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Increasing the Dissolution Rate of USNAC PVP K-30 & PEG-6000 Solid Dissolution Using Solution Method

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ABSTRACT

Usnic acid is a secondary metabolite found in lichen, which has biological activities such as antimicrobial, antiviral, antiprotozoal, antiproliferative, anti-inflammatory and analgesic. Uric acid is very difficult to dissolve in water so that its bioavailability is small. One of the technologies to increase solubility is to create a solid dispersion system. This study aims to determine the effect of Polyvinylpyrrolidone K-30 and Polyethylenglycol-6000 in a solid dispersion system of usnic acid to improve physicochemical properties including changes in functional groups, changes in amorphous form, and degree of crystallinity of usnic acid. Solid dispersion is made in several comparisons between uric acid, polyvinylpyrrolidone K-30 and polyethylenglycol-6000, namely 1; 1;0, 1; 0;01and 1; 0.5; 0.5. As a comparison, a physical mixture was made with a composition of 1; 0.5; 0.5. Powder mixtures of physical and solid dispersions characterized by physical and chemical properties include Differential Scanning Calorimetry Analysis, Infrared Spectrophotometric Analysis, Assay and dissolution test. The dissolution test was determined by the paddle method. Infrared spectrophotometric analysis showed a slight shift in the functional group wave number but no new functional groups were formed. The results of the Differential Scannin Calorimetry show a reduction in the degree of crystallinity which is indicated by a decrease in enthalpy. From the dissolution test results, it was obtained% dissolved pure usnic acid, physical mixture, formula 1, formula 2, and formula 3, respectively, that is 27.20%, 59.42%, 79.42%, 61.40%, 63.01. %.

Keywords: Solid Dispersion; Usnic Acid; PVP-K30; PEG 6000.

INTRODUCTION

Aqueous solubility is one of the most important physicochemical properties of drug. A drug should possess an appropriate aqueous solubility in order to achieve a therapeutic effect. Poor aqueous solubility will exhibit low absorption. In order for a drug to be absorbed, the drug must be dissolved in the fluid where the drug is absorbed (Ansel, 2008).

Usnic acid has good antimicrobial activity against gram-positive bacteria such as Staphylococcusepidermidis, Staphylococcus, Enterococcus faecalis, Mycobacterium tuberculosis and some pathogenic fungus, but its therapeutic use is limited by its low aqueous solubility (Francolini et al., 2013).

Usnic acid is slightly soluble in water, partially soluble in ethanol and freely soluble in organic solvent (Maulidiyah et al., 2015). Usnic acid also exhibits biological activities such as antiviral, antiproliferation, anti-inflammatory and analgesic properties (Ingolfsdottir et al., 2002).

Solid dispersion refers to the dispersion of one or more active ingredients in a inert carrier matrix at solid state prepared by solvent method, melting method, or melting-solvent method. Solid dispersion is a system with a simple method to enhance the solubility, improve the dissolution rate and bioavailability (Nikghalb et al., 2012).

In this study, polyvinylpyrrolidone (PVP) K-30 and polyethylene glycol (PEG) 6000 were used as solid dispersion matrix. PVP K-30 inhibits crystal growth in the phase transformation (Syukri&mulyati, 2007). Polyethylene glycol (PEG) is soluble in water and miscible with other polyethylene glycol. Polyethylene glycol can be used to improve the solubility and dissolution of insoluble compounds by solid dispersion (Rowe et al., 2009). In this study, usnic acid solid dispersion was formulated by solvent method using hydrophilic polymers: PVP-K30 and PEG 6000.

MATERIALS AND METHODS

Tools

Laboratory glassware, digital analytical balance (PrecisaXB 220A), DSC (Differential Scanning Calorimetry) (Type EVO-131, Equivalent), Infrared Spectroscopy (Thermo Scientific), dissolution test apparatus (Copley Scientific NE4-COPD) uv-vis spectroscopy (Shimadzu, 1800), pH meter (Hanna Instruments HI 2211), soxhlet apparatus, rotary evaporators.

Materials

Usnic acid obtained from the isolation of *Usnea misaminensis* (Vain.), polyvinylpyrrolidone K-30 (PVP K30), Polyethylene glycol (PEG) 6000, distilled water, N-hexane, Ethyl acetate, Methanol, Potassium phosphate monobasic, NaOH.

Research Time and Place

The research was carried out from February to July 2020 at Pharmaceutical Technology Laboratory,STIFARM Padang; Central Laboratory of Faculty of Pharmacy, Andalas University Padang; and Herbarium at Andalas University Padang.

