WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 18, 654-680. Research Article ISSN 2277– 7105

FORMULATION, OPTIMIZATION AND EVALUATION OF NIFEDIPINE NANOSPONGES FOR SOLUBILITY ENHANCEMENT

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Article Received on
25 August 2023,

Revised on 15 Sept. 2023,
Accepted on 05 Oct. 2023

DOI: 10. 20959/wjpr202318-29891

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ABSTRACT

The aim and objective of the present study was to formulate, optimize and evaluate Nifedipine Nanosponges for solubility enhancement and Polymeric Nanosponges delivery system was to deliver Nifedipine in a controlled manner. Nine Nifedipine Nanosponges formulations were prepared by emulsion solvent diffusion method by using polymer Ethyl cellulose and polyvinyl alcohol. The prepared Nanosponges formulation was evaluated for particle size and Polydispersity index, Production yield, Drug content, Drug Entrapment efficiency, *In-vitro* Drug release study and Stability studies. Particle size analysis showed that the average particle size of Nifedipine nanosponge using ethyl cellulose was found to be 249.6 nm with Poly Dispersity Index (PDI) value 0.352. Increased in the polymer concentration may increase their % production yield ranged from 65.15% to 85.36%. The drug content of all formulations was in the range of 78.79 %to 92.20%. and entrapment efficiency was in the range of 77.91% to 89.50%. The in-vitro drug release of optimized batch F2 showed the maximum drug release of 85.44% in 12 hrs and 90.86 in 24 hrs and Drug release in a controlled sustained manner and followed First order diffusion mechanism. Optimized Batch F2 formulation was subjected to stability studies for 3 months, it could be concluded that formulation was stable after 3-months stability study. Saturation solubility study was carried out, the result showed that increase in the solubility of Nifedipine as compare to the pure drug.

KEYWORDS: Nifedipine, Nanosponges, Emulsion solvent diffusion method, Solubility, 3^2 Central composite design.

INTRODUCTION

Nanosponges are a part of nanotechnology that is both hydrophilic and hydrophobic in nature. They are made up of microscopic particles with cavities several nanometers wide, in which various medicinal substances can be encapsulated. These particles have the ability to carry both hydrophilic and lipophilic molecules and thereby increase the solubility of drugs that are poorly soluble in water. A study of this nanotechnology proves that tiny network-like structures called nanosponges can revolutionize the treatment of many diseases.[1] A nanosponge is an encapsulating type of nanoparticle that encapsulates drug molecules inside its core. They can be used to target drugs to specific areas, allowing the drug to be released in a controlled and predictable manner.[2] It is possible to control the size of the nano-sponge by changing the part crosslinking agents and polymers.[3] Nano-sponge are non-irritating, non-mutagenic, no allergenic and non-toxic.[4] Nanosponges also improve the bioavailability of the drug, change the pharmacokinetics properties of drugs, enhance the solubility and dissolution rate and provide controlled release.

Nifedipine is chemically known as dimethyl-1, 4- dihydro-2, 6-dimethyl-4-(2-nitrophenyl) pyridine-3, 5 dicarboxylate.[5] Nifedipine is a calcium channel blocker (CCB) belonging to the class of 1,4 dihydropyridines. Calcium channel blockers (CCBs), also known as calcium channel antagonists or calcium antagonists, are a group of drugs that block the movement of calcium through a calcium channel.[6] it is widely used in the treatment of hypertension and angina pectoris.[7] Nifedipine is a yellow crystalline powder, thermostable and hygroscopic in nature, and also practically insoluble in water.[8]

The bioavailability of nifedipine is very low 45-65 % because of its short biological half-life of 2 hours and its poorly water-soluble drug.. It is a highly non-polar compound that is completely absorbed from the gastrointestinal tract, mainly from the jejunum, but has very low bioavailability, mainly due to presystemic metabolism. After absorption, nifedipine is further metabolized in the small intestine and liver to more polar compounds that are primarily eliminated by the kidneys.[10]

The main aim of this work was to formulate, optimize and evaluate of Nifedipine Nanosponges by using Ethyl cellulose and Polyvinyl alcohol for solubility enhancement.

MATERIALS AND METHOD

Materials

The drug Nifedipine was obtained from Unique Pharmaceutical Laboratory, Panoli. Ethyl cellulose, Polyvinyl alcohol and Dichloromethane were obtained from Thermosil Fine Chem Industries, Pune, India.

METHODOLOGY

Formulation of Nifedipine Nanosponges

The emulsion solvent diffusion method was used to formulate Nifedipine nanosponges by using an Ethyl cellulose as a polymer. The dispersed phase consists of the specified amount of drug and polymer which was dissolved in 20ml dichloromethane. The aqueous phase consists of a specified amount of Polyvinyl alcohol dissolved in 100ml of water. The disperse phase was added drop by drop into the aqueous phase by stirring on a magnetic stirrer at 1000rpm for 2 hours. The nanosponges formed were collected by filtration and dried in the oven at 40°C for 24 hours. After they were kept in a vacuum desiccator to remove the residual solvent.[11]

Formulation and optimization of Nanosponges by using 3^2 Central Composite Design (CCD), :(Design of Experiment)

Modern optimization techniques using experimental design are essential aids in formulation development as they help in developing the best possible formulation according to a given set of conditions, saving time, money, and development effort. Current research aims to formulate, optimize, and evaluate nifedipine nanosponges for improving solubility using optimization techniques. CCD is most effective in the estimation of the influence of individual variables (main effects) and their interaction using minimal experimentation.

In the present study, a 3^2 Central Composite Design as shown in table no 1 was employed to study the effect of independent variables, i.e., amount of Ethyl cellulose (X1) and Polyvinyl alcohol (X2) on dependent variables i.e., % Drug release and Entrapment efficiency using DESIGN EXPERT® software Version- 13 powered by State Ease Corporation, USA. A statistical model Incorporating interactive and polynomial terms was utilized to evaluate the responses. 3^2 means 3 level and 2 factor Central Composite Design.

Table No.1: Layout of Central Composite design batches of Nanosponges (F1-F9).

Formulation Code	Coded Values	
	X1	X2
F1	0	+1
F2	-1	+1
F3	-1	-1
F4	-1	0
F5	+1	-1
F6	0	-1
F7	+1	+1
F8	+1	0
F9	0	0

Table No. 2: Translation of coded value in an actual unit.

Coded Values	Actual Values (%)	
	X1	X2
-1	0.3	0.6
0	0.6	0.9
+1	0.9	1.2

(X1- Ethyl cellulose, X2- Polyvinyl alcohol)

Table No.3: Composition of Nanosponges as per 3^2 Central Composite design.

Formulation code	Drug (mg)	Ethyl Cellulose (gm)	Polyvinyl alcohol (gm)	Dichloromethane (ml)	Distilled water (ml)
F1	30	0.6	1.2	20	100
F2	30	0.3	1.2	20	100
F3	30	0.3	0.6	20	100
F4	30	0.3	0.9	20	100
F5	30	0.9	0.6	20	100
F6	30	0.6	0.6	20	100
F7	30	0.9	1.2	20	100
F8	30	0.9	0.9	20	100
F9	30	0.6	0.9	20	100

Organoleptic Properties

The drug sample was evaluated for its Organoleptic Properties like colour, odour, taste and appearance and the result was recorded.

