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Article

Characterization of Hesperidin-PEG 1000 Solid Dispersion Prepared by Freeze Drying Method

Aga Mikail[1], Aditya Trias Pradana[2]*, Endang Wahyu Fitriani[2], Agnes Nuniek Winantari[2], Astridani Rizky Putranti[2], Xandramela Limala Alicya Junaidi Lee[3]

[1]Master of Pharmacy Program, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia
[2]Department of Pharmaceutical Manufacturing, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia
[3]Program Study of Pharmacy, Faculty of Pharmacy, Universitas Surabaya, Surabaya, Indonesia

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Abstract. Hesperidin is a disaccharide-derivative bioflavonoid in BCS class II, insoluble in water but soluble in propylene glycol and polyethylene glycol, and its poor aqueous solubility may impair bioavailability, necessitating modification via solid dispersion. In this study, a hesperidin–PEG 1000 system was prepared at 1:1 and 1:6 hesperidin:PEG 1000 ratios using freeze-drying. The systems were characterised for crystallinity, thermal behaviour, vibrational transitions, and particle morphology. PXRD patterns recorded over 2θ = 5–40° showed that both solid dispersions retained the main diffraction peaks of pure hesperidin with reduced intensities, indicating preservation of a predominantly crystalline structure. DSC thermograms revealed a hesperidin melting peak at 261.0 °C for the pure drug, which shifted to 248.6 °C and 241.0 °C for the 1:1 and 1:6 systems, respectively, without disappearance of the drug melting event. Data from FTIR and SEM further indicated only minor molecular interactions and limited morphological changes, and the characterisation results for both ratios were essentially identical. Taken together, these findings indicate that freeze-drying hesperidin with PEG 1000 under the applied conditions did not convert hesperidin into an amorphous, molecularly dispersed solid dispersion, but yielded a predominantly crystalline, hesperidin-dominated system with minimal PEG 1000 incorporation.

Corresponding Author :
Aditya Trias Pradana
Department of Pharmaceutical Manufacturing, Faculty of Pharmacy,
Universitas Surabaya, Surabaya, Indonesia
Email: aditya_trias@staff.ubaya.ac.id

1. Introduction

Oral administration is the most commonly used route due to its ease of use, relatively low cost, and patient convenience, which ultimately enhances therapeutic compliance. Despite this, low solubility of active ingredients is a major hurdle in oral drug development. More than 40% of new chemical entities are reported to be poorly soluble in water, restricting absorption and bioavailability [1]. This is particularly relevant for the Biopharmaceutical Classification System (BCS) class II drugs, which are highly permeable but poorly soluble in aqueous media.

Hesperidin is a bioflavonoid classified as a BCS class II compound, characterized by its lipophilic nature (log P 1.78 ± 0.72) and very low aqueous solubility [2]. Despite this limitation, hesperidin exhibits diverse pharmacological properties, including antioxidant, anti-inflammatory, antibacterial, cardioprotective, and anticancer effects [3]. Due to the poor solubility of hesperidin, various strategies have been developed to enhance its dissolution. These approaches include preparing amorphous solid dispersions and using polymer-based systems with carriers such as PVP K30 and mannitol. Such methods have demonstrated improved solubility of hesperidin [4].

Different strategies have been applied to increase drug solubility, including chemical modification, physical modification, and micellar-based approaches [5]. One of the most widely applied approaches is the solid dispersion system, in which a hydrophobic drug is dispersed within a hydrophilic matrix. This system can improve the dissolution surface area, reduce crystallinity, and generate amorphous forms that dissolve more readily [6]. The freeze-drying method has become one of the most frequently employed techniques, as it is suitable for thermolabile substances and can be applied both in laboratory and industrial scales [7]. With its favorable molecular characteristics, PEG 1000 has the potential to improve hesperidin solubility through solid dispersion formation.

Polyethylene glycol (PEG) is a hydrophilic carrier commonly utilized in solid dispersion systems due to its water solubility, low cost, and ability to form amorphous dispersions. Previous studies have demonstrated that PEG 1000 effectively enhances the solubility of several hydrophobic drugs, such as dipyridamole, phenacetin, and meloxicam [8]. Compared with previously reported hesperidin formulations employing PVP K30 or mannitol as carriers, the use of PEG 1000 offers a different balance of hydrophilicity, melting behaviour, and processability, making it an attractive alternative for generating solid dispersion systems under mild conditions [9].

Based on these considerations, this study aimed to develop a hesperidin–PEG 1000 solid dispersion system using the freeze-drying method at ratios of 1:1 and 1:6. A 70% ethanol solution (ethanol–water 7:3) was selected as the processing solvent to provide sufficient solubility for PEG 1000 while continuing limited solubility for hesperidin, thereby enabling co-processing of both components under conditions compatible with freeze-drying and with controlled residual water content in the frozen mass. This solvent composition was expected to facilitate intimate contact between hesperidin and PEG 1000 during mixing and freezing, while remaining suitable for subsequent sublimation during lyophilisation [10]. The resulting systems were characterized using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared (FTIR), and scanning electron microscopy (SEM) to evaluate changes in crystallinity, molecular interactions, and particle morphology.

2. Method

2.1. Research Design

This study employed an experimental design to develop solid dispersions of hesperidin with PEG 1000 as the carrier, using two different ratios: 1:1 and 1:6.

