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Research paper

Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics

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Abstract

The aim of the present study was to prepare pulsatile release formulations consisting of two-layered tablets appropriate for preventing ischemic heart diseases. For this reason the active core was constituted by a FELO/PVP 10/90 w/w solid dispersion while for the adjustment of the drug release time the coating layer was composed of PVP/HPMC blends at different compositions, acting as a stimulus responsible layer. These blends as was found by DSC studies are miscible in the entire composition range, ensured by the interactions taking place between hydroxyl groups of HPMC and carbonyl groups of PVP. The miscibility of the system enhances the mucoadhesive properties of the blends, compared with those of pure HPMC, which is desired for such applications. The enhancement was attributed to the higher rate of wetting and flexibility of the new matrices due to the faster dissolution of the PVP macromolecules. Upon exposure of the prepared tablets to the release medium it was found that the coating layer disintegrates first, followed by the immediate release of FELO from the active core. The delaying time is based on a complicated mechanism, which is a combination of swelling and erosion of the PVP/HPMC polymer blends. Varying the PVP/HPMC blend ratios, the exact time that FELO is released during a daytime can be effectively adjusted and this ability is expressed mathematically by the equation $t = 0.028\ C^{1.5}$, where C is the concentration of HPMC in the blend.

Keywords: Felodipine; Poly(vinyl pyrrolidone); Hydroxypropyl methyl-cellulose; Miscible blends; Pulsatile chronotherapeutics; Mucoadhesive polymers

1. Introduction

The main goal of drug delivery research is to develop formulations that fulfil the therapeutic needs related to particular pathological conditions. Up to 1990 this research was governed by the homeostatic theory which was based on the dogma that biological functions display constancy over time. Chronobiology is a science studying how time and seasons affect biological processes [1]. The latest studies on this field have established circadian rhythmicity for almost all body functions. Besides the physiological functions, the symptomatology of several diseases also exhibits circadian rhythms. Results of several epidemiological studies demonstrate the elevated risk of different pathologies during a 24-h cycle. Specifically, symptoms of rheumatoid arthritis and osteoarthritis [2], dyspnoea [3] and epilepsy appear to have a peak during the night or early in the morning. Ischemic heart diseases, such as angina pectoris and myocardial infraction, are manifested more frequently during these times [4]. Blood pressure which arises notably just before waking up [5] is usually responsible for these attacks.

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Felodipine (FELO), which is used in the present study as a model drug, is a dihydropyridine derivative widely accepted for its exquisite anti-hypertension and anti-anginal properties, since it is a calcium antagonist compound [6]. FELO is a typical example of drug, which is used in the therapy of symptoms or diseases as described before. However, for such cases, conventional drug delivery systems are inappropriate for the delivery of FELO, as they cannot be administered just before the symptoms are worsened, because during this time the patients are asleep. Modern views regarding drug delivery systems correspond to the development of chronotherapeutic 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. In order to achieve this goal several studies have been carried out, including the development of enteric-coated systems, osmotic pumps, pulsincap systems and layered systems [7–9]. Chronotherapeutical devices based on osmotic pumps have been developed by MaGruder et al. [10] and Cutler et al. [11]. A pulsincap system [12] corresponds to a more sophisticated approach while it is composed by a capsule with an insoluble body and a hydrogel plug. Multiphasic drug release was achieved by using a three layer [13] tablet while similar devices were also developed and evaluated in a later stage [14,15]. Time controlled coating systems were also developed by Ueda et al. [16] and Narisawa et al. [17], including single and multiple unit dosage forms. The major problem with these formulations is that they concern complicated and not industrially scalable systems.

The simplest pulsatile formulation corresponds to the press-coated tablets comprised of two layers. Solid dosage film coating has been used for more than 30 years in pharmaceutical technology. However, only during the last years scant attention was given for the evaluation of the physicochemical properties and phenomena of the employed polymers. The disadvantage of such formulations is that the rupture time cannot be adjusted as it is strongly correlated with the physicochemical properties of the polymer. Furthermore, the use of physical mixtures of polymers as press coating layers is inappropriate due to the different erosion rates of the substances, which leads to channelling creation and unrepeatable rupture times. The homogeneity of the coated barrier is mandatory in order to assure the predictability of the lag time. Thus, polymer blends could be the solution for the creation of new materials, exhibiting the appropriate flexibility for the adjustment of the drug release [18–21]. In the present study, polymer blends composed of polyvinylpyrrolidone (PVP) and hydroxypropyl-methyl cellulose (HPMC) are investigated in order to create an adjustable system based on the high release rate of PVP and the low one of HPMC. These blends were found to be miscible in the entire composition range creating a new matrix with different physicochemical characteristics [22].

PVP is a water-soluble tertiary amide and a strong Lewis base and with HPMC are used extensively as enhancers of the dissolution behaviour of FELO [23,24]. HPMC 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. This mass gradually dissolves during time. Therefore, from such a system, the release of the active ingredient is expected to be controlled by the dissolution rate of the polymer gel. HPMC was also chosen for one more important reason. Another disadvantage of pulsatile release formulation is that they require a long residence time in the gastrointestinal track. One of the basic mechanisms to extend this time period is the use of bioadhesive polymers. HPMC is well known as one of the most effective mucoadhesive polymers.

The aim of this study was to prepare miscible PVP/HPMC polymer blends with enhanced mucoadhesive properties used in predictable pulsatile formulations of FELO, consisting of two layered tablets. The internal layer contains the active pharmaceutical ingredient (FELO) while the external homogeneous coating layer is composed of different PVP/HPMC blends that adjust to the initiation of FELO release through their rupture. The different blend concentration will act as an alarm clock releasing the drug at the desired time and, mainly, at the period that ischemic heard diseases have the highest possibility of taking place. For this reason the bioadhesion properties of the polymer blends are of highest importance for the development of an integrated system.