Melting point determination

The melting point of Nifedipine was determined by the Capillary Tube Method. Fine powder of Nifedipine was filled in a glass capillary tube (previously sealed on one end). The Melting Point is determined in Thiele's tube using a thermometer.

Solubility studies

The solubility of Nifedipine was checked in different solvents like water, dichloromethane, 0.1N HCL, and phosphate buffer 6.8.

A saturation solubility study of Nifedipine in Nifedipine-NS formulation was carried out. Briefly, 10 mg of Nifedipine-NS formulation was suspended in 1 mL of distilled water packed into a 2ml centrifugation tube and centrifuged at 15000 rpm for 1 h. The supernatant was filtered through Whatman filter paper and Nifedipine content was determined by spectrophotometer at λmax 234.8nm. The test was carried out in comparison with the pure drug.[12]

Compatibility studies between Nifedipine and polymers

- **Fourier Transform Infra-Red Spectroscopy**

The compatibility between Nifedipine and the excipients used was examined using FTIR spectroscopy. In the FTIR spectroscopy technique, significant changes in the shape and position of the absorbance bands are analyzed. It analyzes significant changes in the shape and position of the absorbance bands to show the assumption of different functional groups of present and subsequent molecules.

- **Differential Scanning Calorimetry Analysis**

DSC spectrum of drugs and a mixture of drugs with polymers were obtained. The heat flow into or out of a sample is measured as a function of temperature or time, while a sample is exposed to a controlled temperature program.

Determination of Absorbance Maximum (λmax) of Nifedipine by UV Spectrophotometer

- **Preparation of standard Stock Solution (Phosphate Buffer pH 6.8):** Nifedipine (100mg) was accurately weighed and dissolved in small quantity of Phosphate Buffer pH 6.8 100ml of volumetric flask and final volume was made up to 100ml. 10 ml was taken and diluted further up to 100ml to make stock solution (100µg/ml). The UV spectrum was recorded in the range of 200-400 nm in UV spectrophotometer against blank.
- **Preparation of standard Stock Solution (0.1N HCL):** Nifedipine (100mg) was accurately weighed and dissolved in small quantity of 0.1 N HCl in 100ml of volumetric flask and final volume was made up to 100ml. 10 ml was taken and diluted further up to

100ml to make stock solution (100µg/ml). The UV spectrum was recorded in the range of 200-400 nm in UV spectrophotometer against blank.

Preparation of Calibration Curve for Nifedipine

- **By using 0.1 N HCL**

For calibration curve, standard solutions were prepared by diluting stock solution. From stock solution 0.5, 1.0, 1.5, 2.0 and 2.5ml were transferred to 10ml volumetric flasks and volume were made up to 10ml to get serial dilutions of 5, 10, 15, 20 and 25 µg/ml respectively. The solutions were kept in a fused silica cuvette. The absorbances of these solutions was determine spectrophotometrically at λ max 230.8 nm and the calibration curve was plotted between concentration and absorbance.

- **By using Phosphate Buffer pH 6.8**

For calibration curve, standard solutions were prepared by diluting stock solution. From stock solution 0.5, 1.0, 1.5, 2.0 and 2.5ml were transferred to 10ml volumetric flasks and volume were made up to 10ml to get serial dilutions of 5, 10, 15, 20 and 25 µg/ml respectively. The solutions were kept in a fused silica cuvette. The absorbances of these solutions was determine spectrophotometrically at λ max 234.8 nm and the calibration curve were plotted between concentration and absorbance.

Evaluation of Nanosponges

1. Particle Size and Poly Dispersity Index Determination

The Mean Particle size (MPS) and Poly Dispersity Index (PDI) were determined by PCS (Photon Correlation Spectroscopy), by using Beckman Coulter Counter (Delsa tm Nano). The measurement using PCS based on the light-scattering phenomena in which the statistical fluctuation of the intensity of scattered light from particles in the measuring cells. statistical fluctuation of the intensity of scattered light from particles in the measuring cells are measured. Prior to the measurements, sample were diluted with double-distilled water to produce a suitable scattering intensity.

2. Determination of Production yield OR percentage yield

Nifedipine-loaded Nanosponge was weighed after drying. The percentage yield was calculated by.[13]

Production Yield = Practical mass of nanosponges / Theoretical mass (Drug+polymer) × 100.

3. Drug content

The prepared nanosponge formulations of Nifedipine were tested for their drug content. Drug content was analyzed by taking 10mg of sample and dissolved in 100 ml of phosphate buffer pH 6.8. Each of solution was further diluted in phosphate buffer pH 6.8. Solution was filtered to remove insoluble matter. Absorbance was measured by UV spectrophotometer at 234.8nm.[14]

Drug Content = (Concentration × Dilution Factor × Volume taken) / 1000 × 100

4. Drug entrapment efficiency

The Drug entrapment efficiency of nanosponges were determined by adding 10 ml of phosphate buffer pH 6.8 and sonicated in a Sonicator bath and filtered. 1 ml of filtrate was made up to 10 ml with phosphate buffer and was assayed spectrophotometrically at 234.8nm (UV visible spectrophotometer). The amount of entrapped drug was calculated from the equation.[15]

Drug entrapment efficiency = Practical drug content/Theoretical drug content × 100

5. *In-vitro* Drug release studies

Drug release was determined by a type II dissolution apparatus fitted with eight rotating paddles and vessels. Nine formulations were used for the release study and experiments were carried out in triplicate. The rotation speed was 100 rpm using 900ml of phosphate buffer pH 6.8. The temperature of the dissolution medium was maintained at 37°C.at predetermined intervals, 1ml of the sample was withdrawn and replaced with fresh dissolution media. The experiment is carried out for 24 hours. At specific time intervals, the receptor buffer is completely withdrawn and replaced with a fresh buffer solution. Finally, the amount of release in phosphate buffer were measured by spectrophotometer at 234.8nm and drug release was calculated to determine the release pattern.[16]

6. Stability studies

An Accelerated stability study was carried out for the optimized formulation batch as per the International Conference on Harmonization guidelines. The stability studies were carried out according to ICH guidelines at an accelerated temperature of 40 ± 2°C / 75% + 5% RH for a period of 3 months. The NS were placed in glass vials and stored at 40±2°/75± 5 % RH atmospheric conditions in a stability chamber for a period of 3 months. The sample was periodically withdrawn (1, 2, and 3 months) and evaluated for Drug Content (%), Drug Release (%).

RESULTS AND DISCUSSIONS

Organoleptic Properties

Nifedipine was checked for its colour, odour and taste. Nifedipine is Yellow crystalline powder in appearance, odourless and bitter in taste.

Melting point determination

Melting point of the Nifedipine was determined by capillary Method and found to be 167 ºC.

Solubility studies

The solubility of Nifedipine was checked in different solvents which are shown in following table no 4

Table No. 4: Solubility of Nifedipine in different solvent.

