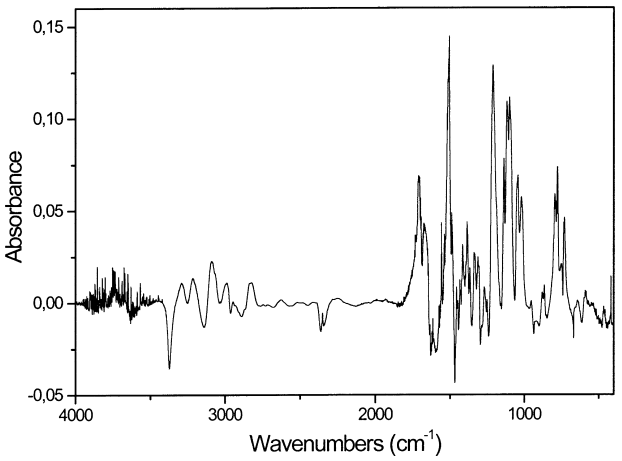


FIGURE 8 **Subtracted Spectrum FTIR Spectrum of FEL/PVP 50/50 w/w Solid Dispersion.**

>N–H or –OH stretching vibrations at lower wave numbers were also observed in other solid dispersions like Piroxicam/PVP (Tantishaiyakul et al., 1996). Furthermore, at the carbonyl group area of FEL/PVP subtracted spectrum there are two positive peaks at 1710 cm^{-1} and at 1678 cm^{-1}. These differences, in comparison with amine groups shifts, are clear evidence that these groups formed intermolecular hydrogen bonds. These bonds are responsible for the fine dispersion of FEL into PVP matrix at the level of nanoparticles and restrict FEL to form crystals. Similar hydrogen bonds between FEL and some used lipophilic excipients were evaluated with FT-IR spectroscopy (Savolainen et al., 2002). Furthermore, it was found that using lipophilic excipients both >N–H and >C=O groups of FEL can involve in interactions, whereas with hydrophilic excipients interactions occur only with >N–H groups.

From FT-IR study, it can be concluded that hydrogen bonding interactions are responsible for the formation of FEL fine dispersion into PVP matrix while they are the basic mechanism for the presence of PVP in FEL rich phase leading to amorphous state.

In Vitro Release Profile

The aim of the present study is the modification of FEL in order to enhance its dissolution rate and to be used in fast release compositions. The release profiles up to 30 min of the prepared solid dispersion systems are presented in Fig. 9, compared to that of pure FEL in order to evaluate the immediate release criteria. The results are given as % w/w dissolved amounts referred to the total amount of each sample, which

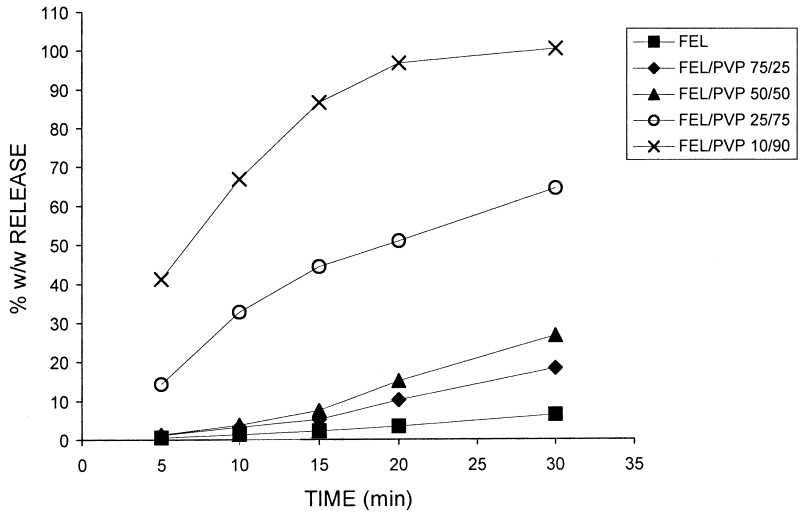


FIGURE 9 **Release Profiles of the Systems as % w/w Amounts of the Initial Quantity of FEL (10 mg).**

