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Felodipine nanodispersions as active core for predictable pulsatile chronotherapeutics using PVP/HPMC blends as coating layer

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Abstract

In the present study predictable pulsatile chronotherapeutics of felodipine (FELO), which is a poorly-water soluble drug, were prepared in the form of two layered tablets. As active core PVP/FELO nanodispersion was used while as effective coating layer different PVP/HPMC blends were added. From dissolution studies of FELO nanodispersions it was revealed that PVP/FELO 90/10 w/w dispersion is an ideal system for pulsatile formulations since the whole amount of FELO is released within the first 30 min. This dissolution enhancement and fast release was attributed to FELO amorphisation, as was found from XRD and DMTA techniques and the effective particle size reduction. Transmission electron microscopy (TEM) studies revealed that FELO creates amorphous nanodispersions into the PVP matrix while particle sizes are directly dependable upon FELO concentration. Drug particles with sizes lower than 150 nm may be the optimal level for a substantial enhancement of FELO dissolution rate. The time of FELO release initiated by the two-layered tablets was adequately adjusted by using different PVP/HPMC blends as coating layer, which is a swellable and erodible barrier. The delaying time of FELO release is directly depended by HPMC concentration and this correlation was mathematically expressed. The significance of these blends is that they are completely miscible over the entire compositional range, thus forming a new matrix with different physicochemical properties, contrary to the initial polymers.

Keywords: Felodipine; Amorphous nanodispersions; Miscible blends; Pulsatile chronotherapeutics

1. Introduction

Felodipine (FELO), which is used in the present study, is a dihydropyridine derivative that is chemically described as ethylmethyl-4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedi-carboxylate, widely accepted for it's excellent anti-hypertension and antianginal properties since it is a calcium antagonist compound (calcium channel blocker) (Edgar et al., 1987). Nevertheless, the formulations of FELO are generally problematic as its dissolution rate is limited by its physicochemical properties. FELO is a typical example of a drug, which can be used for the therapy of symptoms, or diseases that according to circadian rhythms and chronobiology become worse during the night or in the early morning (Fox and Mulcahy, 1991). For these cases conventional drug delivery systems are inappropriate for the delivery of FELO or other suitable drugs, as they cannot be administrated just before the symptoms are worsened because at that time the patients are sleeping.

The achievement of such a release is sometimes limited by the physicochemical properties of the active pharmaceutical ingredients, such as lipophilic character and low solubility or from the use of inappropriate drug carriers. Modern views regarding drug delivery systems correspond to the development of chronotherapeutical formulations and specifically to "time-controlled release dosage forms" in order to achieve the maximum drug concentration in the plasma at the peak time of the symptomatology. Chronotherapeutical devices based on osmotic pumps have been developed by MaGruder (MaGruder et al., 1988) and Cutler (Cutler et al., 1995). Time controlled coating systems were also developed by Ueda (Ueda et al., 1994) and Narisawa (Narisawa et al., 1996), including single and multiple unit dosage forms. The major problem with these formulations is that they concern complicated and not industrially scalable systems. During the last years, the interplay of two or more

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polymers contribute to the development of an acceptable form, resulting, in this way, to the efficient control release of the active compound. (Shi and Tan, 2002; Lele and Hoffman, 2000; Khoo et al., 2003; Ozeki et al., 1999). However, the use of physical mixtures of polymers as press coating layers is inappropriate due to the different erosion rates of the substances, which lead to channelling creation and unrepeatable rupture times. The homogeneity of the coating barrier is mandatory in order to assure the predictability of the lag time.

In the present study, to overcome these disadvantages, polymer blends composed of polyvinylpyrrolidone (PVP) and hydroxypropyl-methyl cellulose (HPMC) are investigated in order to create an adjustable system based on the high solubility and release rate of PVP and the low one of HPMC. PVP is a water-soluble tertiary amide and a strong Lewis base and since it possesses good biocompatibility it has many applications in pharmaceutical technology. HPMC is used extensively as a drug carrier and as an enhancer of the dissolution behaviour of poorly water-soluble drugs as well (Karavas et al., 2001; Okimoto et al., 1997; Mitchell et al., 2003). It is a hardly water soluble polymer carrier with the ability to swell on contact with aqueous solutions creating a hydrocolloid gel mass on the external surface.

The aim of this study is the investigation of predictable pulsatile formulations of FELO consisted of two layered tablets. As coating layer different PVP/HPMC miscible polymer blends with appropriate physical properties will be used acting as an alarm clock releasing the drug amount from the active core at the desired time. In particular, the desired time is defined in terms of the period that ischemic heard diseases have the highest possibility of taking place, during the night or early in the morning. Furthermore, in order to succeed an immediately release of FELO its dissolution enhancement must first be achieved. For this reason dispersions with polyvinylpyrrolidone (PVP), which is the most appropriate drug carrier for dissolution enhancement of poorly water soluble drugs, were prepared (Sethia and Squillante, 2004; Valero et al., 2003; Ford, 1987) and studied extensively in order to select the most appropriate for pulsatile release formulations.

