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Research Article

PREPARATION AND CHARACTERIZATION OF SOLID DISPERSIONS OF NISOLDIPINE

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ABSTRACT

Solid Dispersions have a great potential for improving dissolution rate, and hence possibly bioavailability, of hydrophobic drugs. The objective of this study was to improve the dissolution rate of Nisoldipine by solid dispersion technique. The polymers used at different ratios were Hydroxypropylcellulose (HPC) and Polyvinylpyrrolidone K 29/32 (PVP K 29/32). The solvent method was choosen to prepare different solid dispersions. The solid dispersions were characterized by dissolution studies, solubility studies, DSC (Differential Scanning Calorimetry) and stability studies**.** The release of Nisoldipine was faster from solid dispersions than from pure drug and physical mixtures. The solid dispersions showed increasing percentage cumulative drug release with increasing polymer ratios. PVP K 29/32 solid dispersions gave higher dissolution rate than HPC solid dispersions.DSC thermograms showed change in melting peak of Nisoldipine when formulated as solid dispersions indicating change in crystallinity. The study proved as a promising approach for improvement of dissolution rate and solubility of Nisoldipine**.**

Keywords: Nisoldipine, Solid dispersion, Polyvinylpyrrolidone K 29/32, Dissolution rate.

INTRODUCTION

With the emergence of high throughput screening for agents with potential therapeutic value, the number of poorly soluble drugs has increased considerably[1]. Contrast to highly soluble compounds, poorly soluble drugs results in a number of *in vivo*and *in vitro* consequences. The rate and extent of absorption of BCS class II drugs from the gastrointestinal tract can be improved by various formulation strategies such as by increasing dissolution rate or by introducing the drug in solution and maintaining it in solution in the intestinal lumen[1-3]. Solid dispersion is a promising approach for improving dissolution rate of poorly soluble drugs.Solid dispersion is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent or solvent fusion methods[4-6].When the dispersion is exposed to aqueous media, carrier dissolves and drug releases as fine colloidal particles. The dissolution rate and bioavailability of poorly aqueous soluble drugs improves due to enhanced surface area[7-12].

Nisoldipine, O5-methyl O3-(2-methylpropyl) 2, 6-dimethyl-4-(2- nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate[13], has poor aqueous solubilityresulting in low and often irregular bioavailability. Nisoldipine is used to treat high blood pressure. Nisoldipine is also used to treat patients with angina[14]. It may be used alone or in combination with other agents[15]. Nisoldipine selectively relaxes the muscles of small arteries causing arteries to dilate but has little or no effect on muscles of vein or heart. Dilation of arteries reduces blood pressure[16].Lowering high blood pressure helps prevent strokes, heart attacks and kidney problems[17]. Nisoldipine is available as extended release tablet under the brand name

'Sular'[18,19]. This study involves improving solubility and *in vitro* dissolution of nisoldipine by formulating it as solid dispersions. Hydroxypropylcellulose (HPC) and Polyvinylpyrrolidone K 29/32 (PVP K 29/32) were used as carriers in three different ratios. Faster drug dissolution from solid dispersions has been observed due to increased wettability, improved dispersibility of drug particles and existence of drug in amorphous form with improved solubility and absence of aggregation of drug particles.

MATERIALS AND METHODS

Materials

Nisoldipine was supplied by Shri Ram Chemicals, Ghaziabad. Hydroxypropylcellulose (HPC) andPolyvinylpyrrrolidone K 29/ 32 (PVP K 29/32) were obtained from Across Organics, New Jersey, USA. All the reagents and solvents were of analytical grade.

Preparation of physical mixtures[6,7]

The drug carrier ratios were choosen as 1: 0.5, 1: 1 & 1: 2. Nisoldipine and the selected carriers / polymers Hydroxypropylcellulose (HPC) and Polyvinylpyrrrolidone K 29/ 32 (PVP K 29/32) were first sieved through sieve number 60. They were then mixed with a spatula in a glass mortar for 15 minutes for uniform mixing.

