Dissolution Enhancement of Flavonoids by Solid Dispersion in PVP and PEG Matrixes: A Comparative Study

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ABSTRACT: Polyvinylpyrrolidone (PVP) and poly(ethylene glycol) (PEG) solid dispersion systems with flavanone glycosides, naringin and hesperidin, and their aglycones, naringenin and hesperetin, were prepared, using solvent evaporation method, to enhance their dissolution rates that may affect their bioavailability. Drug release of both flavanone glycosides and their aglycones was directly affected by the physical state of solid dispersions. Powder-XRD technique in combination with scanning and transmission electron microscopy revealed that PVP polymer formed amorphous nanodispersion systems with flavanone aglycones, while such systems could not be formed with their glycosides, which are bulkier molecules. Fourier transform infrared spectra suggest the presence of hydrogen bonds between PVP carbonyl groups and hydroxyl groups of both flavanone aglycones. These interactions prevent the crystallization of naringenin and hesperetin aglycones in PVP matrix. On the other hand, the ability of PEG carrier to form hydrogen bonds with flavanone glycosides or aglycones was limited, and as a result both flavanone glycosides and their aglycones remain in the crystalline form. For this reason, the solubility enhancement of PEG solid dispersions was lower than when PVP was used as drug carrier. At pH 6.8, the % release of naringenin and hesperetin from PVP/naringenin–hesperetin (80/20 w/w) solid dispersion was 100% while in PEG solid dispersions, it was not higher than 60–70%. © 2006 Wiley Periodicals, Inc. J Appl Polym Sci 102: 460–471, 2006

Key words: flavonoids; naringin; hesperidin; hesperetin; naringenin; PVP; PEG; solid dispersions; enhanced dissolution

INTRODUCTION

Flavonoids are a group of naturally occurring polyphenolic compounds that are ubiquitous in all vascular plants and are widely used in the human diet.[1] They are usually present almost exclusively in the form of β-glycosides, and they can be divided on the basis of their molecular structure into four main groups, flavones, flavonols, flavanones, and isoflavones.[2] Naringenin and hesperetin, the aglycones of the flavanone glucosides naringin and hesperidin (Scheme 1), occur naturally in citrus fruits.[3] They exert a variety of pharmacological effects such as antioxidant,[4,5] blood lipid-lowering,[6,7] anti-inflammatory activity through inhibition of the enzymes involved in arachidonate metabolism,[8,9] anticarcinogenic,[10] and inhibit selected cytochrome P-450 enzymes resulting in drug interactions.[11] The physicochemical properties of naringin, hesperidin, and their aglycones, naringenin and hesperetin, indicate that their crystalline phases are poorly soluble in water and show a slow dissolution rate from solid oral forms, restricting their use in therapy. The above properties indicate that the dissolution of either glycosides or their aglycones might be the most critical factor or the rate-limiting step in their bioavailability than the passage through intestinal barrier.

For such insoluble drugs, various methods could be used to enhance their solubility, including micronization,[12] formation of amorphous coprecipitates,[13] or preparation of inclusion complexes using materials such as cyclodextrins.[14] Grinding is also used extensively in pharmaceutical technology to reduce the particle size and some times to produce amorphous drugs. However, it is very difficult to reduce the primary particle size to less than 1 μm, which is critical, to achieve the desired dissolution enhancement. One of the most common approaches to improve the bioavailability of such drugs is to enhance their dissolution rate by the formation of solid dispersions.[15,16] In these formulations, drug is dispersed in fine particles into a polymer matrix, thus increasing the available surface, so that wetting and dissolution can occur more rapidly. Furthermore, in most cases, the drug is

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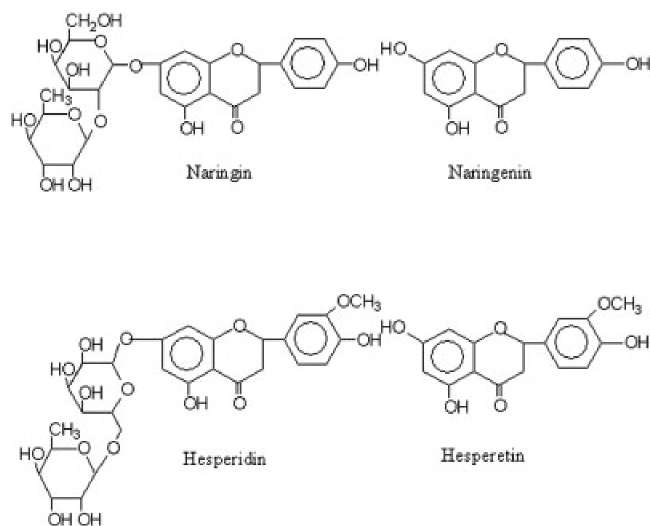


Scheme 1 Molecular structures of flavanone glycosides, naringin and hesperidin, and their aglycones, naringenin and hesperetin.

not in the crystalline but in the amorphous form. From previous studies, it is well established that such different solid forms of drugs can influence the dissolution as well as the stability of the drug.[15,17] Two reviews were cited about solid dispersion systems, concerning methods of preparations, physicochemical properties, mechanism of drug release and dissolution, problems associated with scale up production, and the future prospects of such formulations.[15,17] The advantage of solid dispersion, compared with capsule or 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 the primary particle size, which is higher than 5 μm.[15]

In the present study, flavanone aglycones, naringenin and hesperetin, and their glycosides, naringin and hesperidin, which are poorly water-soluble drugs, were treated with water-soluble carriers, polyvinylpyrrolidone (PVP) and PEG, to improve their dissolution rate. PEG and PVP polymers are the most used drug carriers for solid dispersion preparations,[18–22] owing to their strong hydrophilic properties and their capability to form molecular adducts with many compounds. Furthermore, aims of the present work were also to characterize precisely these systems, and finally to check the effect of particle size distribution on their dissolution profile.

MATERIALS AND METHODS

Materials

Hesperidin (3′,5,7-trihydroxy-4′-methoxyflavanone 7-rhamnoglycoside), 97%, was purchased from Acros Organics (New Jersey), naringin (4′,5,7-trihydroxyflavanone 7-rhamnoglycoside), 97%, naringenin (4′-5,7-trihydroxyflavanone), 95%, and hesperetin (3′,5,7-trihydroxy-4′-methoxyflavanone), 95%, were supplied from Sigma (St. Louis, MO). PVP type Kollidon K30, with a molecular weight of 50.000 g/mol, was supplied by BASF (Ludwigshafen, Germany); poly(ethylene glycol) 4000 (PEG 4000) was obtained from BDH Chemical (Poole, UK), with an average number molecular weight 3470 g/mol. Acetic acid and absolute ethanol used were supplied by Merck. All the other materials and solvents that were used for the analytical methods were of analytical grade.

Preparation of solid dispersions

Solid dispersion systems were prepared using the solvent evaporation method for both flavanone glycosides and their aglycones in two different solvent systems. Acetic acid was used for glycosides and absolute ethanol for their aglycones. As carriers for solid dispersions, two different water-soluble polymers were used, PVP and PEG.

Solid dispersion systems of 80/20, 70/30, 60/40, and 50/50 w/w of PVP/(naringin–hesperidin) and PEG/(naringin–hesperidin) were prepared by dissolving the carrier and drug compounds in proper quantities of acetic acid. Naringin was dissolved completely at room temperature, after 15 min ultrasonication, while hesperidin was dissolved completely only after heating in a mixture of acetic acid/water (80/20 v/v), until boiling, for 20 min with continuous ultrasonication. Acetic acid was used because glycosides are insoluble in other solvents like acetone and especially in alcohol. After this step, the solutions were mixed and subsequently sonicated for 10 min. The solvent was fully evaporated under vacuum by rotary evaporator at 70°C for 30 min because acetic acid is more difficult to be removed at room temperature than is ethanol, and then the created films were pulverized and sieved up to a particle size of 150–200 μm with a laboratory pulverizer (IKA, model A11 basic) and stored in desiccators until studying. Naringin–hesperidin and their aglycones were in equal ratios in all prepared dispersions. For example, in the solid dispersion of PVP/(naringin–hesperidin) 80/20 w/w, naringin and hesperidin were 10 wt % each.

