Research article

Preparation and evaluation of nifedipine solid dispersions

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ABSTRACT:

Oral drug delivery is the simplest and easiest way of administering drugs. However, if the drug being administered has limited aqueous solubility it can result in poor bioavailability.

Solid dispersion method was originally used to improve the dissolution properties and the bioavailability of poorly water- soluble drugs by dispersing them into water-soluble carriers.

This study aims to enhance the solubility of nifedipine, a poorly water-soluble drug, by solid dispersion technique using poloxamer 188 as a carrier. The solid dispersions were prepared by fusion method using various drug to polymer ratios. Moreover, the influence of drug-to-polymer ratio on drug solubility was studied.

The resultant formulations were characterized by Fourier-transformed infrared spectroscopy (FT-IR), Powder X-ray diffractometry (PXRD) as well as solubility study. FTIR results indicated a lack of significant interaction between the drug and the carrier in the solid dispersions.

Compared with pure drug and physical mixtures, the solubility of nifedipine in solid dispersions was enhanced dramatically which indicates that the solubility enhancement is not due to the solubilizing effect of the carrier alone but it may be attributed to the reduction of the crystallinization of nifedipine in the hydrophilic matrix which could be confirmed by PXRD results.

KEY WORDS: Nifedipine; Solid dispersions; Poloxamer 188; Fusion method; Solubility.

INTRODUCTION:

The enhancement of oral bioavailability of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Approximately 40% of the new chemical entities are poorly soluble[1]. Although salt formation, co-solubilization and particle size reduction have been commonly used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs, there are practical limitations for these techniques.[2]

In 1961, Sekiguchi and Obi developed a practical method whereby most of the limitations with the bioavailability enhancement of poorly water-soluble drugs can be overcome, which was termed as Solid Dispersion.

Solid dispersion is defined as Dispersion of one or more active ingredients in an inert matrix in the solid stage to achieve an increased dissolution rate or sustained release of the drug, altered solid-state properties and improved stability.[3, 4]

This method reduces the drug particle size and enhances the dissolution rate, wettability and dispersibility of the drug[5] and it has been used successfully for various poorly aqueous soluble drugs such as disulfiram[6], verpamil[7],ibuprofen[8],valsartan[9] and piroxicam[10]. Many hydrophilic polymers are commonly used as carriers for the preparation of solid dispersions like polyethylene glycol, hydroxyl propyl methylcellulose, and polyvinylpyrrolidone[11-13] using several ways of preparation like fusion[14], co-grinding[15] and solvent evaporation.[16]

In this paper, we report the preparation and characterization of nifedipine solid dispersions in a hydrophilic carrier, poloxamer 188. Preparation and evaluation of nifedipine solid dispersions have been reported by some researchers in carriers, such as HPMC K-4M and Eudragit RS-100[17], PEG 6000-phosphatidylcholine[12] using different methods of preparation.

Nifedipine (Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate) is a calcium channel blocking agent that is used to treat a variety of cardiovascular disorders such as angina pectoris and hypertension.[18, 19]

Due to its low aqueous solubility (5.6 µg/ml at pH=7), nifedipine often shows low and irregular bioavailability after oral administration.[20]

Poloxamer 188 is a closely related block copolymer of ethylene oxide and propylene oxide used in pharmaceutical formulations as an emulsifying, wetting and solubilizing agent.[21]

The block composition of poloxamer with both hydrophilic PEO blocks and hydrophobic PPO blocks enables poloxamer to form micelles in aqueous solutions, thus solubilizing many water-insoluble compounds.[22]

Poloxamers (407,188) have been used successfully to increase the solubility of poorly water-soluble drugs like nifedipine[5], cefuroxime[23], etoricoxib[24] and pioglitazone[25]

MATERIALS AND METHODS:

Materials

A gift sample of nifedipine was received from Tameco. Poloxamer 188 was supplied by BASF (Germany). Sodium dodecyl sulphate (SDS) was obtained from AVONCHEM (UK). Hydrochloric acid was received from Merck (Germany). Double-distilled water was used throughout the study and all the other chemicals used were of analytical grade.

Methods

Preparation of physical mixture (PM)

Physical mixtures of nifedipine and Poloxamer 188 were prepared by mixing the required amount of nifedipine and poloxamer 188 in a mortar until homogenization at 1:3-1:4-1:5-1:6 and 1:8 (nifedipine:poloxamer 188) ratios. The prepared mixture was passed through 250 µm sieve.

