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Physicochemical studies on solid dispersions of poorly water-soluble drugs Evaluation of capabilities and limitations of thermal analysis techniques

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Abstract

Polyvinylpyrrolidone (PVP) and poly(ethylene glycol) (PEG) solid dispersions with Felodipine or Hesperetin having up to 20 wt% drug were prepared using solvent evaporation method. Solid dispersions in comparison with their physical mixtures were studied using differential scanning calorimetry (DSC), wide-angle X-ray diffraction (WAXD), scanning electron microscopy (SEM) and hot stage polarizing light microscopy (HSM). PVP formulations with low drug load proved to be amorphous, since no crystalline Felodipine or Hesperetin drugs were detected using DSC and WAXD. Low and fast heating rates were applied for DSC study, to prevent changes in the samples caused during heating. Similarity between results of WAXD and DSC was also found in the case of physical mixtures, where the drug was in the crystalline state. However, though specific tests showed the high sensitivity of the DSC technique, it was difficult to arrive to reliable results for PEG solid dispersions or physical mixtures with low drug content by DSC, even by high heating rates. Crystalline drug could not be detected by DSC, leading to erroneous conclusions about the physical state of the drug, in contrast to WAXD. On the other hand, HSM proved the presence of small drug particles in the solid dispersions with PEG and the dissolution of the drug in the melt of PEG on heating. In such systems, in which a polymer with low melting point is used as drug carrier, DSC is inappropriate technique and must be used always in combination with HSM. The coupling of WAXD with thermal analysis, allowed complete physicochemical characterization and better understanding which is essential for a first prediction of dissolution characteristics of such formulations.

Keywords: Solid dispersions; Polymers; Poorly water-soluble drugs; Thermal analysis; Hot stage microscopy

1. Introduction

Drug development is a very complex, costly and time-consuming process. Amongst the analyzed compounds, only a few will end up in a commercial formulation. Many in-vitro and in-vivo tests are conducted with the potential drugs to evaluate specific parameters like effectiveness, selectivity, pharmacokinetics, optimal dosage, etc. To avoid wasting time with inappropriate drugs and dosage forms, it is very important to begin the clinical phases with formulations fully characterized from the physicochemical point of view [1–6].

Better understanding of the basic properties of drug, excipient and of their interactions is expected by analyzing these compounds alone and mixed in different proportions under different conditions of temperature, humidity and storage time [7]. All these analyses may be performed in a relatively short time and with the minimal amount of active ingredient, using thermal methods coupled with other techniques, such as spectroscopy, X-rays scattering, and microscopy.

The poor solubility of drug substances in water and their low dissolution rate in the aqueous gastro-intestinal fluids often lead to insufficient bioavailability and is one of the most difficult and non-dissolved problems in pharmaceutical technology. It is estimated that more than 35% of the known drugs and more than 25% of the new discovered appear such problems. An increase in the dissolution rate may be achieved by increasing the surface

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area of the drug, which is accessible for the dissolution medium. The most common, and perhaps the oldest approach to improve the bioavailability of such drugs is to enhance their dissolution rate by the formation of a solid dispersion [8,9]. Fine dispersion will increase the available surface so that wetting and dissolution can occur more rapidly. Furthermore, the drug is not in the crystalline form but in most cases in the amorphous state. It is known that such different solid forms of drugs can influence the dissolution, bioavailability, stability and other drug properties. According to Serajuddin [9], the advantage of solid dispersion, compared with capsule and tablet formulations, is that when the carrier is dissolved the drug is released as very fine colloidal particles with size less than 1 μm. Because of the large surface area, the dissolution rate is enhanced while in conventional formulations the dissolution rate is limited by primary particle size, which is higher than 5 μm.

Detailed investigation of the physicochemical nature of solid-dispersions is essential for an understanding of changes within these systems during preparation and storage. These experiments form the prerequisite for an efficient development of solid dispersions with rapid dissolution and good storage stability. However, there is some question about the adequacy of the common techniques and especially thermal analysis to reveal the real physical state morphology in the case of solid dispersions in polymer matrices. It is suspected that the crystallinity of the drug in such a case is significantly underestimated. In our previous studies, the solid dispersions of flavonoids and Felodipine in polymer matrices were prepared and their dissolution enhancement was studied [10–12].

In the present study a series of physical mixtures and solid dispersions of Felodipine (I) and Hesperetin (II) were prepared having low drug content in order to evaluate the application of thermal analysis in such systems. The chemical structures of these drugs are shown in Fig. 1. The particular drugs, have low solubility in water and exhibit low and high melting points, respectively. Each drug was combined with an amorphous polymer like PVP or a semicrystalline polymer like PEG. These polymers are used extensively in pharmaceutical technology as drug carriers and due to their different physical state, they are expected to show completely different behaviour during thermal treatment.

The aim of this work was to explore the physical state of a variety of new solid dispersions of Hesperetin or Felodipine. The specific solid dispersions have low drug content and thus there are increased demands from the methods of characterization, since routine analysis is not adequate to reveal the features of these systems. Also, in this paper a variety of solid dispersions with large differences referring to their physical characteristics (amorphous, crystalline, etc.) and also drug load, are characterized. Since, the systems are formed by combining an amorphous or a low melting temperature crystalline polymeric carrier, with a low or a high melting point drug, they offer the chance to thoroughly study a wide variety of solid dispersions and extract information for the suitability of the thermal analysis techniques, WAXD and SEM in each case. Finally, in this paper the use of high rate DSC that is a new most promising method for pharmaceutics and is anticipated to expand applications of DSC, is explored. Usually, analyses of solid dispersions involve heating by 10 K/min or slower, for DSC scans or HSM observations. The significance of high rate DSC is that fast heating (100 K/min or faster) prevents changes caused during scanning and enhances signal. The latter is significant for the detection of transitions with weak signal or study of low mass samples. Data from the classical slow rate DSC and hot stage microscopy (using slow and fast rates) are also discussed. The survey is extended by the use of WAXD and SEM, in order to better understand the physical structure of the solid dispersions.

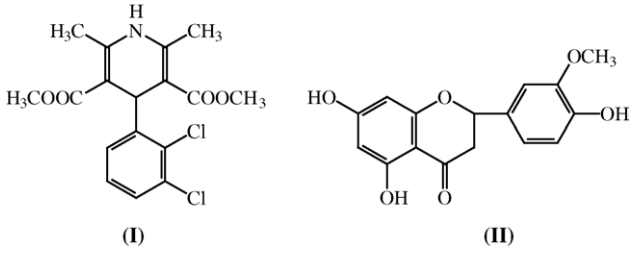


Fig. 1. Chemical structure of Felodipine (I) and Hesperetin (II).