Preparation of solid dispersions[10-12]

Solid dispersions were prepared with solvent method. Drug carrier ratios were 1: 0.5, 1: 1 & 1: 2. The drug and the carriers were dissolved in methanol. They were thoroughly mixed. The solvent was evaporated at 40^{o}C in a tray dryer. The samples were kept in a desiccator for 48 hours. After this period, the samples were pulverized using a glass mortar and pestle, sieved through 60 mesh and kept in a desiccator throughout the experimental period. The samples should be protected from the light.

Drug content analysis

Drug content analysis was done by preparing 1 mg/ml solution of the solid dispersions samples and physical mixtures in methanol. Samples equivalent to 10 mg of Nisoldipine was dissolved in 10ml of methanol. This solution was then kept for 24 hours for complete extraction of the drug. After 24 hrs, the solution was filtered and a 10µg/ml solution was prepared with this solution by dilution with methanol. The solution was assayed through UV spectrophotometer [9,14] (Shimadzu UV-1700) method at 298 nm.

Dissolution studies

Dissolution studies were carried out according to USP using apparatus 2 at 37°C and a rotary speed of 50 rpm. The dissolution medium used was 0.1N Hydrochloric acid, HCl (900ml). The dissolution of Nisoldipine was carried out for one hour. Then the dissolution studies of the prepared solid dispersions were carried out. For this, samples equivalent to 10 mg of Nisoldipine were taken and the dissolution was carried in 0.1 N HCl. At specified times, 5ml samples were withdrawn, filtered, diluted and assayed by the spectrophotometer(Shimadzu UV-1700) at 298 nm. Fresh medium was added to maintain a constant volume after each sampling. Cumulative release and % cumulative drug release after each sampling was determined.

The dissolution studies of the physical mixtures were also carried out for a comparative analysis. The dissolution studies of those physical mixtures whose solid dispersions gave the highest % cumulative drug release were carried out.

Dissolution efficiency ($DE_{30\%}$) was calculated by calculating area under the dissolution curve for 30 minutes (by trapezoidal rule) and expressed as % of area of rectangle described by 100% dissolution in same time.

Solubility studies

The solubility studies were carried out for the drug, solid dispersions and physical mixtures. The solid dispersions and the physical mixtures giving highest % cumulative drug release with each polymer were selected. 1mg/ml solution of the drug was prepared by dissolving 10mg of the drug in 10ml of 0.1N HCl. Solid Dispersions and physical mixtures equivalent to 10mg of the drug were dissolved in 10ml of 0.1N HCl. The solutions were shaken for 5 hours in a wrist action shaker (Hicon)and then the solutions were kept for 24 hours at room temperature. After 24 hours, the solids were filtered off and the liquid was assayed through UV spectrophotometer (Shimadzu UV-1700) at298 nm. Solubility of nisoldipine was 6.2 µg/ml.

Differential scanning calorimetric (DSC) studies[20]

DSC studies were done at IIT, Delhi. The samples were Nisoldipine solid dispersions and physical mixtures**.**

Stability studies of the optimized solid dispersion

The ageing studies[21] were helpful in finding out the physico-chemical stability of solid dispersions. The stability tests were done on the Solid Dispersions batch code SDP3 (drug polymer ratio 1:2) by keeping them at ambient temperature for 60 days. Samples were removed at 0, 30 and 60 days interval and checked for drug content, solubility and dissolution.

RESULTS AND DISCUSSION

The drug content analysis of all solid dispersions and physical mixtures showed that the drug content was in the range of 98% - 100%. The high drug content showed that drug is uniformly dispersed in powder formulation.

From *In –vitro* study, it was observed that dissolution rate of pure drug was low as 22.12% of drug released in 60 minutes. The dissolution rate increased with solid dispersions and physical mixtures. All solid dispersions and physical mixtures showed increasing percentage cumulative drug release (PCR) with increasing polymer ratios (Table 3 and Fig 1 & 2). The HPC solid dispersions showed a much higher percentage cumulative drug releases than drug and physical mixture. (Table 3 and Figure 1). The highest percentage cumulative drug release was shown with batch code SDH3 as 76.32%. The PVP K 29/32 solid dispersions also showed increasing percentage cumulative drug releasesthan drug and physical mixture (Table 3 and Figure 2). The highest percentage cumulative drug release was shown with batch code SDP3 as 82.68%. Among all solid dispersions, PVP K 29/32 solid dispersions gave higher releases in all ratios.

