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ORIGINAL ARTICLE

Dissolution rate and stability study of flavanone aglycones, naringenin and hesperetin, by drug delivery systems based on polyvinylpyrrolidone (PVP) nanodispersions

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Abstract

Objective: To study the dissolution behavior, the release mechanism and the stability of nanodispersion system of aglycones with PVP. *Methods*: The nanodispersion system of polyvinylpyrrolidone (PVP)/naringenin–hesperetin was prepared using the solvent evaporation method. The chemical stability (compatibility) of naringenin and hesperetin in the prepared dispersions was studied under accelerated conditions for 3 months. The evaluation of physical stability was performed by X-ray diffraction analysis (XRD) and by comparing the dissolution profile before and after storage at high temperature and moisture (40°C, RH 75%). *Results*: The dissolution rate of naringenin and hesperetin released was dramatically increased in the nanodispersion system of PVP/naringenin–hesperetin (80/20, w/w). The release mechanism of both flavanone aglycones was better described by the diffusion model (Higuchi model). Also it was found that the rate-limiting step that controlled the release of naringenin and hesperetin in the nanodispersion system was dissolution of the carrier (PVP). *Conclusions*: During accelerated degradation analysis, for 3 months at high temperature and moisture, PVP nanodispersion system showed enhanced chemical compatibility and physical stability. The physical evaluation (obtained from XRD analysis) of PVP/naringenin–hesperetin (80/20, w/w) in the selected storage conditions did not show any crystallization of flavanone aglycones in the PVP nanodispersion system or any change in their release profile.

Key words: *Flavanone aglycones; hesperetin; nanodispersions; naringenin; stability*

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].

Naringenin and hesperetin, the aglycones of the flavanone glycosides naringin and hesperidin, occur naturally in citrus fruits (Figure 1)[2]. They exert a variety of pharmacological effects, such as antioxidant effects[3,4], blood lipid-lowering effects[5–8], anti-inflammatory activity through inhibition of the enzymes involved in arachidonate metabolism[9–11], anticarcinogenic effects[12,13], and inhibit selected cytochrome P-450 enzymes resulting in drug interactions[14].

Naringenin and hesperetin are very poorly soluble in water, indicating that their dissolution might be the rate-limiting step in their absorption. In the two of our previous studies[15,16], the flavanone glycosides, naringin and hesperidin, and their aglycones, naringenin and hesperetin, were prepared as solid dispersions with polyvinylpyrrolidone-K30 (PVP-K30) and polyethylene glycol-4000, using solvent evaporation method, at different

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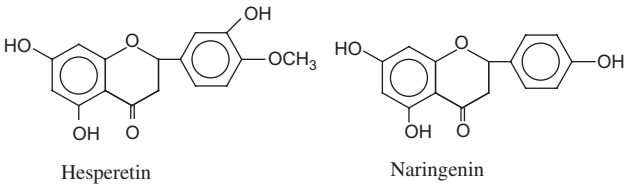

Figure 1. Molecular structures of flavanone aglycones, naringenin and hesperetin.

ratios. These solid dispersions were characterized with X-ray diffraction (XRD), Fourier transform infrared, differential scanning calorimetry, and size analysis, and the interactions between drugs and carriers were studied. Finally the effect of these carriers on the dissolution profile was also studied. It was concluded that the dissolution rate of both flavanone aglycones was directly affected by the physical state of solid dispersions and was dramatically improved in the case of PVP at 80/20 (w/w) concentration level. Hence, the stability of PVP/naringenin–PVP/hesperetin nanodispersions at the optimum concentration level (80/20) has to be further investigated.

The physical instability of solid dispersions because of crystallization of drugs was reported in many studies[17–22]. It is reported that cooling rate of solid dispersion systems influences their aging behavior and crystallinity of the drug (when a slow cooling rate is used, the prepared solid dispersions seem to be more stable compared to faster cooling rates)[23,24]. Glass transition temperature of polymer could also affect the physical stability of the produced solid dispersions. Hancock and Zografi[25] suggested that glass transition temperature should be higher at least by 50°C than storage temperature.

Generally it is accepted that interactions between polymer carriers and drugs can increase the stability of the formulation during storage. These interactions between the components prevent recrystallization of the drug, because drug remains in the amorphous state. It is reported in the literature that PVP can act as a crystallization inhibitor of drugs in solid dispersions at relatively low humidity[26,27] by forming hydrogen bonds with the drug[28].

The aim of this work was to study the dissolution behavior, the release mechanism, and the chemical and physical stability of naringenin and hesperetin from a nanodispersion system with PVP at a ratio of 80/20 (PVP/drugs, w/w) after 3 months of storage at 40°C and 75% RH, based on one of our previous studies[15,16].

