© 2020 Journal of Pharmacy & Pharmacognosy Research, 8 (2), 127-134, 2020
ISSN 0719-4250
http://jppres.com/jppres

Original Article | Artículo Original

Preparation and characterization of quercetin-polyvinylpyrrolidone K-30 spray dried solid dispersion

[Preparación y caracterización de dispersión sólida de quercetina-polivinilpirrolidona K-30 secada por rociado]

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Abstract

Context: The use of quercetin as a potential active pharmaceutical ingredient is limited by low aqueous solubility leading to low bioavailability. A spray-dried solid dispersion technique is used to increase the solubility and dissolution profiles of quercetin.

Aims: To prepare and characterize quercetin solid dispersion using polyvinylpyrrolidone (PVP) K-30.

Methods: Solid dispersions (SDs) were prepared by spray drying technique at quercetin/PVP K-30 ratios of 10/90, 20/80, 30/70, 40/60 and 50/50. A physical mixture of quercetin/PVP K-30 (50/50) and pure quercetin were used as comparisons. The SDs were characterized by powder X-Ray diffraction (XRD), scanning electron microscopy (SEM), Fourier-transform IR (FTIR) spectroscopy, solubility and dissolution studies. The effect of the drug/polymer ratio on the solubility of quercetin was also studied.

Results: Quercetin SDs appeared as amorphous form as confirmed by XRD. Quercetin was better dispersed as the drug/polymer ratio decreased. SD with ratio 10/90 showed regular spherical particles in the size range of 0-35 µm. The solubility of quercetin increased with decreasing drug/polymer ratio. Preparation of SDs influence the solubility significantly ($p<0.01$). The increase in solubility is probably due to a hydrogen bond between quercetin and PVP K30 as confirmed by FTIR spectra. SD with ratio 10/90 showed a high dissolution rate (95.12 ± 1.83%) within 120 min in comparison to pure quercetin (19.37 ± 0.58%) or physical mixture (37.85 ± 0.85%).

Conclusions: Preparation of quercetin SDs with PVP K30 by spray drying technique results in amorphous spherical particles. There was an increase in solubility and percent dissolved with a decrease in drug/polymer ratio.

Keywords: dissolution profile; polyvinylpyrrolidone; quercetin; solid dispersion; solubility.

Resumen

Contexto: El uso de quercetina como un ingrediente farmacéutico activo potencial está limitado por una baja solubilidad acuosa que conduce a una baja biodisponibilidad. Se utiliza una técnica de dispersión sólida secada por pulverización para aumentar los perfiles de solubilidad y disolución de la quercetina.

Objetivos: Preparar y caracterizar la dispersión sólida de quercetina usando polivinilpirrolidona (PVP) K-30.

Métodos: Las dispersiones sólidas (SD) se prepararon mediante una técnica de secado por pulverización en proporciones de quercetina/PVP K-30 de 10/90, 20/80, 30/70, 40/60 y 50/50. Una mezcla física de quercetina/PVP K-30 (50/50) y quercetina pura se utilizaron como comparaciones. Las SD se caracterizaron por difracción de rayos X en polvo (XRD), microscopía electrónica de barrido (SEM), espectroscopía IR de transformada de Fourier (FTIR), estudios de solubilidad y disolución. También se estudió el efecto de la relación fármaco/polímero sobre la solubilidad de la quercetina.

Resultados: Las SD de quercetina aparecieron como una forma amorfa según lo confirmado por XRD. La quercetina se dispersó mejor a medida que disminuyó la relación fármaco/polímero. SD con relación 10/90 mostró partículas esféricas regulares en el rango de tamaño de 0-35 µm. La solubilidad de la quercetina aumentó al disminuir la relación fármaco/polímero. La preparación de SD influye significativamente en la solubilidad ($p<0,01$). El aumento en la solubilidad probablemente se deba a un enlace de hidrógeno entre la quercetina y PVP K30 según lo confirmado por los espectros FTIR. La SD con una relación 10/90 mostró una alta velocidad de disolución (95,12 ± 1,83%) en 120 minutos en comparación con la quercetina pura (19,37 ± 0,58%) o la mezcla física (37,85 ± 0,85%).

