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Formulation of Nifedipine–Polyvinyl Pyrrolidone (PVP) Solid Dispersion System and Intrinsic Dissolution Rate Evaluation

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Abstract

Nifedipine is a drug that acts as an antihypertensive and anti-angina. Nifedipine is known as a drug with poor water solubility. This characteristic will affect the intrinsic dissolution rate so that it can affect the absorption process and reduce the amount of drug that reaches systemic circulation. One of the strategies to increase the intrinsic dissolution rate is developing nifedipine to solid dispersions form. This study aims to observe the intrinsic dissolution rate of nifedipine after it has been made into a solid dispersion. Four samples were prepared, including three solid dispersions of nifedipine-PVP K-30 and one sample of pure nifedipine. The results of the intrinsic dissolution tests are then interpreted through the intrinsic dissolution rate constant (G). The solid dispersions with concentration of nifedipine-PVP K-30 90%:10%; 75%:25%; 60%:40% (w/w), and pure nifedipine produced G values of 3.63; 9.33; 12.63; and 2.08 µg/mm2. min1, consecutively. It shows that the formulation of nifedipine-PVP K-30 solid dispersions has higher G values than pure nifedipine. In addition, increasing PVP K-30 concentration up to 40 % (w/w) can increase the intrinsic dissolution rate of the nifedipine-PVP K-30 solid dispersion system.

Keywords: *Nifedipine, solid dispersion, coprecipitation, intrinsic dissolution.*

INTRODUCTION

Drugs with low solubility are often a problem in developing pharmaceutical preparations. This low solubility has a direct impact on its low dissolution ability. Increasing the rate of dissolution will help increase the rate of absorption, thereby increasing the bioavailability of the drug in systemic circulation (Noval and Malahayati, 2021).

Nifedipine is an antihypertensive and antianginal drug belonging to the class II Biopharmaceutical Classification System (BCS), categorized as having low solubility. Nifedipine has a partition coefficient of 2.2, indicating good permeability (Charalabidis et al., 2019; Nader et al., 2016).

Solid dispersions exist as an alternative method to increase the dissolution rate, especially for poorly soluble drugs in water. This system may consist of one or more active substances in an inert carrier or matrix in the solid state prepared by the solvent method, the melting method, and the melting-solvent method (Shaik et al., 2013).

Co-precipitation is one of the methods for making solid dispersion systems in solids. A dispersion of a drug substance with a carrier which can be prepared by melting at its melting point or dissolving in a suitable solvent can also be prepared by the melt-dissolving method (Huang and Dai, 2014; Shah et al., 2013).

Intrinsic dissolution is one of the in vitro dissolution test techniques used, especially in developing active substances at the preformulation stage. It is because intrinsic dissolution only requires a small number of samples. In addition, it is hoped that the dissolution test results can give researchers an idea of what problems might arise in developing these active substances (Teleki et al., 2020). The intrinsic dissolution rate is defined as the dissolution rate of the pure active substance per unit contact surface area. By knowing the intrinsic dissolution rate, we

can know more deeply about how the rate of dissolution of a drug under physiological conditions (Hadžiabdić, 2013).

This study examines the effect of PVP K-30 with various concentrations in a nifedipine-PVP K-30 solid dispersion system concerning an increase in its intrinsic dissolution rate compared to pure nifedipine. Pure nifedipine is a term that refers to nifedipine non-solid dispersion (no PVP admixture).

RESEARCH METHODOLOGY

Maximum scanning wavelength (λ_{max}) of nifedipine

A total of 10 mg of nifedipine was dissolved in 10 mL of methanol, then put in a 200 mL measuring flask, then added 0.1 M HCl up to the mark. Then 1 mL of nifedipine standard solution was taken and put into a 25 mL measuring flask, and then added dissolution medium up to the mark. The measuring pumpkin is shaken until smooth. The nifedipine solution was then scanned for λmax from 200 nm to 550 nm using a UV-Visible spectrophotometer.

