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SOLUBILITY ENHANCEMENT AND DESIGN EXPERT ASSISTED OPTIMIZATION OF VARIOUS VARIABLES OF FAST DISINTEGRATING TABLETS OF NISOLDIPINE

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ABSTRACT

Solubility and dissolution of a poorly water-soluble drug are the two major barriers for formulation scientists in the development of a successful drug delivery system. Many of the potent drugs do not show the therapeutic effects due to solubility issues but may show toxicity issues when used in high doses. Many techniques and technologies have been used in the past to solve the problems related to poor solubility. Out of all these, Solid dispersion (SD) technology is an excellent tool for enhancing the solubility and dissolution of a drug, which in turns improves the bioavailability. It is defined as the dispersion of one or more active ingredients in an inert carrier at solid state. When the solid dispersion comes in contact with the aqueous medium, the inert carrier dissolves and the drug is released, the increased surface area produces a higher dissolution rate thus increasing the bioavailability of the poorly soluble drug. The aim of the present study was to improve the solubility and dissolution rate of Nisoldipine (N) by formulating a solid dispersion with Polyvinyl pyrollidone (PVP-K30) and Guar gum. Central composite design (CCD) was employed using Design Expert software version 12 to prepare optimized fast disintegrating tablets of Nisoldipine.

INTRODUCTION

Poor drug solubility is the main obstacle in the research and development of a new dosage form designs. Formulation scientist has a major challenge in the formulation of dosage forms of poorly water soluble drugs [1]. Solid dispersion technologies enhance the solubility and dissolution of drugs and thereby improve the oral bioavailability of poorly water soluble drugs [2]. Solid dispersions are molecular dispersions of drug in the carriers and they are formulated by different methods in which drug Is obtained as fine particles by dissolving the carriers in an aqueous fluid [3]. It is a simple and flexible formulation process using various polymers, which in turn enhances the overall bioavailability of the drug [4]. Nisoldipine (N) is a BCS-class II drug with high permeability and low solubility. Chemically it is a 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth

muscle cells, nisoldipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction [5-9]. So improvement of the drug bioavailability and therapeutic efficacy is a crucial parameter which can only be achieved by increasing the solubility of this drug. The aim of the present research work is to increase the solubility and dissolution rate of Nisoldipine by forming solid dispersions using polymers PVP K-30 and Guar Gum in different ratios, and also employing two different methods for their preparation. Then work had been undertaken to optimize the fast disintegrating tablets using central composite design [10-14].

MATERIALS AND METHODS

Materials: Nisoldipine was received as a free gift sample from Torrent Pharmaceutical Pvt. Limited, Baddi, Himachal Pradesh, India. Polyvinyl pyrollidone (PVP-K30) and Guar Gum was purchased from local vendor. Other materials used were of analytical grade [15].

Solubility study

Solubility studies of Nisoldipine was checked in water, phosphate buffer pH 6.8 and HCl buffer pH 1.2. The saturated solutions were prepared by adding excess drug in the solvent system. The solvent system was shaken for 48 hrs at 25ºC. Filtered the solutions through a 0.42 Millipore filter. Samples were analysed by UV spectrophotometer at 237 nm. The solubility data is reported in table 1 [16].

Preparation of solid dispersion: In the present study solid dispersions were prepared with two different methods, Solvent Evaporation Method and Kneading Method using two polymers (PVPK-30 and Guar Gum) in order to study the effect of individual method or polymer on the final formulation.

Solvent Evaporation Method: Drug was mixed with PVPK-30(NP1 to NP4) and Guar Gum(NG1 to NG4) in the ratios of 1:1 to 1:4. The polymers were dissolved separately in an adequate amount of methanol. The solvent was then rapidly evaporated with the aid of mild heat (up to about 50 ℃) and surface airflow with constant vigorous stirring to form a uniform solid mass. The co-precipitate was crushed , sized into different sieve fractions and stored in a desiccators, until further use [17,18].

Kneading Method: A mixture of drug and polymer PVP-K30(NP5 to NP8) and Guar gum(NG5 to NG8) was wetted with water and kneaded thoroughly for 30 min in a glass mortar. The paste formed was dried under vacuum for 24 hrs. Dried powder was passed through #60.

Evaluation of Solid dispersions:

Solubility studies: The solubility study of various Solid dispersions batches was determined in phosphate buffer pH 6.8. Weighed amount of solid dispersion equivalent to drug dose was added in excess quantity of solvent in screw-capped glass vials. The vials were continuously shaken for 2 hrs. Finally the solutions were filtered and analysed spectrophotometrically at 237 nm.