Sr No.	Solvents	Solubility(mg/ml)
1	Water	0.005
2	0.1N HCL	0.025
3	Phosphate Buffer pH6.8	0.012
4	Dichloromethane	10

The results showed that Nifedipine nanosponges reported a significant increase in the solubility of Nifedipine compared to the pure drug in distilled water and also show that the increase in polymer concentration (Polyvinyl alcohol) increased the solubility of drug. The solubility of Nifedipine in water was 0.005 mg/ml or 5 µg/ml. while its solubility in nanosponge particles was in the range of 34.10 µg/ml to 51.31 µg/ml for Nifedipine-NS1 and Nifedipine-NS9 respectively which are represented in Figure no. 1.

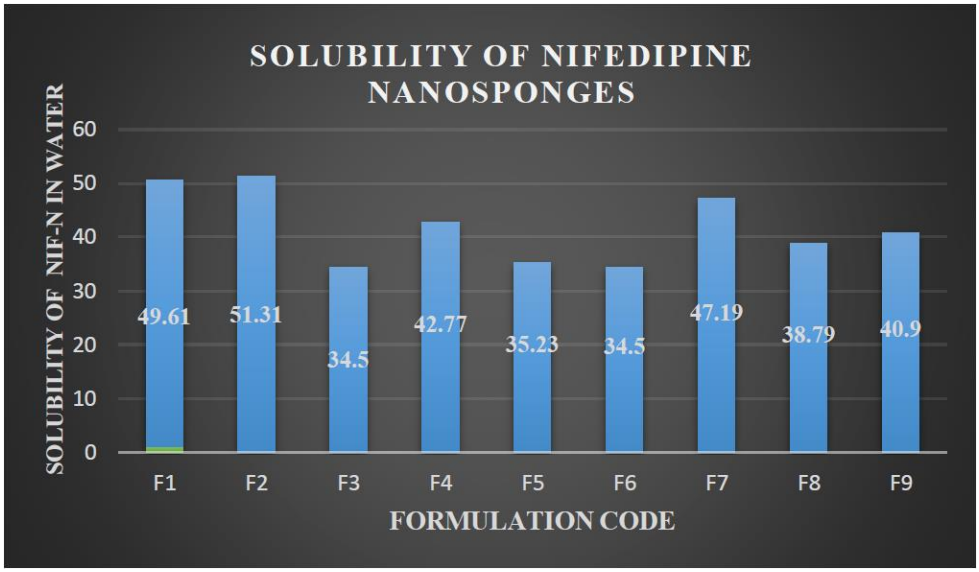


Fig. No. 1: Solubility of Nifedipine-NS formulations in distilled water (µg/ml).

Compatibility studies between Nifedipine and polymers

- **Fourier Transform Infra-Red Spectroscopy**

Fourier transform infrared (FT-IR) spectra of the samples were obtained using a FTIR spectrophotometer by KBr disc method. The spectrums were recorded for the pure drug (Nifedipine), Polymer (Ethyl cellulose) and FT-IR spectra of Blend (Nifedipine+Ethyl cellulose+Polyvinyl alcohol) are shown in following figures no 2, 3.

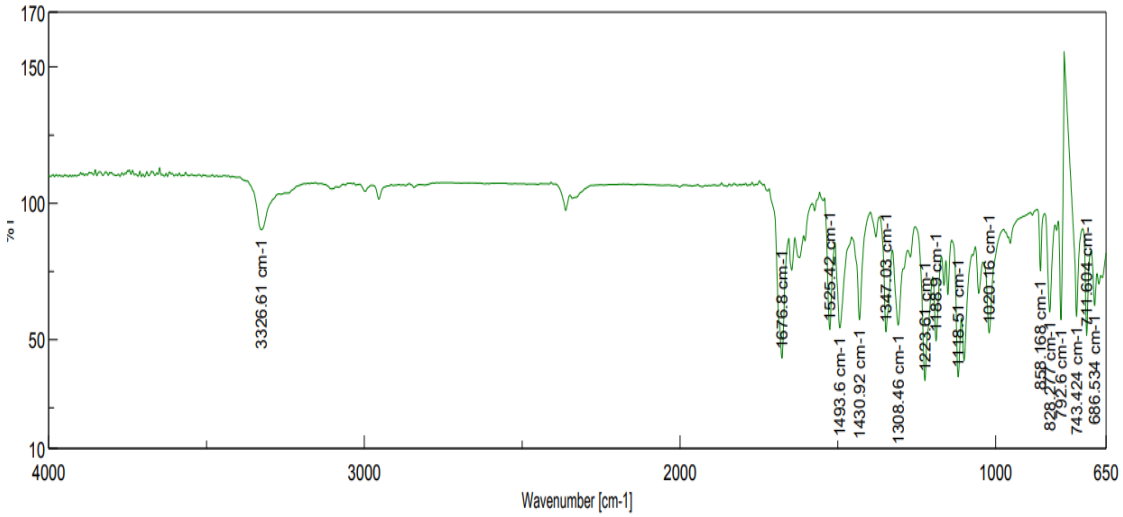


Fig. No. 2: FT-IR spectrum of Polymer [Ethyl cellulose].

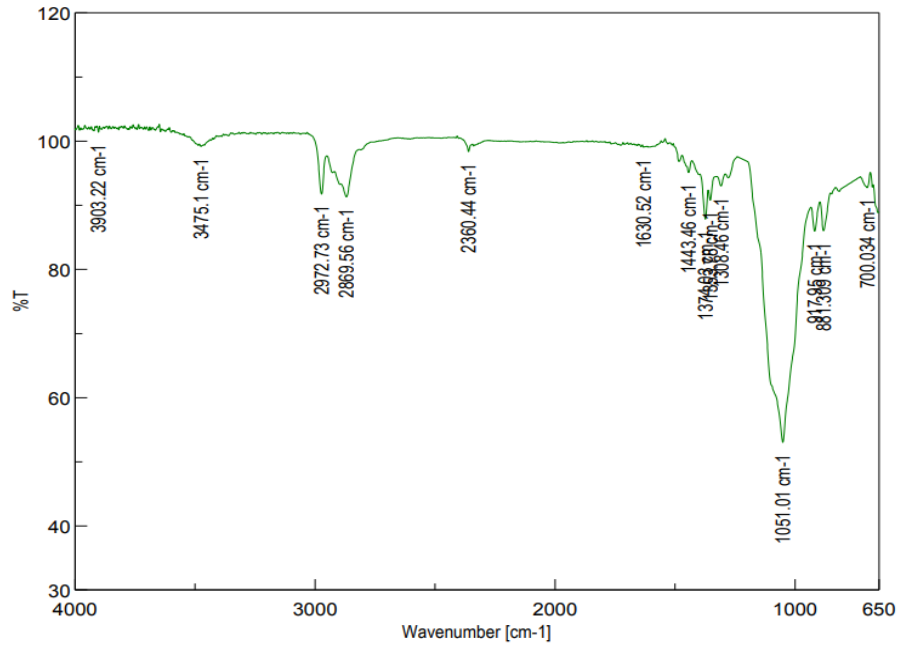


Fig. No. 3: FT-IR spectrum of pure drug Nifedipine.

