ISSN : 2320 4850

BI MONTHLY

Asian Journal of Pharmaceutical Research And Development

(An International Peer Reviewed Journal of Pharmaceutical Research and Development)

AJPRD

Volume - 02 Issue - 03 MAY-JUN 2014

website: www.ajprd.com
editor@ajprd.com

Asian Journal of Pharmaceutical Research and Development
(An International Peer-Reviewed Journal of Pharmaceutical Research and Development)
www.ajprd.com
ISSN 2320-4850

Research Article

DEVELOPMENT, EVALUATION AND CHARACTERIZATION OF SURFACE SOLID DISPERSION FOR SOLUBILITY AND DISSOLUTION ENHANCEMENT OF NIFEDIPINE

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Received: June 2014 ***Revised and Accepted: June 2014***

ABSTRACT

The main objective of the study was to enhance the dissolution of nifedipine, a poorly water soluble drug by surface solid dispersion technique using different carriers and to study the effect of each carrier on the in vitro dissolution profile. The formulations were optimized in the preliminary trials by using various ratios of different carriers like cross carmellose sodium, crosspovidone, and sodium starch glycolate. Resultant formulations were evaluated using FTIR, X-ray diffraction, DSC, SEM and in vitro dissolution. Solid dispersion with at 1:5 ratio gave good release when compared to pure drug and physical mixtures. The optimized dispersion was formulated in to sublingual tablets by using crosspovidone, crosscarmellose sodium and sodium starch glycolate as disintegrants and was evaluated for friability, hardness, weight variation, disintegration and in vitro dissolution

Keywords: Nifedipine; Surface solid dispersion; Sublingual tablets; In vitro dissolution

INTRODUCTION

Bioavailability of poorly water-soluble hydrophobic drugs is limited by their solubility and dissolution rate. Several studies were carried out to increase the dissolution rate of drugs [1]. One such study was solid dispersion which has shown promising results in improving solubility, wettability, dissolution rate of drug and subsequently its bioavailability [2]. The mechanism by which solid dispersion enhances the solubility and dissolution involves particle size reduction to fine form or molecular level, conversion of crystalline form to amorphous form and by enhancing wettability [3].

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This technique has been used for various poorly aqueous soluble drugs such as nimesulide [4], ketoprofen [5], tenoxicam [6], nimodipine [7] and nilvadipine [8].

Despite of having so many advantages, only few commercial solid dispersion products are available [9]. The surface solid dispersion technique overcame the shortcomings of solid dispersion prepared by water soluble carriers like tackiness and difficulty in handling of the product. The carriers used in surface solid dispersion are water insoluble, porous materials and hydrophilic in nature. In this technique drug gets deposited on the surface of the inert carrier leading to reduction in particle size of the drug and thereby enhanced dissolution. The release of drug from the carrier material depends on hydrophilic nature, particle size, porosity and surface area of the

carrier [10]. Larger the surface area available for surface adsorption of the drug better is the release rate [11]. In preparing surface solid dispersion various carriers like crosspovidone, croscarmellose sodium, sodium starch glycolate has been employed. Nifedipine is a dihydro pyridine calcium channel antagonist originally introduced for the treatment of angina pectoris and hypertension. Nifedipine which is a poorly water soluble drug coming under BCS class-2 undergoes first pass metabolism in liver and gut wall. As nifedipine has poor solubility and dissolution, the dissolution was enhanced by surface solid dispersion technique. The surface solid dispersion was prepared with different carriers at different ratios.

MATERIALS AND METHODS

Nifedipine was obtained as gift sample from Pell tech healthcare Pvt.Ltd, Mumbai, crosspovidone, crosscarmellose sodium, sodium starch glycolate were obtained as gift samples from Research-Lab Fine Chem, Mumbai .All the solvents used were of analytical grade from SD
Mumbai, India.