Solid dispersion sample preparation

Nifedipine-PVP K-30 solid dispersions were prepared at three different concentration ratios, as shown in Table 1.

Table 1. Comparison of nifedipine-PVP K-30 solid dispersion concentrations

Mixture	Nifedipine (% w/w)	PVP K-30 (% w/w)
A	90	10
B	75	25
C	60	40

Nifedipine and PVP K-30 was dissolved in 100 mL 95% ethanol in different containers. Next, the nifedipine solution was added to the PVP K-30 solution on a hot plate stirrer at 50°C and a stirring speed of 200 rpm. Ethanol is allowed to evaporate slowly while continuing to stir. Evaporation is continued by using a water bath to evaporate the remaining ethanol until only the co-precipitate is left. Nifedipine-PVP K-30 co-precipitate was then crushed and sieved using sieve number 35.

Pellet production was carried out by inserting approximately 300 mg of nifedipine-PVP K-30 solid dispersion powder into a pellet molding machine, then pressing it with a hydraulic press with a pressure of 6 tons for 3 minutes. Pellets with a diameter of 12 mm were then used to determine the intrinsic dissolution rate.

Intrinsic dissolution test

Dissolution media preparation was carried out by mixing 95% v/v 0.1 M HCl (142.5 mL) and 5% v/v methanol (7.5 mL) so that the total volume of dissolution media used was 150 mL.

The pellet is mounted on a support (Figure 1), then liquid wax is poured until only one side of the pellet surface is not covered by wax, so it will come in direct contact with the dissolution medium. The support is connected to the rotating motor and inserted into the dissolution tube containing the dissolution media solution. The dissolution machine was run at a constant temperature and speed of 37°C±0.5°C, 100 rpm.

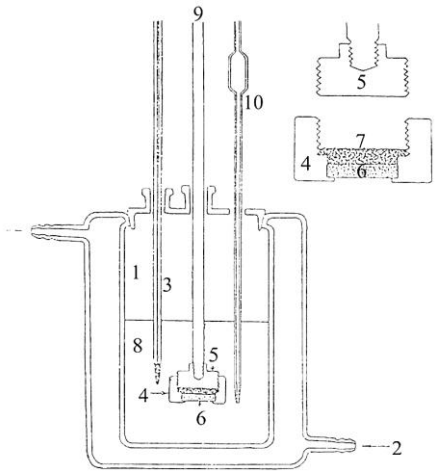

Figure 1. Chart of dissolution test equipment
Figure 1 description: 1. Test tube. 2. Water flow from the thermostat. 3. Thermometer. 4. Pellet holder. 5. Holder cover. 6. Pellet 7. Wax 8. Liquid solvent. 9. Drive shaft. 10. Volume pipette (Yuwono, 1987)

The sampling process was carried out at 5, 10, 15, 30, 45, 60, and 90 minutes. The sampling volume was 2 mL, and for each sampling, 2 mL of dissolution media volume was returned to keep the same volume of medium during the test. After that, the absorbance of each sample was read in a UV-Vis spectrophotometer at λ_{max} nifedipine.

The intrinsic dissolution rate equation is derived from the Noyes-Whitney equation. The simplified form of the intrinsic dissolution rate equation is:

w/s=G.t..... .(1)

where G is the intrinsic dissolution rate constant, and w/s is the dissolved weight per unit area at time t.

W/s is corrected cumulative weight based on sampling volume and total medium volume. At the same time, t is the sampling time. This equation applies when the dissolution test is carried out under sink conditions so that Cs>>>C and a constant contact surface area (Fudholi, 2013).

Results analysis

Analysis of the intrinsic dissolution test results is expressed by G value. G value was obtained by plotting the dissolved weight of nifedipine per unit area (w/s) against the time function. The slope of the curve is the G value. The higher G value of a mixture indicates that the mixture has a higher intrinsic dissolution rate.

RESULTS AND DISCUSSION

Maximum scanning wavelength (λ_{max}) of nifedipine

The nifedipine scanning results produce four wavelengths with large absorption values, namely at wavelengths of 208 nm, 239 nm, 339 nm, and 474 nm, as shown in Figure 2.

