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Formulation and Evaluation of Fast Disintegrating Tables of Nifedipine by QbD Approach

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ABSTRACT

Fast dissolving tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva. Nifedipine is a calcium channel blocker which is used as an antianginal and antihypertensive drug. The aim of this study was to improve the solubility of Nifedipine by solid dispersion technique and increasing its disintegration time by formulation of fast dissolving tablets by Direct Compression method using QbD approach, and various ratios of Cross povidone and Cross Carmellose Sodium as superdisintegrants. The solid dispersions of Nifedipine were formulated with five different polymers as Polyvinylpyrrolidone K 30(PVP k30), Polyethyleneglycol (PEG) 4000, Polyethyleneglycol (PEG) 6000, Urea and Mannitol. The solid dispersions were prepared in five different ratios by solvent evaporation method. The solid dispersion giving the maximum solubility was formulated into fast dissolving tablets using various ratios of cross povidone and cross carmellose sodium (ccs) as superdisintegrants. Tablets pre compression parameters e.g. angle of repose, bulk density, tapped density, Carr's compressibility index and Hauser's ratio and post compression parameters like drug content uniformity, hardness, wetting time, friability, thickness, disintegration time & In vitro dissolution were evaluated for each formulation and found satisfactory. A 23 full factorial design was applied to investigate the combine effect of 3 formulation variables: concentration of cross povidone, concentration of cross carmellose sodium and concentration of microcrystalline cellulose. Here the concentration of cross povidone, concentration of cross carmellose sodium and concentration of microcrystalline cellulose were taken as independent variable X1, X2 & X3 respectively; with their effect of disintegration time was studied as dependent parameter. To represent the data Design Expert software 9 was used.

1. INTRODUCTION

Quality should be built in by design, it cannot be tested in a product, is the main motto of 'Total Quality Management'. To achieve this goal of optimized quality product, the knowledge gained from pharmaceutical development studies and manufacturing provides the scientific background. Although it is based on risks, but it has its fruits that it minimizes the end product testing and increases the chances of regulatory acceptance. Quality by design (QbD) was first proposed by a well known researcher Joseph Moses Juran. Later it has been accepted by ICH, US-FDA and other regulatory bodies. The principles of QbD is best explained by ICH Q8, ICH Q9 & ICH Q10, which gives the guidelines on Science & Risk-based assessment, product's life cycle and its approach, and the various method designs. The method optimization was earlier based on One Factor at a Time (OFAT) approach/ Traditional quality by testing (QbT) approach (Bhoop Bhupinder Singh et al., 2013) where a single component was varied with time and its effect studied. The traditional quality by testing (QbT) approach tests product quality by checking it against the approved regulatory specifications at the end of manufacturing stream at great effort and cost. There is a great deal of unpredictability in scaling up a product from research and development to production scale, and reasons for failure are generally not understood. QbD is a major shift from the traditional approach of QbT in ensuring quality control of products across the manufacturing stream. QbD principles promote innovation and continuous improvement of the product. Knowledge-based commercial manufacturing ensures enough regulatory flexibility for setting specifications and post-approval changes. Product and process are designed using innovative risk-based techniques to meet predefined quality objectives thereby satisfying the most critical patient needs and regulatory requirements at low cost (Peter Devies et al. 2009, Debjit Bhowmik et al. 2009,Velmurugan S.et al 2010).

Formal Experimental Design or DOE is defined as "a structured analysis wherein inputs are changed and differences or variations in outputs are measured to determine the magnitude of the effect of each of the inputs or combination of inputs." Factorial designs allow for the simultaneous study of the effects that several factors like concentration of super disintegrants and diluents concentration may have on the physical characteristics of the tablets. There are several advantages to statistically designed experiments, and when compared with other test methods, the results are striking[4]. (Bharat Parashar et al 2012, Sangshetti Jaiprakash *et al*., 2014)

This approach was not much helpful as it neglected the effect caused due to interaction of more than one factors. Now a day, the approach followed is Quality by Design (QbD) which employs Design of Experiments (DoE) as important concept. DoE approach is a systematic, scientifically analysed better understandable approach. (ICH, 2009 and Sangshetti Jaiprakash et al., 2014).

The aim and objective of the present study is to develop and evaluate FDT of Nifedipine and enhance the onset of action of Nifedipine and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Nifedipine as model drug which is used in the treatment of the hypertension. The study was intended to select the best possible diluents, combination of semi synthetic & natural superdisintegrants to formulate the dispersible tablets among all the diluents and disintegrants used. Finally the impact of the diluents ratio and superdisintegrants on various properties of the tablet were also determined.

2. MATERIALS AND METHODS

2.1. Materials:

Table No. 1: Material and their use with source

Sr. No.	***Material***	***Category***	***Source***
1	Nifedipine	API	Dr. Reddy's Lab., Hyderabad.
2	Mannitol	Carrier	Research-Lab Fine Chem. Industry, Mumbai.
3	PVP K30	Polymer	
4	PEG 4000	Polymer	
5	PEG 6000	Polymer	
6	Urea	Carrier	
7	Crospovidone	Superdisintegrant	
8	CCS	Superdisintegrant	
9	MCC	Diluent, Superdisintegrant	
10	Lactose	Diluent	
11	Talc	Glidant	
12	Mg. Striate	Lubricant	
13	Citric acid	Stabilizer	
14	Sucrose	Sweetening agent	

Preparation of fast dissolving tablets by direct compression technique:

2.2. Method: Fast dissolving tablets of Nifedipine were prepared by direct compression method according to the formula.

Table No. 2: Formulations from F1 to F8

Ingredients	***Quantity in 'mg'***							
	F1	***F2***	***F3***	***F4***	***F5***	***F6***	***F7***	***F8***
Nifedipine	60	60	60	60	60	60	60	60
CP	7	14	7	14	7	14	7	14
CCS	7	7	14	14	7	7	14	14
MCC	70	70	70	70	100	100	100	100
Lactose	45	38	38	31	15	8	8	1
Talc	3	3	3	3	3	3	3	3
Mg sterate	2	2	2	2	2	2	2	2
Citric acid	2	2	2	2	2	2	2	2
Sucrose	4	4	4	4	4	4	4	4

All the ingredients were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed with 7 mm sizes flat round punch to get tablet using Rimek Compression Machine.

Design of Experiment:

Table No. 3. Design of Experiment

3 factors	2 Levels	
	-1	+1
Conc. of CP	7	14
Conc. of CCS	7	14
Conc. of MCC	70	100

3. RESULTS AND DISCUSSION

3.1. API Characterization:

3.1.1. Melting Point:

Melting point of Nifedipine by capillary method was found to be 223-226˚C

3.1.2. Solubility:

The solubility of Nifedipine was checked in different solvents which are shown in following table.

Table No. 4: solubility of Nifedipine in different solvents

S.No	Solvents	Solubility(mg/ml)
1	Water	0.001
2	Acetone	302.7
3	Ethanol	13.81
4	Chloroform	81.6
5	Methanol	32
6	0.1N HCL	0.025
7	Phosphate Buffer pH6.8	0.012

3.2. UV-Visible spectrophotometric study:

3.2.1. λ max determination

The UV spectrum of Nifedipine in 0.1 N HCl scanned in the range of 400-210 nm. The spectrum indicated that the observed λ max of Nifedipine was 237.5 nm which is matched with pharmacopoeial value.

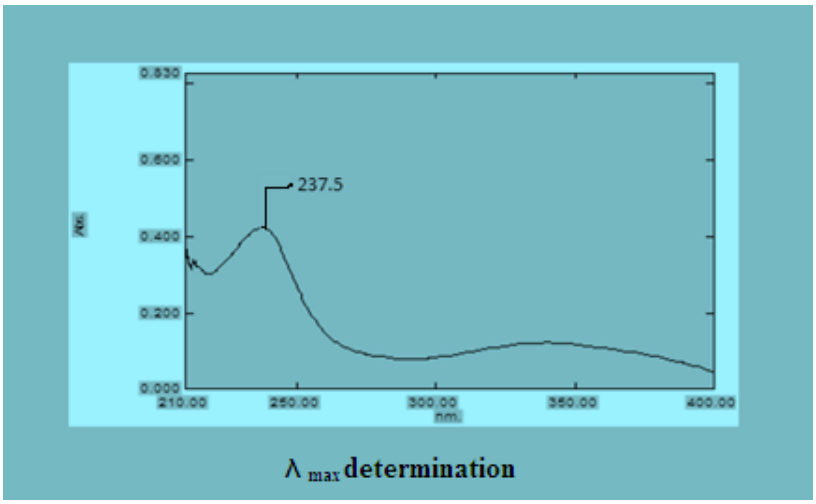

Figure No. 1: UV Spectra of Nifedipine

3.2.2. Preparation of standard calibration curve of Nifedipine

Nifedipine showed maximum absorption at wavelength 226 nm in 0.1 N HCl. Standard curve was plotted by taking absorption of diluted stock solutions (2, 4, 6, 8,10 µg/ml) at wavelength at 237.5 nm.