Infra red Spectral analysis: In FTIR study, the characteristic peak of Nisoldipine has appeared in the spectra of pure drug without any remarkable change in the position. It was confirmed that there was no chemical interaction between the drug and polymer. The FTIR spectra of solid dispersion batch NP3 displayed same characteristic peaks which also reveals that the drug and excipients used in the formulation are stable and posses no interaction [19,20].

Differential scanning calorimetry : The differential scanning calorimetry experiment was performed on the drug and the solid dispersion batch NP3. The samples were analyzed by DSC analyzer. The DSC thermogram of pure nisoldipine showed a sharp endothermic peak at 141.32℃, which was ascribed to drug melting. DSC thermograph of NP3 is shown in Figure 4 which shows no peak i.e. melting point and amorphous state of drug. Disappearance of the drug melting peak confirmed that amorphization had occurred [21,22].

Scanning electron microscopy: The drug and solid dispersion batch NP3 were examined for surface changes using scanning electron microscope as shown in figure 5 and figure 6 respectively. Finally surface topography was studied [23].

Experimental Design: Central composite design (CCD) was employed using Design Expert software version 12 to prepare fast disintegrating tablets of Nisoldipine. The independent variables selected were croscarmellose i.e. X1 (in the range of 0.59-

3.41% w/w) and crospovidone i.e. X2, (in the range of 0.59-3.41% w/w). The response variables studied were friability and disintegration time. Response surface methodology was adopted to study relationship between dependent and independent variables. Composition of all the nine formulations as designed by design expert software are summarized in table 3 [24,25].

Optimization of formulation variables

The optimization of tablet components was done to target the disintegration time and % friability of 30 s and 0.49%, respectively. The optimized amount determined with the help of software is depicted in surface response curves as shown in figure 7.

Formulation of Optimized Fast Disintegrating Tablet:

The tablets were prepared by direct compression method. Solid dispersion batch NP3 equivalent to 17 mg was weighed and added to the fast disintegrating tablet batch.

Evaluation of Optimized Fast Disintegrating Tablet:

Various parameter like weight, hardness, friability, wetting time, disintegration time and drug content were evaluated as shown in table .

Weight variation

Average weight of 20 tablets was determined and then the individual tablet weight was compared with average weight as shown in table 7.

Friability

The tablets were weighed (Winitial) and placed in friabilator (Biolinkz, India). The apparatus was operated at 25 rpm for 4 minutes. Finally the tablets were dedusted and weighed again (Wfinal). The data is reported in table 7.

$$F = \frac{W_{initial} - W_{final}}{W_{final}} \times 100 \quad (5)$$

Hardness

Pfizer Hardness tester was used to check the hardness expressed in kg/cm^2. The data is shown in table 7.

Wetting time

For the determination of wetting time, tissue paper was soaked with 10 ml of water. Tablet was kept over the wet surface and noted down the time required for water to reach at the top of the tablet. The data is reported in table 7.

Disintegration Test

The Disintegration test apparatus was used to calculate the disintegration time and data is reported in table 7.

Determination of drug content

Ten tablets were powdered and the blend equivalent to 17 mg of Nisoldipine was weighed and dissolved in phosphate buffer pH 6.8. The solution was then filtered, diluted and drug content was determined by spectrophotometer at 237 nm [26-28]. The data is recorded in table 7.

***In-vitro* dissolution study**

Dissolution studies were conducted in a beaker having 30 ml phosphate buffer pH 6.8 which was maintained at 37 ± 0.50°C. The assembly was placed on a magnetic stirrer and samples were drawn at appropriate time periods with replacement. The aliquots were filtered, diluted and analyzed by spectrophotometerically at 237nm [29-30].

DISCUSSION

During the preparation of solid dispersions, selection of an appropriate method or polymer has significant effect on the formulation. So, in the present study solid dispersions were prepared with different methods and polymers in order to determine the effect of individual method or polymer on the final formulation. PVP-K30 and Guar Gum were used as natural and synthetic polymers, respectively and their effect on solubility enhancement by formation of solid dispersions was checked. The solubility results are reported in table 1. Solid dispersions were prepared in different drug to polymer ratios ranging from 1:1 to 1:4 using Guar Gum and PVP-K30 as carriers. The data is given in table: 2. Solubility studies data revealed that PVP-K30 polymer increased the drug solubility to a greater extend than the Guar Gum polymer. Based on the solubility results, NP3 batch prepared with Solvent Evaporation Method with PVP-K30 as carrier has shown highest solubility of 418 µg /ml. On further increasing the drug carrier ratio upto 1:4 solubility increased to a non significant level. So, 1:3 drug carrier ratio was selected for further studies.