Preparation of nifedipine surface solid dispersion (SSD) and physical mixture (PM)
The surface solid dispersion of nifedipine with different carriers at different ratios were prepared by solvent evaporation method. The drug to carrier ratios of 1:1 and 1:9 were used for preparing both solid dispersion and physical mixtures. The drug was first dissolved in required quantity of dichloromethane and to this solution, carrier was dispersed. The above prepared mixture was then placed in a rotary flash evaporator for evaporation of the solvent by adjusting the temperature to 40-450C and under reduced pressure. The obtained mass was passed through a 60 # sieve and was dried at 400C in an oven for at least 3 hrs until a constant mass was obtained. The obtained product was stored in desiccators for carrying out evaluation. Physical mixtures (PM) containing one part of drug and 9 parts of carrier were prepared by mixing in a double cone blender for 15 minutes. The prepared mixtures were sifted through 60# sieve and were used for evaluation.

Characterization of Surface Solid Dispersions (SSD):
• Production yield:

Production yield was determined by following formula: Yield = (a x b+c)×100
Where,
a - weight of solid dispersion sifted through# 100.
b - Weight of diclofenac taken for solid dispersion preparation,
c - Weight of polymer taken for solid dispersion preparation.

Calibration curves by blank correction method
In order to correct the interference of the carriers in the UV measurement, some methods reported [10] were employed. Stock solutions were prepared by dissolving 100 mg of drug in few ml of methanol and then made up with the appropriate buffer. Calibration curves in the range of 2 to 20 mcg/ml were obtained by diluting aliquots with appropriate buffer solution. The interference of the carriers on UV measurements was blanked out by preparing stock suspension of the carriers in appropriate buffer solution. Aliquots of suspensions were added to drug solutions to obtain a 1:9 drug-to Excipient ratio on dilution. The suspensions were diluted and filtered through 0.45 mm membrane filter before going for the determination of absorption at a λmax of 238 nm. The blanks were mixtures of corresponding buffers and appropriate carrier. The method obeyed Beer's law in the concentration range of 2 to 20 mcg/ml.

Assay
Accurately weighed samples (n=3) equivalent to 10 mg of drug was taken in a 100 ml volumetric flask, a few ml of methanol was added and shaken for few minutes until the drug gets dissolved. The volume was made to 100 ml with 6.8 pH phosphate buffer containing 0.5% SLS solution and this solution was filtered using0.45 mm membrane filter. A 10ml aliquot of the above prepared solution

was taken and diluted to 100 ml with buffer solution. The absorbance of sample solution was determined at 238 nm against carrier blank by using blank correction method.

***In vitro* dissolution studies**

Nifedipine a pure drug & surface solid dispersions of Nifedipine were subjected to dissolution test using in-vitro dissolution rate apparatus-II. (Paddle method). This test was performed using 900 ml of dissolution medium (0.1N HCL) at 37±20C. Accurately weighed samples (plain drug and surface solid dispersions) of drug were added in 900 ml capacity jar of dissolution apparatus which paddle was rotated at 50rpm. A 5ml aliquot of dissolution medium was withdrawn at appropriate time intervals. An equal volume of fresh dissolution medium was immediately replaced. It was suitably diluted and analyzed spectrophotometrically by measuring absorbance at 285nm.The experiments were performed in triplicate. With the help of standard curve equation concentration were found using absorbance values.

Fourier transforms infrared (FTIR) spectroscopy

FTIR spectra of drug, SSD were obtained. About 1mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer USA Spectrum 65 IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 400 cm-1 in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

Differential scanning calorimetry (DSC)

Thermogram of NIFEDIPINE, and Drug: SSG formulation was recorded by using "Perkin-Elmer differential scanning calorimeter with a pyris workstation". Thermal behavior of the samples was investigated under a scanning rate of 10 0C/ min, covering a temperature range of 100- 3000C.

Powder X-Ray Diffraction Analysis:

X- ray diffraction of drug (Nifedipine), SSG, Drug: SSG in different formulation was recorded by using "PANalytical X'pert pro". The cross section of the samples was exposed to X-ray radiation with scanning range of 50-500.

Solvent residue

The determination of ethanol was performed by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. The packed column was BD-624 capillary column. Temperature of oven was 600C injection port 140 0C and detector 2500C. Oven was programmed at 5 0C/min for 10min, 15 ºC/min up to 250 0C with a hold time of 7min.

RESULTS AND DISCUSSION

Production yield*:* Production yield was calculated according to the formula and Assay was done according to procedure and results are given in table 2 and 3.