Table No. 5: Readings of Standard calibration curve of Nifedipine in 0.1 N HCL

Sr. No.	Concentration (µg/ml)	Absorbance at 237.5 nm
1	0	0
2	2	0.215
3	4	0.399
4	6	0.580
5	8	0.739
6	10	0.915

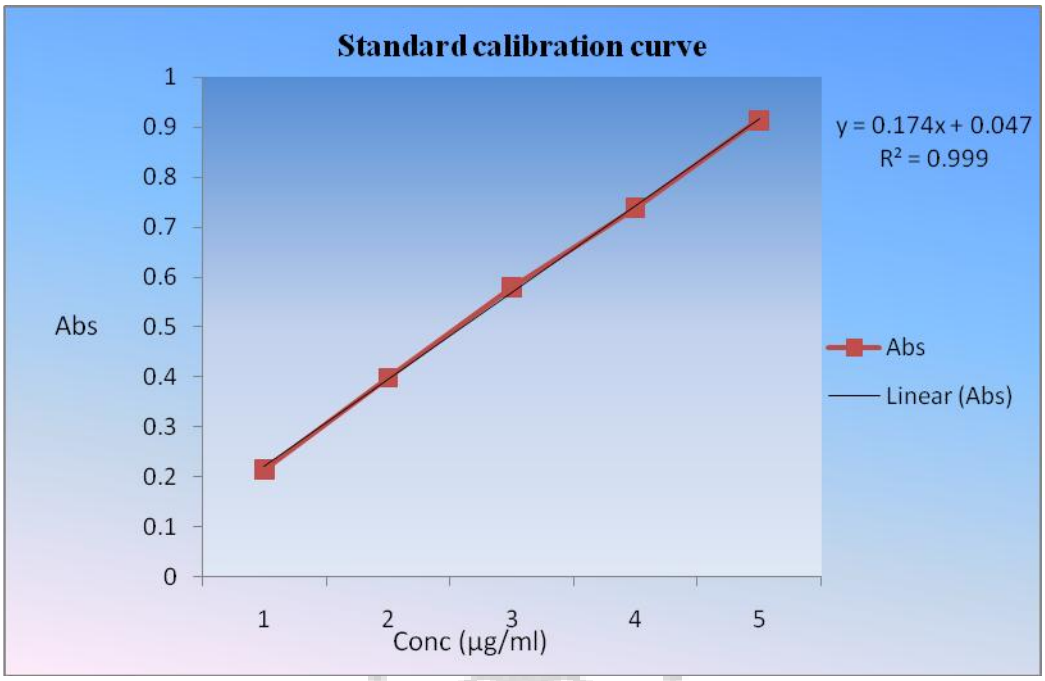

Figure No. 2: Standard curve of Nifedipine in 0.1 N HCL (pH 1.2)

3.3. *Post compression parameter study:* [83, 84]

3.3.1. Thickness:

The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm. (Lachman *et al*, 1991)

3.3.2. Hardness:

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted (Lachman *et al*, 1991).

3.3.3. Friability:

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of

shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre weighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated as follows (Lachman *et al*, 1991)**.**

$$\% F = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

3.3.4. Weight variation test:

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. (Indian pharmacopoeia, 1996)

Table No. 6: Specifications for tablets as per Pharmacopoeia of India

Sr. No.	*Average Weight of Tablet*	*% Deviation*
1	80 mg or less	10
2	More than 80 mg but less that 250 mg	7.5
3	250 or more	5

3.3.5. Uniformity of drug content:

Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 50 mg of Nifedipine was weighed and dissolved in 100 ml of 0.1N HCl (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N HCl. The absorbance was measured at wavelength 237.5 nm using double beam UV-Visible spectrophotometer. Content uniformity was calculated using formula.

% Purity = 10 C (Au / As) -------Equation VII

Where, C - Concentration,

Au and As - Absorbance's obtained from unknown preparation and standard Preparation respectively.

3.3.6. Wetting time:

The method was applied to measure tablet wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 10 ml of water, a tablet was placed on the paper, and the time for complete wetting was measured. Three trials for each batch were performed and standard deviation was also determined.

3.3.7. In vitro disintegration time:

The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. I.P. Specifications: Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C as the immersion liquid. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded.

3.3.8. In vitro dissolution studies:

Dissolution rate was studied by using USP type-II apparatus (50 rpm) using 900ml of 0.1 N HCL as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5°C, aliquot of dissolution medium was withdrawn at every 5 min interval and filtered. The absorbance of filtered solution was measured by UV spectrophotometric method at 237.5 nm and concentration of the drug was determined from standard calibration curve.

In vitro drug release studies details:

- ✓ Apparatus used : USP XXIII dissolution test apparatus
- ✓ Dissolution medium : 0.1 N HCL
- ✓ Dissolution medium volume : 900 ml
- ✓ Temperature : 37 ± 0.5°C
- ✓ Speed of basket paddle : 50 rpm
- ✓ Sampling intervals : 5 min
- ✓ Sample withdraw : 10 ml
- ✓ Absorbance measured : 237.5 nm

Infrared Spectroscopy:

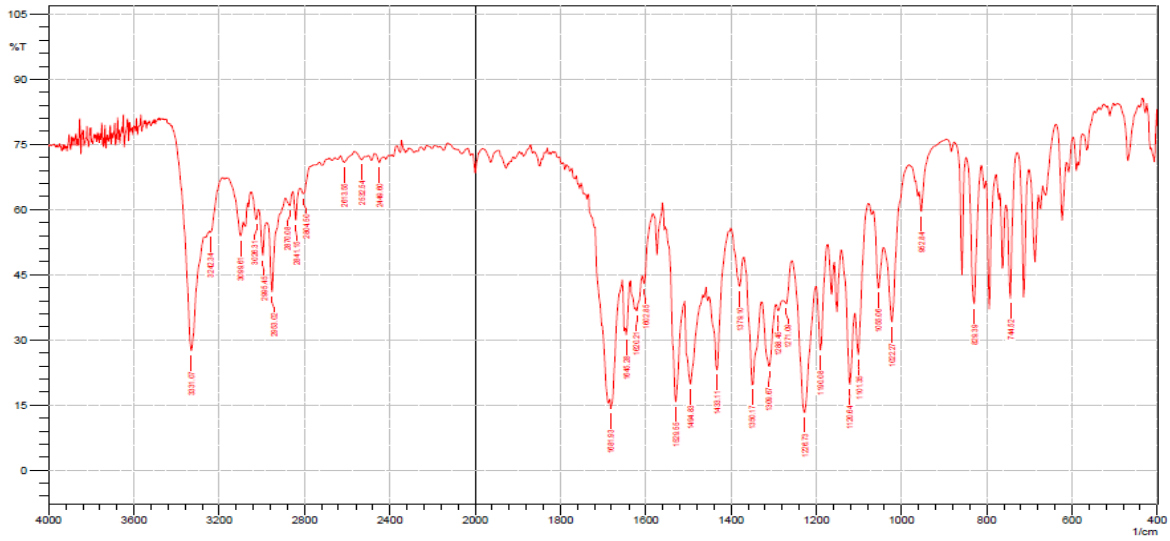

Figure No. 3: FT-IR Spectrum of Nifedipine

Table No. 7: Interpretation of FT-IR of Nifedipine

Peak(cm-1)	Chemical group
2953, 2995	C-H stretching of Methyl
3331	N-H stretching of Amine
829	C-H stretching of penta substitution of Benzene
1529, 1350, 1379	C–O stretching of COOCH3
1681, 1645, 1620	N-O stretching of NO2
744	C-H stretching disubstitution of Benzene
1309	C-N stretching of Aromatic amine

