© 2024 Journal of Pharmacy & Pharmacognosy Research, 12 (1), 175-183, 2024
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres23.1734_12.1.175

Original Article

Enhancing the solubility and dissolution rate of piperine via preparation of piperine–hydroxypropyl methylcellulose 2910 solid dispersion system using freeze-drying method

[Mejora de la solubilidad y la velocidad de disolución de la piperina mediante la preparación de un sistema de dispersión sólida de piperina-hidroxipropilmetilcelulosa 2910 utilizando el método de liofilización]

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Abstract

Context: Piperine is the main secondary metabolite isolated from the family *Piperaceae*. This biologically active ingredient has many pharmacological effects, though its low water solubility limits its absorption in gastrointestinal fluid.

Aims: To improve piperine's solubility and dissolution rate by incorporating it into a solid dispersion system with the hydrophilic polymer hydroxypropyl methylcellulose (HPMC) 2910 via the freeze-drying method.

Methods: Three different piperine:polymer ratios – 1:1, 1:2, and 2:1 (w/w) – were prepared. A physical mixture was also prepared in a 1:1 (w/w) ratio for comparison. The physicochemical properties of the samples were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD) analysis, Fourier transform infrared (FTIR) spectroscopy, and scanning electron microscopy (SEM). The solubility and dissolution tests were conducted in distilled water.

Results: The solid dispersion characterization indicated a decrease in the melting points and endothermic peaks in the DSC analysis, a decrease in peak intensity in the PXRD patterns, no chemical interactions between active substances and polymers in the FTIR analysis, and significant morphological changes in the SEM analysis. The solubility test revealed the highest increase in piperine solubility (7.88-fold increase) for the 1:2 solid dispersion. Moreover, the 1:2 solid dispersion in the dissolution test led to the greatest amount of dissolved piperine (56.445 ± 1.13%).

Conclusions: The piperine–HPMC solid dispersion system improved the solubility and dissolution rate of piperine.

Keywords: dissolution; freeze drying; HPMC 2910; piperine; solid dispersion; solubility.

Resumen

Contexto: La piperina es el principal metabolito secundario aislado de la familia *Piperaceae*. Este ingrediente biológicamente activo tiene muchos efectos farmacológicos, aunque su baja solubilidad en agua limita su absorción en el líquido gastrointestinal.

Objetivos: Mejorar la solubilidad y la velocidad de disolución de la piperina incorporándola a un sistema de dispersión sólida con el polímero hidrófilo hidroxipropilmetilcelulosa (HPMC) 2910 mediante el método de liofilización.

Métodos: Se prepararon tres proporciones diferentes de piperina:polímero: 1:1, 1:2 y 2:1 (p/p). También se preparó una mezcla física en proporción 1:1 (p/p) para comparar. Las propiedades fisicoquímicas de las muestras se caracterizaron mediante calorimetría diferencial de barrido (DSC), análisis de difracción de rayos X en polvo (PXRD), espectroscopia infrarroja por transformada de Fourier (FTIR) y microscopia electrónica de barrido (SEM). Las pruebas de solubilidad y disolución se realizaron en agua destilada.

Resultados: La caracterización de la dispersión sólida indicó una disminución de los puntos de fusión y de los picos endotérmicos en el análisis DSC, una disminución de la intensidad de los picos en los patrones PXRD, ausencia de interacciones químicas entre las sustancias activas y los polímeros en el análisis FTIR, y cambios morfológicos significativos en el análisis SEM. La prueba de solubilidad reveló el mayor aumento en la solubilidad de la piperina (7,88 veces más) para la dispersión sólida 1:2. Además, la dispersión sólida 1:2 mostró un aumento en la solubilidad de la piperina. Además, la dispersión sólida 1:2 en la prueba de disolución produjo la mayor cantidad de piperina disuelta (56,445 ± 1,13%).

Conclusiones: El sistema de dispersión sólida piperina-HPMC mejoró la solubilidad y la velocidad de disolución de la piperina.

Palabras Clave: disolución; liofilización; HPMC 2910; piperina; dispersión sólida; solubilidad.

ARTICLE INFO
Received: July 4, 2023.
Accepted: October 31, 2023.
Available Online: December 1, 2023.

