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Preparation and *in-vitro* evaluation of nifedipine amorphous solid dispersions using mesoporous silica gel

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Abstract
The main purpose of this study was to increase the solubility of poorly soluble drug by preparing solid dispersions. Nifedipine (poorly water soluble drug), when prepared as solid dispersion showed increased solubility and dissolution rate. Solid dispersions of Nifedipine were prepared by using silsol 6035 as carrier in various proportions 10%, 20% and 30% by solvent loading (solvent droplet addition)method and various grades of silica by co-milling method in ratios of (1:1, 1:2 and 2:1). The drug carrier interactions were carried out using Differential Scanning Calorimetry (DSC). Drug release and dissolution profile was studied and it was found that the percentage release of the drug for solid dispersions samples was found to be higher than those of the pure milled drug and co-milled powders.

Keywords: Nifedipine, solid dispersion, co-milling, solvent loading.

Introduction
Nifedipine is a dihydro pyridine calcium channel antagonist originally introduced for the treatment of angina pectoris and hypertension. Nifedipine is BCS class-2 drug having poor solubility and dissolution rate. One of the major problems with this drug is its poor solubility in biological fluids which results in decreased bioavailability. To overcome this problem solid dispersions using mesoporous silica a hydrophilic carrier was prepared. Solid dispersion is a promising approach to improve the dissolution rate and bioavailability of hydrophobic drugs [1]. The term solid dispersion refers to a "group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug" [2]. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chion and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" [3]
Solid dispersion is a well-accepted method to increase solubility of poorly soluble molecules and to improve amorphous state stability. Mesoporous silica (MPS) was used due to its tuneable porosity [4], high surface area, inertness, and good biocompatibility making it a suitable excipient in drug delivery. The porous structure of silica itself can decrease the melting point and crystallinity of entrapped drug [5]. The pore diameter of MPS is 2 and 50nm.MPS has good flow properties. Due to these properties it can minimises the chances of drug converting to crystalline form. The surface of MPS consists of Silanol (Si-OH) and siloxane (Si-O-Si) groups [6]. The internal portion of silica molecule consists of silanol groups which are structurally bounded. Silanol and siloxane groups interact with the drug to form hydrogen bonding. Both physical and chemical interactions influence drug loading on MPS particles. For hydrophobic drugs, physical interactions will occur with silica by hydrogen bonding and electrostatic and hydrophobic interactions. Hydrogen bonding is predominant if the number of surface silanol groups is high; otherwise, dispersive forces are predominant [7].
Solid dispersions were prepared by various methods such as solvent impregnation method, solvent evaporation method, solvent loading with PEG400, co-milling method. The solid dispersion method is extensively used to increase the solubility of poorly water soluble drugs. In these above methods the drug is dissolved in a suitable solvent (acetone) and loaded onto mesoporous silica a hydrophilic carrier. Nifedipine-Silsol 6035 systems, prepared by the solvent loading method show an improvement in dissolution rates of the drug from the solid dispersion compared with pure drug and co-milled powders. This study presents the formulation of solid dispersion of Nifedipine with silsol 6035 as hydrophilic carrier.

Materials and Methods

Materials

Nifedipine (NFD) was received as gift sample from Suchem Laboratories, Ahmadabad, and Silsol 6035, Syloid XDP 3050, 72FP from Grace Davison Chemical India Pvt. Ltd. All reagents and solvents used were of analytical grades.

Methods

Analytical method development

Preparation of stock solution

Stock solution of Nifedipine was prepared by dissolving 1.32 mg of pure drug in 1:1 ratio of methanol and HPLC water and sonicated for 10min. Standard curve was obtained by making 100 dilutions to the stock solution with methanol and water mixture which finally gives 132 µg/ml and absorbance was checked at 238 nm using Agilent 1100 HPLC apparatus.

HPLC Analysis

The amount of dissolved Nifedipine was determined by HPLC analysis (Agilent 1100, Agilent). The mobile phase consisted of methanol and HPLC water in a volume ratio of 1:1 and the flow rate was maintained at 1 ml/min. For a HPLC column, Rocket HL 53 mm *7 mma C18 column (HL (high load) 3µ 53*7 mm Rocket) was used at 40 °C. The detection wavelength was set to 238 nm. The injection volume was 20 µl with pressure 20bars and run time of 5min.