2. Materials and methods

2.1. Materials

Felodipine (FELO) with an assay of 99.9% was obtained from PCAS (Longjumeau, France) having 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 was obtained from BASF (Ludwigshafen, Germany), $T_g = 167$ °C (DSC), moisture content 1.95% (TGA), bulk density 0.410 g/cm^3 and particle size distribution 10% < 50 μm and 5% > 250 μm. HPMC type Methocel K4M was obtained from Colorcon Italy with a $T_g = 202$ °C (DSC), moisture content 2.1% (TGA) and particle size distribution 99% < 425 μm. Cross caramelose sodium was obtained from Blanver (Sao Paulo, Brazil) and 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 the other materials and reagents were of analytical grade.

2.2. Preparation of the polymer blends

Polymer blends were prepared by using the solvent evaporation method. Both polymers were dissolved in

double distilled water. PVP was dissolved almost immediately (5 wt%), while HPMC (2 wt%), in order to be dissolved, was first immersed in water for 7 days in order to swell while complete dissolution was achieved through gently heating at 60 °C for 2 h. The two solutions were mixed at different amounts under sonication for 10 min. 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 complete drying of the blends, the prepared films were heated in a vacuum oven for 24 h at 80 °C. The final amounts of each one-blend composition were approximately 30 g. All these blends were used as coating layers for the preparation of two-layered tablets as is described further down.

2.3. Blend characterization

2.3.1. Thermal analysis

Thermal analysis of the samples was carried out through the use of 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, while placed in aluminium seal without closing the cover and heated up 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 200 °C using the previous heating rate. From this second scan the glass transition temperature of the blends (T_g) was measured.

2.3.2. Fourier transformation-infrared spectroscopy

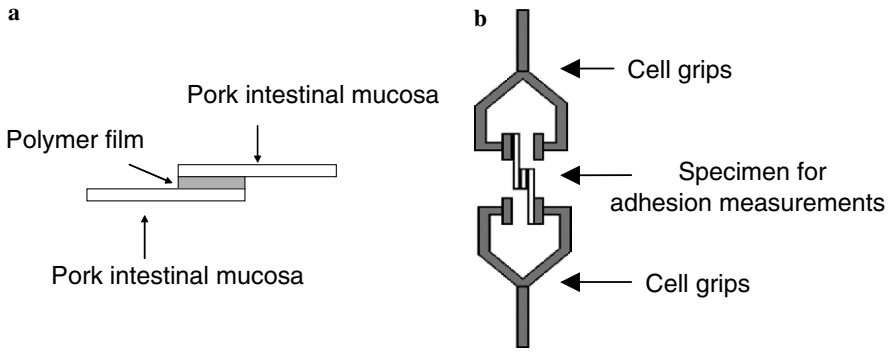
Fourier transformation-infrared spectroscopy (FT-IR) spectra were obtained using a Perkin-Elmer FTIR spectrometer, model Spectrum 1000. In order to collect the spectra, a small amount of each material was used (1 wt%) and compressed in KBr tablets. To avoid the effect of moisture all samples were dried overnight in a vacuum oven at 110 °C. The IR spectra, in absorbance mode, were obtained in the spectral region of 450–4000 cm^{-1} using a resolution of 4 cm^{-1} and 64 co-added scans.

2.4. Assessment of the mucoadhesive force

The estimation of the adhesive force was performed on an Instron 1122 dynamometer, using full-scale load cell of 10 kg. Polymer specimens prepared by solution casting, were used in the form of films 1.5×1.5 cm (2.25 cm^2). Before measurements the films were immersed into a phosphate buffer solution (pH 7) for 2 min for wetting and placed on a fresh pig intestinal mucosa, which had the form of a rectangular bar 1.5×6 cm (9 cm^2). After that, another intestinal mucosa was superimposed on the free polymer surface, so the polymer lay between the two intestinal mucosa bars (Scheme 1). The width of the polymer plates and the intestinal mucosa bars was exactly the same avoiding the intestines attaching to each other. Finally, the plates were subjected to a pressure of 0.2 kg for 10 min. The whole system was mounted by the instrument of cell grips from the free edges of each intestinal mucosa and the force of detachment was measured with a crosshead speed of 1 mm/min. For each sample three measurements were conducted, and the results were averaged to obtain a mean value.

2.5. Preparation of the Felodipine/PVP solid dispersion system

Felodipine is practically insoluble in water. Thus, in order to increase its solubility, solid dispersions using PVP as a drug carrier were prepared. Solid dispersion systems of 10/90 w/w FELO/PVP, respectively, containing 1% sodium docusate, were prepared by dissolution of accurately weighed appropriate quantities of the drug substance and the polymer, in equal quantities of absolute ethanol [23]. The solutions were sonicated for 15 min. After dissolution the samples were maintained at 40 °C for 48 h in order to slowly evaporate the solvent. The resulting films were pulverized and milled to a particle size of 109 μm to 250 μm. The final granules were assayed spectrophotometrically (UV–Vis) for FELO content, at 362 nm, using a Shimadzu UV 1601 apparatus.



Scheme 1. (a) Illustration of the final sample used for the estimation of the mucoadhesive force and (b) its attachment on the Instron cell grips.

