CRYSTAL ENGINEERING TECHNIQUE FOR THE ENHANCEMENT OF NIFEDIPINE SOLUBILITY

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***Abstract*:** Nifedipine is a calcium channel blocker used to manage angina, high blood pressure. It has poor aqueous solubility and slow dissolution rate lead to a lack of dose proportionality. The aim of this study was to improve the biological performance of the drug by enhancing its solubility. In the present study an attempt has been made to enhance solubility of nifedipine using β-cyclodextrin (β-CD). The complex were prepared by different methods like Physical mixture, Kneading and Solvent evaporation with different ratio.The prepared complexes were characterized using FT-IR and X-ray Diffractometry (XRD). The complex were evaluated for phase solubility, saturation solubility, drug content and powder yield. The Saturation solubility study of optimized formulation was found to be 16.07µg/ml. The Drug content of optimized formulation was found to be 97.3%. The powder yield of optimized formulation was found to be 98.45%. *In vitro* dissolution study was carried out phosphate buffer solution of pH 6.8, Formulation prepared by kneading method F5 (1:2) and solvent evaporation F8 (1:2) showed 88.51% and 90.23 % drug release respectively.

Key words: **Nifedipine, β-cyclodextrin, physical mixture, kneading, solvent evaporation, phase solubility, saturation solubility, dissolution rate.**

1. Introduction

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown.[1] The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution.[2]The solubility is commonly expressed as a concentration, either by mass (g of solute per kg of solvent, g per dL (100 mL) of solvent), molarity, molality, mole fraction, or other similar descriptions of concentration. The maximum equilibrium amount of solute that can dissolve per amount (volume) of solvent is the solubility of that solute in that solvent under the specified conditions.[3]

Oral drug delivery is the most accepted administration rout because of the greater stability, smaller bulk, accurate dosage and easy production.Therefore, most of the new chemical entities (NCE) under development are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration. However, most NCEs are poorly water soluble drugs, after oral administration, despite their high permeability they are only absorbed in the upper small intestine having small absorption window. Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability. Therefore, one of the major current challenges of the Pharmaceutical industry is related to strategies that improve the water solubility of drugs.

Nifedipine is insoluble in water which causes lead to limited absorption. Also during storage the excipients may interact with the drug and affect its dissolution characteristics.To overcome these

difficulties, several approaches have been used namely, the formation of complex between nifedipine and β-cyclodextrin. Nifedipine is in a group of drugs called calcium channel blockers. It works by relaxing the muscles of your heart and blood vessels. Nifedipine is used to treat hypertension and angina (chest pain)[4].

Techniques for Solubility Enhancement:

Solubility improvement techniques broadly categorized into physical modification, chemical modifications of the drug substance, and other techniques.

1.Physical Modifications- Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions,

2.Chemical Modifications- Change of pH, use of buffer, derivatization, complexation, and salt formation.

3.Miscellaneous method- Supercritical fluid process, use of adjuvant like surfactant, Solubilizer, Coslovency**.**

2. Materials and methods

2.1 Materials

Nifeddipine was purchased from Yarrow Chem Pvt. Ltd. Mumbai. B- cyclodextrin (β-CD)was obtained from Gangwal Chemicals, Mumbai. Methanol,ethanol,sodium hydroxide were obtained from loba chemie pvt. Ltd. Mumbai.

Preparation of Solid dispersion

Solid dispersion was prepared by following method.

1. Physical mixture
2. Kneading method
3. Solvent evaporation method

Physical mixture[5]

The physical mixtures of nifedipine and β-cyclodextrin were prepared by homogeneous blending of previously pulverized powder of both components (#60) together in a mortar pestle for 30 min. These powdered physical mixtures were then stored in the room at controlled temperature (25°±2°C) and humidity conditions (Relative humidity 40-50%) for comparison with the corresponding solid complex powders.

Kneading method[6]

In this method weigh amount of nifedipine and chosen carrier i.e. β-cyclodextrin, were mixed and moistened with a small volume of ethanol - water system.The mixture was ground thoroughly in pestle and mortar and kneaded like paste by addition of solvent drop wise upto 45 minute.The dried mass was pulverized and passed through a sieve of 120 mesh size and and stored in desiccators at 25^0C.