corresponds to 10 mg of FEL. Pure FEL shows negligible dissolution until 30 min, while in the dispersion systems containing 75 and 50% w/w of FEL the dissolution increased very little. However, a remarkable increase was observed for solid dispersions containing 25 and 10% w/w of FEL. At the late system, the release reaches the 100% w/w almost 20 min after treatment, which is the scope of the study. The enhancement of the release profile is possibly caused by several parameters. Such parameters are: 1) the strong hydrophilic character of PVP, which improves the water penetration and the wettability of the hydrophobic FEL, 2) the optimal dispersion of FEL to PVP, which corresponds to a minimum particle size value in the level of colloidal dispersion, 3) the absence of crystals (amorphous dispersions) corresponds to lower required energy for dissolution and 4) the hydrogen bonds and the molecular adduction of FEL on PVP leads to partial miscibility, improving the hydrophilic characteristics of the drug substance via interactions within the polymer.

From these results it can be concluded that the release amount of FEL from the prepared systems is controlled by two main factors. The first factor is the crystallinity of the system, since in all amorphous material the rate of release is higher than the crystalline, which are pure FEL and the system containing 75% w/w of FEL. The second factor is clearly the particle size of the dispersed FEL into PVP matrix. Comparing the amorphous systems (10, 25, and 50% w/w of FEL), it can be seen that as the particle size decreases, the release rate becomes higher. This finding is further proof that in solid dispersion systems the amorphous state may not be enough to enhance the dissolution rate and the particle sizes is the main factor that controls the release profile.

As representative factors for the comparison of the systems, the parameters of T_{50} and T_{80} were selected. T_{50} and T_{80} are defined as the time required for the dissolution of 50% and 80% w/w of FEL, respectively. In order to calculate these parameters, the equations with the optimal correlation coefficient were evaluated. It was found that the function of the relative release amount (M_t/M_∞) versus time (t) was linear for pure FEL and the systems with drug concentration up to 50% w/w according to the equation:

$$M_t/M_\infty = at + b \tag{3}$$

On the contrary, the fitting is changing to Logarithmic for the systems 25/75 and 10/90 w/w of FEL/PVP according to the equation:

$$M_t/M_\infty = a\ Ln(t) + b \tag{4}$$

Normally, the insoluble substances follow a zero order kinetic while the soluble ones follow a first order. This significant change of the pattern indicates that the treatment described in the present study leads to the optimization of the dissolution properties of the drug substance.

The experimental results were in high correlation with the above functions. The factors a,b and the correlation coefficients are presented in Table 2.

TABLE 2 Parameters of the Eqs. 3 and 4 for the Relative Release Amount of Felodipine (M_t/M_∞) for FEL/PVP Systems

FEL/PVP [w/w]	Fitting	a	b	R^2
100/0	Linear	0.23	−0.99	0.98
75/25	Linear	0.70	−3.66	0.97
50/50	Linear	1.05	−6.01	0.97
25/75	Logarithmic	27.70	−30.63	0.99
10/90	Logarithmic	35.02	−12.89	0.97

TABLE 3 The Release Parameters T_{50}, T_{80}, and Relative Released Amount of Felodipine at 30 min for Felodipine/Polyvinylpyrrolidone (FEL/PVP) Systems

FEL/PVP [w/w]	T_{50} [min]	T_{80} [min]	Released [% w/w]
100/0	218.66	347.31	6.30
75/25	76.22	118.82	18.30
50/50	53.07	81.50	26.74
25/75	18.37	54.29	64.56
10/90	6.02	14.19	100.30

The relative standard deviation (RSD) was found to be between 1.3 and 1.7 for all samples. Due to the low RSD and the optimal correlation coefficient (R^2), the parameters T_{50} and T_{80} were calculated by using the Eqs. 3 and 4. The values of T_{50} and T_{80} and the relative release amount at 30 min are presented in Table 3. From these calculations it is clear that the system 10/90 w/w of FEL/PVP corresponds to optimal dissolution profile for the drug substance. Additionally, any requirement for fast release formulations is covered, as T_{80} is less than 15 min.