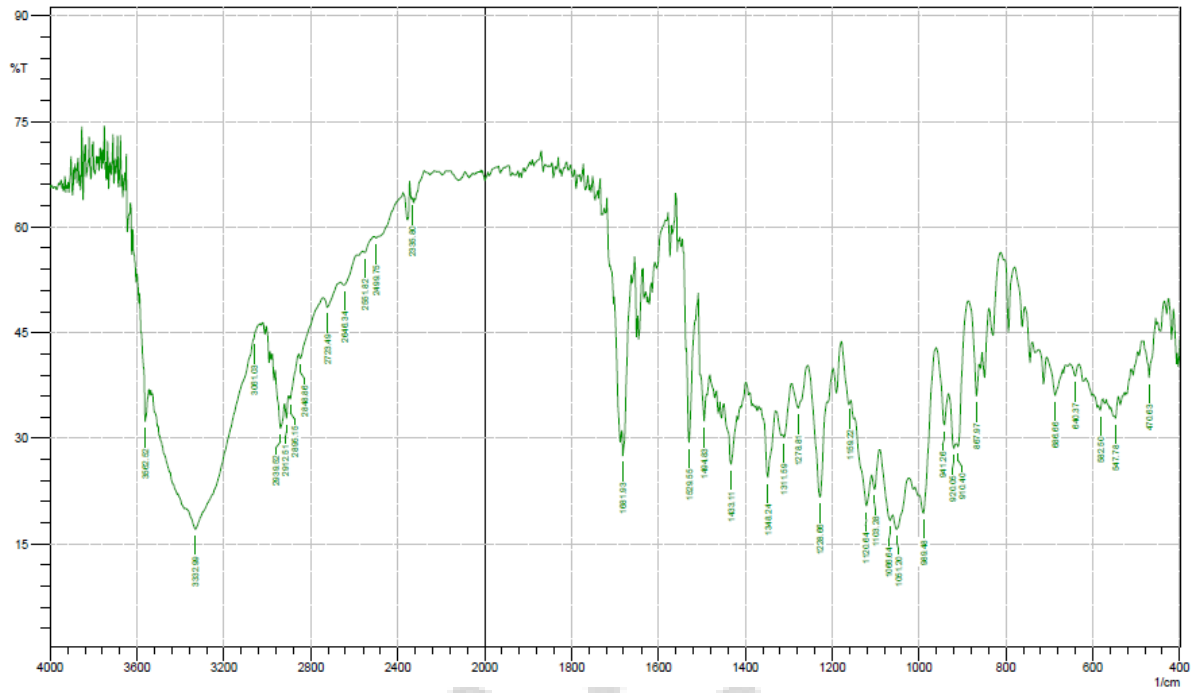

Figure No. 4: FT-IR Spectrum of Solid Dispersion of Nifedipine: PEG 4000

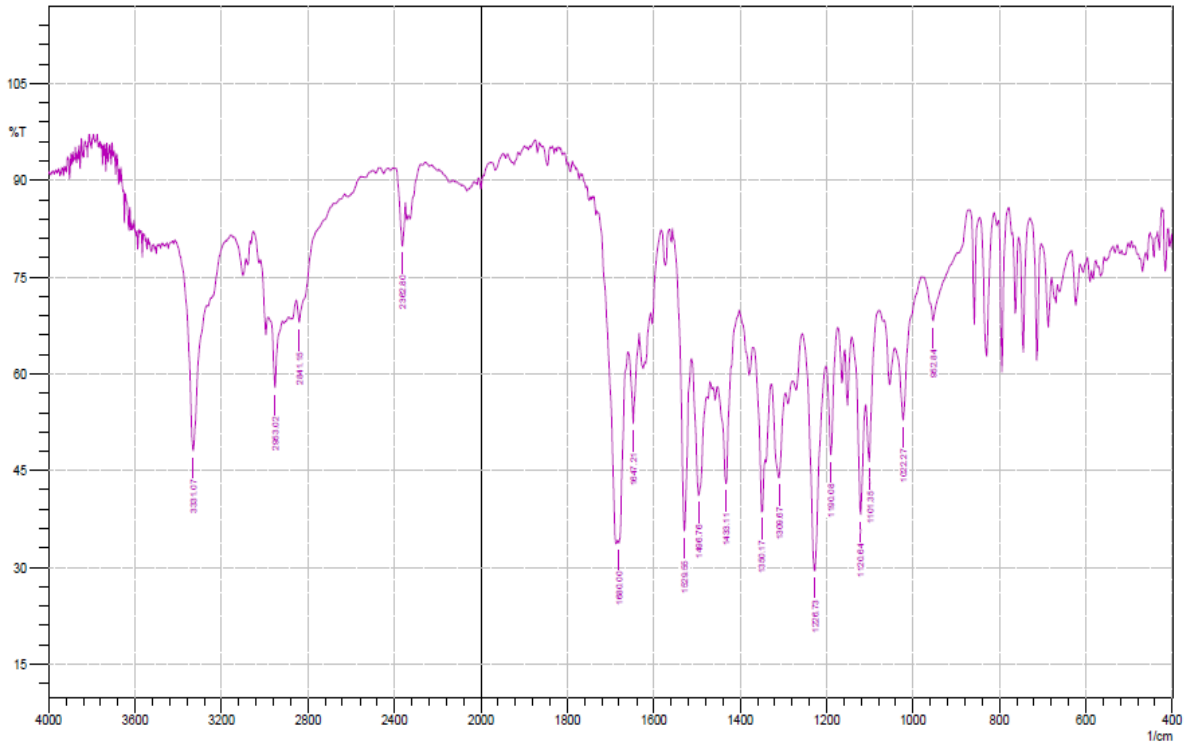

Figure No. 5: FT-IR Spectrum Drug and Crospovidone

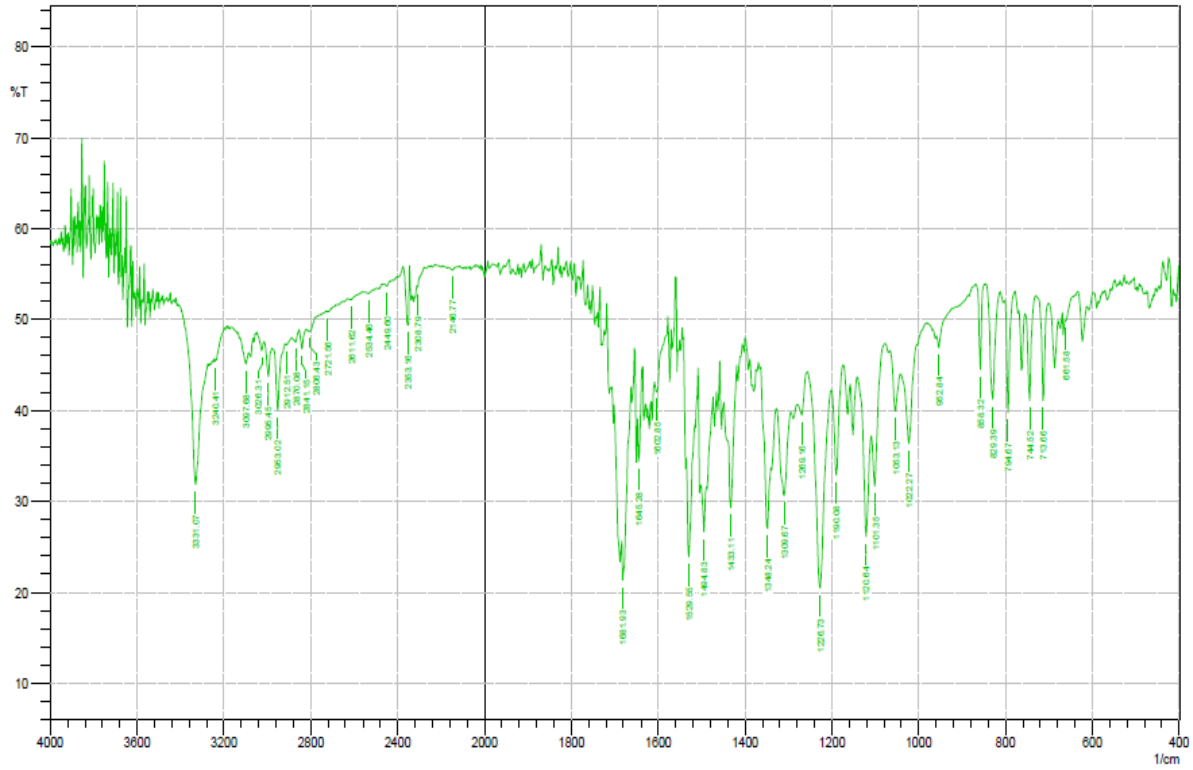

Figure No. 6: FT-IR Spectrum Drug and CCS

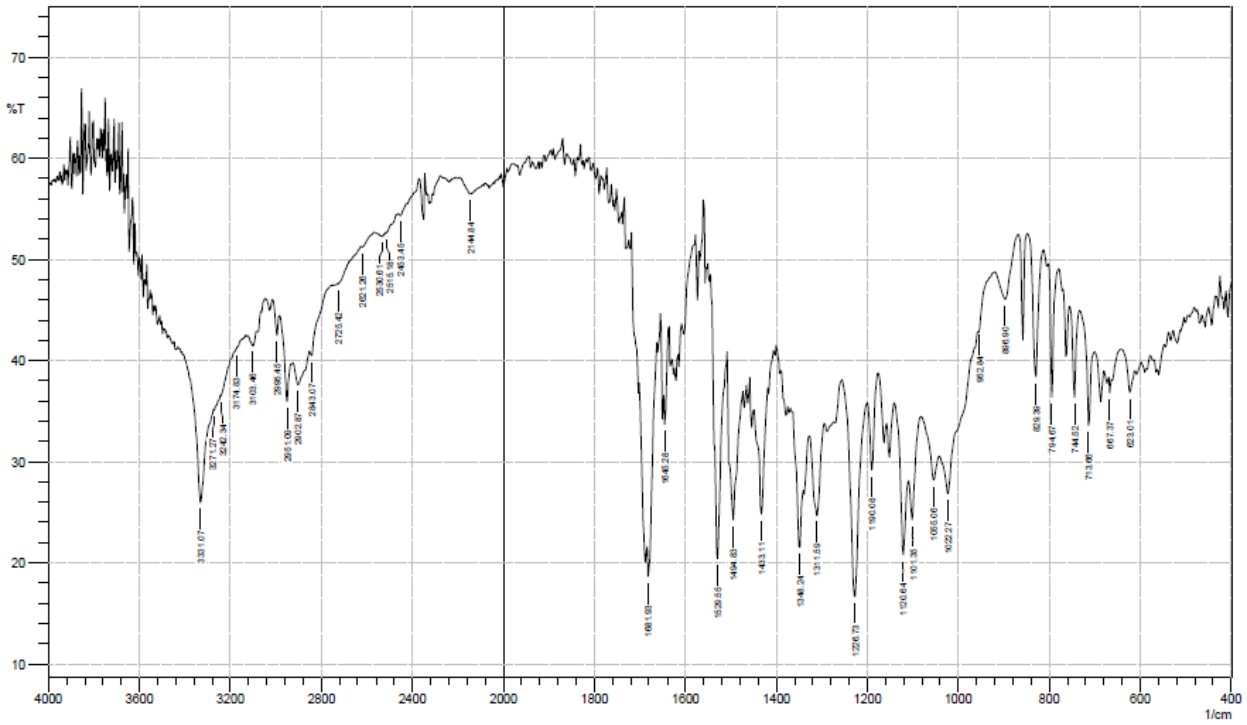

Figure No. 7: FT-IR Spectrum Drug and MCC

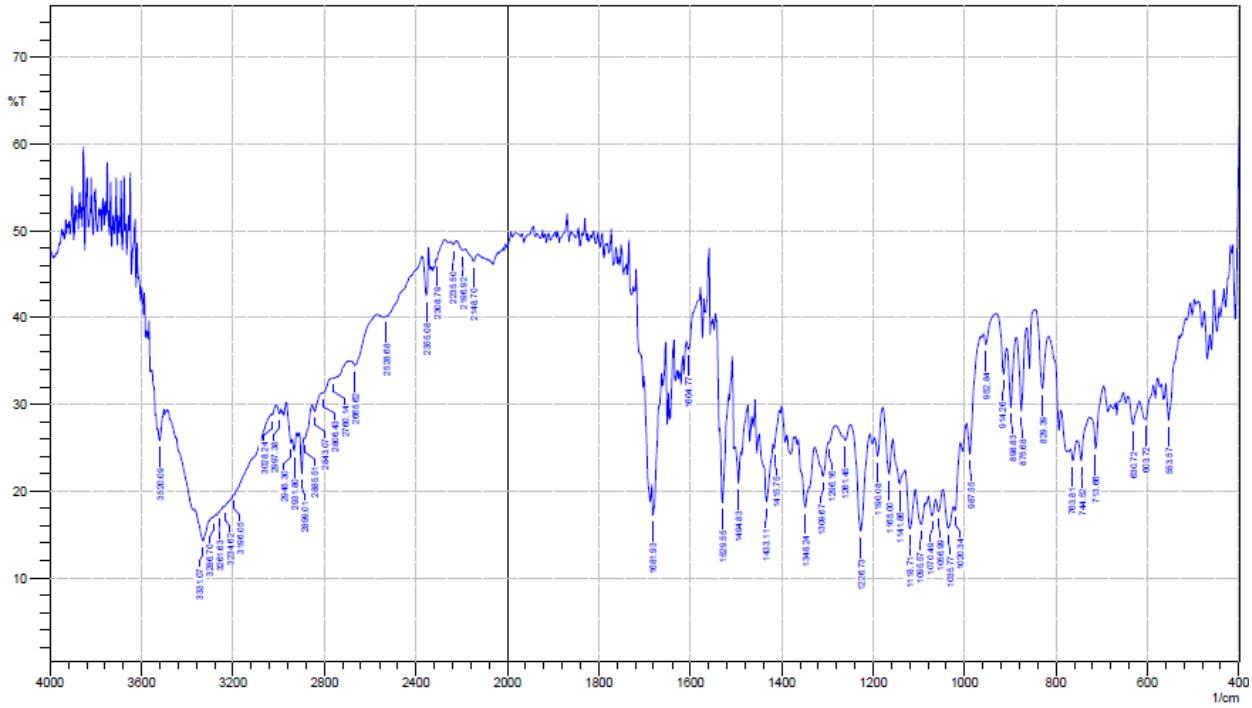

Figure No. 8: FT-IR Spectrum Drug and Lactose

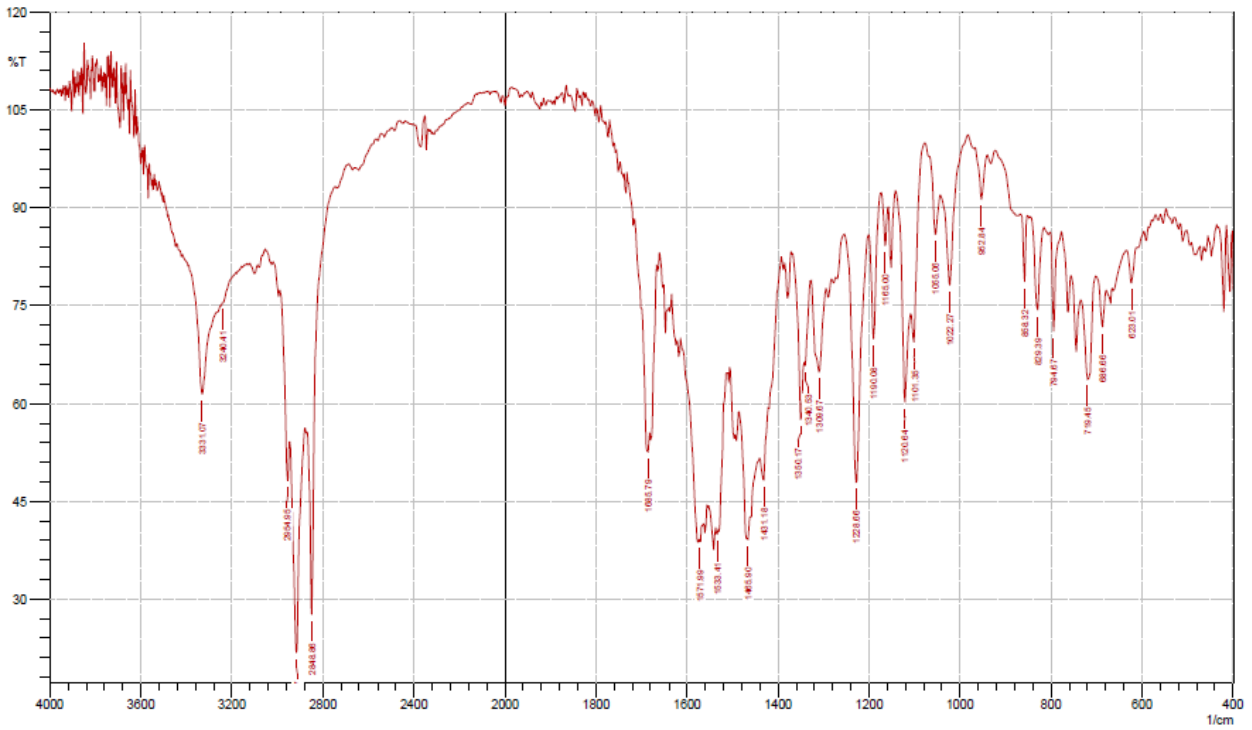

Figure No. 9: FT-IR Spectrum Drug and Magnesium stearate

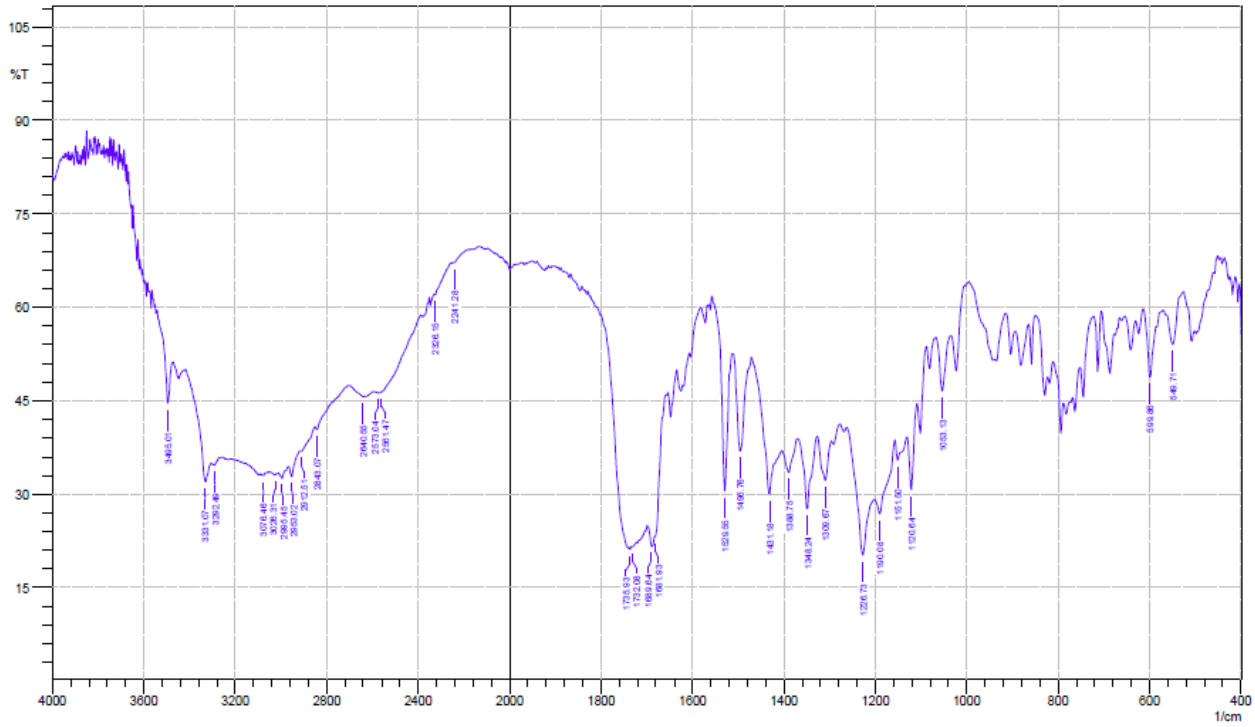

Figure No. 10: FT-IR Spectrum Drug and Citric acid

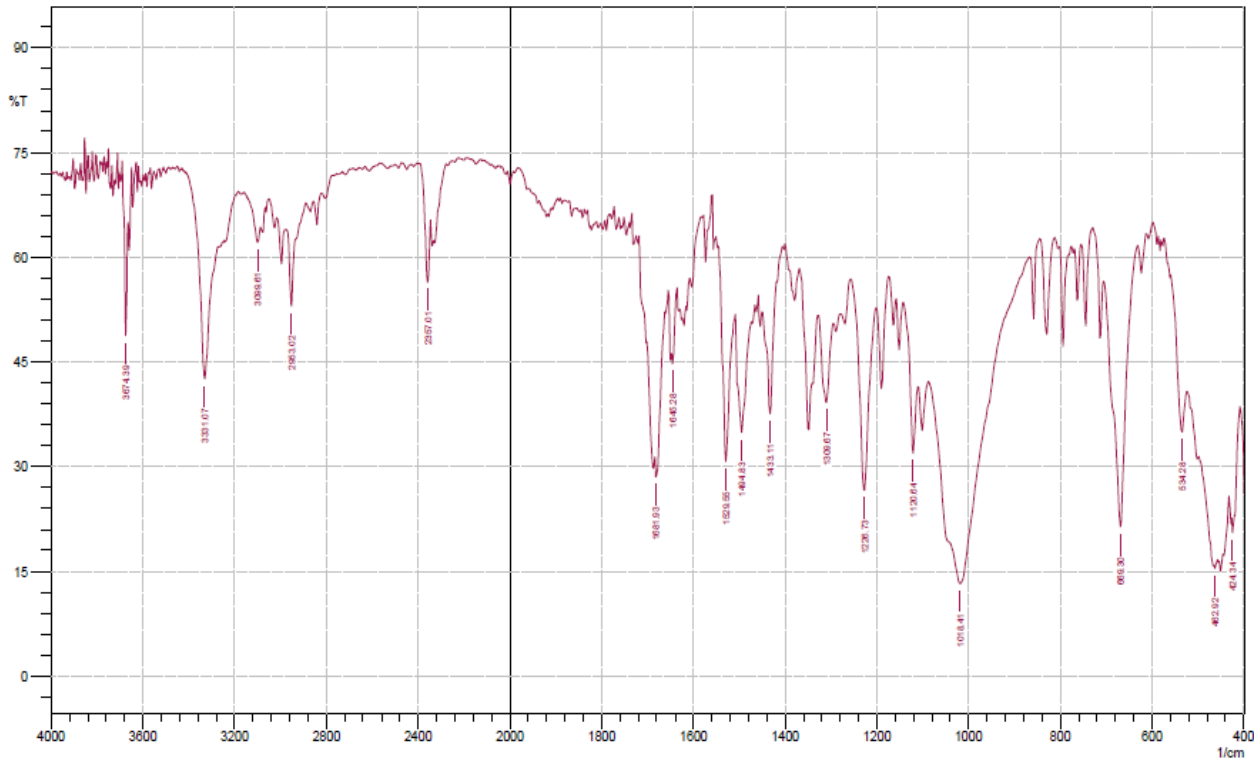

Figure No. 11: FT-IR Spectrum Drug and Talc

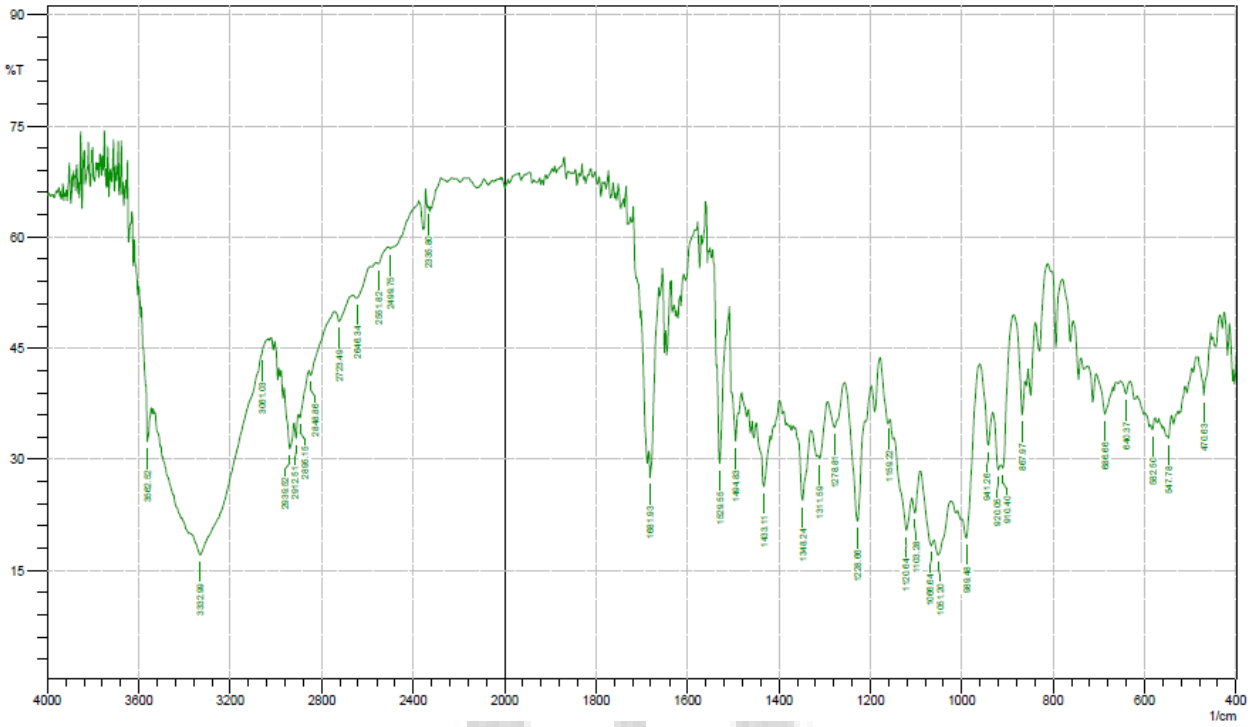

Figure No. 12: FT-IR Spectrum Drug and Sucrose