Pre-formulation studies

Pre-formulation studies like Angle of repose, bulk density, tapped density, carr's index and hausner's ratio were done according to IP 2007 procedure.

Preparation of Solid Dispersion

Co-milling

In this method Drug and Silica were co-milled together in a mortar and pestle by taking varying ratios of accurately weighed quantities of Drug: Silica like 1:1, 1:2 and 2:1 for about 5 min, 10 min and 25 min respectively [8].

Solvent Droplet addition method: (10% load on silsol 6035)

A concentrated drug solution (10%) near its saturation point was prepared and added drop wise to the silica under stirring and allowed to evaporate the solvent (acetone) from silica during the addition procedure itself [4].

Incipient Impregnation method: (10% load on silsol 6035)

Dilute drug solution was prepared and silica was added at once to the solution to form slurry of silica. Silica slurry was evaporated by constant stirring at room temperature [4].

Solvent Evaporation method: (30% load on silsol 6035)

Drug solution was poured on the silica and the prepared suspension was stirred for 15 min. The solvent was evaporated using rotary evaporator and all the dried material is recovered at the end of process. As the solvent starts evaporating, the drug concentration in the loading solution increases slowly which creates a concentration gradient and drug loading in the silica pores is initiated [9].

Characterization of Samples

Drug Content Study: (10%, 20%, 30% load on Silica grades)

Accurately weighed samples equivalent to 10mg of drug of solvent loaded solid dispersion (Silsol 6035, Syloid XDP and Syloid 72 FP) were taken in a 25 ml volumetric flask and volume was made upto the mark by adding methanol and kept for sonication for about 15min until the drug gets dissolved. A 1ml aliquot of the above prepared solution was taken. From this 10µl was pipette out and diluted with 990 µl of methanol solution which finally gives 1 ml of drug solution. The absorbance of sample solutions was determined at 238nm using Agilent Technologies 1260 infinity HPLC instrument [10].

In-vitro **dissolution studies:** The *in-vitro* dissolution studies of the solid dispersions were performed for a period of 2h in USP II apparatus (Lab India DS 8000). The studies were carried out in 900 ml of water as dissolution media and rotated at stirring speed of 50 rpm in the dissolution media maintained at 37±0.5 °C. Aliquots of samples were withdrawn at every predetermined time intervals and filtered through 0.45 µm filters, and analysed in Agilent 1260 infinity HPLC. The dissolution data recorded was analyzed to calculate the amount of drug released and percentage cumulative drug released at different time intervals [11].

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetric (DSC) analysis was performed by taking 3 mg samples of pure Nifedipine, Silica and selected formulations. Samples were heated in an open aluminium pan at a rate of 10 °C/min in a 0 to 200 °C temperature range under a nitrogen flow of 40 ml/min as purging gas using the instrument Texas, C2000 [12].

Stability studies

Stability studies were performed according to ICH guidelines Q1C. The stability studies were carried out on the optimised formulation F5in a humidity chamber maintained at 40 ± 2 °C/75 ± 5% relative humidity (RH) for 1 month. At the end of the studies, the samples were analyzed for percentage drug release and drug content [13].

Results

Table 1: Evaluation of pre formulation parameters

Parameter	Syloid 72FP	Syloid XDP 3050	Silsol 6035
Bulk density (gm/cm^3)	0.14±0	0.22±0.005	0.35±0.01
Tapped density (gm/ml)	0.206±0.001	0.293±0.002	0.453±0.002
Carr's Index (%)	29.29±0.88	20.14±1.07	20.24±1
Hausner's ratio	1.41±0.01	1.21±0.01	1.20±0.01
Angle of Repose	32.57±0.86	27.16±0.69	25.48±0.53

Data represents mean ±S.D (n=3)

Table 1: Composition of batches containing Nifedipine and silica by solvent loading method

Formulation code	Silica Grades	% composition	Drug composition (mg)	Silica composition (mg)
F2 F5 F8	Syloid XDP 3050 Silsol 6035 Syloid 72FP	10%	10	90
F3 F6 F9	Syloid XDP 3050 Silsol 6035 Syloid 72FP	20%	20	80
F4 F7 F10	Syloid XDP 3050 Silsol 6035 Syloid 72FP	30%	30	70

Table2: Dissolution profile of Nifedipine solvent loading on Silsol 6035 SD batches (Droplet addition method)