Maximum wavelength scanning results in nifedipine readings having to be performed at a wavelength of 339 nm. The wavelengths of 208 nm and 239 nm were not chosen because readings of levels at these wavelengths could be disturbed due to the influence of the cut-off wavelength of the methanol solvent, which also has a UV cut-off wavelength of 205 nm (Khoder et al., 2018).

Solid dispersion sample preparation

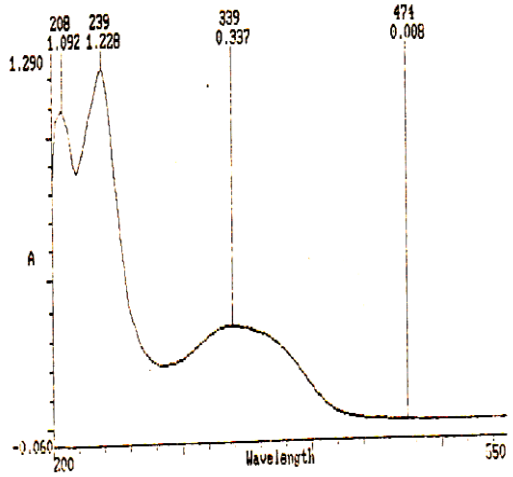

Figure 2. The results of scanning the wavelength of the nifedipine solution

The results of making nifedipine-PVP K-30 solid dispersions from each mixture were as follows: Mixture A 3.30 grams, Mixture B 3.44 grams, and Mixture C 2.88 grams. The result obtained is a fine yellow dry powder.

The interaction between nifedipine molecules and PVP K-30 can occur during the process of making solid dispersions. Nifedipine molecules will be dispersed and trapped in the PVP polymer network, and when heated, the physical state of nifedipine can change into an amorphous form (Kothari et al., 2015; Saraf et al., 2022).

Intrinsic dissolution test

The results of the nifedipine intrinsic dissolution test and nifedipine-PVP K-30 solid dispersion can be seen in Figure 3.

The nifedipine-PVP K-30 solid dispersion mixture generally has a higher intrinsic dissolution rate than pure nifedipine. The increased level of dissolved nifedipine in nifedipine-PVP K-30 solid dispersion system proves the effect of PVP K-30, which is highly hydrophilic (Zidan et al., 2019). The dissolution rate of PVP-based solid dispersion is related to the molecular weight and

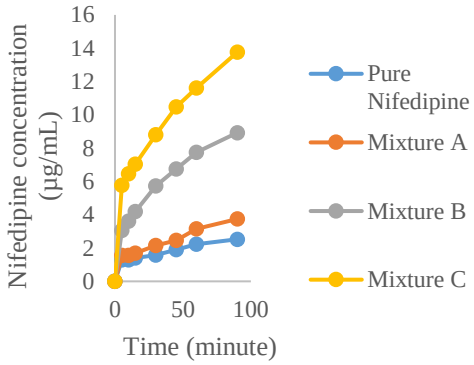

Figure 3. Dissolution profile curves of pure nifedipine and nifedipine in nifedipine-PVP K-30 solid dispersion

concentration of PVP employed in the system. An increase in the molecular weight and concentration of PVP correlated negatively with the dissolution rate. The higher PVP molecular weight and concentration increases the viscosity and swelling of PVP within the solution phase. It consequently decreases the diffusion of drug molecules from the surface boundaries of the viscous material into the bulk of the solution, leading to reducing the dissolution rate of drug (Nair et al., 2020).

Results analysis

Comparative analysis of the intrinsic rate of dissolution constant was carried out using to equation (1). The experimental conditions that met the intrinsic dissolution rate equation criteria included: the experiment was carried out under sinking conditions, the total dissolved weight of substance per unit volume was constant, the contact area was constant, and the initial dissolution weight per unit volume was empty (Fudholi, 2013).