In the same way, solid dispersion systems of 80/20, 70/30, 60/40, and 50/50 w/w of PVP and PEG /(naringenin–hesperetin) were prepared by dissolving the carrier and drug compounds in proper quantities of absolute ethanol at room temperature. The solutions were mixed, were subsequently ultrasonicated for 20 min, and then were let in aluminum plates for 24 h in a gentile stream of air, at room temperature, until the solvent was fully evaporated. The created glassy films

were pulverized and studied. All solid dispersions were sieved and the 50–250 mesh was used.

Characterization of solid dispersions

X-ray

X-ray diffraction (XRD) analysis was performed on solid dispersion powders, scanned over the 2θ from 5 to 50°, at steps of 0.05 ° and counting time 5 s, using a Philips PW1710 diffractometer, with Bragg–Brentano geometry (θ, 2θ) and Ni-filtered CuK_α radiation.

Ft infrared spectroscopy

Fourier transform infrared (FTIR) spectra were obtained using a Perkin–Elmer FTIR spectrometer model Spectrum 1000. To collect the spectra, a small amount of each material was used (1% weight) by compression in KBr tablets. The IR spectra, in absorbance mode, were obtained in the spectral region 550–4000 cm^{-1} using resolution 4 cm^{-1} and 64 coadded scans.

Scanning electron microscopy

The morphology of the prepared solid dispersions as well as the initial materials was examined in a scanning electron microscopy (SEM) type Jeol (JMS-840). The films were covered with a carbon coating to have good conductivity of the electron beam. Operating conditions were as follows: accelerating voltage 20 KV, probe current 45 nA, and counting time 60 s.

Transmission electron microscopy

Electron diffraction and transmission electron microscopy (TEM) investigations were made on ultrathin film samples prepared by ultramicrotome deposited on copper grids. TEM micrographs were obtained using JEOL 120 CX microscope operating at 120 kV. The specimens were stained with OsO_4 before thin sections were microtomed for TEM.

Release profile

A modified dissolution apparatus Pharma Test PT-DT7, with a stationary disk at 100 rpm and 1000 mL capacity, was used. Samples of solid dispersions equivalent to 180 mg content of each glycoside, naringin and hesperidin, and their aglycones, embedded into hard gelatin capsules were placed in each vessel and were maintained at 37 ± 0.5°C. Phosphate buffers containing 2% Tween 20, pH 7.5 and 6.8 to resemble the physiological pH of intestine and human colon, respectively, were used, while aqueous hydrochloric acid solution, pH 1.2, was used to resemble the physiological pH of stomach.

The disintegration time of the capsules was 5 min. The samples were analyzed according to the RP HPLC methods developed by Kanaze et al.[3,23] Aliquots of 100 μL were withdrawn through 0.2 μm filter at appropriate times, and equal volumes of fresh dissolution medium were replaced. The analyses were performed in triplicate using an HPLC system (Varian, Palo Alto, CA) consisting of two high-pressure solvent delivery pumps (Model 2510), a static high-pressure mixer (Model 2584), a variable wavelength UV–Vis detector (Model 2550), a manual injector with a 20-μL loop (Rheodyne, Cotati, CA), and an integrator (Model 4290). Separation was performed on a Macherey Nagel Nucleosil C8 analytical column (5 μm particle size, 250 × 4.6 mm I.D.), proceeded by a guard column (20 × 4.6 mm I.D.) dry packed with pellicular ODS material (37–53 μm).

The mobile phase for the determination of naringin and hesperidin and their aglycones, naringenin and hesperetin, was tetrahydrofuran/water/acetic acid (21:77:2 v/v/v) at 280 nm, and (43:55:2 v/v/v) at 288 nm, respectively. The flow rate of the mobile phase was 1 mL/min and the column temperature was 45°C.

RESULTS AND DISCUSSION

In the case where PEG was used as carrier with flavonoid drugs, it was observed that all created films were sticky and not transparent; this might be due to the low melting point of PEG and the immiscibility between the components, respectively. However, this was not the case when PVP was used as a carrier with flavanone aglycones. The prepared films were very clear and transparent, indicating compatibility between PVP and the used compounds at all ratios. Comparing the prepared PVP and PEG solid dispersions, it was observed that PVP created glassy films after their complete drying, which are easily collected; on the other hand, PEG solid dispersion films were difficult to handle, owing to their sticky nature. All the prepared solid dispersion systems were characterized precisely by several techniques, to check their physical state (crystalline or amorphous) before the dissolution studies.

X-ray difractometry

From our previous study, it was found that XRD, owing to its high sensitivity, is probably the most appropriate method for the study of the physical state of such systems.[24] Figure 1 presents the XRD patterns of naringin, hesperedin (glycosides) and naringenin, hesperetin (aglycones). All compounds are crystalline with several characteristic diffraction peaks. These peaks can be used to verify if the above compounds

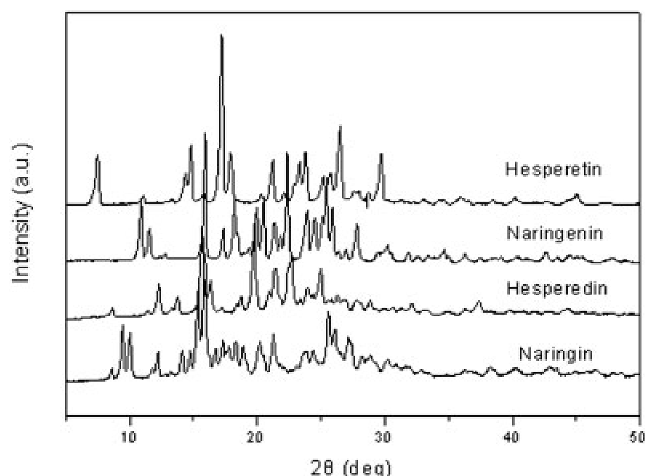


Figure 1 XRD patterns of flavanone glycosides, naringin, hesperedin, and their aglycones, naringenin and hesperetin, crystals.

were present in crystalline form into the prepared solid dispersions.

XRD diffraction patterns of PVP/flavanone glycosides [Fig. 2(a)] revealed that naringin and hesperedin were partially crystalline in solid dispersions, since several diffraction peaks were recorded at the same angles (2θ) compared with that of the pure compounds. The most characteristic peaks are at $2\theta = 19.7$, 21.4, and 22.6°, which are attributed to hesperedin, while $2\theta = 15.9°$is attributed to naringin. On other hand, XRD patterns of PVP/flavanone aglycones [Fig. 2(b)] showed only two broad peaks that correspond to the diffraction pattern of pure PVP. The XRD patterns of these solid dispersions show typical profiles of amorphous material. Peaks that correspond to aglycones completely disappeared, suggesting that the PVP matrix inhibited the crystallization of both aglycones. Furthermore, the position and the magnitude of the PVP broad peaks were shifted compared with that of pure PVP, indicating that the morphology of PVP particles changed, and this in turn showed the existence of some interactions between PVP and aglycone compounds. Comparing the different physical state of flavanone glycosides with their respective aglycones in PVP solid dispersions, it is realized that the first are bulky molecules crystallizing easily in solid dispersions. This finding is in accordance with DSC data[25] and it might be due to the difficulty in hydrogen bond formation.