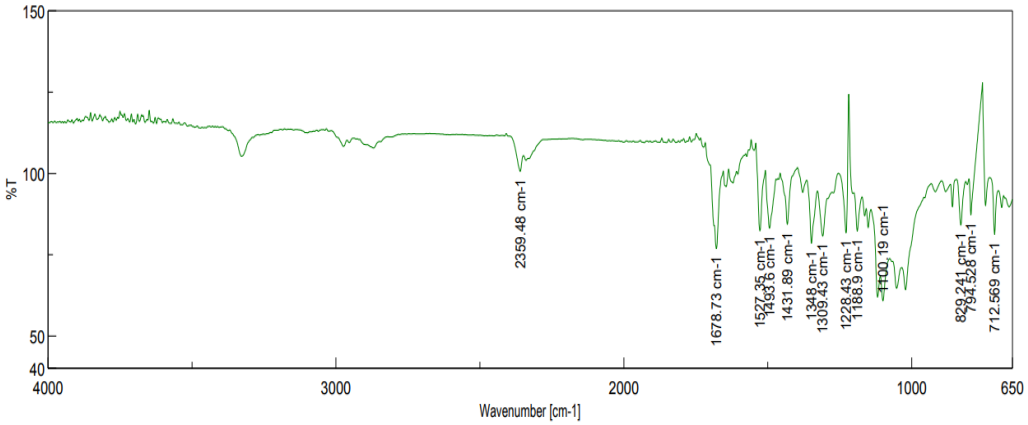


Fig.No.4: FT-IR spectrum of Blend [Nifedipine+Ethyl cellulose+Polyvinyl alcohol]

Differential Scanning Calorimetry Analysis

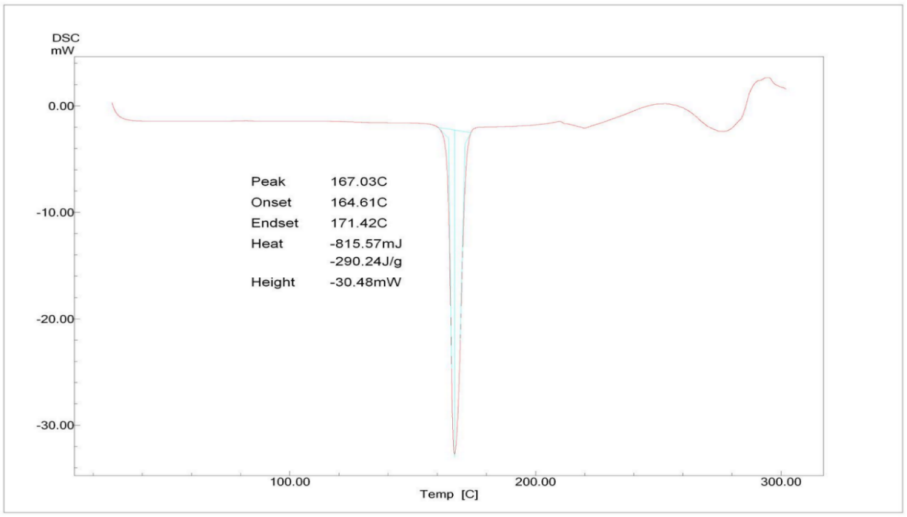


Fig.No.5: Differential Scanning Calorimetry of Nifedipine.

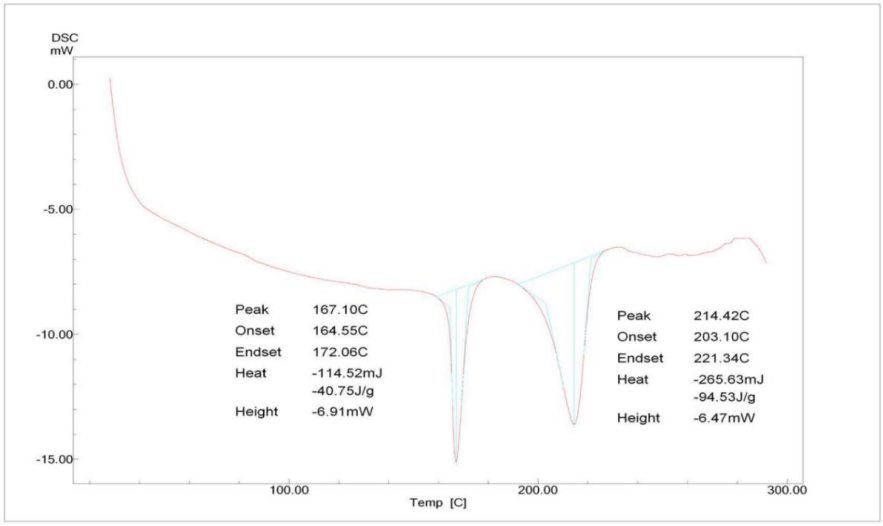


Fig.No.6: Differential Scanning Calorimetry of Blend.

DSC studies were carried out for Nifedipine and Blend. Fig.5 and 6 showed DSC thermogram of Nifedipine and blend respectively. The DSC thermogram of Nifedipine showed sharpen endothermic peak with onset temperature 164.61 ºC and peak temperature 167.03 ºC corresponding to melting point, while the Blend of drug and excipients exhibited an endothermic peak at 214.42 ºC. The presence of same peak in the blend indicates that there was no interaction between drug and excipient during the formulation process. By comparing the thermograms of drug and drug- excipients it was found that it has a suitable compatibility for further formulation.

Determination of Absorbance Maximum (λmax) of Nifedipine by UV Spectrophotometer

The Nifedipine was analysed by using spectrophotometrically in between 200-400nm. The maximum absorbance (λ_{MAX}) was found to be at **230.8nm in 0.1N HCL** and **234.8nm in Phosphate Buffer pH 6.8**. The UV spectrum of Nifedipine was measured in following figures no 7 & 8.

