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Original Article

INVESTIGATION OF NIFEDIPINE SOLID DISPERSION WITH SOLVENT PVP K-30

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ABSTRACT

Objective: The objective of this study was to investigate solid dispersions of nifedipine and polyvinylpyrrolidone K-30 in different drug loads.

Methods: Solid dispersions with drug loads 20%, 30%, 50% were prepared by spray dried method. Drug-carrier interaction was analyzed with FT-IR, X-ray Powder Difractometry (XRPD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM), and *In-vitro* drug release.

Results: The results were as follows: (1) solid dispersions was granulated, yellow, and had a free flowing nature. (2) FT-IR spectra had no interaction between nifedipine with PVP K-30, (3) the assay of formulas met all the requirements of 90%-110%, (4) XRPD patterns of all PVP-based solid dispersions with nifedipine incorporated showed no distinctive peaks of crystalline nifedipine, (5) thermograms of these physical mixtures showed broad melting peak of nifedipine and shifted to the lower temperature indicating the partial miscibility of drug in carrier during DSC scan, (6) Scanning electron microscopy study releaved that the solid dispersion were spherical and porous in nature.

Conclusion: Dissolution behavior of solid dispersion based on the PVP K-30 was determined by dissolution of the carrier. A lower drug load will increase drug dissolution of solid dispersions.

Keywords: Spray dried method, Nifedipine, Amorphous solid dispersions, Dissolution, Polyvinylpyrrolidone K-30.

INTRODUCTION

Amorphous solid dispersions can be used to improve the dissolution rate of poorly soluble drugs [1]. In general, a solid dispersion consists of a hydrophilic carrier in which the drug was dispersed molecularly or as very small particles [2-4].

In a previous study, fully amorphous solid dispersions using PVP K-30 was prepared as hydrophilic carriers and nifedipine as a model drug. Dissolution behavior these solid dispersions were evaluated by determining the dissolution rate of the PVP K-30 as well as the drug. However, when the drug load was high and or when the PVP K-30 dissolved fast, the dissolution rate of the drug was slowed [4, 5].

This phenomenon was attributed to an uncontrolled crystallization of the drug in the near vicinity of the dissolving tablet due to a high supersaturation. This uncontrolled crystallization resulted in the formation of large crystals which obviously dissolved slowly. Furthermore, it was found that the drug and the carrier in the solid dispersions did not interact [6].

It is well known that polyvinylpyrrolidone (PVP) can interact with many lipophilic drugs [6–11]. PVP K-30 is a hydrophilic polymer that can lead to increase solubility in water [11]. This study was therefore to investigate the dissolution behavior of tablets prepared from solid dispersions in which drug and carrier do interact and to compare that with the dissolution behavior of tablets prepared from solid dispersions that lack such an interaction. Nifedipine was used as model drugs.

MATERIALS AND METHODS

Materials

The following materials used: nifedipine was purchased from Kimia Farma, Bandung, Indonesia; and polyvinylpyrrolidone (PVP) K-30 was supplied by BASF, South East Asia Pte. Ltd. Since nifedipine is a photosensitive drug, it had been protected from light during all tests.

Preparation of solid dispersion (SD)

To produce the solid dispersions with different drug loads, the concentrations of drug and methods were suitably adjusted (table 1). Solid dispersion were prepared by spray dried technique with inlet temperature 90 °C, exhaust temperature 60 °C, and pump speed 4.

Preparation of physical mixtures (PM)

Physical mixture prepared by mixing nifedipine and PVP K-30 physical and crushed in the corresponding ratio of solid dispersions were prepared by gently mixing using mortar and spatula. This samples were placed in a vacuum desiccator over silica gel at room temperature for at least one day before use.

Table 1: Formulation variable of nifedipine solid dispersion

Formula	Method of Preparation	Drug load Nifedipine (%)	PVP K-30 (%)
F I	Solid Dispersion	20	80
F II	Solid Dispersion	30	70
F III	Solid Dispersion	50	50
F IV	Physical Mixtures	20	80
F V	Physical Mixtures	30	70
F VI	Physical Mixtures	50	50

Scanning electron microscopy (SEM)

The morphology of particles was examined by scanning electron microscopy (Jeol JSM T300).

