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Original Article

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IMPROVEMENT OF DISSOLUTION RATE AND SOLUBILITY OF NIFEDIPINE BY FORMULATION OF SOLID DISPERSIONS

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ABSTRACT

The objective of this study was to improve the dissolution rate of Nifedipine by solid dispersion technique. The Solid Dispersions of Nifedipine were formulated with four different polymers as Hydroxypropylcellulose (HPC), Polyvinylpyrrolidone K 29/32 (PVP K 29/32), Polyethyleneglycol 6000 and Gelucire 44/14. The solid dispersions were prepared in six different ratios. The solvent method was choosen to prepare different solid dispersions. However, solid dispersions with PEG 6000 could be formulated with both melting and solvent method. The combination solid dispersions of PEG 6000 and Gelucire 44/14, and PVP K 29/32 and Gelucire 44/14 were also prepared.

The evaluation of solid dispersions was done with dissolution studies, DSC, FT-IR and stability studies. HPC and PVP K 29/32 solid dispersions gave higher dissolution rate than other solid dispersions. The combination solid dispersions do not markedly enhance dissolution as compared to PEG 6000 and PVP K 29/32 alone. The optimized solid dispersions were HPC solid dispersions. They were formulated into capsule dosage form and evaluated through dissolution and stability studies.

Keywords: *Nifedipine; Solid dispersion; Hydroxypropylcellulose (HPC); Gelucire 44/14; Dissolution rate.*

INTRODUCTION

The enhancement of oral bioavailability of poorly soluble drugs is an important aspect of drug development. A poorly soluble compound is defined as one dissolving in less than 1 part per 10,000 of water. It takes more time to dissolve in gastrointestinal fluids than it takes to be absorbed in the gastrointestinal tract.[1]

Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from dosage form and higher inter-patient variability. Poorly soluble compounds also present many in-vitro formulation obstacles, such as severely limited choices of delivery technologies and increasing

complex dissolution testing with limited or poor correlation to in-vivo absorption. [1, 2]

The solid dispersion methodology is the widely applied technology for solving the bioavailability problems of poorly aqueous soluble drugs. The technology overcomes the limitations of conventional methods for reducing particle size and increasing bioavailability. [3, 4, 5, 6, 7]

Nifedipine, 1, 4- dihydropyridine[8], with calcium channel blocking activity[9] has poor aqueous solubility[10] resulting in low and often irregular bioavailability. Incorporation of such a substance into a water-soluble matrix results in solid dispersion systems[3, 4, 5, 6] where the dissolution rate of active ingredient is expected to be significantly improved.

The rate-limiting step in the absorption of Nifedipine is its dissolution rate in gastrointestinal fluids. If its aqueous solubility is increased it will give higher dissolution rate and improved bioavailability. [9, 10] The Solid Dispersion Technique[3, 4, 5, 6] can be applied to Nifedipine for increasing its solubility and dissolution rate.

MATERIALS AND METHODS

Materials

Nifedipine was received as a gift sample from Shilpa Medicare Limited, Raichur, Karnataka. Polyethylene glycol 6000 (PEG6000) was obtained from CDH, New Delhi. Hydroxypropylcellulose (HPC) Polyvinylpyrrrolidone K 29/ 32 (PVP K 29/32) were obtained from Across Organics, New Jersey, USA. Gelucire 44/14 was a gift sample from Colorcon Asia Pvt. Limited, Goa. All the reagents and solvents were of analytical grade.

Preparation of physical mixtures

The drug carrier ratios were choosen as 1: 0.5, 1: 1, 1: 2, 1: 3, 1: 4, and 1:5. Nifedipine and the selected carriers / polymers (Polyethylene glycol 6000 (PEG6000) [11], Hydroxypropylcellulose (HPC) [11], Polyvinylpyrrrolidone K 29/ 32 (PVP K 29/32) [11] and Gelucire 44/14) [3, 15] 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

Melting method[4, 5, 6, 12, 13]

Only PEG 6000 Solid Dispersions could be prepared by this method. The drug and the carriers were taken in the ratios of 1: 0.5, 1: 1, 1: 2, 1: 3, 1: 4 and 1:5. PEG 6000 melted at 65°C. Then the drug was added. This mixture was heated at 65-70°C for one and a half hours until completely melted. The molten mixture was then cooled rapidly in an ice bath and solidified.