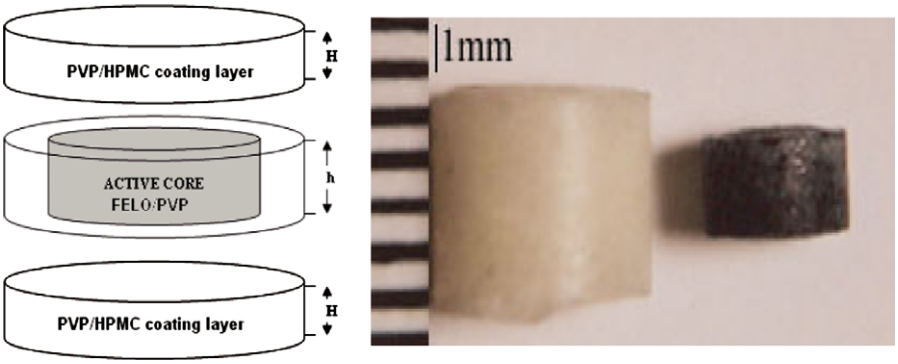


Fig. 1. Design of the press-coated system composed of FELO/PVP 10/90 w/w (black colour) and an inactive and adjusting coating layer containing different PVP/HPMC ratios (h = expected rupture area).

2.6. Design of the device – tablet preparation

Press-coated tablets were prepared using an IR press. The device was composed of an active core placed in the centre of a double layered tablet (Fig. 1). The active core contains a FELO/PVP 10/90 w/w solid dispersion while the coating layer was composed of the different polymer blends described in the respective paragraph, which were pulverized and sieved up to a particle size of 100–150μm. The weight of the active core was 40 mg composed by a triplex solid 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 boosters in order to enhance the rupture of the external layer. Furthermore, indigocarmine (EPSA Valencia, Spain) was used as a colorant in an amount of 0.1 wt%. The tablets (4 mm in diameter) were compressed under a compression force of 500 kP while the final mean height was 2.65 mm (RSD 1.63%, range 0.13 mm). The hardness was found to be more than 60Nt. The coating layer was applied using the compression technique while blends with different polymer ratios were used. The device was designed targeting to homogeneous thickness of the layers although the expected rupture area was the one corresponding to the sides of the tablets as shown in Fig. 1. The total height of the tablet was adjusted to a minimum of 4.7 mm, which corresponds to a minimum thickness of 1 mm on the top and bottom surfaces, and a standard thickness of 1 mm on the sides of the tablet. The total weight of the external tablet was about 116 mg and the diameter was 6 mm.

2.7. In vitro release profile

The release of FELO from the press-coated tablet systems was measured by a modified dissolution apparatus II (paddles) USP. A stationary disc 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 0.1 M phosphate buffer, pH 6.5, containing 2% polysorbate 20 as a dissolution medium [25]. According to the sampling plan, 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 the UV method as described above. The tests were 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. Blends' characterization

The prepared films, after drying, exhibit a light brown colour, characteristic of both polymers and are transparent in the whole composition range. This observation is an indication that the two polymers may possibly be fully miscible creating a new polymer matrix constituted by one single phase. In the case of inhomogeneous systems the film of the blends should be opaque due to different light scattering of each different phase. Experimentally, the least ambiguous criterion for polymer miscibility of two amorphous polymers is the detection of a single glass transition temperature (T_g) ranged at temperatures between those corresponding to the initial polymers, or at even higher temperatures. The precise position depends on the extent of interactions that take place between the reactive groups of the two polymers. On the other hand, phase separation is judged by the existence of two distinct T_g close to the T_g of the pure polymers. For this reason a detailed analysis of the T_g of the prepared polymer blends is necessary to identify blend miscibility. HPMC has a T_g value of about 202 °C, and PVP shows one at 167 °C. Even though this difference is very small (35 °C) it has been proved that differential scanning calorimetry is a sensitive technique as far as the study of the miscibility of such blends is concerned [26]. In prepared blends it is observed that in all compositions there is only one T_g, which ranges between the glass transitions of the two initial polymers, which is in accordance with the previous study in similar blends [22]. This is a strong proof that the two polymers are fully miscible, creating a massive interpenetrating network.

In the past, several theoretical and empirical equations have been proposed to adequately describe the dependence

of glass transition of a miscible blend from the weight fractions and the glass transitions of the initial polymers and to estimate the extent of interactions between the different components. Among them, the Fox equation can be used to evaluate the T_g/composition relationship, which was one of the first proposed [27]

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

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} and T_{g2} are their glass transition temperatures. Gordon–Taylor proposed an equation taking into account the evolved interactions that cannot be predicted by the Fox equation [28]

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

where k is a constant representing a semi-quantitative measure of the interaction strength between the reactive groups. If k takes values close to 1 or higher then it is suggested that strong interactions take place as in the PVP/PVAL and PVP phenoxy blends [29,30]. These classic equations predict that T_g can continuously and monotonically increase with blend composition. However, in several polymeric blend systems it was observed that such a variation is not always the case. For this reason Couchman examined the thermodynamic behaviour of both polymers in order to obtain a more accurate prediction of the T_g-composition dependence [31]

$$\ln T_g = [(w\Delta C_p \ln T_g)_1 + (w\Delta C_p \ln T_g)_2]/[(w\Delta C_p)_1 + (w\Delta C_p)_2], \quad (3)$$

where w is the weight fraction of each component and ΔC_p represents the heat capacity change at T_g.

By using the above equations, as it can be seen in Fig. 2, only the Gordon–Taylor and Couchman–Karasz fit well with the experimental data. By applying the Gordon–Taylor with $k = 0.25$, a very good correlation with the experimental data is obtained. This value is inferior to 1, implying that the interactions between the hydroxyl groups of HPMC and the carbonyl groups of PVP are rather weak. However such a low value does not exclude the formation of completely miscible blends. Such a small value ($k = 0.41$) was calculated in PVP/PAN blends which are also miscible [32]. 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. These values were calculated from the thermograms of both polymers measured with a DSC over the area of the glass transition temperatures and the value of PVP is very close to that mentioned for PVP 0.26 J g^{-1} K^{-1}. Thus, it can be concluded that both equations outline the large negative T_g deviations from the weight average values calculated from the DSC thermograms.