Dissolution efficiency ($DE_{30\%}$) was also greater for physical mixtures and solid dispersions when compared to only 7.76 % for pure drug (Table 3).

All solid dispersions showed higher amounts of drug being released compared with the pure Nisoldipine and the corresponding physical mixtures. The increased dissolution rate of solid dispersions can be attributed to solubilization effect of the carrier and conversion of the drug to the amorphous state. Dry mixing of Nisoldipine with various carriers in physical mixtures brought the drug in close contact with the hydrophilic carriers. The increased dissolution rate observed in these cases could be attributed to several factors such as solubilization effect of the carrier, inhibition of particle aggregation etc. During dissolution, when solid dispersion comes in contact of dissolution medium, hydrophilic carrier dissolves and precipitation of embedded drug into fine particles occurs and thus surface available for dissolution increases.

Solubility studies indicated that solubility of nisoldipine increased in presence of carriers when compared to 6.2 µg/ml of pure drug. The rapid dissolution of drug is due to presence of drug in amorphous form. The other factors as absence of aggregation, good wettability and dispersibility might be responsible for improved solubility.

The DSC curves of pure drug, physical mixtures and solid dispersions are shown in Figure 4,5,6,7 and 8. The thermal curve of Nisoldipineindicated its crystalline nature as melting peak of drug was shown at 150.68ºC (Figure 4). In the cases of physical mixtures as HPC physical mixtures (PMH3), this melting endotherm shifted as peak at 149.41ºC (Figure 5). The same was the case with PVP K 29/32 physical mixtures (PMV2). The melting endotherms showed peak at 143.55ºC (Figure 6). Solid dispersions SDH3 showed peak at 140.56 ºC (Figure 7) and SDP3 showed peak at 134.93 ºC (Figure 8). The shifting of peaks indicated that the drug has attained amorphous form in SDs. This amorphous state was responsible for increased dissolution rate of the drug.

The insignificant change in the drug content, solubility and dissolution indicated that solid dispersions were stable.

Table 1: Formulation of Solid Dispersions and Physical Mixtures

Solid dispersions	Physical mixtures	Drug polymer ratio
Carrier-HPC		
SDH1	PMH1	1:0.5
SDH2	PMH2	1:1
SDH3	PMH3	1:2
Carrier-PVP K 29/32		
SDP1	PMP1	1:0.5
SDP2	PMP2	1:1
SDP3	PMP3	1:2

Table 2:Drug Content Analysis

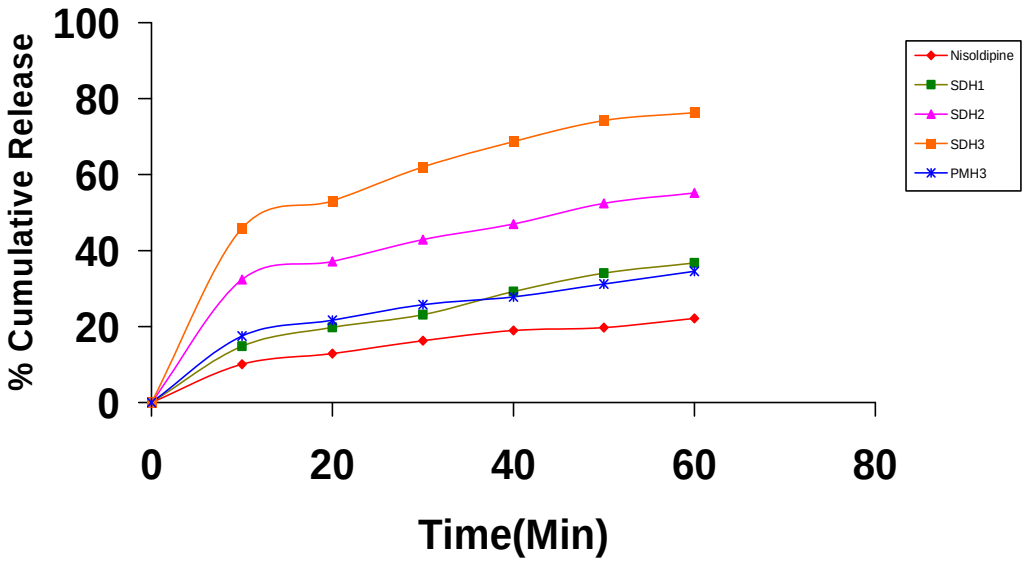
Batch code (Solid dispersions)		Drug content(%)
HPC	SDH1	98.70
	SDH2	99.23
	SDH3	98.45
PVP K29/32	SDP1	99.53
	SDP2	99.23
	SDP3	99.23