Experimental methods

Materials

Naringenin (4′,5,7-trihydroxyflavanone) 95% and hesperetin (3′,5,7-trihydroxy-4′-methoxyflavanone) 95% were supplied from Sigma (St. Louis, MO, USA). PVP-type Kollidon K30 with a molecular weight of 50,000 was supplied by BASF (Ludwigshafen, Germany), cross-linked carboxymethylcellulose sodium (Croscarmellose Sodium, AcDiSol®) was from FMC Corp. (Philadelphia, PA, USA), sodium starch glycolate, Primojel (Avebe, Veendam, Holland), sodium lauryl sulfate (J.T. Baker, Phillipsburg, NJ, USA), magnesium stearate (Mallinckrodt, Hazelwood, MO, USA), and colloidal silicon dioxide (Aerosil® 200; Degussa, Frankfurt, Germany). Acetic acid and absolute ethanol were purchased from Merck (Darmstadt, Germany). All the other materials and solvents used were of analytical grade.

Preparation of nanodispersion system

The nanodispersion system of PVP/naringenin–hesperetin (80/20, w/w), which had the highest dissolution rate, was prepared using the solvent evaporation method mentioned in our previous studies[15,16]. Briefly, absolute ethanol was used as a solvent. The nanodispersion system was prepared by the dissolution of PVP and both flavanone aglycones in proper quantities of absolute ethanol at room temperature. The solutions were mixed, subsequently ultrasonicated for 20 minutes and then were let in aluminum plates for 24 hours in a gentle stream of air, at room temperature, until the solvent was fully evaporated. Naringenin and hesperetin were in equal amounts in the prepared dispersion. The created glass films were pulverized and stored in a desiccator until use. Finally, the nanodispersions were sieved using 50–250 mesh.

Preparation of capsules and tablets

For the dissolution studies, hard gelatine capsules (size 0) were directly prepared by filling each with 450 mg of pulverized nanodispersion. Each capsule contained 45 mg of each flavanone aglycone. The dissolution tests were done each time for two capsules in each dissolution vessel (theoretical weight, 90 mg of each flavanone aglycone). Because capsules tend to float on the top of the dissolution medium, a wire sinker was used in order to hold the capsules at the bottom of the dissolution vessel.

Twenty-seven grams of granules (50–250 mesh size) of nanodispersion were mixed with 2.25 g of sodium starch glycolate (Primojel), 0.3 g of magnesium stearate, 0.3 g of sodium lauryl sulfate, and 0.15 g of colloidal silicon dioxide in a polyethylene bag for 15 minutes. Tablets of a net weight of 1 g (Table 1) were compressed in flat punches with diameter 12.5 mm using a hydraulic press by applying 1.25, 2.5, 4, 5, 10, and 20 N/mm^2 load for 5 seconds. Each tablet contained 90 mg of each flavanone aglycone. The reason for preparing tablets was to maintain

Table 1. Composition of tablet formulation.

Components	Weight (mg)	Weight (%)
Nanodispersion system (PVP/ naringenin–hesperetin, 80/20, w/w)	900	90
Sodium starch glycolate (Primojel)	75	7.5
Magnesium stearate	10	1
Sodium lauryl sulphate	10	1
Colloidal silicon dioxide	5	0.5
Total weight	1000	100

the initial surface area constant, investigating the potential dissolution behavior of the polymer (e.g., gelling).

Release profile

A modified dissolution apparatus Pharma Test PT-DT7 (paddle rotating method) with a stationary disk at 100 rpm and 1000 mL capacity was used. Samples corresponding to 90 mg of each naringenin and hesperetin, in hard gelatin capsules or tablets, were placed in each vessel and maintained at 37 ± 0.5°C. Phosphate buffer (pH 6.8) was used based on the previous studies[15,16]. The introduction of tablets or capsules inside the dissolution vessels was done carefully, so that all the tested forms had the same orientation in the vessel's bottom and to ensure that they did not had any air bubbles affecting the dissolution results. Each time six tablets or capsules were tested and the mean value of released percentage was used. Perfect sink conditions prevailed during the drug release.

High-performance liquid chromatography analysis

The samples were analyzed according to a high-performance liquid chromatography (HPLC) method reported previously[29]. Aliquots of 100 µL were withdrawn and filtered through a 0.2-µm filter at appropriate times, and equal volumes of fresh dissolution medium were replaced. The analyses were performed using an HPLC system (Varian, Palo Alto, CA, USA), 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, USA), 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 used was methanol/water/acetic acid (43:55:2, v/v/v), and the analytes were detected at 288 nm. The flow rate of the mobile phase was 1 mL/min and the column temperature was 45°C. The presence of PVP and the other excipients used did not interfere with the chromatographic analysis of both flavanone aglycones.

Mechanism and modeling of drug release

In order to describe the drug kinetics release from the capsules and tablets, various mathematical equations are used.