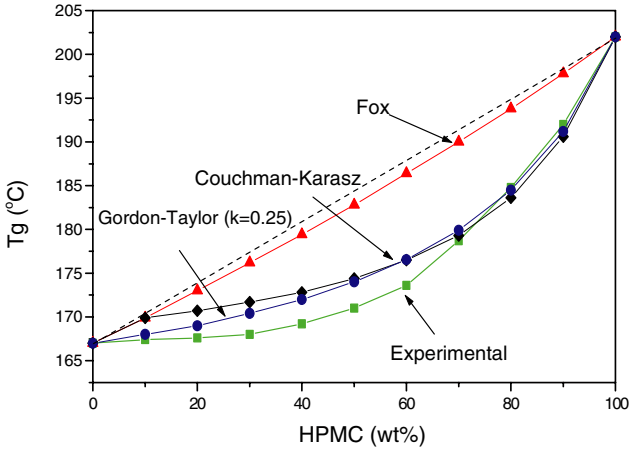


Fig. 2. Prediction of the T_g-composition dependence using several equations.

3.2. Estimation of the nature of the interactions

In the prepared miscible blends, it is expected that intermolecular hydrogen bonding between the hydroxyl groups of HPMC and the carbonyl groups of PVP might be created. To gain a deeper understanding of these interactions the FTIR spectra of all prepared blends were studied. From all spectrum areas two regions are of great importance. The carbonyl group area situated between 1600 and 1750 cm^{-1} and the respective of the hydroxyl groups at 3350–3700 cm^{-1}, where the hydrogen bonding takes place (Fig. 3).

In the PVP spectrum the characteristic peaks are at 1662 cm^{-1} and at 1291 cm^{-1} attributed to the stretching of amide >C=O and >N–C groups, respectively. Since PVP is very hygroscopic, to avoid any plasticizing effect of the present water the sample was extensively dried for 24 h at 130 °C. On the other side the characteristic peaks of HPMC are at 3050–3750 cm^{-1} and are attributed to the –O–H stretching and the triple peak in the so-called fingerprint spectrum area of >C–O– at 960–1230 cm^{-1} (Figs. 3a and b). A broad band at 3442 cm^{-1} denotes the superposition of stretching for two types of hydroxyl groups in HPMC. Free at 3585 cm^{-1} and self-association hydroxyl groups through intermolecular and intramolecular hydrogen bonding at 3444 cm^{-1} that is not easily observed due to the peak broadness. The intensity and the position of these characteristic peaks of both polymers permit us to interpret rather easily the influence of interactions between these polymer groups.

From the FTIR spectra of the prepared blends it can be seen that as the amount of HPMC increases the hydroxyl band moves to lower wavenumbers. In PVP/HPMC blend containing 20/80 w/w the peak can be found at 3418 cm^{-1} while as the amount of PVP increases it seems that the peak moves again at higher wavenumbers (Fig. 3a). Thus in PVP/HPMC blends containing 80/20 w/w, the peak is detected at 3444 cm^{-1} which is similar to that of the initial HPMC. This indicates that the hydrogen bonding between the carbonyl groups of PVP and the hydroxyl groups of HPMC is stronger when HPMC is used in excess rather than PVP (Fig. 3b). A similar trend is exhibited for the C-O groups recorded at the fingerprint area. These findings can be directly related to the DSC data where glass transition of these blends is well predicted from the

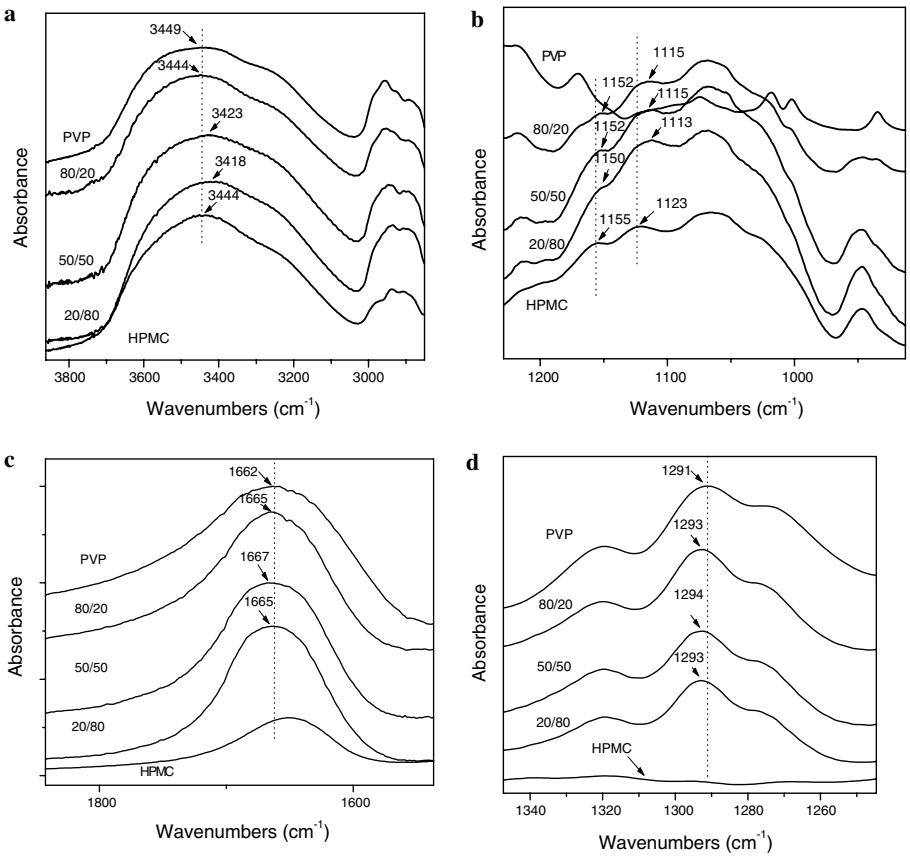
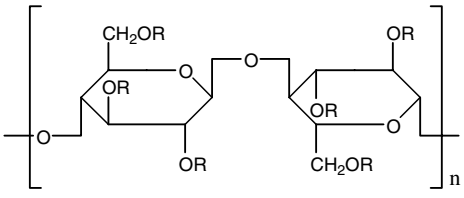


Fig. 3. FTIR spectra of PVP/HPMC blend at characteristic wavenumber positions.