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INTRODUCTION

Piperine (1-piperoylpiperidine) is an alkaloid and secondary metabolite found in black pepper (*Piper nigrum*), long pepper (*Piper longum*), and other pepper species belonging to the Piperaceae family. This compound has been widely used in traditional medicine in many Asian countries to treat conditions such as rheumatism, muscle pain, dyspepsia, flatulence and indigestion, and sore throat and coughing; in addition, it is used as a digestive tonic and exhibits antipyretic, antiseptic, bactericidal, insecticidal, and diuretic effects and activities (Gorgani et al., 2017; Meghwal and Goswami, 2013; Smilkov et al., 2019; Srinivasan, 2007). Studies have indicated that piperine increases the bioavailability of foods, drugs, anticarcinogens, and phytochemicals and inhibits drug-metabolizing enzymes (Meghwal and Goswami, 2013). Several studies have also investigated the pharmacological effects of piperine, such as its anti-inflammatory, analgesic, antidepressant, cytoprotective, antileukemic, and antioxidant properties (Ashour et al., 2016).

However, piperine is poorly soluble in aqueous media and has a melting point of 135°C, limiting its utilization in the preparation of pharmaceutical dosages (Ashour et al., 2016; Chonpathompikunlert et al., 2010). Most active pharmaceutical ingredients (APIs) that exhibit poor water solubility likely result in a low absorption profile after oral administration. Thus, increasing the solubility and dissolution rate of these drugs is one of the key ways to increase drug bioavailability, which can be regarded as the greatest challenge in the pharmaceutical industry (Savjani et al., 2012). Various techniques have been used to improve the solubility and release profile of piperine, including its incorporation into microparticles (Bonepally et al., 2008), inclusion complexes (Alshehri et al., 2020), multicomponent crystals (Zaini et al., 2020), nanosuspensions (Zafar et al., 2019), and solid dispersion systems (Thenmozhi and Yoo, 2017; Zaini et al., 2021).

In pharmaceutical manufacturing, solid dispersion (SD) is a simple and effective method for increasing the solubility of poorly water-soluble APIs. SDs are systems in which hydrophobic APIs are molecularly dispersed in one or more hydrophilic carriers to reduce the particle size, enhance the surface area, improve wettability, and convert the crystalline APIs to amorphous states (Bhujbal et al., 2021). Various carriers employed in the generation of SDs, including acids, sugars, soluble polymers, surfactants, and inert carriers, among other compounds, have appeared in the literature with the technological advancement of the pharmaceutical sector (Bhujbal et al., 2021).

In our previous work, we prepared the piperine–hydroxypropyl methylcellulose (HPMC) 2910 solid dispersion using the spray-drying technique, which successfully increased the solubility of piperine sevenfold compared to intact piperine (Zaini et al., 2021). Therefore, this study aimed to prepare a solid dispersion system of piperine with the hydrophilic polymer HPMC 2910 via the freeze-drying method, which is a promising and suitable technique for drug incorporation into a stabilizing matrix due to the minimal thermal stress induced during solid dispersion preparation (Vo et al., 2013). The solid-state properties of the solid dispersion system were then characterized by differential screening calorimetry (DSC) thermal analysis, Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction (PXRD), and scanning electron microscopy (SEM) for the microscopic analysis. Furthermore, aqueous solubility tests were performed, and *in vitro* dissolution rate profiles in an aqueous medium were generated.

MATERIAL AND METHODS

Materials

Piperine was supplied by BOC Science (USA), HPMC 2910 was purchased from Shin-Etsu Chemical (Japan), and pro-analysis-grade ethanol and distilled water were purchased from Merck (Germany).

Preparation of solid dispersions by freeze-drying

Solid dispersions with piperine:HPMC 2910 ratios of 1:1, 1:2, and 2:1 (w/w) were prepared. HPMC was first dispersed in 40 mL of distilled water, and piperine was dissolved in 10 mL of 20% ethanol. The piperine and HPMC mixture was homogenized using a magnetic stirrer and then frozen using liquid nitrogen. Prior to the primary drying process, the freeze dryer (Christ Alpha 1-2 LD Plus, France) was set to a temperature of -50°C and a pressure of 0.056 atm. Primary drying was carried out for 14 hours, and the secondary drying process was conducted at -53°C for the next 14 hours (Fitriani et al., 2018). The dried powder was then removed from the freeze-dried flask, sieved, and finally stored in a desiccator for further characterization.