1. Zero-order kinetics

Equation (1) describes systems where drug release rate is independent of its concentration, assuming that the area does not change and no equilibrium conditions are obtained[30]:

$$Q_t = k_0 \times t. \tag{1}$$

2. First-order kinetics

Equation (2) describes the release from systems where the release rate is concentration-dependent[31,32]:

$$\ln Q_t = \ln Q_0 - k_1 \times t. \tag{2}$$

3. Higuchi model

Higuchi[33] described the release of drugs from insoluble matrix as a square root of time-dependent process based on Fickian diffusion (Equation 3):

$$Q_t = K \times S\sqrt{t} = k_{\mathrm{H}} \times \sqrt{t}. \tag{3}$$

4. The Hixson–Crowell model

Equation (4) describes the release from systems where there is a change in surface area and diameter of the particles or the tablets[34,35]:

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = k_{\mathrm{HC}} \times t. \tag{4}$$

where Q_t is the amount of drug released at time t, Q_0 the initial amount of the drug in tablet or capsule, S the surface area of the tablet, and k_0, k_1, k_{H}, and k_{HC} are release rate constants for zero-order, first-order, Higuchi, and Hixson–Crowell rate equations, respectively. In addition to these basic release models, there are several other models and equations described in the literature to characterize the drug release kinetics and mechanisms from different types of systems[36].

Chemical and physical stability

In order to investigate the compatibility (chemical stability) between the drugs and the used excipients, pure

flavanone aglycones and the nanodispersion system of PVP/naringenin–hesperetin (80/20, w/w), either alone or with one excipient each time (Table 1), were stored for 3 months under accelerated chemical stability conditions. The nanodispersion system was packed in glass vials with Teflon caps and silicone liners. Specifically an Angelatoni stability oven was used, the temperature was set at 40 ± 1°C and a relative humidity at 75 ± 5%. The samples were analyzed each month for assay and chromatographic purity.

Portions of powdered samples equivalent to 50 ± 0.01 mg (PVP/naringenin–hesperetin, 80/20, w/w) were carefully weighed from each bottle, supplemented with exactly 1 mL (400 μg/mL I.S., 7-ethoxycoumarin) solution, and then diluted to 100 mL by a mixture of methanol:water (50:50, v/v), sonicated for 20 minutes and then centrifuged for 10 minutes (3500 rpm). The supernatant solution was used for the analysis and the concentrations of naringenin and hesperetin were determined immediately. Moreover, the percentage of remaining drug was calculated using Equation (5):

$$\%\ \text{Remaining of N and H} = \frac{C_{t=0} - C_t}{C_{t=0} \times 10}, \qquad (5)$$

where N and H are the naringenin and hesperetin, respectively, $C_{t=0}$ is the concentration at $t = 0$, and C_t is the concentration at time t.

The physical stability was evaluated by comparing the dissolution profile of three tablets or capsules, before and after their storage at a temperature of 40°C and a humidity of 75% for 3 months. XRD analysis was also carried out in order to ensure that naringenin and hesperetin did not recrystallize in the solid dispersions and in the examined storage conditions. Samples were scanned over the interval 5–50° 2θ, using a Philips PW1710 diffractometer, with Bragg–Brentano geometry (θ, 2θ) and Ni-filtered CuKα radiation.

Results and discussion

Release profile from capsules and tablets

According to our previous studies[15,16], the dissolution profile of the nanodispersions depended on the concentration of PVP indicating carrier-controlled release. Also hydrogen bonding between the PVP and the flavanone aglycones played an important role in controlling the drug release profile.

Comparisons of the dissolution profiles of the prepared nanodispersions at the optimum concentration level (PVP/drugs: 80/20, w/w) prepared as capsules and tablets are shown in Figures 2 (for capsules) and 3 (for tablets). From these figures, it was observed that in the case of capsules the release of both naringenin and hesperetin was completed in less than 2 hours, whereas for tablets at the same time of 2 hours, the concentration of the two drugs, naringenin and hesperetin, was 52% ± 4.6 (SD) and 55% ± 4.3 (SD), respectively. Hence, it can be concluded that the dissolution rate of both drugs was faster in the case of capsules compared to tablets, despite the fact that in the latter a super disintegrant (sodium starch glycolate) was used.