Methods

Usnic Acid Raw Material Test

1. Organoleptic testing of usnic acid was done visually by observed its colour and shape.
2. Determination of melting point of usnic acid with Differential Scanning Calorimetry (DSC).
3. Determination of the maximum wavelength of usnic acid with uv-vis spectroscopy (Maulidiyah et al., 2015).
4. Thin layer chromatography (TLC) test.

PVP K-30 Raw Material Test

PVP K-30 raw material test was carried out according to the Handbook of Pharmaceutical Excipients 6th Edition, including: organoleptic testing.

Polyethylene glycol (PEG) 6000 Raw Material Test

PEG 6000 raw material test was carried out according to the Handbook of Pharmaceutical Excipient 6th Edition, including organoleptic, solubility, and identification.

Preparation of Physical Mixture and Solid Dispersion

Solid dispersion of usnic acid were prepared in various mixtures and can be seen in Table 1.

Table 1. Formulation mixtures (gram)

Formulation	Usnic acid	PVP-K30	PEG 6000
Physical Mixture	1	0.5	0.5
F1	1	1	0
F2	1	0	1
F3	1	0.5	0.5

Physical mixture of usnic acid, PVP-K30 and PEG 6000

The physical mixture of usnic acid, PVP-K30 and PEG 6000 was prepared at ratio of 1:0.5 :0.5 (w/w). The components were mixed and homogenized in the mortar. Then the mixture is placed on parchment paper and divided into 5 parts. The various mixtures were taken and put back into the mortar. This experiments were performed in triplicate. The homogeneous mixture was sieved with a 70 mesh sieve, and then stored in a tightly closed container and stored in a desiccator.

Preparation of usnic acid -PVP K-30 solid dispersion by solvent method

Usnic acid and PVP-K30 were mixed in a ratio of 1:1 (w/w). Methanol was added slowly to usnic acid until dissolved (M_1). PVP-K30 was dissolved in methanol until homogen (M_2). PVP-K30 solution (M_2) then added into the usnic acid solution (M_1) then homogenized with sonication. The mixture was then evaporated on the water bath and then put into a vacuum oven at a temperature of 40ºC-50ºC until dry. The solid then grounded and passed through a sieve.

Preparation of usnic acid-PEG-6000 solid dispersion powder by solvent method

Usnic acid and PEG 6000 were mixed in a ratio of 1:1 (w/w). Methanol was added slowly to usnic acid until dissolved (M_1). PEG 6000 was dissolved in methanol until homogen (M_2). PEG 6000 solution (M_2) then added into the usnic acid solution (M_1) then homogenized with sonication. The mixture was then evaporated on the water bath and then put into a vacuum oven at a temperature of 40ºC-50ºC until dry. The solid then grounded and passed through a sieve.

Preparation of usnic acid solid dispersion of PVP-K30 and PEG-6000 by solvent method

Usnic acid, PVP-K30 and PEG 6000 were mixed in a ratio of 1:0.5:0.5 (w/w). Methanol was added slowly to usnic acid until dissolved (M_1). PVP-K30 and PEG 6000 were dissolved separately in methanol until homogen, (M2) and (M3) respectively. PVP-K30 (M_2) and PEG 6000 (M_3) solution then added into usnic acid solution (M_1), then homogenized with sonication. The mixture was then evaporated on the water bath and then put into a vacuum oven at a temperature of 40ºC-50ºC until dry. The solid then grounded and passed through a sieve.

Evaluation of Solid Dispersion and Physical Mixture of Usnic Acid, PVP-K30 and PEG 6000

Differential Scanning Calorimetry (DSC) Analysis

The thermal properties of the samples were carried out using a differential scanning calorimetry which has been calibrated with Indium temperature. 3 mg of sample was placed on an aluminum pan. The instrument temperature was set in a range from 20°C to 360°C at 10°C per minute of heating rate. This analysis was performed for usnic acid, PVP-K30, PEG-6000, solid dispersion, formulation 1, formulation 2 and formulation 3 (Lira et al., 2009).

Infrared Spectrophotometric (FT-IR) Analysis

FT-IR spectroscopy analysis was done forusnic acid, PVP-K30, PEG 6000, solid dispersion formulation 1,2 and 3, This analysis was performed to study the presence or absence of functional groups formed during the process of usnic acid solid dispersions and also to observed the shift at wave numbers of the usnic acid functional groups. Approximately 1-2 mg of sample was placed and compressed onto a disc under vacuum condition at a pressure of 800 kPa. The absorption spectra were recorded in the region of 400-4000 cm-1 (Watson, 2009)

Determination of Usnic AcidLevels

Preparation of usnic acid mother liquor in methanol solution

The mother liquor of usnic acid was prepared in a volumetric flask with 50 mg of usnic acid put in a 100 mL flask dissolved with methanol, then made up to the mark, so that the concentration of the mother liquor was 500 g/mL.