2.2. Research Location

The study was conducted at the Solid Dosage Form Manufacture (University of Surabaya), the Microorganism Biotechnology Laboratory (University of Surabaya), the Research Laboratory (University of Surabaya), the Metallurgical Engineering Laboratory (Sepuluh Nopember Institute of Technology), and the Energy and Environment Laboratory (Sepuluh Nopember Institute of Technology). In this work, a hesperidin–PEG 1000 solid dispersion was prepared using the freeze-drying method.

2.3. Research Implementation Report

The study began with the preparation of the hesperidin–PEG 1000 solid dispersion, followed by physical characterization of the resulting solid dispersions, including crystallinity, vibrational transition, thermal analysis, and morphological changes.

2.4. Materials

Hesperidin (pro analysis, Sigma-Aldrich®), PEG 1000 (Sigma-Aldrich®), ethanol pro analysis (EMSURE®), and aquadest were used in this study.

2.5. Instruments

The instruments employed included a freeze dryer (SCANVAC), X-ray diffractometer (Philips Analytical PW3710), differential scanning calorimeter (Mettler Toledo, Germany), Fourier-transform infrared spectrophotometer (Agilent Cary 630), scanning electron microscope (Zeiss), analytical balance (OHAUS), magnetic stirring hot plate (Cirnarec SP 131320), Buchner funnel, Erlenmeyer flask, filter paper, and glass rod.

2.6. Preparation of Solid Dispersions

Hesperidin and PEG 1000 were weighed according to the predetermined ratios (1:1 and 1:6). Each material was dissolved in 70% ethanol, prepared by mixing ethanol pro analysis with distilled water at a 7:3 ratio. The two solutions were mixed under continuous stirring at room temperature using a magnetic stirrer until until homogeneous. After filtering the mixture via a Buchner funnel with vacuum, the resulting precipitate was subjected to freeze drying at −53 °C to obtain the solid dispersion. For comparison, physical mixtures of hesperidin and PEG 1000 at ratios of 1:1 and 1:6 were also prepared by simple mixing with a glass rod.

2.7. Characterization of Solid Dispersions

Various analytical methods were applied to characterize the solid dispersions and evaluate their physical and chemical features. PXRD helped determine the samples' degree of crystallinity. Approximately 250 mg of each sample was analyzed over a 2θ range of 5–40° with a Cu target and Kα filter, running at 45 kV and 40 mA. The thermal characteristics, including glass transition and melting point, were assessed using DSC. About 4 mg of each sample—including pure hesperidin, PEG 1000, physical mixture, and solid dispersion—was enclosed in aluminum pans and analyzed across a temperature range of 30–300 °C at 10 °C/min.

Fourier-transform infrared (FTIR) spectroscopy was employed to investigate possible molecular interactions among components by scanning approximately 5 mg of each sample within the wavenumber range of 400–4000 cm^{-1}. The particles' surface morphology was analyzed through SEM

at the final step of the study. Specimens were mounted on stubs with double-sided tape and examined in a vacuum to visualize particle shape and surface characteristics. All characterization results were analyzed descriptively to determine changes in crystallinity, thermal behavior, molecular interactions, and particle morphology of the solid dispersions compared with the physical mixtures and pure components.

3. Results and Discussion

3.1. Characterization Results of the Solid Dispersion System

The physical appearance of the freeze-dried product is shown in Figure 1. The powder formed has a yellowish color. The characterization results of the hesperidin–PEG 1000 solid dispersion system were obtained from crystallinity testing, vibrational transition analysis, thermal analysis, and morphological evaluation.

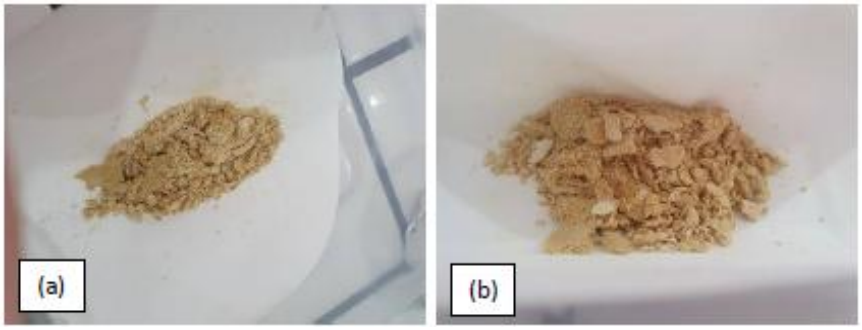

Figure 1. Results of the hesperidin–PEG 1000 solid dispersion system: (a) solid dispersion system at a 1:6 ratio; (b) solid dispersion system at a 1:1 ratio

3.2. Crystallinity

Crystallinity was analyzed using a PXRD (powder X-ray diffraction) instrument. At the same diffraction angle, a decrease in peak intensity implied the conversion from crystalline to amorphous form, confirming the formation of the solid dispersion. Crystallinity parameters were assessed for hesperidin, PEG 1000, physical mixtures of hesperidin–PEG 1000 (1:1) and (1:6), as well as solid dispersions of hesperidin–PEG 1000 (1:1) and (1:6). The diffractograms are presented in Figure 2.