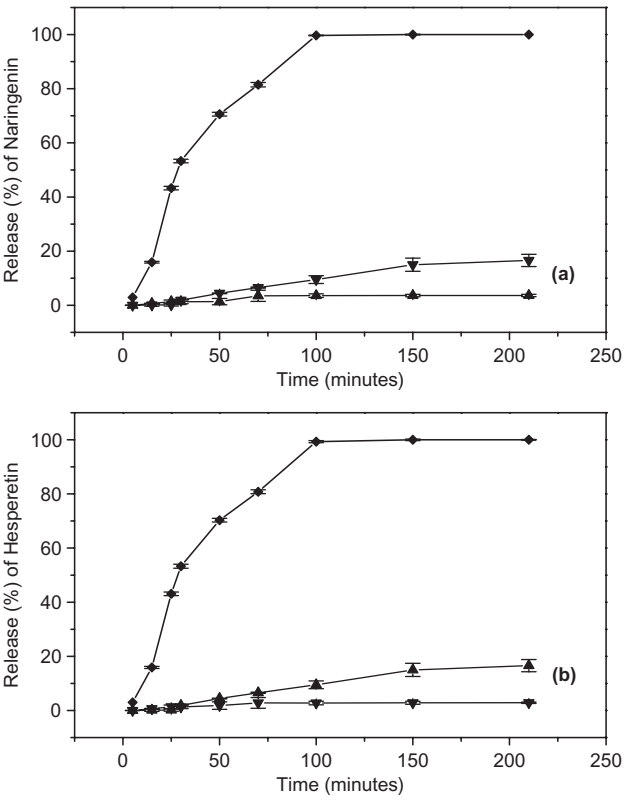

Figure 2. Dissolution profiles of (a) naringenin (◆) from nanodispersion, (▼) physical mixture of PVP/naringenin and hesperetin (80/20, w/w), (▲) crystals and (b) hesperetin (◆) from nanodispersion, (▲) physical mixture of PVP/naringenin and hesperetin (80/20, w/w), (▼) crystals, from capsule formulation.

This difference of dissolution behavior for capsules and tablets can be attributed to the applied compression force (when preparing tablets). This force brought the granules much closer to each other decreasing the porosity and reducing wettability. Further, the controlled release of flavanone aglycones from the nanodispersion system can be attributed to the creation of a thin film (like gel) formed around the tablets. This film controlled the diffusion of dissolution medium inside the matrix, resulting in a delay of the release of the drugs. This was an indication that the release of drugs was mainly controlled by diffusion through the slightly swollen nanodispersion matrix.

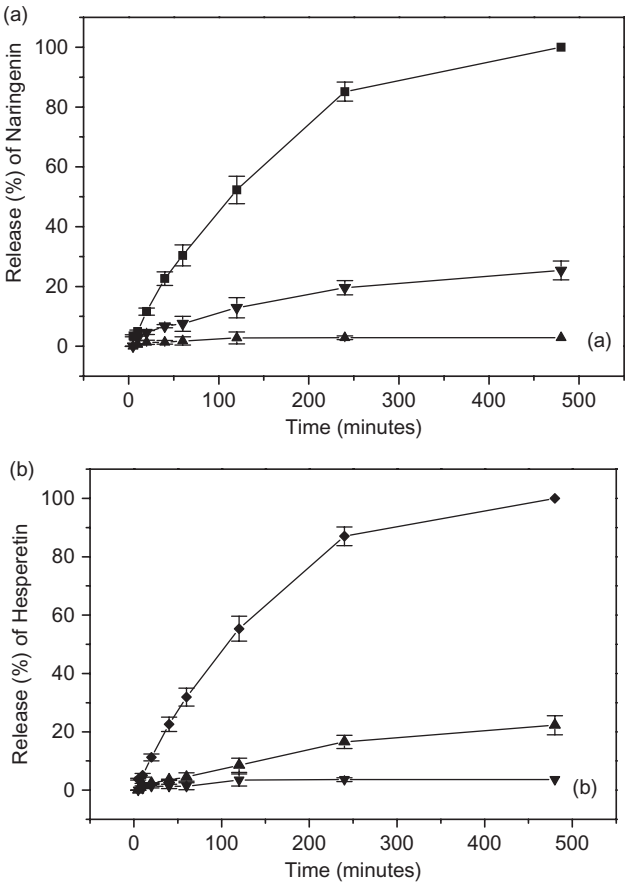

Figure 3. Dissolution profiles of (a) naringenin (◆) from nanodispersion, (▼) physical mixture of PVP/naringenin and hesperetin (80/20, w/w), (▲) crystals and (b) hesperetin (◆) from nanodispersion, (▲) physical mixture of PVP/naringenin and hesperetin (80/20, w/w), (▼) crystals, from tablet formulation with a compression force (5 N/mm^2).

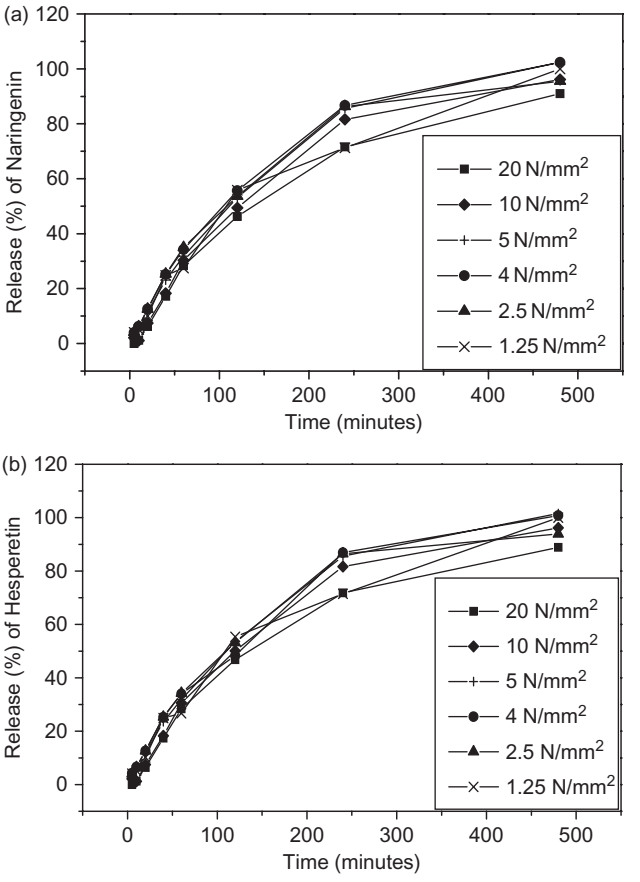

Figure 4. The effect of the used compression force (N/mm^2) on the dissolution profiles of (a) naringenin and (b) hesperetin from tablets.