2. Experimental

2.1. Materials

Felodipine (FEL) with an assay of 99.9% was obtained from PCAS (Longjumeau, France). Hesperetin (3′,5,7-trihydroxy-4′-methoxyflavanone), 95%, was supplied from Sigma (St. Louis, MO, USA). Poly(ethylene glycol) 4000 (PEG 4000) was obtained from BDH Chemical Ltd. (Poole, UK). Polyvinylpyrrolidone (PVP) type Kollidon K30 with a molecular weight of 50,000–55,000 was obtained from BASF (Ludwigshafen, Germany). Ethanol absolute was obtained from Merck. All the other materials and reagents were of analytical grade of purity.

2.2. Preparations of solid dispersions and physical mixtures

Solid dispersions of Felodipine and Hesperetin with the two different water-soluble polymers PVP and PEG were prepared using the solvent evaporation method in weight ratios 1/99, 5/95, 10/90 and 20/80 (w/w). For this reason the drug and the carriers were dissolved in proper quantities of absolute ethanol separately to form solutions of the drug 1 wt% or the polymer 5 wt%. Solid dispersion was formed after mixing of the proper volumes of these solutions. After mixing the solutions were ultrasonicated for 20 min and finally let in aluminium plates for 24 h in a gentile stream of air at room temperature for solvent evaporation. The created films were pulverized and stored at 25 °C in desiccator for 1 month before study. Preparation of physical mixtures with the same weight ratios as solid dispersions was performed by mixing the appropriate amounts of the components for 10 min in a mechanical mixer.

2.3. Differential scanning calorimetry

DSC study was performed on a Perkin-Elmer Pyris 1 DSC, equipped with Intracooler 2P cooling accessory. Accurately weight samples (5 mg) were placed in standard aluminium pans and sealed with a lid. Heating rates of 20 or 100 K/min were applied with a nitrogen purge of 20 ml/min. Fast heating rates should be preferred in order to prevent changes and to reveal the original morphology of the samples [14]. Changes during heating scan, like dissolution of the drug in the melt of PEG do not permit direct investigation of the morphology.

2.4. Hot stage microscopy

Microscopic observations of morphological features and changes during heating were carried out using a polarizing optical microscope (Nikon, Optiphot-2) equipped with a Linkam THMS 600 heating stage and a TP 91 control unit. Several heating rates were applied to evaluate influence of temperature and time on the structure of the samples under study.

2.5. Wide-angle X-ray diffractometry

WAXD study was performed over the range 2θ from 5 to 60°, at steps of 0.05° and counting time 5 s, using a Philips PW1710 powder diffractometer, with Cu Kα Nickel-filtered radiation.

2.6. Scanning electron microscopy

The morphology of the prepared solid dispersions as well as the physical mixtures was examined by a scanning electron microscopy system (SEM) Jeol (JMS 840). The films were covered with carbon coating in order to increase conductivity of the electron beam. Operating conditions were accelerating voltage 20 kV, probe current 45nAmp and counting time 60 s.

3. Results and discussion

3.1. PVP solid dispersions

DSC measurements showed that Felodipine drug is a crystalline compound with a melting point of about 145–155 °C, depending on the heating rate. To increase signal and also to prevent phenomena occurring during heating scan, which may alter the original morphology of the samples, especially in solid dispersions, high rate heating scans were also performed. As it is well known, when heating rates are increased though peak onset remains constant, superheating effects cause an increase in melting peak temperature [13,14] or glass transition in amorphous drug compounds [15]. In Fig. 2, the DSC traces of crystalline as well as of amorphous Felodipine, as recorded at a heating rate 100 K/min are shown. In this case, crystalline compound exhibited a melting point of 155 °C while using lower heating rate (20 K/min) the recorded melting point was 144.5 °C. Amorphous Felodipine was obtained by cooling from the melt in the DSC instrument at a nominal rate 250 K/min. At subsequent heating scan, Felodipine showed a glass transition temperature

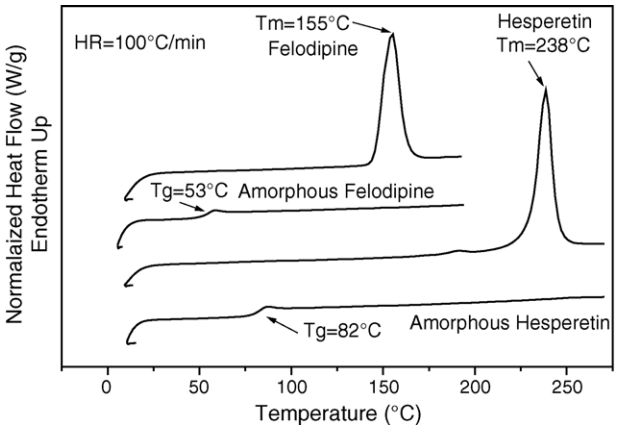


Fig. 2. DSC traces of crystalline and amorphous Felodipine and Hesperetin. Heating rate 100 K/min.

T_g about 53 °C. Also, fast heating scan by 100 K/min did not allow cold-crystallization of the substance. In the same figure, the DSC traces of crystalline and amorphous Hesperetin are also presented. The tests were performed at the same conditions as for Felodipine. Hesperetin exhibited a melting peak temperature 238 °C for scanning by 100 K/min. However, measurement at 20 K/min resulted in a peak temperature 231 °C. Hesperetin, as it is also proved by the absence of any melting peak in the respective trace after the quenching process, can be obtained as purely amorphous. Its glass transition temperature was found to be 82 °C.

As it was described before, a series of solid dispersions of each drug was prepared using PVP or PEG as carrier. The respective physical mixtures with these polymers, having the same drug content were also prepared. Felodipine solid dispersions in PVP showed no melting peak that could be related with melting of the drug crystals. In the DSC traces for Felodipine/PVP solid dispersion for scanning at a usual scanning rate 20 K/min, only the glass transitions of PVP and Felodipine were detected [12]. This is an indication that the prepared solid dispersions are immiscible systems and Felodipine is dispersed into PVP matrix having particle sizes higher than 10 nm. Melting of Felodipine could also not been observed even for fast scanning at 100 K/min. Consequently, it might be supposed that the drug was obtained only in the amorphous state in the solid dispersions in PVP. Such a case can be attributed to the formation of hydrogen bonds between the carbonyl group of PVP and the hydroxyl groups of Felodipine. In the molecular structure of Felodipine there are polar groups, i.e. >C=O, –Cl and mainly >N–H which are able to interact with the functional groups of PVP, like the carbonyl groups, to form hydrogen or Van der Waals bonds [12].

The DSC traces of the physical mixtures of Felodipine and PVP are shown in Fig. 3. In contrast to what was reported for the solid dispersions, in the traces for mixtures with 5 wt% drug content or higher, the melting of Felodipine was easily detected, even though slow heating by 20 K/min was applied, while with heating rate 100 K/min the peaks are more obvious. The observed peak temperature was reduced by reducing drug content. This is because of dissolution taking place by increasing temperature, due to the interactions with the polymeric environment.