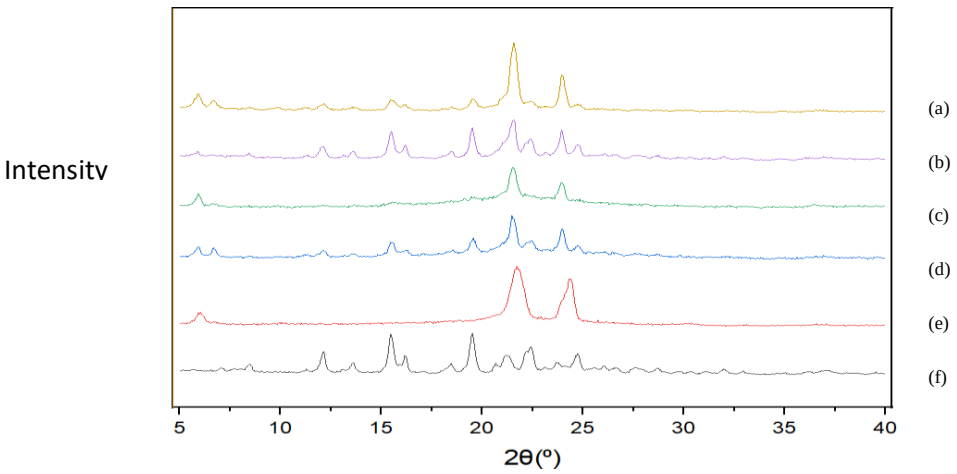

Figure 2. PXRD diffractograms: (a) hesperidin–PEG 1000 solid dispersion (1:6); (b) solid dispersion (1:1); (c) physical mixture (1:6); (d) physical mixture (1:1); (e) PEG 1000; (f) hesperidin

3.3. Thermal Behavior

DSC was employed for thermal analysis to identify the system's crystallinity by measuring melting point depression and enthalpy change (ΔH). Significant changes in ΔH and the decrease in the endothermic peak indicated interaction between the active ingredient and the carrier, serving as a marker of solid dispersion formation. Thermal analysis was carried out on hesperidin, PEG 1000, the physical mixture of hesperidin–PEG 1000 (1:1), the physical mixture of hesperidin–PEG 1000 (1:6), the solid dispersion system of hesperidin–PEG 1000 (1:1), and the solid dispersion system of hesperidin–PEG 1000 (1:6), as shown in Figure 3 and Table 1.

Table 1. Melting point data and enthalpy change (ΔH) of hesperidin, PEG 1000, physical mixtures, and solid dispersion systems of hesperidin–PEG 1000.

No.	Material	Melting Point °C	ΔH (J/g)
1	Hesperidin	71.74	-21.91
		130.78	-81.95
		261.00	-92.97
2	PEG 1000	58.19	-109.31
		250.69	63.53
3	Physical Mixture (1:1)	60.04	-28.32
		118.51	-48.12
		241.41	-6.91
		251.01	-1.83
4	Physical Mixture (1:6)	60.34	-50.77
		108.71	-5.33
		225.29	-1.48
		235.50	-1.25
5	Solid Dispersion (1:1)	63.45	-46.25
		127.61	-58.15
		248.55	-85.63
6	Solid Dispersion (1:6)	58.17	-125.07
		108.70	-11.23
		240.98	-15.69

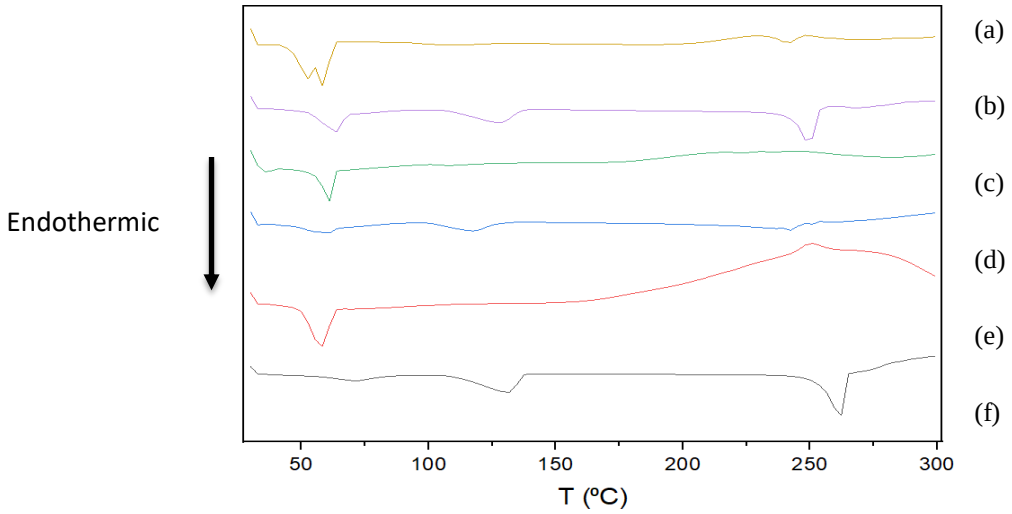

Figure 3. DSC thermograms: (a) solid dispersion system (1:6); (b) solid dispersion system (1:1); (c) physical mixture (1:6); (d) physical mixture (1:1); (e) PEG 1000; (f) hesperidin

3.4. Vibration Transition

Vibrational transitions were carried out using FTIR to examine the functional groups and chemical interactions present in hesperidin, PEG 1000, the physical mixtures, and solid dispersions. The results are shown in Figure 4 and Table 2. Functional groups and chemical bonds were identified from the % transmittance at wavenumbers. Differences in *band positions* between the solid dispersion system and pure hesperidin indicated chemical interactions between the active ingredient and the carrier in the solid dispersion system.