The effect of the used compression force on tablet dissolution was also studied. A number of tablets (having the same composition as stated in Table 1) were prepared by applying a load of 1.25, 2.5, 4, 5, 10, and 20 N/mm^2 for 5 seconds. The dissolution profiles of six tablets for 8 hours are shown in Figure 4. It was observed that there were only small differences in the dissolution profiles of naringenin and hesperetin when applying different tableting forces. After 4 hours, it was observed that the mean percentage release of naringenin and hesperetin, at the different applied forces, was 80.5% ± 7.2 (SD) and 80.7% ± 7.1 (SD), whereas after 8 hours, the release was 97.9% ± 4.5 (SD) and 96.9% ± 4.9 (SD), respectively. It was also noticed that in all the prepared tablets there was no disintegration.

In order to study the effect of the excipients on the dissolution profile of tablets, two batches of tablets (consisting of three tablets each), one without and the other with excipients (as stated in Table 1), were prepared at 5 N/mm^2 tableting force. Their mean dissolution profiles, for 8 hours at pH 6.8, are shown in Figure 5. The percentage of drug release for both flavanone aglycones after 8 hours was 91% ± 1.7 (SD) in the batch prepared without excipients, whereas in the batch with excipients, the release was 100% (for both aglycones). This study revealed that the presence of excipients had a little effect on the magnitude and the release kinetics of both flavanone aglycones. In order to improve the wettability of the tablets and to accelerate the dissolution rate or the disintegration of the tablets, another super disintegrant was also tested. Cross-linked carboxymethylcellulose sodium (AcDiSol) was used in the same ratio instead of Primojel, but there was no change in the dissolution profile for both flavanone aglycones. The dissolution profiles of naringenin and hesperetin from six tablets containing AcDiSol and Primojel are shown in Figure 6. It was observed that Primojel acted as AcDiSol and did not show any disintegration effects, leading to controlled release of the drugs.

The lack of disintegration and the slow dissolution of tablets prepared from solid dispersions could be related

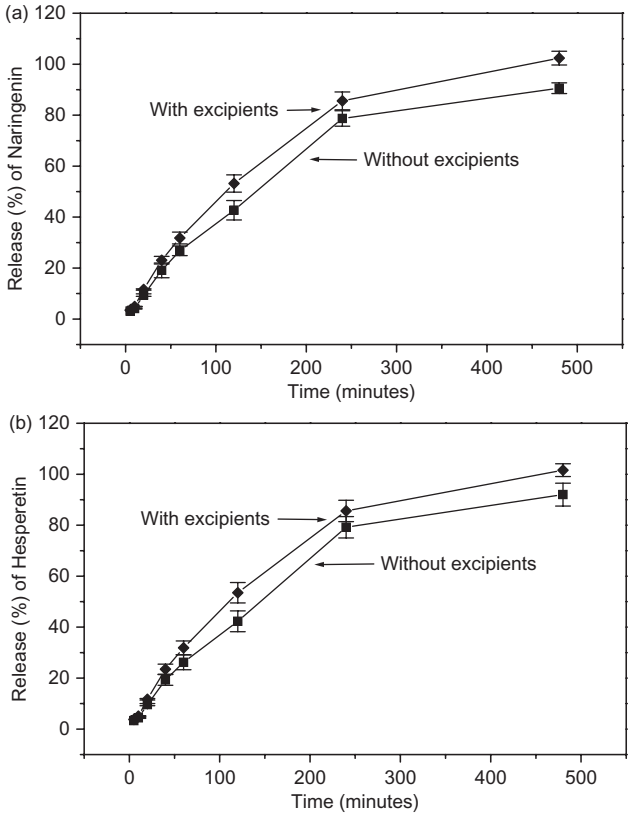

Figure 5. The effect of excipients on the dissolution profiles of (a) naringenin and (b) hesperetin from tablets (compression force 5 N/mm^2).