X-ray powder difractometry (XRPD)

Samples were analyzed using difractometer (Philip PW 1800, Gadjah Mada University, Yogyakarta, Indonesia) with copper anode (Cu Kα

radiation, λ = 0.15405 nm, 40 kV, 40 mA). The difraction pattern was measured with step size of 0.008° and dwell time of 45s.

FT-IR analysis

Nifedipine, physical mixtures, and nifedipine spray dried were performed with FT-IR spectrophotometer (IR-Prestigo 21). The samples were made into pellet shape with KBr crystals (pressure 7 torr, 5 minute); and then samples were analyzed with FT-IR at a wavelength of 4000-500 cm^{-1}. [12]. FT-IR analysis is useful to explain the interaction between nifedipine with PVP K-30 which has been seen from the parameters of functional groups formed on the solid dispersion spectra.

Differential scanning calorimetry (DSC)

A modulated differential scanning calorimeter (ASTM D 3418-08, BPPT, Serpong, Jakarta, Indonesia) was used to measure glass transition temperature (*Tg*) of the solid dispersions. About 5 mg of sample was weighed in a standard open aluminium pan. An empty pan of the same type was used as a reference. Samples were heated from 30–200°C at a heating rate of 10°C/min, a modulation amplitude of 0.318°C and a modulation period of 60 s. Modulated Differential Scanning Calorimetry (MDSC) while being purged with pure nitrogen gas. Calibrations of temperature and heat flow were carried out with indium. The inflection point of the transition was taken as the *Tg*. Furthermore, samples were run at a heating rate of 20°C/min without modulation to measure the degree of relative crystallinity of the drug in solid dispersions (DSC). All measurements were conducted at least in triplicate.

***In-vitro* drug release**

Dissolution of samples was performed using USP dissolution apparatus II (Veego) with paddles at 100 rpm and 37°C. This samples was filtered through 0.35 µm filters prior to analysis. Concentration of nifedipine in the medium was measured at a wavelength of 237 nm with UV-Vis Spectrophotometer mini 1240 (Shimadzu). HCl pH 1, 2 (900 mL) was used as the dissolution medium. In a number of cases when PVP based-solid dispersions or PVP based-physical mixtures were evaluated, 1.0 mL samples were taken at different time intervals. Measurements were performed in triplicate.

RESULTS AND DISCUSSIONS

Physical characteristics of the test conducted on the formula of solid dispersions, physical mixtures, and obtained data such as nifedipine powder were shown in table 2.

Table 2: Nifedipine solid dispersion characteristics

Formula	Type test			
	Organoleptic	Flow rate* (gram/sec)	Moisture content* (%)	Melting point* (°C)
F I	Granule, yellow, *free flowing*	20.69±0.30	6.37±0.08	172.03±3.06
F II	Granule, yellow, *free flowing*	22.80±0.28	3.90±0.11	173.05±3.06
F III	Granule, yellow, *free flowing*	21.70±0.43	4.70±0.11	172.22±2.00
F IV	Yellow powder	No flow	7.10±0.11	172.68±1.15
F V	Yellow powder	No flow	6.13±0.10	172.70±2.31
F VI	Yellow powder	No flow	5.30±0.11	172.91±1.15
Nifedipine	Fine powder, light yellow	No flow	0	174.97±0.58

Note: *Mean±SD; n= 3

a b

Fig. 1: SEM Picture of Nifedipine (a) and Solid Dispersion Nifedipine with PVP K-30 (b)

Scanning electron microscopy (SEM)

The morphology of microparticles was examined by scanning electron microscopy (Jeol JSM T300). Samples were mounted on metal stubs and sputter-coated with gold for 4 prior to examination under. The SEM picture was seen in fig. 1, that the shape of the microspheres was spherical and smooth surface with less porosity.