Preparation of physical mixture

A 1:1 (w/w) mixture of piperine and HPMC 2910 was prepared by physical mixing in a jar, and the resultant powder was then stored in a desiccator until analysis (Zaini et al., 2021).

Differential scanning calorimetry (DSC) analysis

The thermal properties of piperine, HPMC, the physical mixture, and the solid dispersions were analyzed using DSC apparatus (Shimadzu DSC-60 Plus, Japan). The samples were placed on aluminum pans precalibrated using indium before taking measurements. The DSC apparatus was set to a temperature range of 30–260°C with a heating rate (heat flow) of 10°C/min (Zaini et al., 2021).

Powder X-ray diffraction (PXRD) analysis

The crystallinity of piperine, HPMC, the physical mixture, and the solid dispersions was analyzed using an X-ray diffractometer (X'Pert XRD Powder type PW 30/40 PANalytical, The Netherlands) with the following settings: Cu as the target metal, a Kα filter, a voltage of 45 kV, and a current of 40 mA. The samples were placed in a sample holder, and the analysis was carried out at room temperature at a 2θ angle ranging from 5°–50° (Zaini et al., 2021).

Fourier transform infrared (FTIR) spectroscopy

FTIR analysis was performed for piperine, HPMC, the physical mixture, and the solid dispersions using a spectrophotometer (Shimadzu IRTracer-100AH, Japan). The samples were placed on the ATR crystal to cover the entire crystal surface, a small amount of pressure was applied, and the IR absorption spectrum was then generated for the samples over the wave number range of 4000–600 cm^{-1} (Zaini et al., 2021).

Scanning electron microscopy (SEM) analysis

Prior to the SEM analysis, piperine, HPMC, and the solid dispersions were sieved using a 425-µm sieve. A small amount of each sample was then placed in an aluminum sample holder of the SEM apparatus (Hitachi S-3400 N, Japan) and coated with gold approximately 10 nm in thickness to observe the surface morphology of the samples. The SEM instrument was set to a voltage of 10 kV and a current of 12 mA (Zaini et al., 2021).

Solubility test

Saturated solutions of the intact piperine, the physical mixture, and the piperine–HPMC 2910 solid dispersion in distilled water were prepared to measure the solubility of each sample. The solubility test was carried out over 24 hours using an orbital shaker at a speed of 100 rpm and a temperature of 25°C. Each sample was subsequently filtered using Whatman filter paper, and the filtrate was analyzed using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan) at 341 nm, the maximum absorption wavelength of piperine. The test was conducted in triplicate (Zaini et al., 2021).

In vitro dissolution rate profile

Dissolution testing of the piperine, physical mixture, and solid dispersions was performed using a paddle-type dissolution apparatus (Hanson Research SR08, USA) (Zaini et al., 2021). Prior to the measurements, the dissolution flask was filled with 900 mL of distilled water and set to a temperature of 37 ± 0.5°C and a speed of 50 rpm. The powders were then added to the medium, and 5 mL aliquots of the dissolution solution were pipetted at 5, 10, 15, 30, 45, and 60 minutes. After pipetting each aliquot, the medium taken was replaced with a fresh medium. The amount of dissolved piperine was calculated using UV-Vis spectrophotometric analysis (Shimadzu UV-1700, Japan) at 341 nm. The dissolution test was carried out in triplicate.

Statistical analysis

The result of the solubility test and *in vitro* dissolution test of piperin, physical mixture, and solid dispersions were presented as mean ± SD and then analyzed using one-way analysis of variance (ANOVA) with a significance level at $p<0.05$.