The same behavior was also noticed in PEG/glycosides solid dispersions, for which characteristic diffraction peaks corresponding to naringenin and hesperetin were recorded beside to those of PEG [Fig. 3(a)]. However, rather unexpectedly, characteristic peaks corresponding to aglycone drugs are also present in PEG/aglycones dispersions. This was in contrast to what was observed for the same compounds in the PVP solid dispersions. Low intensity peaks corresponding to both aglycones were observed, suggesting that they partially existed in the crystalline form. However, for the solid dispersion PEG/naringenin–hesperetin, 80/20 w/w, only peaks that correspond to PEG were observed, while those of naringenin and hesperetin were absent [Fig. 3(b)]. This is evident because in the particular solid dispersion, both aglycones might be in the amorphous state.

FT-IR spectroscopy

FTIR analyses in the present study were carried out to investigate the interactions between carriers and flavanone glycosides or their aglycones in solid dispersion systems. This is very important, since it is believed that the extent of interactions between drug and carriers, in solid dispersion systems, has the greatest effect for taking the drug fully amorphous or reducing its particle size. FTIR spectroscopy has been successfully used for exploring the differences in molecular conformations, crystal packing, and hydrogen bond

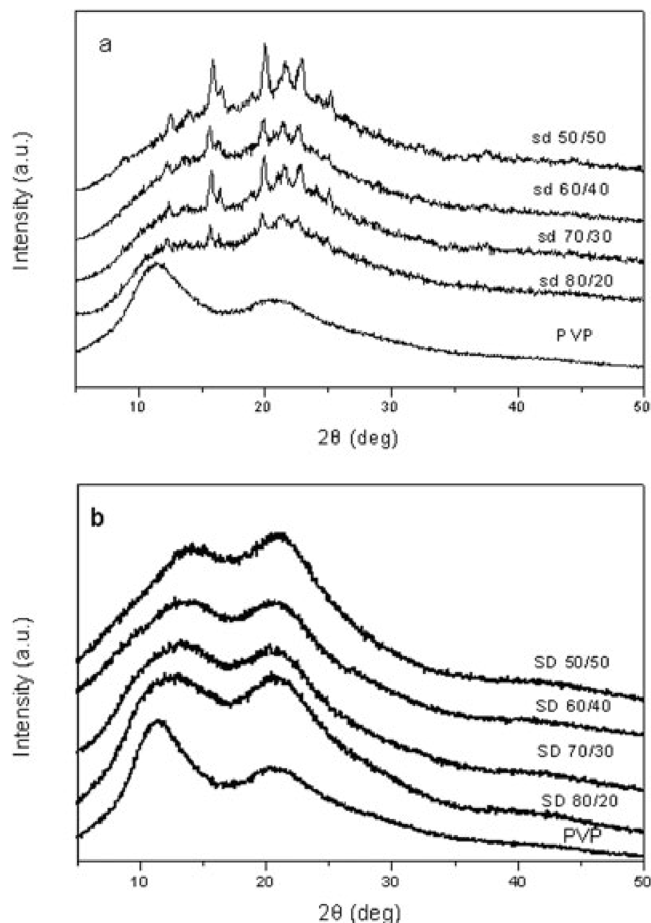


Figure 2 XRD patterns of PVP solid dispersion systems with (a) flavanone glycosides, naringin and hesperidin, and (b) their aglycones, naringenin and hesperetin.

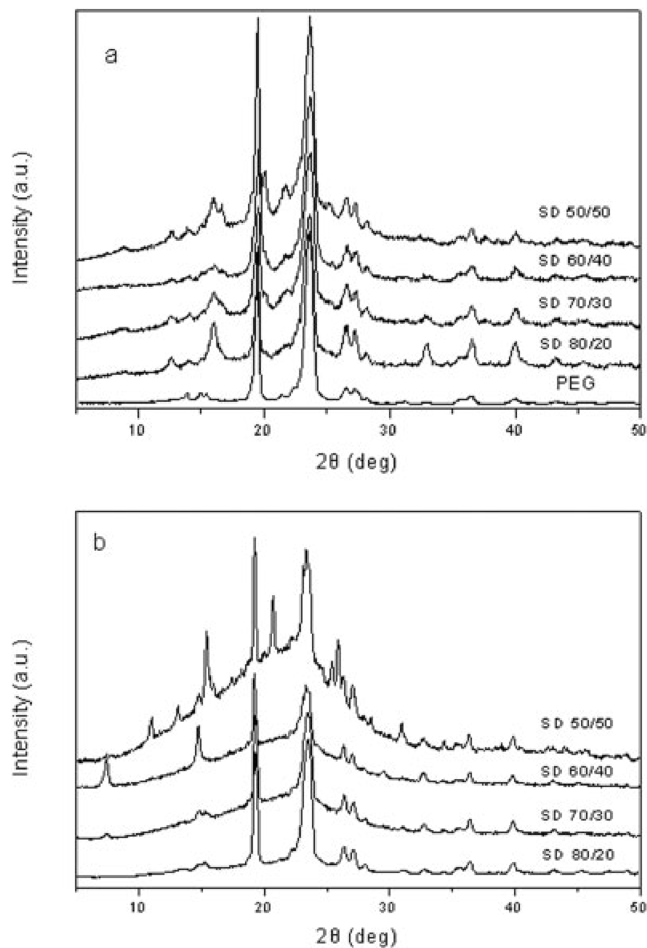


Figure 3 XRD patterns of PEG solid dispersion systems with (a) flavanone glycosides, naringin and hesperidin, and (b) their aglycones, naringenin and hesperetin.

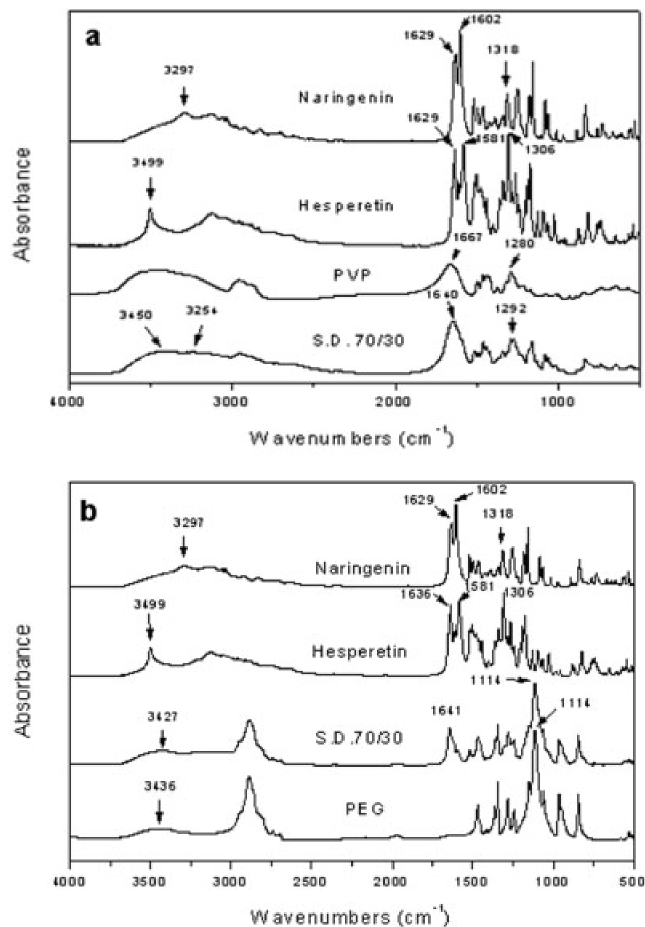
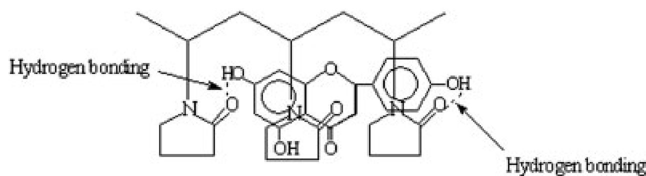
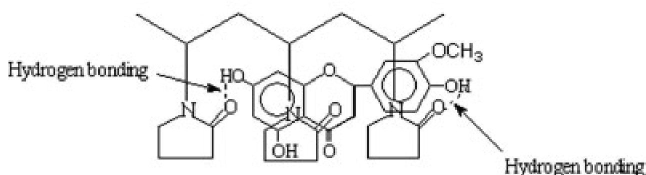


