



Development and characterization of solid dispersion to enhance the dissolution profile of Nifedipine with PVP K30 and Poloxamer 407

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Received: 23-10-2014
Review completed: 21-11-2014
Accepted: 17-12-2014

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ABSTRACT

The purpose of this study is to develop and characterize the nature of a solid dispersion system of nifedipine in a polymer matrix consisting of PVP K30 and poloxamer 407. Dispersions consist of drug, polymeric carrier and surfactant carrier. Binary solid dispersions consisting of nifedipine and PVP K30 were developed by solvent evaporation method. Poloxamer 407, surfactant carrier was incorporated into binary solid dispersions as the third component to prepare ternary solid dispersions. Solid dispersions were characterized by differential scanning calorimetry, Fourier transform infrared spectroscopy, and dissolution tests. Both the binary and ternary solid dispersions enhanced the dissolution of nifedipine. Moreover, the dissolution of ternary solid dispersion was faster compared with that of binary solid dispersion. Poloxamer 407 played an important positive role in dissolution of the solid dispersion.

Key words: Nifedipine, Surfactant carrier, Dissolution, Solubility enhancement.

INTRODUCTION

Nifedipine is the prototype nitro-dihydropyridine calcium channel antagonist that is used to treat a variety of cardiovascular disorders, such as angina pectoris and hypertension^{1, 2}. Nifedipine exists in the form of crystals of melting point of 172–174 °C that is poorly soluble in water³. The dissolution of pure drug is the slowest step during absorption process and leads to variation in the bioavailability and it has to be administered thrice a day because of immediate release oral solid dosage forms because of the short half-life which leads to significant fluctuation in the plasma drug concentration and drug toxic effect^{4, 5}. The oral route of drug administration is the most common and preferred method of delivery of drugs for systemic effects because of simplest and easiest way of administering drugs⁶. There are a large percentage of drugs which having low aqueous solubility and low dissolution rate that leads to low drug concentrations at absorption sites and result obtained is low oral bioavailability^{7, 8} first devised the Biopharmaceutical Classification System and categorized such drugs in the Biopharmaceutical Classification System as class II compounds. To overcome

these class II compounds limitations, several methods have been opted such as complexation, solubilization, formulation of solid dispersions etc. Except solid dispersions, every method has their own limitations but solid dispersions are the effective approach to achieve the solubility and dissolution of the drug. Solid dispersions is defined as dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by fusion, hot-melt, solvent and supercritical fluid method⁹. This is the method which reduces the drug particle size and hence enhanced the dissolution rate, wettability and dispersibility of the drug¹⁰. Many hydrophilic polymers are being commonly used as carriers for preparation of the solid dispersions like polyvinylpyrrolidone (high aqueous solubility and low toxicity), polyethylene glycol, hydroxy propyl methylcellulose. In this study, BCS II drug nifedipine has low solubility 5.6 µg per ml was used as model drug and polyvinyl pyrrolidone K30 was used as the carrier for the preparation of the binary solid dispersions, in ternary solid dispersions PVP K30 and poloxamer 407 were used. Solid dispersions were prepared by solvent

evaporation method. In these dispersions, PVP K30 and Poloxamer 407 will reduce the particle size and enhance the dissolution rate of the drug

MATERIALS AND METHODS

Materials

Nifedipine was provided as a gift sample by Medicamen Biotech limited, Bhiwadi (Rajasthan). Poloxamer were provided by Central drug house pvt. Ltd., New delhi. PVP K30 were provided by Central drug house pvt. Ltd., New delhi. Acetone were provided by Loba chemie pvt. Ltd. Mumbai. All the reagents were of analytical grade.

Methods

Preparation of physical mixture

Physical mixtures of nifedipine and PVP K30 were prepared by mixing the required amount of nifedipine and PVP K30 in a glass mortar for 5 min at 1:1 and 1:8 (nifedipine/PVP K30) ratios. The prepared mixture was passed through sieve no. 60. Physical mixtures of nifedipine PVP K30 and poloxamer 407 were prepared by mixing the required amount of nifedipine, PVP K30 and poloxamer 407 in a glass mortar for 5 min at 1:8:1 and 1:8:2.