Conclusiones: La preparación de SD de quercetina con PVP K30 mediante la técnica de secado por pulverización da como resultado partículas esféricas amorfas. Hubo un aumento en la solubilidad y porcentaje disuelto con una disminución en la relación fármaco/polímero.

Palabras Clave: dispersión sólida, perfil de disolución; polivinilpirrolidona, quercetina, solubilidad.

ARTICLE INFO
Received: August 29, 2019.
Received in revised form: November 13, 2019.
Accepted: November 14, 2019.
Available Online: November 15, 2019.
Declaration of interests: The authors declare no conflict of interest.
Funding: This research was supported by University of Andalas (contract No. 10/UN.16.17/PP.HGB/LPPM/2017).

INTRODUCTION

Quercetin (3,3′,4′5′-7 pentahydroxy flavon) is a potential nephron-protector (Aldemir et al., 2014), however, the benefit is limited by poor aqueous solubility and low rate of dissolution leading to low bioavailability in rats (<17%) and in human (1%) (Moon et al., 2008; Cai et al., 2013). Various techniques have been developed to improve the physicochemical properties of quercetin including particle size reduction (Nam et al., 2016), formation of binary mixture (Zaini et al., 2016) and preparation of solid dispersion (Costa et al., 2011; Sahoo et al., 2011).

Spray-dried solid dispersion has been reported as an efficient way to increase the solubility of poorly water-soluble drugs (Martins et al., 2012; Paudel et al., 2013; Tran et al., 2013). The advantage of this technique is that it obtains smaller spherical particles with homogeneous particle size distribution, which consequently increases flowability and compressibility. Commonly used carrier polymers are polyethylene glycol (PEG), polyvinylpyrrolidone (PVP) and hydroxypropylmethylcellulose (HPMC) (Patel et al., 2015).

The choice of carrier and preparation method have a significant effect on increasing the solubility and stability of the amorphous form of the drug in solid dispersion. Previous workers reported the preparation of flavonoids solid dispersion using a solvent evaporation method with PEG and PVP as carriers. Kanaze et al. (2006b) found that the PVP K30 matrix increased the rate of flavonoids release better than the PEG 4000 matrix. Furthermore, Costa et al. (2011) prepared quercetin - PVP K25 solid dispersion with a solvent evaporation method that resulted in an increase in the solubility of quercetin 436 times. The aim of this study is to prepare quercetin solid dispersion with PVP K30 using the spray-drying method and to evaluate the effect on the solubility and dissolution profile of quercetin.

MATERIAL AND METHODS

Materials

Quercetin was purchased from Sigma-Aldrich (Singapore); PVP K30 was purchased from Bratachem Ltd. (Indonesia). Ethanol pro analysis (Merck), and hydrochloric acid (Merck) were also used.

Preparation of spray dried solid dispersion

Solid dispersions were prepared by using a various ratio of quercetin-PVP K30 as in Table 1. The ethanolic solution of quercetin was added to the aqueous solution of PVP K30 and was sonicated for 10 minutes. The solution was maintained at 200 rpm with a magnetic stirrer and spray-dried (BUCHI Mini spray dryer B-290) at a controlled temperature (inlet 145°C, outlet 65°C, aspirator 85%, pump 30% and flow rate 30 mL/minutes). Physical mixtures of quercetin-PVP K30 were prepared in the ratio of 1:1. The solid dispersions (F1-F5), the physical mixture (PM), and pure quercetin (Q) were analyzed by XRD, FTIR and SEM.

X-Ray diffraction

XRD analysis was performed by using X-ray diffractometer (X'pert PRO, PAN analytical) equipped with copper Kα radiation (40 kV, 20 mA). The scanning was done from 5° to 50° 2θ for quercetin solid dispersion and pure quercetin respectively.

Fourier Transform IR spectroscopy

The FT-IR spectra were obtained on a Perkin Elmer Spectrum 1000 FT-IR Spectrophotometer. Scans were done at the wavenumber range of 4000-600 cm^{-1}.

Scanning Electron Microscopy

The morphology of pure quercetin and QSD was characterized by using Scanning Electron Mi-

croscope (HITACHI type S-3400N) at 100 kV accelerating voltage. Pure quercetin or quercetin in the dried original dispersion medium was dispersed in distilled water; 5 µL was dropped onto SEM grid carbon film and dried for 30 minutes at 25°C respectively.