Table 1. Solubility of Nisoldipine in various solvents

Solvents	Solubility (µg/ml)
Water	9.11±0.048
Phosphate buffer pH 6.8	1.97±0.082
0.1 N HCl	31.32±0.078

Table 2. Solubility data of solid dispersion batches

Polymer	Drug:Polymer Ratio	Formulation Batch	Method used	Solubility (µg/ml)
PVP-K30	1:1	NP1	Solvent Evaporation Method	198
	1:2	NP2	Solvent Evaporation Method	307
	1:3	NP3	Solvent Evaporation Method	418
	1:4	NP4	Solvent Evaporation Method	436
	1:1	NP5	Kneading Method	149
	1:2	NP6	Kneading Method	268
	1:3	NP7	Kneading Method	371
	1:4	NP8	Kneading Method	391
Guar Gum	1:1	NG1	Solvent Evaporation Method	147
	1:2	NG2	Solvent Evaporation Method	233
	1:3	NG3	Solvent Evaporation Method	345
	1:4	NG4	Solvent Evaporation Method	359
	1:1	NG5	Kneading Method	117
	1:2	NG6	Kneading Method	208
	1:3	NG7	Kneading Method	319
	1:4	NG8	Kneading Method	342

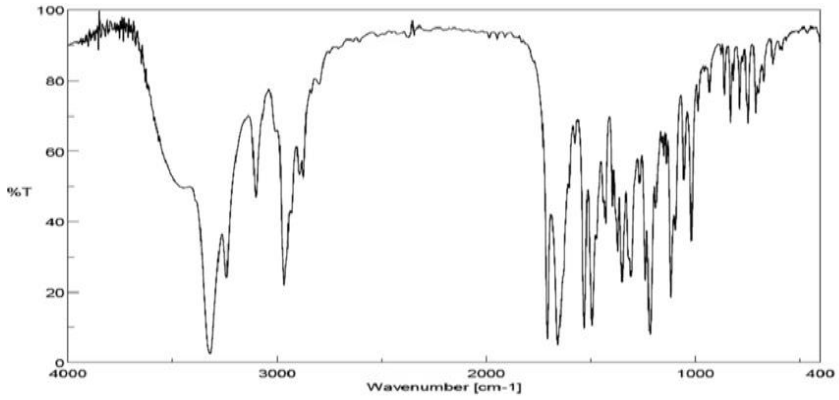

Figure 1. FTIR Spectra of Nisoldipine

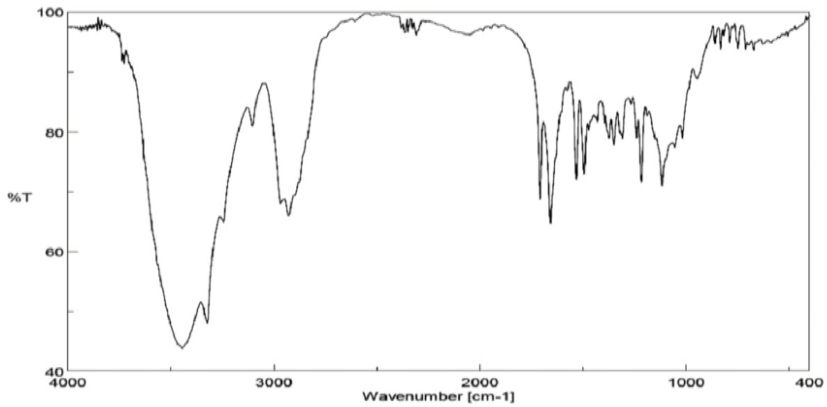

Figure 2. FTIR Spectra of batch NP3

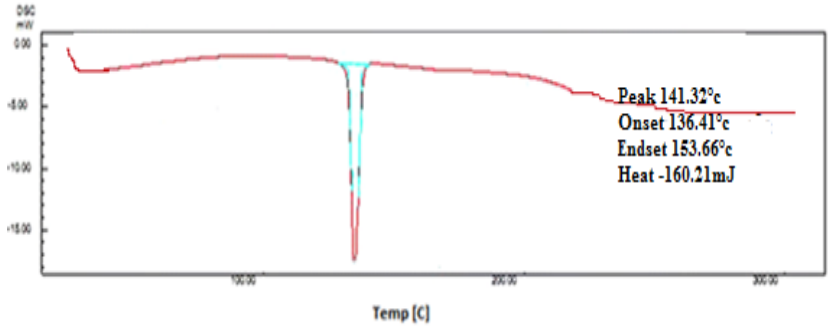

Figure 3. DSC of Nisoldipine

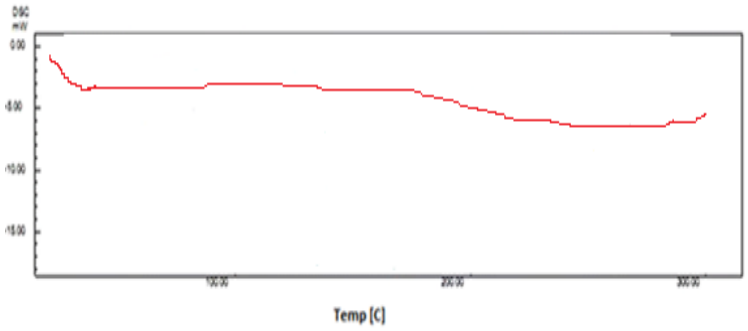

