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Original Research Article

The Preparation and Characterization of the Solid Dispersion of Piperine with Hydroxypropyl Methylcellulose (HPMC) 2910 Using Spray Drying

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ABSTRACT

Piperine is an alkaloid belonging to the Piperaceae family that has long been used in traditional medicine and has many pharmacological activities. However, piperine does not dissolve easily in aqueous media, resulting in low bioavailability. This study aims to prepare solid dispersions of piperine-HPMC 2910 in order to increase its solubility and dissolution rate. Spray drying was used to prepare solid dispersions in three formulations, with ratios of piperine:HPMC 2910 of 1:1, 1:2, and 2:1 (w/w). The samples were characterized by their solid-state properties using Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy, and Scanning Electron Microscope (SEM). Solubility test and dissolution rate were conducted in aqueous medium. The results of the characterization showed a decrease in the intensity of the diffraction peak in the PXRD analysis; a decrease in melting point and a reduction in the endothermic peaks in the DSC analysis; no chemical interactions between piperine and the hydrophilic polymer (HPMC 2910) in the FTIR spectroscopy analysis; and significant changes in crystal morphology in the SEM analysis. The results of the solubility test showed that the highest increment in solubility was in the 1:1 formula, which increased solubility 7.296 times. The highest dissolution rate studies was also shown in the 1:1 formula, where dissolution rate increased 6.284 times. In summary, formation of piperine in solid dispersion with HPMC 2910 by spray drying technique significantly improved the solubility and dissolution rate of piperine.

***Keywords*:** *Piperine, HPMC 2910, Solid dispersion, Spray drying, Solubility, Dissolution rate.*

Introduction

Piperine is an alkaloid found in black pepper (*Piper nigrum*), long pepper (*Piper longum*), and other Piperaceae families and is known for its sharp, pungent flavor.[1,2] Piperine in black pepper is well known for its pharmacological benefits, such as increasing the body's absorption of nutrients, and also has potential as an antibacterial, anti-asthmatic, anti-oxidant, anti-inflammatory, antidepressant, and antihyperlipidemic additive.[3–5] However, piperine has low solubility in water, resulting in poor bioavailability. Generally, drugs with low solubility but good permeability are classified as Class II drugs, according to the Biopharmaceutics Classification System (BCS).[6] In Class II drugs, the dissolution rate is the determining step for drug absorption. Therefore, the dissolution rate needs to be improved, which can be done by increasing the drug's solubility to accelerate the absorption process and the onset of the drug's activity.[7] Various approaches have been developed to improve the solubility and dissolution rate of piperine, including polymorphism,[8] multicomponent crystals,[9,10] self-emulsifying drug delivery systems (SEDDS),[11] inclusion complexes,[12] solid dispersions,[13] nanosuspensions,[14] and nanoparticles.[15] One of the most popular techniques is solid dispersion, where one or more active ingredients, which can be in a fine crystalline, dissolved, or amorphous state, are dispersed in an inert excipient or matrix (carrier).

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Solid dispersion is simple method with high manufacturability in improving the psychochemical properties of active pharmaceutical ingredients (APIs) particularly in solubility and dissolution rate. Moreover, solid dispersions consist of two or more components, generally a carrier polymer and a drug, often with the addition of a stabilizing agent.[16]

This study aims to prepare a solid dispersion of piperine-HPMC 2910 by using spray drying in order to increase the solubility and dissolution of piperine. HPMC is a hydrophilic and biodegradable polymer, commonly used as a dispersing agent and is used as a matrix in the formulation of immediate-release tablets in oral products.[17–19] Spray drying can facilitate the preparation of solid dispersions due to its ability to form amorphous structures and increase particle surface area. Spray-dried powder can increase the dissolution rate of an oral drug, thereby increasing its bioavailability.[20] In this study, solid dispersion was prepared in three formulations, with piperine-HPMC 2910 ratios of 1:1, 1:2, and 2:1 (w/w). The solid dispersion systems were characterized using Powder X-ray Diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy, Scanning Electron Microscope (SEM), and solubility and dissolution rate studies.