Determination of particle size

A microscope (Nikon ECLIPSE E100) equipped with OptiLab® Viewer 2.2 (Micronos Nusantara, Indonesia) at 400 magnifying power was used to observe the particle size distribution of F1. The size of at least 500 particles was observed.

Solubility studies

Excess quercetin solid dispersions were added into 100 mL of distilled water. The suspensions were pre-homogenized for 1 minute by sonication (Elmasonic S 80 (H)) and filtered by Whatman paper. The solutions were analyzed by spectrophotometer UV-Visible (Shimadzu UV-1700) for quercetin concentration. The method of analysis was validated by measuring the absorbance of quercetin at concentration range 6 – 14 µg/mL at the maximum wavelength of 255.8 nm. Experiments were carried out in triplicate; data were presented as the average value ± standard deviation. The aqueous solubility of PM and Q were also determined respectively.

Dissolution studies

The dissolution rate profile was obtained by using the type II USP apparatus (SR08 Dissolution Station, Hanson Research) at 100 rpm speed in 0.1 N hydrochloric acid medium at 37 ± 0.1°C for 120 minutes. Drug concentration was determined by spectrophotometer UV-Vis (Shimadzu UV-1700) at time intervals. The dissolution profiles of PM and Q were also determined under the same conditions.

Statistical analysis

Data were expressed as (Mean ± Standard Deviation) and analyzed by two-way ANOVA (α = 0.05) to determine the significant differences between means followed by Duncan Multiple Range Test at 5% significance level.

RESULTS AND DISCUSSION

Quercetin is a naturally occurring flavonoid found in fruits and vegetables, which is safe to consume and has numerous health benefits to humans (Nam et al., 2016, Kaulmann and Torsten, 2016). In an effort to develop quercetin as a nephron-protector, it was formulated as QSD to improve its aqueous solubility as well as the dissolution rate. Previous studies showed that the QSD is practically non-toxic with LD_{50} of >16 g/kg (Lucida et al., 2019a). The QSD at a dose of one fifth of pure quercetin provides a comparable effect in nephron-protection on the ARF induced mice (Lucida et al., 2019b). In this study, the prepared QSDs were characterized by several techniques to check their physical state (crystalline or amorphous) before the solubility and dissolution studies.

X-Ray diffraction

Diffractogram profiles showed in Fig. 1 refers to PVP K30, Q, PM, F1, F2, F3, F4 and F5. Pure quercetin and the physical mixture show crystalline nature as confirmed by sharp peaks at 12.6831° and 26.2551° at 2θ position. PVP K30 was characterized by an absence of any diffraction peak indicating that it was present as an amorphous polymer. F1 – F5 showed the same diffraction pattern with the peaks of PVP K30, indicating that they were in the amorphous state. These results confirmed that quercetin has been well dispersed in PVP K30 and converted to amorphous forms, which could contribute to increased solubility (Kanaze et al., 2006b).

Fourier Transform IR spectroscopy

FTIR analyses were carried out to investigate the interactions between PVP K30 and quercetin in the solid dispersion systems. This is also to obtain information on how the interactions influence the solubility of quercetin in SDs. The FTIR spectra of pure quercetin, PVP K30, the physical mixture and solid dispersions F1 are shown in Fig. 2.

Table 1. The ratio of quercetin-PVP K30 solid dispersions.

Weight	Quercetin:PVP K30 ratios (w/w)						
	F1	**F2**	**F3**	**F4**	**F5**	**PM**	**Q**
Quercetin	10	20	30	40	50	50	100
PVP K30	90	80	70	60	50	50	0