Solvent evaporation[7]

In solvent evaporation technique nifedipine was dissolved in a mixture of dichloromethane and ethanol (50:50 V/V) to produce a clear solution .Carrier substance was dispersed in the above clear solution, by stirring at 37^0 C in a magnetic stirrer. Further clear solution was poured into the aluminium foil and solvent was allowed to evaporate at 40^0C in a hot air oven. Finally, the resultant mass was dried at 37^0C for 24hour. This dried material was pulverized and passed through a sieve with a mesh number of 120.

Table 1 Composition of various formulations

Method of Preparation	Drug & carriers Used	Drug to Carrier Ratio	Batch Code
Physical mixture	Nifedipine: β-cyclodextrin	1:1	F1
	Nifedipine: β-cyclodextrin	1:2	F2
	Nifedipine: β-cyclodextrin	1:3	F3
Kneading method	Nifedipine: β-cyclodextrin	1:1	F4
	Nifedipine: β-cyclodextrin	1:2	F5
	Nifedipine: β-cyclodextrin	1:3	F6
Solvent Evaporation	Nifedipine: β-cyclodextrin	1:1	F7
	Nifedipine: β-cyclodextrin	1:2	F8
	Nifedipine: β-cyclodextrin	1:3	F9

Preparation of tablet of solid dispersion

Tablet containing complex of equivalent nifedipine to equivalent 30 mg was compressed on a 16 station rotary machine (cadmach Ahmadabad) using round shaped concave punches. The composition of tablet is given in Table 2.

Table 2.Composition of tablet formulations

Ingredient	Formulation Batch(mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nifedipine	30	30	30	30	30	30	30	30	30
Hydroxy methyl propyle cellulose	100	100	100	100	100	100	100	100	100
Microcrystalline Cellulose	130	130	130	100	100	100	70	70	70
Talc	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5

2.2 FTIR spectroscopy:

The compatibility between pure drug and polymer was detected by IR spectra obtained using Zink Selenium cell by IR spectrophometer (Bruker Alpha T). The spectra were recorded over the wave number range of 4000 to 600 $^{cm-1}$. Disappearance or shifting of nifedipine peak in any of the spectra was studied.

2.3 Powder X-ray Diffractometry [PXRD]

The powder X-ray diffraction technique has been extensively utilized along with DSC to study the interaction between drug and β- cyclodextrin.The diffraction studies were carried out on a powder X-ray diffractometer (STOESTADI-P). The samples were rotated during data collection to reduce orientation

effects. PXRD patterns of pure drug and physical mixture were recorded between 2θ = 5 to 50° at 40 kV and 30 mA.

2.4 Phase Solubility Studies[8]

Phase solubility studies were carried out according to the method reported by Higuchi and Connors. An excess of Nifedipine (20 mg) was added to 15 ml portions of distilled water, each containing variable amount of β -cyclodextrin in 0, 1, 3, 6, 9,12, and 15 x 10^{-3} moles/liter. All the above solutions with variable amount of β-cyclodextrin were shaken for 72 hours. After shaking, the solutions were filtered and their absorbance was noted at 238 nm. The solubility of the Nifedipine in every β - cyclodextrin solution was calculated and phase solubility diagram was drawn between the solubility of nifedipine and different concentrations of β-cyclodextrin as shown in fig.1 The apparent stability constant (Ka) according the hypothesis of 1:1 stoichiometric ratio of complexes was calculated from the slope of the linear portion of the phase solubility diagrams using the following equation

$$Ka = Slope / S_0 (1- Slope)$$

Where, S_0 is intrinsic aqueous solubility of nifedipine

2.5 Saturation Solubility Studies[9]

The saturation solubility study was carried out to determine increase an in the solubility of pure nifedipine as compared with the physical mixture (PM) and inclusion complexes. The known excess amount of drug, PM and inclusion complexes were added to the 250 ml conical flasks containing 25 ml of phosphate buffer solution (pH 6.8). Then the sealed flasks were maintained at 25°C for 48 hours. The saturated solution was sonicated for 20 min and then centrifuged. Then, the supernatant were withdrawn through Whatman filter paper. The concentration of Nifedipine was determined by UV spectrophotometer at 238 nm .