Table 3: Percentage Cumulative Release and Dissolution Efficiency

Parameters	Solid dispersions						Physical mixtures	
	HPC			PVP K29/32			HPC	PVP K29/32
	SDH1	SDH2	SDH3	SDP1	SDP2	SDP3	PMH3	PMP3
PCR	36.77	55.18	76.32	43.37	66.41	82.68	34.55	40.7
$DE_{30\%}$	15.39	30.31	43.31	18.70	33.09	46.1	17.34`	20.17

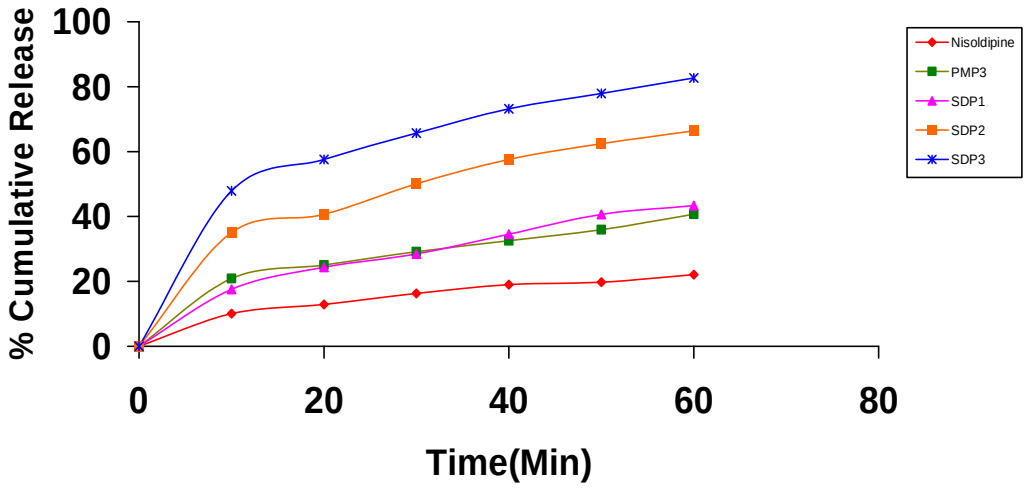
Table 4:Stability Study

Days	Drug Content (%)	Solubility (µg/ml)	Percentage Cumulative Release
0	99.2	21.6	82.7
30	99.2	21.2	81.4
60	98.7	21.2	80.7



SDH3> SDH2 > SDH1 > PMH3 >Nisoldipine

Fig.1:Comparative Dissolution Profiles of Nisoldipine, HPC Physical mixture and HPC Solid Dispersions



SDP3> SDP2 > SDP1 > PMP3 >Nisoldipine

Fig.2: Comparative Dissolution Profiles of Nisoldipine, PVP K 29/32 Physical Mixture and PVP K 29/32 Solid Dispersions