Materials and Methods

Materials

The materials used were piperine (BOC Sciences, the US), HPMC 2910 (Shin-Etsu Chemical, Japan), ethanol pro analysis (Merck, Germany), and distilled water.

Preparation of solid dispersion by spray drying[18]

Piperine and HPMC 2910 were mixed at ratios of 1:1, 1:2, and 2:1 (w/w) as shown in Table 1. Piperine was dissolved in 2 ml of 96% ethanol, while HPMC 2910 was dispersed in 200 mL distilled water. They were then mixed and homogenized using a magnetic stirrer.

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Table 1: The ratio of piperine-HPMC 2910 solid dispersions

Weight (g)	Piperine:HPMC 2910 ratios (w/w)		
	F1 (1:1)	F2 (1:2)	F3 (2:1)
Piperine	3	2	4
HPMC 2910	3	4	2

The mixture was spray-dried (BUCHI Mini spray dryer B-290, Switzerland), with an inlet temperature of 120ºC, an outlet temperature of 60ºC, and a flow rate of 35 m^3/hour. The dried powder then was then kept in a desiccator.

Preparation of the physical mixture[18]
The physical mixture of piperine-HPMC was prepared at a ratio of 1:1 (w/w) and mixed homogenously. The mixture was stored in a tightly closed container and kept in a desiccator prior to further characterization.

Powder X-ray Diffraction (PXRD) analysis[9]
PXRD analysis of samples was conducted on piperine, HPMC 2910, physical mixtures, and solid dispersions by using an X-ray diffractometer (PANanalytical MPD PW3040/60 type X'Pert Pro, The Netherlands). The measurement conditions were a Cu metal target and a Kα filter, with 40 kV voltage and a current of 30 mA. The analysis was conducted for intact piperine, intact HPMC, physical mixtures, and solid dispersions at 2θ range of 5–50°. The samples were then placed in a sample holder (glass) and leveled to prevent particle orientation during analysis.

Differential Scanning Calorimetry (DSC) analysis[9]
Thermal analysis of the samples was performed using a DSC instrument (Shimadzu DSC-60 Plus, Japan) that had been calibrated at temperature. Intact piperine, HPMC 2910, physical mixtures, and solid dispersions were weighed to the nearest 4 mg and placed in a closed aluminum pan. The DSC apparatus was programmed with a temperature range of 30–260ºC.

Fourier Transform Infrared (FTIR) analysis[9]
The piperine, HPMC 2910, physical mixtures, and solid dispersions were analyzed using an FTIR spectrophotometer (Thermo Scientific, the US). The sample was placed in an ATR crystal and the tip of the cover was positioned parallel to the sample hole. The absorption spectra were recorded at a wavenumber of 4000–400 cm^{-1}.

Scanning Electron Microscopy (SEM) analysis[18]
The microscopic analysis was performed on piperine, HPMC 2910, and solid dispersions. The samples were placed in a sample container made of aluminum and were observed at various magnifications using an SEM (Hitachi FLEXSEM 100, Japan). The device was set with a 15–20 kV voltage and 12 mA current.

Solubility test[18]
Solubility tests were conducted triplicate on piperine, physical mixtures, and solid dispersions, which were made into a saturated solution. An excess amount of samples was put into a 100 mL Erlenmeyer flask, along with 100 mL of distilled water. The test was conducted over 24 hours using an orbital shaker and filtered using Whatman filter paper. The concentration of piperine was determined from the absorbance measurement at 341 nm using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan).