Couchman–Karasz equation. Examining the corresponding absorbance it was found that as the amount of HPMC increases the maximum of the carbonyl group is shifted towards higher positions (Fig. 3c). This is an indication that the electron change of the carbonyl group is somewhat suppressed due to the hydrogen bonds and cannot be dispersed to the neighbouring >N–C groups. Furthermore, this reveals that these interactions are rather weak since in the case where strong interactions are involved, as in poly(acrylic acid)/poly(vinyl pyrrolidone) blends, a clear shift of the carbonyl group absorbance to lower wavenumbers appears [33]. The formation of hydrogen bonds in the present study weakened the strength of the carbonyl bond of PVP in the prepared blends, shifting the carbonyl stretching vibration to a higher frequency.

The HPMC used for the blend preparation is substituted cellulose with different substitutes. Methoxy groups are predominates with a degree of substitution ranging between 1.36 and 1.42. The hydroxy-propyl group is the second but less important side group with a low degree of substitution, between 0.18 and 0.23. This means that almost half of the hydroxyl groups of cellulose are not substituted. These groups, together with the hydroxy-propyl groups, can be involved in hydrogen bonding with the carbonyl groups of PVP (Fig. 4). These interactions are responsible for the observed polymer miscibility.



where R: is H, CH_3 or $CH_2CH(OH)CH_3$
ds=1.36-1.42 for CH3 and ds = 0.18-0.23 for $CH_2CH(OH)CH_3$

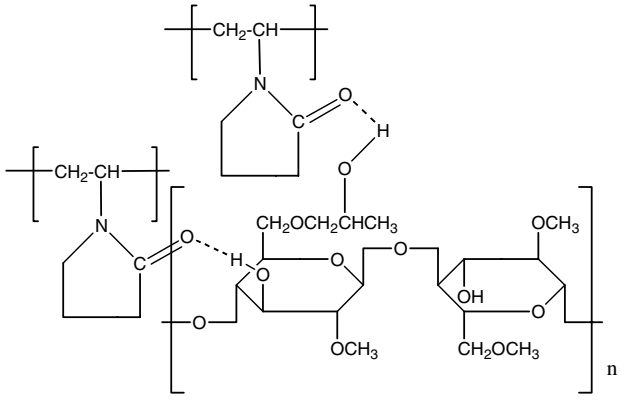


Fig. 4. Hydrogen bonds taking place between the hydroxyl-groups of HPMC and carbonyl groups of PVP.

3.3. Estimation of the mucoadhesive strength of the blends

Most of the hydrophilic polymers have the ability to absorb water and swell. This can increase the ability to adhere onto mucosal surfaces. PVP has a high water solubility that critically limits its application as an effective mucoadhesive polymer, because after hydration, the formed gel starts to disintegrate due to dissolution. This leads to slippery mucilage and loss of the adhesive properties. On the other hand HPMC is a nonionic polymer containing only hydroxyl groups which can form weak hydrogen bonds with mucous layers. Furthermore, due to its slow rate of hydration it can form a strong surface gel that efficiently adheres onto the mucosal surface and remains in contact for a longer time. For this reason it can be characterized as one of the most effective mucoadhesive polymers. However it has a very high T_g (higher than 200 °C), which practically lowers its flexibility and its extensive application as a mucoadhesive polymer. In the present study, miscible blends were prepared between PVP/HPMC in order to create a new matrix with an enhanced mucoadhesion accompanied by the individual properties of each polymer. Mixing with a second polymer can enhance the mucoadhesive properties of a novel polymer. This was observed in the case of PPA prepared with a template polymerisation in the presence of poly(ethylene glycol) or chitosan [34,35]. In the present study, in order to obtain a more reliable estimation of the PVP/HPMC mucoadhesive force, fresh pig intestinal mucosa was used. The stress required to detach the polymer films of the prepared PVP/HPMC blends from the mucous surface is presented in Fig. 5a.

The curves in the graph show that the increase of the applied stress, in perspective with the respective strain increase, is relatively slow. This is due to the fact that initially there is a resistance of the film against its detachment from the intestinal mucosa, forcing the intestine to elongate. Since the intestine is soft, the strain required for its elongation is relatively small. Thus, initially the stress increases slowly, versus the applied strain, taking the highest value when the polymer film is detached from the intestinal mucous surface. After detachment, the polymeric films slip across the mucosal surface and stress is reduced. From these stress–strain curves it can be safely concluded that PVP has the lowest mucoadhesive strength. The curves of the rest of the polymeric films tested show that the strain of the intestine detachment is related to the compositions of the blends and takes the highest values for HPMC concentrations of 50 up to 70 wt%. The adhesive force was determined from the maximum of each curve and the results are presented in Fig. 5b.