Formulation of solid dispersions (SD)

Solid dispersions were prepared by melting (fusion) method. Different weights of poloxamer 188 were heated while stirring in a water bath maintained at 70°C then to each fused mixture an appropriate weight of nifedipine powder was added to produce the required proportion (1:3-1:4-1:5-1:6-1:8) drug:carrier.

The mixture was then stirred until all the nifedipine was dissolved and uniformly dispersed in the matrix. The fused mixture was rapidly quenched by placing the container in an ice bath. The solidified melts were grounded in a mortar and passed through 250 µm sieve.[26]

Drug loading determination

For nifedipine loading determination, an appropriate amount of solid dispersions was dissolved in methanol to obtain a specific theoretical nifedipine concentration (20 mg/100mL). The drug concentration was then analyzed using a UV-visual spectrophotometer at 238 nm with a standard curve prepared using sequential concentrations of nifedipine methanol solution. . No interference from the polymer on nifedipine assay was found at 238 nm.[27, 28]

Solubility study

The solubility of drug, physical mixtures and solid dispersions was determined by adding excess amount into simulated gastric fluid containing SDS (0.5% w/v) at room temperature. This was then agitated for 24 hrs in shaker until saturation. The saturated solution was filtered through a 0.45 µm cellulose acetate filter to obtain a clear solution and was analyzed by using spectrophotometer at 238 nm. Drug concentration was calculated with a standard curve prepared using sequential concentrations of nifedipine aqueous solution 0.5% SDS with pH=1.2.[5]

X-Ray diffraction

The X-ray diffraction studies were carried out to determine the physical state of the drug, carriers ,and drug in the solid dispersions using STOE Powder Diffraction System (Germany), supplied with a CuKa radiation source, with a voltage of 40 KV and a current of 30 mA, over the 2Theta ranges 0-50°, with a step size of 0.020 and a dwell time of 30.0 s at each step.

FTIR

FTIR Spectra were obtained using a FTIR spectrophotometer (Thermo Nicolet AVATAR; LabX Midland, ON, Canada) in the range of 4000-400 cm^{-1} with an optical resolution of 4 cm^{-1}. The samples (nifedipine, solid dispersions, physical mixtures, and polymer) were grounded and mixed thoroughly with potassium bromide KBr, discs were prepared by compressing the powders, then the FTIR spectra were compared in order to check the interaction between drug and carriers.

RESULTS AND DISCUSSION:

Drug loading determination

The actual drug content of solid dispersion systems was determined within the range of 92.33±10.7% to 100.37±8.41% (Table 1). The drug content was found to be uniform in all solid dispersion and was in good agreement with theoretical drug content.

Table 1: Solid dispersion drug loading

formulation Code	Drug:polymer	Drug loading (%)
SD3	1:3	92.33±10.7
SD4	1:4	94.9±11.96
SD5	1:5	86.25±3.76
SD6	1:6	92.70±7.19
SD8	1:8	100.37±8.41

Solubility study

The solubility of nifedipine from physical mixtures and solid dispersion systems was found to be greater than pure nifedipine as shown in Table 2. The solubility of nifedipine was 48.61 mg/L and physical mixtures solubility was between 69.13 to 114.66 mg/L and in case of solid dispersions was between 99.85 to 199.36 mg/L. Table (2) clearly shows that increasing the poloxamer ratio leads to improvement in the solubility.

The improvement of the solubility of physical mixtures could be attributed to the hydrophillicity and surfactant property of poloxamer which results in greater wetting. It also increases the surface available to dissolution by reducing the interfacial tension between the hydrophobic drug and dissolution medium.

As the solubility of nifedipine from solid dispersions was found to be greater than from physical mixtures, this indicates that SD enhanced dissolution is not only due to the solubilizing effect of the polymer, but can also be attributed to other factors such as a reduction in the particle size and/or reduction of the crystallinization of nifedipine in the hydrophilic matrix which could be confirmed by the PXRD results.