Infrared Spectroscopy Result:

The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between Nifedipine, carrier (PEG 4000) & the used excipients. The observed peaks along with assignment of functional groups to the peak are in above table: Solubility Studies of Nifedipine with various carriers

Table No.8: Solubility study of Nifedipine with various carriers in 0.1N HCl

Drug: Carries ratio	Solubility of Mannitol (µg/ml)	Solubility of PVP K30 (µg/ml)	Solubility of PEG4000 (µg/ml)	Solubility of PEG 6000 (µg/ml)	Solubility of Urea (µg/ml)
1:1	3.04	2.02	7.82	5.8	2.02
1:2	3.80	2.73	9.49	5.99	3.30
1:3	5.71	3.00	7.82	4.65	2.79
1:4	4.80	2.89	12.07	9.07	4.70
1:5	7.01	3.71	28.49	15.77	3.99

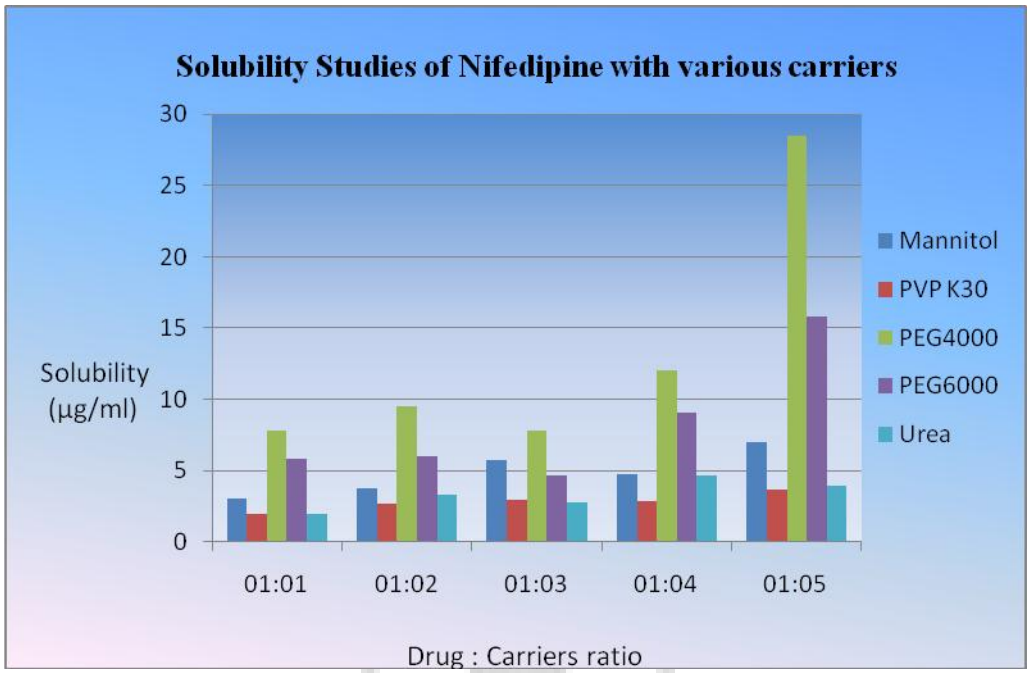

Figure No. 13: Graphical representation of solubility of Nifedipine with various Carriers in 0.1N HCl