2. Experimental part

2.1. Materials

Felodipine (FELO) with an assay of 99.9% was supplied from PCAS (Longjumeau, France) with a melting point of 143–145 °C and solubility in water approximately 0.5 mg/l while it is freely soluble in ethanol. Polyvinylpyrrolidone (PVP) type Kollidon K30 with a molecular weight of 50,000–55,000, T_g = 167 °C (DSC analysis), moisture content 1.95% (TGA analysis) and bulk density 0.410 g/cm^3 was obtained from BASF (Ludwigshafen, Germany). HPMC type Methocel K4M was obtained from Colorcon Italy with a T_g = 202 °C (DSC) and moisture content 2.1% (TGA). Cross caramelose sodium was obtained from Blanver (Sao Paulo, Brazil) while dioctyl sodium sulfo-succinate (sodium docusate) was obtained from Cytec (Botlek RT, Holland). Sodium starch glycolate (Primogel type A) was obtained from DMV International (Veghel, The Netherlands). All other materials and reagents were of analytical grade of purity.

2.2. Preparation of PVP/FELO nanodispersions and characterization

Felodipine is practically insoluble in water. Thus, in order to enhance its solubility, nanodispersions of 10–30 and 50 wt.% into the PVP matrix were prepared by dissolving the appropriate quantities of the dry substances separately in ethanol absolute, according to our previous paper (Karavas et al., 2005). The solutions were mixed, subsequently ultrasonicated for 20 min and then the solvent was fully evaporated by rotary evaporator at 60 °C.

For the characterization of their physical state XRD analysis were performed on randomly oriented samples, scanned over the interval 5–55° 2θ, using a Philips PW1710 diffractometer, with Bragg-Brentano geometry (θ, 2θ) and Ni-filtered Cu Kα radiation.

The dynamic thermomechanical properties of the PVP/FELO dispersions were measured with a Tritec 2000 dynamic mechanical analyser (DMA)(Triton Technology Ltd., Nottinghamshire, UK). Approximately 50 mg of each sample were heated from −150 to 200 °C with applied frequency 1 Hz, a strain level of 0.04% and heating rate 4 °C/min.

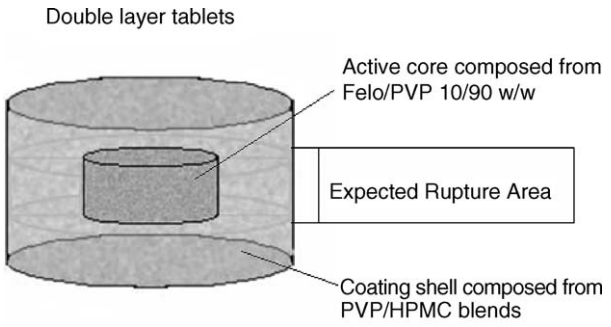
The morphology of the prepared nanodispersions was determined by a transmission electron microscopy (TEM) using a JEOL 120 CX microscope operating at 120 kV. TEM microphotographs were taken from ultra thin film samples of nanodispersions prepared by an ultra-microtome. To avoid the destruction of PVP films after exposure to electron irradiation, an adequate sample preparation is required and the thin films were carbon coated.

2.3. Preparation of polymer blends and characterization

PVP/HPMC polymer blends were prepared by using the solvent evaporation method. Both polymers were dissolved in double distilled water. PVP dissolved almost immediately (5 wt.%), while HPMC (2 wt.%) was immersed in water for 7 days to swell while complete dissolution was achieved with gentle heating at 60 °C. The two solutions were mixed at different amounts under sonication. Blends with concentrations 10/90, 20/80, 30/70, 40/60, 50/50, 60/40, 70/30, 80/20 and 90/10 w/w, in the form of thin films were prepared after water evaporation at room temperature. For the complete drying of the blends, the prepared films were heated in a vacuum oven for 24 h at 80 °C.

The morphology of the prepared blends as well as that of the initial materials, was examined using a scanning electron microscope (SEM), type Jeol (JMS 840).

Tensile strength and elongation at break of the prepared PVP/HPMC blends were studied on the prepared thin films. Dumbbell-shaped tensile-test specimens (central portions, ~5 × 1.5 mm thick; gauge length, 22 mm) were used. The stress–strain data were received by using an Instron tensile testing machine model 1122 according to ASTM D 1708-66. At least five specimens were tested for each sample and the average



Scheme 1. Design of the press coated tablet composed of an active FELO/PVP core and an inactive PVP/HPMC coating layer.

values reported. Typical standard deviation values were found for all samples.

Thermal analysis of the samples was carried out by using a Perkin-Elmer, Pyris 1 differential scanning calorimeter (DSC). For each measurement a sample of approximately 6 mg was used, placed in aluminium seal and heated to 135 °C at a heating rate of 20 °C/min. The sample remained at that temperature for 15 min in order to remove the moisture traces of PVP and HPMC. Following, the samples were cooled to 0 °C with a cooling rate of 20 °C/min and scanned again up to 230 °C using the previous heating rate. From this second scan the glass transition temperature of the blends (T_g) was measured.