Table 2: Result of Production Yield & Assay of Surface solid dispersion

Drug	Diclofenac	Diclofenac	Diclofenac
Carrier	SSG	CCN	CP
Code	SSD-S1	SSD-C1	SSD-P1
Code	SSD-S2	SSD-C2	SSD-P2
Code	SSD-S3	SSD-C3	SSD-P3
Code	SSD-S4	SSD-C4	SSD-P4
Code	SSD-S5	SSD-C5	SSD-P5
Drug: Carrier ratio	1:1	1:1	1:1
Drug: Carrier ratio	1:3	1:3	1:3
Drug: Carrier ratio	1:5	1:5	1:5
Drug: Carrier ratio	1:7	1:7	1:7
Drug: Carrier ratio	1:9	1:9	1:9

Table 3: Result of Production Yield & Assay of Surface solid dispersion

Drug	Carrier	Code	Ratio	Production Yield (%)	Assay (%)
Nifedipine	Sodium Starch Glycolate	SSD-S1	1:1	95.04	97.64
		SSD-S2	1:3	95.40	91.67
		SSD-S3	1:5	92.50	96.33
		SSD-S4	1:7	96.38	94.92
		SSD-S5	1:9	96.20	98.85
	Cross Carmellose Sodium	SSD-C1	1:1	96.04	98.34
		SSD-C2	1:3	93.20	91.57
		SSD-C3	1:5	88.43	97.34
		SSD-C4	1:7	96.70	92.98
		SSD-C5	1:9	89.20	94.56
	Cross Povidone	SSD-P1	1:1	95.20	95.39
		SSD-P2	1:3	93.80	102.04
		SSD-P3	1:5	97.80	98.93
		SSD-P4	1:7	91.56	90.33
		SSD-P5	1:9	92.51	96.36

In Vitro Dissolution Studies:

Dissolution data of surface solid dispersions on excipients were reported in Fig 1 All the prepared surface solid dispersion showed an enhancement in the dissolution rate of the drug compared to plain drug. Surface solid dispersions prepared by using sodium starch glycolate (1:5ratio) showed enhanced dissolution rate when compared to other carriers. Surface solid dispersions of diclofenac were prepared with various carrier concentrations and the effect of increasing carrier concentration on dissolution rate was determined. The rank order of dissolution rate improvement for various carriers are; SSG>CCS>CP. The D: SSG 1:5 ratio, both showed near 100% drug release in 20 min. So Drug: SSG 1:5 selected as optimized formulation. From drug release pattern it was concluded that Drug: SSG at the ratio 1:5 shows good result.

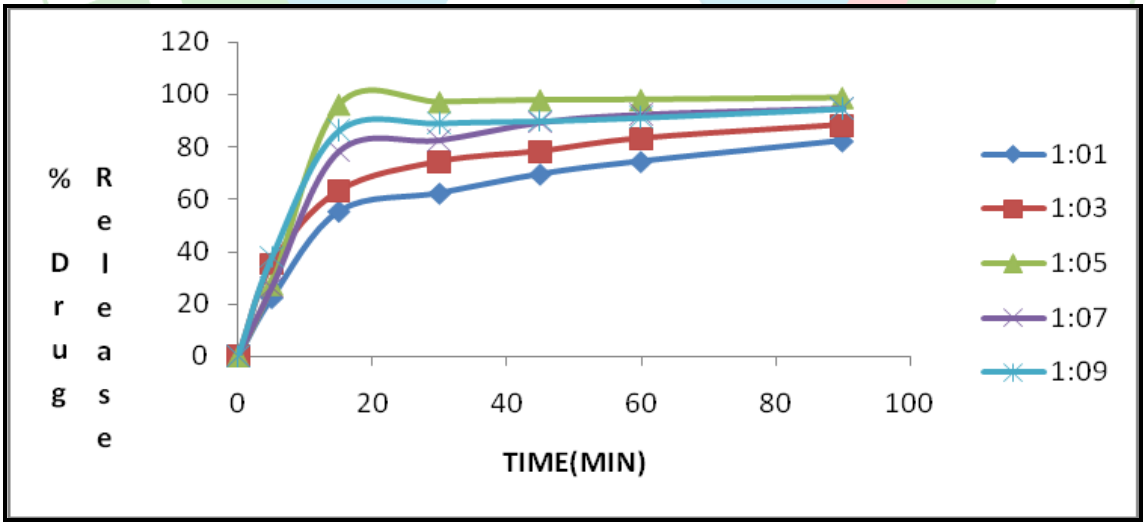

Fig No: 1 Dissolution profiles of Nifedipine with SSG in 0.1 N HCL

FTIR Study:

Fig. 2 to 5 shows the FTIR spectra of the I) drug II) carrier III) Surface Solid Dispersion. There was no significant change in the spectrum of Surface solid dispersions, as incorporation of Nifedipine into the carrier (SSG) did not modify the position of its functional groups.

