RESEARCH ARTICLE

Enhancement of water solubility of felodipine by preparing solid dispersion using poly-ethylene glycol 6000 and poly-vinyl alcohol

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In the present study, solid dispersion (SD) of felodipine was prepared to enhance its water solubility. The SD was prepared by using polyethylene glycol (PEG 6000) and polyvinyl alcohol (PVA) as a carrier with different drug polymer ratios using different techniques (physical mixing and solvent evaporation). The product was characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD) and *in vitro* dissolution rate studies. Phase solubility analysis was performed in aqueous solution for drug polymer interactions. DSC and XRD analysis demonstrated the conversion of felodipine to amorphous form with both physical mixture (PM) and SD. SD with PVA released 95% of the drug in 85 min as compared with 89% of drug released in 90 min by SD with PEG 6000. Thus, SD with both polymers increased drug release, particularly greater in the case of PVA than PEG 6000.

Key words: *Felodipine, PEG 6000, Polyvinyl alcohol, solid dispersion*

INTRODUCTION

Felodipine (4 RS)-4-(2,3-dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3,5-dicarboxylate is a calcium channel blocker used as antihypertensive and antianginal drug.[1,2] According to Biopharmaceutics Classification System, felodipine is class II drug, i.e., low solubility and high permeability. Felodipine has poor water solubility and hence poor dissolution and bioavailability after oral administration. Felodipine undergoes extensive first- pass metabolism with a bioavailability of about 15%.[3] The major drawback in the therapeutic application and efficacy of felodipine as oral dosage form is its low aqueous solubility, which is expressed to be approximately 19.17 mg/L at 25°C. Hence, improvement of its water solubility and dissolution is of therapeutic importance.[4,5]

The enhancement of the solubility of poorly water-soluble drug is one of the major current challenges to pharmaceutical sciences. Several techniques have been developed over the years to enhance the dissolution of the drug, such as inclusion complexation, salt formation, andcogrinding.[6-8] Among other techniques, solid dispersion (SD) is the popular method for enhancing the solubility and dissolution rate of an insoluble drug. In the SD method, a drug is dispersed in a carrier to make it amorphous. The particle size is reduced from crystalline to microcrystalline or molecular state,[9] which enhances solubility. There are three major methods for the preparation of SD: Melting method, solvent method and solvent evaporation method. The melting method and solvent method have a number of drawbacks. The melting method requires high temperature, which may result in the decomposition of the drug. In the solvent method, the issue of difficulty in selection of common volatile solvents arises coupled with chemical instability of drugs.[10]

In the present study, SD was prepared by solvent evaporation method using polyethylene glycol (PEG 6000) and polyvinyl alcohol (PVA) as carriers. By using different drug polymer ratios and through different techniques (physical mixing, solvent evaporation method), SD and physical mixture (PM) were prepared. After assessing the drug content of the solid dispersions, the products were characterized by differential scanning calorimetry (DSC), X-ray diffraction (XRD) and *in vitro* dissolution rate studies. Drug polymer interactions in aqueous solution were investigated by phase solubility analysis.

MATERIALS AND METHODS

Materials

Felodipine was obtained from Wockhardt Ltd., Chikhalthana (India); PEG 6000 was purchased from

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Research Lab Ltd., Pune: PVA, NaOH, ethanol, pottasium dihydrogen phosphate, disodium hydrogen phosphate, HCl, lactose, magnesium state, Tween 80, and talc were obtained from Cipla Ltd, Mumbai, India.

Methods

Phase solubility study

Initially, phase solubility study was performed to prove that the solubility of the drug increases with the polymers at different ratios. The effect of concentration of PEG 6000 and PVA on equilibrium solubilities of felodipine in distilled water at 37 ± 0.5°C was carried out by adding an excess of drug (20 mg) into a screw capped glass vial containing 20 ml of 0.1N HCl (pH 1.2) and various amounts of the carrier (1-6% w/v). The samples were placed on a water bath shaker and agitated at 37 ± 0.5°C for 72 h, which was previously determined to be the adequate time for equilibration. An aliquot of each solution was withdrawn and filtered with syringe holder. The assay of felodipine was determined spectrophotometrically at 362 nm, a wavelength at which PEG6000 or PVA does not interfere.