2.6 Percentage Powder yield

The percentage powder yield for the solid dispersion was calculated using the following equation

$$\%\ Powder\,yield = \frac{Weight\,of\ powder}{Totol\,weight\,of\ solid} X100$$

2.7 Drug Content Estimation[10]

50 mg of solid dispersion was accurately weighed and transferred to 50 ml volumetric flask and volume was made up to the mark with methanol. From this 1ml was taken in 10 ml volumetric flask and the volume is adjusted up to the mark with phosphate buffer pH 6.8 solvent. The absorbance of the solution was measured at 238nm against solution of the carrier substance without drug as blank. The drug content of Nifedipine was calculated using calibration curve.

2.8 *In- vitro* dissolution studies

The dissolution studies of Nifedipine ER tablet were performed on a paddle – stirrer type of apparatus. The dissolution studies were performed according to dissolution procedure recommended for single – entity product in 900 ml of P^H 6.8 phosphate buffer (50 rpm) . The temperature of the cell was maintained at 37^0 C by using thermostatic bath. Aliquot of 1 ml was withdrawn at predetermined time intervals of 1, 2, 3, 4, 5, 6 and 7 Hr and replaced with the same volume of drug free buffer. The aliquot were diluted suitably and the concentration of Nifedipine was determined at the 238 nm wavelength by UV-visible spectrophotometer (Lab India 3200) against blank.

3. Result and discussion

3.1 Phase Solubility Study:

Table 3. Phase Solubility Study

Concentration of β-CD(mM)	Concentration of Nifedipine (mM)
0	0.038
3	0.042
6	0.045
9	0.05
12	0.053
15	0.059

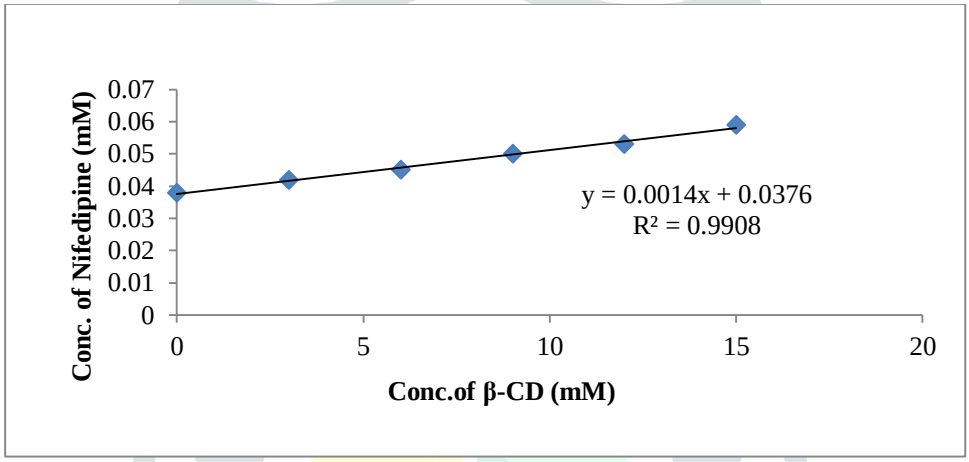

Figure 1 Phase solubility study of nifedipine

Phase solubility studies were carried out for an assessment of the affinity between β-CD and drug molecule in water before preparation of inclusion complex. The phase solubility diagram for the complex formation of nifedipine with β-CD [Fig.1] illustrates linear increase of aqueous solubility of the drug (R^2 = 0.990) as the concentration of β-CD increased over the entire concentration range studied and can be classified as AP-type following the Higuchi and Connors classification. The linear correlation coefficient of Nifedipine :β-CD with a slope smaller than 1 indicated the increase in solubility was due to the formation of 1:1 water soluble complex in solution with respect to β-CD concentrations. The apparent stability constant (Ka) calculated was found to be 575 M^{-1} which was inside range of 200-5000 M^{-1}. This value of stability constant (Ka) indicated that the complex formed is a bit stable and recommended that β-CD is appropriate for the improved dissolution properties and hence better bioavailability of Nifedipine.