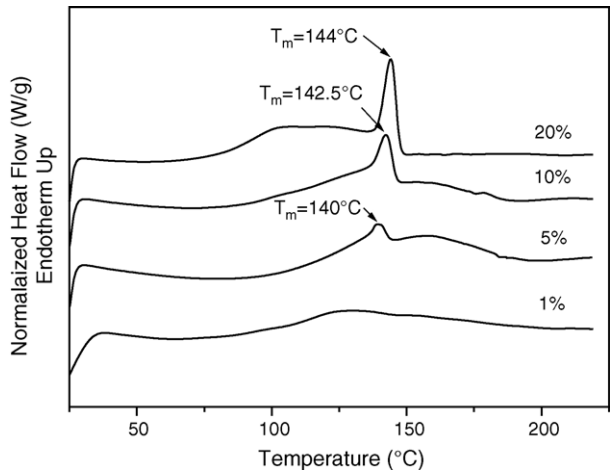


Fig. 3. DSC traces of Felodipine/PVP physical mixtures with different drug content. Heating rate 20 K/min.

However, enhanced dissolution is normally anticipated to occur above the glass transition of the polymer. Since the temperature was lower than the T_g of pure PVP, the observed effect should be also attributed to the moisture of the samples (see continuous endothermic phenomena around or above 100 °C in the traces). Moisture is known to promote drug dispersion in PVP, which is very hydroscopic. The absorbed moisture may increase the free volume and decrease the T_g of PVP. Thus, the macromolecular chain motions begin at lower temperatures promoting drug-polymer interactions. Finally, observations showed clear differences between solid dispersions and physical mixtures.

In order to test the validity of the above assumption and also the resolution capability of the DSC instrument one more task was taken. Physical mixtures of Felodipine with an inert material, namely talc, were prepared having very low drug content, less than 2 wt%. These mixtures were prepared by mixing very low amounts of drug and talc in a pestle. The respective traces (in proper scale) are presented in Fig. 4. Increased mass of physical mixture about 30 mg was used in the DSC pan for testing. As one can see, the DSC scans showed small melting peaks even for such low content of drugs and at the same temperature as in the case of pure Felodipine. Consequently, since DSC is a quite sensitive technique, appropriate to characterize mixtures with very low drug content the initial morphology of the drug in the above solid dispersions and physical mixtures or the interactions with the polymeric carrier are responsible for the disappearance of any sign of crystal melting. These interactions seem to be very effective in physical mixtures containing 1 wt% Felodipine, and its melting point was not possible to be detected.

Though in general DSC can give safe results about the physical state of a polymer/drug mixture and thus has been used extensively to characterize solid dispersions, physical stability and possible drug-excipient interactions [16–23] its accuracy and sensitivity were limited for the characterization of specific systems, compared with other techniques. For example, in naproxen/PVP (30/70, w/w) physical mixtures, the DSC technique could not detect any crystalline structure, while WAXD was able to detect the presence of residual naproxen crystals [24]. So to further investigate the morphology of the Felodipine/PVP solid dispersions the respective WAXD patterns were studied. These patterns showed only two amorphous halos, like those in the diffraction pattern of pure PVP, while the crystalline reflections of Felodipine could not be observed (Fig. 5). Thus, it is proved that PVP macromolecules inhibited the drug crystallization in the solid dispersions. This finding is in agreement with

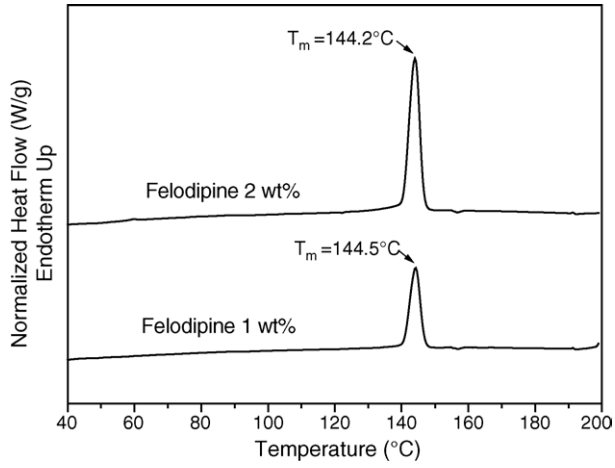


Fig. 4. DSC traces for Felodpine-talc mixtures containing 1 and 2 wt% of drug.

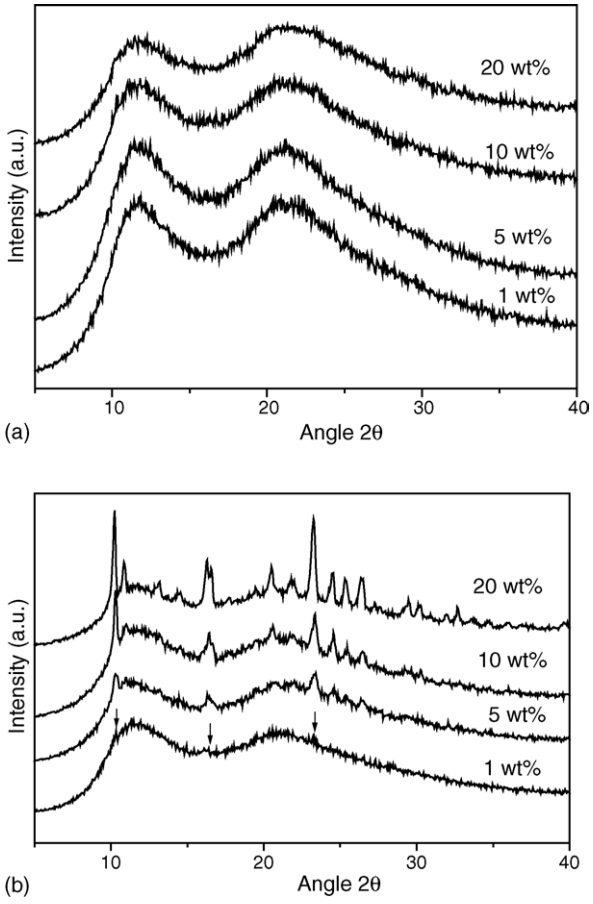


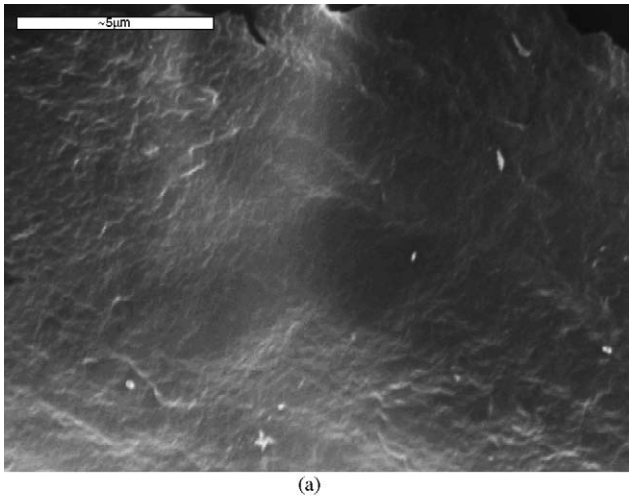
Fig. 5. WAXD patterns of: (a) solid dispersions of Felodipine in PVP with different drug content; and (b) physical mixtures of Felodipine in PVP with different drug content.