Time(min)	Nifedipine milled drug F1	Solvent loading on 10% silsol 6035 F5	Solvent loading on 20% silsol 6035 F6	Solvent loading on 30% silsol 6035 F7
0	0.00	0.00	0.00	0.00
2.5	0.00	89.87±1.54	26.57±1.58	11.03±1.64
5	0.17±1.52	95.39±1.52	33.97±1.54	14.95±1.58
10	0.24±1.56	98.43±1.54	32.81±1.54	21.20±1.66
15	0.45±1.58	94.88±1.56	46.46±1.50	24.83±1.60
30	1.09±1.52	96.40±1.52	57.78±1.52	32.38±1.58
45	1.93±1.52	98.07±1.58	65.04±1.56	37.31±1.54
60	2.86±1.62	97.71±1.52	70.56±1.54	41.38±1.54
90	4.16±1.54	99.67±1.52	74.91±1.62	49.07±1.60
120	5.87±1.62	101.63±1.54	81.88±1.62	51.54±1.60

Data represent means ±S.D (n=3)

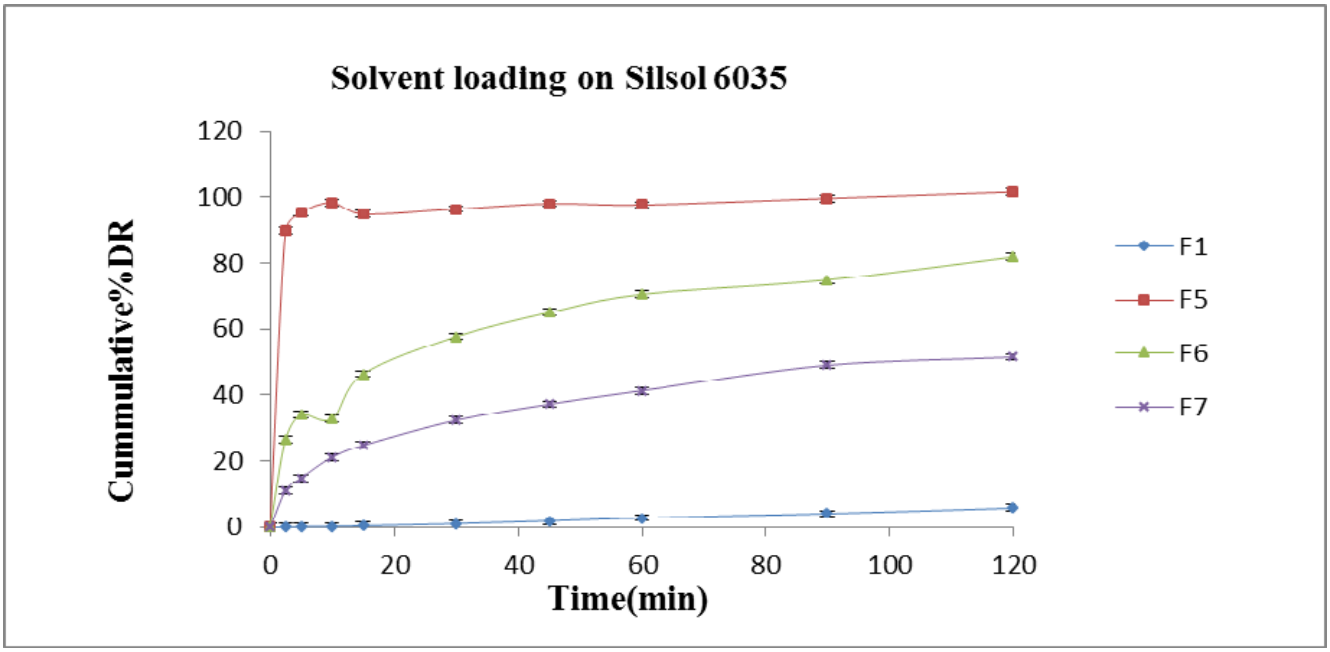

Fig 1: Dissolution Profiles of Nifedipine solvent loading on Silsol 6035 SD batches

Table 3: Nifedipine Content Study

Drug Loading % on Silica	Actual amount(mg) present in the powder that used for dissolution
10%Drug Load Syloid 72FP	8.59±0.02
10%Drug Load Syloid 3050	9.11±0.08
10%Drug Load Silsol 6035	9.44±0.04
10%Drug Load Syloid 72FP	8.39±0.06
10%Drug Load Syloid 3050	8.71±0.02
10%Drug Load Silsol 6035	8.91±0.12
10%Drug Load Syloid 72FP	9.28±0.16
10%Drug Load Syloid 3050	9.60±0.08
10%Drug Load Silsol 6035	8.23±0.12

The drug content was determined by using the method mentioned above in materials and methods and the results are presented in (Table-3).