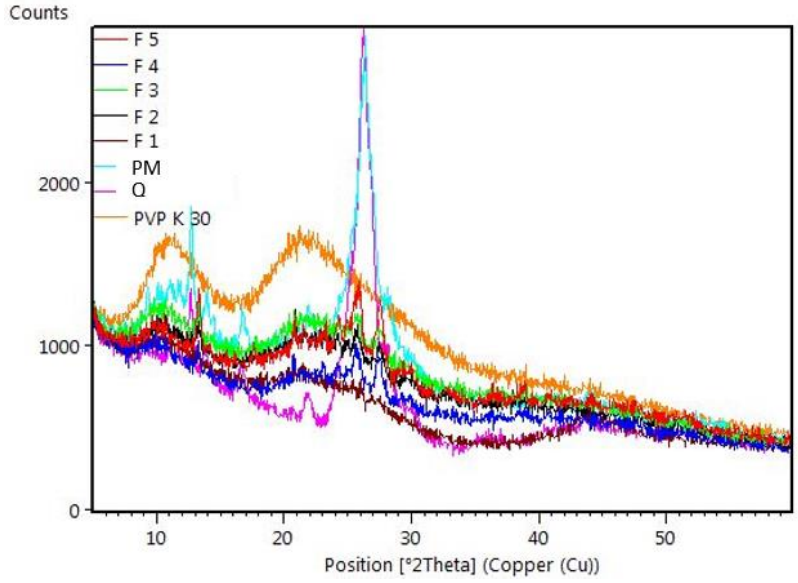

Figure 1. Diffractograms of PVP K30; Q (quercetin); PM (physical mixture); solid dispersions F1; F2; F3; F4 and F5.

The spectrum of pure quercetin presented characteristic peaks at 3266 cm^{-1} (O-H stretching vibration), and 1611 cm^{-1} (carbonyl C=O stretching vibration). PVP K30 showed stretching bands at 3429 cm^{-1} (O-H stretching); 2944 cm^{-1} (C–H stretching) and at 1651 cm^{-1} (C=O stretching). There were shifts of C=O band from 1611 cm^{-1} (pure quercetin) to 1641 cm^{-1} (SD) and the O-H band from 3266 cm^{-1} (pure quercetin) to 3384 cm^{-1} (SD) suggesting that a physicochemical interaction was formed between quercetin and PVP K30 in SD. The phenolic group of quercetin was capable of forming hydrogen bonds with the C=O group of PVP to which extent that has a role for quercetin to be dispersed into the PVP matrix and keep it in an amorphous state (Brough and Williams, 2013). These results are in agreement with previous report about hydrogen bonding formation of naringenin and hesperetin aglycones with PVP, which results in increased solubility, and rate of dissolution (Kanaze et al., 2006a).

SEM analysis

Morphological analysis by SEM (Fig. 3) shows crystalline forms of pure quercetin needles and irregularly spherical particles of PVP K30. Solid dispersions are seen as irregular shape particles. The particle shape looks more regular with decreasing drug/polymer ratio, the most regular is at the lowest drug/polymer ratio (10/90). The SEM of F1 shows that the drug is well dispersed in the polymer, obtaining relatively regular spherical particles with a size distribution in the range of 0-35 µm. These are in agreement with the previous study that spray drying technique results in spherical shaped particles (Febriyenti et al., 2014).