Table 2. FTIR spectra of pure materials, physical mixtures, and solid dispersions

Hesperidin	PEG 1000	Physical Mixture (1:1)	Physical Mixture (1:6)	Solid Dispersion (1:1)	Solid Dispersion (1:6)	Functional Group
1089.82 cm^{-1} 1126.47 cm^{-1} 1176.62 cm^{-1} 1273.06 cm^{-1}	-	1092.00 cm^{-1}	1092.00 cm^{-1}	1094.00 cm^{-1}	1096.00 cm^{-1}	CO aromatic *stretch*
-	1464.00 cm^{-1}	1465.00 cm^{-1}	-	-	1463.00 cm^{-1}	Alkanes CH *bend* (1485-1445)
1517.00 cm^{-1}	-					C=C aromatic *stretch*
1641.48 cm^{-1}	-	1646.00 cm^{-1}	1646.00 cm^{-1}	1646.00 cm^{-1}	1647.00 cm^{-1}	Carbonyl C=O *stretch*
-	2945.40 cm^{-1}	2917.00 cm^{-1}	2917.00 cm^{-1}	2917.00 cm^{-1}	2917.00 cm^{-1}	Alkanes CH *stretch* (2935-2915)
3471.91 cm^{-1}	-	3476.00 cm^{-1}	3470.00 cm^{-1}	3476.00 cm^{-1}	-	OH *stretch*

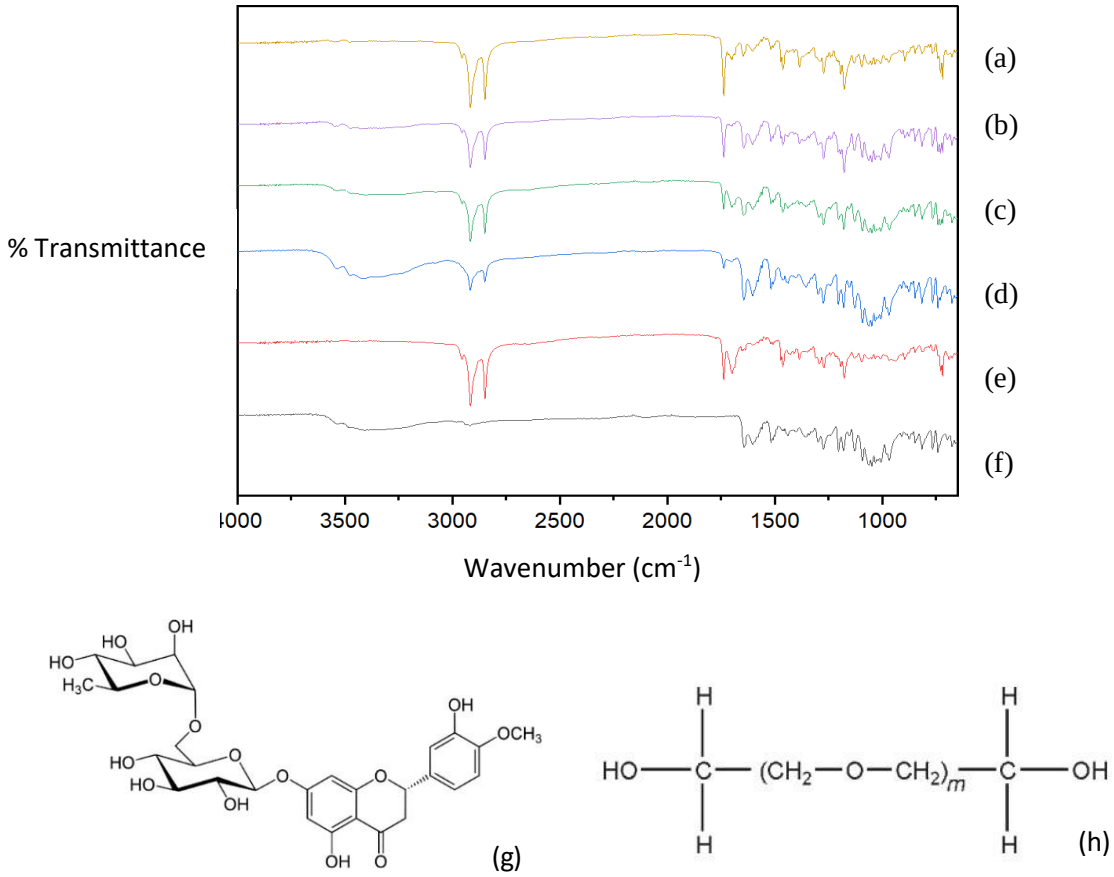

Figure 4. FTIR spectra: (a) solid dispersion (1:6); (b) solid dispersion (1:1); (c) physical mixture (1:6); (d) physical mixture (1:1); (e) PEG 1000; (f) hesperidin; (g) hesperidin structure; (h) PEG 1000 structure

3.5. Morphology Change

SEM results were used to indicate the presence of morphological changes from crystalline to amorphous forms, compared to hesperidin. Morphological change analysis was carried out on hesperidin, PEG 1000, a physical mixture of hesperidin–PEG 1000 (1:1), a physical mixture of hesperidin–PEG 1000 (1:6), the hesperidin–PEG 1000 (1:1) solid dispersion system, and the hesperidin–PEG 1000 (1:6) solid dispersion system. The surface morphology obtained from SEM observations is shown in Figure 5.