PVP has a negligible mucoadhesive force (0.006 N/cm^2) compared to HPMC (0.157 N/cm^2). As the concentration of HPMC increases in the blends, the mucoadhesive force of the PVP/HPMC complex also increases. Similar improvements in duration of the mucoadhesion were observed in HPMC when it was mixed with polymers with weak mucoadhesion, which may promote the wetting of the polymeric disc surfaces [36]. As can be seen in Fig. 5, blends with 50 up to 70 wt% of HPMC show the highest mucoadhesive force (approximately 0.30 N/cm^2), which is double compared to the force of pure HPMC. It can be deduced that blending the two homopolymers, the mucoadhesive behaviour of either pure PVP or pure HPMC is improved. The reason for such an improvement is not well established. Several theories exist and the most dominant is the increase of macromolecular flexibility by decreasing the glass transition temperature of the main mucoadhesive polymer and the quicker wetting of the polymer surface in order to efficiently adhere onto the mucous surface. Furthermore, bioadhesion ability of polymers is affected by several factors including the concentration of polar groups (strong anionic or cationic charged), which are able to form hydrogen bonds with the membrane surface, high molecular weight, polymer surface microstructure and chain flexibility. Thus polymers with higher bioadhesion properties are those containing carboxylic or amine groups, such as poly(acrylic acid) and chitosan interacting with mucin [37,38]. It is believed that the use of drug carriers with adhesive properties, which can interact with gastrointestinal mucosa, could lead to drug delivery systems with higher bioavailability [39]. In the present blends such new reactive groups were not introduced in order to justify such an improvement. Nikolas Peppas just recently extended these theories and proposed another based on the increased matrix flexibility and the insertion of more flexible macromolecules into mucous membrane [40,41]. In our prepared blends this mucoadhesion improvement may be the result of the higher flexibility of the new matrix due to the faster dissolution of the PVP macromolecules and the quicker wetting of HPMC, in order to form faster, or a higher extent, the gel on its surface.

3.4. Release mechanism – profile

As was already found above, the studied blends have satisfying mucoadhesive properties, which is essential in order to be used as an effective tablet coating barriers for the creation of pulsatile formulations. Even blends containing 10–30 wt% HPMC have familiar mucoadhesive strength with that of pure HPMC. The macroscopic observation of the prepared tablets during the dissolution procedure revealed that the coating layer, composed of the polymer complexes, is indeed a swellable and erodible barrier. The swelling of the tablet follows the opposite direction than the compression force. This behaviour could be explained by the fact that the polymer blend tends to recover its initial geometrical characteristics before compression (Fig. 6a).

The release mechanism of FELO from active core follows three different stages:

(a) In the first stage of dissolution, penetration of the dissolution media is achieved in a short time interval (less than 1 h for all the polymer ratios). This can

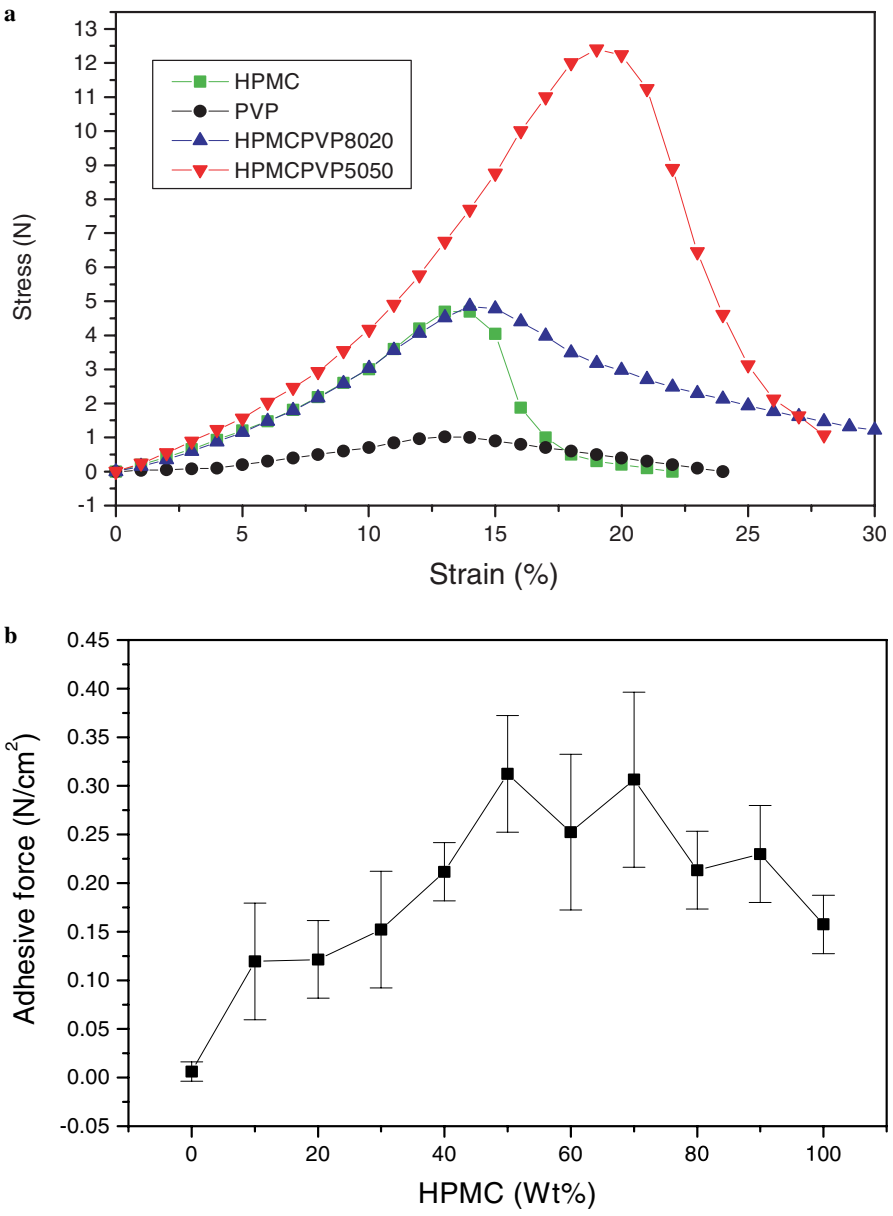


Fig. 5. (a) Variation of the applied stress for the polymer film detachment from the intestinal mucous surface versus the strain of the used sample and (b) effect of the composition on the mucoadhesive force of the prepared blends, measured using an intestinal mucosa.