XRPD studies

XRPD patterns of all PVP-based solid dispersions with nifedipine incorporated showed no distinctive peaks of crystalline nifedipine. Fig. 2 showed the XRPD patterns of nifedipine solid dispersion and the corresponding physical mixture with 20%, 30%, 50% drug load respectively. The XRPD pattern of nifedipine had sharp peaks. As expected, the physical mixture showed the typical sharp peaks of crystalline nifedipine. Compared to the corresponding physical mixture, the solid dispersion showed a broad diffraction peak and lack of the typical sharp peaks of crystalline nifedipine. This indicates clearly that nifedipine incorporated in PVP K30 was fully amorphous [13].

FT-IR studies

FT-IR analysis was used to examine the interaction between nifedipine and PVP K-30 which has been seen from the parameters of functional groups performed on the solid dispersion spectra. Table 3 showed that there is no interaction between nifedipine with PVP K-30. Wave number shift was happening, but still met the requirements. For the OH group is at wave number 3400-2400 cm^{-1}, C = O group is at wave number 1820-1600 cm-1, and nitro groups is at wave number 1600-1500 cm^{-1}.

DSC studies

To investigate whether the drugs were incorporated in the solid dispersions molecularly, as amorphous particles or as crystalline particles, all samples including drugs, solid dispersions and corresponding physical mixtures were evaluated by (M)DSC. The melting points (*Tm*) of nifedipine were 174.94°C and the *Tgs* of PVP K30 was 173°C, respectively. Thermograms of these physical mixtures showed broad melting peak of nifedipine and shifted to the

lower temperature indicating the partial miscibility of drug in carrier during DSC scan. For instance, as shown in fig. 2, the solid dispersion with nifedipine incorporated at a drug loads of 20% in PVP K30 showed one single *Tg* at 132.24°C indicating that nifedipine was molecularly dispersed in these solid dispersions. When the concentration of nifedipine in PVP K30 was increased, multiple *Tg* were observed at 130.15°C for a drug loads of 30%, and at 133.04°C for a drug loads of 50%. These results indicate that in these solid dispersions of nifedipine was partially molecularly mixed with PVP K30 and partially distributed as amorphous clusters [14-16].

***In-vitro* drug release**

Table 4 indicated that solid dispersion can increase this solubility of the pure drug substances. FI consists of 20% drug loads which have the greatest level of dissolved. It is because of the higher concentration of PVP K-30 in these formula.

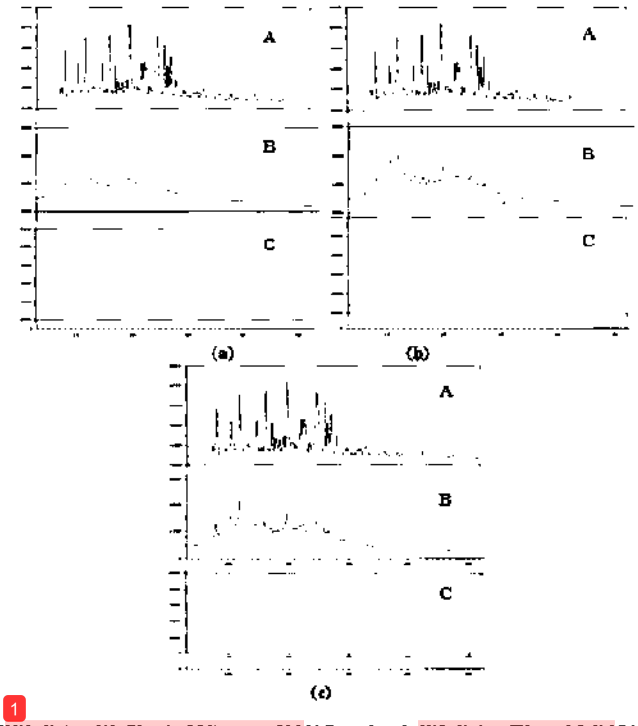

Fig. 2(a): XRD Patterns of Nifedipine (A), Physical Mixture of 20% Drug Loads Nifedipine (B), and Solid Dispersion of 20% Drug Loads Nifedipine (C) 2(b). Nifedipine (A), Physical Mixture of 30% Drug Loads Nifedipine (B), and Solid Dispersion of 30% Drug Loads Nifedipine (C) 2(c) Nifedipine (A), Physical Mixture of 50% Drug Loads Nifedipine (B), and Solid Dispersion of 50% Drug Loads Nifedipine (C)