RESULTS

Differential scanning calorimetry (DSC) analysis

Thermal analysis is generally used to measure the energy absorbed and emitted by a sample as a function of time and temperature. The DSC apparatus can record the change in enthalpy (ΔH) and melting temperature of the sample (Zaini et al., 2021). The presence of interactions between samples is indicated by a change in the melting point of the analyzed material, which is used to assess the interactions between the active substance and polymer. Fig. 1 and Table 1 reveal a reduction in the endothermic peak, which indicates that piperine is in an amorphous state (Karataş et al., 2005). Generally, the greater the amount of polymer used, the greater the decrease in the melting point. This can occur due to the dispersion of piperine in its molecular state into the polymer matrix, where the piperine tends to form an amorphous state, commonly called partial amorphization. Thus, piperine forms amorphous solid dispersions with the hydrophilic HPMC polymer.

Powder X-ray diffraction (PXRD) analysis

PXRD is a simple method for examining solid APIs and excipient crystal structures. All solid materials have their own set of atoms and repeating units.

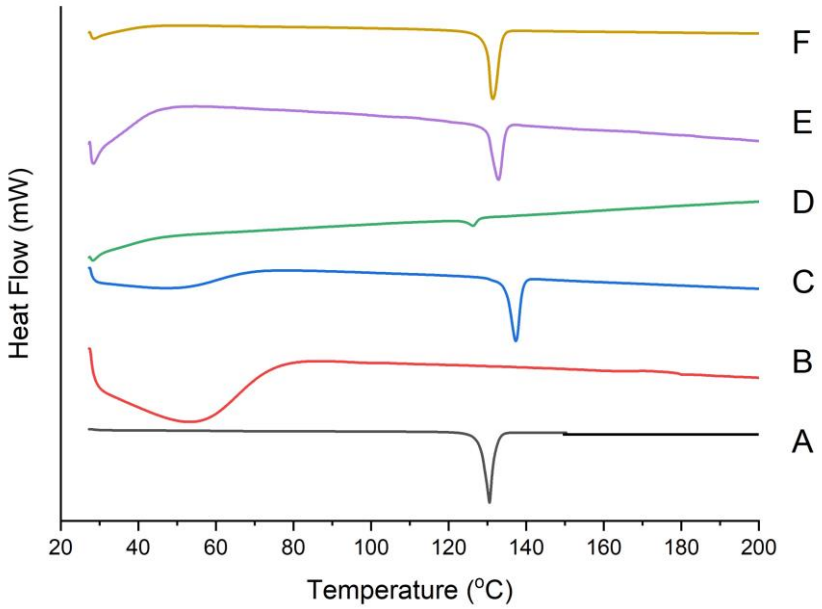

Figure 1. Thermograms of **(A)** piperine, **(B)** HPMC 2910, and **(C)** the physical mixture and those of the **(D)** 1:1, **(E)** 1:2, and **(F)** 2:1 solid dispersion.

Table 1. Melting points of piperine, the physical mixture, and the solid dispersions.

Samples	Melting point (°C)
Piperine	131.63
Physical mixture	131.61
Solid dispersion 1:1	130.08
Solid dispersion 1:2	129.87
Solid dispersion 2:1	130.71

When X-rays are utilized, these atoms are bombarded, resulting in a succession of unique peaks that may be used to identify the crystalline components. Since PXRD allows for rapid measurements of pharmaceutical solids, so it has become a popular analytical method in industry and academia (Vasconcelos et al., 2007). The results of this analysis are given as diffractograms, which show the typical peak intensity for each material (see Fig. 2 and Table 2).

As shown in Fig. 2 and Table 2, the physical mixture and solid dispersions still show some typical peaks of piperine, with a decrease in the peak intensities of crystalline solids. The numbers in Table 2 are the highest peak intensity of each sample (compound) that correlates to the crystallinity. The decrease in peak intensity indicates a change in the crystallinity of piperine; the bonds between the piperine molecules likely become weaker, which correlates to the solubility and dissolution of piperine (Okonogi and Puttipipatkhachorn, 2006). In addition, the greater the amount of HPMC 2910 used, the greater the decrease in peak intensity in the solid dispersion. This results in the change of the crystalline phase of piperine to a partial amorphous state occurs during the process of solid dispersion formation in the freeze-drying method. Similarly, solid dispersion of piperine with HPMC prepared by spray drying technique showed a decrease in peak intensity (Zaini et al., 2021). This is likely due to the effect of HPMC used in this work, which is known as a hydrophilic polymer and shows an amorphous state in the diffractogram. The amorphous or metastable forms dissolve the most rapidly due to their higher internal energy and greater molecular mobility (Zaini et al., 2017). Another study also reported the change in crystallinity of piperine prepared by a solvent evaporation method using PEG as the carrier in which some of the specific peaks intensity of piperine decreased significantly and also dismissed in the diffractogram, which indicated the solid dispersion was in an amorphous state (Thenmozhi and Yoo, 2017).