Figure 4 (a) FTIR spectra of pure naringenin, hesperetin, PVP, and their solid dispersion PVP/naringenin–hesperetin (70:30 w/w) and (b) FTIR spectra of pure naringenin, hesperetin, PEG, and their solid dispersion PEG/naringenin–hesperetin (50:50 w/w).

arrangement for different solid-state forms of organic compounds.[26]

The FTIR spectra of pure PVP, naringenin and hesperetin, and their solid dispersion PVP/naringenin–hesperetin (70/30 w/w) are shown in Figure 4(a). PVP has stretching band in the carbonyl frequency region at 1667 cm^{-1}, which is attributed to the stretching of >C=O group, and at 1280 cm^{-1}, which is attributed to the >*N*—C group. In their solid dispersion systems, characteristic peaks of both flavanone aglycones and PVP were observed. However, in all cases, there were shifts of carbonyl band to a lower wavelength at 1630–1640 cm^{-1}, which suggest that there was a physicochemical interaction between PVP and the two aglycones. To confirm this, hydroxyl group absorbances of naringenin and hesperetin were studied, since only these groups were capable of forming hydrogen bonds with carbonyl group of PVP. The stretching bands of phenolic hydroxyl groups of these aglycones were recorded at 3297 and 3499 cm^{-1}, respectively. In the prepared solid dispersions, these peaks are shifted to 3254 and at 3450 cm^{-1}, respectively. Also, similar





Scheme 2 The possible hydrogen bond formation between the hydroxyl groups (—OH) of both aglycones with carbonyl groups of PVP (>C=O).

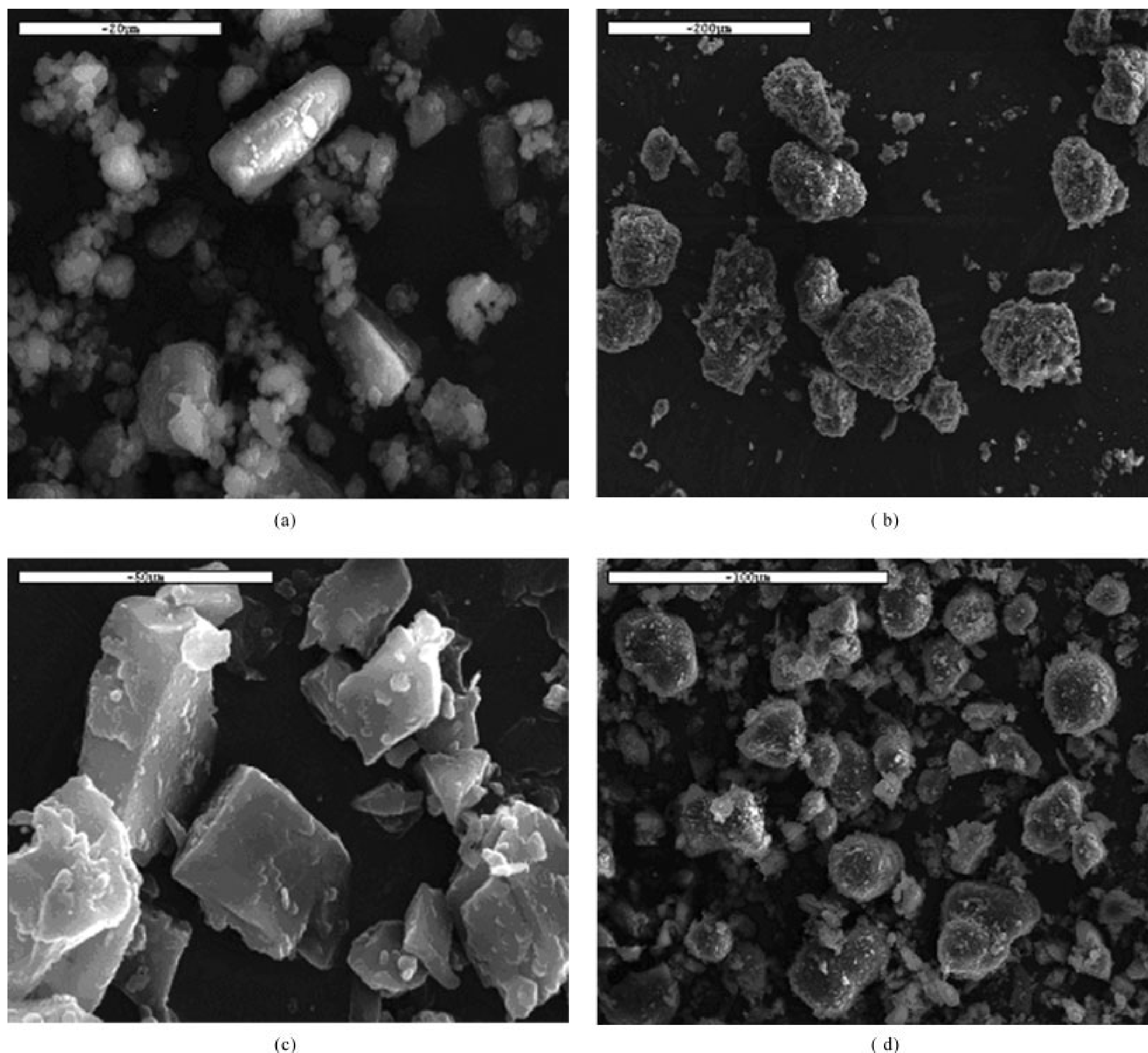


Figure 5 SEM micrographs of (a) naringin, (b) hesperidin, (c) naringenin, and (d) hesperetin particles.

shifts to lower wavelengths occurred in the bending region bands of these phenolic hydroxyl groups. Pure compounds have strong peaks at 1318 and 1306 cm^{-1}, respectively. In all solid dispersion systems, these two bands merged into one peak, with a maximum at 1292 cm^{-1}. These shifts in FTIR spectra in comparison with the recorded shift of PVP carbonyl group confirm the ability of hydrogen bond formation between the hydroxyl groups of both flavanone aglycones with carbonyl groups (>C═O) of PVP (Scheme 2). Similar reports suggested hydrogen bond formation between PVP polymer with other drugs.[27,28] The extent of interactions between drugs and polymers in such dispersions systems seems to play the most important role for the drug to be fully amorphous. These bonds enhance miscibility between PVP and aglycones, inhibiting them to form crystals and keeping them in molecular dispersion into the PVP matrix. However, in the case of PVP solid dispersions with glycosides, such extensive interactions were not observed and this might be the reason that these compounds remained in the crystalline state as was proved by XRD.