Dissolution rate studies[18]
The dissolution rate profiles of the samples were determined using a type II dissolution test apparatus (Hanson Research SR08, the USA) with 900 mL of distilled water used as a medium, at 37 ± 0.5 ºC and a speed of 50 rpm. A 5 mL sample of dissolution solution was pipetted after 5, 10, 15, 30, 45, and 60 minutes. After each pipetting, the medium taken was replaced with a dissolution medium (at the same volume and temperature). The amount of piperine dissolved in the medium was determined from the absorbance measurement at a maximum wavelength of 341 nm using a UV-Vis spectrophotometer (Shimadzu UV-1700, Japan). The dissolution test was carried out on the piperine, physical mixtures, and solid dispersions powders and conducted in triplicate.

Statistical Analysis
The data from the solubility test was presented as mean ± SD and analyzed statistically with one-way ANOVA with significance level at $p < 0.05$.

Results and Discussion

X-ray diffraction analysis is a reliable method for characterizing solid-state interactions. It can be used to determine changes in the degree of crystallinity and to distinguish whether the solid dispersion formed is in a crystalline or amorphous form.[21] Based on the diffractogram shown in both Figure 1 and Table 2, the X-ray diffraction peaks of piperine showed that it was in the crystalline phase, which is characterized by sharp, distinctive peaks. However, HPMC showed no distinctive and sharp peaks, which is typical of the amorphous phase. The diffraction pattern of piperine-HPMC 2910 solid dispersion is different from the active substance and polymer. There was also a decrease in specific peaks throughout the diffractogram in solid dispersions for all the formulations. These indicated that the solid dispersion of piperine-HPMC 2910 underwent a decrease in the degree of crystallinity. [18,22,23]
DSC analysis is used to characterize the thermal properties of solid substances by measuring the energy absorbed or emitted by the sample as a function of time or temperature. DSC analysis also provides information about changes in the thermal properties of solid dispersions as well as heat energy, which is indicated by the appearance of endothermic peaks on the thermogram caused by melting, phase transition, recrystallization, and dehydration.[24] The thermal analysis showed a decrease in the melting point of the physical mixture and solid dispersion. The solid dispersion formation, using the spray-drying technique, has a broad, single, and distinct endothermic peak, and a lower melting point compared with intact piperine, as shown in Figure 2. The shift in the endothermic peak indicates interactions between the piperine and HPMC. The endothermic peak in solid dispersion was also lower than intact piperine, indicating that the solid dispersion system formed was in an amorphous or partially amorphous phase. The decrease in melting point indicates a decrease in the degree of crystallinity, which can increase solubility.[25]

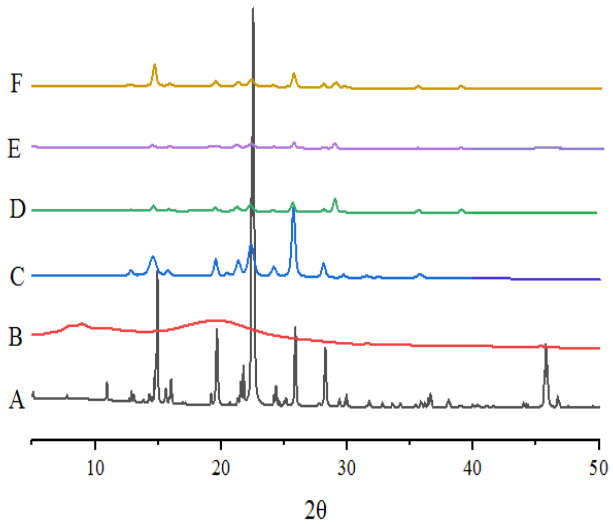

Figure 1: Diffractogram of (A) piperine, (B) HPMC 2910, (C) physical mixture, (D) solid dispersion F1, (E) solid dispersion F2, (F) solid dispersion F3

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Table 2: Peak intensity of piperine, physical mixture and solid dispersions