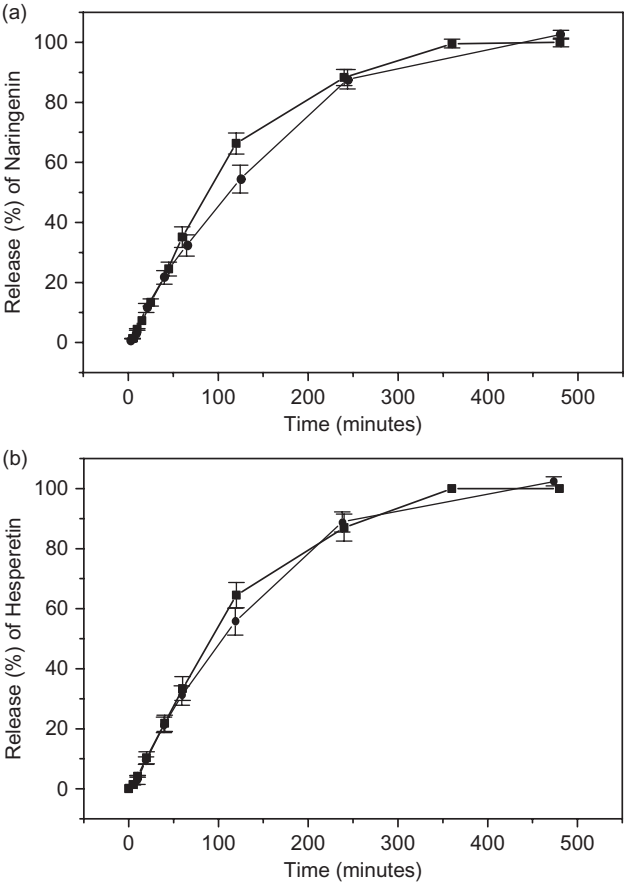

Figure 6. Dissolution profiles when adding super disintegrant, AcDiSol (■), compared to the nanodispersions with Primojel (●) from tablets of (a) naringenin and (b) hesperetin. Compression force was 5 N/mm^2.

to the soft and waxy nature of the carrier used (PVP). Such carriers essentially act as strong binders within tablets. It is also possible that the softened and melted carriers coated the disintegrants and other ingredients used in tablets, and such a coating, along with the reduction of porosity of tablets, made the disintegrants ineffective. The use of a very high ratio of solid dispersion to added excipient might alleviate the problem.

Mechanism and modeling of drug release

Release data obtained from tablets and capsules were subjected to different drug release models in order to predict the release mechanisms and kinetics. A criterion for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals.

A model-dependent approach was employed in order to calculate and compare the dissolution kinetics of both tablets and capsules, and the release data were fitted to nonlinear models using Excel computer program. Three popular release models were implemented in the program: first-order, Higuchi, and Hixson–Crowell kinetic models. The results are summarized in Tables 2 and 3.

The curvilinear nature of the cumulative percentage of drug released versus time plots (Figures 2–6) suggested that none of the studied formulation followed zero-order drug release kinetics. The poor correlation of the first-order model suggested that the drug release was not matrix drug load-dependent. Moreover, the poor correlation of the drug release (for both tablets and capsules) to Hixson–Crowell cube root law suggested that there was no change in surface area and diameter of tablets or particles with the progressive dissolution of the matrix as a function of time. On the other hand, the high correlations of the release data of both tablets and capsules to the equation of Higuchi suggested that the drug release can be described as a diffusion process based on Fick's squared root time-dependent law.

Thus, the release mechanism of both naringenin and hesperetin from tablets or capsules of nanodispersion system (PVP/naringenin–hesperetin) is controlled by diffusion. Dissolution medium diffuses into the tablet matrix and dissolves the drug. Then the dissolved drug diffuses out of the matrix. It can be concluded that the

Table 2. Modeling of naringenin and hesperetin release from capsules according to first-order, Higuchi, and Hixon–Crowell (cube root) release kinetic models.

	Naringenin			Hesperetin		
Capsules	First-order model	Higuchi model	Cube root	First-order model	Higuchi model	Cube root
Correlation	0.76423	0.94377	−0.81213	0.76577	0.94518	−0.81390
Slope	0.01024	9.80325	−0.01269	0.01024	9.78287	−0.01269
Intercept	−1.19511	−6.54508	1.50562	−1.19828	−6.62213	1.50972

Table 3. Modeling of naringenin and hesperetin release from tablets according to first-order, Higuchi, and Hixon–Crowell (cube root) release kinetic models.

	Naringenin			Hesperetin		
Tablets	First-order model	Higuchi model	Cube root	First-order model	Higuchi model	Cube root
Correlation	0.75856	0.96921	−0.82212	0.75974	0.97182	−0.82519
Slope	0.00512	5.50904	−0.00549	0.00520	5.50338	−0.00554
Intercept	−1.92303	−8.95349	2.11788	−1.95477	−9.48258	2.14360

rate-determining step of the dissolution process was the diffusion of the dissolution medium through the polymer matrix.

Chemical stability (compatibility)

The accelerated stability tests are designed to increase the rate of chemical degradation or physical change of an active drug by using exaggerated storage conditions. The presence of moisture could potentially cause recrystallization of the drug substances[20] or chemical degradation because of the plasticizing effect of water, which increases the mobility of the systems by decreasing the transitional glass temperature (T_g) as reported by Hancock and Zografi[37]. In this study, 40°C and 75% RH were chosen as storage conditions and the effect of each excipient on the PVP/naringenin–hesperetin system was examined.