3.2 Saturation solubility study:

Table 4. Saturation solubility study in Phosphate buffer pH 6.8(ug/ml)

Batch Code	Solubility in Distilled Water(ug/ml)
Drug	5.75
F1	6.6
F2	8.39
F3	8.75
F4	9.32
F5	14.67

F6	15.17
F7	10.1
F8	14.92
F9	16.07

The saturation solubility data for Nifedipine and complexes of nifedipine - β-CD are shown in Table 4. The whole inclusion complexes prepared were found to be fine and free flowing powders. Formulation F9 was found to be highest increased in solubility i.e 16.07 µg/ml.

3.3 Drug Content Estimation:

Table 5.Drug Content Estimation

Batch Code	Percentage Drug Content
F1	85 ±0.94
F2	94±0.56
F3	85 ±0.94
F4	94±0.20
F5	89±0.76
F6	97±0.13
F7	96±0.24
F8	97±0.13
F9	96±0.24

Percentage drug content of the nifedipine formulations F1-F9 were found to be in the range of 85 ±0.94 to 97±0.13%.The result shown in Table 5. All the formulations showed satisfactory drug content. However F6 formulation batch showed 97.3 %. The drug content of nifedipine was found to be uniform.

3.4 Percentage powder yield

Table 6 Percentage Powder Yield

Batch Code	Percentage Powder Yield
F1	91.7
F2	96.6
F3	90.1
F4	97.2
F5	96
F6	93.7
F7	96.2
F8	98.45
F9	97.55

Percentage powder yield of the nifedipine formulations F1-F9 were found to be in the range of 90 to 98.The result shown in Table 6. The powder yield of optimized formulation was found to 98.45%.