This solidified mass was kept in a desiccator for 48 hours. After this period, the samples were pulverized using a glass pestle and mortar, sieved through 60 mesh and kept in a

desiccator over silica gel throughout the experimental period.

Solvent method[4, 5, 6, 13, 14]

The solid dispersions of Nifedipine with all carriers were prepared with solvent method. Drug carrier ratios were 1: 0.5, 1: 1, 1: 2, 1: 3, 1: 4 and 1:5.

The drug and the carriers were dissolved in methanol. The solution was stirred for 1 hour. The solvent was evaporated off at 40°C in a tray dryer. After solvent removal, 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.

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 Nifedipine 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 10 µg/ml solution was prepared with this solution by dilution with methanol. The solution was assayed through UV spectrophotometric method at 236.5nm.

Dissolution studies

Dissolution studies[8] were carried out using USP apparatus 2 at 37 ± 0.5°C at a speed of 50 rpm. The dissolution medium used was 0.1N Hydrochloric acid, HCl (900ml). The dissolution of Nifedipine 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

Nifedipine were taken and the dissolution was carried in 0.1 N HCl. At specified times, 5ml samples were withdrawn, filtered, and assayed by the spectrophotometric method at 236.5nm. 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.

Solubility studies

The solubility studies[15, 16, 17] 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 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 at 236.5 nm.

Differential scanning calorimetric (DSC) studies

DSC[18, 19, 20] studies of Nifedipine, solid dispersions and physical mixtures were done at NIPER, Mohali.

Fourier –transformation Infrared studies

FT-IR[18, 19, 20] studies were done by ARBRO Pharmaceuticals, New Delhi. The samples were Nifedipine, polymer, solid dispersions and physical mixtures.

Ageing studies[15, 17] of the optimized solid dispersion

The ageing studies were helpful in finding out the physico-chemical stability of solid dispersions. The stability tests were done on the Hydroxypropylcellulose Solid Dispersion batch code H3 (drug polymer ratio 1: 2). The ageing studies were done by first keeping the samples for 1month (30 days) at room temperature and then shifting it at 40°C/ 75%RH for 1 month (30 days). The total period of stability analysis was two months (60 days). Before and after storage, the samples were examined for drug content and dissolution rate i.e. on day of keeping the samples, after 30 days and after 60 days.

RESULTS AND DISCUSSION

The formulation studies

The melting method resulted in only PEG 6000 solid dispersions Solid dispersions with Gelucire 44/14 were difficult to be formulated so, PEG 6000 and Gelucire 44/14 were combined in different ratios to formulate solid dispersions. PVP K 29/32 and Gelucire 44/14 were also combined to formulate solid dispersions.

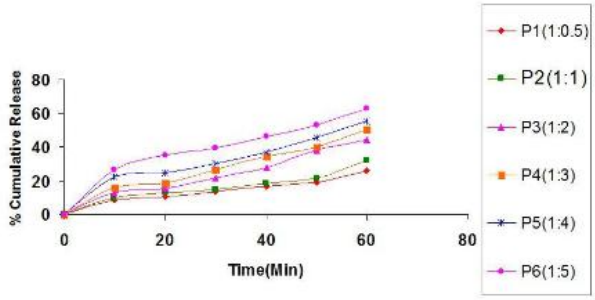
Drug content analysis

The drug content analysis of all solid dispersions and physical mixtures showed that the drug content was in the range of 98% - 102%.

Dissolution studies

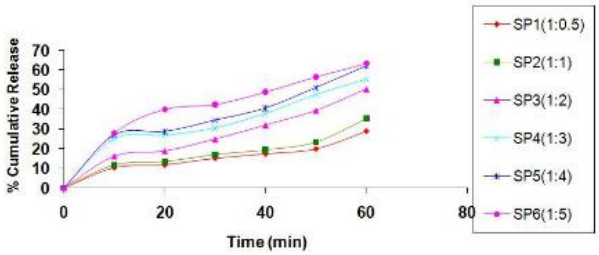
Nifedipine PEG 6000 solid dispersions prepared with melt and solvent method showed increasing percentage cumulative drug release with increasing polymer ratios. The solid dispersions prepared with solvent method gave better results than by the fusion method. The solid dispersions batch code P6 gave 62.73 and the solid dispersions batch code SP6 gave 63.34 percentage cumulative drug releases at the end of 60 minutes (Fig.1. and Fig.2).