Figure 4. DSC of Solid Dispersion batch NP3

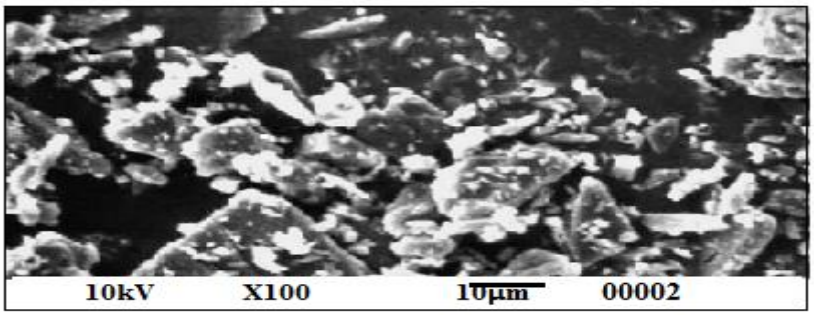

Figure 5. SEM image of the Nisoldipine

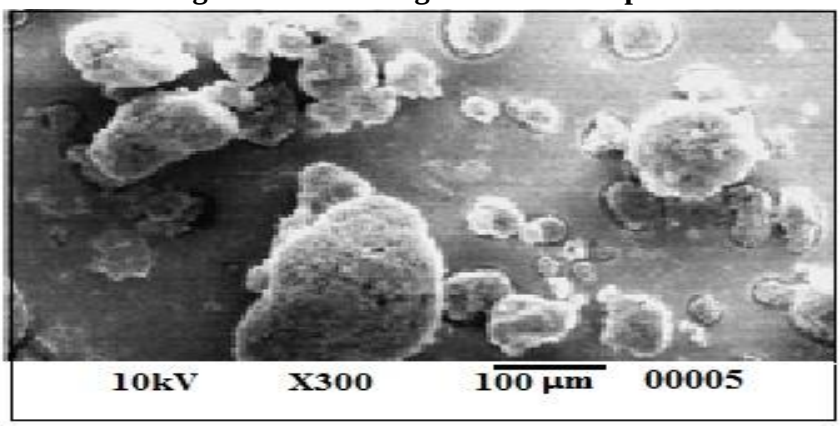

Figure 6. SEM image of Solid dispersion batch NP-3

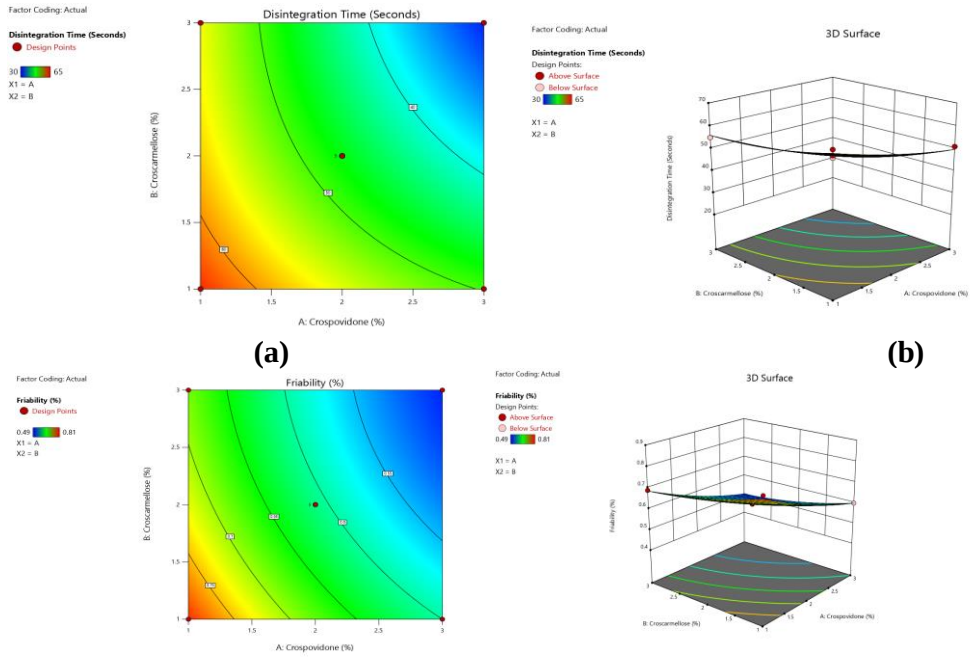

Figure 7. Images of contour plots (a,c) and three dimensional surface response plots (b,d) showing the effect of croscarmellose and crospovidone on the disintegration time and friability of Fast Disintegrating Tablets.

Table 3. Central composite design with two factors, nine runs

Formulation Code	Factor 1 Crospovidone(%)	Factor 2 Croscarmellose(%)	Response 1 Disintegration Time(Secs)	Response 2 Friability (%)
NFDT1	2	0.585786	58	0.71
NFDT2	2	2	47	0.61
NFDT3	3	3	30	0.49
NFDT4	0.585786	2	63	0.77
NFDT5	1	1	65	0.81
NFDT6	1	3	55	0.69
NFDT7	3	1	51	0.6
NFDT8	3.41421	2	36	0.52
NFDT9	2	3.41421	43	0.58

Table 4. Results of ANOVA for Disintegration Time

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1146.74	5	229.35	131.80	< 0.0001	significant
A-Crospovidone	744.67	1	744.67	427.94	< 0.0001	
B-Croscarmellose	340.78	1	340.78	195.83	< 0.0001	