Formulation of solid dispersions

Binary and ternary solid dispersions were prepared by solvent evaporation method. In binary solid dispersions, different weight of nifedipine and PVP K30 (1:1, 1:2, 1:4, 1:6, 1:8 and 1:10) were dissolved in 20 ml chloroform, then the solvent was removed in water bath at 60°C. The residues were dried in an oven at 50 °C for 24 hours, then ground in a mortar and passed through sieve no. 60. The resultant granules were kept in desiccators. In ternary solid dispersions, poloxamer 407 was incorporated into nifedipine and PVP K30 to obtain the dispersions with weight ratios of 1:8:1, 1:8:2, 1:8:4, 1:8:6, 1:8:8, 1:8:10 (nifedipine/PVP K30/poloxamer 407).

Solubility study

Drug and solid dispersions solubility was determined by adding excess amount of nifedipine or equivalent to 20 mg of nifedipine into pH1.2 buffer at 37±0.5°C. This was agitated for 48 hr in shaker upto saturation and then saturated solution was withdrawn, filtered to obtain clear solution and analyzed by using Double beam spectrophotometer (Systronics model no. 2203, India) at 239.8nm.

Differential scanning calorimetry

DSC was performed on a Diamond DSC (Perkin, USA) with a thermal analyzer. Samples were heated in sealed aluminium pans with heating rate of 10°C/min from 20 to 200°C. An empty aluminium pan was used as reference.

X-Ray diffraction

The X-ray diffraction (XRD) studies were carried out to determine the physical state of the drug, carriers and drug in the solid dispersions. The XRD was investigated by

scanning powder samples using X' Pert PRO instrument (Philips, The Netherland), equipped with X' Pert PRO Data Collector software. The radiation used was generated by a CuK α source fitted with a Ni filter operated at voltage of 45 kV. Samples were analyzed in the 2 θ angles range from 5 - 45°, at a scanning rate of 10°/min. The peak intensities of diffractograms of powdered samples of pure drug, PVP K30, poloxamer 407 and solid dispersions were compared.

FTIR spectroscopy

FTIR spectra were obtained by using a FTIR spectrophotometer- 4800S (Shimadzu, Japan) in the region of 500-4000 cm⁻¹ using a resolution of 2 cm⁻¹. The samples (nifedipine, solid dispersions, physical mixtures and polymers) were ground and mixed thoroughly with potassium bromide at 1:5 (sample: KBr). KBr discs were prepared by compressing the powders under force of 6 tons for 5 min in hydraulic press. The FTIR spectra were compared to check the interaction between drug and carriers.

In-vitro dissolution of solid dispersions

Dissolution study was conducted in triplicate on the pure drug, binary and ternary physical mixture, binary and ternary dispersions. Dissolution tests were performed by using USP dissolution apparatus- II/ 8000 (Labindia). To simulate the dissolution of the compound in stomach, 900 ml of pH 1.2 buffer was used as dissolution media at a temperature of 37±0.5°C and basket speed of 100 rpm. Amount of powdered samples, equivalent to 20 mg nifedipine was added to the dissolution medium. Ten ml samples were taken and immediately replaced with fresh dissolution medium. At predetermined intervals (15, 30, 45, 60, 90, 120, 180 min), 10 ml samples were withdrawn from each vessel, filtered with whatman filter paper. The samples were analysed for nifedipine content by using Double Beam spectrophotometer (Systronics model no. 2203, India) at 239.8nm. The results of dissolution studies were statistically analyzed using ANOVA.