A comparative analysis of dissolution rate of drug, solid dispersion and physical mixtures was also done. The solid dispersions showed a much higher percentage cumulative drug releases than drug and physical mixture as drug D 12.79%, physical mixture PP6 27.99% and solid dispersion SP6 63.34%(Fig.3).



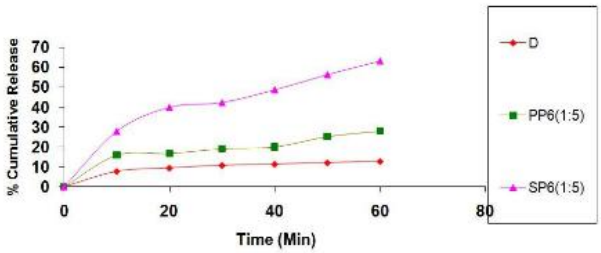
P6 > P5 > P4 > P3 > P2 > P1

Fig 1: *Comparative dissolution profiles of PEG 6000 solid dispersions prepared by the melt method (figures in brackets indicate drug polymer ratios)*



SP6 > SP5 > SP4 > SP3 > SP2 > SP1

Fig 2: *Comparative dissolution profiles of PEG 6000 solid dispersions prepared by the solvent method*



SP6 >PP6 >D

Fig 3: *Comparative dissolution profiles of Nifedipine D, physical mixture PP6 and solid dispersion*

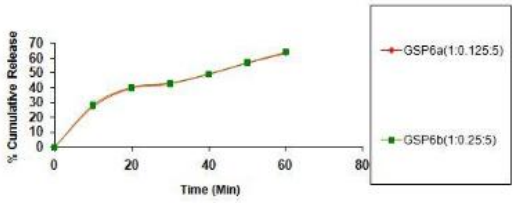
Nifedipine PEG 6000 Gelucire 44/14 solid dispersions were prepared with solvent method. The drug polymer ratios were 1:0.125:5 and 1: 0.25:5. The batch GSP6b gave higher dissolution results 64.11% than GSP6a 63.35% (Fig.4). But the results were not much higher than PEG 6000 alone.

Nifedipine HPC solid dispersions were prepared with solvent method. The solid dispersions showed increasing percentage cumulative drug release with increasing polymer ratios. The highest percentage cumulative drug release was shown with batch code H3 as 72.45% (Fig.5).

The solid dispersions showed a much higher percentage cumulative drug releases than drug and physical mixture as drug D 12.79%, physical mixture PH3 15.69% and solid dispersion H3 72.45% (Fig.6).

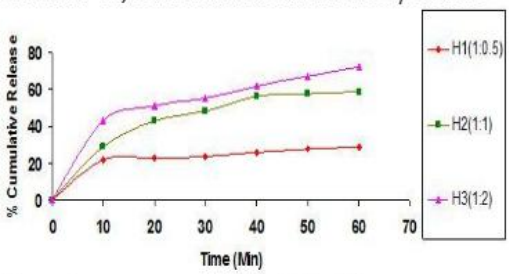
Nifedipine PVP K 29/32 solid dispersions were prepared with solvent method. The solid dispersions showed increasing percentage cumulative drug release with increasing polymer ratios**.** The highest percentage cumulative drug release was shown with batch code V2 as 62.21% (Fig.7).

The solid dispersions showed a much higher percentage cumulative drug releases than drug and physical mixture as drug D 12.79%, physical mixture PV2 13.67% and solid dispersion V2 62.21%.(Fig.8). Nifedipine PVP K 29/32 Gelucire 44/14 solid dispersions were prepared with solvent method. The drug polymer ratio was 1:1:0.25. The batch GV2 gave 63.39% cumulative drug release but the results were not much higher than PVP K 29/32 alone (Fig.9).



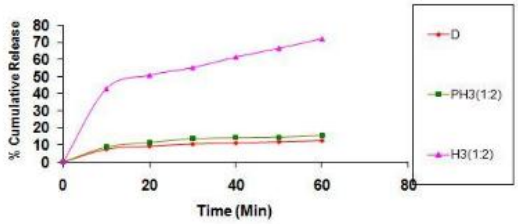
GSP6b ≈ GSP6a

Fig 4: *Dissolution profiles of PEG 6000 and Gelucire 44/14 combination solid dispersions*