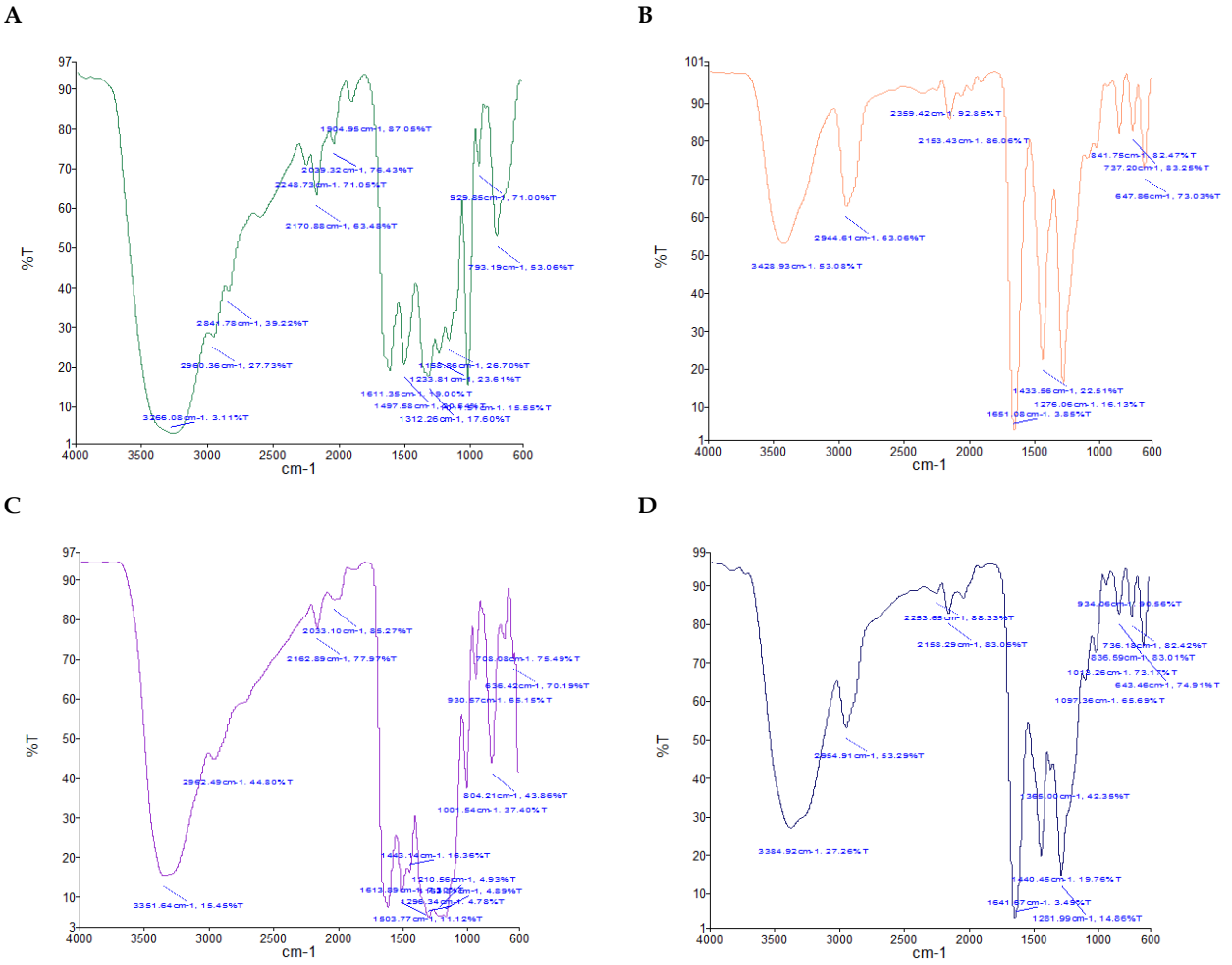

Figure 2. FTIR spectra of pure quercetin **(A)**; PVP K30 **(B)**; physical mixture **(C)**; solid dispersions F1 **(D)**.

Solubility studies

Validation of the analytical method showed a linear correlation between absorbances and concentrations with the regression equation of y = 0.0519 x + 0.0364 (r = 0.9995). Data in Table 2 shows the effect of the formulation on the solubility of quercetin. The solubility of pure quercetin (23.2381 ± 2.0850 µg/mL) is significantly different than PM (48.2976 ± 2.1601 µg/mL) ($p<0.01$). Quercetin solubility in solid dispersion is improved gradually with decreasing drug/polymer ratio in the solid dispersions. The solubility of F1 is the highest (116.6309 ± 7.6522 µg/mL), which is significantly different from other formulations ($p<0.01$). The increase in quercetin solubility is attributed to the amorphous state of the drug in the solid dispersion system. These results were in agreement with the previous reports (Kanaze et al., 2006b; Costa et al., 2011). The former showed that PVP K30 improved the solubility and dissolution profiles of aglycone flavonoids (naringenin and hesperetin) solid dispersions at the drug/polymer ratio of 1:4 (w:w). The latter found that solid dispersion of quercetin - PVP K25 showed a remarkable increase in quercetin solubility compared to pure quercetin. However, a 436-fold increase in quercetin solubility was obtained from a drug/polymer ratio of 1:105 (w:w). In this study, the highest increase (5-fold) in quercetin solubility resulted from a drug/polymer ratio of 1:9 (w:w). High proportions of polymer and drug ratios are not preferred in solid dispersion systems because

they may be troublesome in the formulation of high-dose tablets or capsules (Silva et al., 2010).