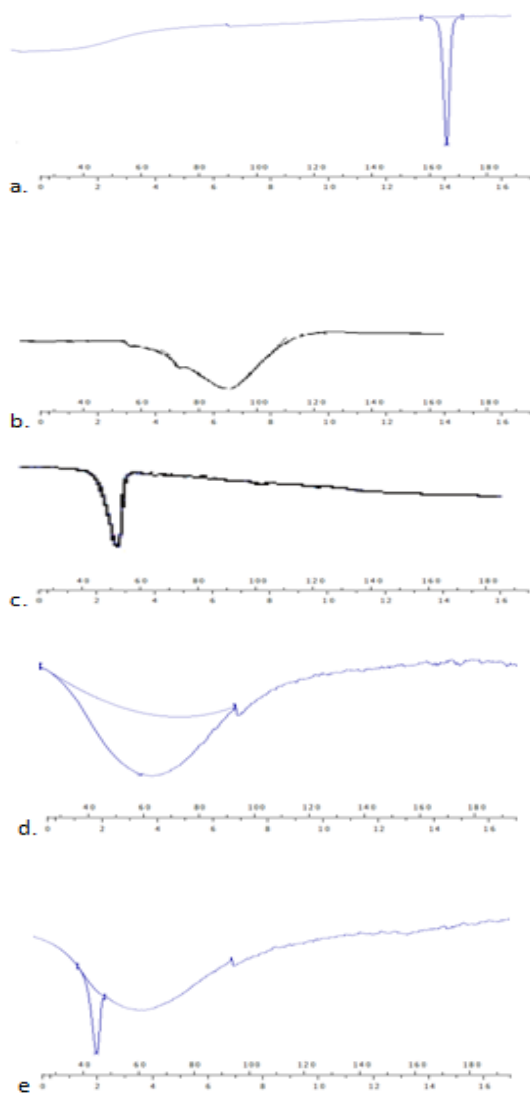
RESULTS AND DISCUSSION

Solubility study

The solubility of nifedipine from solid dispersions system in pH 1.2 buffers at 37 ± 0.5 °C is found to be greater than pure nifedipine shown in table 1. The solubility of nifedipine was 2.3 µg/ml and binary solid dispersions solubility was found 14.9 µg/ml and in case of ternary solid dispersion was 24.7 µg/ml. Solubility might have enhanced by micellar solubilization or by reducing the activity coefficient of the drug by reducing the hydrophobic interaction or by both processes. In addition, improvement of the wetting of the hydrophobic nifedipine crystals may occur.

Table 1. Solubility of nifedipine and nifedipine solid dispersion system at 37 ± 0.5 °C

Medium	Type of nifedipine	Solubility (µg/ml)
pH 1.2 buffer	Pure nifedipine	2.3
pH 1.2 buffer	Binary solid dispersion	14.9
pH 1.2 buffer	Ternary solid dispersion	24.7



observed. This result suggest that on heating in DSC, nifedipine progressively dissolves in poloxamer 407 and PVP K30 below melting temperature of crystalline nifedipine (Fig. 2e). The sharp peak of nifedipine shows the cyrstallinity of the pure drug and solid dispersions shows complete absence of drug peak at 174.21 °C indicated that the crystalline form of the nifedipine had transformed into amorphous form.

X-Ray diffraction

The XRD of pure nifedipine, PVP K30, poloxamer 407 and solid dispersions is shown in Fig. 3. The XRD pattern of nifedipine displayed sharp peaks at 7.35, 8.22, 10.49, 11.89, 13.05, 14.78, 16.31° (2θ) etc. with percent intensity 0.16, 79.39, 1.82, 53.80, 0.65, 1.58, 100.00 etc. respectively indicating that drug is present in the highly crystalline nature. Relative decrease in crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the binary system with those of a reference (pure nifedipine). Nifedipine solid dispersions with PVP K30 did not show the crystalline peaks. The peaks of nifedipine disappeared in all solid

dispersions systems. The absence of intense peaks in solid dispersions suggested that drug has lost crystalline nature and possibly might have transformed into amorphous form. Nifedipine solid dispersions with PVP K30 and poloxamer show nifedipine peaks disappeared in ternary solid dispersions; the poloxamer 407 peaks appeared; possibly may have achieved highest degree of bioavailability and stabilized solid dispersions, avoiding recrystallisation.

FTIR spectroscopy

FTIR spectra of nifedipine, PVP K30, poloxamer 407, physical mixture and solid dispersions systems are shown in Fig. 4. The IR spectrum of nifedipine (Fig. 4a) is characterized by principal absorption peaks at 3330.84 cm^{-1} (NH stretch), 3103.25 cm^{-1} (C=O stretch), 1689.53 cm^{-1} (C-H stretch), 1529 cm^{-1} (NO_2 stretch). The IR spectrum of physical mixture (Fig. 4d, 4e) displayed the superimposition pattern of nifedipine and polymer peaks with decreased peaks intensity and little shift in peaks. The IR spectrum peaks of binary system (Fig. 4f) shows disappearance of peaks at 3330.84 cm^{-1} and the presence of all other nifedipine peaks with decreased intensity. The IR spectrum peaks of ternary system (Fig. 4g) shows disappearance of peaks at 3330.84 cm^{-1} and some other peaks are not visible while the peak at 3103.25 cm^{-1} and 1689.53 cm^{-1} were shifted to 3023.19 cm^{-1} 1660.77 cm^{-1} . The peak of 3103.25 cm^{-1} of CH appeared consistently but slightly shifted in binary and ternary solid dispersions. All other nifedipine peaks were smoothed indicating a strong physical interaction of nifedipine with polymers and drug-polymers are compatible to each other. However, no additional peak was observed in any binary and ternary system indicating absence of any chemical interaction between nifedipine and polymer.