Similar interactions of PEG with flavanone aglycones were found, but in lower extent than that of PVP. Comparing the FTIR spectra of pure PEG, naringenin, hesperetin with their solid dispersion [Fig. 4(b)], it could be said that the solid dispersion exhibited some differences and shifts in the corresponding wavelengths, especially in the stretching band of hydroxyl groups (3250–3700 cm^{-1}). PEG had a broad peak with a maximum absorbance at 3436 cm^{-1}, while in the solid dispersion this peak was shifted to 3427

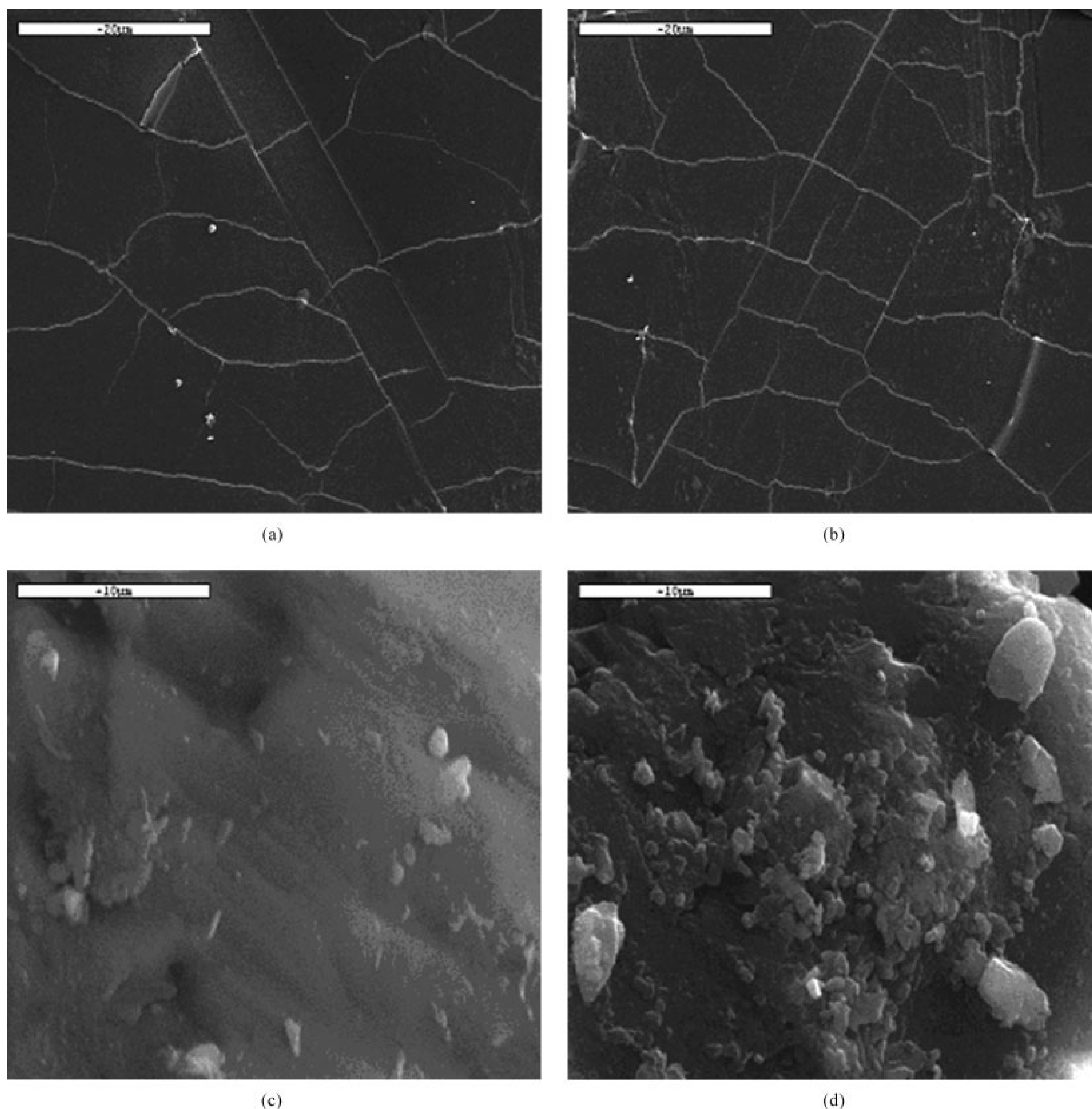


Figure 6 SEM micrographs of PVP-naringenin/hesperetin solid dispersion films at different ratios (a) 80/20 and (b) 50/50 w/w.

cm^{-1}, but this was not a considerable change. Explanation for this behavior could be the strong ability of PEG to form self-associated hydrogen bonds (PEG–PEG bonds). Thus, high energy must be supplied to break the PEG–PEG bonds first and then to form new ones with groups such as the carbonyl or phenolic hydroxyl of the flavanone aglycones.

Sem and tem study

SEM is a technique that can provide information about the crystal shape and particle size of pure compounds, as well as their morphology in the solid dispersions. Figure 5 shows the morphology of naringin, hesperidin, naringenin, and hesperetin. Naringin particle sizes ranged from 2 to 20 μm, while hesperidin has large particles with a wide particle size distribution (20–160 μm). Naringenin appears as small, smooth crystals of three-dimensional parallelogram ranging from 10 to 60 μm. Hesperetin appears as spherical particles with a wide size distribution ranging from 5 to 40 μm.

Examining solid dispersion films of PVP/naringenin–hesperetin, smooth surfaces were observed and

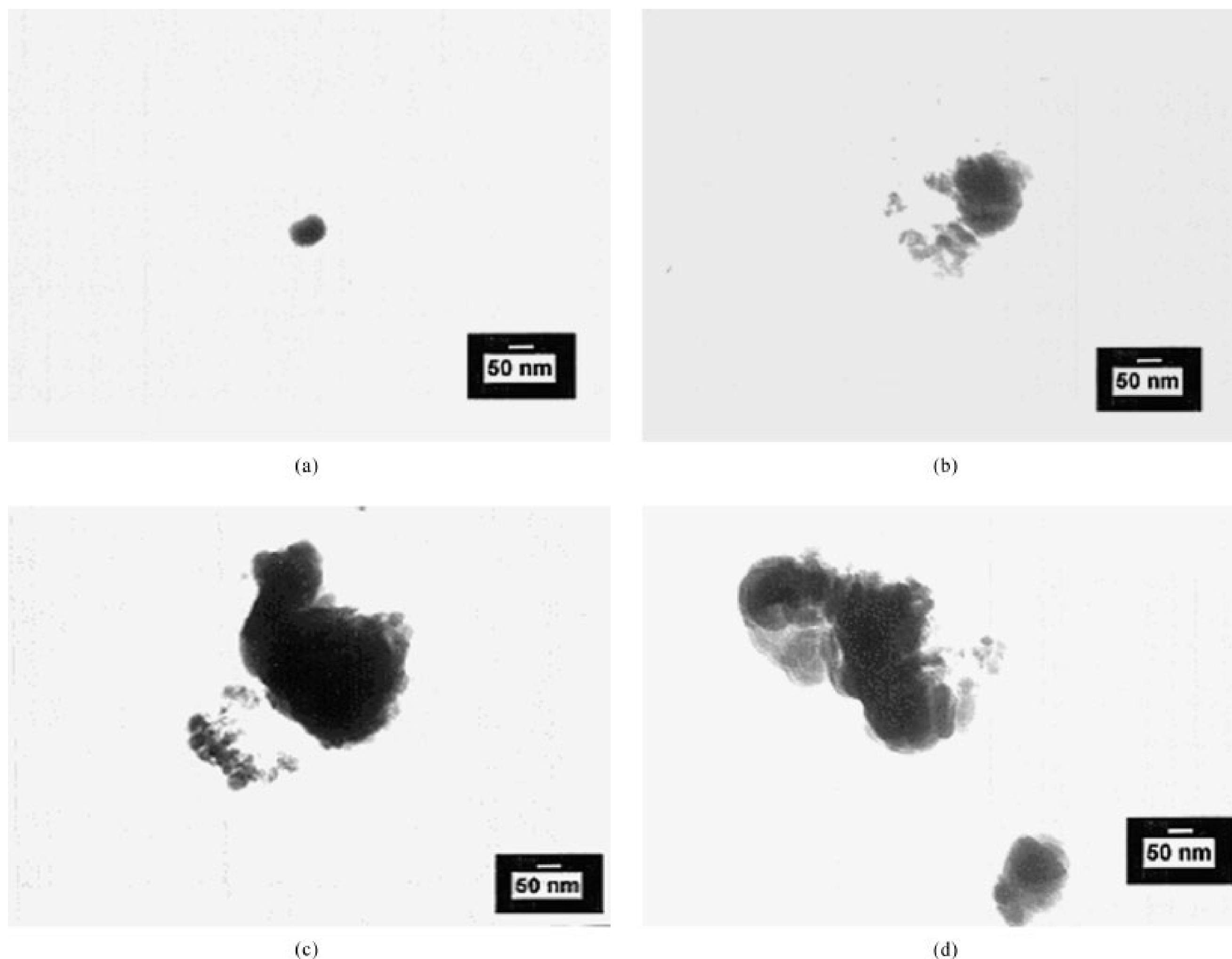


Figure 7 TEM micrographs of PVP-naringenin/hesperetin solid dispersion ultrathin films at different ratios: (a) 80/20 (b) 70/30, (c) 60/40, and (d) 50/50 w/w.