A further objective of this study was the effect of the described treatment with PVP and sodium docusate to the dissolution profile of FEL, targeting an optimization of the said profile. From such prepared systems, no significant modification was observed for solid dispersions 75/25 and 50/50 w/w of FEL/PVP. The reason is that the quantity of PVP in this system is not enough to modify the lipophilic character of the drug substance. On the contrary, the dissolution profile was drastically improved for the systems 25/75 and 10/90 w/w of FEL/PVP relative to the one of the pure FEL. In relation to the effect of sodium docusate in the formulation, the optimal system of 10/90 w/w of FEL/PVP was tested more extensively by the addition 0.1%, 0.5%, and 1.0% w/w of sodium docusate. An extra improvement on the dissolution profile is observed. For comparison reasons, the same parameters T_{50} and T_{80} were calculated in the same way as described above. The systems are well fitted with the Eq. 4. The equation factors are presented in Table 4.

The experimental results were in high correlation with the above functions. The parameter T_{50} was decreased according to the concentrations 0.1%, 0.5%, and 1.0% w/w of surfactant. Higher concentrations corresponded to lower T_{50} values. Similar behavior was also observed for the parameter T_{80}. It was found that the presence of sodium docusate optimizes the dissolution profile of FEL even more. This extra optimization is possibly caused by the effect of the surfactant on the surface tension, which improves the

TABLE 4 Parameters a and b of the Release Equations and the Release Parameters T_{50} and T_{80} of Felodipine for the FEL/PVP System of 10/90 Contain Varying Concentrations of Sodium Docusate

Sodium docusate [% w/w]	a	b	R^2	T_{50}	T_{80}
0.1	35.86	−15.02	0.997	6.12	14.15
0.5	36.57	−13.73	0.999	5.71	12.94
1.0	35.86	−5.43	0.992	4.69	10.80

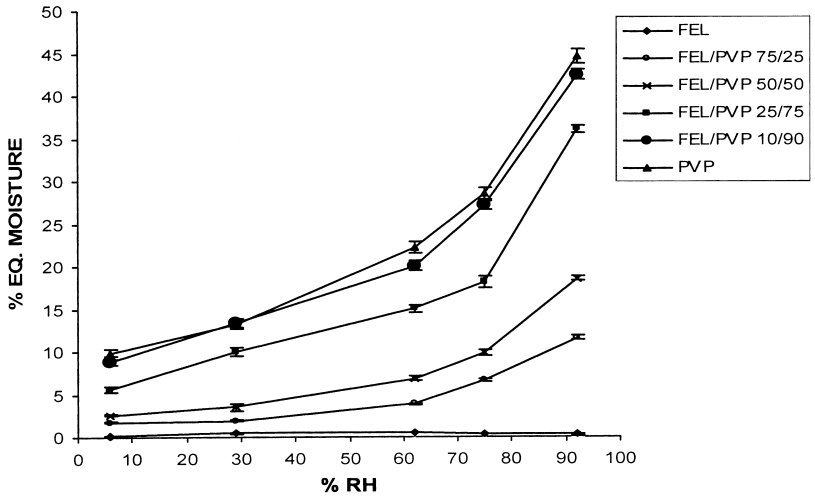


FIGURE 10 **Moisture Sorption Isotherms at 25°C of the Pure Materials (FEL, PVP) and the Solid Dispersion Systems (FEL/PVP).**

wettability of the systems. Specifically, according to the Eqs. 3 and 4, the concentration of PVP in the solid dispersion affects strongly the dissolution kinetics as it causes the pattern to change from linear to logarithmic, while significant changes are observed in the slopes of the curves. On the contrary, no change in the slope is observed for the equations describing the effect of the concentration of sodium docusate. The optimization of the dissolution kinetics is caused by the distribution of the drug on the polymer chains whilst the effect of the surfactant is focused mainly on the wettability enhancement.