AB	30.25	1	30.25	17.38	0.0042	
A^2	11.98	1	11.98	6.89	0.0342	
B^2	22.85	1	22.85	13.13	0.0085	
Residual	12.18	7	1.74			
Lack of Fit	12.18	3	4.06			
Pure Error	0.0000	4	0.0000			
Cor Total	1158.92	12				

Table 5. Results of ANOVA for friability

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	0.0984	5	0.0197	203.38	< 0.0001	significant
A-Crospovidone	0.0729	1	0.0729	753.49	< 0.0001	
B-Croscarmellose	0.0214	1	0.0214	221.35	< 0.0001	
AB	0.0000	1	0.0000	0.2585	0.6268	
A^2	0.0023	1	0.0023	23.63	0.0018	
B^2	0.0023	1	0.0023	23.63	0.0018	
Residual	0.0007	7	0.0001			
Lack of Fit	0.0007	3	0.0002			
Pure Error	0.0000	4	0.0000			
Cor Total	0.0990	12				

Table 6. Composition of Optimized Fast Disintegrating Tablet

Ingredients	Amount(mg)
Nisoldipine SD (NP3)equivalent to 17 mg	58
Crospovidone	4.5
Croscarmellose	4.5
Avicel pH 102	qs 150
Magnesium stearate	3
Talc	3
Total weight	150

Table 7. Evaluation of Optimized NFDT

Parameters	Optimized NFDT
Weight (mg)	150.54±1.65
Hardness (kg/sq.cm.)	2.5±0.63
Friability (%)	0.49±0.76
Wetting time (sec)	19±1.23
Disintegration time (sec)	30±0.43
Drug content (%)	98.43±0.87