3.5 Compatibility study FT- IR

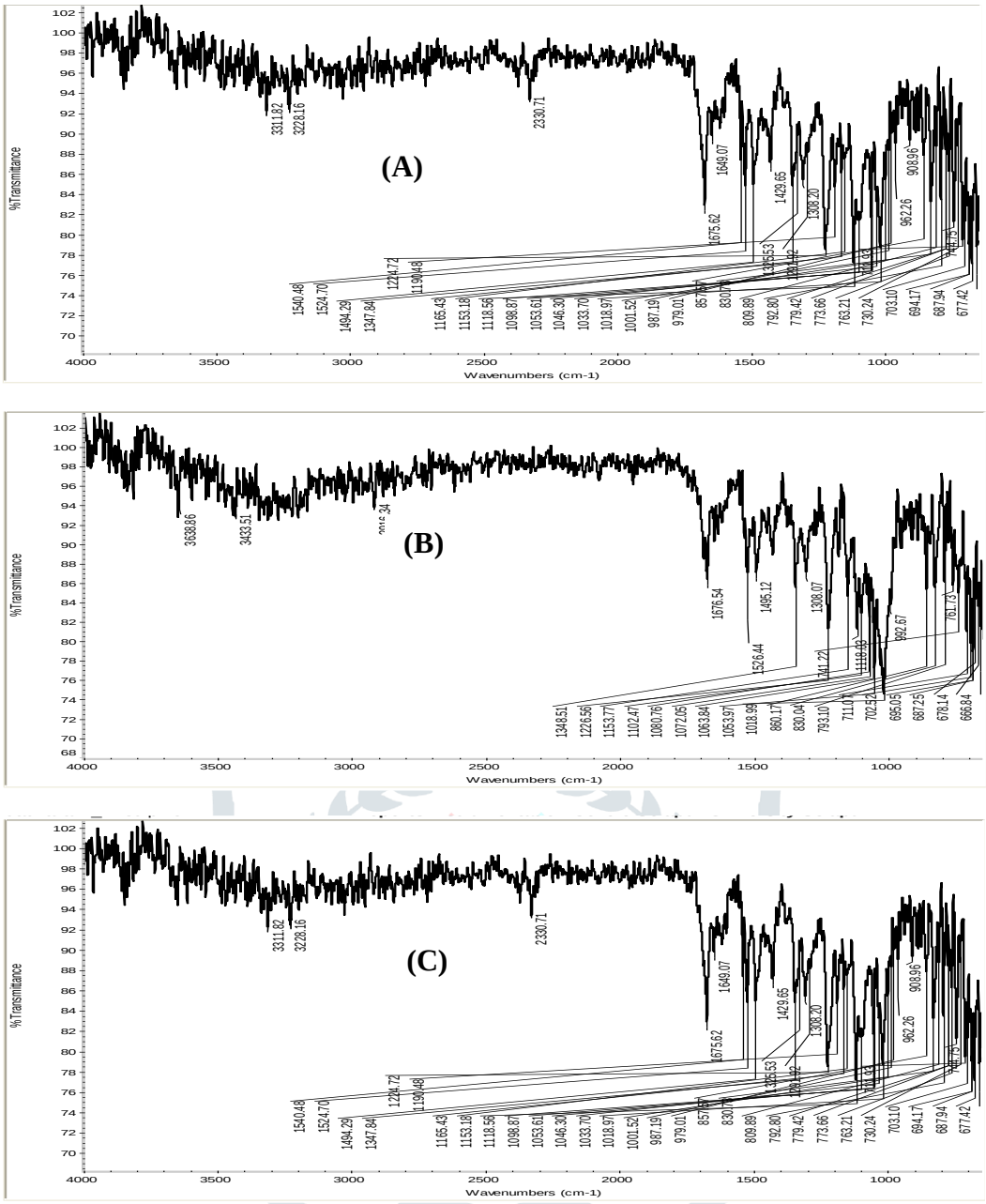

Figure 2 IR (A) Nifedipine; (B) β-CD; (C) Batch F9.

The FT-IR spectra of nifedipine showed a N-H stretching vibration at 3331.82 $^{cm-1}$, C-H aromatic vibration at 3226.16 $^{cm-1}$,C-H aliphatic stretching at 2330.71 $^{cm-1}$, C=O stretching at 1649.07 $^{cm-1}$, C-O ester stretching at 1326.53 $^{cm-1}$ and 1300.20 $^{cm-1}$. Sharp peak of N=O stretching was observed at 1675.62 $^{cm-1}$. Nifedipine has N-H function that is capable of forming hydrogen bonds. In crystalline nifedipine, N-H group is weakly hydrogen bonded to a carbonyl function to another molecule. The study reveals that there is no any interaction between nifedipine and polymers mixture.