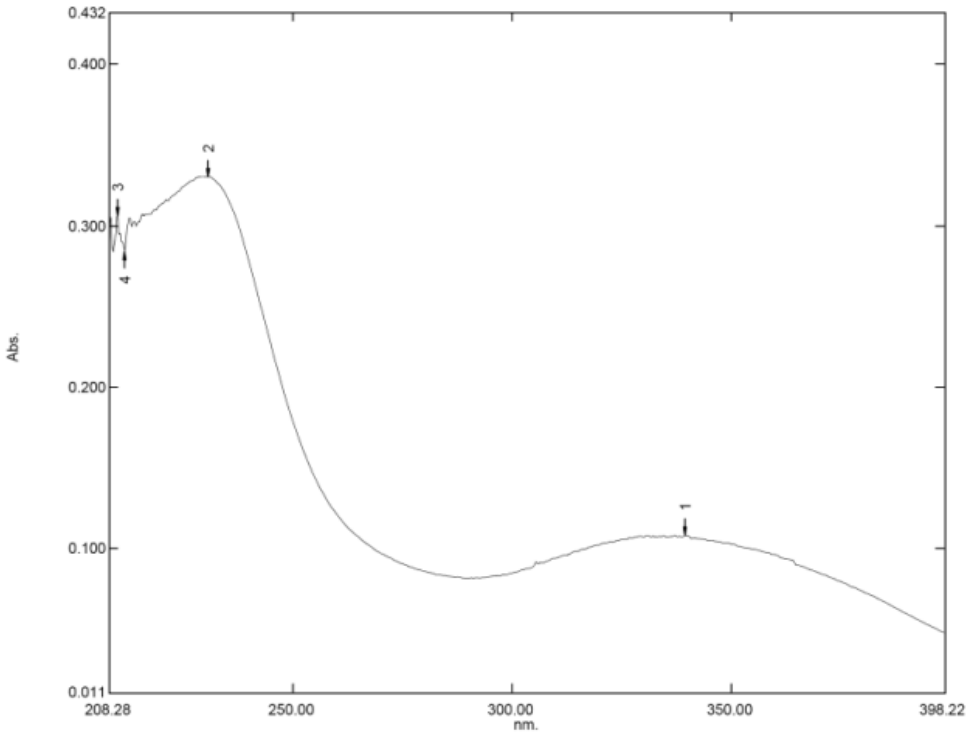


Fig.No.7: Absorbance Maximum (λ_{MAX}) of Nifedipine in 0.1N HCL.

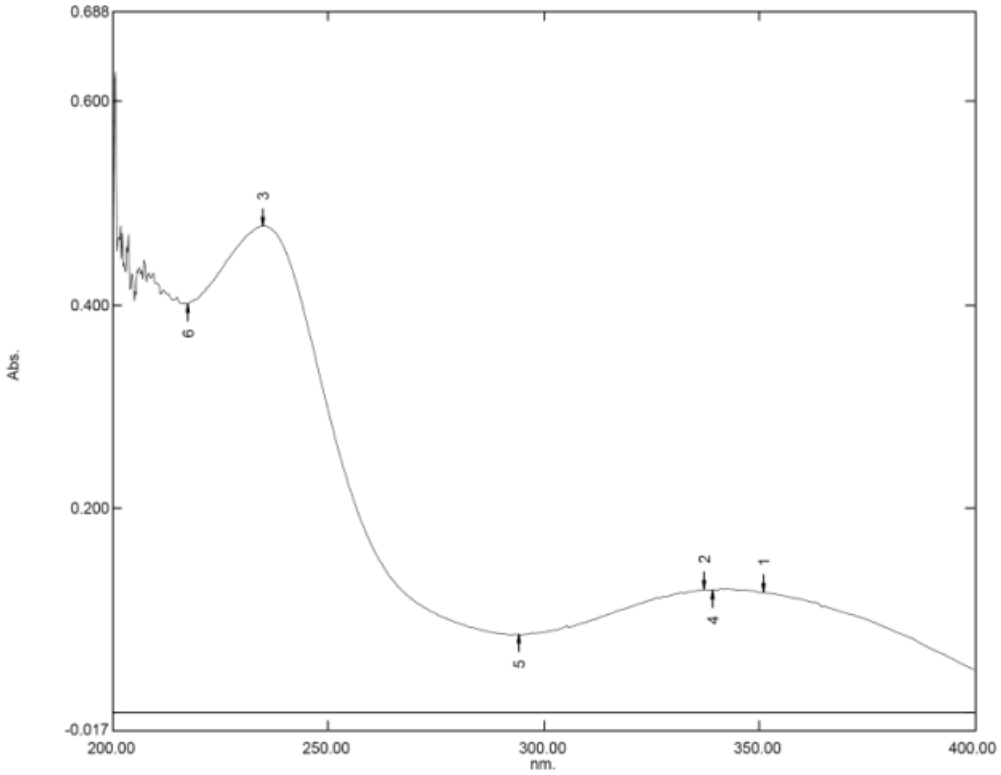


Fig.No.8: Absorbance Maximum ($\lambda_{MAX)}$ of Nifedipine in Phosphate Buffer pH 6.8.

Preparation Of Calibration Curve for Nifedipine:

- **By using 0.1 N HCL**

The standard calibration curve of Nifedipine was taken in 0.1 N HCL at wavelength 230.8nm. In the calibration curve, linearity was obtained between 5-25µg\ml concentration of Nifedipine and the correlation coefficient value (R^2) was found to be 0.99588. It was observed that the concentration range of 5-25µg /ml obeyed the Beer's Lambert's law. The results are shown in Table no 5 and figure no 9.

Table No. 5: Standard Calibration Curve of Nifedipine in 0.1 N HCL.

Sr no.	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.291
2	10	0.347
3	15	0.407
4	20	0.465
5	25	0.506

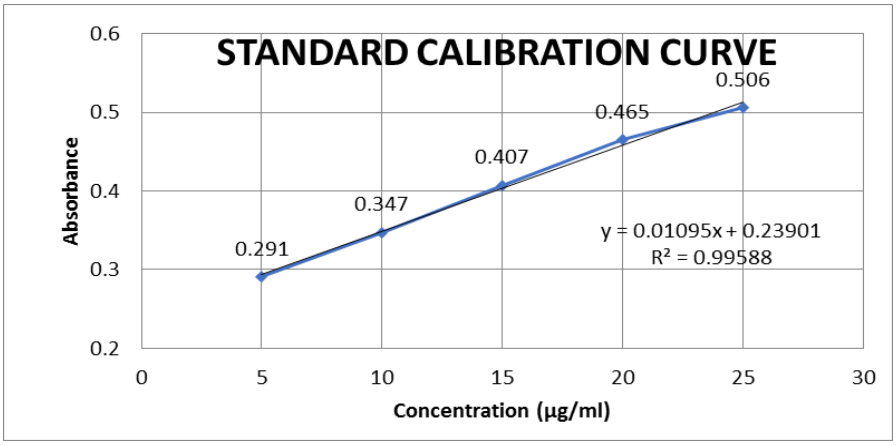


Fig.No.9: Standard Calibration Curve of Nifedipine in 0.1N HCL.

- **By using Phosphate Buffer pH 6.8**

The standard calibration curve of Nifedipine was taken in Phosphate Buffer pH 6.8 at wavelength 234.8nm. In the calibration curve, linearity was obtained between 5-25µg\ml concentration of Nifedipine and the correlation coefficient value (R^2) was found to be 0.99518. It was observed that the concentration range of 5-25µg /ml obeyed the Beer's Lambert's law. The results are shown in Table no 6 and figure no 10.