Table 2: Solubility of nifedipine,PM and SD

Type of Nifedipine	Drug:poloxamer ratio	Solubility (mg/L)
Pure nifedipine	-	48.61±2.57
PM	1:3	69.13±5.21
PM	1:4	85.71±2.27
PM	1:5	95.89±3.17
PM	1:6	108.28±3.2
PM	1:8	114.66±8.99
SD	1:3	99.85±3.38
SD	1:4	116.50±4.81
SD	1:5	133.47±12.71
SD	1:6	141.48±10.46
SD	1:8	199.36±15.48

FTIR

FTIR spectra of nifedipine, poloxamer 188, physical mixture and solid dispersions are shown in Fig.1. The IR spectrum of nifedipine (Fig.1a) is characterized by principle peaks at 3320 cm^{-1} (N-H stretch), 3100-3000 cm^{-1} (=C-H stretch), 2960 cm^{-1} (C-H stretch), 1730 cm^{-1} (c=o stretch), 1100 cm^{-1} (c-o stretch) while it shows that the characteristic peaks of pure poloxamer 188 were at 3500, 2870, 1100 cm^{-1} due to the stretching of O-H, C-H, and C-O groups respectively (Fig 1b). FTIR spectrum of physical mixture (Fig.1c) illustrates the superimposition pattern of nifedipine and polymer peaks. All the characteristic peaks were also observed in the corresponding solid dispersion (Fig 1d). Furthermore,the absence of shifts in the wavenumbers of the FTIR peaks of the solid dispersion compared to the physical mixture indicates a lack of significant interaction between the drug and the components in the solid dispersion.

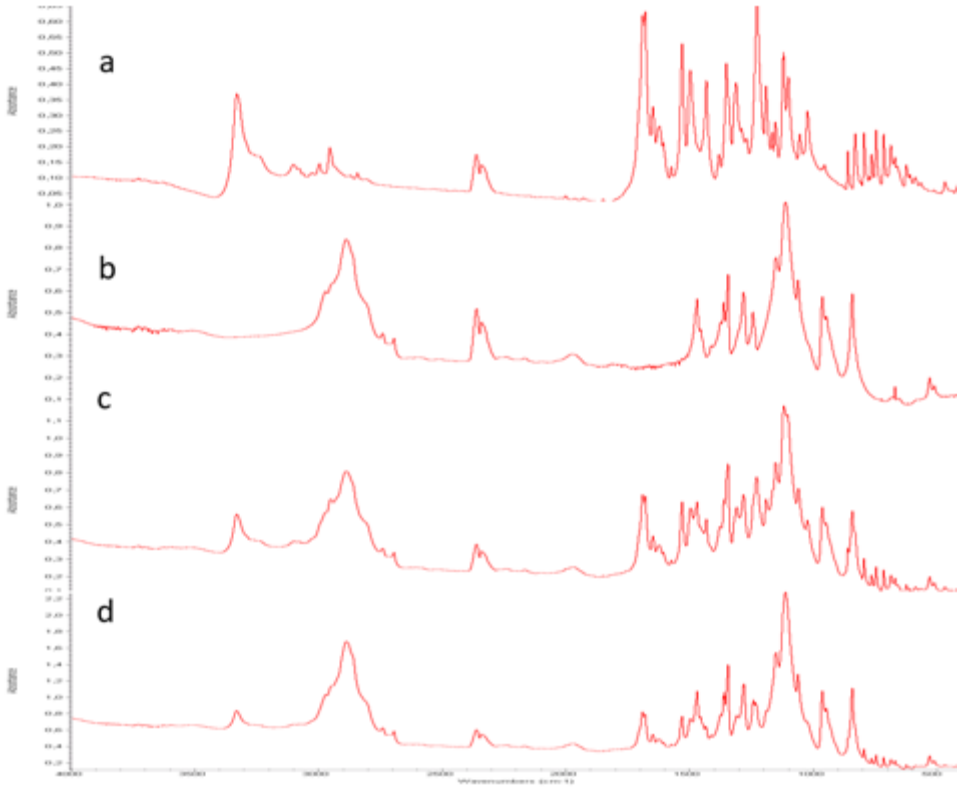

Fig. 1: FTIR of (a) pure nifedipine, (b) pure poloxamer 188, (c) physical mixture of nifedipine and poloxamer 188, (d) solid dispersion of nifedipine and poloxamer 188

X-Ray diffraction

The PXRD patterns of pure nifedipine, Poloxamer 188, and the solid dispersions are shown in Fig.2,3, and 4 respectively. The powder X-ray diffractogram of pure nifedipine drug powder showed numerous distinctive peaks at 8.5°, 10.6°, 11.9° 2-Theta that indicated a high crystallinity. Poloxamer 188 also exhibited some crystallinity, as indicated by the two peaks of high intensity at 19.25°, 23.5° 2-Theta (Fig.3). The PXRD pattern of the solid dispersions exhibits all the characteristic diffraction peaks of poloxamer and crystalline nifedipine, but with lower intensity. It is remarkable that these characteristic peaks of nifedipine gradually decrease with decreasing nifedipine concentration in the solid dispersions (increasing poloxamer concentration) as shown in Fig.4.