DSC results, showing no melting of crystalline material. On the other hand, in the patterns for the corresponding physical mixtures the peaks of crystalline Felodipine could be observed for a Felodipine content of 5 wt% or higher, in accordance to the observation of drug melting in the DSC traces. In the case of the mixture containing 1 wt% Felodipine very small peaks of drug reflections were recorded, in fact comparable to the usual noise (Fig. 5b).

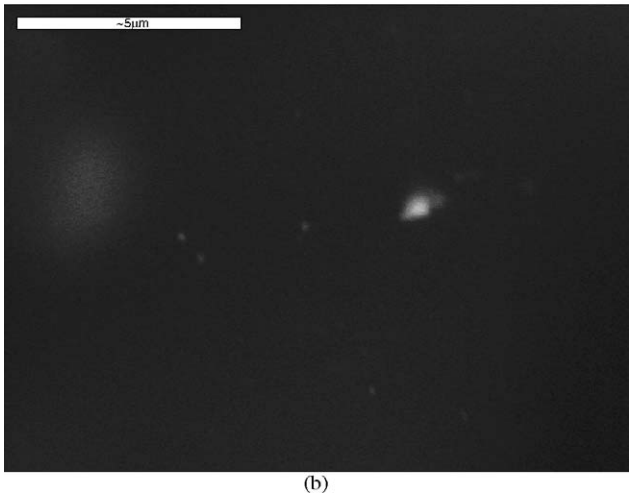
Consequently, it was found that data taken from both techniques in the case of solid dispersions, as well as in the case of physical mixtures are in good agreement. PVP/Felodipine solid dispersions are completely amorphous while in physical mixtures crystalline Felodipine can be detected. The sensitivity of DSC proved to be comparable and maybe even better than that of WAXD, since even limited crystalline amounts can be detected, though the conditions of the experiments are so different. DSC tests involve by their nature, dynamic conditions, in contrast to standard WAXD experiments, which are carried out at room temperature. The interactions that take place at increased temperatures between PVP and Felodipine during a heating scan, especially in the presence of water traces may cause changes in the sample under investigation. Such interactions, not pre-existing at room temperature, were also found to play an important role in similar physical mixtures at increased temperatures [25]. Application of high-rate DSC will possibly extent the use of DSC.

DSC, as well as WAXD, examines the macroscopic characteristics of materials. Thus, microscopic study with SEM was also performed. Though SEM cannot be used for crystallinity estimations, it allows the study of the geometry of the particles and their dispersion in the polymer matrix. SEM microphotographs revealed the presence of drug particles dispersed in the polymer matrix. However, it was clear in the photographs that the dimensions of the drug particles were much smaller in the solid dispersions, maybe even in nanosizes (Fig. 6). These observations show that the above findings from DSC and WAXD study are reasonable. Pure Felodipine was in the form of large cubic crystals with sizes up to 100 μm. The average particle size was 20–30 μm. In contrast in the solid dispersions only Felodipine particles with sizes not exceeding 200–300 nm were observed. Even, in the case that the drug was not in the amorphous phase, as WAXD revealed, such a fine dispersion would be a goal. It is expected to reflect in improved dissolution of the drug from the solid dispersions into aqueous media. Actually, in a previous study it was found that the dissolution reached 100% for solid dispersions with 10 and 20% (w/w) Felodipine at almost 30–40 min, due to the particle size reduction and the amorphous state at which the drug was kept in the dispersions [12]. Also, SEM showed that in solid dispersions the particle size increased with drug content, but in all cases the size was less than 300 nm.

As was referred before, Felodipine has melting point lower than the T_g of PVP. In order to evaluate the efficiency of DSC to characterize drug formulations based on high melting temperature drugs, Hesperetin was used. Hespertin has a melting point about 70 °C higher than the glass transition of PVP. Like Felodipine, the melting peak of crystalline Hesperetin, was not detected in DSC traces in its solid dispersions in PVP by using slow



(a)



(b)

Fig. 6. SEM microphotographs of Felodipine/PVP solid dispersions: (a) 10/90 (w/w); and (b) 20/80 (w/w).

(20 K/min) or fast heating (100 K/min) rates (Fig. 7). Also, neither in the WAXD patterns crystalline drug was evidenced. Peaks corresponding to reflections of crystalline Hesperetin could not be detected for any of the solid dispersions, but the shape of the amorphous halos in the patterns altered with increasing drug content. This change in the shape should be attributed to the increased content of amorphous drug. Besides, SEM micrographs showed that in the case of solid dispersions of Hesperetin in PVP, the drug was in fine dispersion and only particles of nanodimensions could be observed (data not shown), as was also found for the dispersions of Felodipine in PVP. So, PVP develops effective interactions with the particular drug, which has three hydroxyl groups in its molecule, and these results in reducing the dimensions of the drug particles [12].

In the DSC traces for the respective physical mixtures even for 20 K/min heating rate, melting of Hesperetin could be observed for drug content as low as 5 wt% at temperatures close to that for the pure Hesperetin (Fig. 8). However, in these traces which were recorded at usual (20 K/min) and not high scanning rates, there was a peak broadening and in the mixture containing 5 wt% Felodipine its melting point is hard detectable. Finally, the heat