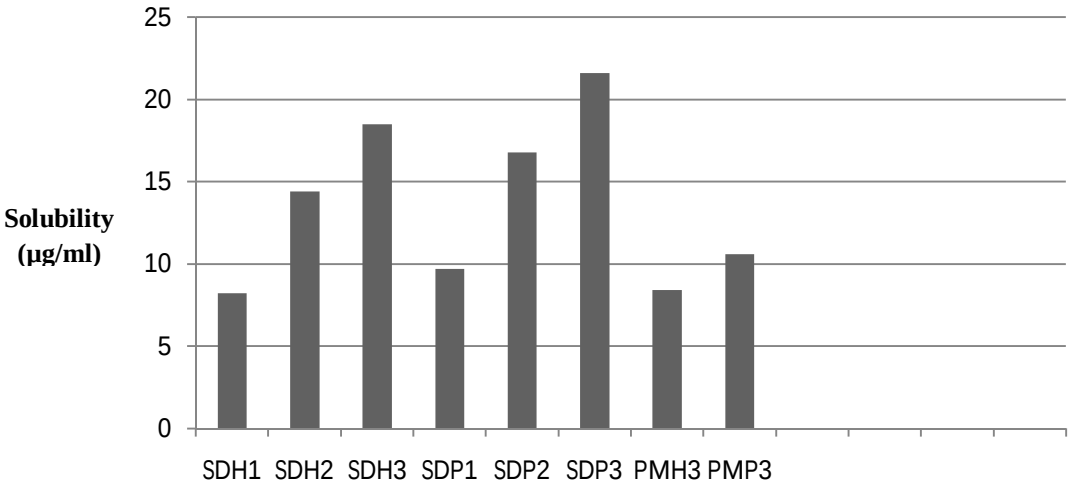


Fig. 3: Solubility of Nisoldipine Solid Dispersions and Physical Mixtures

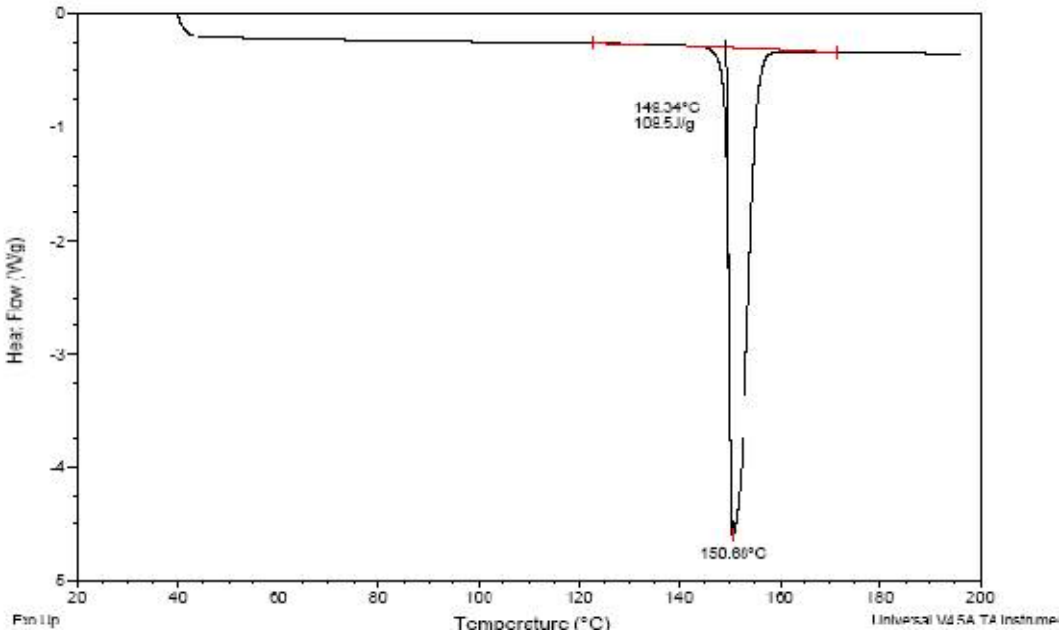


Fig.4:DSC Curve of Nisoldipine

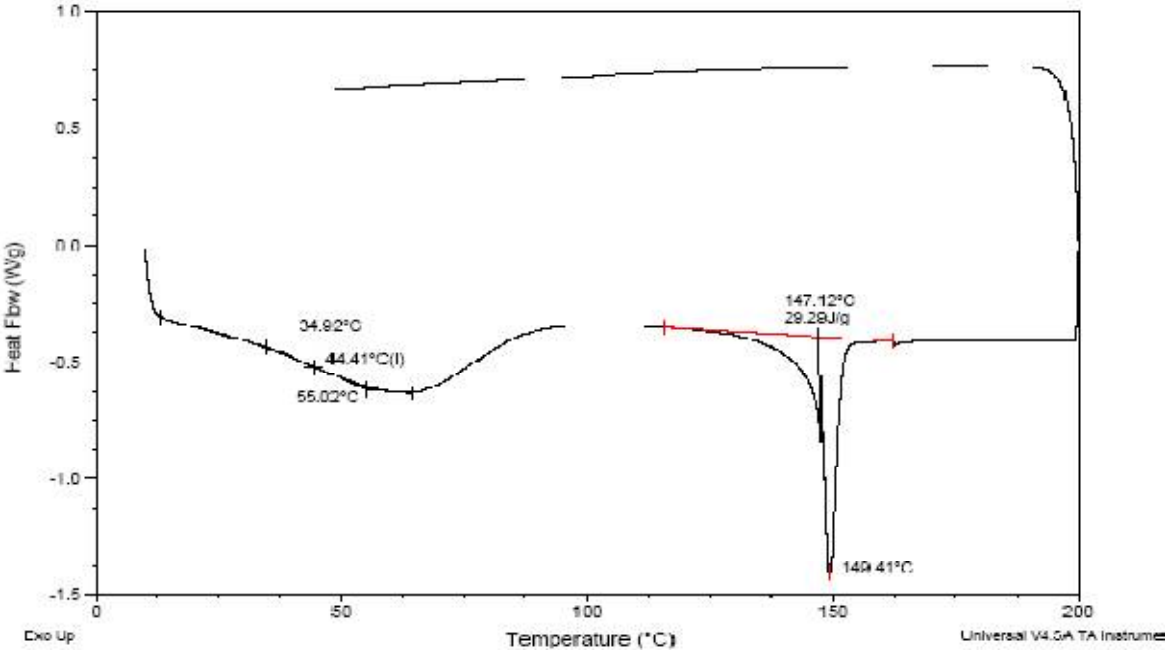


Fig.5:DSC Curve of Nisoldipine HPC Physical Mixture PMH3

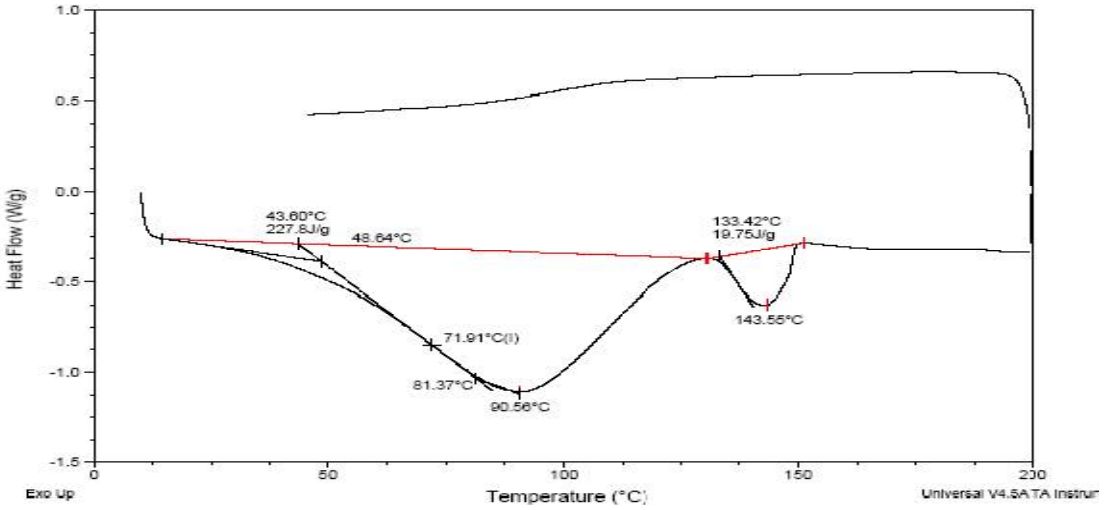


Fig. 6:DSC Curve of Nisoldipine PVP K 29/32 Physical Mixture PMP3

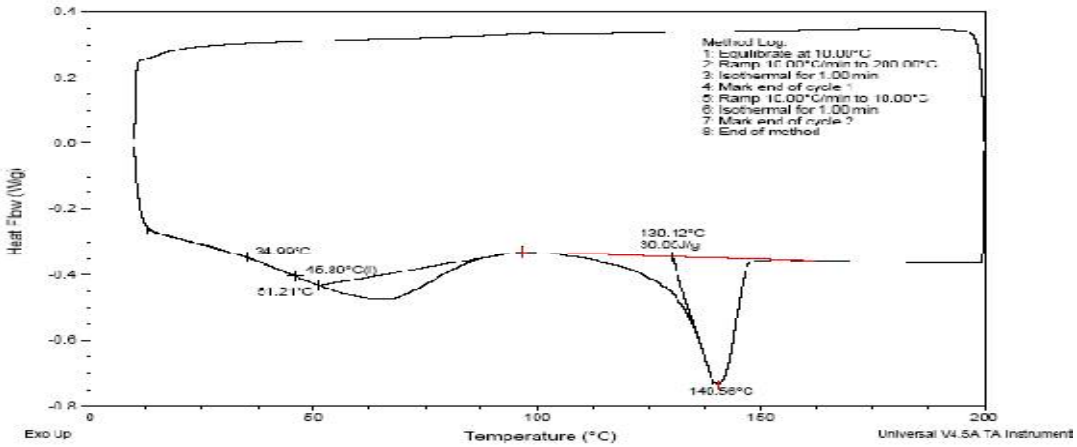