Preparation of felodipine solid dispersion particles

Solid dispersion of felodipine in PEG 6000 and PVA are prepared in three different ratios (1:1, 1:3 and 1:6) by using solvent evaporation method. Felodipine was dissolved in an appropriate amount of ethanol (2.5 times the total weight of drug and polymer). After complete dissolution; solutions were transferred into a container in which the polymeric carriers PEG 6000 and PVA were present. The solvent was evaporated at 45°C, and resulting residue was dried in hot air oven for 1 h and stored for 24 h in a desiccator. Subsequently, the dispersion was ground in a mortar and passed through sieve no. 100.

Further a, physical mixture of felodipine is prepared by mixing the drug with PEG 6000 and PVA in the following ratios: 1:1, 1:3 and 1:6.

Analysis of drug content in solid dispersion

The content of felodipine in PM and SD (in ratios 1:1, 1:3 and 1:6 with PEG and PVA) was determined using UV spectroscopy and compared with drug alone. Accurately weighed solid dispersion or PM equivalent to 10 mg of felodipine was transferred to 100 ml volumetric flask and diluted to 100 ml with ethanol and sonicated for 30 min for complete solubilization of the drug. Solution was filtered with membrane filter paper 0.45 μm; 1 ml of filtrate was taken and diluted to 100 ml with ethanol, and the absorbance was noted at 362 nm. The concentration of felodipine was determined by using the calibration curve of felodipine in ethanol.

For further evaluation of PM and SD of felodipine, ratio of the polymer was selected depending on maximum release in UV spectroscopy.

Differential scanning calorimetry

DSC was performed on felodipine (pure drug), PM and SD (each containing 5 mg of felodipine), which were sealed in aluminum pans. DSC thermograms were recorded from 50 to 200°C at a heating rate of 10°C/min. An empty pan was used as a reference. Prior to each experiment, the DSC baseline temperature and enthalpy were calibrated using Indium and a heating rate of 5°C/min. A nitrogen flow rate of 20 ml/min was used for each DSC run.

X-ray diffraction

X-ray powder diffraction (XRD) pattern of the drug in pure form and of PM and SD were obtained by using Philips PW1700 X-ray diffractometer with Cu k-a (l = 1.54056 AO) radiation and a crystal monochromator, with a voltage of 45 mV and a current of 20 A. The diffraction patterns run at 5-10°/min terms of 2q angles.

Preparation of tablets

Tablet formulation

Ingredients	Weight of ingredient
SD of PVA (1:6)	70 mg
Microcrystalline cellulose	32 mg
Lactose	45 mg
Talc	2 mg
Magnesium stearate	1 mg
Total weight	150 mg

All the ingredients were accurately weighed. Then, these ingredients were thoroughly sieved through sieve no. 60, mixed in plastic vessel and subjected to direct compression on single flat punches with 8 mm in diameter in a tablet compression machine.

Evaluation of tablets

Disintegration time of tablets was determined by using an apparatus (UC-21 Disintegration Test System) according to US Pharmacopoeia standards. The disintegration medium was degassed distilled water at 37°C. The friability of the tablet samples was measured using the Roche friabilator, which complies with USP testing standards. Pre-weighed 20 tablets were placed in friabilator, which was then operated for 100 revolutions, i.e., 4 min. The tablets were then dedusted and re-weighed. Friability of the tablets was calculated as a percentage according to the following equation:

Friability in percentage = (initial weight – final weight/initial weight) $\times$100

Thickness was determined using a micrometer; 10 individual tablets were used. Content uniformity was ensured by weighing the 10 tablets individually and dissolved in ethanol, which was then analysed spectrophotometrically at 362 nm. The drug content was determined by UV analysis at 362 nm.