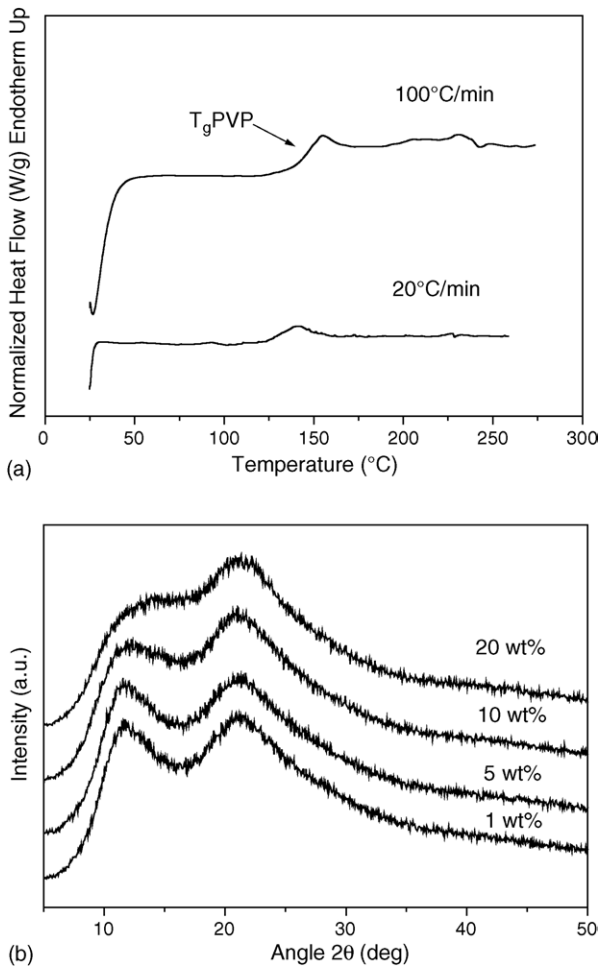


Fig. 7. (a) DSC traces of Hesperetin/PVP 20/80 (w/w) solid dispersion at different heating rates; and (b) WAXD patterns of Hesperetin/PVP solid dispersions with different drug content.

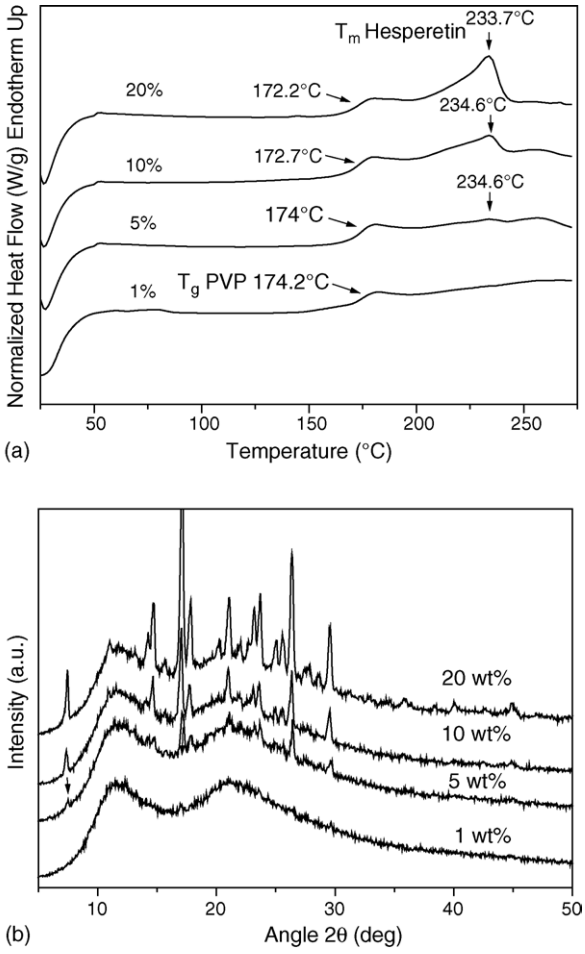


Fig. 8. (a) DSC traces obtained at heating by 20 K/min; and (b) WAXD patterns of physical mixtures of Hesperetin in PVP with different drug content.

of fusion was lower than the anticipated. As was reported before, PVP always absorbs very easily significant amounts of water and this facilitates appearance of drug-polymer interactions. However, in these mixtures interactions may be favoured by macromolecular motions since Hesperetin melts at temperature almost 70 °C above the T_g of PVP and not by moisture. These interactions induce dissolution of the drug and this may affect drastically its melting. Furthermore, unlike for solid dispersions, crystalline reflections were obvious in the WAXD patterns of the physical mixtures, containing up to or more than 5 wt% Hesperetin (Fig. 8). Even for the physical mixture containing 1 wt% drug, a very small peak appeared in the position where the strong reflection for Hesperetin was anticipated, at about $2\theta = 16.92^\circ$, showing that even at such low amounts crystalline material can be possibly detected by WAXD. The other feature, which should be pointed out, is that the shape of the amorphous halos did not change with the addition of crystalline drug. This confirms that the change in the shape of the halos in the solid dispersion patterns was due to the presence of amorphous drug. From the above, it is concluded that DSC may lead to erroneous conclusions in the case that the pharmaceutical compound has higher melting point than the T_g of PVP. In all mixtures, a portion of the amount of the drug dissolved in the polymer matrix during heating. This is easy to observe especially in the case in which the drug content was lower than 5 wt%.

3.2. PEG solid dispersions

PVP is an amorphous polymer, which is extensively used for the preparation of solid dispersions. Another polymer, which is also used as drug carrier, is PEG. This is semicrystalline and exhibits a very low melting point, so it can be used to prepare solid dispersions by the melt method [26,27]. The latter offers the advantage of the large-scale production comparing to the solution method. Besides, due to its low melting point, PEG, after its melting, dissolves drugs before reaching their own melting temperatures and which may be much higher. Furthermore, some drugs decompose after their melting and dissolving in PEG melt could be a way to avoid decomposition. Consequently, it is of special interest to study solid dispersions in PEG in comparison to those in PVP.

First, the thermal behavior of the solid dispersions of Felodipine or Hesperetin in PEG was studied. The main feature was that sign of drug melting was not detected in the DSC traces even for high scanning rates. Since PEG has a low melting temperature, it

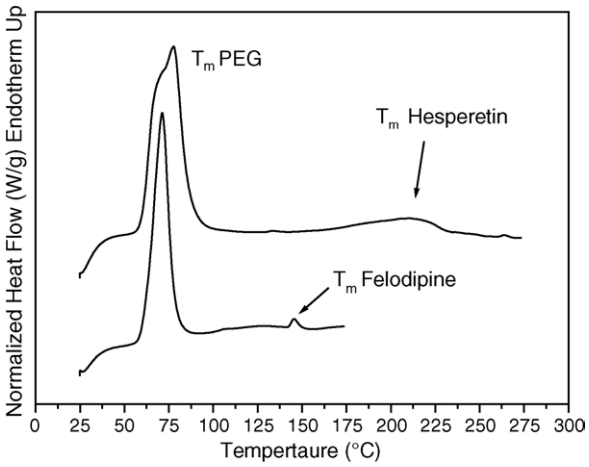


Fig. 9. DSC traces of Felodipine/PEG 50/50 and Hesperetin/PEG 50/50 physical mixtures. Heating rate 100 K/min.

is expected the drugs to dissolve in PEG melt during heating, as has already been mentioned. However, this was the case not only for the solid dispersions, but also for the physical mixtures of the specific drugs. Only for high drug content, its melting peak was observed, as one can see in Fig. 9. In this figure, the DSC traces of physical mixtures of PEG, containing 50 wt% Hesperetin (upper curve) or Felodipine (lower curve) are shown. But, even in these mixtures, the peak corresponding to drug melting is very small indicating that the highest drug amount was dissolved in the melt and only limiting crystalline particles were remained. Furthermore, these peaks were not recorded by using slower heating rates (20 K/min). Similar data were also reported in the case of PEG/carbamazepine physical mixture where melting point of carbamazepine could be detected only when the drug load was higher than 50 wt% [28]. Though for solid dispersions one could suppose that the drug was in the amorphous state, and/or effective drug particle size reduction has been achieved, the thermal behaviour of the physical mixtures could only be attributed to dissolution of the drug in the polymer melt. Consequently, the appearance or not of drug melting peak in the DSC traces, has rather to do with the solubility of the specific drug in the melt of PEG, which is usually significant at temperatures exceeding 60 °C.