Fig. 7: DSC Curve of Nisoldipine HPC Solid Dispersions SDH3

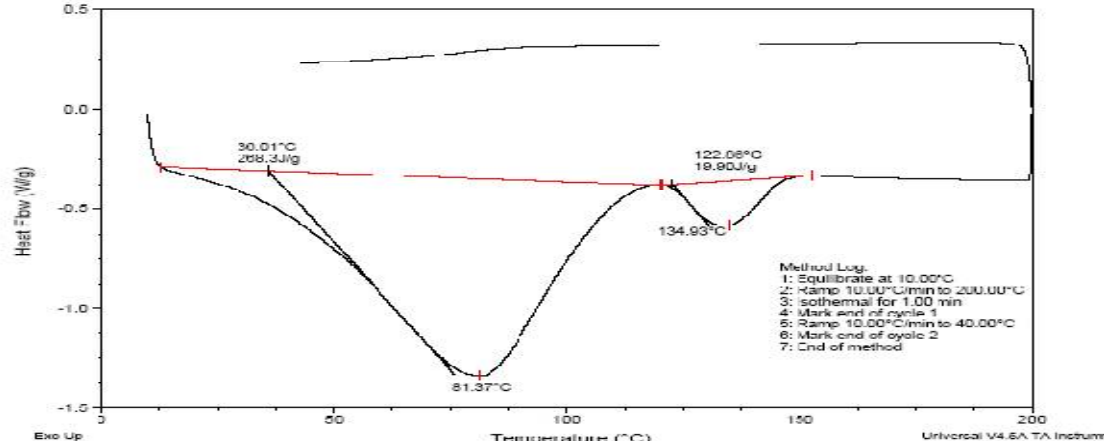


Fig. 8:DSC Curve of Nisoldipine PVP K 29/32 Solid Dispersions SDP3

CONCLUSION

Solid dispersions using solvent method were effective in improving dissolution rate of nisoldipine. Solid dispersions prepared with PVP K29/32 gave higher dissolution rate than HPC solid dispersions. Increase in polymer concentration increased drug release with both polymers. The studies indicated that polymer inhibited crystallization of drug, resulting in amorphous form of drug in solid dispersions. DSC studies supported attainment of amorphous state for nisoldipine. Thus, the results indicate dispersion technique can be an effective delivery system to improve dissolution and hence, bioavailability of poorly soluble drugs.

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