Dissolution rate studies

Dissolution studies of felodipine from SDs and tablets were performed according to the method described in USP. Using apparatus 2 with the paddle rotating at 50 rpm along with 1.5% Tween 80 was used as a dissolution medium at pH 1.2 buffer and pH 6.8 buffer. A sample of SD equivalent to the 10 mg of felodipine was dispersed in 900 ml of dissolution medium at different time intervals; 5 ml samples were withdrawn through a filter. The amount of released felodipine was determined by UV analysis at 362 nm. It was found that PVA and PEG 6000 did not interfere with the assay at this wavelength.

RESULT AND DISCUSSION

Phase solubility studies

Figure 1 shows the effect of concentration of PEG6000 and PVA on solubility of felodipine. Saturation stability of drug was enhanced in all cases as compared to the control sample felodipine. A 4.66-fold increase in solubility of felodipine was observed in 18% w/v solution of PEG 6000. Further, a 4.68-fold increase in drug solubility was observed in 18% w/v solution of PVA. The phase solubility in pH 1.2 (0.1N HCl) was found to be linear in a wide range of PEG 6000 or PVA concentrations and corresponded to A_L type. It can also be noted that the solubility significantly increases when the concentration is increased to 6% as compared to 4%. The increased solubility of drug is due to the formation of soluble complexes between the hydrophobic drug and hydrophilic carrier.

Analysis of drug content

Figure 2 shows the analysis of SD and PM of PVA and PEG with felodipine in various ratios (1:1, 1:3, 1:6) vs. % of drug content. The solubility of drug is increased with PM and SDs as compared with drug alone. The drug solubility is increased as the concentration of polymer is increased in the ratios from 1:1 to 1:6, and the solubility of drug is more with SD than PM. It can be noted that drug content is maximum with SD with PVA and PEG 6000 in the ratio 1:6. The solubility is more in pH 1.2 buffer than that in pH 6.8 buffer. This is a preliminary test that gives an early prediction of the drug solubility.

Polymers (PVA and PEG6000) in the ratio 1:6 used for PM and SD had released maximum drug; therefore further analysis of PM and SD in the ratio 1:6 were done with by using, DSC XRD, tablets prepared , by preparing tablets preparation and dissolution studies.

Evaluation of differential scanning calorimetry curve

DSC curve of felodipine, PEG 6000, and their PM and SD in 1:6 ratio shows that the thermogram of felodipine exhibited an endothermic peak at about 145.6°C corresponding to its melting point. The endothermic peak corresponding to melting peak of felodipine disappeared in the case of PM and SD with the PEG 6000. Similarly with PVA, the endothermic peak corresponding to melting peak of felodipine shifted to lower temperature (144.9°C) with reduced intensity in SD [Figure 3]. The disappearance of drug melting in lesser amount of drug is due to its dissolution in the melted carrier. Felodipine homogenizes with the carriers in an amorphous form.[11-13]

X-ray diffraction studies

Figure 4 shows the XRD pattern of felodipine, PEG 6000 and their PM and SD in molar ratio 1:6. Many diffraction peaks with high intensity were observed in the diffraction patterns of pure felodipine, PEG 6000 and PVA due to its crystalline nature. The intensity of peaks decreased in PM and furthermore decreased in SD. The intensity of felodipine peak at 10.090 remarkably reduced in SD of felodipine with PEG 6000 at ratio 1:6. In addition, the intensity of felodipine peaks at 26.120 remarkably reduced in SD with PVA, indicating amorphous state of the drug.[9]

Based on this data, we can confirm that a structural modification occurred in molecular state felodipine. the

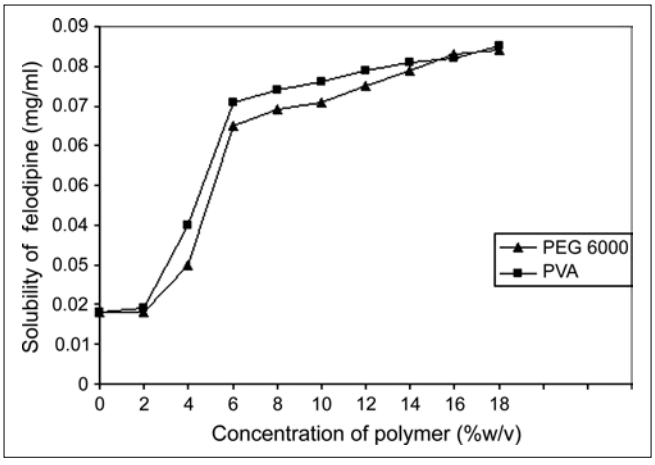

Figure 1: The effect of concentration of PEG 6000 and polyvinyl alcohol on solubility of felodipine