Stability Studies

Amorphous state is usually preferable in pharmaceutical formulations as it is well established that it leads to enhanced dissolution rate and bioavailability of the drug substances. Nevertheless, there are several disadvantages which have to be taken into consideration during the development of amorphous systems (Giron, 1988). There is a specific review reporting the instability of amorphous materials relative to the corresponding crystals as well as the polymorphic transition of amorphous materials to crystalline as the latter corresponds to systems with lower energy (Yu, 2001).

The presence of moisture could potentially cause recrystallization of the drug substances (Yu, 2001) or chemical degradation due to the plasticizing effect of water, which increases the mobility of the systems by decreasing the T_g value (Hancock & Zografi, 1994). Additionally, water could cause degradation of amorphous materials by acting as a plasticizer, reactant product, or medium (Shalaev & Zografi, 1996). Taking into consideration the above studies and the fact that T_g of FEL in the systems is near the storage temperature, the solid state and chemical stability could be characterized as the most critical issue of this study as it is mandatory for every pharmaceutical product in order to remain unchanged during the whole shelf life. For this reason, the ability of the prepared solid dispersion systems to absorb water during storage at physical conditions were measured.

The moisture absorption curves, presented in Fig. 10, show that increasing the content of PVP increases the hygroscopicity of the systems dramatically, while FEL is very hydrophobic. As the moisture absorption is an indication of the hygroscopicity of the systems, it could be suggested that the prepared systems appear to have an intermediate behavior between FEL and PVP. The moisture content increases by increasing the polymer concentration. Specifically, for the system 10/90 w/w of FEL/PVP, the hygrophobic effect of FEL has been absolutely minimized and the absorption content is almost similar to that of pure PVP.

The accelerated chemical stability studies (6 months at 40°C and 75% RH) of the dispersion systems, when compared with those of pure FEL, show that FEL is compatible with both excipients PVP and sodium docusate, whilst this treatment does not cause any extra degradation risk of the drug substance. This behavior indicates the chemical stability of the systems. Specifically, neither any significant change in chromatographic purity nor any assay modification was observed for the systems after 6 months storage in

accelerated conditions, while the HPLC chromatograms of the dispersion systems were found to be identical to those of pure FEL. Furthermore, in order to investigate the solid-state stability of the dispersion systems and the inhibition of any recrystallization, the samples were analyzed after 6 months storage at 40°C and 75% RH by using the DSC and XRPD methods. Before analysis, the samples were dried at 105°C for 4 h.

The DSC analysis did not show any endotherm corresponding to recrystallization of the substance. In order to have more results and to exclude the possibility of the existence of some crystalline material into solid dispersions, these systems were studied with XR-diffraction. Figure 11 shows the X-ray diffractograms for the FEL solid dispersions with PVP, compared to that of pure components and 50/50 w/w physical mixture after 6 months storage at 40°C and 75% RH in open vials. PVP is fully amorphous and two large peaks attributed to the two different size particles are recorded. On the other hand, pure FEL is a crystalline compound which showed a very strong diffraction peak at 2θ of 29.2 and a lot of others with lower intensity at 2θ of 11.6, 12.8, 13.6, 20.4, 20.8, 30.90, 31.9, 33.4, and 37.2. Such peaks are not observed in solid dispersions. This is further evidence after DSC studies that the prepared solid dispersions are remaining at amorphous state and are stable during storage.

From the above results, it is concluded that the prepared dispersion systems show an enhanced physical, chemical, and solid state stability in accelerated conditions. These findings were unexpected, taking into consideration the hygroscopicity of the systems and the plasticizing effect of PVP to FEL as it reduces the T_g of the drug substance to lower temperatures (near the storage conditions) as it has been found in the DSC experiments. Nevertheless, the stabilization effect of PVP on amorphous FEL could be explained by the presence of interactions taking place in the systems. The creation of heteromolecular hydrogen bonds keep the molecules of the drug substances frozen in the polymer matrix decreasing their mobility. This mechanism results in the inhibition of any recrystallization or chemical reaction due to the vitrification of the amorphous state. Solid state stability of the pure amorphous FEL was not investigated as it is unstable and appears to transition to crystalline form (Kerč et al., 1991). Similar behavior of PVP as a stabilization substance has been observed by several researchers. Specifically, Matsumoto and Zografi (1999) observed that low level polymeric additives could inhibit the crystallization of amorphous indomethacin. Similar results in stabilization of amorphous ketoconazole with PVP k25 have been given (Van dem Mooter et al., 2001), while systems composed by Carbamazepine/PVP remain amorphous after one year storage at 35°C (Sethia & Squillante, 2004). Nevertheless, no results are available after long term direct explosion to high values of RH (worst case scenario) as it is known that moisture accelerates the recrystallization of amorphous materials.