The above assumption was tested with WAXD and SEM and the observations will be discussed in the following text. In the WAXD patterns of Fig. 10a for the solid dispersions of Felodipine, peaks corresponding to drug crystals appeared when the dug content exceeded 10 wt%. This finding could be in disagreement with the respective DSC scans, since no melting of crystalline drug was detected in the latter. But, in fact, this has only to do with measurement conditions. WAXD reveals the physical state of the drug at room temperature while DSC during heating. Furthermore, for all solid dispersions the WAXD patterns showed no changes in spacing values of both components, and thus there was no indication for substantial interactions evolved between the functional groups of PEG and Felodipine. After all, WAXD showed that in solid dispersions where the solubility of Felodipine in PEG at room temperature was exceeded (supersaturation), the excess of the drug could crystallize. This was the case when Felodipine content was higher than 10 wt%. Solubility of the drug is obviously much lower at room temperature (at which WAXD measurements were performed), and when also PEG is solid, than at temperatures above 60 °C (like during the DSC experiments), where also PEG is in the liquid state. In general, it is also known that solid solutions of a drug in polymeric carriers turn to solid suspensions with increasing drug content. This explains the similarities between the behavior of most solid dispersions and physical mixtures of Felodipine.

In the WAXD patterns of the physical mixtures, the reflections of Felodipine crystals could be observed in the patterns for lower content, i.e. 5 wt% (Fig. 10b). This is in complete disagreement with DSC measurements where in particular mixtures no melting of Felodipine was detected and maybe this behaviour is a limiting factor that restricts the use DSC technique in such carriers having low melting point. In this case, by increasing the temperature, the polymer starts to melt and dissolves the drug crystals. PEG has a low melting point with a result to melt at low temperatures before that of encountered drugs, so most of the used drugs can dissolve in the melt before reaching their melting points [29,30]. For this reason DSC must be used in combination with WAXD technique, which seems to be more accurate and

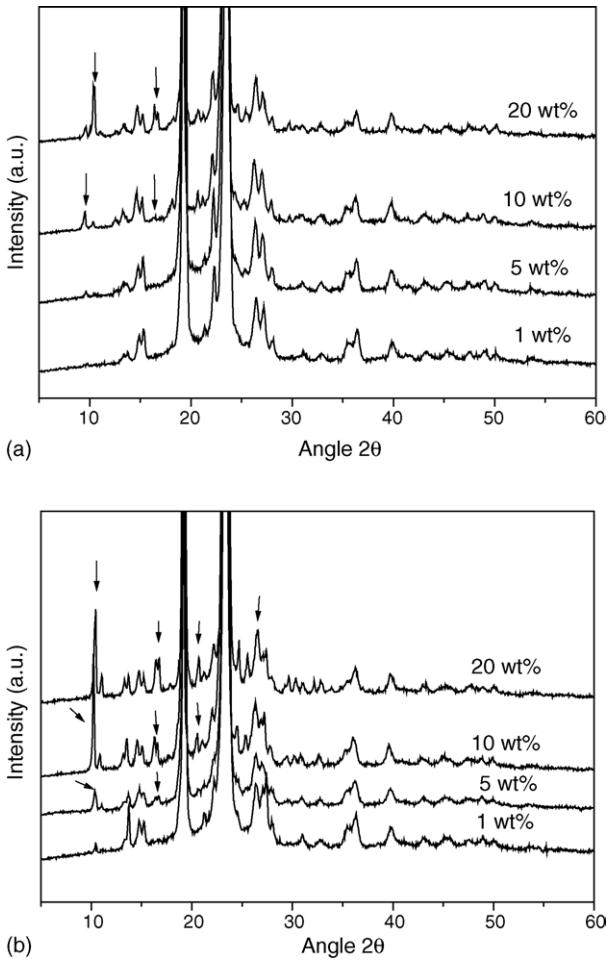


Fig. 10. WAXD patterns of: (a) solid dispersions of Felodipine in PEG with different drug content; and (b) physical mixtures of Felodipine and PEG with different drug content. Arrows indicate drug crystalline reflections.

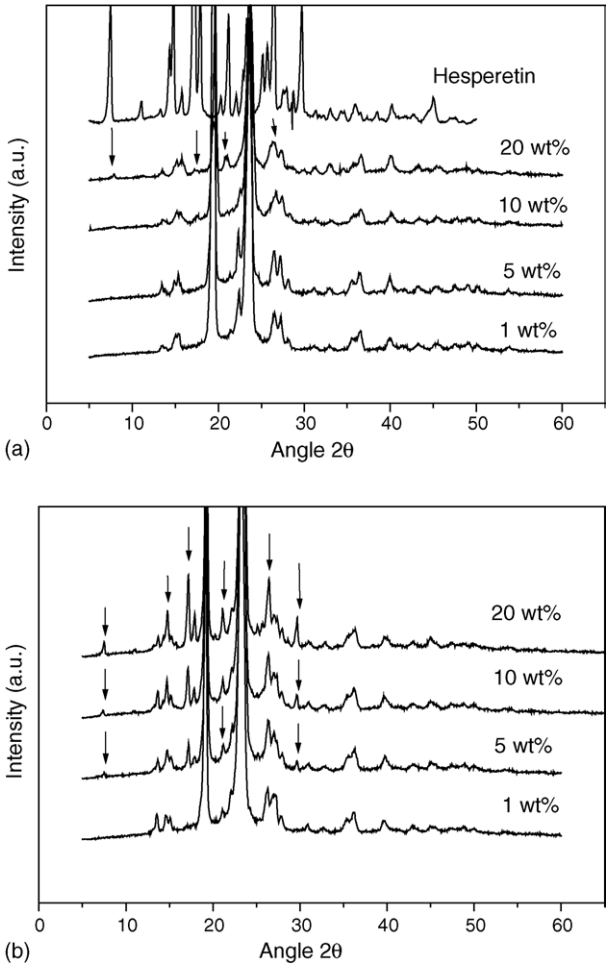


Fig. 11. WAXD patterns for (a) solid dispersions of Hesperetin in PEG with different drug content; and (b) physical mixtures of Hesperetin and PEG with different drug content. Arrows indicate drug crystalline reflections.