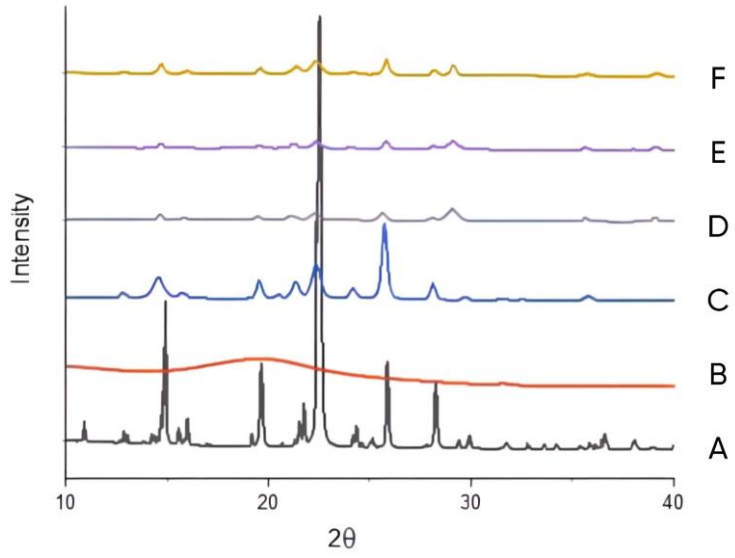

Figure 2. Diffractograms of **(A)** piperine, **(B)** HPMC 2910, and **(C)** the physical mixture and those of the **(D)** 1:1, **(E)** 1:2, and **(F)** 2:1 solid dispersion.

Table 2. Peak intensities from the PXRD analysis of piperine, the physical mixture, and the solid dispersions.

Position 2θ (°)	Peak intensity				
	Piperine	Physical mixture	Solid dispersion 1:1	Solid dispersion 1:2	Solid dispersion 2:1
5.0066	1109.480	493.399	449.111	389.859	410.472
15.8616	1009.276	799.023	411.522	355.279	474.856
19.1766	1185.018	527.459	357.625	327.956	369.066
22.3876	14288.530	2757.926	728.056	725.680	1199.020
27.6786	431.199	413.028	256.112	255.990	259.193
35.8426	704.656	572.841	268.438	261.346	327.269

Fourier transform infrared (FTIR) analysis

FTIR spectroscopy was used to analyze the chemical interactions between the solid molecules. The analysis was carried out by considering the spectral shifts in the FTIR transmission bands arising from the solid dispersion of piperine in HPMC. Infrared spectra are notably sensitive to changes in molecular structure and conformation; thus, they can be used to compare the structures of compounds in different solid phases (Dwichandra Putra et al., 2016). The FTIR spectral results are depicted in Fig. 3.

The spectra in Fig. 3 indicate that the physical mixture and solid dispersions contain functional groups similar to those in piperine and HPMC 2910. Although there are slight shifts in the wave numbers, the signals still occur in the same range of functional groups, which indicates the absence of chemical interactions in the solid dispersion of piperine and HPMC 2910. This result was presumed since solid dispersion is not prepared to yield new substances (Zaini et al., 2021). The slight shifts in the wave numbers are likely caused by the formation of hydrogen bonds arising from the interaction between two solid compounds. These hydrogen bonds facilitate the breaking of bonds between molecules when in contact with water such that one can expect an increase in the solubility and dissolution rate of piperine (Sinha et al., 2010). Compared to solid dispersion prepared by the spray drying method, the same pattern in the infrared spectrum was observed, which indicated the physical interaction between piperine and HPMC (Zaini et al., 2021). Furthermore, research on hydrophilic polymers, such as PEG and PVP, used in the solid dispersion of piperine, has revealed that the drug and carrier exhibit hydrogen bonding, which may be the primary factor promoting the drug's miscibility and molecular level distribution in solid dispersion which impeding phase separation and recrystallization (Thenmozhi and Yoo, 2017).