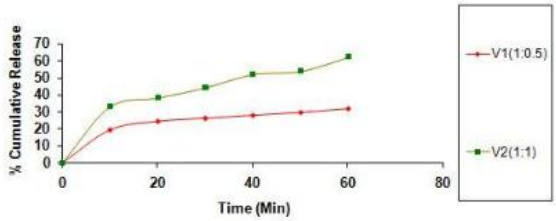
The release pattern **H3 >H2 >H1**

Fig 5: *Dissolution profiles of HPC solid dispersions*



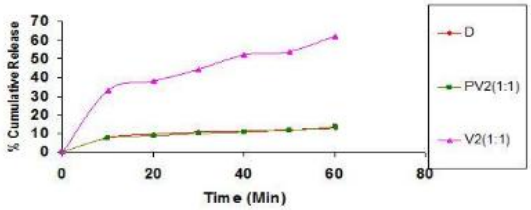
The release pattern **H3 >PH3 >D**

Fig 6: *Comparative dissolution profiles of drug, physical mixture PH3 and solid dispersion*



The release pattern **V2 > V1**

Fig 7: *Comparative dissolution profiles of PVP K 29/32 solid dispersions*



The release pattern **V2 >PV2 >D**

Fig 8: *Comparative dissolution profiles of drug, PVP K 29/32 physical mixture PV2 and solid dispersion*

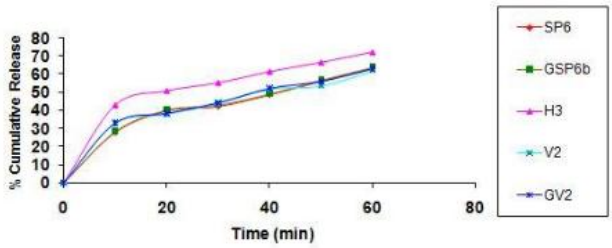


Fig 9: *Comparative dissolution profiles of different solid dispersions (different polymers)*

All solid dispersions showed higher amounts of drug being released compared with the pure Nifedipine and the corresponding physical mixtures. Possible explanations for the increased dissolution rate of solid dispersions include solubilization effect of the carrier and conversion of the drug to the amorphous state.

Dry mixing of Nifedipine 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.

The dissolution studies for three batches H3a, H3b, H3c of HPC solid dispersion having drug to polymer ratio 1:2 were conducted. The parameters for the dissolution studies were same as for previous studies (Table 1).

Table 1: *Dissolution studies of three batches of Hydroxypropylcellulose solid dispersion H3 (H3a, H3b, H3c)*

Cumulative % drug release	**Time (min)**					
	10	20	30	40	50	60
Mean ± standard deviation	43.02 ± 0.322	50.87 ± 0.295	55.19 ± 0.344	61.86 ± 0.147	66.84 ± 0.204	72.40 ± 0.328

Coefficient of variation (c.v.) for the percentage cumulative release at the end of 60 minutes = 0.00453. Coefficient of variation is very less so, there was not much significant difference between the dissolution studies of three batches.

Solubility studies

The solubility of Nifedipine is 8.60µg/ml (in 0.1N HCl). The physical mixtures as SPP8, PH3 and PV2 gave higher solubility than the drug. The solid dispersions as SP8, H3 and V2 gave higher solubility than the drug and the physical mixtures (Table 2).

Table 2: *Solubility analysis of Physical mixtures and Solid dispersions*

Batch Code	**Solubility (µg/ml)**	**Relative Solubility (wrt. Drug)**
PP6	11.46	1.33
PH3	15.79	1.84
PV2	10.03	1.17
SP6	22.92	2.67
H3	25.78	3.00
V2	21.49	2.50

The aqueous solubility of Nifedipine and HPC solid dispersion H3 was determined by same procedure as in 0.1 N HCl. Solubility of Nifedipine was 5.46µg/ml and H3 was 17.20µg/ml. So, relative solubility was 3.16. Thus, increase in solubility was observed.

Differential scanning calorimetric (DSC) studies

DSC thermograms of drug showed endotherms at 173.36ºC corresponding to melting of drug, Nifedipine (Fig.10). In case of physical mixtures (PMs), this endotherm broadened and shifted slightly to lower temperature (Fig.12 and Fig.14). No peak corresponding to melting point of the drug was observed in the thermograms of solid dispersions (SDs) indicating amorphous form of the drug (Fig.11 and Fig.13).