original crystals of narngenin or hesperetin could not be detected, indicating miscibility between the two components (Fig. 6). On the contrary, on the film surfaces of PVP/naringin–hesperedin solid dispersions, crystals of aglycone compounds are detected, which is in good agreement with XRD data. Drugs in amorphous dispersions, as in our case, may exist in two forms, molecularly dispersed, which is more desired, or nanodispersed, with particle sizes less than 1 μm. These forms are difficult to be characterized by SEM, which seems to be inappropriate technique. For this purpose, TEM was also used.

It is observed from micrographs (Fig. 7) that aglycone compounds could be differentiated into PVP matrix, which appeared as black spots. Sizes of these particles were strongly affected by aglycone load into the PVP matrix. Particle sizes, in the solid dispersion of PVP/naringenin–hesperetin (80/20 w/w), were close to 50–60 nm. By increasing the aglycone load in solid dispersions, particle sizes became progressively larger; they ranged from 200 to 300 nm, 600 to 700 nm, and 1 μm in solid dispersions containing 30, 40, and 50 wt % of both aglycones, respectively. Similar nanodispersions were also observed with TEM in Felodipine, which is also a poorly water-soluble drug, dispersed into a PVP matrix and it is believed that this technique can adequately characterize such nanodispersions.[29] From this study, it was realized that aglycone flavonoids are nanodispersed into PVP matrix and this is the main reason for the substantial enhancement of dissolution rate that will be discussed in the following text.

In the case of PEG solid dispersion systems (Fig. 8), film surfaces were different form those of PVP, since irregularities dominated. However, even at such surfaces, it was possible to distinguish aglycone crystals of average particle size ranging from 1 to 15 μm, depending on their weight percent in the dispersions. This is in agreement with XRD results, revealing that aglycones in PEG matrix remained in the crystalline form. It was also noticed in SEM micrographs of PEG solid dispersions that crystal sizes of aglycones were

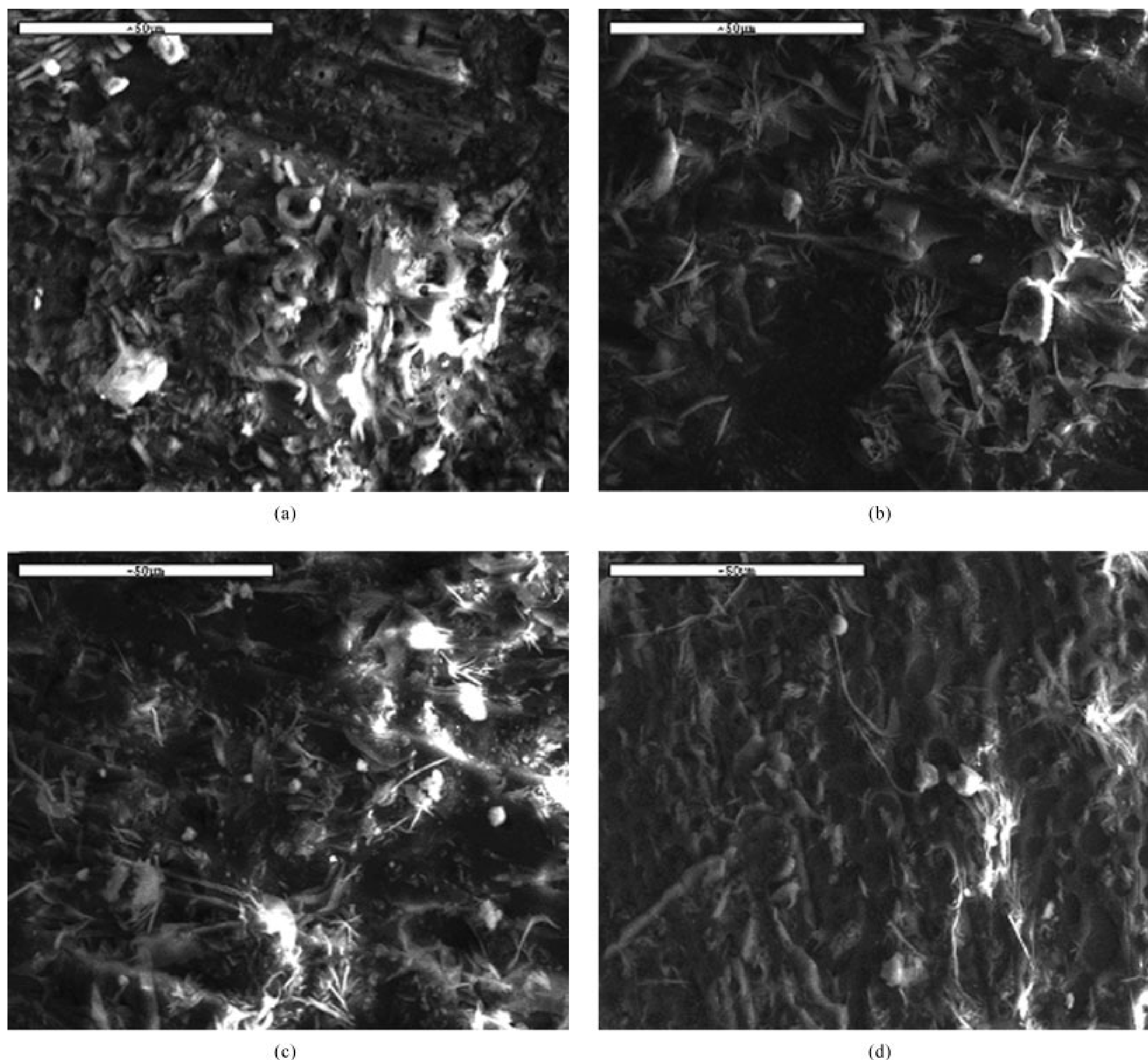


Figure 8 SEM micrographs of PEG-naringenin/hesperetin solid dispersion films at different ratios (a) 80/20, (b) 70/30, (c) 60/40, and (d) 50/50 w/w.

drastically reduced compared with that of pure ones. However, it seems that crystals were not adequately reduced and remained above the critical particle size needed to ensure the complete dissolution of aglycones.