Compatibility of the nanodispersions (PVP/naringenin–hesperetin, 80/20, w/w) with all excipients (mentioned in Table 1) for 3 months are shown in Table 4. The HPLC chromatograms of the nanodispersion systems were found to be identical to those of the pure flavanone aglycones as shown in Figure 7. From the chromatograms it was concluded that there were not any assay modifications or significant chromatographic purity alternations for the examined systems.

From the above results, it can be concluded that PVP nanodispersion system of naringenin and hesperetin showed enhanced chemical stability during accelerated degradation analysis with all used excipients. The formation of hydrogen bonds, as mentioned in a previous study[16], keeps the molecules of both flavanone aglycones stable in the polymer matrix with a result to decrease their mobility. These bonds play an important role in the inhibition of any recrystallization or

Table 4. Results of percentage remaining of naringenin and hesperetin, after accelerated chemical stability studies for 3 months at 75% RH and at 40°C.

	Naringenin				Hesperetin			
Sample number	Assay percentage found	Percentage remaining after 1 month	Percentage remaining after 2 months	Percentage remaining after 3 months	Assay percentage found	Percentage remaining after 1 month	Percentage remaining after 2 months	Percentage remaining after 3 months
(1)	100.56	100.48	100.04	101.46	99.89	99.57	99.96	101.44
(2)	101.22	100.54	101.33	100.91	100.45	100.81	102.73	101.44
(3)	100.42	101.62	102.12	100.88	102.22	102.06	98.04	100.95
(4)	101.25	102.52	103.67	99.89	100.95	101.81	99.38	99.85
(5)	99.84	101.13	100.04	100.76	99.76	100.22	98.15	100.13
(6)	101.33	98.99	103.45	101.21	100.76	99.79	101.53	101.99
(7)	100.65	102.29	102.33	101.47	101.09	101.74	102.07	101.87

(1) Nanodispersion (PVP/naringenin–hesperetin, 80/20, w/w), (2) pure physical mixture (naringenin/hesperetin, 50/50, w/w), (3) nanodispersion (PVP/naringenin–hesperetin, 80/20, w/w) + 7.5% Na starch glycolate, (4) SD (PVP/naringenin–hesperetin, 80/20, w/w) + 1% Na lauryl sulfate, (5) nanodispersion (PVP/naringenin–hesperetin 80/20, w/w) + 1% Mg-stearate, (6) nanodispersion (PVP/naringenin–hesperetin, 80/20, w/w) + 0.5% colloidal silicon dioxide, (7) nanodispersion (PVP/naringenin–hesperetin, 80/20, w/w) + 7.5% Na-cross-linked carboxymethylcellulose.

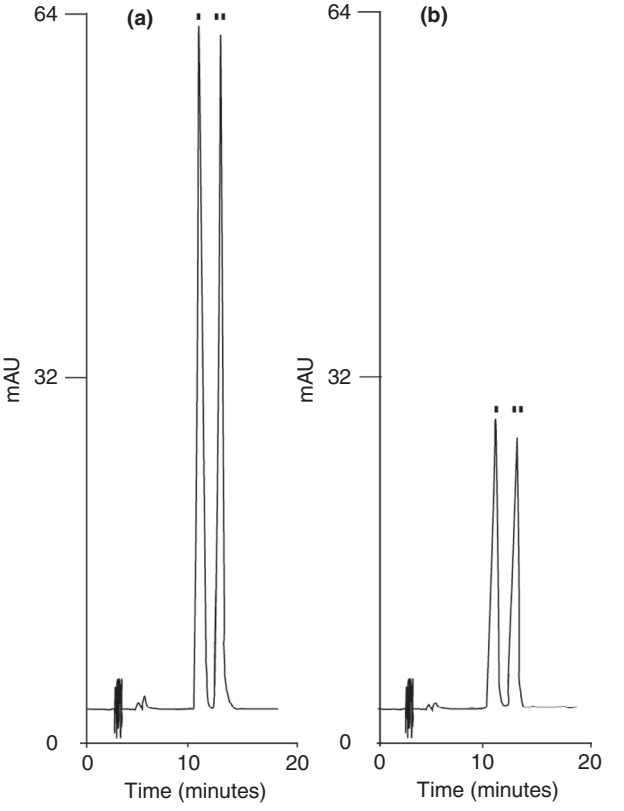

Figure 7. Examples of HPLC chromatograms of (a) pure crystals of naringenin (I) and hesperetin (II) at a concentration of 12.5 μg/mL and (b) naringenin (I) and hesperetin (II) from the nanodispersion system (PVP/naringenin and hesperetin, 80/20, w/w), at 6 μg/mL concentration, with all the excipients after 3 months of stability studies.