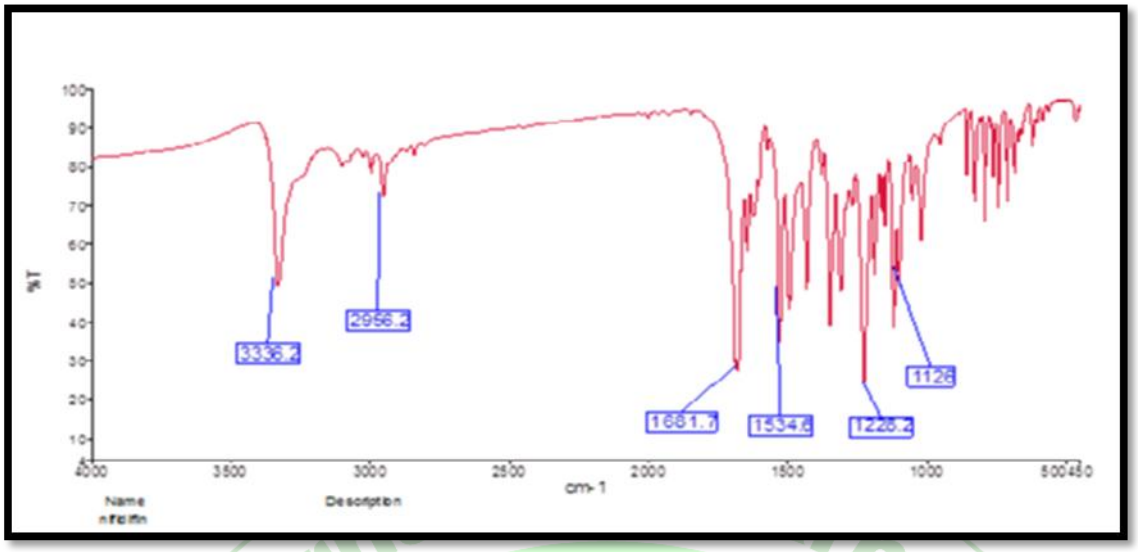

Fig No: 2 FTIR Spectra of Nifedipine

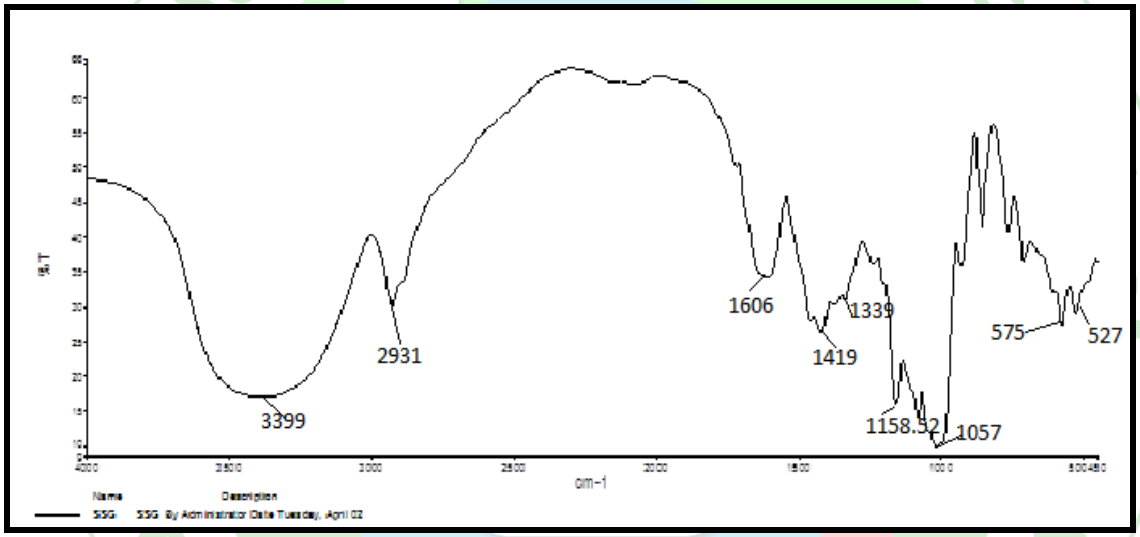

Fig No: 3 FTIR spectra of sodium starch glycolate

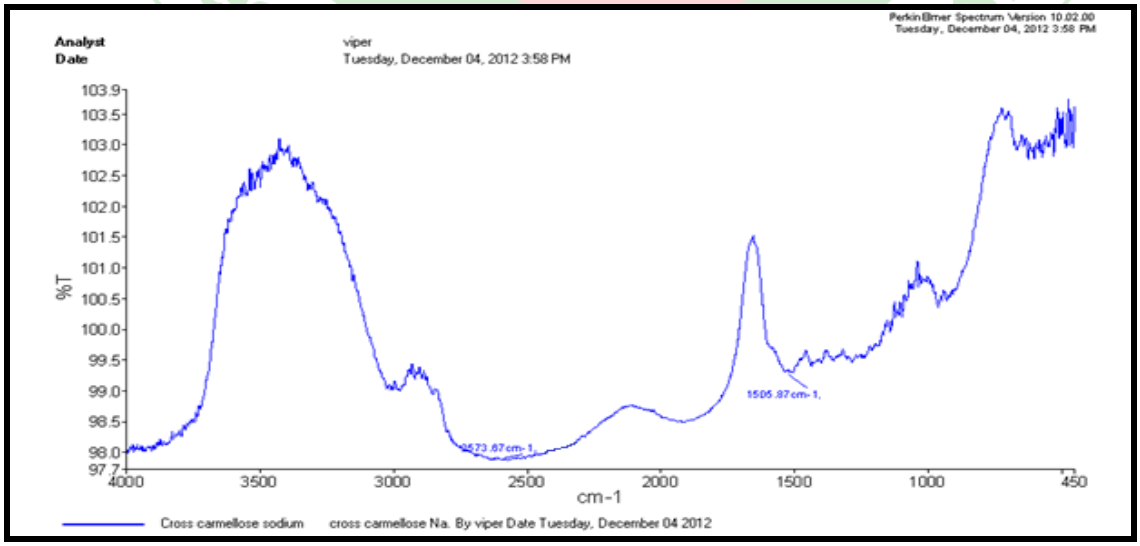

Fig No: 4 FTIR Spectra of cross carmellose sodium

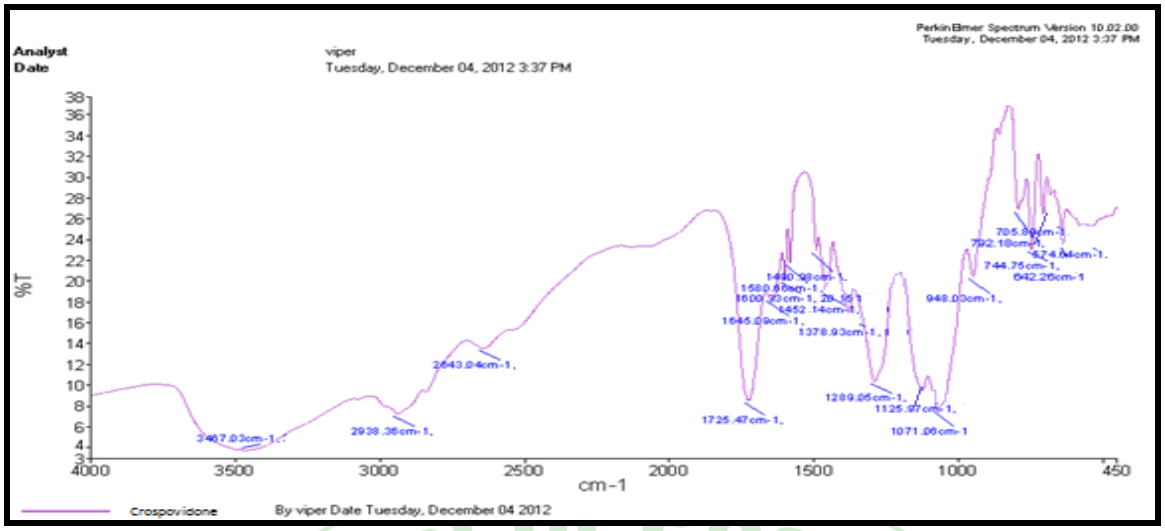

Fig No: 5 FTIR Spectra of cross povidone

X-Ray diffraction studies:

X-ray diffraction patterns revealed that pure Nifedipine was in crystalline state as it showed sharp distinct peaks notably at 2 diffraction angles of 7.43º, 9.73º, 16.18º, 24.27º. The reflections (specific peaks) corresponding to the