Solubility Studies of Nifedipine with PEG 4000 in 1:1 to 1:9 ratios:

Table No. 9: Solubility Studies of Nifedipine with PEG 4000 in 1:1 to 1:9 ratios

Drug:PEG 4000 Ratio	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
Solubility (µg/ml)	7.82	9.49	7.82	12.07	28.49	17.56	21.52	22.59	22.13

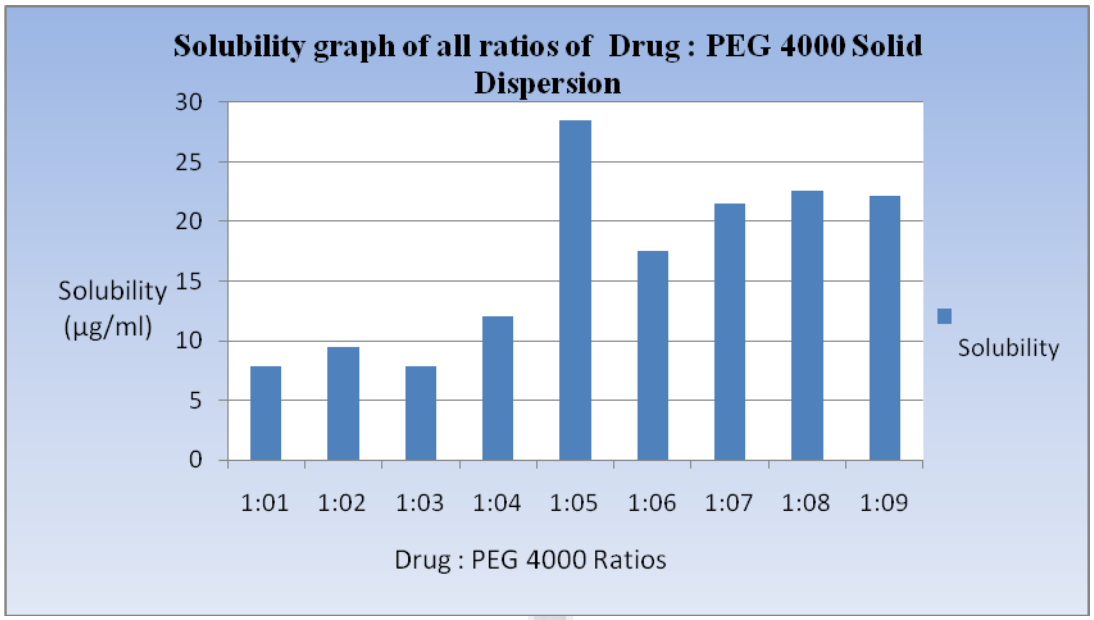

Figure No. 14: Graphical representation of Solubility of Nifedipine with PEG 4000 in 1:1 to 1:9 ratios

Therefore the efficiency of carrier in various ratios in improving the solubility of Nifedipine is in the following order

1:5 > 1:8 > 1:7 > 1:9 > 1:4 > 1:2 > 1:1=1:3

In-vitro dissolution study data for Solid Dispersion of PEG 4000

Table No.10: *In-vitro* dissolution study data for Solid Dispersion of PEG 4000 from 1:1 to 1:4 ratios