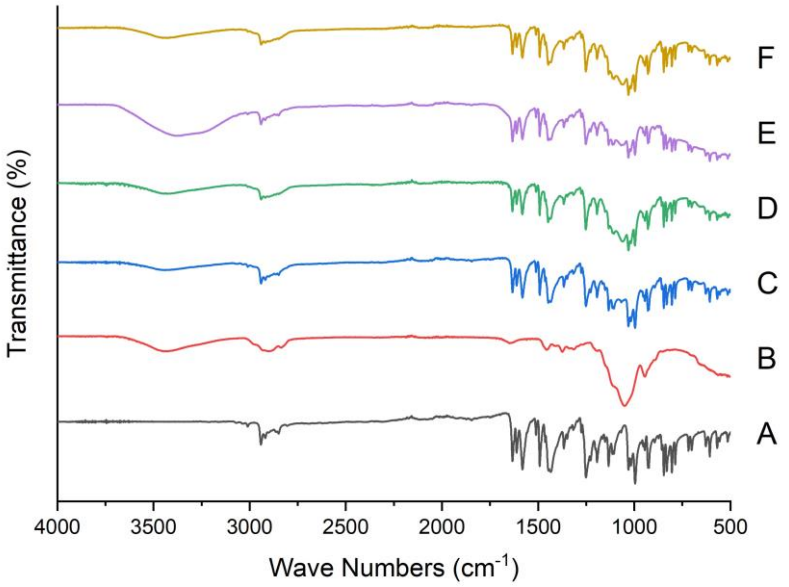

Figure 3. FTIR spectral overlays for **(A)** piperine, **(B)** HPMC 2910, **(C)** the physical mixture, and the **(D)** 1:1, **(E)** 1:2, and **(F)** 2:1 solid dispersion.

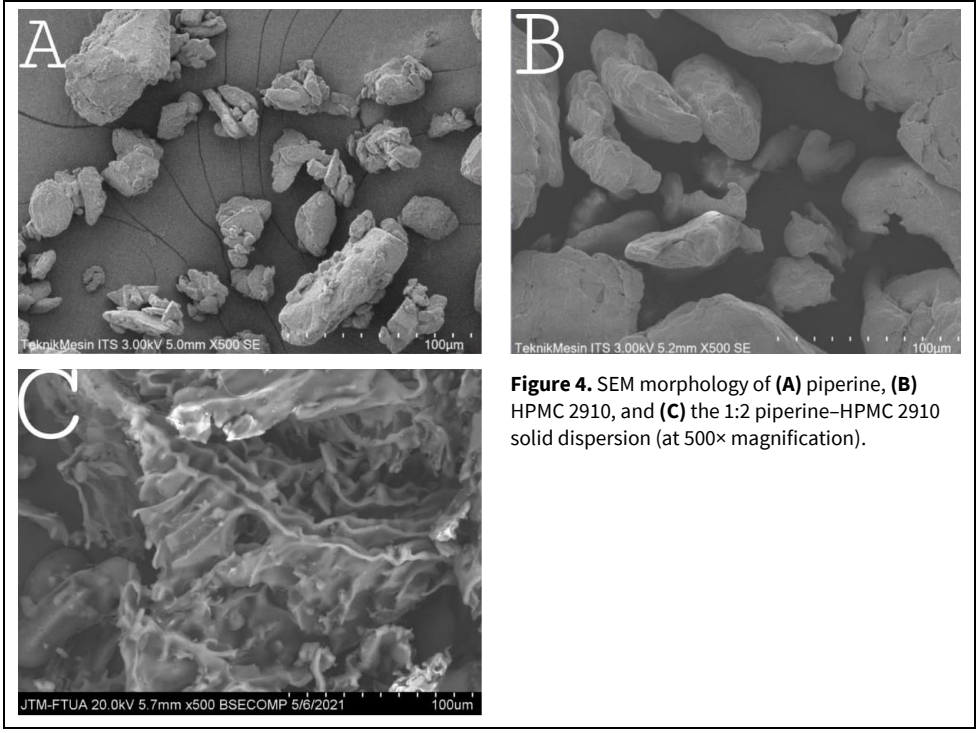

Figure 4. SEM morphology of **(A)** piperine, **(B)** HPMC 2910, and **(C)** the 1:2 piperine–HPMC 2910 solid dispersion (at 500× magnification).