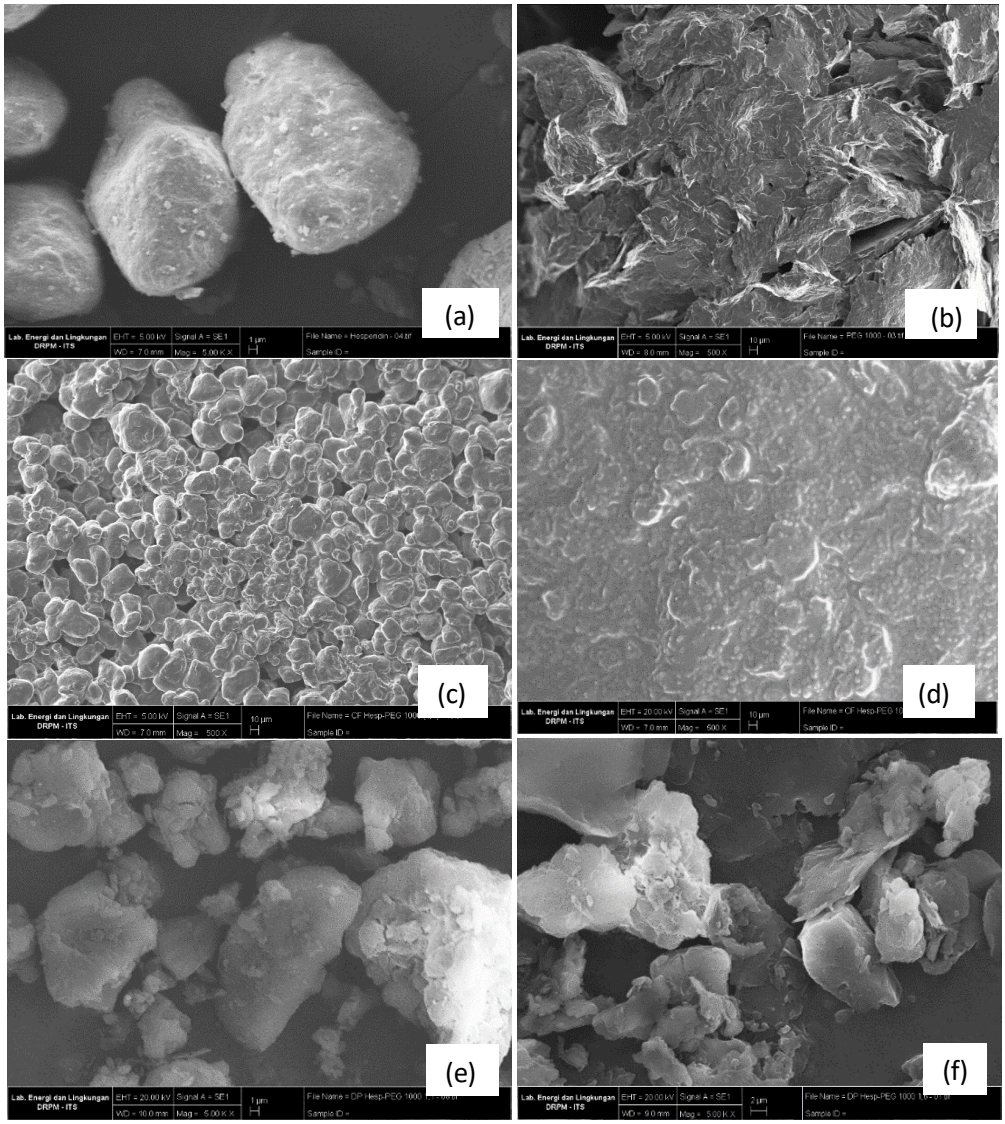

Figure 5. SEM photomicrograph at 5000× magnification: (a) hesperidin; (b) PEG 1000; (c) physical mixture of hesperidin–PEG 1000 (1:1); (d) physical mixture of hesperidin–PEG 1000 (1:6); (e) solid dispersion of hesperidin–PEG 1000 (1:1); (f) solid dispersion of hesperidin–PEG 1000 (1:6)

Hesperidin is a bioflavonoid glycoside of the flavanone group that can function as an antioxidant, anti-inflammatory agent, and is effective in preventing cardiovascular disease [11] Although it has many pharmacological benefits, hesperidin has low water solubility, resulting in low bioavailability in the body [12]. The established formula was chosen with PEG 1000 as a carrier, referring to earlier work that employed the same polymer with different active ingredients. The selected ratios were 1:1 and 1:6. The selected ratios were 1:1 and 1:6. The 1:1 ratio had previously been reported as the most optimal among ten tested ratios, as no separate crystalline phase of dipyridamole remained and the maximum drug concentration was achieved. At this ratio, the concentration of drug dissolved in water increased up to five-fold. In addition, studies on solid dispersions of Phenacetin–PEG 1000 identified the 1:5 and 1:6 ratios as the most favorable [13].

Freeze drying is one of the methods for making solid dispersions that has many advantages, namely, it is suitable for thermolabile materials and relies on the sublimation process to remove solvents without changing the structure of the active ingredient. In preparing solid dispersions, hesperidin and the PEG 1000 carrier were each dissolved in 70% ethanol, and then the two solutions were mixed in a beaker [14]. The beaker was stirred on a magnetic stirrer for about 30 minutes until the mixture appeared fully dissolved and there were no lumps. The mixture was then poured into a Buchner funnel attached to an Erlenmeyer flask connected to a suction pump. After about 45 minutes, the remaining solid on the filter paper in the Buchner funnel was scraped off and stored in a closed container. The solid was then subjected to the freeze-drying process. During freeze drying, the remaining water in the solid was frozen and removed by sublimation.