Time (min)	% drug release of solid dispersion of PEG4000 in different ratios			
	1:1	1:2	1:3	1:4
0	0	0	0	0
5	10.05	12.17	10.11	15.17
10	15.75	19.25	14.70	22.98
15	21.07	25.18	21.97	29.00
20	30.00	36.15	29.73	38.70
25	37.17	42.00	38.19	48.63
30	47.90	53.50	47.45	59.73

Table No.11: *In-vitro* dissolution study data for Solid Dispersion of PEG 4000 from 1:5 to 1:9 ratios

Time (min)	% drug release of solid dispersion of PEG4000 in different ratios				
	1:5	1:6	1:7	1:8	1:9
0	0	0	0	0	0
5	19.86	16.63	18.21	17.27	18.18
10	35.21	23.66	25.27	26.29	24.17
15	65.07	29.00	34.20	35.07	35.29
20	72.85	38.95	42.47	41.40	41.01
25	80.37	49.53	51.99	52.43	53.07
30	84.86	62.47	64.47	65.93	63.99

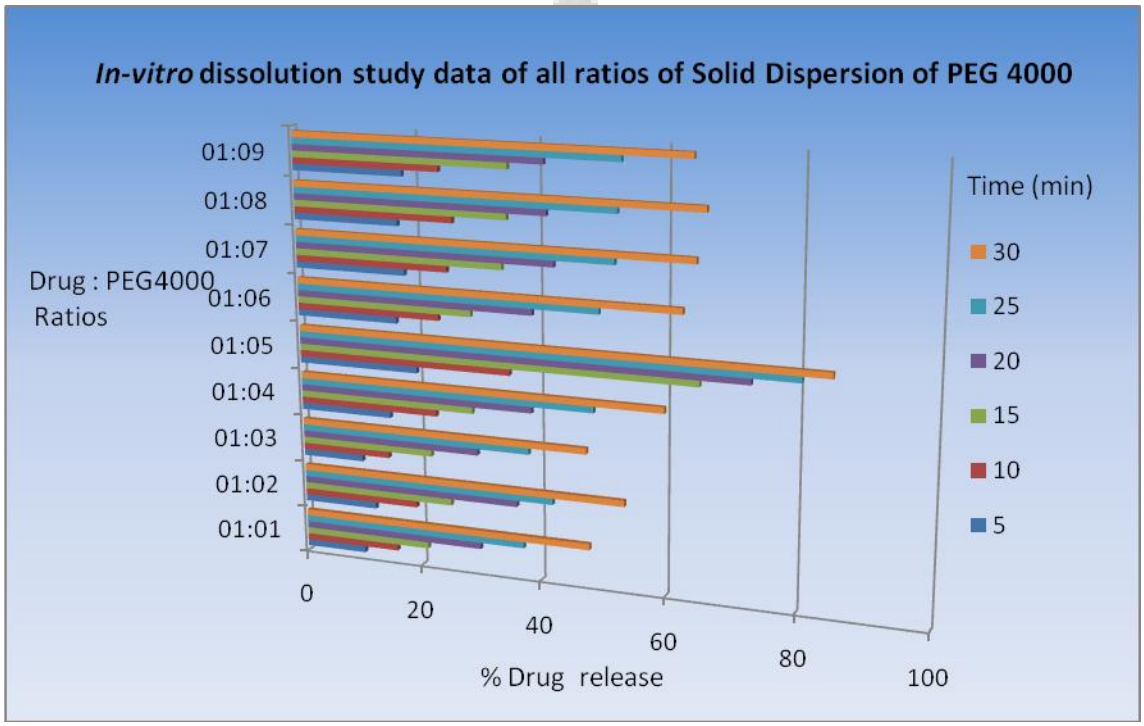

Figure No. 15: Graphical representation of *In-vitro* dissolution study of all ratios of Solid Dispersion of PEG 4000

Precompression parameter study:

Table No. 12: Precompression parameter study

Formulation code	Angle of repose	Bulk density (wt/ml)	Taped density (wt/ml)	Hausner's ratio (%)	Compressibility index (%)
F1	27.92±0.70	0.41±0.02	0.49±0.04	1.17±0.01	15.00±0.46
F2	26.10±0.56	0.42±0.03	0.48±0.02	1.14±0.02	13.47±0.23
F3	28.36±0.63	0.42±0.03	0.49±0.04	1.14±0.02	12.82±0.45
F4	25.74±0.45	0.41±0.02	0.48±0.02	1.18±0.04	14.91±0.36
F5	27.40±0.69	0.42±0.03	0.48±0.02	1.13±0.03	11.86±0.17
F6	26.56±0.60	0.43±0.02	0.51±0.01	1.16±0.05	14.03±0.21
F7	28.23±0.14	0.42±0.03	0.49±0.04	1.15±0.06	13.67±0.11
F8	28.17±0.85	0.42±0.03	0.48±0.02	1.16±0.07	13.44±0.17

The values represents mean±SD, n = 3

Post compression parameter study:

Table No. 13: A-Post compression parameter study

Formulation	Hardness	Friability	Weight	Thickness
F1	3.2±0.12	0.34±0.08	202.1±0.05	3.20±0.03
F2	3.0±0.11	0.42±0.03	200.0±0.03	3.35±0.02
F3	2.9±0.15	0.43±0.09	199.6±0.09	3.00±0.04
F4	2.7±0.09	0.38±0.08	201.3±0.08	3.25±0.05
F5	2.4±0.13	0.44±0.04	200.1±0.06	3.28±0.02
F6	3.5±0.10	0.39±0.06	200.0±0.03	3.30±0.02
F7	2.9±0.15	0.36±0.05	200.3±0.02	3.20±0.03
F8	2.8±0.11	0.41±0.03	201.1±0.05	3.25±0.01

The values represents mean±SD, n = 3

Post compression parameter study:

Table No. 14: B-Post compression parameter study

Formulation	Drug content (%)	Wetting time (sec)	Disintegration
F1	97.61±1.23	3±0.01	7±0.02
F2	99.32±1.18	4±0.02	11±0.01
F3	99.60±1.84	4±0.01	11±0.01
F4	98.10±1.95	3.5±0.02	10±0.02
F5	99.12±1.19	2±0.01	5±0.01
F6	99.21±1.43	2±0.01	5±0.01
F7	98.01±1.46	3±0.02	7±0.02
F8	95.23±1.26	2±0.01	6±.0.02

The values represents mean±SD, n = 3

Hardness:

The hardness of the tablets prepared was determined by Monsanto Hardness tester and found to be within the range of 2.4 kg/cm2 to 3.5 kg/cm2.

Friability test:

The friability was found in all designed formulations in the range 0.36% to 0.44% to be well within the approved range (<1%).

Weight variation test:

The weight variation was found in all designed formulations in the range 199.6 to 202.1 mg and % deviation was in a range of 0.03 to 1.22. All the tablets passed weight variation test as the average percentage weight variation was within 7.5 % i.e. in the pharmacopoeia limits.

Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 3.20 mm. to 3.35 mm. The standard deviation values indicated that all the formulations were within the range.

In- vitro disintegration time:

The *in-vitro* disintegration time was measured by the time taken to undergo complete disintegration. Rapid disintegration within 1 minute was observed in all the formulations. The disintegration time of all the formulations is checked & is found within the range of 5 sec. – 11 sec.

Wetting time:

Wetting time is closely related to the inner structure of the tablet. The wetting time of Nifedipine tablets prepared were found to be in the range of 2 to 4 sec.

Drug Content:

The drug content uniformity was performed for all the formulations. The average value and standard deviations of all the formulations were calculated. The percentage drugs content of the tablets were found to be between 95.23 ±1.26 to 99.60 ±1.84

In-vitro dissolution study of F1 to F8 Formulation batches:

Table No. 15: *In-vitro* dissolution study of F1 to F8 Formulation batches

Time (min)	% Drug release							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	22.31	18394	19.86	17.81	19.26	18.31	16.21	15.82
10	41.28	37.71	38.21	36.25	37.21	36.85	35.75	33.71
15	69.37	64.24	66.04	63.26	65.34	64.26	62.38	60.44
20	78.25	73.05	74.85	72.81	74.15	73.31	71.72	69.51
25	91.57	86.62	89.37	84.96	88.37	85.16	83.43	81.21
30	99.23	96.93	97.86	94.17	97.23	95.10	93.27	92.81

Percentage (%) Drug release:

The *in-vitro* drug release from fast dissolving tablets prepared by direct compression method was found to be in the range of 92.81 to 99.23%. 2^3 Factorial design with upper & lower limits of all factors Statistical Optimization technique.