Position (2Θ)	Peak Intensity				
	Intact Piperine	Physical mixture	Solid Dispersion F1	Solid Dispersion F2	Solid Dispersion F3
14.574	952.602	1,872.274	714.317	491.248	1,341.326
14.925	10,287.840	1,067.277	394.980	365.496	869.054
19.553	2,113.423	1,645.544	548.417	454.104	730.959
19.657	6,038.736	1,329.157	463.620	433.152	702.058
22.374	15,604.770	2,767.070	763.987	593.219	904.819
22.530	29,634.360	2,161.050	531.525	523.031	802.034
25.741	945.697	5,503.240	852.575	637.826	1,289.100
25.871	6,149.013	3,440.010	516.713	577.245	1,109.530
28.120	878.125	1,399.720	454.293	352.925	561.456
28.263	4,624.801	958.716	411.737	336.255	467.219

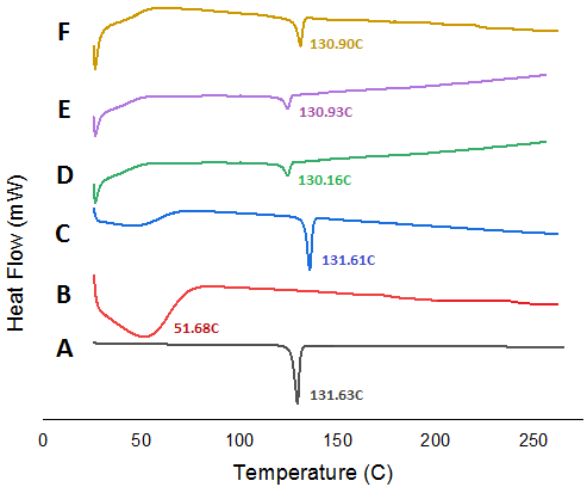

Figure 2: Thermogram of (A) piperine, (B) HPMC 2910, (C) physical mixture, (D) solid dispersion F1, (E) solid dispersion F2, (F) solid dispersion F3

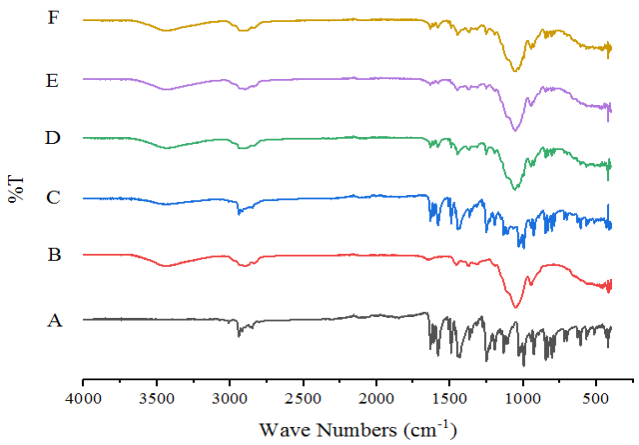

Figure 3: FTIR spectrum of (A) piperine, (B) HPMC 2910, (C) physical mixture, (D) solid dispersion F1, (E) solid dispersion F2, (F) solid dispersion F3

Enthalpy is the amount of energy required to fuse a solid substance by decreasing the degree of crystallinity of the compound.[26] Regarding the decreasing melting point and shifting endothermic peaks, the physical mixture and solid dispersion of piperine-HPMC 2910 also showed a decrease in enthalpy of fusion. As shown in Table 3, a decrease in the enthalpy value is associated with a decrease in the degree of crystallinity, meaning that the solubility of piperine in a solid dispersion of piperine-HPMC 2910 is likely to increase.

FT-IR spectroscopy analysis was conducted to support the results of the analysis of XRD and DSC. FT-IR spectroscopy analysis is often used to determine the intermolecular interaction between solid drugs and polymers.[27] In this study, the analysis was conducted in order to observe the shift in the spectrum of solid dispersion samples, which are likely to form hydrogen bonds. The results of the FT-IR spectrum are shown in Figure 3. The spectrum of the physical mixture and solid dispersions show the same functional groups as intact piperine and HPMC 2910. The shift in wavenumber that occurs is still at the same functional group, which indicates that there were no chemical interactions between piperine and HPMC 2910.