Scanning electron microscopy (SEM) analysis

SEM can provide information about crystal morphologies, which can be used as qualitative evidence for phase transition studies (Kanaze et al., 2006). The morphology of a sample can be viewed from its surface (Vasconcelos and Costa, 2007). SEM results can also indicate the interactions between two substances, which would affect the crystal morphology of each substance. Fig. 4 depicts the SEM morphologies of selected compounds investigated herein.

Piperine contains crystals with irregular shapes, while HPMC is an amorphous powder containing irregular shapes. However, the 1:2 piperine–HPMC solid dispersion shows a different morphology to its two constituent compounds, as shown in Fig. 4. The solid dispersion of piperine in HPMC exhibits many pores on the surface, indicating a larger surface area,

Table 3. Solubility test results of piperine, the physical mixture, and the solid dispersions in distilled water.

Sample	Mean solubility (mg) ± SD	Increase in solubility (change factor)
Piperine	0.349 ± 0.014	-
Physical mixture	1.760 ± 0.040	5.05[a]
Solid dispersion 1:1	2.680 ± 0.103	7.69[b]
Solid dispersion 1:2	2.747 ± 0.066	7.88[b]
Solid dispersion 2:1	2.673 ± 0.123	7.67[b]

Analyzed using a one-way ANOVA with a significance level $p<0.05$.

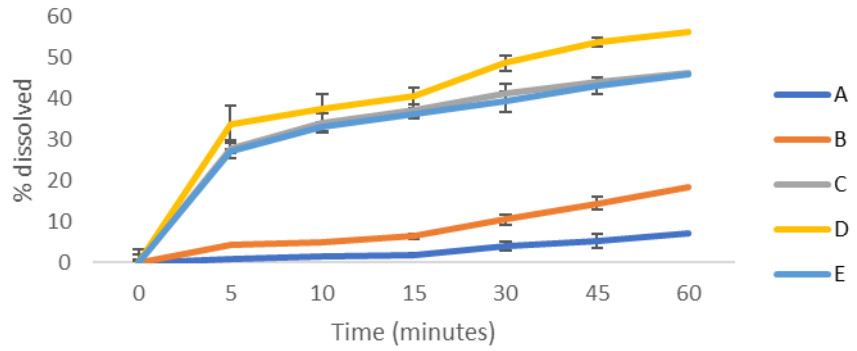

Figure 5. Dissolution rate profiles of **(A)** piperine and **(B)** the physical mixture and those of the **(C)** 1:1, **(D)** 1:2, and **(E)** 2:1 solid dispersions in distilled water (n = 3, mean ± SD).

which likely contributes to increasing the solubility and dissolution rate of piperine (Fitriani et al., 2018). It is generally known that in the freeze-drying process, pores were generated during the sublimation process in primary and secondary drying. These pores correspond to the greater surface area and follow the Noyes-Whitney equation (Thenmozhi and Yoo, 2017). These results support the PXRD ones, which reveal a decrease in the peak intensities of the solid dispersions compared to piperine, indicating the formation of a crystal lattice at a lower symmetrical height than its components.

Solubility test

The solubility test results, as shown in Table 3, indicate an increase in the water solubility of piperine for the physical mixture and solid dispersions. The highest enhancement in piperine solubility is present in the 1:2 solid dispersion, showing a 7.88-fold increase compared to intact piperine. The ratio of piperine to HPMC in the formation of the solid dispersions does not significantly influence the enhancement in piperine solubility ($p>0.05$). This result agrees with that of our previous study, where the formation of solid dispersions led to an increase in the solubility of the active substance by 3.8 times (Zaini et al., 2021). Compared to spray drying, the solid dispersion prepared by feeeze drying had higher solubility. This impact is due to the pores generated in freeze-dried solid dispersion, as seen in the SEM photomicrograph. However, the different concentrations of polymers used in these studies contribute to a different value in the solubility of piperine. In this study, solid dispersion at a ratio of 1:2 showed the highest solubility, whereas at the same ratio solid dispersion prepared by spray drying exhibited the least solubility as HPMC covered the spray-dried solid dispersion; thus, it prevented the molecules from dissolving (Zaini et al., 2021). Furthermore, the increase in solubility can be attributed to the increase in the wettability of the drug and the change of the drug's crystalline phase to an amorphous state, which is supported by the PXRD results and the DSC thermograms (in the form of a decreasing melting point) (Fan et al., 2018; Yuliandra et al., 2020).