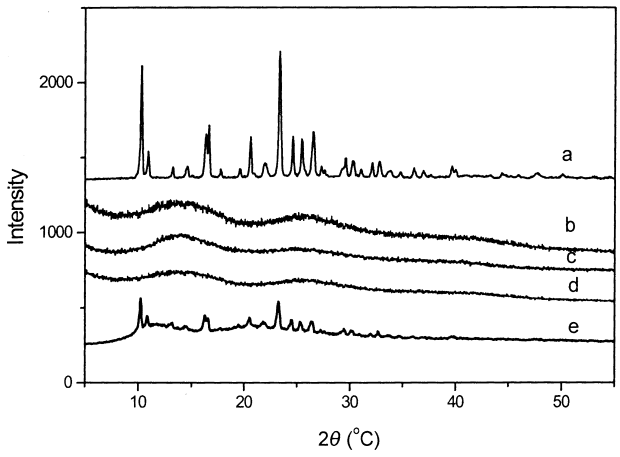


FIGURE 11 **WAXD Patterns of: a) FEL, b) PVP, c) FEL/PVP 10/90 w/w, d) 50/50 w/w Solid Dispersions, and e) 50/50 w/w Physical Mixtures.**

CONCLUSION

The investigated solid dispersion systems are characterized as amorphous solid dispersions of FEL into PVP matrix over a polymer concentration of 50% w/w in the systems. FEL/PVP w/w ratios and the extent of interactions that take place affected the particle size distribution. The compounds are not fully miscible. However, a partial miscibility between the two phases was observed, due to the formation of a hydrogen bond between the carbonyl group of PVP and the amino group of FEL resulting in amorphous systems as it was verified by XRPD and DSC experiments.

The advantage of these amorphous systems is that they require lower energy for their dissolution than the crystalline materials whilst the total surface, exposed to the dissolution media, is increased. According to the dissolution kinetics, the solid dispersion system

containing 10% w/w of FEL is the optimum system. The main factor affecting the dissolution kinetics is the particle size distribution of FEL and not the amorphous state. The rapid dissolution achieved could be characterized as critical because although FEL requires a sustained release formulation its rapid dissolution is appropriate for future use in a chronotherapeutical formulation which requires fast release periods at definite times during the day. Additionally, the release optimization could improve the bioavailability of the drug substance. Nevertheless, the dissolution enhancement described in this study is much more impressed than the one described by Kerč, comparing crystalline with amorphous FEL even though they used different dissolution mediums and conditions, indicating the critical role of the polymer.

The materials are compatible resulting in a system with acceptable stability (chemical and physical) whilst the process and materials are suitable for pharmaceuticals and readily scalable.

The presence of small amounts of the surfactant sodium docusate further improves the dissolution profile but it is classified as a secondary factor.

ACKNOWLEDGMENTS

This study was supported by the Pharmaceutical Company Pharmathen S.A, 6 Dervenakion Str., P.C. 15351 Pallini Attikis, Athens, Greece. Also, we would like to acknowledge the vital contribution of Dr. D.D. Leonidas on XRPD analysis.

REFERENCES

Abrahamsson, B., Johansson, D., Torstensson, A., & Wingstrand, K. (1994). Evaluation of solubilizers in the drug release of hydrophilic matrix extended-release tablets of felodipine. *Pharmaceutical Research*, *11*, 1093–1097.

Acartürk, F., & Sencan, A. (1996). Investigation of the effect of different adjuvants on felodipine release kinetics from sustained release monolithic films. *International Journal of Pharmaceutics*, *131*, 183–189.