Dissolution studies

The dissolution profiles of pure quercetin, the physical mixture and the solid dispersions in Fig. 4 showed an improved release rate of quercetin from solid dispersion systems. At fifth minutes of dissolution, more than 35 – 51% quercetin dissolved from solid dispersions, whereas Q and PM dissolved 10.43% and 33.56% respectively. After 30 minutes, 41 – 78% of drug dissolved from solid dispersions compared to 37% PM and 16% Q. There was a remarkable increase in the amount of quercetin solid dispersion dissolved compared to pure quercetin or the physical mixture. The dissolution rate increased as the drug/polymer ratio decreased. The highest rate of dissolution was F1 (95.12 ± 1.83%) in 120 min (Fig. 4), this was attributed to the amorphous form of the solid dispersion. Molecules present in a random arrangement in the amorphous state, therefore need less energy for molecule separation. Consequently, the amorphous form shows higher solubility, higher rate of dissolution and better bioavailability than the crystalline structure (Salman et al., 2015).

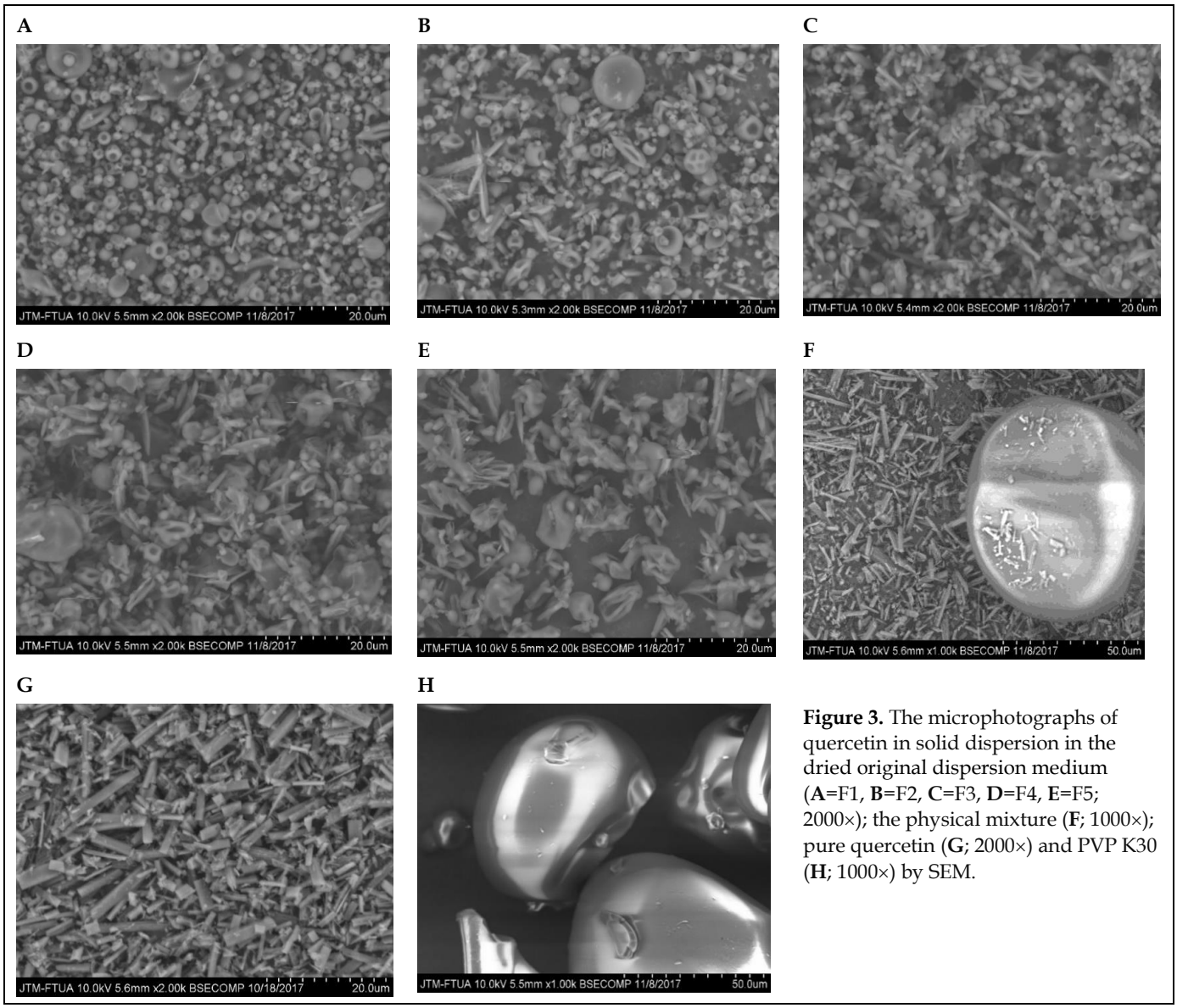

Figure 3. The microphotographs of quercetin in solid dispersion in the dried original dispersion medium (**A**=F1, **B**=F2, **C**=F3, **D**=F4, **E**=F5; 2000×); the physical mixture (**F**; 1000×); pure quercetin (**G**; 2000×) and PVP K30 (**H**; 1000×) by SEM.

Table 2. The solubility of quercetin solid dispersions in comparison to the physical mixture (PM) and pure quercetin (Q).

No.	Formulations	Solubility (µg/mL)			Mean solubility ± SD (µg/mL)
		1	2	3	
1.	Q	22.8214	25.5000	21.3929	23.2381 ± 2.0850[a]
2.	PM	49.9642	49.0714	45.8571	48.2976 ± 2.1601[b]