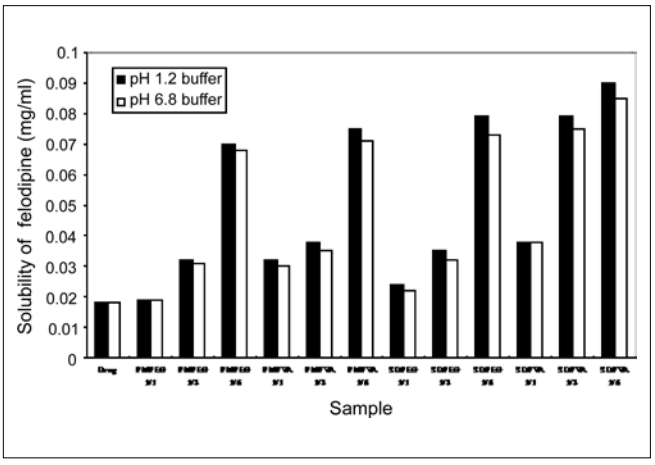

Figure 2: Analysis of solid disperison and physical mixture

physical state of felodipine is crystalline, but that of carrier is amorphous. The molecular state of felodipine prepared as drug carrier SD changed from crystalline state to microcrystalline stat, and the presence of some peaks of the drug might be due to some amount of drug that was present outside the SD, i.e., it was not dispersed monomolecularly. The diffused peaks in SD shows entrapped drug molecules that were monomolecularly dispersed in the carrier bed. [14,15]

Evaluation of tablets

The evaluation of felodipine tablets is shown in Table 1. All the parameters of the tablets were found to be within IP limits.

Dissolution studies

The results of *in-vitro* dissolution studies of felodipine, its PM and SD with carriers in pH 1.2 and 6.8 buffer are shown in Figures 5 and 6. Inspection of the reported data reveals that the dissolution rate of pure felodipine is very slow. The dissolution of a poorly water-soluble drug requires a dissolution medium that is entirely different from that used for water-insoluble drugs. One of the techniques that have been useful in that dissolution of insoluble drugs is the incorporation of a small amount of surfactant in the dissolution medium. Hence, Tween 80 is used as surfactant for improving dissolution. The

Table 1: Evaluation of tablet (n = 3)

Parameters	Formulated tablet (± SD)
Weight uniformity (mg)	149.5 ± 0.5
Friability (%)	0.790 ± 0.005
Thickness (mm)	2.70 ± 0.06
Hardness (kg/cm^2)	4.20 ± 0.05
Content uniformity (%)	99.0 ± 0.5
Disintegration time (min)	10.00 ± 0.05