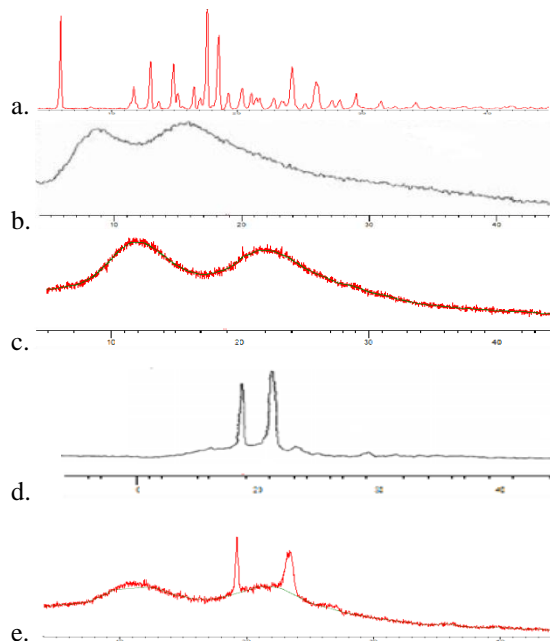


Figure 3: X-ray diffraction of (a) nifedipine (b) PVP K30 (c) solid dispersions consisting of nifedipine and PVP K30 (1:8) (d) poloxamer 407 (f) Solid dispersions consisting of Nifedipine, PVP K30 and poloxamer 407 (1:8:2)