3.	F5	54.6071	47.2857	56.7500	52.8809 ± 4.9627[b]
4.	F4	52.2857	55.8571	56.2143	54.7857 ± 2.1724[b]
5.	F3	71.9285	69.2500	69.9643	70.3809 ± 1.3870[c]
6.	F2	84.7857	85.5000	81.9286	84.0714 ± 1.8898[d]
7.	F1	115.5000	109.6071	124.7857	116.6309 ± 7.6522[e]

Data with different superscripts showed significant differences ($p<0.01$).

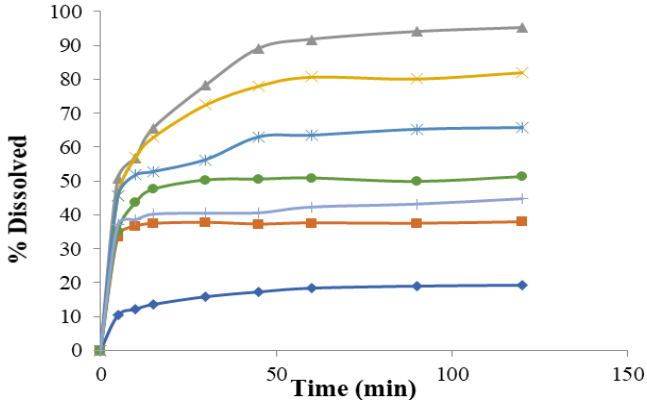

Figure 4. The dissolution profile of quercetin solid dispersion (F1-F5), the physical mixture (PM) and pure quercetin (Q).

CONCLUSIONS

Preparation of quercetin solid dispersion with PVP K30 by spray drying technique results in amorphous spherical particles. Formulation of solid dispersion increase the solubility of quercetin significantly ($p<0.01$). The amount of quercetin dissolved also increased from 19.37% (pure quercetin); 37.85% (the physical mixture) to 95.12% in 120 min.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The authors acknowledged University of Andalas for financial support through a research grant. Contract No. 10/UN.16.17/PP.HGB/LPPM/2017.

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AUTHOR CONTRIBUTION:

Contribution	Febriyenti	Indra P	Zaini E	Ismed F	Lucida H
Concepts or ideas					x
Design	x		x		x
Definition of intellectual content					x
Literature search		x			x
Experimental studies		x			x
Data acquisition		x			x
Data analysis		x		x	x
Statistical analysis		x			
Manuscript preparation	x			x	x
Manuscript editing	x		x	x	x
Manuscript review	x	x	x	x	x

Citation Format: Febriyenti, Indra P, Zaini E, Ismed F, Lucida H (2020) Preparation and characterization of quercetin-polyvinylpyrrolidone K-30 spray dried solid dispersion. J Pharm Pharmacogn Res 8(2): 127–134.