Controlled release profile

In the above studies, efforts were concentrated on the preparation and characterization of physicochemical properties of solid dispersion systems. However, the main objectives of this study were to enhance the dissolution rate of the two flavanone glycosides or their aglycones and to correlate this behavior directly with the physical state and the particle size distribution of dispersed drugs. Dissolution profiles, at different pH values, were studied to have more data for better correlation. It is well known that the release profile of a drug depends mainly on the selected carrier.[30]

Flavanone glycosides, naringin and hesperidin, remain in the crystalline form in solid dispersions of both carriers (PVP and PEG), as shown in their XRD analysis [Figs. 2(a) and 3(a)]. This physical state directly affected their dissolution profiles; which in PVP and PEG solid dispersion systems remained almost the same with pure components after 10 h treatment. In particular, the solubility of hesperidin remained very low; there was no noticeable enhancement in its dissolution compared with its pure crystals. Further-

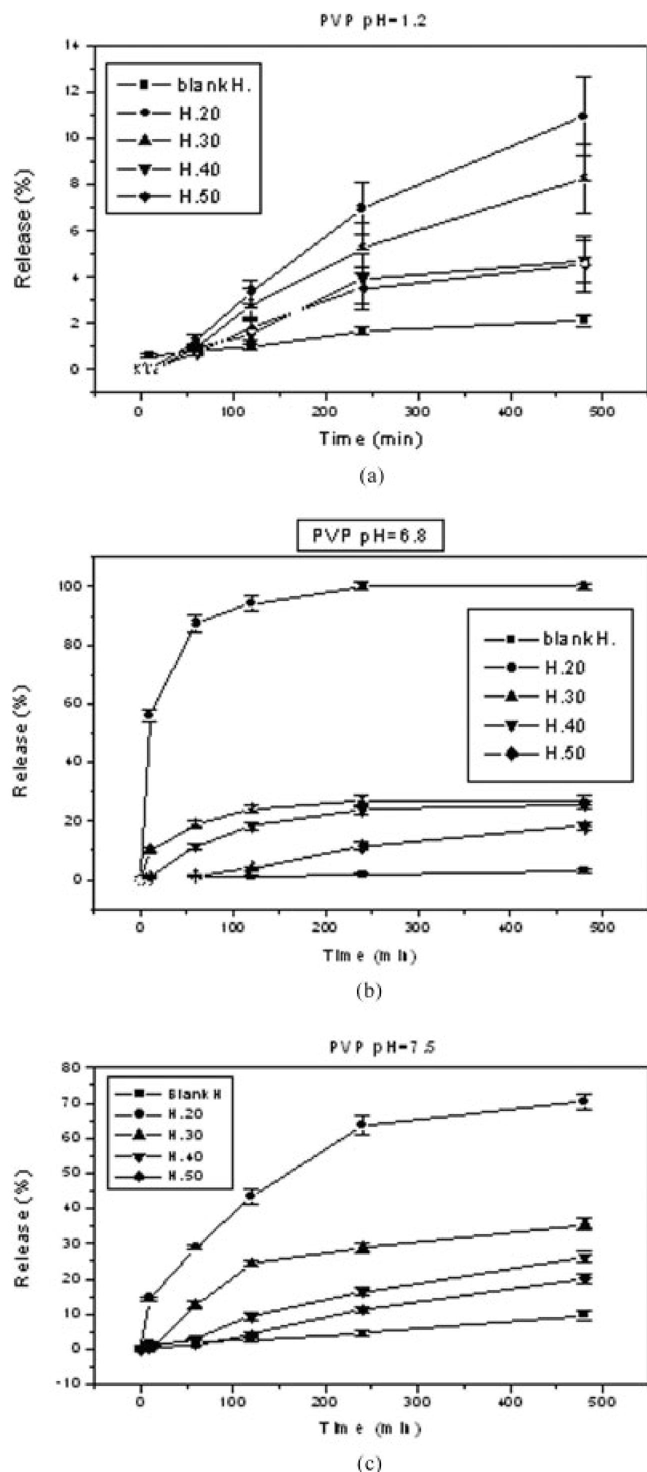


Figure 9 Release profiles of hesperetin from PVP solid dispersion systems at pH (a) 1.2, (b) 6.8, and (c) 7.5.

more, pH values influence very slightly their rate of dissolution. These compounds are bulky compared with their aglycones and it might be difficult to dissolve into the polymer matrix or they need higher concentrations of the carrier. For this reason, our interest was directed toward their aglycones, naringenin, and hesperetin.

Release profiles of naringenin and hesperetin from their PVP solid dispersion systems, at pH 1.2, 6.8, and 7.5 for 8 h, are presented in Figures 9 and 10. The results were given as % release or dissolved drug. It was verified, from these figures, that the release pro-

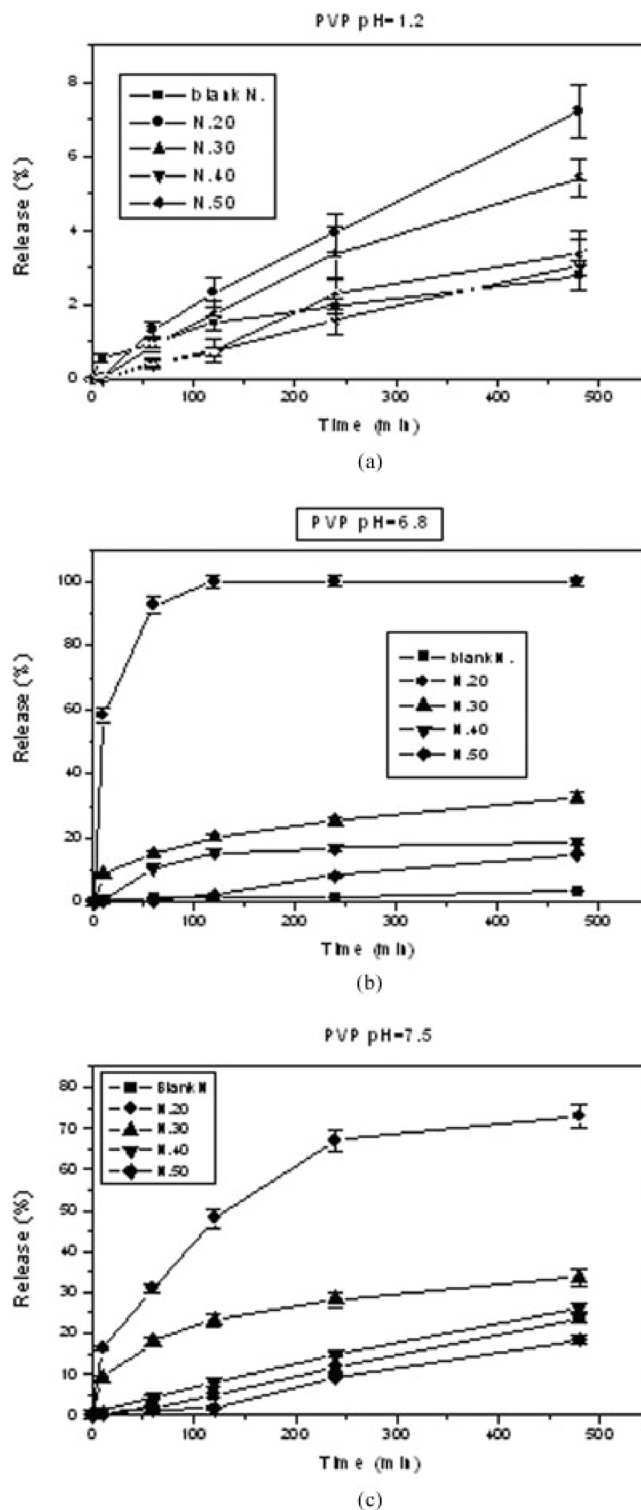
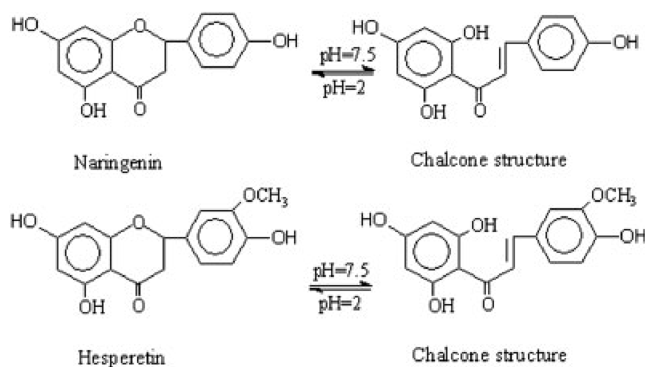


Figure 10 Release profiles of naringenin from PVP solid dispersion systems at pH (a) 1.2, (b) 6.8, and (c) 7.5.