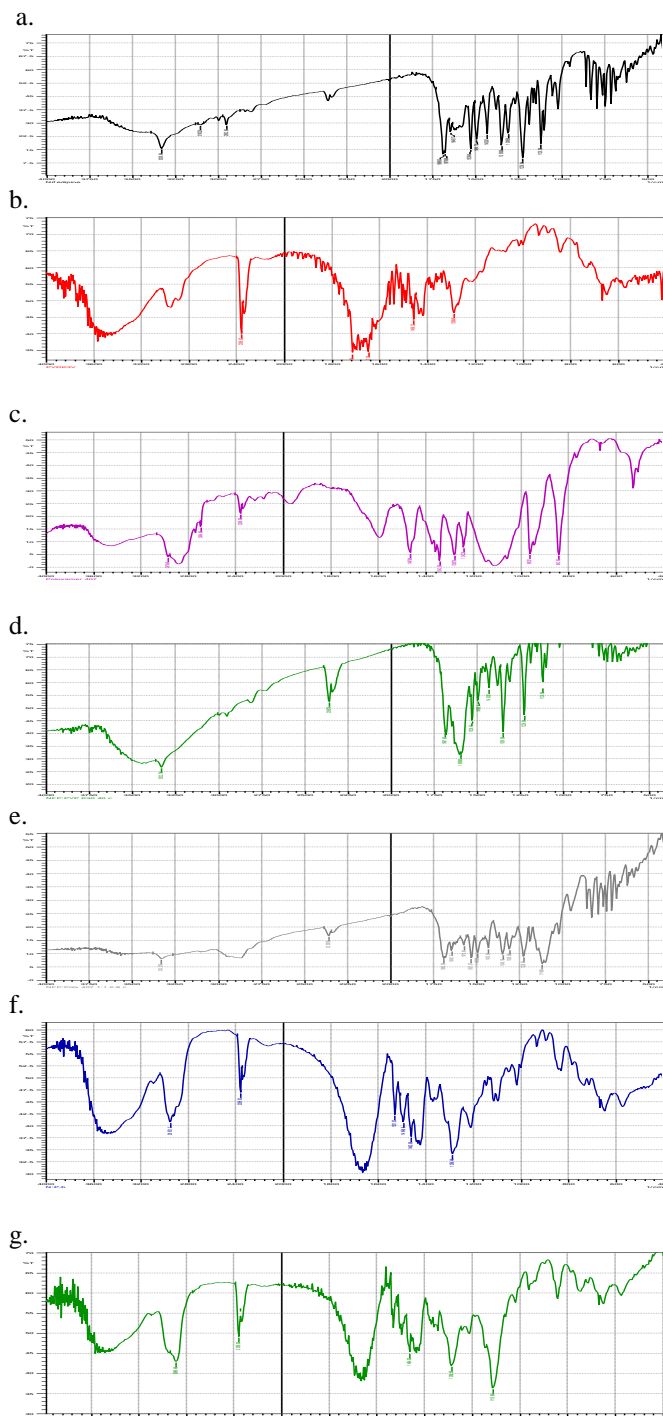


Figure 4: FTIR spectra of (a) nifedipine (b) PVP K30 (c) poloxamer 407 (d) physical mixture consists nifedipine and PVP K30 (e) physical mixture consists nifedipine, PVP K30 and poloxamer 407 (f) solid dispersions of nifedipine consisting PVP K30 (g) solid dispersions of nifedipine consisting PVP K30 and poloxamer 407.

In-vitro dissolution of solid dispersions

The dissolution profiles of nifedipine, binary and ternary physical mixtures, binary and solid dispersions were plotted in Fig. 5 and 6. The statistical analysis was performed between the dissolution data. The physical mixtures as well as solid dispersions system of nifedipine with poloxamer 407 have significant improved the drug

dissolution rate ($p < 0.05$ for PM; $p < 0.05$ for SD). The percentage of nifedipine dissolved was 0.99% in 30 min and only 2.82% in 3 hour. Comparing with the nifedipine, the dissolution rate of the physical mixtures was slightly higher: the percentage drug dissolved of binary physical mixture consisting nifedipine and PVP K30 (1:8) was 23.54% in the 30 min, it might be due to increase in drug wettability and dispersibility¹¹ with PVP K30 and in the case of ternary physical mixture consisting nifedipine, PVP K30 and poloxamer 407 (1:8:2) was 29.58% in the 30 min, This demonstrates the solubilizing effects of the Poloxamer 407.¹² In the case of binary solid dispersions, nifedipine: PVP K30 (1: 8) the percentage drug dissolved was 50.76% in the 30 min. It might be PVP K30 reduces the crystallization of nifedipine in the solid dispersions, which could be attributed to improved wettability by the carrier^{13, 14}. Further in case of 1:10 ratio, decrease in the dissolution rate of the solid dispersions containing higher proportion of the polymer might be caused by leaching out of the carrier during dissolution which could form a concentrated layer of solution around the particles, therefore the migration of the released drug particles to the bulk of the dissolution medium was slowed down.^{15, 16}

Table 2. Dissolution data of nifedipine and its binary and ternary systems with PVP K30 and poloxamer 407

System	DP ¹⁵ (%)	DP ³⁰ (%)	DP ⁴⁵ (%)	DP ⁶⁰ (%)	DP ⁹⁰ (%)	DP ¹²⁰ (%)	DP ¹⁸⁰ (%)
Nifedipine	0.48±1.8	0.99±1.5	1.26±2.2	1.91±4.2	2.26±3.1	2.60±2.7	2.82±3.8
1:8 PM	10.76±2.1	23.54±1.4	35.64±4.1	43.86±1.8	54.90±2.5	58.28±1.2	61.95±2.7 ^a
1:8:2 PM	17.79±3.1	29.58±4.7	49.55±2.7	57.84±1.7	69.03±2.5	70.76±1.2	72.76±1.3 ^b
1:8 SD	38.83±2.5	50.76±4.6	62.09±2.3	70.56±1.2	76.73±1.1	78.79±2.5	82.23±3.9 ^c
1:8:2 SD	68.18±1.2	77.55±1.5	81.64±3.2	89.70±2.5	95.25±4.1	97.34±3.5	100.70±2.2 ^d

Temperature: 37 ± 0.5 °C

Mean ± SD (n=3)

PM - Physical mixture, SD – Solid dispersions, DP – drug dissolved at 15, 30, 45, 60, 90, 120 and 180 min (%)