3.6 XRD:

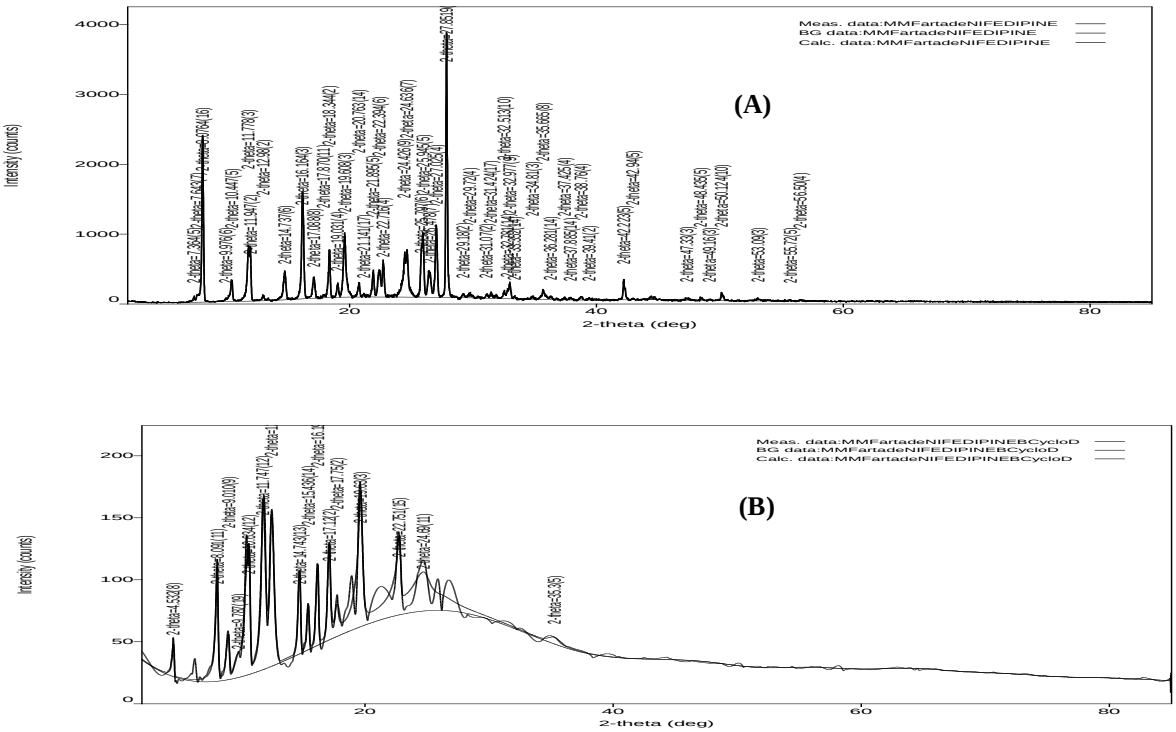

Figure 3. XRD of (A) Nifedipine; (B) complex

The XRD patterns of nifedipine and physical mixture (Nifedipine: β-CD) were shown in Figure 3. In the X-ray differactogram of pure nifedipine, a sharp peak is presented at a diffraction angle (2θ), are presented and it confirms that the drug is in the crystalline form. Typical diffraction peaks of Nifedipine in physical mixture indicating the presence of free crystalline drugs, which were revealed by few broad peaks of low intensity which that emerged on the background of β-CD as an amorphous carrier. The reduction in intensity and number of typical diffraction peaks of nifedipine in Physical mixture.X-ray diffractogram suggests the formation of complex.

3.7 *In vitro* Dissolution study:

Table 8.*In-vitro* drug release profile of F1 to F5 formulations

Time (Hr)	Cumulative amount of drug released					
	Microgram	Percentage	Microgram	Percentage	Microgram	Percentage
	F1		F2		F3	
1	5.34	17.79	5.85	19.5	6.13	20.44
2	12.61	42.05	8.5	28.32	9.98	33.25
3	13.98	46.6	13.07	43.58	13.53	45.09
4	15.86	52.87	16.63	55.43	17.12	57.06
5	18.26	60.87	18.51	61.71	18.77	62.58
6	20.15	67.16	20.01	66.71	19.57	65.22
7	21.46	71.52	21.97	73.22	23.13	77.09

Table 9.*In-vitro* drug release profile of F4 to F6 formulations

Time (Hr)	Cumulative amount of drug released					
	Microgram	Percentage	Microgram	Percentage	Microgram	Percentage
	F4		F5		F6	
1	6.24	20.79	6.49	21.64	6.78	22.59
2	10.36	34.54	10.88	36.25	11.39	37.97
3	16.87	56.24	15.72	52.38	17.45	58.18
4	18.63	62.1	18.89	62.95	21.33	71.11
5	19.94	66.46	23.09	76.97	23.42	78.06
6	20.73	69.11	23.82	79.41	24.09	80.29
7	24.94	83.13	26.55	88.51	25.98	86.60

Table 10.*In-vitro* drug release profile of F7 to F9 formulations

Time (Hour)	Cumulative amount of drug released					
	Microgram	Percentage	Microgram	Percentage	Microgram	Percentage
	F7		F8		F9	
1	6.36	21.21	6.88	22.93	7.26	24.21
2	10.49	34.97	10.81	36.04	9.72	32.39
3	12.95	43.16	13.85	46.16	14.36	47.87
4	20.69	68.95	19.08	63.59	19.91	66.38
5	22.64	75.46	23.35	77.82	22.25	74.17
6	24.4	81.34	24.92	83.05	24.08	80.26
7	25.59	85.29	27.07	90.23	26.49	88.29