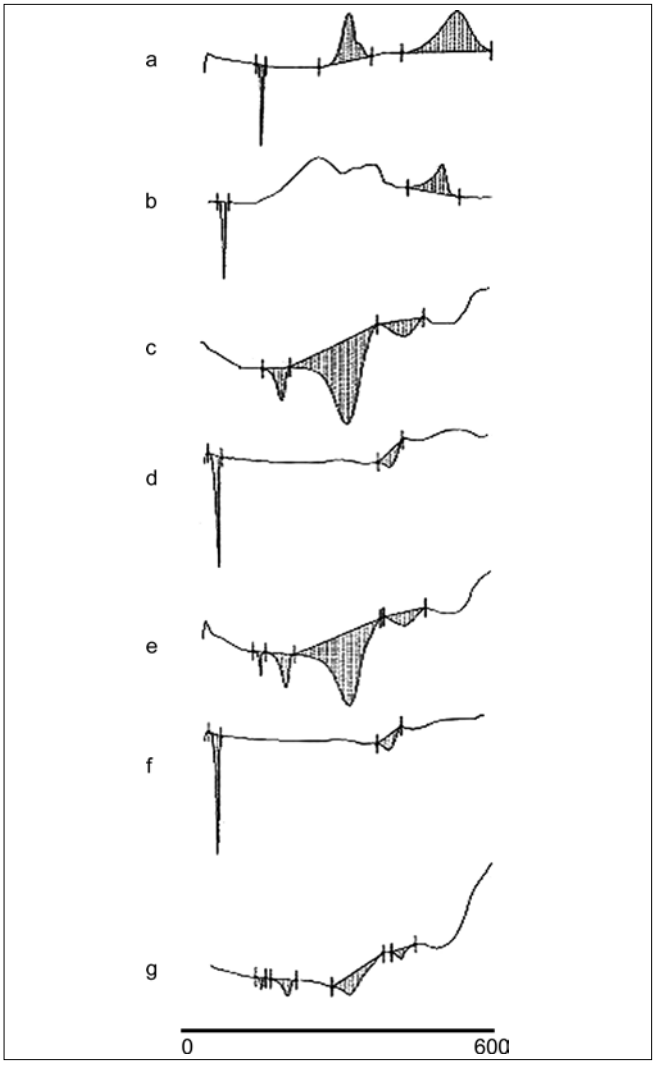

Figure 3: DSC analysis of felodipine, PEG 6000, PVA, PM and SD. (a: Felodipine, b: PEG 6000, c: PVA, d: PM of PEG 6000, e: PM of PVA, f: SD of PEG 6000 (1:6), g: SD of PVA)

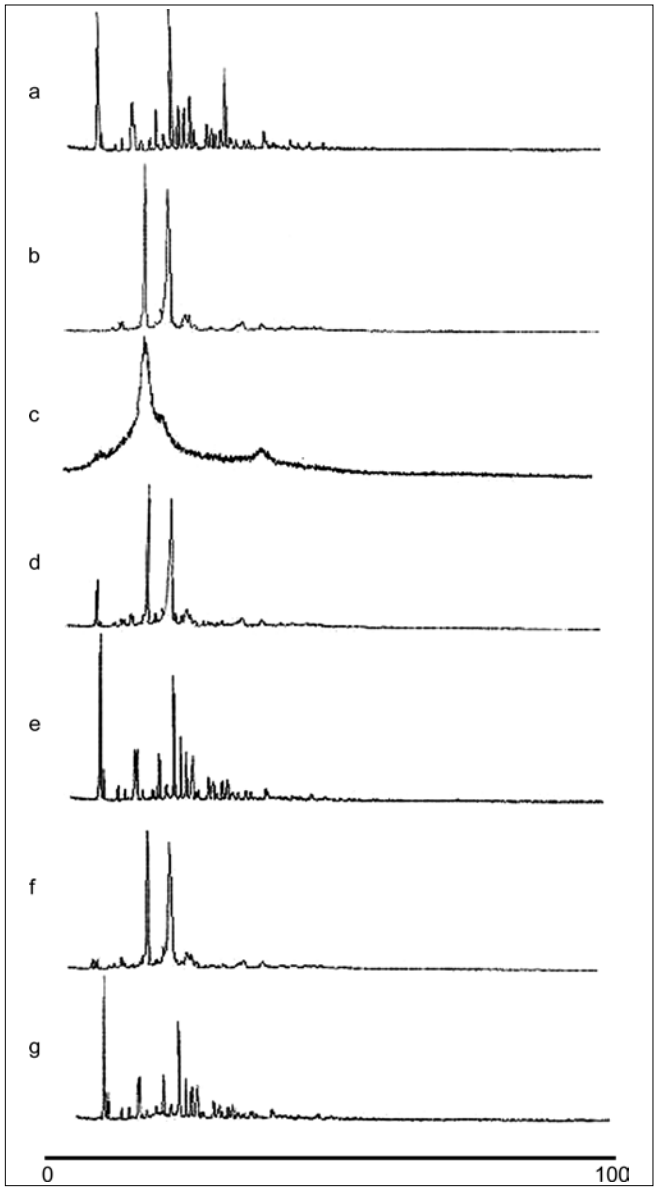

Figure 4: X-ray diffraction analysis of felodipine, PEG 6000, PVA, PM and SD. (a: Felodipine, b: PEG 6000, c: PVA, d: PM of PEG 6000, e: PM of PVA, f: SD of PEG 6000 (1:6), g: SD of PVA)