drug and SSG were also found in the formulation diffractogram with reduced intensity as compared to drug alone. The reduction in intensity and number of typical diffraction peaks in formulation diffractogram Suggests reduction in crystalline nature of drug and may be converted from crystalline to amorphous form.

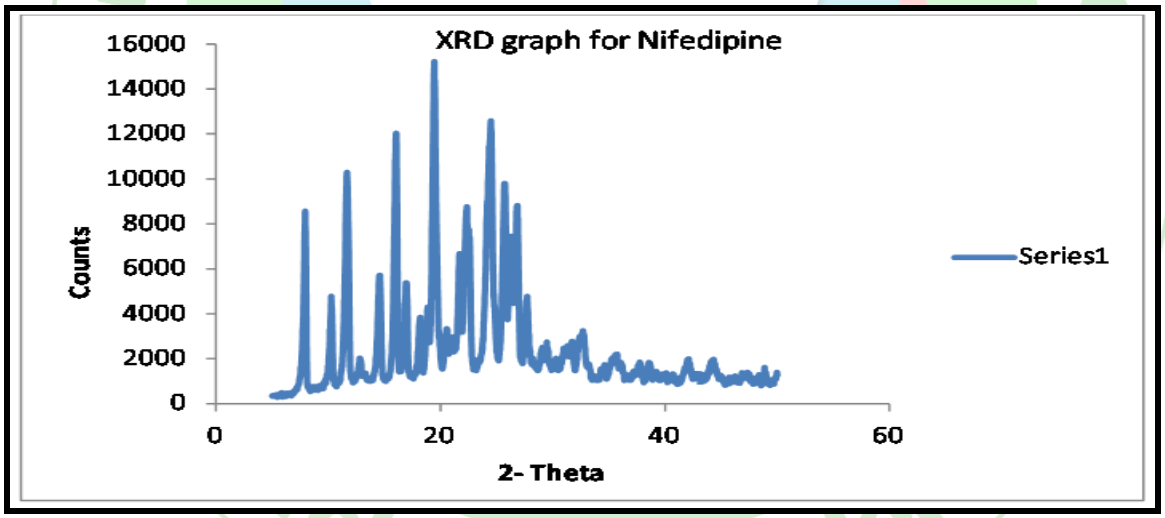

Fig No: 6 XRD of Nifedipine

Differential scanning calorimeter:

The Thermogram of pure Diclofenac showed a sharp peak at 178.9 ºC, which corresponds to the melting temperature of Diclofenac, sharpness of the peak indicating crystalline nature of the drug. The Thermogram of sodium starch glycolate (SSG) showed a peak at 82ºC, which corresponds to the melting temperature. In the optimized formulation Drug: SSG (1:7) 2 peaks were observed one at 82.36ºC, another one at 185.47ºC, which corresponds for SSG and Diclofenac respectively. And the area and sharpness of the peaks were decreased, which indicated that the crystallinity of the drug was reduced and might be converted to amorphous form. There was no change in the peak temperature of the optimized formulation (SSD-S3) when compared to the pure drug, which indicates no interaction between drug and Excipient.