Significant differences compared to pure nifedipine: ^a $p < 0.05$; ^b $p < 0.05$; ^c $p < 0.05$; ^d $p < 0.05$

It was evident that the dissolution rate of nifedipine from ternary solid dispersions was higher than that from binary solid dispersions (Fig. 6). In first 30 minutes, the percentage drug dissolved of binary solid dispersions was approximately 50.76 % at the ratio of 1:8 compared with 77.55 % of ternary solid dispersions with the ratio of 1:8:2. The rapid dissolution of nifedipine from solid dispersions may be attributed to the decrease in the drug crystallinity and formation of molecular colloidal dispersion in the hydrophilic carrier matrix. The wetting properties are also greatly increased due to the surfactant property of the polymer, resulting in decreased interfacial tension between the medium and the drug. It was observed that the higher ratios of poloxamer 407 (1:8:4, 1:8:6, 1:8:8, 1:8:10) retarded the drug release system even though the drug crystallinity was reduced to greater extent in the solid dispersions. This might be due to the gelling property of the poloxamer 407 at higher concentration.¹⁷ Higher hydrophilicity and surfactant property of the poloxamer 407 result in greater wetting and increase the surface

available to dissolution by reducing the interfacial tension between the hydrophobic drug and dissolution medium.

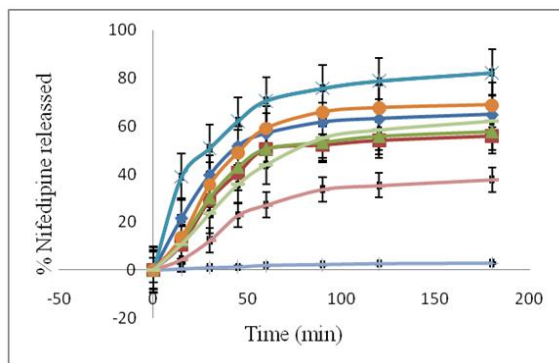


Figure 5: Release profile of nifedipine (○), solid dispersions consist of nifedipine and PVP K30 (1:1) (◆), solid dispersions consist of nifedipine and PVP K30 (1:2) (■), solid dispersions consist of nifedipine and PVP K30 (1:4) (▲), solid dispersions consist of nifedipine and PVP K30 (1:6) (×), solid dispersions consist of nifedipine and PVP K30 (1:8) (⊗), solid dispersions consist of nifedipine and PVP K30 (1:10) (●), physical mixture consists nifedipine and PVP K30 (1:8) (n=3 error bars indicate SD).

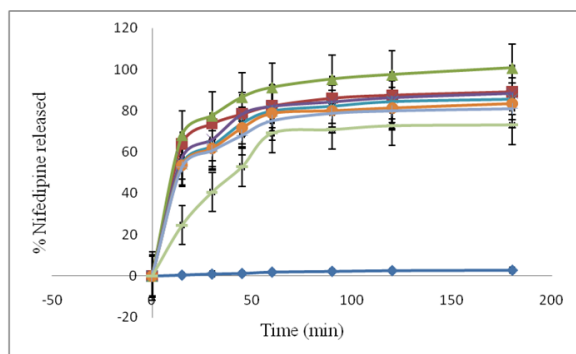


Figure 6: Release profile of nifedipine (○), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:1) (■), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:2) (▲), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:4) (×), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:6) (⊗), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:8) (●), solid dispersions of nifedipine with PVP K30 and poloxamer 407 (1:8:10) (○), physical mixture of nifedipine consisting PVP K30 and poloxamer 407 (1:8:2) (—) (n=3 error bars indicate SD).

CONCLUSION

In the present investigation, DSC of nifedipine in binary and ternary solid dispersions did not indicate the presence of crystalline nifedipine because nifedipine dissolved completely below its melting point. However, of nifedipine solid dispersions indicated decrease in the crystallinity of nifedipine and the possibility of the presence of the amorphous form of nifedipine in solid dispersion systems. Among the ratios used, 1:8:2 ratio of solid dispersion was found to be optimal for its superior performance in dissolution enhancement. This indicated that an increase in

the mass fraction of polymer could not offer any advantage for dissolution enhancement. Based on these results, it can be concluded that solid oral dosage forms of nifedipine with PVP K30 and poloxamer 407 could be formulated with high dissolution rate, faster onset action and improved bioavailability.

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