be easily observed by the change of colour of Indigocarmine, included in the active core which becomes even more darkened after its wetting. Previous studies from other scientific groups have shown that once the solvent penetrates into the interior core, the core tablet dissolves or swells, breaking the outer shell and resulting in rapid drug release [42–44]. Such rapture is not observed in our case although the active core is composed by highly swellable components. This behaviour is due to the high flexibility of the outer layer, as has already been shown in the investigation of the thermal properties, gained from the introduction of PVP. The complexation of PVP with HPMC results in an alteration of the physicochemical characteristics of the latter and the preparation of a new matrix with completely different erosion properties. According to the literature data the delay in the kinetics is strongly influenced by the presence of a gellable or expandable polymeric shell. This type of coating hydrates and gels completely but does not get removed from the surface of the core, acting as a reservoir system and leading to a slow release kinetic through diffusion and relaxation phenomena [45–48]. Our system differs significantly from this behaviour and no release of the drug is observed up to the erosion time of the external barrier. This difference is due to the low solubility of FELO, which does not allow diffusion phenomena to take place during

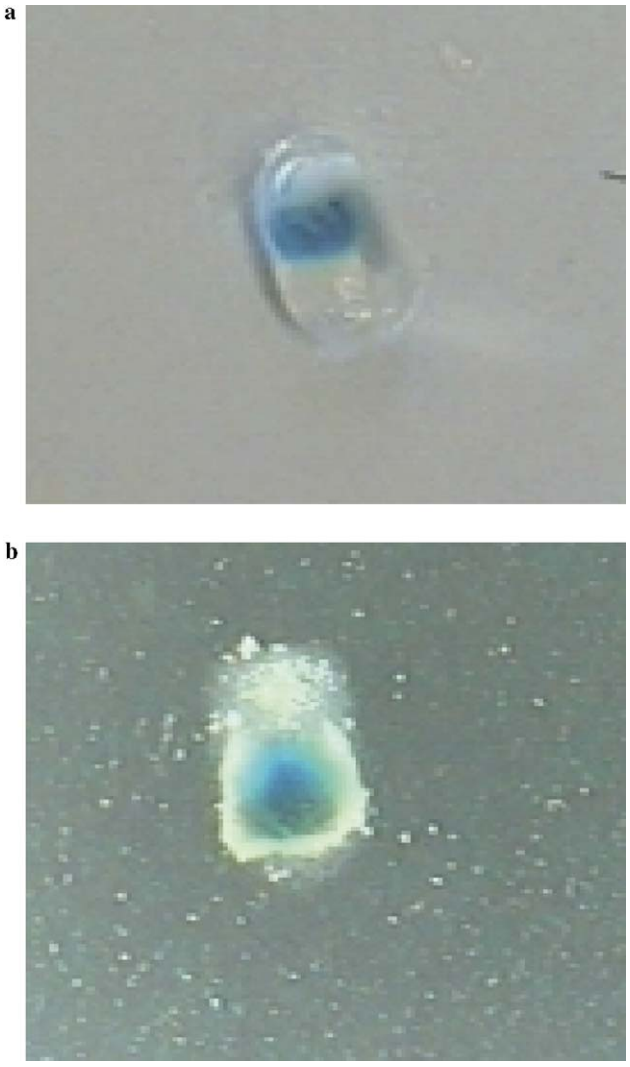


Fig. 6. (a) The swelling of the tablet follows the opposite direction than the compression force while hydration of the active core is achieved readily and (b) The coating layer is ruptured after achieving a critical thickness.

this process. Furthermore, its interaction with PVP carbonyl groups, as was found in our previous study, may contribute to this behaviour [24].

(b) In the second stage of the dissolution procedure, the coating barrier is gradually eroded up to a limited thickness. After that stage a rupture of the shell is observed under the pressure applied by the swelling of the active core (Fig. 6b). According to the device design, the rupture always develops on the sides of the tablet as the initial thickness of the coating layer in these points is lower than on the top and bottom surfaces of the tablet and also, as aforementioned, the swelling is applied at the direction of the top and bottom surfaces of the tablet. All of this process corresponds to a lag time capable of exhibiting a pulsatile release of the drug.

(c) After the delay time, the third stage of dissolution takes place, which corresponds to a rapid release of the drug. Apart from the time lag, the release kinetics of the active core is not significantly influenced by the presence of the erodible barriers, as all the compositions showed similar behaviour, but depends on the core formulation. In FELO/PVP solid dispersions containing 10 wt% of FELO it was found that FELO is dispersed in the form of amorphous nanoparticles in the polymer matrix and except for the substantial bioavailability enhancement, FELO is released almost immediately within 30 min [24]. On the contrary, the delay at the start of the release does not exhibit any dependency upon the active core and is totally influenced by the barrier formulation. As shown in Fig. 7 the delay at the start of the release is increased by increasing the concentration of HPMC in the polymer complex. This behaviour was expected as the solubility of HPMC is lower than the one of PVP and matrices with higher HPMC concentrations have as a result a lower solubility.

The profiles of the prepared tablets showed a repeatable delaying time for the initiation of the drug release (RSD $< 3\%$). This repeatability has to be attributed to the homogeneity of the blends' microenvironment as the two polymers compose only one phase. It has to be pointed out that the compression force of the tablets does not significantly affect the lag time and the release kinetics of the system. Preliminary experiments showed that no significant differences of the release profiles was observed with the application of a compressive force of 500, 1000 and 1500 kP. Normally, the release rate of the drug decreases and the lag time increases by increasing the compression force until a critical point due to the reduction of the porosity [42]. In our case, this does not occur, possibly due to the fast gellation of the blends, while there is a possibility that the common compression force range (500–1500 kP) is over the critical point discussed above.