The crystalline profile was observed using a powdered X-ray diffraction (PXRD) instrument by monitoring the decrease in peak intensity in the solid dispersion compared to pure hesperidin. A decrease in peak intensity was observed in the hesperidin–PEG 1000 (1:1) solid dispersion compared with pure hesperidin. Similarly, the hesperidin–PEG 1000 (1:6) solid dispersion exhibited a reduction in peak intensity relative to hesperidin. The consistent decrease in peak intensity at the same diffraction angles, along with the attenuation of characteristic peaks, suggests the occurrence of molecular interactions between hesperidin and PEG 1000. When compared, the hesperidin–PEG 1000 solid dispersions at ratios of 1:1 and 1:6 showed similar crystallinity [15].

DSC was employed for thermal analysis, showing a decline in melting point and enthalpy values. The thermal analysis of hesperidin presents a well-defined peak at 261 °C. In the solid dispersion systems (1:1) and (1:6), there is a decrease in the endothermic peak and ΔH compared to hesperidin. The solid dispersion system exhibits melting points of 248.55 °C for the 1:1 ratio and 240.98 °C for the 1:6 ratio. This shift indicates an interaction between hesperidin and PEG 1000. Vibrational transition analysis was carried out using FTIR (ATR) to observe functional groups and molecular interactions [16]. The hesperidin spectrum displays a sloping signal at 3471.91 cm^{-1}, reflecting an O–H group [17]. Conversely, the PEG 1000 spectrum features a well-defined peak at 2945.40 cm^{-1}, corresponding to an alkane C–H group [18]. The spectra of the physical mixtures (1:1 and 1:6) show properties of both hesperidin and the carrier, with a sloping peak at 3470 cm^{-1} (O–H) [19] and a sharp peak at 2935–2915 cm^{-1} (C–H) [20]. The spectrum of the solid dispersion system (1:1) shows a sharp peak at 2917 cm^{-1} (C–H) and a gentle O–H peak with a smaller % transmittance [21]. The spectrum of the solid dispersion system (1:1 and 1:6) shows a sharp peak at 2917 cm^{-1} (C–H), but no gentle peak at 3470 cm^{-1} (O–H) [22-23].

This confirms interaction between hesperidin and PEG 1000. Morphological analysis using SEM compared the differences in size and shape between hesperidin particles and solid dispersions. SEM was carried out at 5000× magnification [22]. In Figure 5, the surfaces of the solid dispersion particles (1:1 and 1:6) show little difference in shape and surface compared with hesperidin and the physical mixtures. All characteristic changes (crystallinity, thermal analysis, vibrational transitions, and surface morphology) indicate similarities between hesperidin and the formed system [24]. Between the two systems (1:1 and 1:6), identical characteristics were observed. The initial objective of this study was to obtain a hesperidin–PEG 1000 solid dispersion. However, the processing steps introduced a significant limitation in interpreting the results. During Buchner filtration, PEG 1000, which is highly soluble in 70% ethanol, remained mostly in the filtrate. In contrast, hesperidin, being practically insoluble in this solvent, precipitated and was collected as the solid fraction for freeze-drying.

As a result, the freeze-dried material characterised by PXRD, DSC, FTIR, and SEM consisted primarily of precipitated hesperidin, with only a minimal amount of PEG 1000 incorporated. This outcome explains the observed crystallinity, thermal behaviour, vibrational transitions, and morphology of the resulting systems. These properties closely resembled those of pure hesperidin and were essentially indistinguishable between the 1:1 and 1:6 ratios. Based on these findings, the preparations obtained should be classified as hesperidin-dominated crystalline systems with limited carrier contribution, rather than classical amorphous molecularly dispersed solid dispersions [25]. In

the future, avoid the filtration step and instead remove the solvent directly from the entire hesperidin–PEG 1000 mixture. Methods such as slow evaporation followed by freeze-drying will help ensure both components remain in the solid matrix throughout processing [26].

In this study, hesperidin is insoluble in ethanol, even though the literature reports it should be soluble [27]. Meanwhile, PEG 1000 is soluble in ethanol [28]. In Buchner filtration, PEG 1000 dissolved in ethanol becomes the filtrate, while hesperidin precipitates. This precipitate is then freeze-dried and characterized, so the observed properties in both ratios are dominated by hesperidin [28]. As a suggestion, future research is recommended to slowly evaporate ethanol from the entire system without filtration. Evaporation should continue until a concentrated solid mass is formed, which can then be freeze-dried and characterized [29,30]. From a thermodynamic and physicochemical perspective, the combination of 70% ethanol and Buchner filtration employed in this study is not conducive to the formation of solid dispersions. In conventional solid dispersion processes, both the drug and the carrier are typically co-dissolved or uniformly dispersed in a common solvent or solvent mixture [31].

The solvent is subsequently removed from the entire system, resulting in the drug being molecularly dispersed within the solidified carrier matrix. In contrast, the solvent system used here produced a pronounced solubility disparity. PEG 1000 dissolved readily in 70% ethanol, whereas hesperidin remained essentially insoluble under the experimental conditions [32]. Vacuum filtration then induced phase separation: the PEG-rich solution passed into the filtrate, while the hesperidin-rich solid was retained on the filter. Consequently, the subsequent freeze-drying step acted primarily on a suspension dominated by crystalline hesperidin, rather than on a homogeneous hesperidin–PEG 1000 solution [33] . This phase behavior aligns with the PXRD, DSC, FTIR, and SEM data, which collectively indicate that the final solids retained the crystallinity and morphology of hesperidin, with only minor contributions from PEG 1000.