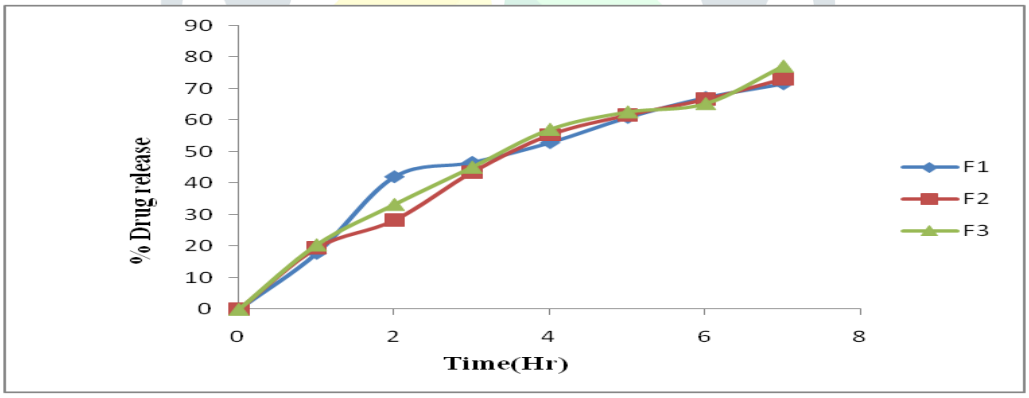

Figure 4.Comparison of in-vitro drug release graph profile of F1 to F3.