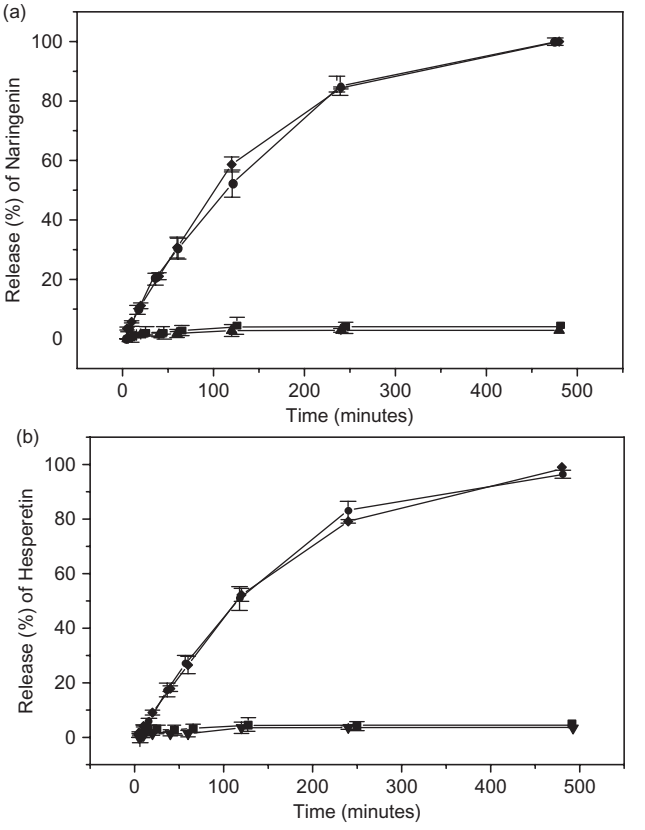

Figure 8. Dissolution profiles of (a) naringenin (◆) from nanodispersion and (▲) crystals after 3 months storage according to Table 1, compared to the nanodispersions (●) and crystals (■) dissolution profiles immediately after their preparation and (b) hesperetin (◆) from nanodispersion, (▼) crystals after 3 months storage according to Table 1, compared to the nanodispersions (●) and crystals (■) dissolution profiles immediately after their preparation. Compression force was 5 N/mm^2.

chemical reaction. Similar behavior of PVP as a recrystallization inhibitor has been reported by several researchers[19,26,27].

Physical stability

The high degree of molecular mobility in solid dispersion systems leads to their spontaneous reversion to the thermodynamically stable crystalline form. Solid dispersion systems often show poor stability during storage, because of partial or complete crystallization[38,39]. Therefore, physical stability was tested after 3 months for three tablets by checking the dissolution rate of naringenin and hesperetin, as shown in Figure 8. Also the crystallization of naringenin or hesperetin in the nanodispersion systems was tested by XRD, as shown in Figure 9.

It was observed (Figure 8) that the dissolution profiles of naringenin and hesperetin from PVP nanodispersion after 3-month storage at 40°C and 75% RH did not change with respect to the initial profiles.

Moreover, from the XRD patterns (Figure 9) of pure PVP and PVP nanodispersion of naringenin and hesperetin

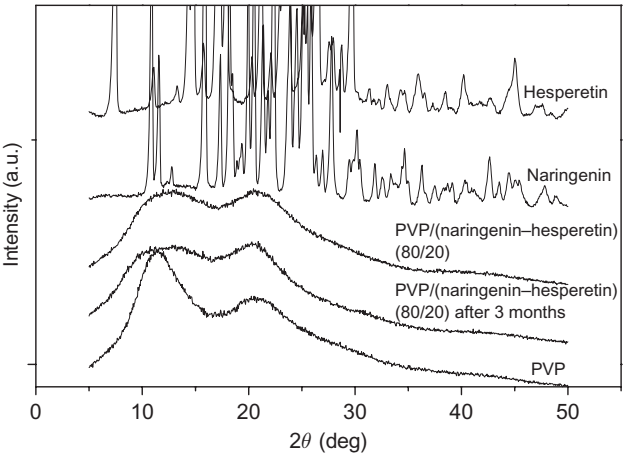

Figure 9. XRD patterns of PVP, PVP nanodispersion systems with flavanone aglycones before and after 3 months.

before and after 3 months, it was concluded that there were only two broad peaks corresponding to the diffraction pattern of pure PVP. Peaks corresponding to naringenin or hesperetin were completely disappeared, suggesting that the crystallization of the drug was inhibited by the PVP. Similar observations of PVP solid dispersions with other drugs were also reported[26,27]. This can be attributed to PVP, which is a strong proton acceptor able to form easily hydrogen bonds with other proton donor groups[28]. This indicates that there was a large margin of safety with respect to potential crystallization of compounds in the formulation of PVP solid dispersion.

Conclusion

In this study, the dissolution rate and the mechanism of release of the flavanone aglycones, naringenin and hesperetin, in a nanodispersion system with PVP were investigated. Differences between capsule and tablet release profiles were attributed to the applied tableting force. The release mechanism for both capsules and tablets was described by the diffusion model (Higuchi model). Physical and chemical stability was investigated for the examined system and all used excipients under accelerated storage conditions (40°C and 75% RH) for 3 months. HPLC analysis, powder XRD, and dissolution testing revealed that the examined formulations were stable (no degradation or recrystallization of the two drugs was observed).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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