Therefore, the product did not fulfill the criteria for an amorphous, molecularly dispersed solid dispersion [34]. A further limitation of this study is the absence of direct solubility or dissolution testing. Although solid dispersion technology is primarily intended to enhance the solubility and dissolution rate of poorly water-soluble drugs, the present investigation focused exclusively on solid-state and morphological characterization of the hesperidin–PEG 1000 systems [35,36]. As a result, no definitive conclusions can be drawn regarding improvements in hesperidin solubility or dissolution performance based solely on these data. To comprehensively assess the effectiveness of future hesperidin solid dispersion formulations, quantitative solubility and/or dissolution studies in relevant media should be conducted in parallel with PXRD, DSC, FTIR, and SEM analyses [37].

4. Conclusion

The results indicate that preparation of hesperidin–PEG 1000 systems at 1:1 and 1:6 ratios by freeze-drying under the applied conditions did not produce an amorphous, molecularly dispersed solid dispersion of hesperidin. PXRD, DSC, FTIR, and SEM analyses demonstrate that both formulations remained predominantly crystalline and were primarily influenced by the solid-state properties of hesperidin, with only minor contributions from PEG 1000. The nearly identical solid-state characteristics observed for both ratios suggest that the current process parameters were inadequate to achieve a true solid dispersion within the PEG 1000 matrix. Future studies should optimise the solvent system, eliminate the filtration step, and incorporate quantitative solubility or dissolution testing to more definitively evaluate the potential of PEG 1000-based solid dispersions to enhance the biopharmaceutical performance of hesperidin.

References

[1] Bhalani, D. V., Nutan, B., Kumar, A., & Singh Chandel, A. K. (2022). Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. *Biomedicines*, *10*(9).

[2] Kumar, S. V. P., Vishwanath, B. A., & Swapna, D. (2024). Enhancement of solubility and dissolution rate of BCS class II drugs. *International Journal of Pharmaceutical Sciences Review and Research*, *84*(7).

[3] Shekaari, H., Zafarani-Moattar, M. T., Mokhtarpour, M., & Faraji, S. (2023). Solubility of hesperidin drug in aqueous biodegradable acidic choline chloride-based deep eutectic solvents. *Scientific Reports*, *13*(1).

[4] Swarup, P., & Agrawal, G. P. (2024). Development of hesperidin solid dispersion for improved solubility and dissolution using mannitol and PVP K30 as carriers. *Journal of Applied Pharmaceutical Research*, *12*(6), 192–202.

[5] Xie, B., Liu, Y., Li, X., Yang, P., & He, W. (2024). Solubilization techniques used for poorly water-soluble drugs. *Acta Pharmaceutica Sinica B*, 14(11), 4683–4716.

[6] Hashmi, A. R., Sekar, M., Zahra, F., Molugulu, N., & Wong, L. S. (2025). Advanced drug delivery strategies to overcome solubility and permeability challenges: Driving biopharmaceutical advancements toward commercial success. *ACS Omega*, *10*(36), 40769–40792.

[7] Tekade, A. R., & Yadav, N. J. (2020). A review on solid dispersion and carriers used therein for solubility enhancement of poorly water soluble drugs. *Advanced Pharmaceutical Bulletin*, 359–369.

[8] Pisano, R., & Fissore, D. (2023). New trends in freeze-drying of pharmaceutical products. *Pharmaceutics*, *15*(7).

[9] Bessarabov, V., Lisovyi, V., Lyzhniuk, V., Kostiuk, V., Smishko, R., Yaremenko, V., ... & Melnyk, V. (2025). Development and characterisation of polymeric solid dispersed systems of hesperidin, obtained by centrifugal fibre formation. *Heliyon*, *11*(4).

[10] Pardeshi, S. R., Deshmukh, N. S., Telange, D. R., Nangare, S. N., Sonar, Y. Y., Lakade, H. S., ... & Sangshetti, J. N. (2023). Process development and quality attributes for the freeze-drying process in pharmaceuticals, biopharmaceuticals and nanomedicine delivery: A state-of-the-art review. *Future Journal of Pharmaceutical Sciences*, *9*(1).

[11] Khorasanian, A. S., Fateh, S. T., Gholami, F., Rasaei, N., Gerami, H., Khayyatzadeh, S. S., ... & Asbaghi, O. (2023). The effects of hesperidin supplementation on cardiovascular risk factors in adults: A systematic review and dose–response meta-analysis. *Frontiers in Nutrition*, *10*.

[12] Paczkowska-Walendowska, M., Miklaszewski, A., & Cielecka-Piontek, J. (2023). Improving solubility and permeability of hesperidin through electrospun orange-peel-extract-loaded nanofibers. *International Journal of Molecular Sciences*, *24*(9).

[13] Gerasimov, A. V., Ziganshin, MA., Gorbatchuk, V. V., & Usmanova, L. S. (2013). Formation of solid dispersion of PEG-1000 with phenacetin according to differential scanning calorimetry. *Der Pharma Chemica*, *5*(4), 133–139.

[14] Mundada, A. S. (2021). Solid dispersion: A review. *International Journal of Pharmacy Research & Technology*, *11*(2).

[15] Almeida, H., Ferreira, B., Fernandes-Lopes, C., Araújo, F., Bonifacio, M. J., Vasconcelos, T., ... & Soares-da-Silva, P. (2024). Third-generation solid dispersion through lyophilization enhanced oral bioavailability of resveratrol. *ACS Pharmacology & Translational Science*, *7*(3), 888–898.

[16] Bessarabov, V., Lisovyi, V., Lyzhniuk, V., Kostiuk, V., Smishko, R., Yaremenko, V., ... & Melnyk, V. (2025). *Development and characterisation of polymeric solid dispersion systems of hesperidin obtained by the method of centrifugal fibre formation*.