This reveals that some nifedipine still exists in the crystalline state in the solid dispersions and that, at the employed concentrations, the proportion of the drug may be equal to or exceed its solid solubility.

However, Nifedipine at low concentrations may have either converted to a metastable amorphous form, dissolved in the matrix system to form a solid solution, or exists in a microcrystalline form in the matrix system.

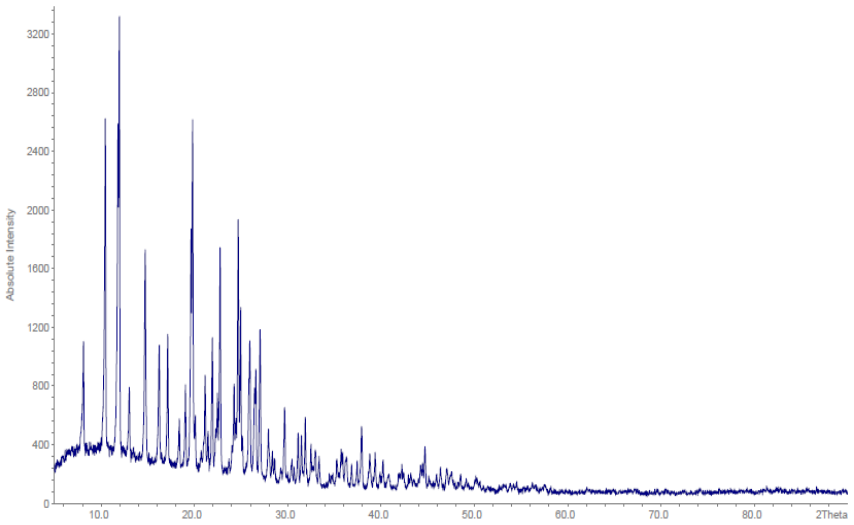

Fig. 2: PXRD of pure Nifedipine

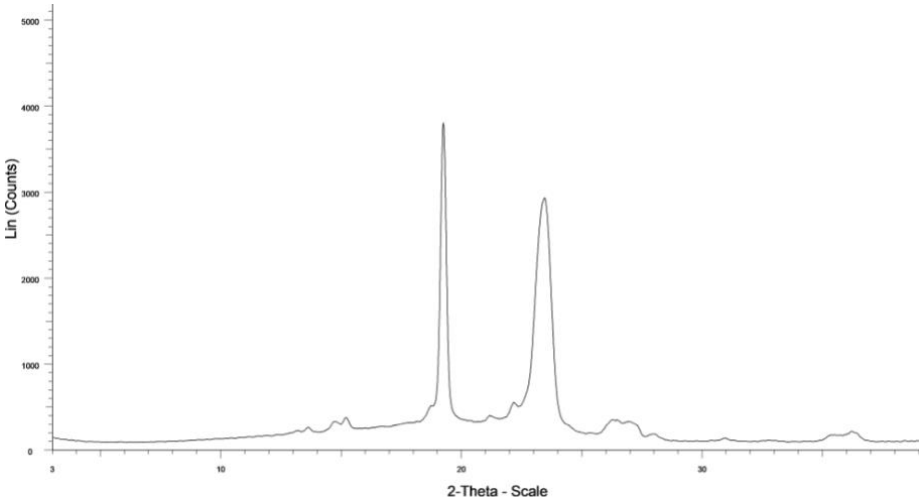

Fig. 3: PXRD of pure poloxamer 188

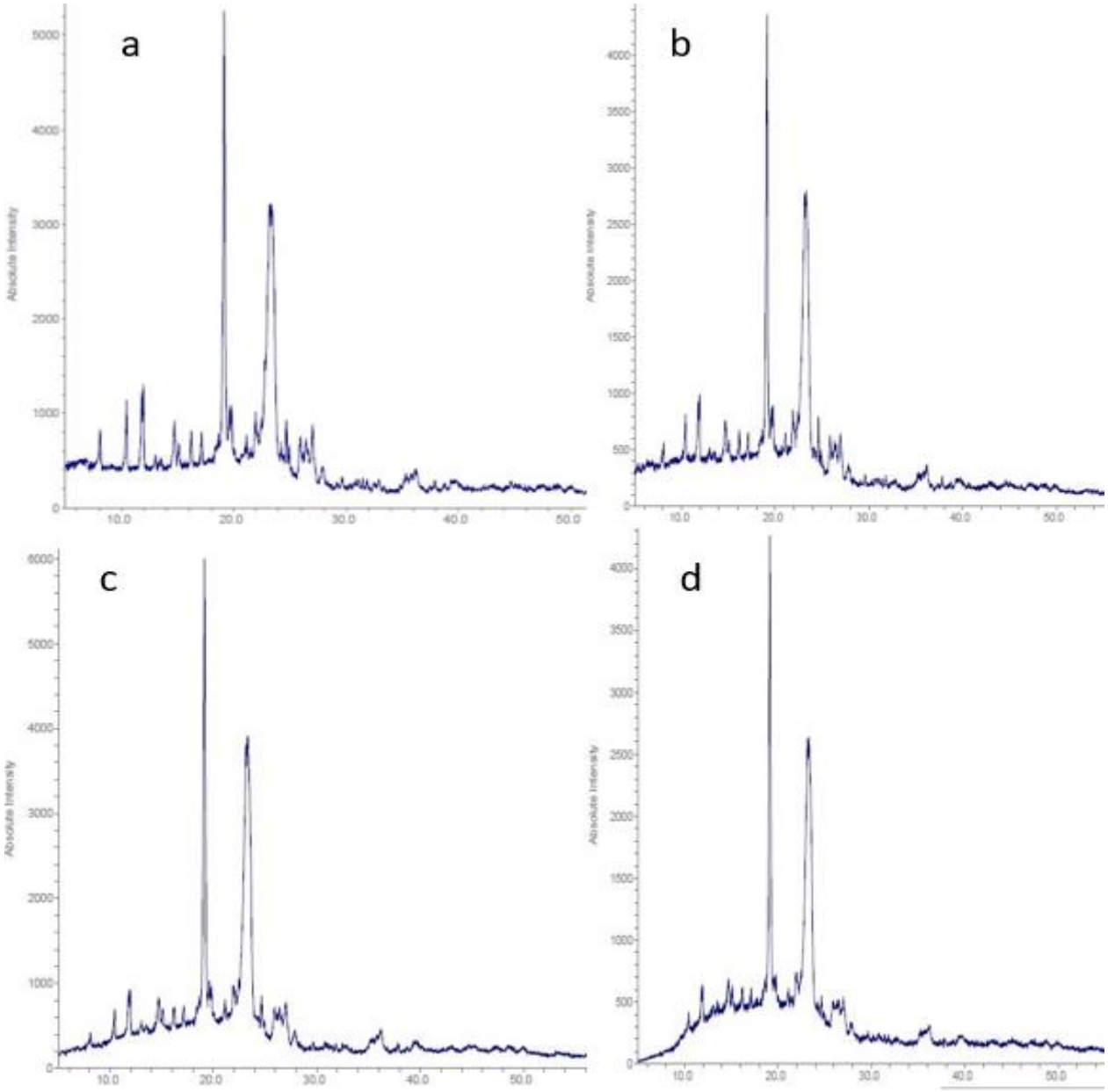

Fig. 4: PXRD of (a) solid dispersion of nifedipine:poloxamer (1:4), (b)) solid dispersion of nifedipine:poloxamer (1:5), (c)) solid dispersion of nifedipine:poloxamer (1:6), (d)) solid dispersion of nifedipine:poloxamer (1:8)

CONCLUSION:

Solid dispersion improves the solubility of nifedipine compared to the physical mixture or to the pure drug. PXRD was adopted in this research to identify the physical state of the drug in SD and it revealed the reduction in crystallinity of pure drug. Furthermore, the absence of shifts in the wavenumbers of the FTIR peaks of the solid dispersion compared to the physical mixture indicates lack of significant interaction between the drug and the components in the solid dispersion.

In conclusion, This study proves that it is possible to increase the solubility of poorly water-soluble drug Nifedipine by preparing it as solid dispersion with poloxamer 188 using fusion method. Further studies are needed to transform the crystalline drug completely into the amorphous state and monitor long-term stability.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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