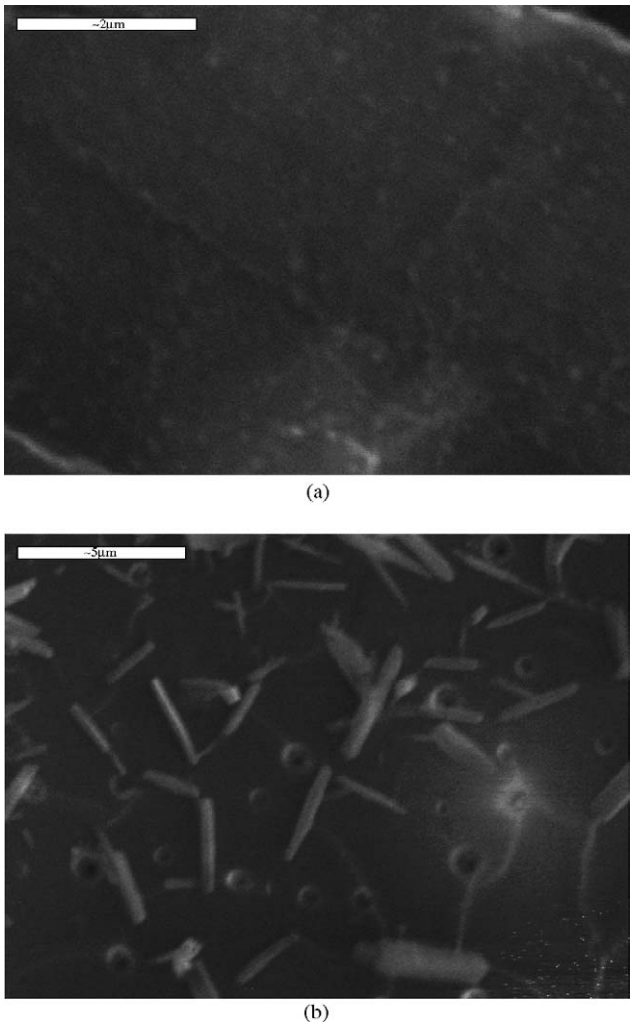


Fig. 12. SEM microphotographs of Felodipine/PEG solid dispersions: (a) Felodipine/PEG 5/95 (w/w); and (b) 10/90 (w/w).

sensitive to study the crystalline state of the compounds when drug carriers with low melting point are used.

Similar behaviour has also been detected in PEG/Hesperetin samples. WAXD study of Hesperetin's solid dispersions in PEG showed that crystalline drug was present only in dispersions containing at least 20 wt% drugs. In the physical mixtures drug crystalline reflections were easily detected for much lower drug content (5 wt%) as one can see in Fig. 11b. So, it was proved that for solid dispersions where PVP was used as carrier, since there was no melting of the polymer during the scan, DSC could reveal the real morphology when high heating rates were applied. Thus, DSC and WAXD findings were in agreement. On the other hand, when PEG was the excipient, during a DSC scan fusion of the polymer occurred and the drug was dissolved in that melt. Thus, the DSC traces could not give information about the morphology of the solid dispersions or even the physical mixtures. In contrast, even in this case WAXD patterns could reveal the morphology and detect the presence of crystalline drug directly.

Fig. 12 shows SEM micrographs of solid dispersions of Felodipine in PEG. As one can see for 5% Felodipine content small particles could be observed, with a size less than 200 nm. In the microphotograph of the solid dispersion containing 10 wt% Felodipine, thin needles with a length of about 5 μm and thickness less than 500 nm were clearly detected. Such large particles were also observed in higher concentrations. Thus, PEG did not promote as effectively as PVP did, a fine dispersion of Felodipine down to a nanoscale. PEG is a crystallizing polymer in contrast to PVP. It was proved that the crystallization of PEG did not facilitate miscibility with pharmaceutical substances.

To visualize the changes in the samples of physical mixtures with PEG, during heating, hot stage optical microscopy (HSM) was used. This technique is complementary to DSC and may help the interpretation of DSC results. In the photographs of Fig. 13, the morphology of a Felodipine/PEG physical mixture is shown before heating (left) and after heating to 90 °C at a rate 60 K/min (right picture). Magnification was ×100 in these photos. By increasing the temperature PEG began to melt and above 65 °C its melting was complete. As one can see Felodipine particles were dispersed in that melt and subsequently dissolved with rising temperature. During heating, drug particle size was steadily reduced showing its dissolution in PEG melt. The two materials were miscible in the molten state providing a uniform liquid. Felodipine, in this physical mixture with 20 wt% drug,

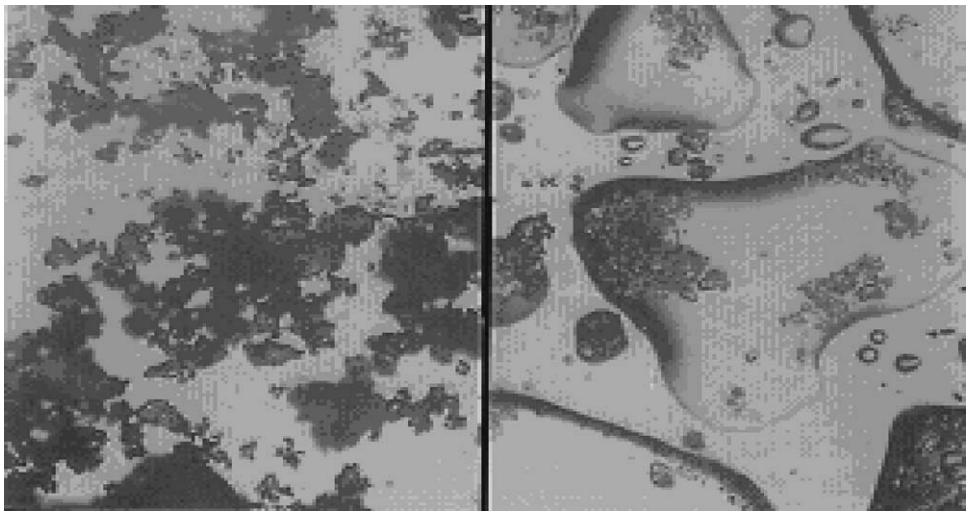


Fig. 13. HSM photographs of Felodipine/PEG 20/80 (w/w) physical mixture at 50 °C (left) and after heating to 90 °C (right) by 60 K/min.

was completely dissolved in the melt of PEG close to 120 °C, a temperature which is at about 20–25 °C lower than the melting point of pure Felodipine. This finding can explain the absence of any melting sign in DSC thermograms when low heating rates were used, since Felodipine had already been completely dissolved in PEG melt before reaching its usual melting temperature. Only in the case that a high drug content (e.g. 50 wt%), and also fast heating rate 100 K/min was used, Felodipine crystals could be detected till the melting temperature. This was in accordance with the observation of a small endothermic peak in the respective DSC trace.