Scheme 3 Formation of insoluble chalcone structures pH from soluble flavanones, at slight alkaline.

files of aglycones from PVP solid dispersions, at all ratios, were dramatically improved comparing with the pure aglycones crystals alone; it was also observed that the release profiles at pH 6.8 or 7.5 were the highest for all solid dispersion systems. In particular, the release of naringenin and hesperetin, at pH 6.8, from the solid dispersion system PVP/naringenin–hesperetin, 80/20 w/w, was 100% after almost 2 h, which means that there was 51.4- and 64.3-fold increase in their dissolution compared with their pure crystals, respectively. Usually, such enhancement of dissolution profile results in an increased bioavailability of the particular drugs. The dissolution profile of both components, as can be seen in Figures 9 and 10, is almost identical without any clear differences. The order of increasing solubility of both aglycones was at pH 6.8 > 7.5 > 1.2 and at the ratios 80/20 > 70/30 > 60/40 > 50/50 PVP/naringenin–hesperetin, w/w. This enhancement in dissolution rate of both aglycones could be attributed to the crystal destruction of these compounds and mainly to the formation of solid nanodispersions. Comparing the particle size distributions of flavanone aglycones in PVP solid dispersions (Fig. 7), it can be concluded that particle sizes must be lower than 200 nm for a substantial enhancement of the dissolution rate, e.g., PVP/naringenin–hesperetin, 80/20 w/w. This also seems to be the critical particle size, since for higher particle sizes of aglycones in solid dispersion systems > 30 wt %, the dissolution rate was limited. This behavior could be attributed to the effective surface area available for the dissolution, which is limited by increased particle size.

Furthermore, it was found that in addition to the particle size distribution, pH had a strong effect on the dissolution rate. The release profile of naringenin and hesperetin from all solid dispersion systems, at pH 1.2, was lower than that of pH 7.5 or 6.8. It is well known that flavanones are phenolic compounds with slightly acidic character, and their solubility depends on the pKa value of the dissolution medium ($pKa = pH + \log(S_{tot}-S_o)/S_o$), where S_{tot} is the pH-dependent solubility and S_o the intrinsic solubility.[31] When the pH of the medium was lower than their pKa, the majority of their phenolic hydroxyl groups were nonionized and the hydrogen bonds between carriers and aglycones in solid dispersion systems were kept, leading to a slower dissolution rate. However, when the pH of the medium was higher than their pKa, the majority of the phenolic hydroxyl groups were ionized and the hydrogen bonds could not be kept, leading to a higher dissolution rate. Flavanones were less soluble at pH 7.5 than 6.8, because flavanones at slightly alkaline pH form chalcone structures (Scheme 3), which are extremely insoluble, with a result to precipitate quickly.[32]

In the same way, the release profiles of naringenin and hesperetin from PEG solid dispersion at different ratios 80/20, 70/30, 60/40, and 50/50 PEG/naringenin–hesperetin, w/w, were studied only at pH 6.8 (Fig. 11). Similar improvements in dissolution profiles of both aglycones from PEG solid dispersions were also observed, especially in the first 2–3 h, even

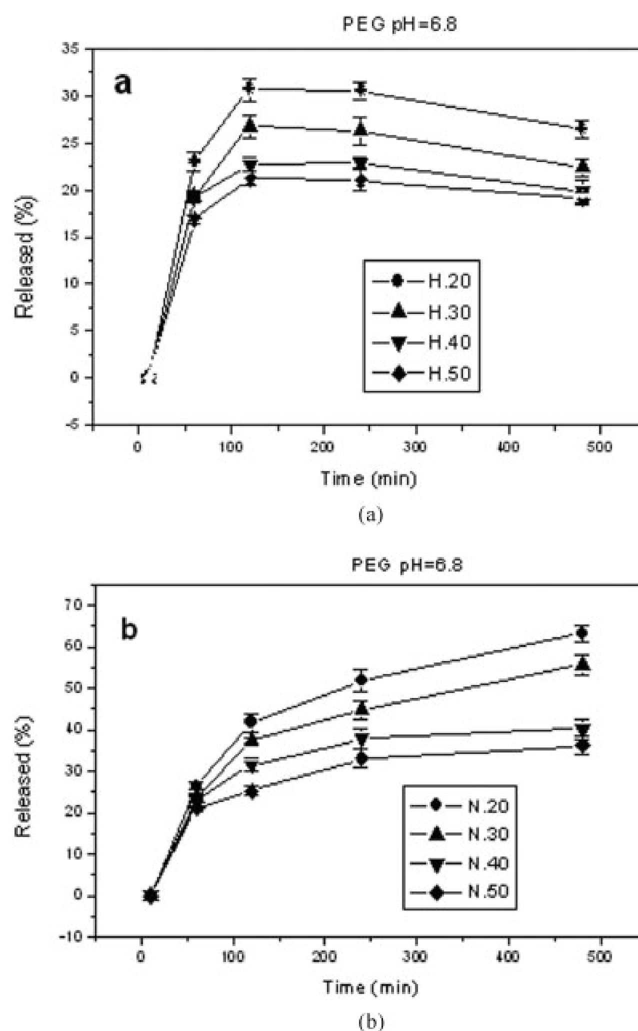


Figure 11 Release profiles from PEG solid dispersion systems at pH 6.8 of (a) hesperetin and (b) naringenin.

though the drugs are in semicrystalline form. A possible explanation for this dissolution enhancement, except the particle size reduction, is the improved wetting of the drugs in the PEG microenvironment created at the surface of drug crystals after dissolution of the polymer.[33] The highest % release of naringenin and hesperetin was from the solid dispersion of PEG/naringenin–hesperetin, 80/20 w/w. Their releases after 2 h were 41.2% (12-fold increase) and 31% (11-fold increase), and after 8 h were 63% (18-fold increase) and 27% (10-fold increase), respectively. The small decrease that appears after 8 h is due to the crystallization and precipitation of hesperetin. However, compared with PVP solid dispersions, it can be seen that the % release was in all ratios lower than in the case of PVP and thus it can be concluded that PVP is better drug carrier than PEG. These differences in dissolution rate can be attributed to the different physical state that drugs are dispersed in each one different carrier and the particle size distribution. In PEG, drugs are in crystalline form and particles with average diameter higher than 5 μm are observed. On the contrary, in PVP carrier, these compounds are amorphous and dispersed in nanodimensions, which means that higher amount is available for dissolution.

CONCLUSIONS

In the present study, dissolution enhancement of flavonoid aglycone drugs naringenin and hesperetin was achieved by the solid dispersion technique. The dissolution was up to 100% after 2 h using PVP as drug carrier while in the case of PEG the value was somewhat lower (<70%). This difference is attributed to the amorphous form and nanodispersions of the flavanoid drugs into the PVP matrix, while into PEG the compounds were partially crystalline with particle sizes higher than 1 μm.

FTIR spectra showed the presence of hydrogen bonds between PVP carbonyl groups and hydroxyl groups of both flavanone aglycones. These interactions prevent crystallization of naringenin and hesperetin aglycones in the PVP matrix. On the other hand, the ability of PEG carrier to form hydrogen bonds with flavanone glycosides or aglycones was limited, thus both flavanone glycosides and their aglycones remained mainly in the crystalline form.

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