The optimization phase was designed statistically using 2^3 factorial design in which three variables namely concentrations of Isabgol mucilage, S.S.G and M.C.C. were kept at two levels. Main interactive influences were tested using statistical methods. The eight formulations of optimization phase were categorized in to four groups for ease of analysis and comparison as follows:

1. Group I: All variables at low level (Formulation F1).

2. Group II: Any one of three variables at high level (Formulations F2, F3 & F5).

3. Group III: Any two of three variables at high level (Formulations F4, F6, & F7).

4. Group IV: All three variables at high level (Formulation F8).

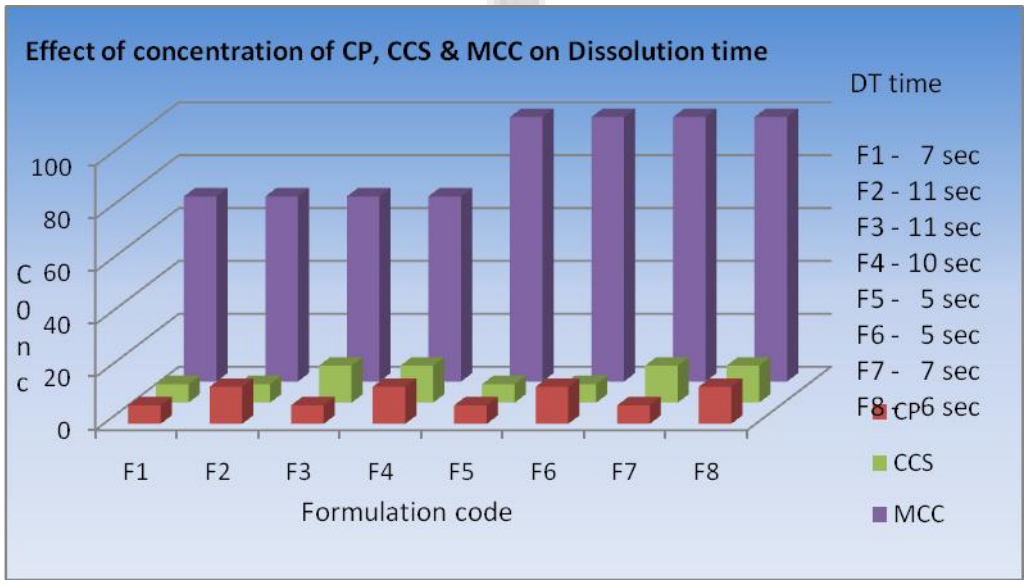

Figure No. 16: Effect of concentration of CP, CCS & MCC

Although all formulation were analyzed for disintegration time, amount of drug release at the end of 30minutes, and mechanism of drug release, and all of these parameters were considered for selection of best formulation in the optimization phase.

All these interpretations and implications of disintegrants characteristics over release profile were supported statistically and the results of main effects, interactive (two and three way) effects, were enlisted in Table.

Table No. 16: Effects of CP, CCS, MCC and their average estimates in the formulation

Effect	Estimate
Main effect	
Effect of CP	0.5
Effect of CCS	1.5
Effect of MCC	-4
Two Factor Interactions	
Effect of CP & CCS	-1.5
Effect of CP & MCC	0
Effect of MCC & CCS	-1
Three Factor Interactions	
Effect of CP, CCS & MCC	-1

Pareto chart:

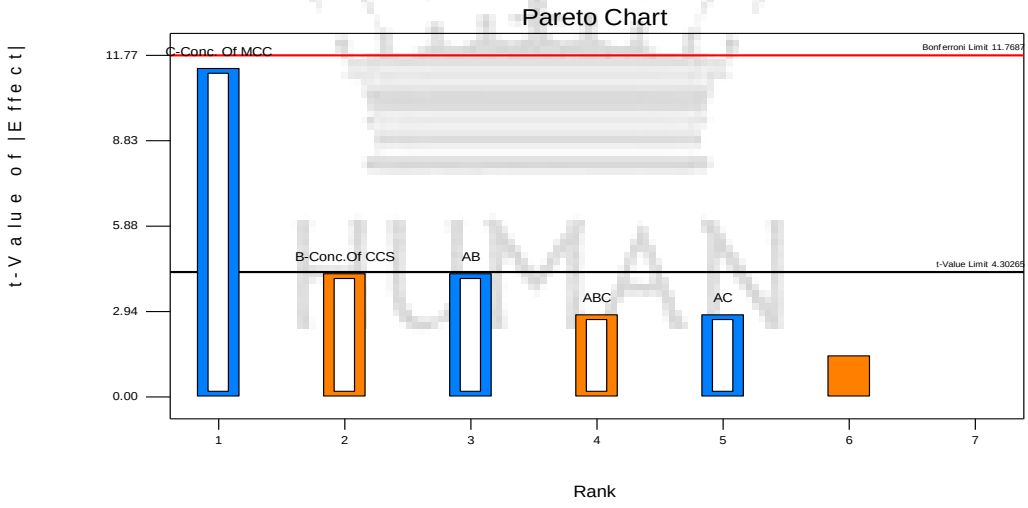

Figure No. 17: Pareto chart for responsible factor

Response surface methodology:

Table No. 17: Signs to calculate effects in a 23 Factorial Experiment Calculation of coefficient

Formulation	Level of factor in Experiment			Interaction				Total
	X1	X2	X3	X1X2	X1X3	X2X3	X1X2X3	
F1	-1	-1	-1	1	1	1	-1	-1
F2	1	-1	-1	-1	-1	1	1	1
F3	-1	1	-1	-1	1	-1	1	1
F4	1	1	-1	1	-1	-1	-1	1
F5	-1	-1	1	1	-1	-1	1	1
F6	1	-1	1	-1	1	-1	-1	1
F7	-1	1	1	-1	-1	1	1	1
F8	1	1	1	1	1	1	1	1
	+ Factor for high level			Multiply signs of factors to obtain signs of interaction terms in				

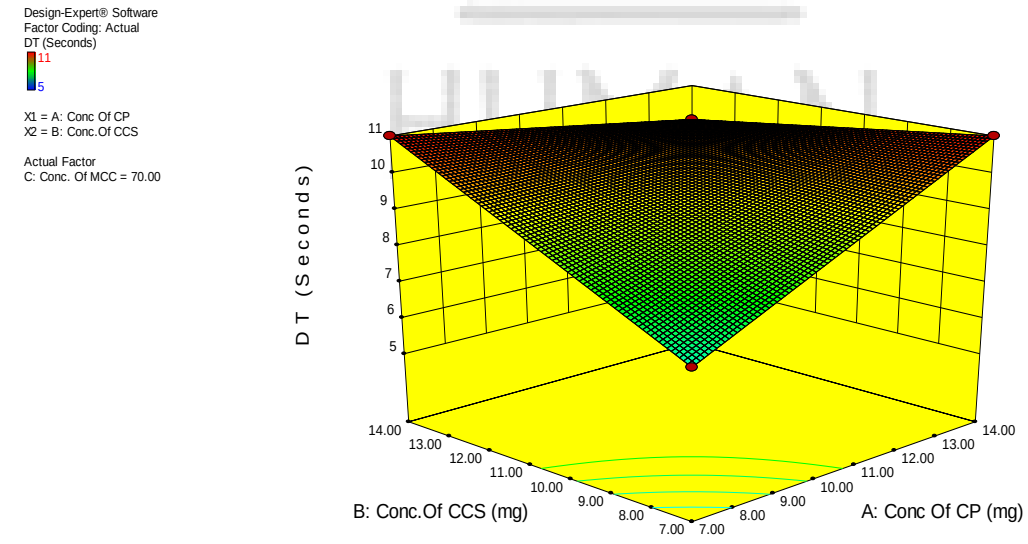

Figure No. 18: Response surface diagram showing combined effect of CP & CCS When MCC kept at lower level i.e. 70 mg

Response surface methodology:

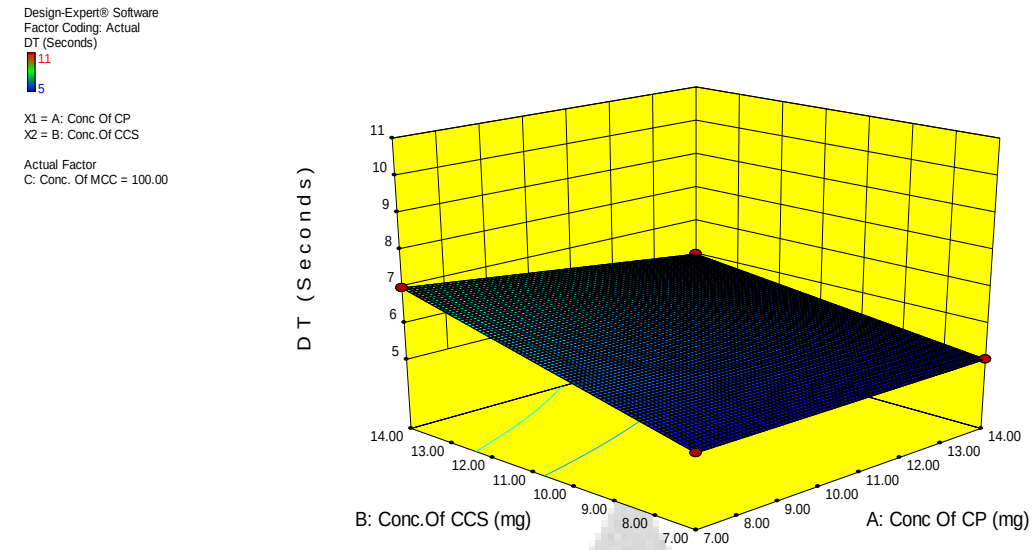

Figure No. 19: Response surface diagram showing combined effect of CP & CCS When MCC kept at higher level i.e. 100 mg

Response surface methodology:

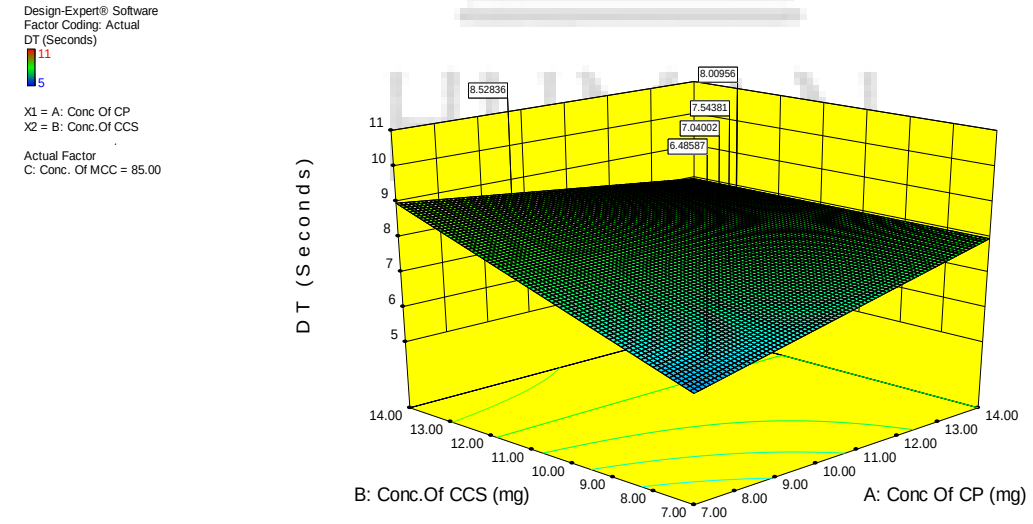

Figure No. 20: Response surface diagram showing combined effect of CP & CCS When MCC kept at middle level i.e. 85 mg