SEM analysis was performed in order to observe the morphology of the sample particles. The results of the SEM analysis at 2000x magnification can be seen in Figure 4. The morphology of piperine is like a blade in the crystalline phase, while HPMC has irregular lumps on its surface. The solid dispersions of piperine-HPMC 2910 were almost spherical with smaller particle sizes.

The results of the SEM analysis of piperine-HPMC 2910 solid dispersion support the X-ray diffraction results that show a decrease in peak intensity, which implies the formation of a crystal lattice that has a lower level of symmetry than its constituent components.

From the SEM microphotograph in Figure 4, we can see that the particle size of solid dispersions was greater compared with the nozzle size on the spray dryer, which was approximately 1.4–1.5 µm. This is likely due to the atomization process of the samples through the nozzle, which passed the hot gas stream through a tube, which then makes contact with both the sprayed powder and the air in the drying chamber. A powder that passes through a spray of atomized gas is likely to form an agglomeration.[28]

Table 4 shows the data from the solubility test. There was a significant increase ($p<0.05$) in the solubility of piperine in the physical mixture and solid dispersions. The greatest increase in solubility was F1, which increased 7.296 times. The increase in solubility of piperine in F1 may be caused by the increase in the wettability of piperine and its change from a crystalline to an amorphous state—results which are supported by the X-ray diffraction and thermal DSC analyses.[29,30] By contrast, the solubility of piperine in F2 is lower among the solid dispersions, which is probably due to the addition of more concentrated polymers, which may have then enveloped the piperine, preventing its molecules from dissolving fully.[31]

Finally, a dissolution rate profile of piperine was conducted to compare it with the dissolution rate profiles of the physical mixtures and solid dispersions.

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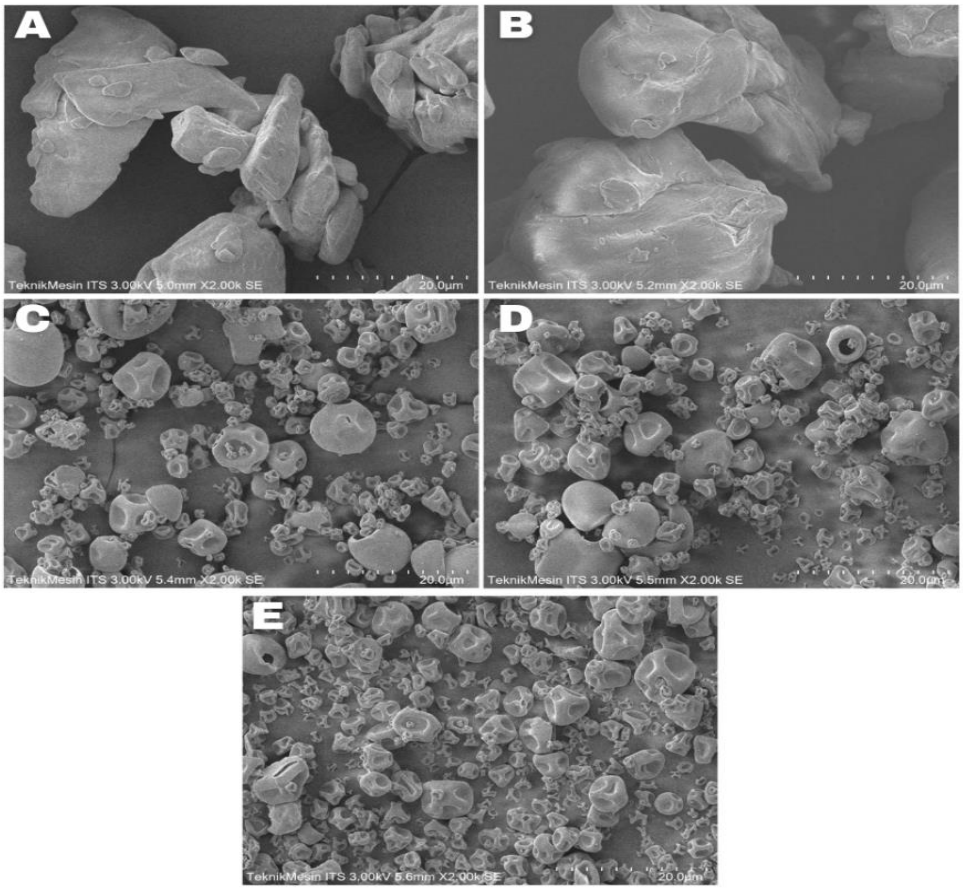