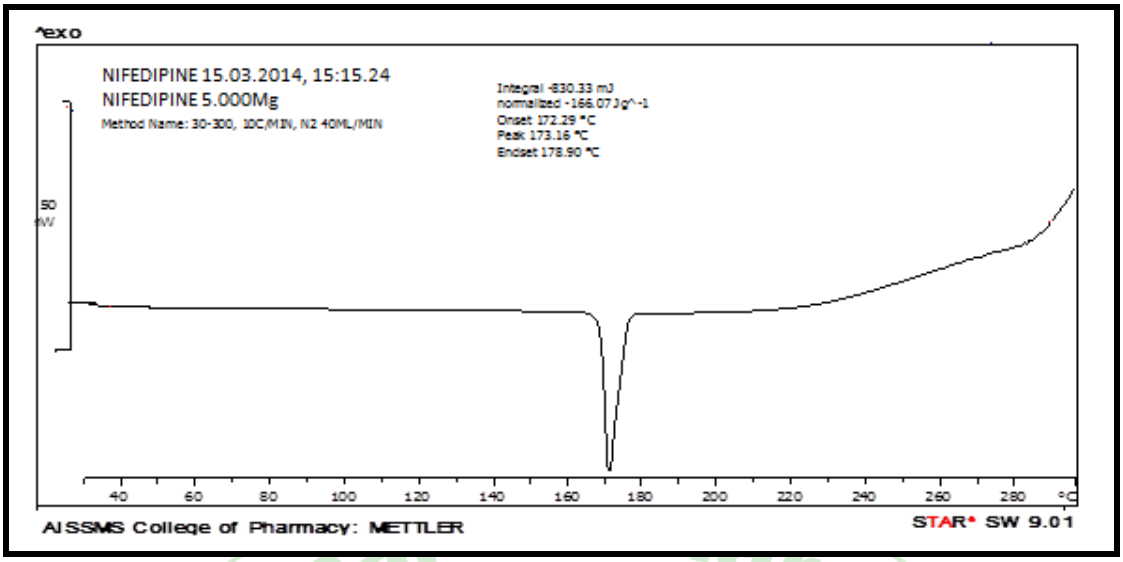

Fig No: 7 DSC of Nifedipine

Residual Solvent Study:

Residual solvent concentration in surface solid dispersion of Diclofenac prepared using ethanol was performed by gas chromatography. The level of ethanol was below detectable limits that is 5000ppm Hence, can be concluded that solvent evaporation method was efficient in removal of solvents from SSD well below permissible levels.

Table 3: Comparison studies of Dissolution profiles of different SSD in 0.1 N HCL

Code	D:C ratio	T 5	T 20	T 30	T 45	T 60	T 90
SSD–S1	1:1	34.03	71.30	77.98	86.10	92.03	99.20
SSD-S2	1:3	43.26	74.70	82.05	90.40	99.26	-
SSD-S3	1:5	36.80	99.93	-	-	-	-
SSD-S4	1:7	34.20	91.30	94.87	99.70	-	-
SSD-S5	1:9	33.97	97.85	99.87	-	-	-
SSD-C1	1:1	43.26	74.70	82.05	90.40	99.26	-
SSD-C2	1:3	25.20	47.57	59.50	64.48	74.93	78.60
SSD-C3	1:5	30.06	49.50	57.43	63.70	78.20	83.55
SSD-C4	1:7	25.60	63.02	72.16	80.50	87.14	92.60
SSD-C5	1:9	35.03	69.30	75.30	81.45	91.50	97.51
SSD-P1	1:1	43.80	77.66	86.10	97.20	-	-
SSD-P2	1:3	20.50	44.30	47.00	59.10	68.60	79.36
SSD-P3	1:5	23.45	54.10	62.70	72.20	78.20	83.40
SSD-P4	1:7	19.65	57.20	65.82	74.41	79.72	89.55
SSD-P5	1:9	30.12	60.59	65.89	75.60	83.90	93.98

CONCLUSION

The dissolution rate of nifedipine was successfully achieved by surface solid dispersion technique. The type and the amount of the carrier played a very important role in the enhancement of the dissolution rate. This enhancement in dissolution rate helped in providing rapid onset of drug. The sublingual administration of prepared SSD tablets help in bypassing the first pass effect.

ACKNOWLEDGEMENT

The author is thankful to pelltech healthcare, Mumbai for providing gift sample of nifedipine and also thankful to university of pune for carrying out DSC & XRD.

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