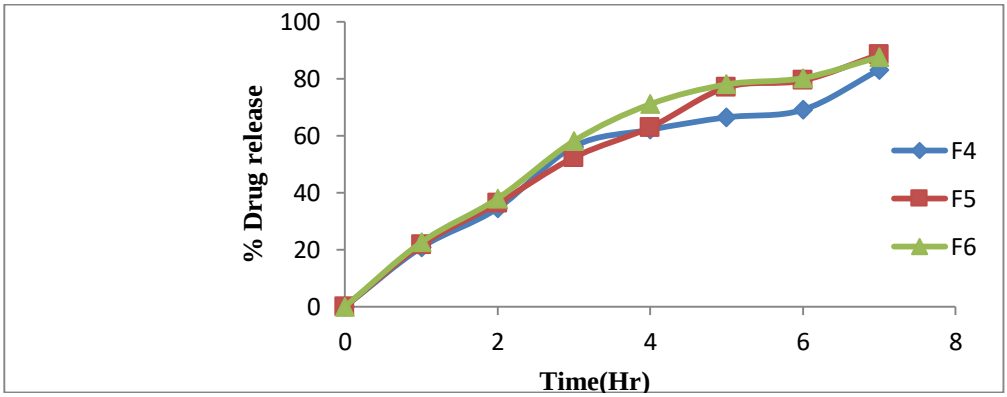

Figure 5. Comparison of in-vitro drug release graph profile of F4 to F6

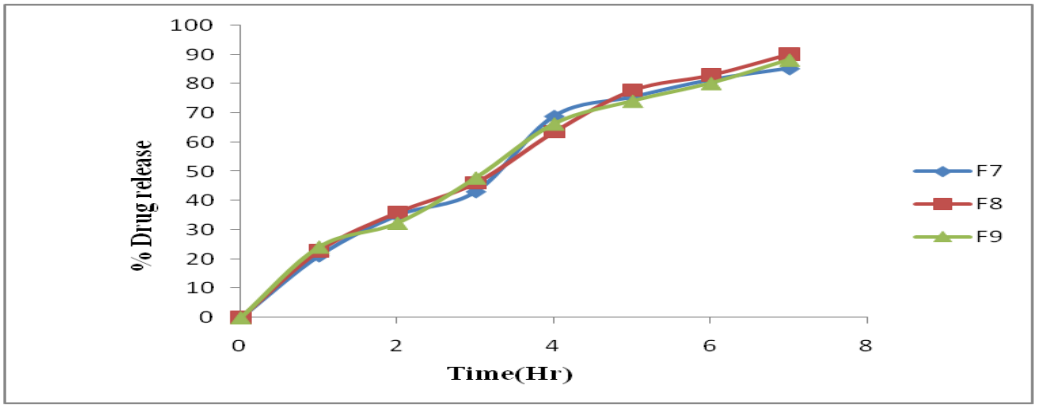

Figure 6. Comparison of in-vitro drug release graph profile of F7 to F9

Dissolution studies of all formulations were carried out in PBS of pH 6.8 as dissolution medium. The cumulative (%) release of nifedipine tablet after 7 Hr were 71.52, 73.22 and 77.09 for formulation F1, F2 and F3 respectively. The order of retardation from these tablet was F1< F2< F3. The results are given in Table 8 and fig. 4. The cumulative (%) release of nifedipine tablet after 7 Hr were 83.13, 88.51 and 86.60 for the formulation F4, F5 and F6 respectively. The order of retardation from different tablet was F5>F6>F4. The results are given in Table 9 and fig. 5. The cumulative (%) release of nifedipine tablet after 7 Hr were 85.29, 90.23and 88.29 for the formulation F7, F8 and F9 respectively at the end of 7 Hr. The order of retardation from different films were F8>F9>F7. The results are given in Table 10 and fig.6.

3.8 Kinetics of drug release:

Batch	Zero order	First order	Higuchi	Korsmeyer-peppas model
F5	y = 12.04x + 12.78 R^2 = 0.971	y = -0.135x + 2.068 R^2 = 0.978	y = 42.50x - 21.63 R^2 = 0.989	y = -1.347x + 1.957 R^2 = 0.632

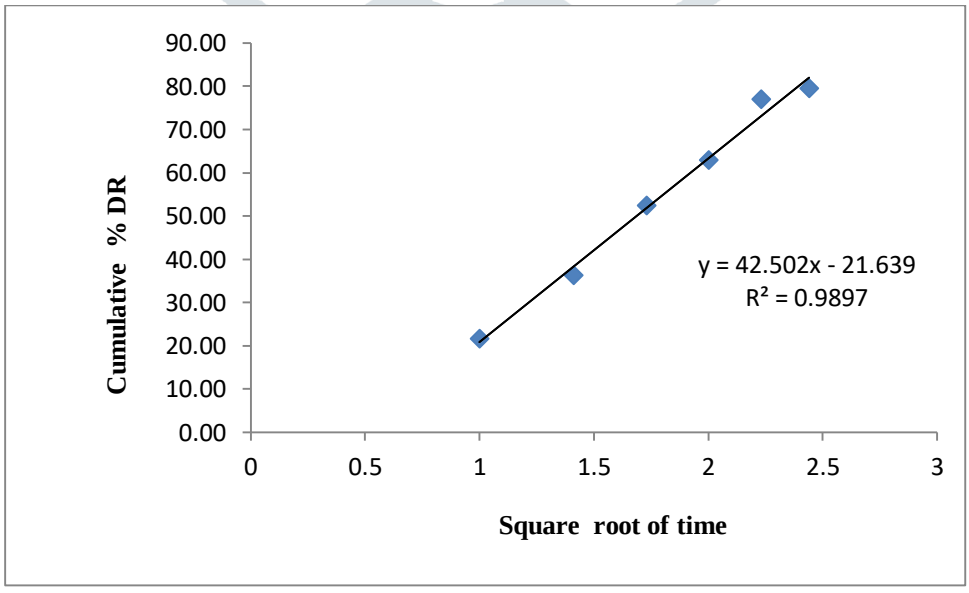

Figure 7. Higuchi plot of Nifedipine F5

In order to elucidate the release mechanism for formulation F5 tablet through dissolution profile, the data was fitted in to the model representing zero-order, first order, higuchi and korsemeyer-Peppas equations.

When data was plotted according to higuchi's equation; a linear plot was obtained for the formulation F5 with its regression coefficient value of 0.98 suggesting the mechanism of release from formulation F5 was obtained as per higuchi kinetics model.This indicate drug release by diffusion mainly.It also showed encapsulation of nifedipine in β-CD complex.

4. Conclusion:

The complex were prepared by different methods like physical mixture, kneading and solvent evaporation .The phase solubility analysis indicated the formation of 1:1 molar complex of nifedipine with β-CD .The complex prepared with β-CD by Solvent evaporation showed greatest enhancement in solubility. The complex prepared with β-CD by kneading & Solvent evaporation showed highest enhancement in dissolution profile. Among all formulations F8 showed highest *In-vitro* release as 90.23%.

5. Acknowledgement:

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