Bikiaris, D., Prinos, J., Botev, M., Betchev, C., & Panayiotou, C. (2004). Blends of polymers with similar glass transition temperatures: a DMTA and DSC study. *Journal of Applied Polymer Science*, *93*, 726–735.

Conte, U., & Maggi, L. (1997). Geomatrix tablets for the pulsatile release of drugs. *Proceedings of the International Symposium on Controlled Release of Bioactive Materials*, *24*, 291–292.

Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *International Journal of Pharmaceutics*, *231*, 131–144.

Daniel Mwambete, K., Torrado, S., Cuesta-Banbera, C., Ponce-Gordo, F., & Torrado, J. T. (2004). The effect of solubilization on the oral bioavailability of three benzimidazole carbamate drugs. *International Journal of Pharmaceutics*, *272*, 29–36.

Diez, I., Colom, H., Moreno, J., Obach, R., Peraire, C., & Domenech, J. (1991). A comparative in vitro study of transdermal absorption of a series of calcium channel antagonists. *Journal of Pharmaceutical Sciences*, *80*, 931–934.

Edgar, B., Collste, P., Haglund, K., & Regardh, C. G. (1987). Pharmacokinetics and haemodynamic effects of felodipine as monotherapy in hypertensive patients. *Clinical and Investigative Medicine*, *10*, 388–394.

Ford, L. J. (1987). The use of thermal analysis in the study of solid dispersions. *Drug Development and Industrial Pharmacy*, *13*(9–11), 1741–1777.

Fox, T. G. (1956). Influence of diluent and copolymer composition on the glass transition temperature of a polymer system. *Bulletin of the American Physical Society*, *1*, 123.

Giron, D. (1988). Impact of solid state reactions on medicaments. *Molecular Crystals and Liquid Crystals Incorporating Nonlinear Optics*, *161*, 77–100.

Hancock, B. C., & Zografi, G. (1994). The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharmaceutical Research*, *11*, 471–477.

Horn, D., & Ditter, W. (1982). Chromatographic study of interactions between polyvinylpyrrolidone and drugs. *Journal of Pharmaceutical Sciences*, *71*, 1021–1026.

Karavas, E., Georgarakis, E., Bikiaris, B., Thomas, T., Katsos, V., & Xenakis, A. (2001). Hydrophilic matrices as carriers in felodipine solid dispersion systems. *Progress in Colloid & Polymer Science*, *118*, 149–152.

Kerč, J., Srčič, S., Mohar, M., & Šmid-Korbar, J. (1991). Some physicochemical properties of glassy felodipine. *International Journal of Pharmaceutics*, *68*, 25–33.

Kerč, J., Srčič, S., Knez, Ž., & Senčar-Božič, P. (1999). Micronization of drugs using supercritical carbon dioxide. *International Journal of Pharmaceutics*, *182*, 33–39.

Lemmer, B. (1991). Circadian rhythms and drug delivery. *Journal of Controlled Release*, *16*, 63–74.

Lin, Y. K., & Ho, H. (2003). Investigations on the drug releasing mechanism from an asymmetric membrane-coated capsule with an in situ formed delivery orifice. *Journal of Controlled Release*, *89*, 57–69.

Matsumoto, T., & Zografi, G. (1999). Physical properties of solid molecular dispersions of indomethocin with poly(vinylpyrrolidone) and poly(vinylpyrrolidone-co-vinylacetate) in relation to indomethacin crystallization. *Pharmaceutical Research*, *11*, 1722–1728.

Mura, P., Faucci, M. T., Manderioli, A., Bramanti, G., & Parrini, P. (1999). Thermal behaviour and dissolution properties of naproxen from binary and ternary solid dispersions. *Drug Development and Industrial Pharmacy*, *25*, 257–264.

Nielsen, P. B., Müllertz, A., Norling, T., & Kristensen, H. G. (2001). The effect of α-tocopherol on the in vitro solubilisation of lipophilic drugs. *International Journal of Pharmaceutics*, *222*, 217–224.