2.4. Design of the predictable pulsatile device

Press coated tablets were prepared by using an IR press. The device was composed by an active core placed in the center of a double layered tablet (Scheme 1). The active core (2 mm in diameter, black colour in Scheme 1) contained PVP/FELO 90/10 w/w nanodispersion while the coating layer was composed by the different PVP/HPMC polymer blends described before, which were pulverized and sieved up to a particle size of 100–150 μm. The weight of the active core was 40 mg composed by a triplex dispersion −2.5 mg FELO, 22.5 mg PVP, 0.25 mg sodium docusate, while 4.75 mg cross caramelose sodium and 10 mg sodium starch glycolate were used as disintegration agent, in order to enhance the rupture of the external layer. The tablets (4 mm in diameter) were compressed under a compressional force of 500 Kp while the mean height was 2.65 mm (R.S.D. 1.63%, range 0.13 mm). Resistance to crashing (hardness) was found to be more than 60 Nt. The device was designed targeting to a homogenous thickness of the layer although the expected rupture area was the one corresponding to the sides of the tablets as shown in Scheme 1.

2.5. In vitro release profile of felodipine

The release rate of FELO from PVP nanodispersions as well as from the press coated tablet systems were measured by a modified dissolution apparatus II (paddles) USP (Karavas et al., 2005) (Wingstrand et al., 1990). A stationary disk was used in order to achieve hydrodynamic equilibration. The test was performed in 37 ± 1 °C with a rotation speed of 100 rpm using 500 ml of a 0.1 M phosphate buffer having pH 6.5 and containing 2% polysorbate 20 as a dissolution medium. According to the sampling plan, samples of 5 ml were withdrawn and immediately replaced by an equal volume of the respective dissolution medium maintained at 37 ± 1 °C. The samples were filtered (0.20 μm) and assayed according to the UV method described above. The test was performed in triplicate. The instrumentation used for the dissolution test was an apparatus type DISTEK 2100B equipped with an auto sampler.

3. Results and discussion

3.1. Dissolution enhancement of FELO via nanodispersions in PVP matrix

Oral drug delivery continues to be the preferred gateway of a drug administration into the blood stream. However for effective delivery, the candidate therapeutic agent must first be dissolved in the gastrointestinal lumen. FELO is a compound with a strong lipophilic character whilst it appears as a crystalline powder practically insoluble in aqueous solutions (solubility less than 0.5 mg/l) (Karavas et al., 2005; Abrahamsson et al., 1994). On the contrary, FELO is rapidly absorbed by the gastrointestinal tract after dissolution. However, even though it is highly permeable through biological membranes (Diez et al., 1991) the physicochemical characteristics of FELO indicate that its dissolution profile is the limiting factor of its bioavailability (Wingstrand et al., 1990). In order to increase its dissolution rate several attempts were carried out in the past (Kerč et al., 1991; Kim et al., 2005; Lee et al., 2003). From our previous study it was found that dissolution enhancement of FELO can be achieved using hydrophilic matrices such as modified celluloses (Karavas et al., 2001). However the particular systems are appropriate for retarded release and not for immediate as is desired for chronotherapeutics. This statement seems to be satisfied with the prepared PVP/FELO dispersions in the present study. The release rates of FELO from these dispersions, in comparison with those of the pure compound, are presented in Fig. 1.

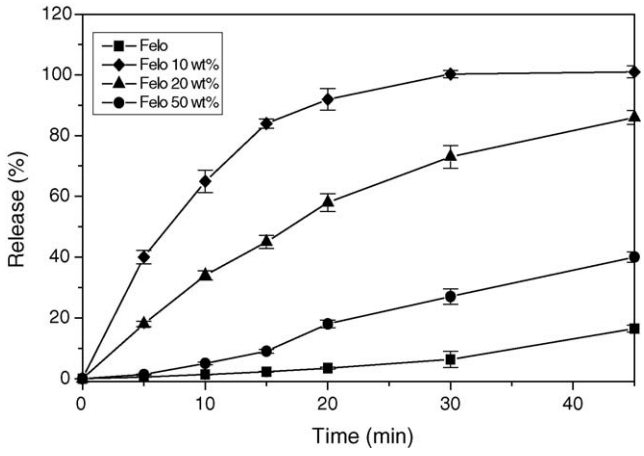


Fig. 1. Dissolution rates at 45 min of pure FELO and its solid dispersions as a function to FELO concentration.

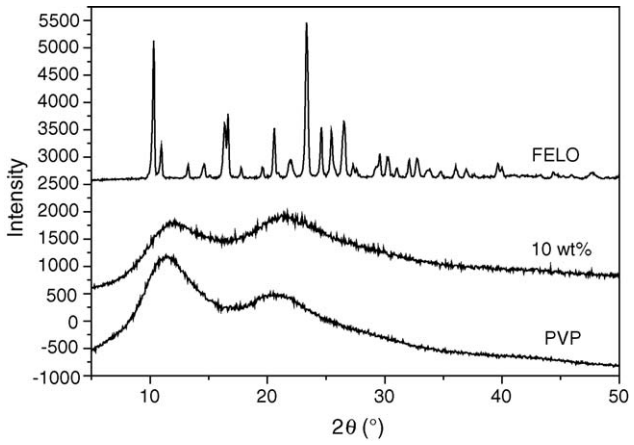


Fig. 2. XRD patterns of pure PVP, FELO and its solid dispersions within PVP containing 10 wt.% FELO.