[17] Yaghoubi, N., Gholamzad, A., Naji, T., & Gholamzad, M. (2024). In vitro evaluation of PLGA loaded hesperidin on colorectal cancer cell lines: An insight into nano delivery system. *BMC Biotechnology*, *24*(1).
[18] Brogly, M., Bistac, S., & Bindel, D. (2024). Adsorption and structuration of PEG thin films: Influence of the substrate chemistry. *Polymers*, *16*(9).
[19] Rosiak, N., Wdowiak, K., Tykarska, E., & Cielecka-Piontek, J. (2022). Amorphous solid dispersion of hesperidin with polymer excipients for enhanced apparent solubility as a more effective approach to the treatment of civilization diseases. *International Journal of Molecular Sciences*, *23*(23).
[20] Invernizzi, C., Rovetta, T., Licchelli, M., & Malagodi, M. (2018). Mid and near-infrared reflection spectral database of natural organic materials in the cultural heritage field. *International Journal of Analytical Chemistry*, *2018*.
[21] Sip, S., Sip, A., Miklaszewski, A., Żarowski, M., & Cielecka-Piontek, J. (2023). Zein as an effective carrier for hesperidin delivery systems with improved prebiotic potential. *Molecules*, *28*(13).
[22] Dai, F., Zhuang, Q., Huang, G., Deng, H., & Zhang, X. (2023). Infrared spectrum characteristics and quantification of OH groups in coal. *ACS Omega*, *8*(19), 17064–17076.
[23] Campanale, C., Savino, I., Massarelli, C., & Uricchio, V. F. (2023). Fourier transform infrared spectroscopy to assess the degree of alteration of artificially aged and environmentally weathered microplastics. *Polymers*, *15*(4).
[24] Patel, K., Shah, S., & Patel, J. (2022). Solid dispersion technology as a formulation strategy for the fabrication of modified release dosage forms: A comprehensive review. *DARU Journal of Pharmaceutical Sciences*, 165–189.
[25] De Oliveira Cardoso Melo, M. E., Castro da Silva, C., Dos Santos Dantas, T., Barbosa Machado, JC., Assunção Ferreira, M. R., & Lira Soares, L. A. (2026). Amorphous solid dispersions as a strategy to enhance the bioavailability and stability of formulations containing plant active ingredients: An integrative review. *DARU Journal of Pharmaceutical Sciences*.
[26] Xiao, H., Feng, Y., Goundry, W. R. F., & Karlsson, S. (2024). Organic solvent nanofiltration in pharmaceutical applications. *Organic Process Research & Development*, 891–923.
[27] Rosiak, N., Wdowiak, K., Tykarska, E., & Cielecka-Piontek, J. (2022). Amorphous solid dispersion of hesperidin with polymer excipients for enhanced apparent solubility as a more effective approach to the treatment of civilization diseases. *International Journal of Molecular Sciences*, *23*(23).
[28] Bertoni, S., Albertini, B., & Passerini, N. (2023). Investigating the physicochemical properties of solid dispersions based on semicrystalline carriers: A case study with ketoprofen. *International Journal of Pharmaceutics*, *632*.
[29] Malkawi, R., Malkawi, W. I., Al-Mahmoud, Y., & Tawalbeh, J. (2022). Current trends on solid dispersions: Past, present, and future. *Advances in Pharmacological and Pharmaceutical Sciences*, *2022*.
[30] De Mohac, L. M., Caruana, R., Cavallaro, G., Giammona, G., & Licciardi, M. (2020). Spray-drying, solvent-casting and freeze-drying techniques: A comparative study on their suitability for the enhancement of drug dissolution rates. *Pharmaceutical Research*, *37*(3).
[31] Thomas, M., Nabais, A. R., Burggraef, M. J., Peeva, L., Murray, J., & Livingston, A. G. (2025). Enabling High-Boiling-Point Green Solvent Recycling Using Organic Solvent Nanofiltration Membranes. *ChemSusChem*, *18*(21), e202501117.
[32] Xie, B., Liu, Y., Li, X., Yang, P., & He, W. (2024). Solubilization techniques used for poorly water-soluble drugs. *Acta Pharmaceutica Sinica B*, 4683–4716.

[33] Le Khanh, H. P., Haimhoffer, Á., Nemes, D., Józsa, L., Vasvári, G., Budai, I., ... & Fenyvesi, F. (2023). Effect of molecular weight on the dissolution profiles of PEG solid dispersions containing ketoprofen. *Polymers*, *15*(7).
[34] Jelić, D. (2021). Thermal stability of amorphous solid dispersions. *Molecules*, *26*(1).
[35] Joshi, S., Dhingra, A. K., Chopra, B., Dass, R., Guarve, K., & Sapra, S. (2023). Formulation and evaluation of solid dispersions of poorly water-soluble drug-hesperidin. *Letters in Applied NanoBioScience*, *12*(2).
[36] Kanaze, F. I., Kokkalou, E., Niopas, I., Georgarakis, M., Stergiou, A., & Bikiaris, D. (2006). Dissolution enhancement of flavonoids by solid dispersion in PVP and PEG matrixes: A comparative study. *Journal of Applied Polymer Science*, *102*(1), 460–471.
[37] Akram, A., Irfan, M., Abualsunun, W. A., Bukhary, D. M., & Alissa, M. (2022). How to improve solubility and dissolution of irbesartan by fabricating ternary solid dispersions: Optimization and in-vitro characterization. *Pharmaceutics*, *14*(11).