A similar behaviour was observed also for physical mixtures containing Hesperetin. Also, the temperature at which the drug was completely dissolved increased with increasing its content in physical mixtures, and finally approximated the melting temperature of the drug. This has to do with the solubility of the drug in the polymer melt. Large amounts cannot dissolve at low temperatures due to limited solubility. Since solubility increases with temperature dissolution may be possible at increased temperatures. Furthermore, for a given drug content the temperature for complete dissolution increased with increasing heating rate. Slow heating rates means larger times for dissolution of the drug.

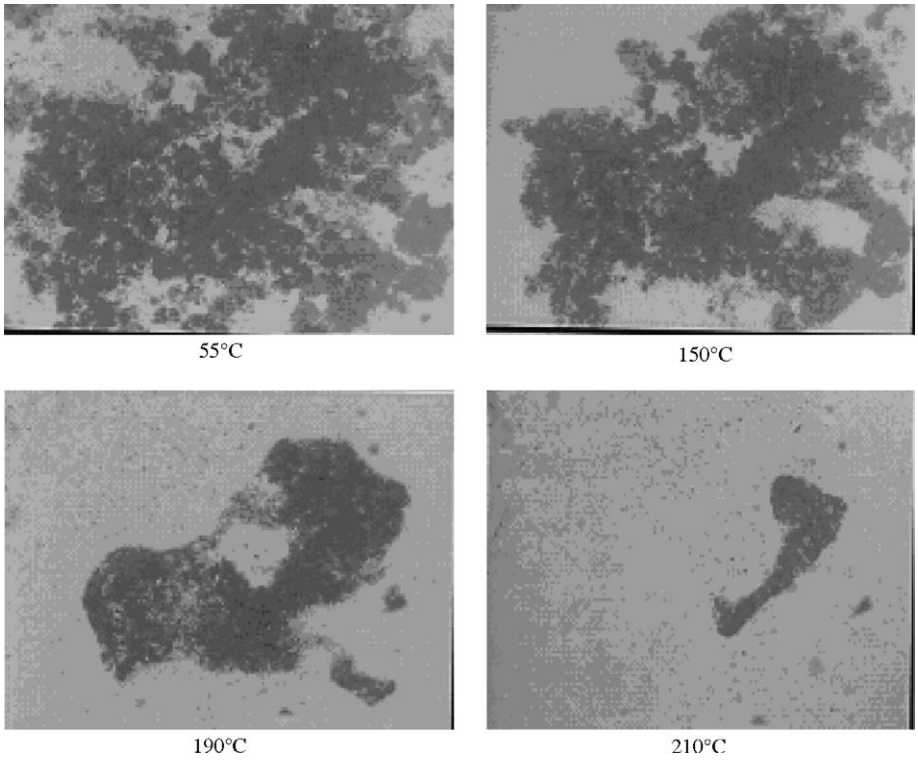


Fig. 14. HSM photographs presenting Hesperetin particles in Hesperetin/PEG 20/80 (w/w) solid dispersion. Photos were taken at 55, 150, 190 and 210 °C, respectively.

Fig. 14 shows the changes in morphology of Hesperetin/PEG 20/80 solid dispersion during heating from 55 to 150, 190, and finally 210 °C by 60 K/min (magnification was ×100). To take these photos the sample was first heated to 65 °C to melt PEG for obtaining a thin film. Then it was quickly cooled to 55 °C, before final heating. PEG was in the melt state at the temperatures at which the photos were taken. Thus, only the Hesperetin particles and their aggregates could be observed. These photographs evidenced (a) that Hesperetin particles could be observed in the dispersions and (b) that the drug was progressively dissolved before reaching its melting temperature. Also, smaller particles were observed for the dispersions comparing to physical mixtures with the same drug content, and the complete dissolution of the drug, for given heating rate, occurred at lower temperatures for the dispersions.

4. Conclusions

Polyvinylpyrrolidone (PVP) and poly(ethylene glycol) (PEG) solid dispersions with Felodipine or Hesperetin with low drug load, up to 20 wt% drug were prepared using the solvent evaporation method. Felodipine, in contrast to Hesperetin, exhibits a melting temperature lower than the glass transition of PVP. Also, both drugs melt above the melting temperature of PEG. These combinations offered the opportunity to analyse the physicochemical characteristics of a variety of solid dispersions in comparison to the respective physical mixtures and evaluate the efficacy of the techniques of characterization in each specific case.

The above formulations were studied using differential scanning calorimetry (DSC), wide-angle X-ray diffractometry (WAXD), scanning electron microscopy and hot stage polarizing light microscopy. For solid dispersions in PVP, with low drug content, melting of crystalline drug was not detected by DSC. Also, crystalline reflections of the drug could not be recorded in WAXD patterns. This however has not to do with the resolution of the techniques. In contrast the drug could be effectively detected even at very low concentrations (1% or lower) in its mixtures with inert carriers like talc. Also, melting was observed for the physical mixtures with PVP, despite the fact that some dissolution effects took place at temperatures close or above the glass transition of the polymer, especially in the case of Hesperetin, that is the high melting point drug. Complementary investigations with microscopic techniques (SEM) showed fine dispersion of the drug in the polymer matrix since only drug nanoparticles were observed. Thus, the drug could not be detected because attractive interactions of its molecules with the carrier ones resulted in fine dispersion of the drug. Furthermore, in such a case the dissolution rates were enhanced.

In the case of dispersions in PEG as well as the physical mixtures, DSC, though fast rates were used, could not detect the presence of crystalline drug. This was not because the drug was amorphous, but because of the increased solubility of the drugs in the liquid PEG at elevated temperatures. In contrast, crystalline reflections of the drugs were observed in WAXD patterns, obtained at room temperature. For the specific formulations, hot stage microscopy proved to be appropriate, and like SEM, showed that small drug particles were dispersed in the PEG matrix. These reduced size particles could easily dissolve in the polymer melt at heating, and complete dissolution of the drug was achieved at temperatures lower than those for the respective physical mixtures, because of the smaller particle size and lower crystallinity.

Physicochemical characterization can be used for valid preliminary study of solid dispersions. However, proper combination of thermal analysis with X-ray scattering and microscopic techniques is recommended for better understanding.

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