As can be seen an impressive enhancement of solubility is achieved for dispersions containing 20 and mainly 10 wt.% FELO in which FELO releases immediately almost in 100% at a time less than 30 min. Increased dissolution rate was also observed in the samples containing 30 and 50 wt.% FELO. This behaviour could be explained by the modification of the particle size and, theoretically, of their substantial reduction due to the existence of interactions between the two components of the systems (Craig, 2002). Furthermore, one of the most common approaches to improve the bioavailability of poorly water soluble drugs is to enhance their dissolution rate by the formation of amorphous dispersions and, preferably, molecular dispersions (Craig, 2002). XRD diffraction patterns of PVP/FELO dispersions revealed that FELO, even thought it is a crystalline material with characteristic peaks at 2θ 10.30, 10.95, 16.35, 16.65, 20.60, 13.34, 24.60, 25.46 and 26.54, its dispersions in a PVP matrix are completely amorphous (Fig. 2). XRD patterns show typical profiles of amorphous material while peaks that correspond to FELO crystals completely disappeared, suggesting that the PVP matrix inhibited the crystallization of FELO. Only two broad peaks that correspond to the diffraction pattern of pure PVP are recorded.

XRD analysis can give substantial results about the physical state of the prepared dispersions. However, it is not possible to distinguish if there are one or two separate amorphous phases (Bikiaris et al., 2005). For this reason, the prepared PVP/FELO formulations were studied with dynamic thermomechanical analysis (DMA). This technique was preferred from DSC because it is more sensitive and thus appropriate to detect very weak molecular motions as well as drug amorpization (Royall et al., 2005). In the prepared amorphous dispersions, as can be seen from Fig. 3a, the storage modulus decreases sharply at the temperature area between 25 and 75 °C, and in tan δ there is a recorded high intensity peak at 52 °C corresponding to the glass transition temperature (T_g) of amorphous FELO. T_g of pure FELO alone ranges between 40 and 55 °C and becomes dependable upon the rate. (Kerč et al., 1991; Karavas et al., 2005). Except of this peak two other smaller are recorded at 114 and 162 °C. The first one corresponds to the absorbed moisture by the PVP matrix and is recorded in all samples at the same temperature range while the second one to the glass transition temperature of PVP. From these data it is realized that felodipine is not completely miscible with PVP forming a single matrix but remains as a separate finely dispersed phase with sizes higher than 10 nm. However, the small movement of both T_g's in solid dispersions to lower temperatures, compared to the initial pure FELO and PVP materials, is a strong indication that some interactions between PVP and FELO are taking place during the preparation of FELO nanodispersions.

In order to determine the exact morphology of PVP/FELO dispersions, TEM analysis was performed, thus having higher spatial resolution than SEM and thus it is easier the differentiation between molecular dispersion and nanodispersion. Since FELO is the minor component in the PVP matrix, FELO particles well dispersed into PVP matrix are expected. In Fig. 4 TEM photomicrographs obtained from different PVP/FELO nanodispersions are presented. As can be seen FELO nanoparticles, which appear as black spots, can be satisfactorily differentiated from the PVP matrix. Sizes of these particles were directly affected by drug ratios into the PVP matrix. The prepared PVP/FELO systems are more close to the described ones by Savolainen et al. (2002), who assumed that FELO exists as a

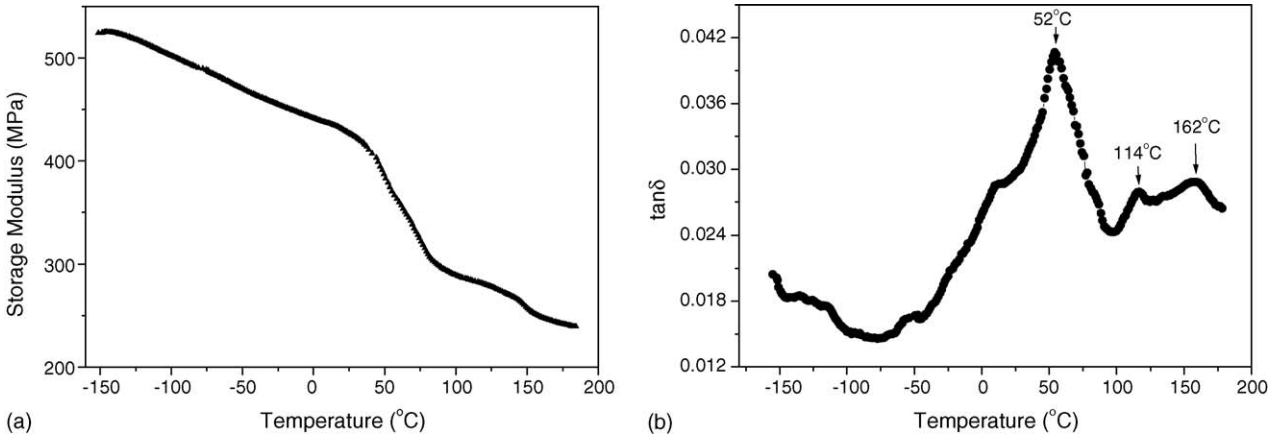


Fig. 3. Variation of (a) storage modulus E′ and (b) tan δ of PVP/FELO 90/10 w/w amorphous nanodispersions.