Measurement of the maximum absorption of usnic acid

A total of 5 mL of usnic acid mother liquor was put in a 10 mL volumetric flask and made up to the mark to obtain a concentration of 250 g/mL of usnic acid analyte solution. Then pipette 2 ml of a solution with a concentration of 250 g/mL into a 10 mL flask and fill it up to the mark so that the analyte concentration of usnic acid is 50 g/mL. Then pipette 1.6 mL from a concentration of 50 g/mL. Measure the absorption at a wavelength of 200-400 nm.

Preparation of usnic acid calibration curve in methanol solution

Pipette from a solution of 50 g/mL concentration, a series of usnic acid solutions with graded concentrations (4,6,8,10, and 12 g/mL) was made by pipetting 0.8; 1,2; 1.6; 2 and 2.4 mL put in a 10 mL volumetric flask. Then it was made up to the mark with methanol. The absorption of each solution was measured using a UV-VIS spectrophotometer. Determined the regression equation between the concentration and absorbance obtained.

Determination of usnic acid content in solid dispersions and physicalmixtures

Each formula was weighed equivalent to 50 mg of usnic acid, then dissolved in methanol in a 100 mL volumetric flask and made sufficient to mark the concentration limit (500 g/mL), take 5 mL of the solution, put it into a 10 mL volumetric flask and make enough volume using methanol to the mark (concentration 250 g/mL). Pipette 2 mL again from a concentration of 250 g/mL, put it in a 10 mL volumetric flask, make sure the volume is up to the mark (concentration 50 g/mL) and then add a 2 mL pipette into a 10 mL flask and fill it up to the mark (concentration 10 g/mL). Each solution was analyzed using a UV-VIS spectrophotometer and the percent recovery was determined using a linear regression equation. The test for determining the recovery rate was repeated three times.

Determination of Dissolution Profile of Usnic Acid Solid Dispersion Powder (Lira, et al., 2009)

CO_2-free aqua production

Heat the distilled water in a suitable closed container until it boils over the bath, leave it for 5-10 minutes then lower it from the bath and wait until it cools down.

Preparation of dissolution medium

Potassium dihydrogen phosphate was weighed as much as 27.218 g dissolved in CO2-free aquadest in a 1000 mL volumetric flask. 8 g of NaOH was weighed dissolved in CO2-free aquadest in a 1000 mL volumetric flask, from a 0.2 M 1000 mL potassium dihydrogen phosphate solution taken 250 mL and from a NaOH solution0.2N 1000 mL was taken 173.5 mL then shaken homogeneously in a 1000 mL volumetric flask.The dissolution medium was measured with a pH meter to pH 7.4, then supplemented with CO2-free aquadest to 1000 mL.

Determination of the maximum absorption wavelength of usnic acid in phosphate buffer pH 7.4

Usnic acid mother liquor was prepared by dissolving 50 mg of usnic acid in 50 mL of phosphate buffer pH 7.4. The concentration was 1000 g/mL. Pipette 1 mL of mother liquor, put into a 10 mL volumetric flask and dissolve with dissolution medium to the mark (100 g/mL). Then 2 mL of a solution of 100 m/mL was pipetted, put into a 10 mL volumetric flask and dissolved with dissolution medium to the mark. Take measurements at an absorption wavelength of 200 nm – 400 nm using a UV-Vis spectrophotometer.

Preparation of usnic acid calibration curve in phosphate buffer pH 7.4

Pipette 1 ml of the mother liquor with a concentration of 1000 g/mL, put in a 10 mL flask and fill it up to the mark with phosphate buffer 7.4 (concentration 100 g/mL). Perform dilutions with concentrations of 10, 20, 40, and 50 g/mL in a 10 mL volumetric flask, then measure the absorbance at the maximum absorption wavelength of usnic acid. Determine the regression equation between concentration and absorbance.

Dissolution test

Determination of the dissolution profile of usnic acid was carried out using the paddle method. The dissolution flask was filled with 900 mL of phosphate buffer pH 7.4 with a temperature of 37° ± 0.5 0C at 100 rpm, 50 mg of usnic acid and 50 mg equivalent to usnic acid solid dispersion system. and rotated. The dissolution solution was pipetted as much as 5 mL at 5,10, 15, 30, 45, and 60 minutes. In each pipetting, the solution in the flask was replaced with dissolution medium (the same volume and temperature at the time of pipetting). The absorption of the solution that has been pipetted from the dissolution medium is measured at the maximum wavelength. The concentration of usnic acid that was dissolved at any time can be calculated using a calibration curve (Ministry of the Republic of Indonesia, 1979).