Table.No.6: Standard Calibration Curve of Nifedipine in Phosphate Buffer pH 6.8

Sr no.	Concentration (µgm/ml)	Absorbance (nm)
1	5	0.292
2	10	0.422
3	15	0.526
4	20	0.622
5	25	0.715

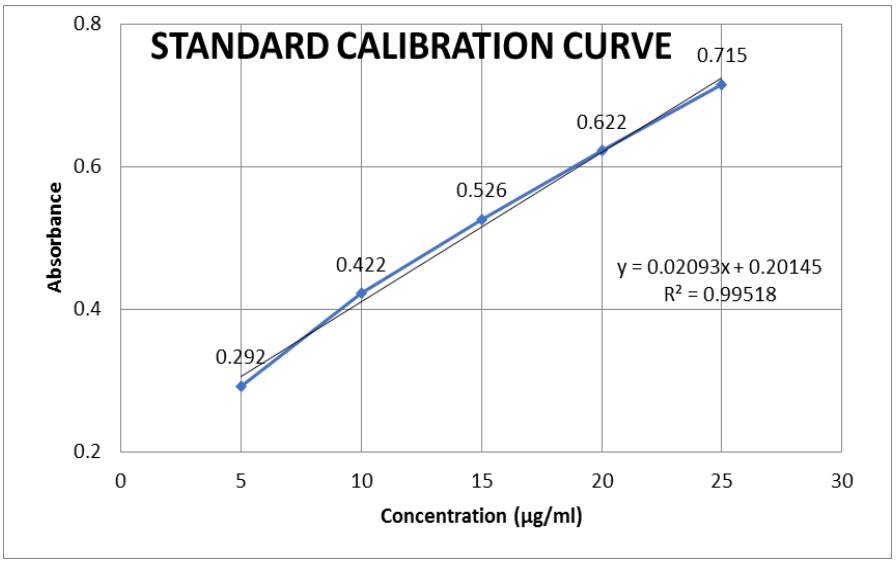
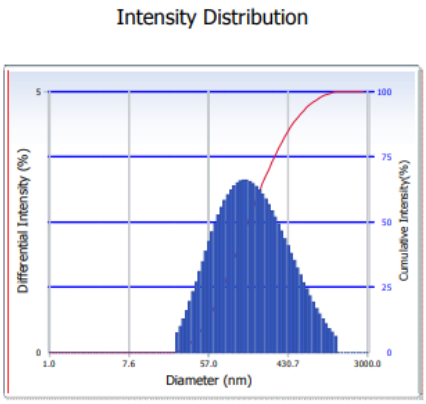


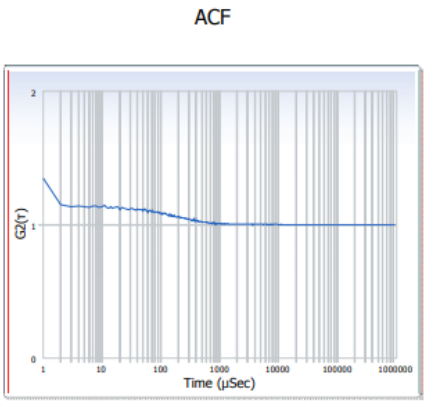
Fig.No.10: Standard Calibration Curve of Nifedipine in Phosphate Buffer pH 6.8.

Evaluation of Nifedipine Nanosponges

1. Particle Size and Poly Dispersity Index Determination

The particle size is one of the most important parameter for the Evaluation of nanosponges. Optimized batch F2 was evaluated for Particle Size and Poly Dispersity Index. The particle size and Poly Dispersity Index of the prepared Nifedipine nanosponge (F2) was measured using Beckman Coulter Counter (Delsa t^{m} Nano) Particle size analyzer and depicted in Figure No.11. Particle size analysis showed that the average particle size of Nifedipine nanosponge using ethyl cellulose was found to be **249.6 nm** with Poly Dispersity Index (PDI) value **0.352**.





Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	249.6	246.5
2	0.0	0.0
3	0.0	0.0
4	0.0	0.0
5	0.0	0.0
Average	249.6	246.5
Residual :	4.056e-003	(O.K)

Cumulants Results

Diameter	(d)	: 136.2	(nm)
Polydispersity Index	(P.I.)	: 0.352	
Diffusion Const.	(D)	: 3.621e-008	(cm²/sec)

Measurement Condition

Temperature	: 25.1	(°C)
Diluent Name	: WATER	
Refractive Index	: 1.3328	
Viscosity	: 0.8858	(cP)
Scattering Intensity	: 10550	(cps)

Fig.No.11: Particle size and PDI of Optimized batch F2.

2. Determination of Production yield OR percentage yield

Production yield or Percentage yield of the formulated Nifedipine Nanosponges were calculated using the formula:

Production Yield = Practical mass of nanosponges / Theoretical mass (Drug+polymer) × 100.

The range of the production yield of the prepared Nanosponge was found to be between 65.15% to 85.36% as shown in Table no 7. The production yield of all formulations is

depicted in Figure no 12. From the results, we can conclude that as the concentration of polymer increases the percentage yield also increases.

Table.No.7: Production yield or percentage yield of nanosponges formulations (F1-F9)

Formulation code	Production yield (%)
F1	66.66%
F2	81.46%
F3	73.65%
F4	67.57%
F5	79.36%
F6	65.15%
F7	85.36%
F8	75.39%
F9	82.27%

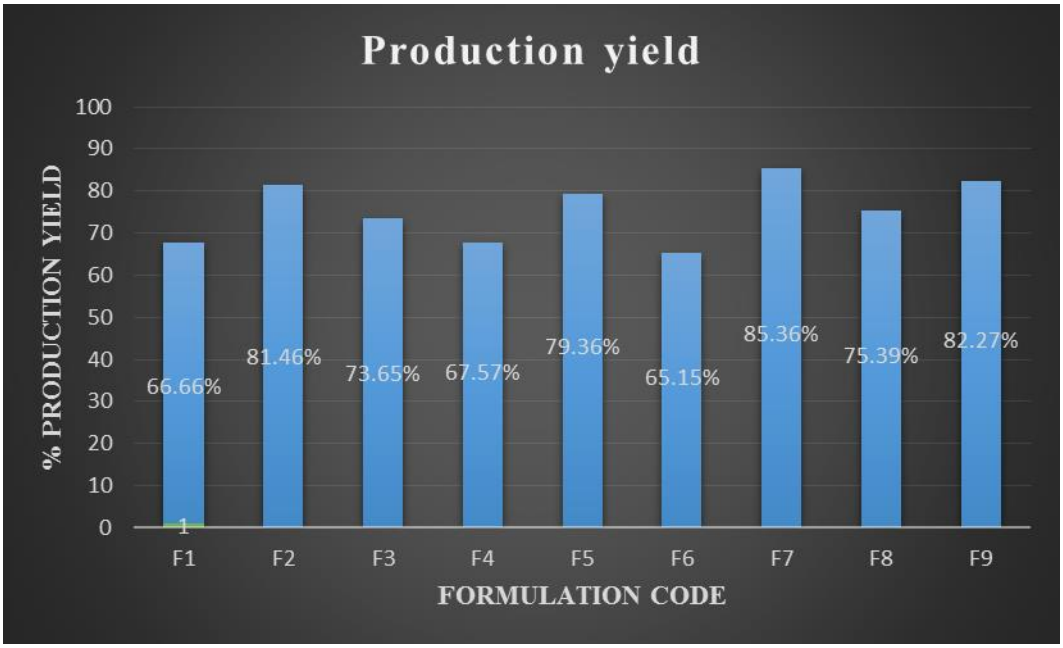


Fig.No.12: Production yield of Nifedipine Nanosponges (F1-F9).