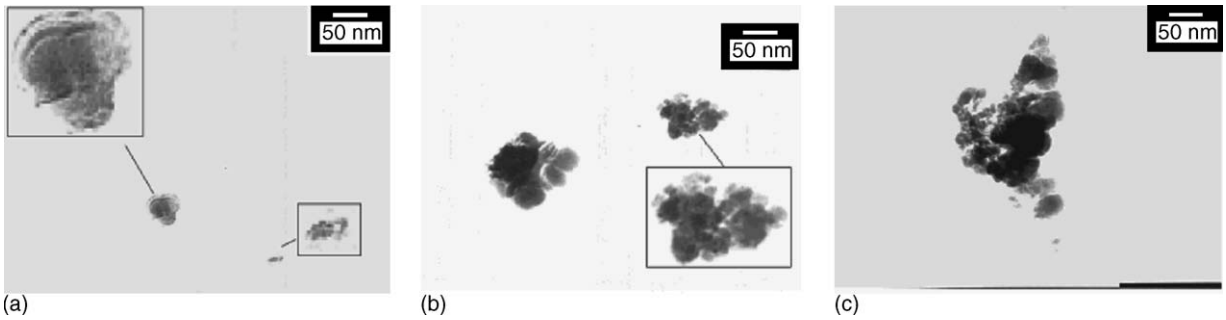


Fig. 4. Transmission electron photomicrographs of PVP/FELO nanodispersions containing differed drug concentrations: (a) PVP/FELO 90/10 (40–50 nm), (b) PVP/FELO 80/20 (100–110 nm) and (c) PVP/FELO 50/50 (500–550 nm).

partially solid solution. Particle sizes, in the solid dispersion of PVP/FELO 90/10 w/w, were 20–130 nm. By increasing the FELO ratio in solid dispersions, particle sizes became progressively larger; they ranged from 50 to 200 nm, and 500–1000 nm in solid dispersions containing 20 and 50 wt.% of FELO, respectively. In all cases it is noticeable that these nanoparticles are not united particles, as appeared in SEM micrographs in our previous study (Karavas et al., 2005), but aggregates from individual particles in sizes ranging from 5 to 10 nm and may be even lower than that. Furthermore, there seems to be another basic morphological difference that was not possible to be distinguished by SEM. At high magnifications it can be seen that FELO nanoparticles have circular shape and consisted of a dark core with a light shell. This is due to the fact that the shell is thinner than the core or because of the interactions taken place between PVP and FELO and an intermediate interphase is produced in the boundaries between the two components. This is more obvious in the first photomicrograph of PVP/FELO 90/10 w/w nanodispersion. Similar nanodispersions were also observed with TEM in flavonoids dispersed into a PVP matrix (Kanaze et al., in press) and it is strongly believed that this technique can adequately characterize such nanodispersions.

3.2. Preparation of PVP/HPMC polymer blends and characterization

After the preparation of FELO formulations that can release the drug in a sort time, corresponding to an immediate release, an appropriate system that could adjust the exact time of FELO release was investigated. For this reason PVP/HPMC blends were prepared and studied taking into account the high dissolution rate of PVP and the very low one of HPMC. However, in order to create a new matrix capable of combining the different physicohemical properties of the initial polymers the prepared blends must be miscible or at least compatible. Otherwise the prepared blends will behave as physical mixtures, which are not desired for uses in pulsatile systems. The prepared PVP/HPMC films are transparent, which is an indication that they may be miscible in the entire compositional range. In order to verify this, the blends were studied with several techniques. Examining the SEM micrographs of fractured films it is observed that they reveal only one smooth surface, thus revealing the complete miscibility of the particular blend (Fig. 5). This miscibility is maybe the result of strong interactions taking place between the reactive groups of both polymers. PVP is a strong Lewis base and due to its polar carbonyl groups it is a powerful proton acceptor, easily creating hydrogen bonding interactions with other polymers like HPMC, with the latter containing hydroxyl groups. This effect enhances polymer miscibility since hydrogen bonding induces a negative, favourable enthalpic contribution to the Gibbs free energy of mixing.