W/s of nifedipine was obtained from dissolution test results of pure nifedipine, Mixture A, Mixture B, and Mixture C pellets. The increase of w/s value occurred according to the increase in the concentration of PVP K-30. W/s value of Mixture C was up to six times that of the w/s value of pure nifedipine, three times that of the w/s value of Mixture A, and one and a half times that of the w/s value of Mixture B. Furthermore, plotting was carried out between w/s against time, where the results are shown in Figure 4.

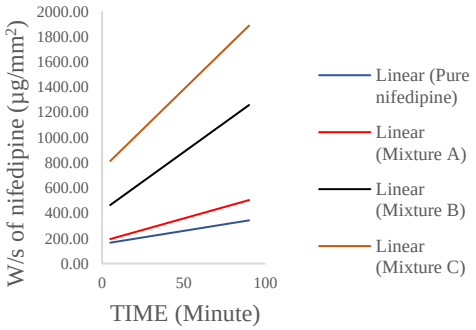

Figure 4. The curve of the relationship between w/s and the time function

The results of plotting between w/s and the time function will produce a linear regression equation, where the slope is the value of the intrinsic dissolution rate constant. The value of the intrinsic dissolution rate constant (G) and the correlation coefficient can be seen in Table 2.

Table 2. Intrinsic dissolution rate constant (G)

Campuran	G value ($\mu g\ mm^{-2}\ min^{-1}$)	Correlation Coefficient (r)
Pure Nifedipine	2,08	0,992
Mixture A	3,63	0,993
Mixture B	9,33	0,981
Mixture C	12,63	0,992

The solid dispersion of nifedipine-PVP K-30 has a higher G value than pure nifedipine at all concentration variations. It proves that the formation of solid dispersions has successfully increased the intrinsic dissolution rate of nifedipine. In addition, it is also seen that the greater the ratio of PVP K-30 to nifedipine will increase its G value. It proves that the concentration of PVP K-30 in the solid dispersion mixture increases the intrinsic dissolution rate of solid nifedipine dispersion.

An increase in dissolution rate can occur through two mechanisms: withdrawing and wetting. A carrier material that dissolves easily after interacting with the drug substance will be bound around the substance

so that the solid dispersion system will dissolve rapidly in a solution by carrying (withdrawing) the drug. It is called the withdrawal mechanism (Sareen et al., 2012; Van den Mooter, 2012).

Another mechanism is the wetting mechanism. It occurs because of the interaction between nifedipine and PVP K-30 through hydrogen bonding with water in the medium which causes the solid dispersion to dissolve quickly (Huang and Dai, 2014). Each PVP K-30 molecule contains elements that can hold hydrogen bonds (oxygen) (Fitriani et al., 2016). PVP K-30 is easily soluble in water, so it can increase the penetration of the dissolution medium into solid dispersions (Febriyenti et al., 2019; Salman et al., 2015). It is because PVP K-30 has good hydrophilic properties so that it can form water-soluble complexes with drug compounds that have slight solubility in water (Jagtap et al., 2019; Nair et al., 2020).

The limitations in this study are related to increasing the concentration of PVP K-30 as a hydrophilic inert carrier in forming the Nifedipine-PVP K-30 solid dispersion system. The concentration of PVP K-30 above 40% w/w will form a gel that cannot develop a solid dispersion system. Its phenomena inform us that the concentration of PVP K-30 is under 40%, which we could only use to develop a solid dispersion system. So, in this research, 40% w/w was the maximum concentration in preparing nifedipine-PVP K-30 solid dispersions using the coprecipitation method. The greater the concentration of PVP K-30, up to 40% w/w, the greater the amount of water attracted by PVP K-30 so that the combination of solid dispersion mixtures hydrates faster and affects the intrinsic dissolution rate of nifedipine (Alves et al., 2014; Frizon et al., 2013).

CONCLUSION

The formation of a nifedipine-PVP K-30 solid dispersion system can increase nifedipine's intrinsic dissolution rate compared to pure nifedipine's. The higher concentration of PVP K-30, up to 40% w/w, in the solid dispersion system can increase the intrinsic dissolution rate of nifedipine.

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