3. Drug content

The amount of drug content was calculated from the equation

Drug Content = (Concentration × Dilution Factor × Volume taken) / 1000 × 100

The percentage drug content of the formulated Nano-sponge (F1-F9) as shown in table no 8. The drug content was found to be highest for formulation (F2) which is 92.20 % and the lowest drug content was found to be 78.79 % (F5). The results show that the increase in polymer concentration (Ethyl cellulose) increased the drug content.

Table.No.8: Drug content of Nifedipine nanosponges (F1-F9)

Formulation code	% Drug content
F1	85.90
F2	92.20
F3	83.23
F4	89.13
F5	78.79
F6	83.68
F7	84.10
F8	82.05
F9	84.57

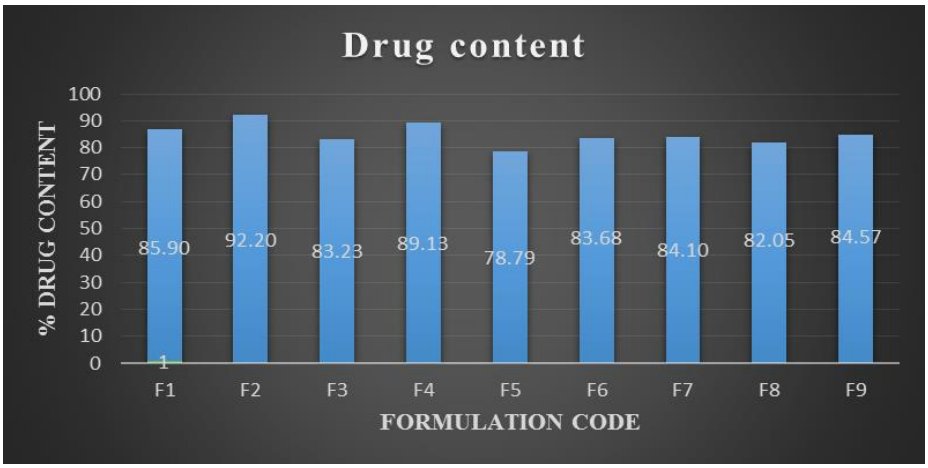


Figure No.13: % Drug content of Formulations (F1-F9).

4. Drug entrapment efficiency

The Entrapment Efficiency was found to be highest for formulation (F8) which is 89.50 % and the lowest entrapment of drug in formulation (F4) which is 77.91%. The variation in entrapment efficiency was due to the changes in the polymer concentration and the difference in the degree of cross-linking. In general, all nano-sponge formulations showed prolonged sustained and controlled release up to 24 hours. This may be due to a higher concentration of the polymer would have provided more space and also reduced the escaping of the drug into the external phase.

Table.No.9: Drug entrapment efficiency of Nifedipine nanosponges (F1-F9).

Formulation code	Drug entrapment efficiency (%)
F1	80.20
F2	82.45
F3	79.54
F4	77.91
F5	86.11
F6	81.66

F7	88.78
F8	89.50
F9	82.95

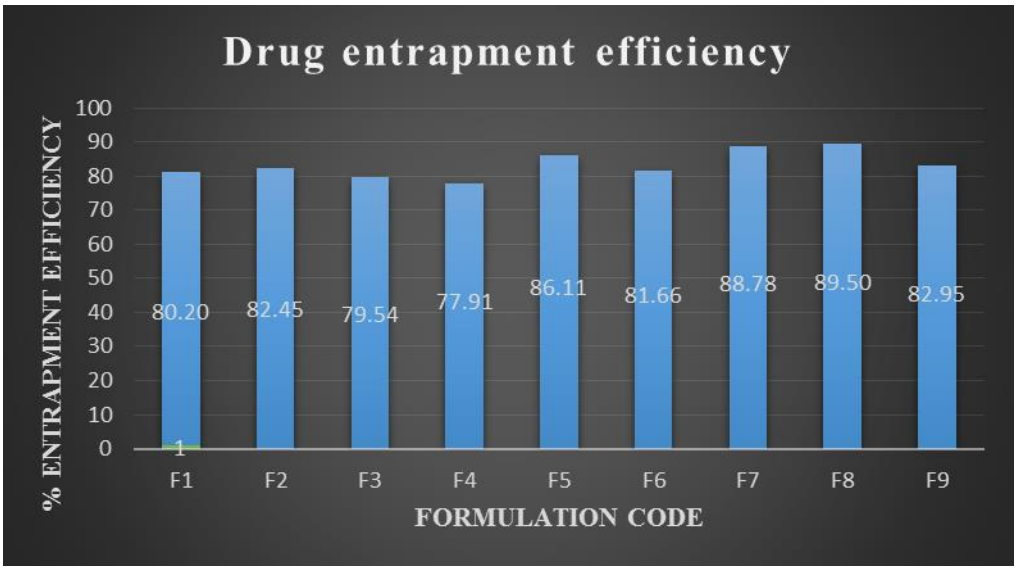


Fig.No.14: Entrapment efficiency of formulations (F1-F9).

***In vitro* Drug release studies**

An *in-vitro* drug release study of the prepared formulations (F1-F9) was carried out using a type II dissolution apparatus. The amount of drug released in different time intervals were observed.

In-vitro drug release profile data obtained for Nifedipine Nanosponges containing Ethyl cellulose are given in Table no 10 and figures no 15,16 and 17.

The amount of drug released from Nifedipine Nanosponges ranges from 69.21 to 85.44% at different time intervals for a period of 12 h and the total amount of drug released is 79.81 to 90.86 at 24 h. The results revealed that the release profile of Nifedipine Nanosponges shows drug release as given in Table no 10. Batch F1 to F9 showed drug release as 85.10 %, 79.81 %, 83.90 %, 88.35 %, 82.01 %, 90.86 %, 81.77 %, 80.98 % and 81.97 % respectively. In the first drug, the release was found to range from 4.30% to 11.12%. In general, all nano-sponge formulations showed prolonged sustained and controlled release up to 24 hours. It could be concluded from that Results showed that nanosponges with a decreased concentration of polymer increase the % Drug release. The rate of drug release decreased significantly upon increasing the Concentration of polymer.

Batch no 2 was selected as the optimized batch because it has the highest drug release of 90.

86% for further studies like kinetic study and stability study.

Table.No.10: Percentage cumulative drug release of Nifedipine nanosponges (F1-F9).