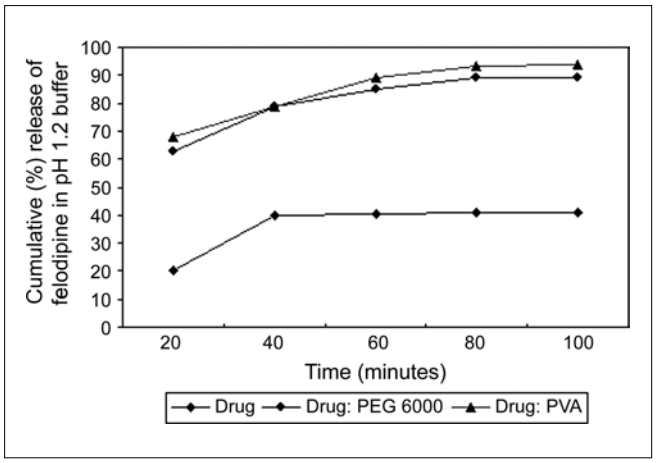

Figure 5: *In-vitro* dissolution of solid disperison of felodipine with carriers in pH 1.2 buffer

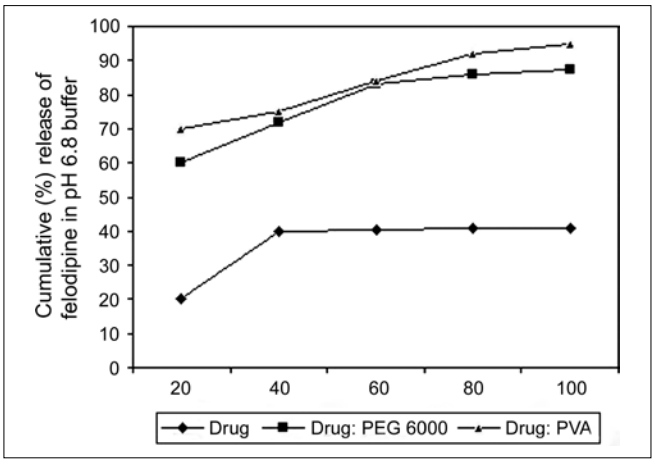

Figure 6: *In-vitro* dissolution of solid disperison of felodipine with carriers in pH 6.8 buffer

improved dissolution by using surfactant is contributed by its various actions such as wetting, molecular solubilization and or deflocculation. Solubility of drug is increased with PM and SD (SD > PM).

The results have shown that SD using PEG 6000 released about 89% of drug in 90 min, while 95% of drug is released with PVA. This shows that SD using PVA has more dissolution rate than PEG 6000. This study confirmed previous observations that the dissolution rate is dependent on drug concentration in the SD.[13]

CONCLUSION

After comparing the solubility and the dissolution profile of various solid dispersions, it was observed that SD of felodipine with PEG 600 and PVA in the drug-carrier ratio of 1:6 gave the desired dissolution profile. Changes of drug-to-carrier interactions in the solid state were confirmed by XRD and DSC studies. The phase solubility studies indicated the existence of drug-to-carrier interactions in liquid state. The drug release was found to be better when PVA was used as carrier as compared with PEG 6000. Increasing the drug- carrier ratio from 1:1 to 1:6 improved drug release profiles. The improvement in dissolution profile with increase in the concentration of polymer was found to be more in case of PVA than PEG 6000 SD at a ratio of 1:6. Felodipine tablets of SD at ratio 1:6 showed drug release in IP limits. The preparation of solid dispersion of felodipine with PVA released 95% of the drug in 85 min and solid dispersion of felodipine with PEG 6000 released 89% of drug in 90 min. Thus, the solid dispersion of felodipine with PVA showed a greater increase in dissolution rate than that of PEG 6000.

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