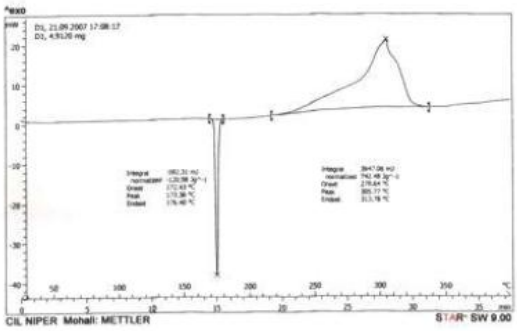


Fig 10: *DSC curve of Nifedipine*

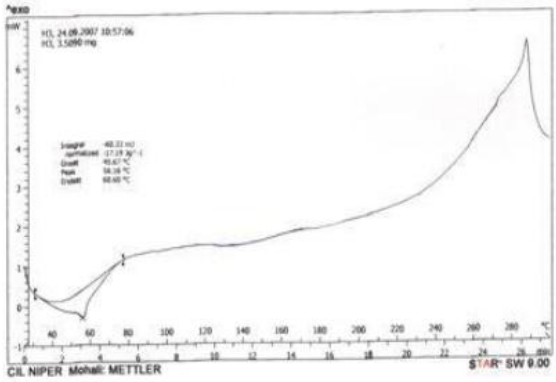


Fig 11: *DSC curve of HPC solid dispersion H3*

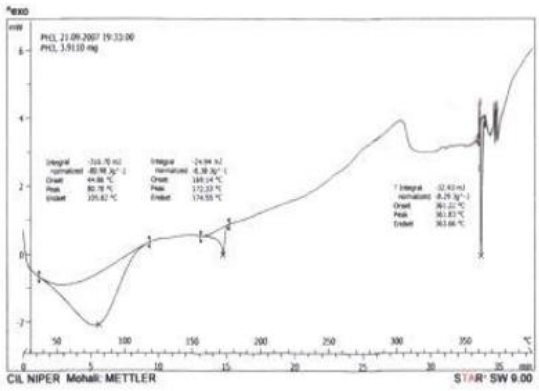


Fig 12: *DSC curve of HPC physical mixture PH3*

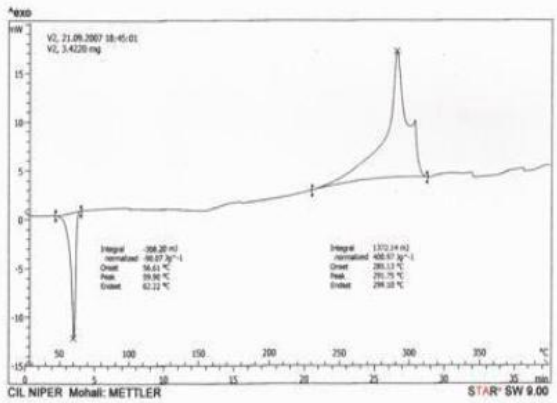


Fig 13: *DSC curve of PVP K 29/32 solid dispersion V2*

The melting peak of drug, Nifedipine (D1), was shown at 173.36ºC. In the cases of physical mixtures as HPC physical mixtures (PH3), this melting endotherm broadened, onset at 169.14ºC, peak at 172.33ºC and endset at 174.55ºC. The shifting is slightly to lower temperature. The same was the case with PVP K 29/32 physical mixtures (PV2). The melting endotherms of drug showed onset at 161.58ºC, peak at 172.18ºC and endset at 174.60ºC.

In the case of solid dispersions, H3 and V2, no peak was observed corresponding to melting

point of the drug. This indicated that the drug has attained amorphous form in SDs. This amorphous state was responsible for increased dissolution rate of the drug.

Thus, in both HPC and PVP K 29/32 solid dispersions, the drug has attained amorphous form.

Fourier –transformation Infrared (FT-IR) studies

The FT-IR spectra of Nifedipine showed a N-H stretching vibration at 3330.46 cm^{-1}(peak no.3), C-H aromatic vibration at 3100.97 cm^{-1}, C-H aliphatic stretching at 2952.48 cm^{-1}, C=O stretching at 1683.55 cm^{-1}(peak no.7), C-O ester stretching at 1227.47 cm^{-1}, and 1120.44 cm^{-1}. Sharp peak of NO_2 stretching was seen at 1529.27 cm^{-1} (Fig.15).

Nifedipine has an N-H function that is capable of forming hydrogen bonds. In crystalline Nifedipine, N-H group was weakly hydrogen bonded to a carbonyl function to another molecule.