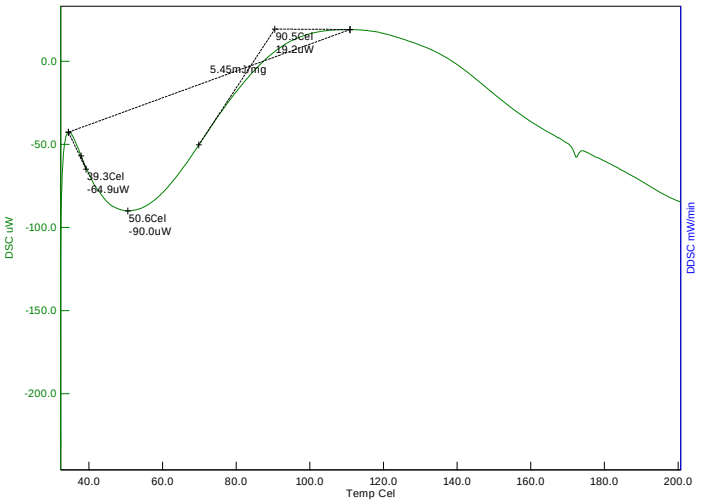

Fig 2

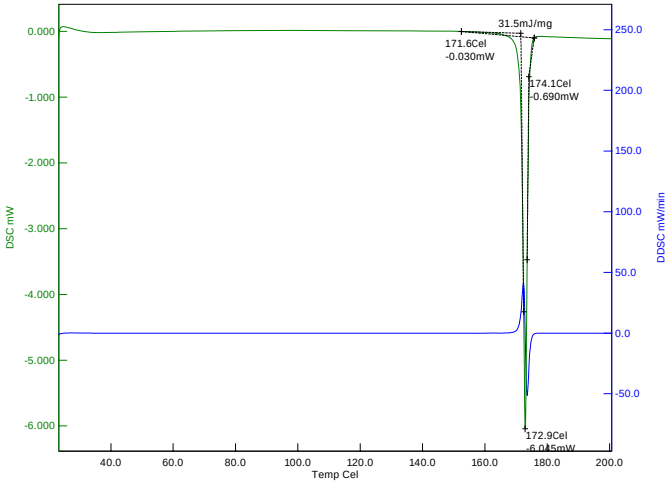

Fig 3

DSC spectra of Nifedipine pure drug DSC spectra of 10% solvent loaded silsol 6035

Table 5: Stability testing data of Nifedipine solvent loading on silsol 6035 kept at 40°C/75% RH

Time (min)	F1	10%solvent loading		20%solvent loading		30%solvent loading	
		Initial F5	1 month X5	Initial F6	1 month X6	Initial F7	1month X7
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.17 (±1.52)	95.39 (±1.52)	56.04 (±1.54)	33.97 (±1.54)	21.49 (±1.52)	14.95 (±1.58)	22.21 (±1.54)
10	0.24 (±1.56)	98.43(±1.54)	66.78 (±1.52)	32.81 (±1.54)	33.10 (±1.52)	21.20 (±1.66)	27.15 (±1.52)
15	0.45 (±1.58)	94.88 (±1.56)	74.04 (±1.54)	46.46 (±1.50)	42.68 (±1.54)	24.83 (±1.60)	30.78 (±1.58)
30	1.09 (±1.52)	96.40 (±1.52)	81.30 (±1.52)	57.78 (±1.52)	55.17 (±1.56)	32.38 (±1.58)	36.30 (±1.54)
45	1.93 (±1.52)	98.07 (±1.58)	85.80 (±1.52)	65.04 (±1.56)	64.61 (±1.52)	37.31 (±1.54)	40.94 (±1.54)
60	2.86 (±1.62)	97.71 (±1.52)	87.40 (±1.50)	70.56 (±1.54)	70.70 (±1.56)	41.38 (±1.54)	44.14 (±1.52)
90	4.16 (±1.54)	99.67 (±1.52)	89.29 (±1.54)	74.91 (±1.62)	74.33 (±1.58)	49.07 (±1.60)	45.44 (±1.54)
120	5.87 (±1.62)	101.63 (±1.54)	88.13 (±1.58)	81.88(±1.62)	81.01 (±1.58)	51.54 (±1.60)	52.99 (±1.60)