RESULTS AND DISCUSSION

Results of inspection of usnic acid raw materials The results of the inspection of usnic acid raw materials are in accordance with the requirements listed in (The Merck Index An Encyclopedia of Chemicals Drugs and Biologicals) and those listed in the research journal Maulidiyah, et al., (2015). The results of the examination can be seen in Appendix 1, Table II and Figure 13. Includes examination of description in the form of needle crystal shape and yellow color, identification of wavelength and melting point, determination of Rf (Retention factor) value and yield then identification of functional groups using FT-IR (Fourier transform Infra-Red) and those listed in the research journal Maulidiyah, et al., (2015). The results of the examination can be seen in Figure 1 and Table 2.

Then the identification of the raw material for usnic acid obtained by inspection includes examination of the description in the form of the results of the isolation of usnic acid in the form of needle crystals and yellow in color. 281.60 nm with an absorbance of 0.483 can be seen in Figure 1 and Table 2. Then the TLC test was carried out, the RF value was 0.65, then a melting point test was carried out using DSC. The melting point of usnic acid was 205o C. This is in accordance with the literature of Maulidiyah et al., (2015) the melting point range of usnic acid is 203-205. Then the identification of functional groups in usnic acid was carried out, there were -O-H, -C=O, -C=C, -C-H and -C-O-C groups, the groups obtained were the same as the literature Maulidiyah et al., (2015).

Inspection of Polyvinyl pyrrolidone (PVP-K30) was carried out according to the method listed in (Handbook of Pharmaceutical Excipient)(6thed). The examination of Polyvinyl pyrrolidone (PVP-K30) material was carried out according to the method listed in the (Handbook of Pharmaceutical Excipient)(6thed). The results of the examination of Polyvinyl pyrrolidone (PVP-K30) can be seen in (Figure 1 and Table 2).

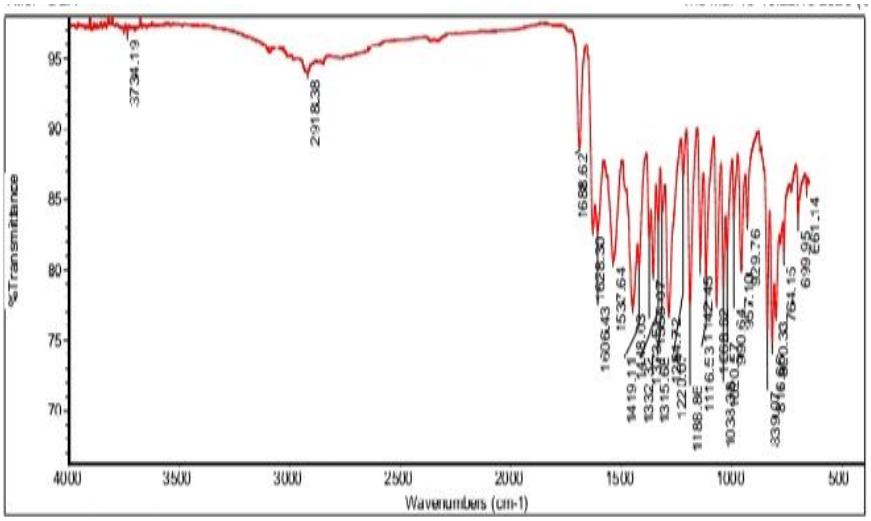

Figure 1. Pure Usnic Acid Infrared Spectrum

Table 2 Dissolution Efficiency

FORMULA	Dissolution efficiency			average (%)	± SD
	Repeater 1	Repeater 2	Repeater 3		
AU	27.294	27.334	26.976	27.201	0.196
CF	59.325	59.287	59.654	59.422	0.201
F1	79.121	79.440	79.705	79.422	0.292
F2	60.792	61.447	61.984	61.408	0.596
F3	62.907	63.166	62.970	63.014	0.135

CONCLUSIONS

The addition of PVP K-30 and PEG-6000 can affect the physicochemical characteristics of usnic acid, the functional group does not form chemical bonds or new groups, and for thermal analysis shows a decrease in enthalpy which indicates a change from crystal to amorphous. The addition of PVP K-30 and PEG-6000 can affect the dissolution rate of usnic acid where the use of PVP-K30 alone increases the dissolution rate compared to PEG-6000 or in combination.The increase in the dissolution rate was indicated by the percentage of dissolution content at the 60th minute for formula 1, The results of the statistical analysis of the dissolution test showed a significant difference in the dissolution efficiency, it can be said that there has been an increase in the dissolution efficiency of the usnic acid solid dispersion formula.The best dissolution efficiency in formula 1 is usnic acidterdisolusi79,422 %dalamwaktu 60 menit.

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