Figure 4: The microphotographs of (A) piperine, (B) HPMC 2910, (C) solid dispersion F1, (D) solid dispersion F2, (E) solid dispersion F3

Table 3: Melting point and enthalpy of piperine, HPMC 2910, physical mixture and solid dispersions

Samples	Melting point (°C)	ΔH fusion (J/g)
Intact piperine	131.63	4.530
HPMC 2910	51.68	118.44
Physical mixture	131.61	25.425
Solid Dispersion F1	130.16	2.805
Solid Dispersion F2	130.93	1.887
Solid Dispersion F3	130.90	3.802

Table 4: Data of solubility test

Materials	Mean Solubility (mg/100ml)	Increase in solubility (times)
Piperine	0.349 ± 0.015	-
Physical mixture	1.760 ± 0.040	5.050
Solid Dispersion F1	2.543 ± 0.047	7.296
Solid Dispersion F2	2.325 ± 0.020	6.670
Solid Dispersion F3	2.515 ± 0.049	7.215

(Analyzed with one-way ANOVA with 95 confidence interval, $p < 0.05$)

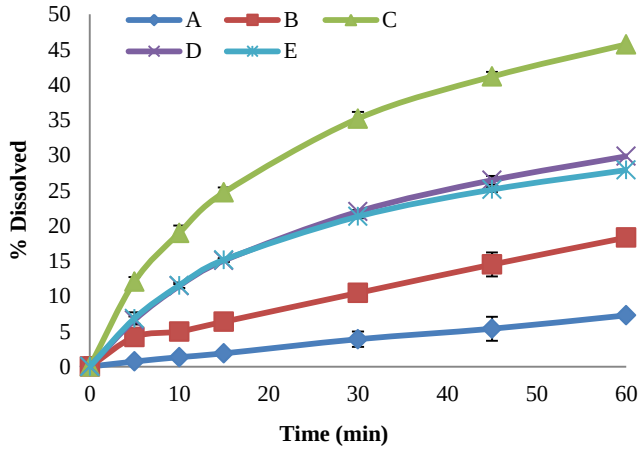

Figure 5: The dissolution profile of (A) piperine, (B) physical mixture, (C) solid dispersion F1, (D) solid dispersion F2, (E) solid dispersion F3

The dissolution profile data can be seen in Figure 5. Based on the results, solid dispersions of piperine-HPMC 2910 increased the dissolution rate of piperine. The average percentage of piperine dissolved at 60 minutes in intact piperine, physical mixture, and solid dispersions F1, F2, F3 were 7.276% ± 1.694; 18.305% ± 1.703; 45,728% ± 0.665; 29.844% ± 0.603; 27.891% ± 0.341, respectively. The results of the dissolution rate study matched those of the solubility test, described previously.

Conclusion

The solid dispersion of piperine with HPMC 2910 was successfully achieved by spray drying technique and characterizing the samples. Solid dispersions have been shown to enhance the solubility and dissolution rate of piperine. The solid dispersion in F1 showed the highest solubility and dissolution rate for piperine, with a 7.296-fold increase in solubility, and a 6.285-fold increase in the dissolution rate, after 60 minutes.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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