Counter plots:

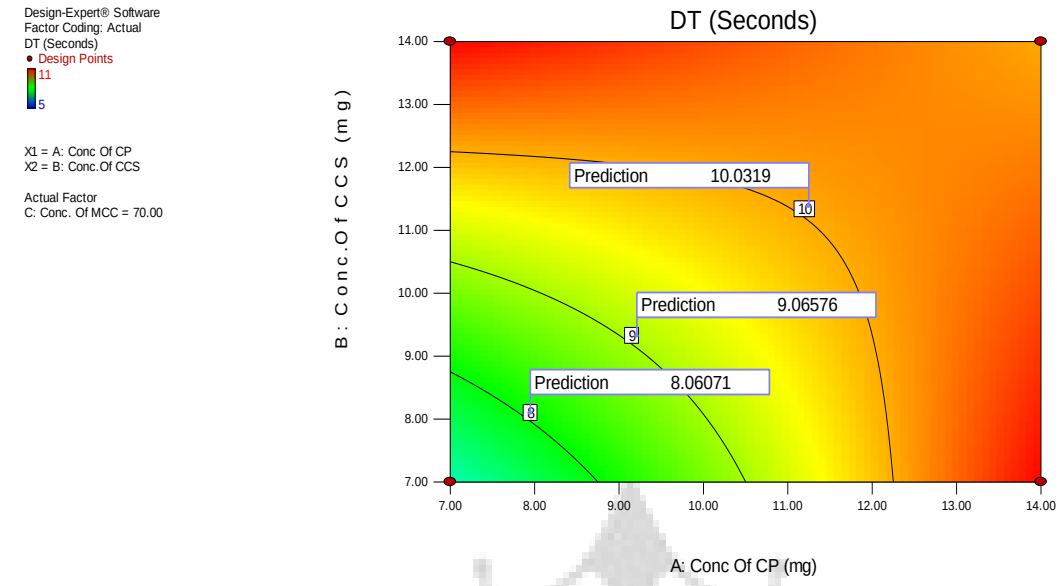

Figure No. 21: Counter plot showing combined effect of CP & CCS when MCC kept at lower level i.e. 70 mg

Counter plots:

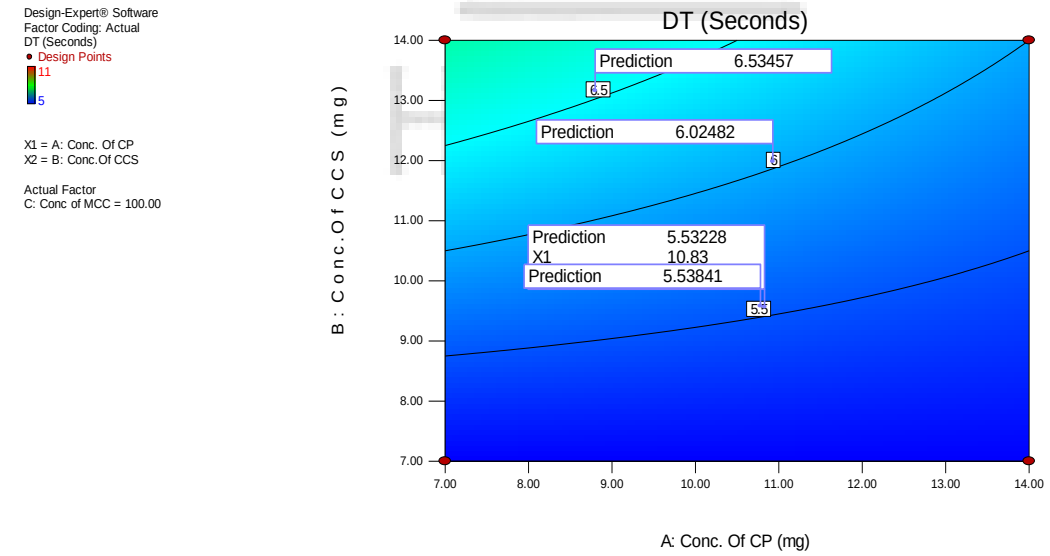

Figure No. 22: Counter plot showing combined effect of CP & CCS when MCC kept at higher level i.e. 100 mg

Counter plots

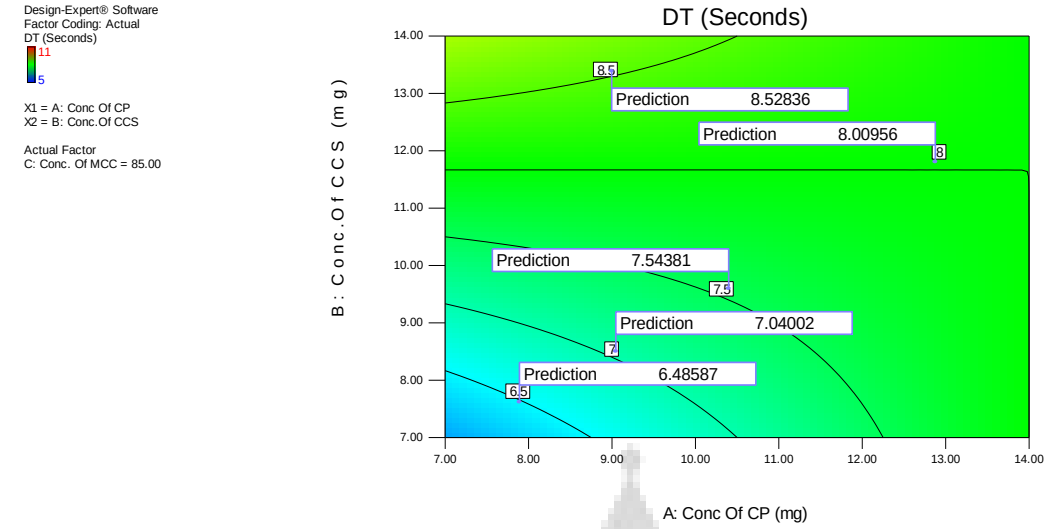

Figure No. 23: Counter plot showing combined effect of CP & CCS when MCC kept at middle level i.e. 85 mg

Standard Error:

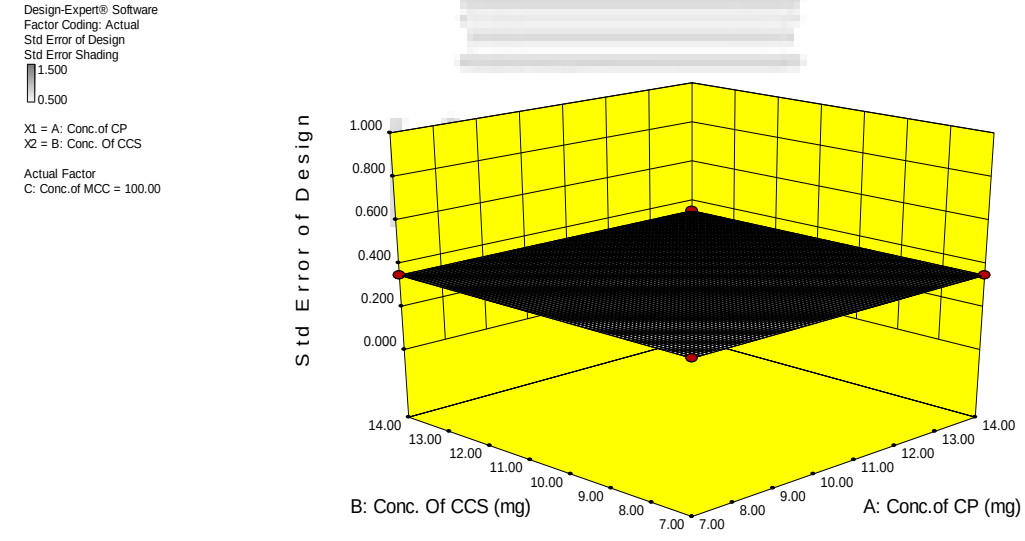

Figure No. 24: Standard Error of design

4. CONCLUSION

At the end, from the experiments carried out and results obtained, it can be concluded that the developed formulations achieved the objective of the investigation. The data obtained from the study of "Formulation and Evaluation of Fast Disintegrating Tablets of Nifedipine by QbD Approach" reveals following conclusion:

✓ IR spectroscopy studies indicated that the drug was compatible with the PEG 4000 and all excipients used.

✓ Fast Disintegrating Nifedipine Tablets were successfully prepared by direct compression method.

✓ The flow properties and uniformity of all the prepared tablets were good as indicated by good fluff density, tapped density, low angle of repose (<30°) , low compressibility index (I<35).

✓ The hardness of the prepared tablets by direct compression, sublimation and effervescent method was found to be in the range of 2.4 kg/cm^2 to 3.5 kg/cm^2

✓ The Thickness of the prepared tablets by all three methods was found between 3.0 mm. to 3.35 mm.

✓ The friability values of the prepared tablets by all three methods were found to be less than 1%.

✓ The *in-vitro* disintegration time of tablets prepared by direct compression method were found to be in the range of 5 to 11 sec. Formulation F5 and F6 showed *in-vitro* disintegration time 5 Sec.

✓ Based on the *in-vitro* disintegration time**,** Promising formulations F5and F6, which facilitate the faster disintegration in the mouth.

✓ The *in-vitro* percentage drug releases from fast dissolving tablets of Nifedipine prepared by direct compression method were found to be in the range of 92.81 to 99.23%.

Hence, finally it was concluded that the prepared fast dissolving tablets of Nifedipine may prove to be potential candidate for effective fast disintegrating tablet dosage form.

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