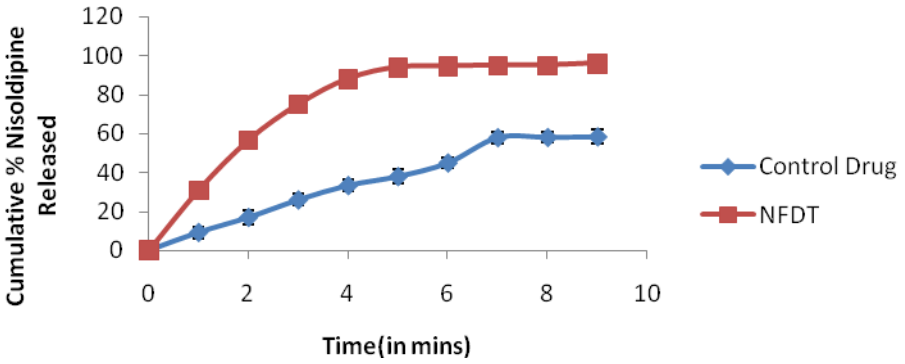

Figure 8. *In vitro* drug release data of NFDT

The FTIR spectra of pure drug and solid dispersion batch NP3 displayed same characteristic peaks and revealed no chemical interaction between the drug and excipients as depicted in figure 1 and figure 2 respectively. Thermograms of drug and batch NP3 are depicted in figure 3 and figure 4 respectively**.** DSC reports also revealed that the disappearance of the drug melting peak is a result of amorphization as shown in figure 6. The reduction in drug peak height and its broadening can be considered as a result of the change in the crystalline state to amorphous one. SEM photographs are shown in figure 5 and figure 6. Central composite design (CCD) was employed using Design Expert software version 12 to check the effects of independent variables on formulation properties of Fast Disintegrating Tablets. Response surface methodology was adopted to study relationship between dependent and independent variables.The formulations (n=9) were designed by design expert having two independent variables, croscarmellose and crospovidone concentration respectively. The response variables studied were friability and disintegration time Adequacy and good fit of the models were tested using analysis of variance (ANOVA). Mathematical relationship generated for the studied response variables were expressed as equations for Disintegration time (X) and wetting time (Y).

The following equations were generated when disintegration time was correlated with independent variables (A and B).

$X = 47 - 9.65A - 6.53B - 2.75AB + 1.31A^2 + 1.81B^2$ (1)

($R^2 = 0.98$, Quadratic model).

The equation generated that correlates friability with independent variables (A and B) is:

$X = 0.61 – 0.09A – 0.05B + 0.00AB + 0.01A^2 + 0.01B^2$ (2)

Both coefficients A and B bear a negative sign as shown in equation 1, which indicate that on increasing the concentration of either superdisintegrant, crospovidone or croscarmellose, disintegration time decreases. This is due to the fact that the higher percentage of superdisintegrat induces higher porosity facilitating higher water uptake which lead to reduced disintegration time. From equation 2, it is again evident that on increasing the concentration of either superdisintegrants, the friability also decreases and mechanically strong tablets were produced . RSM plots were constructed using design expert to study the interaction between independent and dependent variables. The combined effect of croscarmellose and crospovidone on friability and disintegration time can be seen in figure 7. It is suggested that crospovidone and croscarmellose produced a combined effect of improving disintegration and dissolution. Both the disintegrants work well through swelling and capillary action. The optimized Nisoldipine fast disintegrating tablet NFDT was formulated as shown in table 6. Weight of the tablet batch NFDT was 150.54±1.65 mg. Friability was reported to be 0.49%±0.76 and hardness of 2.5±0.63 kg/cm^2. The accreditation for fast wet ability and disintegration could be assigned to the capillary action mechanism of the superdisintegrant which leads to fast puffiness of the dosage form. The drug content was found to be 98.43±0.87% w. The wetting time and disintegration time was 19±1.23 and 30±1.43 secs respectively. This may be credited to the brisk dissolution of the tablet, which is due to the usage of super disintegrant and carrier all together.

CONCLUSION

The above carried research work revealed that the solid dispersion technique could be a lucrative way for solubility enhancement of Nisoldipine, using Poly vinyl pyrollidone (PVP K-30) and guar gum as carriers. From the preliminary screening for polymers, PVPK30 was selected for the further formulation studies. Finally, Nisoldipine Fast Disintegrating Tablets were successfully prepared applying central composite design with the most appropriate combination of crosscarmellose and crospovidone as super disintegrants. Batch NFDT was formulated with maximum 96.1±3.65 % drug release within 10 min. At last, it was summarised that fast disintegrating tablet formulation can be an innovative and promising approach for the delivery of Nisoldipine with enhanced dissolution and bioavailability, and also as an effective therapy for the treatment of hypertension.

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Conflict of Interest: The authors declare no conflict of interest.

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