In the case of HPC solid dispersion (Fig.17), N-H stretching vibration and C=O stretching were shown at 3331.43 (peak no.3), and 1683.15(peak no.5), respectively and they were broadened. The shifting of these bands to higher wave number and also, broadening of bands indicated that rupture of intermolecular hydrogen bonding took place between the two functional groups evidenced in the crystalline structure of Nifedipine. This showed that the drug had attained amorphous form. This amorphous state was responsible for increased dissolution rate of the drug.

In the case of HPC physical mixture (Fig.18), the shifting of N-H and C=O stretching vibration were not observed. But the broadening was observed. The spectrum was the superimposed spectra of HPC (Fig.16). and Nifedipine.

The absence of any other new peaks in the solid dispersion indicated that Nifedipine was not undergoing any polymorphic change during its preparation and also there was no intermolecular interaction between drug and carrier.

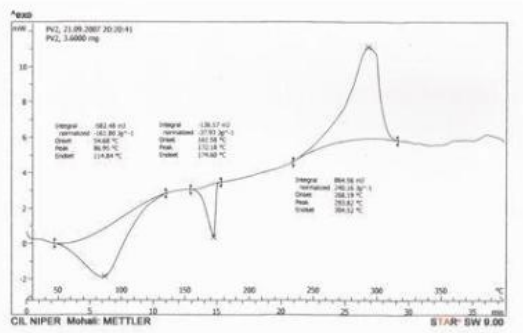


Fig 14: *DSC curve of PVP K 29/32 physical mixture PV2*

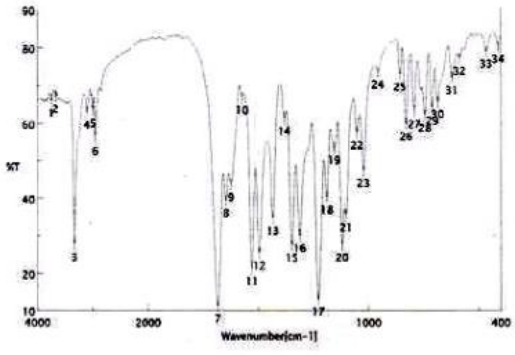


Fig 15: *FT-IR spectra of Nifedipine*

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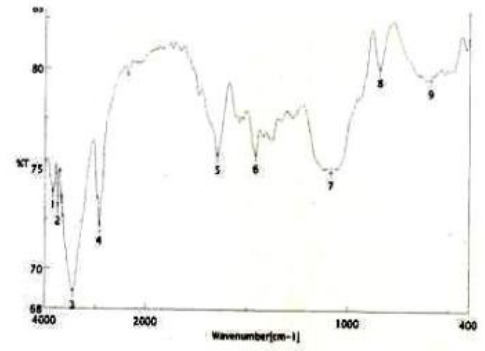

Fig 16: *FT-IR spectra of HPC*

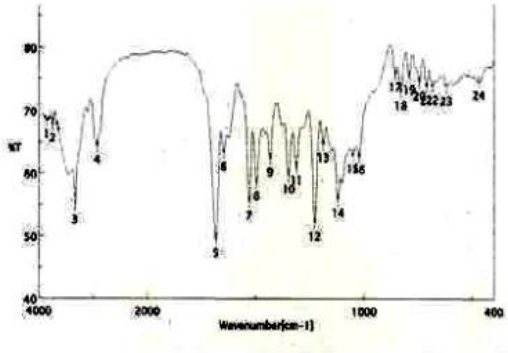

Fig 17: *FT-IR spectra of HPC solid dispersion H3*

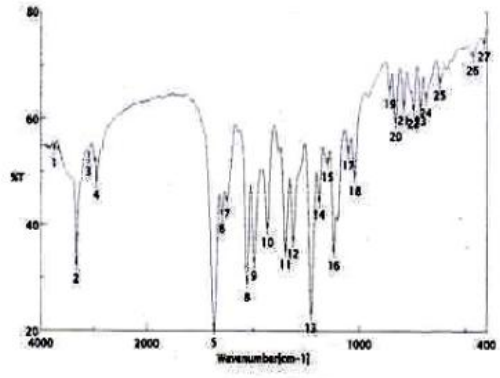

Fig 18: *FT-IR spectra of HPC physical mixture PH3*

Stability studies

Effect of ageing on drug content and dissolution rate of HPC solid dispersion was studied (Table 3 and 4).