Table 3: FT-IR Analysis

Formula	Wave number (cm^{-1})		
	-OH	C=O	Nitro
FI	3448.72	1658.78	1658.78
FII	3448.72	1681.93	1651.07
FIII	3417.86	1681.93	1527.62
FIV	3448.72	1681.93	1651.07
FV	3448.72	1681.93	1643.35
FVI	3448.72	1681.93	1651.07
Nifedipine	3332.99	1681.93	1527.62

Table 4: Profile dissolution of nifedipine (%)

Formula	Nifedipine (%)					
	10 min	20 min	30 min	40 min	50 min	60 min
FI	76, 69±2, 36	89, 48±3, 17	93, 23±3, 48	95, 65±3, 84	96, 47±3, 28	97, 84±3, 54
FII	40, 99±1, 64	51, 75±0, 38	54, 40±2, 23	57, 53±2, 89	65, 73±4, 08	70, 60±0, 89
FIII	17, 27±2, 45	22, 58±0, 71	30, 91±2, 96	33, 84±1, 76	34, 54±2, 04	36, 74±1, 32
FIV	9, 26±1, 88	12, 88±0, 42	17, 51±2, 33	20, 25±3, 54	26, 45±1, 58	27, 04±2, 16
FV	10, 89±2, 28	24, 07±2, 56	31, 24±2, 62	35, 43±2, 93	38, 29±2, 63	40, 14±2, 27
FVI	13, 75±2, 25	26, 34±3, 44	35, 42±1, 32	39, 64±1, 32	43, 63±1, 90	44, 69±1, 38
Nifedipine	10, 25±4, 01	24, 95±0, 34	30, 15±1, 61	34, 91±2, 19	37, 53±1, 60	40, 16±1, 06

Dissolution profiles are intended to describe the drug release at any given time. fig. 3 shows the release of different drug loads in each formula.

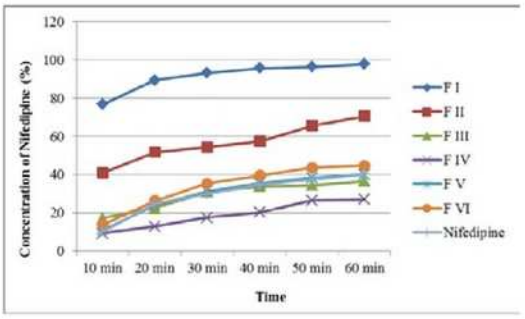

Fig. 3: Dissolution profiles

Both FI and F II had higher drug release than pure nifedipine because nifedipine was fully distributed as amorphous. Metastable amorphous form is a form which has the lower activation energy than the crystal, this can be increased solubility of drugs [10]. F III has lower drug release than control. It may be caused that the amount of PVP K-30 which were used to disperse nifedipine was not enough. All of the physical mixtures (F IV, F V, and F VI) has lower solubility than solid dispersion due to physical mixture between nifedipine and PVP K-30 only physically mixed which does not changes their molecular shape. Increase in drug loads causes a decrease in prosentase drug dissolved, because of the amount of PVP K-30 was reduced. PVP K-30 is one of substances that helps solubility of nifedipine. The less amount of PVP K-30 makes the lower solubility of nifedipine.

CONCLUSION

Dissolution behavior of solid dispersion based on the PVP K-30 has been determined by dissolution of the carrier. The lower drug loads will increase dissolution of solid dispersions. It could refers to the fact that a higher drug loading in PVP K-30 based solid dispersion, gives a stronger tendency of the drug for recrystallization in the vicinity of a drug dissolving line. As a drug and carrier do not interact, a dissolution process will be difficult.

CONFLICT OF INTERESTS

Declared None

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