According to the above, the main critical parameter for the predictability of the systems is the polymer ratio in the blends if the initial thickness of the coating layer remains constant. In order to mathematically express this predictability, the function between the delaying time and the HPMC concentration in the blend was calculated according to the experimental results (Fig. 8). This function is in full correlation (correlation coefficient $R^2 = 0.99$) with the equation

$$t = 0.028C^{1.5}, \tag{4}$$

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

The non-linear pattern is possibly due to the modification of the physicochemical characteristics of the initial pure polymers. Additionally, the critical thickness at which the rupture takes place may differ for the different polymer ratios causing deviations from the linear plot. The above equation could be easily used for the accurate definition of the lag time of the chronotherapeutic formulation.

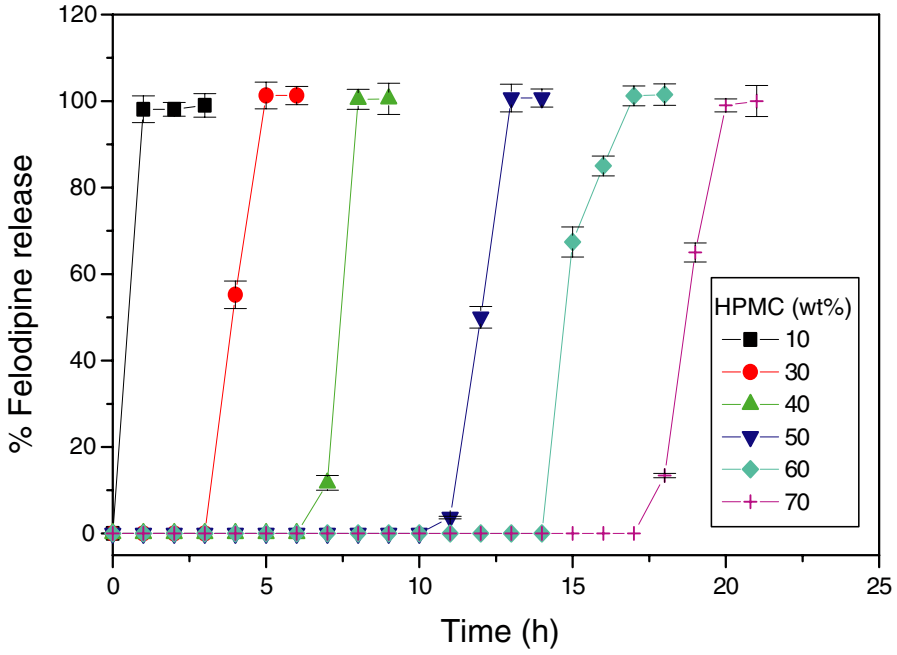


Fig. 7. The release profile of the prepared tablets corresponds to pulsatile kinetics strongly depended on the PVP/HPMC ratio.

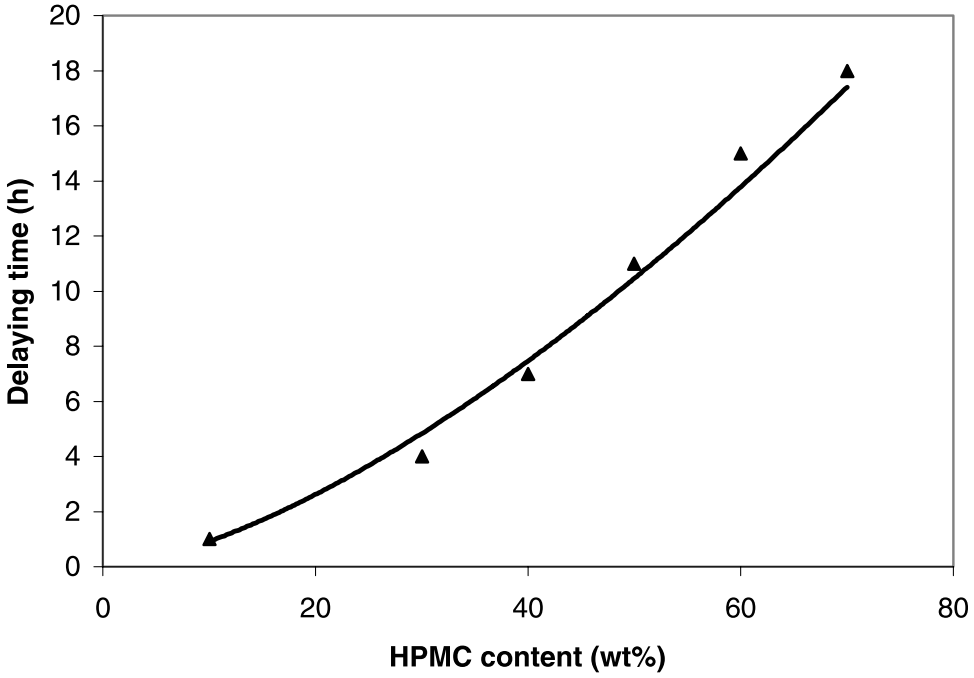


Fig. 8. Delaying time (h) of the systems versus HPMC content (%w/w).

4. Conclusions

From the above study, it was verified that prepared blends between PVP and HPMC are fully miscible over the entire composition range due to the weak interactions taking place between the carbonyl groups of PVP and the hydroxyl groups of HPMC.

The newly prepared materials have different physical properties compared with the initial polymers used for their preparations. The most remarkable alteration is the substantial enhancement of the mucoadhesive force on the intestinal mucosa. This is attributed to the higher flexibility of the prepared blends, compared with HPMC, which is the main mucoadhesive constituent in the blends.

The present PVP/HPMC miscible blends provide an effective and easily prepared system for the creation of a pulsatile chronotherapeutic formulation, consisted of two layered press-coated tablets. The delay time of Felodipine

release, which was used as a drug model, can be decisively adjusted using blends with different HPMC concentrations.

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