Table 3: *Effect of ageing on Drug content (%) on three H3 batches*

Batch	Drug content (%)		
	0 Day	30 Days	60 Days
H3a	99.14	99.14	98.85
H3b	98.42	98.42	98.28
H3c	99.14	98.85	98.85

Table 4: *Cumulative percentage drug release after 60 minutes for three H3 batches (effect of ageing on dissolution rate)*

Batch no.	0 Day	30 Days	60 Days
H3a	72.70	72.05	71.40
H3b	72.45	72.45	72.05
H3c	72.45	72.05	71.40

For statistical analysis, ANOVA (analysis of variance) [21] was applied on the results of dissolution studies of stability samples (Table 5).

Table no 5: *ANOVA table for effect of ageing on dissolution rate of three H3 batches*

SOURCE	df	SS	MS	F
CSS	2	1.284	0.692	12.140
RSS	2	0.201	0.1005	1.763
C x R	4	0.228	0.057	
TSS	8	1.713		

SS = Sum of squares
MS = Mean sum of squares = SS/df

F (Tabulated) > F (Calculated) for both F(a) & F(b).

Thus, the dissolution readings of three batches did not have a significant difference on three different days. Also, the batches did not have a significant difference among themselves for the dissolution readings for the same day. The result supported the null hypothesis.

The results of drug content analysis showed that there was not much difference in drug content before and after storage conditions. The difference was even much less than 0.5%.

The dissolution results also proved that there was not significant difference among the percentage cumulative drug release.

Thus, Solid Dispersions were stable.

Formulation of the optimized solid dispersion into suitable dosage form

The solid dispersion system, H3 (1:3), was formulated into capsules by using various excipients (Table 6).

A comparative study of the dissolution rate (basis for selection of final capsule dosage form) of different formulations was done. The dissolution of solid dispersion system H3 containing 10 mg of the drug was compared with the formulation having solid dispersion H3 and either lactose only or lactose and microcrystalline cellulose (MCC) both (Table 7).

The dissolution parameters were same as in previous cases evaluating solid dispersions.

Table 6: *Dosage form development (Capsules)*

FORMULATION	F1	F2	F3
SOLID DISPERSION(H3)	30	30	30
LACTOSE	-	60	40
MCC	-	-	20
TOTAL (mg)	30	90	90

Table 7: *Dissolution studies of three Capsule formulations*

Batch no.	Cumulative % drug release at the end of 60 minutes
F1	72.42
F2	72.67
F3	72.02

Drug content uniformity analysis for final capsule formulation (Solid dispersion and Lactose)

The contents of six capsules (batch 1) were taken out and mixed. Then the amount equivalent to dose of the drug (10mg) was taken. A 10µg/ml solution was prepared. It was analyzed through UV spectrophotometry. The drug content was then calculated as for solid dispersion. The same procedure was repeated with two more batches of six capsules (Table 8).

All capsules had drug content more than 98%

Table 8: *Drug content uniformity analysis of final capsule formulation F2 (three batches 1,2and 3 with six capsules each)*

Batch	Drug content (%)	Mean ± standard deviation
1	98.42	
2	98.85	98.61 ± 0.219
3	98.56	

Stability study on final Dosage form

The capsule dosage form was kept for 30 days under accelerated stability conditions of 40°C/75%RH. The dissolution study of the formulation was carried out before and after storage. The dissolution results did not show much difference, dosage form was stable.

CONCLUSION

The aim of the present work was preparation of Solid Dispersions of Nifedipine so as to increase the dissolution of the active drug .Hydroxypropylcellulose (HPC) was found to be the most efficient polymer among the four polymers studied. The dissolution kinetics of Nifedipine dissolved from the HPC solid dispersions revealed high rates in comparison to Polyvinylpyrrolidone (PVP K 29/32), Polyethyleneglycol 6000 (PEG 6000) and PEG 6000 and Gelucire 44/14 (in combination), PVP K 29/32 and Gelucire 44/14 (in combination) solid dispersions.

The physical mixtures showed better release than pure drug but less than the solid dispersions. The solubility of Nifedipine was also increased by formulating solid dispersions.

DSC and FT- IR studies for Nifedipine and solid dispersions showed that Nifedipine had attained amorphous form in solid dispersions. This amorphous state may be responsible for increased dissolution rate of the drug.

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