The miscibility of the two polymers with strong interactions can improve tensile strength of the blends. Both homopolymers according to the stress–strain data could be characterized as strong materials since their tensile strength is very high. However, they break before yield point is recorded and it appears to have very low elongation at break. For this reasons both polymers can be safely characterized as strong and brittle materials. HPMC has a tensile strength of about 50 MPa while PVP has a somewhat higher one, close to 65 MPa (Fig. 6). The curve in the plot of tensile strength versus concentration shows that these blends are completely miscible. The values of tensile strength

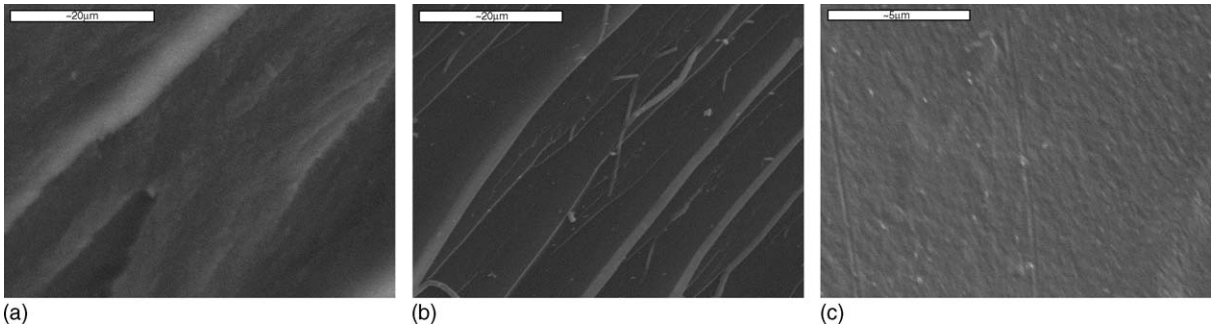


Fig. 5. SEM micrographs of PVP/HPMC blends with different composition ranges: (a) 80/20, (b) 50/50 and (c) 10/90 w/w.

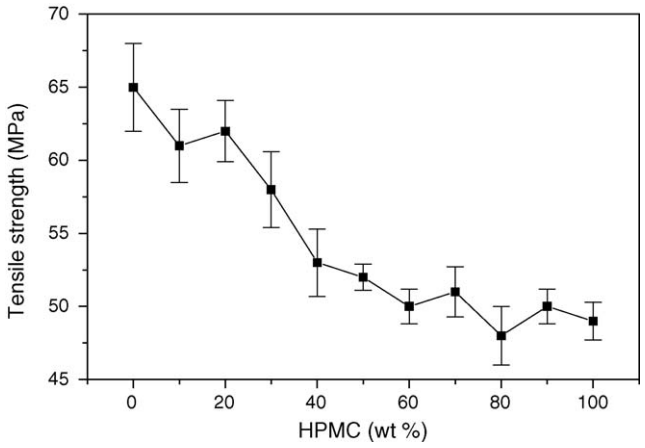


Fig. 6. Tensile strength of the prepared blends containing different compositions of HPMC.

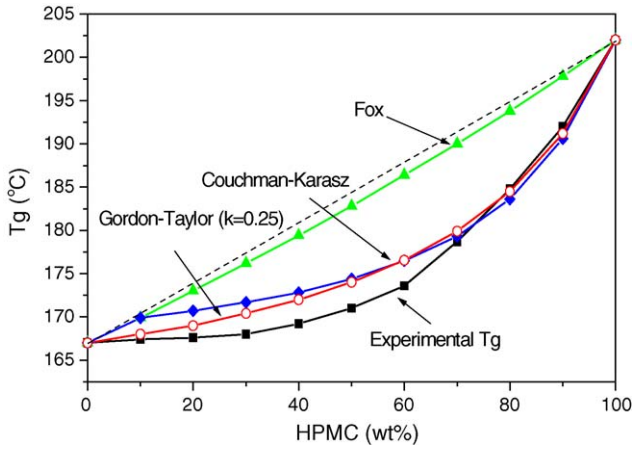


Fig. 7. Prediction of T_g-composition dependence by using several equations in comparison with the experimental data as was calculated from DSC thermograms.

of the mixtures range between the values of tensile strength of the pure polymers, a condition that appears in compatible and miscible blends while the existence of strong interaction shall be excluded (Prinos et al., 1997).

Experimentally, the most ubiquitous criterion to characterize that two amorphous polymers are completely miscible, is the detection of a single glass transition temperature (T_g) ranging at temperatures between the corresponding ones of the initial polymers, or at even higher temperatures. For this reason homopolymers as well as their blends were studied by DSC. HPMC has a glass transition temperature of about 202 °C while PVP shows one at 167 °C. Both polymers are amorphous materials and even thought this difference is very small (35 °C) it has been proven by our previous work that DSC is a sensitive technique to study the miscibility of such blends (Bikiaris et al., 2004). In all DSC thermograms recorded form PVP/HPMC blends only one T_g was found, which ranges between the glass transitions of the two initial polymers which is in accordance with a previous study in similar blends (Nyamweya and Hoag, 2000). This is a further proof that the two polymers are fully miscible in the entire compositional range, as was already postulated by SEM and mechanical properties study. This miscibility is the result of strong interactions taking place between the carbonyl groups of PVP and hydroxyl groups of HPMC (Karavas et al., in press JTA). To predict the extent of the interactions taking place between the reactive groups of the two polymers the Fox (1) (Fox, 1956) Gordon–Taylor (2) (Gordon and Taylor, 1952) and Couchman–Karasz (3) (Couchman and Karasz, 1978) equations were applied:

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \quad (1)$$

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \quad (2)$$

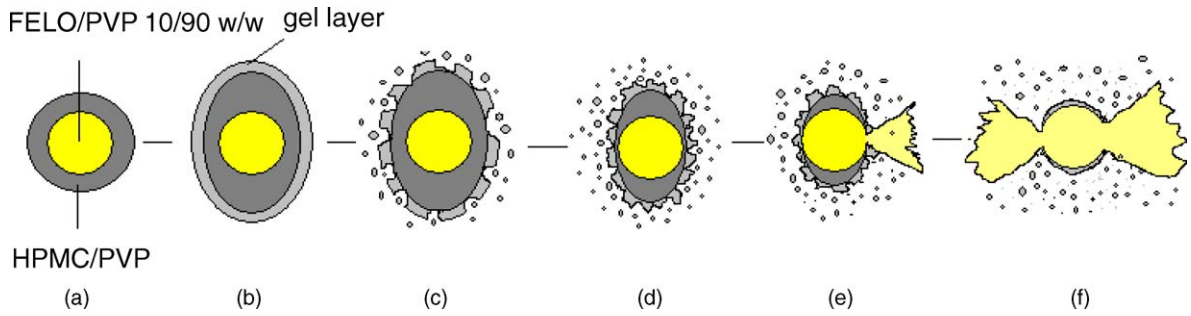
$$\ln T_g = \frac{(w\Delta C_p \ln T_g)_1 + (w\Delta C_p \ln T_g)_2}{(w\Delta C_p)_1 + (w\Delta C_p)_2} \quad (3)$$

where T_g is the glass transition of the blend, w_1 and w_2 are the weight fractions of the initial polymers forming the blend and T_{g1}, T_{g2} are their glass transition temperatures, k is a constant representing a semi-quantitative measure of the interaction strength between the reactive groups and ΔC_p represents the heat capacity change at T_g. In Fig. 7 the experimental data of T_g calculated from DSC thermograms are presented in comparison with those of theoretical predictions by using the above equations. As can be seen only the Gordon–Taylor and Couchman–Karasz equations fit well with the experimental data. By applying in the Gordon–Taylor equation a value $k = 0.25$ a very well correlation with the experimental data is obtained. The Couchman–Karasz equation gives similar fittings by using as ΔC_p values for PVP and HPMC, 0.37 and 0.07 J g^{-1} K^{-1} respectively, which were calculated from DSC thermograms. Both equations outline the large negative T_g deviations from the weight average values calculated from the DSC thermograms, which is an indication that hydrogen bond formed between the reactive groups of both polymers is rather weak and not as strong as was believed.

3.3. Preparation and study of pulsatile chronotherapeutics in the form of two layered tablets

From the extensive study of PVP/HPMC blends it was verified that these are miscible in the entire compositional range, which was also the target of their preparation in the present study. These blends will be used as effective coating layers for the preparation of two layered tablets in order to release FELO in a pulsatile manner. The active core consisted of PVP/FELO 90/10 w/w nanodispersions, since this formulation corresponds to immediate release of FELO (Fig. 1), while in the coating layer different PVP/HPMC blends were used. The target of this coating application is to act as alarm clock, thus releasing the drug at the desired and strictly determined time.

The macroscopic observation of the tablets during dissolution procedure showed that the coating layer composed by the polymer complexes is simultaneously a swellable and erodible barrier. This complicated behaviour is attributed to the different physicochemical properties of each one of the used polymers. HPMC is a hardly water soluble polymer carrier with the ability



Scheme 2. Rupture mechanism of double wall tablets. (a) Initial tablet, (b) gel forming on the coating layer due to the water penetration and tablet swelling (c) erosion inception of the coating layer (d) extended erosion (e) rapture of coating layer and initiation of core dissolution and (f) extended FELO release.

to swell on contact with aqueous solutions, resulting to the creation of a hydrocolloid gel mass on the external surface. Thus the gel that appears in the external tablets layer arises from this polymer while at its erosion contributes to the PVP amount. Based on these different dissolution rates coating layers behave in a complex way (Scheme 2). At the beginning, the coating layer hydrates rapidly and the internal penetration of the dissolution media is achieved in a short time, less than 1 h for the entire polymer ratios, depending from PVP/HPMC variation. During this process the tablet is expanded to an opposite direction than the compression force (Scheme 2b). This behaviour could be explained by the fact that the polymer blend tends to recover its initial geometrical characteristics before compression. In the second phase of the dissolution procedure, the coating layer gradually starts to erode up to a limiting thickness (Scheme 2c and d). After this stage, a rapture of the shell is observed under the pressure applied by the swelling of the active core and FELO releases (Scheme 2e and f). All of this process corresponds to a lag time capable of exhibiting a pulsatile release of the drug. After the delaying time, the last phase of FELO dissolution takes place, which corresponds to a rapid release of the drug. It is very important at this point to note that there isn't any released amount of FELO detected before the rapture of the coating layer. Maybe this is due to the strong interactions taken place between PVP and FELO that restricts a release based on diffusion (Karavas et al., accepted for publication).