In vitro dissolution rate profile

Fig. 5 depicts the dissolution rate profiles of various compounds studied herein, where the average percentages of dissolved piperine at 60 minutes for the intact piperine, physical mixture, and 1:1, 1:2, and 2:1 solid dispersion are 7.276 ± 1.68%, 18.305 ± 1.7%, 46.446 ± 1.09%, 56.445 ± 1.13%, and 46.164 ± 2.08%, respectively. These results indicate that the 1:2 piperine–HPMC 2910 solid dispersion has the highest dissolution percentage, which is in accordance with the solubility result. The increase in the dissolution rate of piperine in the solid dispersions is supported by other

data reported herein, such as the decrease in the melting points (DSC results) and PXRD peak intensities of the solid dispersions.

HPMC 2910 is an amorphous hydrophilic polymer that is water soluble, and when mixed with a crystalline compound, it contributes to decreasing the compound's crystallinity (Fitriani et al., 2018; Zaini et al., 2017). Due to its lower crystal lattice energy, the amorphous phase shows greater solubility and a larger dissolution rate than the crystalline phase (He et al., 2011). Moreover, a photomicrograph of a solid dispersion obtained via the freeze-drying method exhibited open-porous particles, which impact both the solubility and dissolution rate when the particles come into contact with water (Fitriani et al., 2016; 2018).

Similar to another study, the impact of hydrophilic polymers in solid dispersion also increased the dissolution of piperine. This was likely due to the higher dispersibility of piperine in the polymer, which improves wettability since the polymer has an important role in inhibiting crystallization or crystal growth (Thenmozhi and Yoo, 2017).

In this study, both solubility and dissolution tests presented higher values than intake piperine, as also shown in the previous study, solid dispersion prepared by the spray drying process. All of the solid-state characterization that has been carried out supports this result. As described recently, this increase is influenced by several factors, including the choice of the hydrophilic polymer and the freeze-drying method. Although the dissolution in this study was not as high as a study using PEG and PVP (Thenmozhi and Yoo, 2017), this revealed that freeze drying is a proper method for increasing the solubility and dissolution of piperine.

CONCLUSION

The solid dispersions of piperine and HPMC 2910, prepared via the freeze-drying method, showed enhanced physicochemical properties compared to the intact compounds, as revealed by the thermal analysis, X-ray diffraction, and microscopy results. The piperine–HPMC 2910 solid dispersion prepared in a 1:2 (w/w) ratio increased the aqueous solubility of piperine 7.88 fold ($p<0.05$) and increased its dissolution rate to achieve a dissolved piperine percentage of 56.445 ± 1.13% after 60 minutes ($p<0.05$), the highest percentage from the investigated compounds.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

The authors would like to thank Andalas University for funding this research with a grant under the scheme Riset Publikasi Terindeks (T/30/UN.16.19/PT.01.03/KO-RPT/2023) in 2023.

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AUTHOR CONTRIBUTION:

Contribution	Fitriani L	Tirtania S	Umar S	Zaini E
Concepts or ideas	x			x
Design		x	x	x
Definition of intellectual content	x	x	x	x
Literature search	x	x		x
Experimental studies	x	x		
Data acquisition	x	x	x	
Data analysis	x	x	x	x
Statistical analysis		x	x	
Manuscript preparation	x	x	x	x
Manuscript editing	x			x
Manuscript review	x	x	x	x

Citation Format: Fitriani L, Tirtania S, Umar S, Zaini E (2024) Enhancing the solubility and dissolution rate of piperine via preparation of piperine–hydroxypropyl methylcellulose 2910 solid dispersion system using freeze-drying method. J Pharm Pharmacogn Res 12(1): 175–183. https://doi.org/10.56499/jppres23.1734_12.1.175