Data represent means ±S.D (n=3)

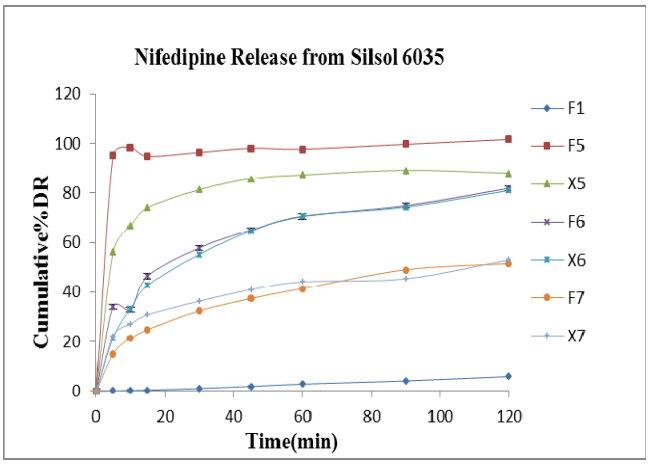

Fig 4: Comparison of dissolution profile of initial and 1 month samples of 10%, 20%, 30% Nifedipine solvent loading on solsol6035 SD batches

Table 6: Nifedipine content study for stability samples

Formulation code	Actual amount (%) present in the solid dispersion that used for dissolution
F5	94.3(±0.02)

Data represent means ±S.D (n=3)

Discussions

Pre-formulation studies were carried out on different grades of silica and their results were shown in the table-1 and all are within the range. Nifedipine solid dispersions were prepared by co-milling and solvent loading methods. F1 is the pure Nifedipine milled powder and F2,F5,F8 are prepared by 10% loading onto silica using XDP3050, silsol 6035and 72FP.F3,F6,F9 are prepared with 20% loading onto silica and F4,F7,F10 are prepared by 30% loading onto silica and for these formulations evaluation studies were carried out.

According to the dissolution profiles plotted in (Figure-1), the dissolution rates of nifedipine were increased by solvent (droplet addition) loading solid dispersion technique when compared to pure milled drug. Different loading concentrations were performed and *in-vito* dissolution studies were performed with different grades of silica. From all the solid dispersion batches F5 formulation showed (Table-2) 101.63% release in 120 min i.e. 20 folds increase in drug release when compared with pure milled drug with only 5.87% drug release. Hence F5 was selected as optimised formulation.

Conversion of crystalline drug into amorphous form was confirmed by DSC curves when compared with pure Nifedipine drug and silica along with selected formulations. 10% solvent loading Silsol 6035 DSC curve showed no peak formation as the pure drug at 170 °C shown in figures-2 and 3.

The stability testing of optimized formulation F5 were carried out as per the ICH guidelines. The optimized formulation was subjected to stability studies at 40 °C and 75% RH for a period of one month. The physical stability was assessed by the physical appearance and there was no change in the colour of powder and the chemical stability by determining drug content. The results showed that there was no change in the physical and chemical properties of the formulations. So F5 formulation was stable at the end of one month shown in table-5. The drug content of the formulation F5 for stability studies was found to be 94.3% shown in table-6.

Conclusion

An attempt was made to develop Nifedipine solid dispersion using mesoporous silica grades (SyloidXDP3050, Silsol 6035, and Syloid72FP) by various methods like co-milling, solvent droplet addition method, solvent impregnation method and solvent evaporation method. Nifedipine solid dispersion prepared by solvent (droplet addition) loading method was selected as the optimized formula based on the percentage drug release compared with other methods. The prepared solid dispersions were evaluated for DSC studies for the conformation of conversion of crystalline drug into amorphous form for the optimised formulation. From the *in-vitro* dissolution studies at a time point of 120 min (Table-4), formulation F5 showed 20 folds increase in dissolution compared with pure Nifedipine milled powder. Accelerated stability studies proved that the formulation is stable. Optimised Nifedipine solid dispersion was prepared for the treatment of Angina and Hypertension.

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