Otwinowski, Z., & Minor, W. (1997). Processing of x-ray diffraction data collected in oscillation mode. In: C. W. J. Carte & R. M. Sweet (Eds.), *Methods Enzymology* (pp. 307–326). New York: Academic Press.

Paradkar, A., Ambike, A. A., Jadhav, B. K., & Mahadik, K. R. (2004). Characterization of curcumin-PVP solid dispersion obtained by spay drying. *International Journal of Pharmaceutics*, *271*, 281–286.

Savolainen, M., Khoo, C., Glad, H., Dahlqvist, C., & Juppo, A. M. (2002). Evaluation of controlled-release polar lipid microparticles. *International Journal of Pharmaceutics*, *244*, 151–161.

Savolainen, M., Herder, J., Khoo, C., Lövqvist, K., Dahlqvist, C., Glad, H., & Juppo, A. M. (2003). Evaluation of polar lipid-hydrophilic polymer microparticles. *International Journal of Pharmaceutics*, *262*, 47–62.

Sekiguchi, K., & Obi, N. (1961). Studies on absorption of eutectic

mixture. I. A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. *Chemical and Pharmaceutical Bulletin*, *9*, 866–872.

Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *Journal of Pharmaceutical Sciences*, *88*, 1058–1066.

Sethia, S., & Squillante, E. (2004). Solid dispersion of capbamatepine in PVP k30 by conventional solvent evaporation and supercritical methods. *International Journal of Pharmaceutics*, *272*, 1–10.

Shalaev, E. Y., & Zografi, G. (1996). How does residual water affect the solid state degradation of drugs in the amorphous state. *Journal of Pharmaceutical Sciences*, *85*, 1137–1141.

Sharma, V. K., Srivastav, A. K., Hussain, J., & Khorakiwala, H. F. (July 4, 2002). Preparation of Micron-Size Felodipine Particles by Microfluidization. US Patent 2002/0086061 A1.

Sonne, M. (November 23, 1995). Tocopherol Compositions for Delivery of Biologically Active Agents. WO Patent 95/31217.

Srcic, S., Kerc, J., Urleb, U., Zupancic, I., Lahajuar, G., Kofler, B., & Smid-Korbar, J. (1992). Investigation of felodipine polymorphism and its glassy state. *International Journal of Pharmaceutics*, *87*, 1–10.

Streubel, A., Siepmann, J., Peppas, N. A., & Bodmeier, R. (2000). Bimodal drug release achieved with multilayer matrix tablets: transport mechanisms and device design. *Journal of Controlled Release*, *69*, 455–468.

Sumnu, M. (1986). Increasing dissolution rate and gastrointestinal absorption of nifedipine via solid dispersion. *STP Pharma*, *2*, 214–220.

Tantishaiyakul, V., Kaewnopparat, N., & Ingkatawornwong, S. (1996). Properties of solid dispersions of pinoxicam in polyvinylpyrrolidone K-30. *International Journal of Pharmaceutics*, *143*, 59–66.

Valero, M., Perez Revuelta, B. I., & Rodrigues, L. J. (2003). Effect of PVP k-25 on the formation of the naproxen: B-ciclodextrin complex. *International Journal of Pharmaceutics*, *253*, 97–110.

Van dem Mooter, G., Wuyts, M., Blaton, N., Busson, R., Grobet, P., Augustijns, P., & Kinget, R. (2001). Physical stabilisation of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *European Journal of Pharmaceutical Sciences*, *12*, 261–269.

Weber, M. A., Goldberg, A. I., Faison, E. P., Lipschutz, K., Shapiro, D. A., Nelson, E. B., & Irvin, J. D. (1994). Extended-release felodipine in patients with mild to moderate hypertention. Felodipine ER Dose-Response Study Group. *Clinical Pharmacology and Therapeutics*, *55*, 346–352.

Wingstrand, K., Abrahamson, B., & Edgar, B. (1990). Bioavailability from felodipine extended-release tablets with different dissolution properties. *International Journal of Pharmaceutics*, *60*, 151–156.

Yu, L. (2001). Amorphous pharmaceutical solids: preparation, characterization and stabilization. *Advanced Drug Delivery Reviews*, *4*, 27–42.