The delay time for beginning the FELO release can be shift to higher times by increasing the concentration of HPMC in the polymer complex (Fig. 8). This behaviour was expected as the solubility of HPMC is lower than the one of PVP and matrices with higher HPMC concentrations have lower solubility. Compared with PVP, HPMC can be characterized as the retarding polymer since the release of the active ingredient is expected to be controlled by the dissolution rate of the polymer gel.

The profiles of the prepared tablets showed a repeatable delay time for the initiation of the drug release (RSD < 3%) while the main critical parameter for the predictability of the systems is the polymer ratio of the blends. In order to mathematically express this predictability, the function between the delay time and the HPMC concentration in the blend was calculated according to the experimental results. This function is in full correlation (correlation coefficient $R^2 = 0.99$) with the equation:

$$t = 0.028\, C^{1.5} \quad (4)$$

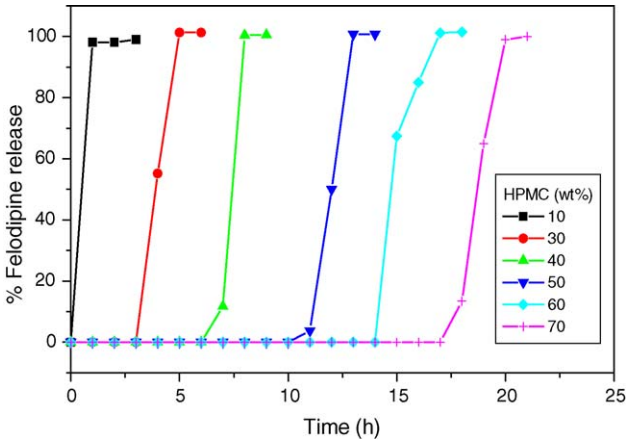
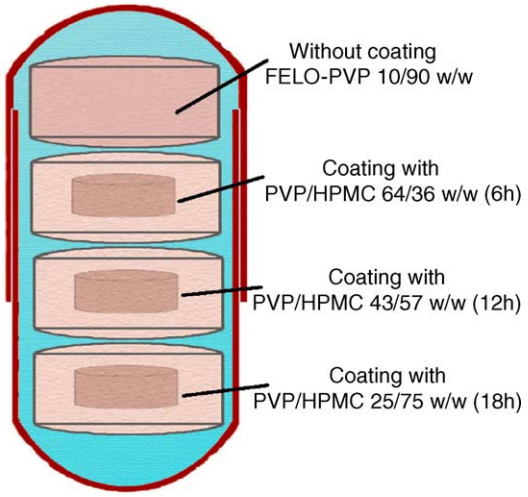


Fig. 8. Release profile of felodipine from the prepared tablets containing PVP/HPMC with different polymer ratios as coating layer. The release profile corresponds to pulsatile kinetics strongly depended on the PVP/HPMC ratio.

where t is the delaying time and C the concentration of HPMC in the blend.

The above equation could be easily used for the definition of the lag time of the chronotherapeutic formulations. These formulations could be consisted of a capsule containing 2–4 tablets, each one having different miscible PVP/HPMC blends



Scheme 3. Scalable pulsatile chronotherapeutic formulations consisted of a capsule containing tablets with different coating layers adjusting precisely the time of FELO release.

as a coating layer, in order to release FELO at the predetermined and desired time. For example if a pulsatile release of FELO every 6 h during daytime is desired, the capsule would be comprised of four tablets (Scheme 3). The first composed only from a FELO/PVP nanodispersion (0 h) without having any coating layer, the second having a PVP/HPMC 64/36 w/w coating layer (6 h), the third composed from PVP/HPMC 43/57 w/w coating layer (12 h) and the forth being a PVP/HPMC 25/75 w/w coating layer (18 h). The advantage of such a system is that it can be easily be prepared in research labs as well as that it is also scalable for industrial applications.

4. Conclusions

In all PVP/FELO prepared solid dispersions it is proved by TEM analysis that FELO is dispersed within amorphous nanoparticles and not in a molecular dispersion.

The drug release rate is directly attributed to the size of these nanodispersions while PVP/FELO 90/10 w/w corresponds to an immediate release at an interval less than 30 min.

PVP/HPMC miscible blends provide an effective and easily prepared system for the creation of a scalable pulsatile chronotherapeutic formulation, consisted of two layered press-coated tablets. An active core of FELO nanodispersions in a PVP matrix are the ideal solid dispersions corresponding to a fast release of FELO from the PVP matrix while the coating layer consists of PVP/HPMC blends.

The delay time of felodipine release can be decisively adjusted during daytime by varying the PVP/HPMC concentrations.

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