Time in hours	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	2.50	3.80	2.50	3.10	1.90	2.45	2.75	1.50	3.45
1	6.20	11.12	6.55	9.17	5.35	4.64	6.12	4.30	10.60
2	15.13	22.78	13.34	19.24	12.40	18.17	17.10	11.14	17.32
3	30.40	34.75	24.54	28.56	22.98	25.91	31.60	24.35	32.18
4	36.50	40.51	29.20	37.14	27.50	37.34	35.65	31.34	39.67
5	45.13	52.11	40.12	50.30	37.20	44.56	48.40	38.11	47.80
6	56.65	61.52	48.41	61.13	46.56	53.17	58.27	49.43	55.57
8	68.40	72.19	63.90	70.15	60.41	61.22	66.30	63.81	66.89
12	78.61	85.44	72.95	82.93	69.21	71.33	78.30	74.48	73.82
24	85.10	90.86	82.10	88.35	79.81	81.77	83.90	80.98	81.97

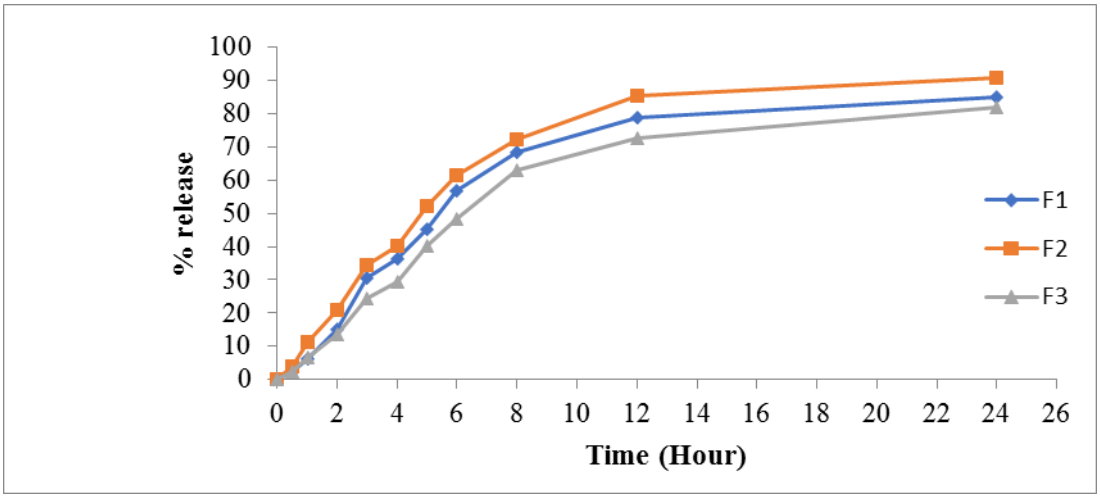


Fig.No.15: %Drug Release in Graphical Presentation (F1 TO F3).

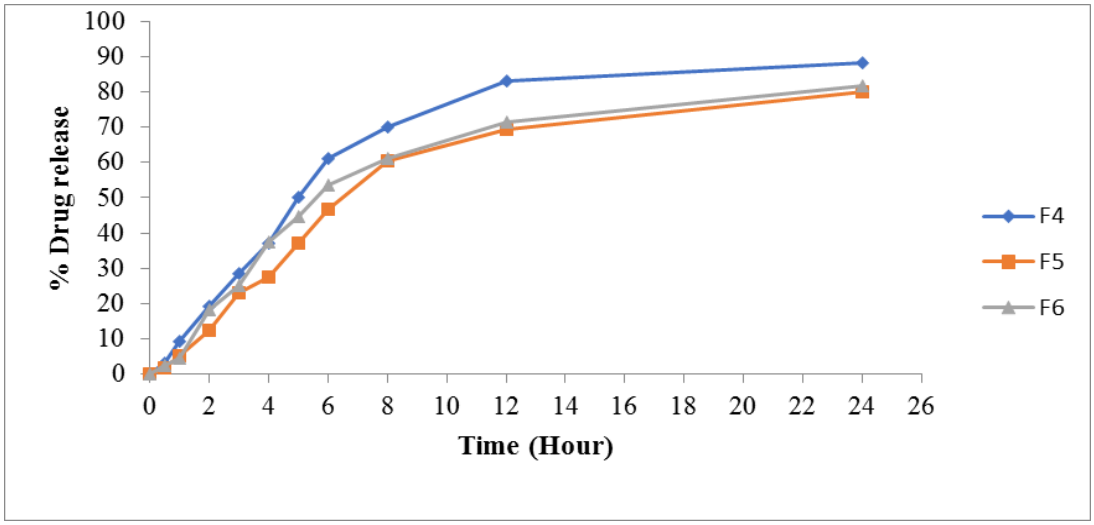


Fig.No.16: %Drug Release in Graphical Presentation (F4 TO F6).

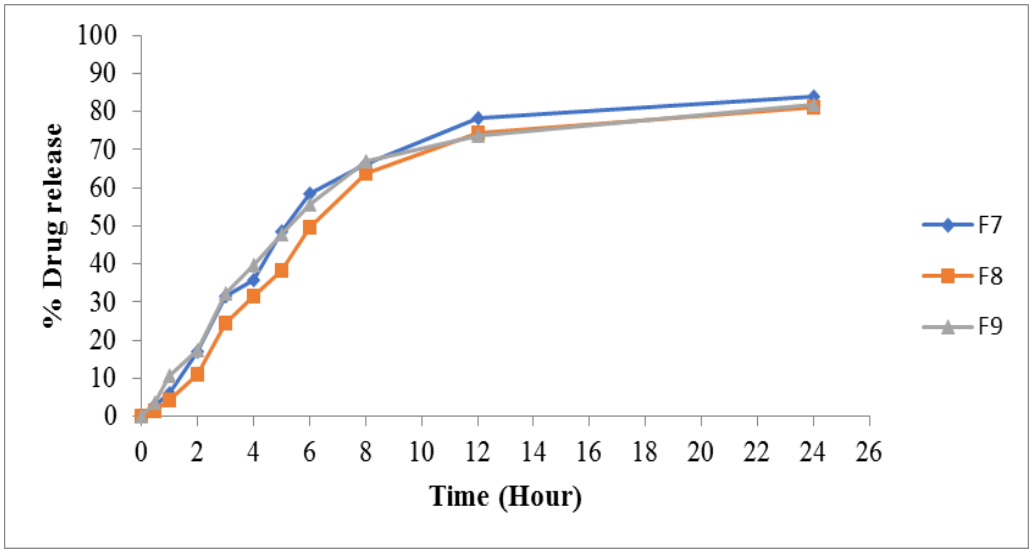


Fig.No.17: %Drug Release in Graphical Presentation (F7 TO F9).

***In-Vitro* Drug Release Kinetics**

Batch no 2 was selected as optimized batch because it has highest drug release for kinetics studies.

The data obtained from the in vitro release study was used to fit into kinetic models. This was done to find out the mechanism of drug release from Nifedipine nanosponges. In order to determine the release model, the in vitro release data were analysed according to zero order, first order, Higuchi model and peppas model. The preference of a certain mechanism was based on the coefficient of determination (r^2) for the parameters studied, where the r^2 value is higher for First order, it is selected as the best fitted model. This was confirmed by r^2 value range for First order model 0.936. It is observed that the Optimized Batch (F2) followed Fickian diffusion.

Table.No.11: Kinetic Drug Release Study of Optimized Batch F2

Batch Code	Zero order R^2value	First order R^2value	Higuchi R^2value	Korsmeyer Peppas R^2value	'n' value
F6	0.720	0.936	0.911	0.783	0.5

a. Zero order Drug Release kinetics

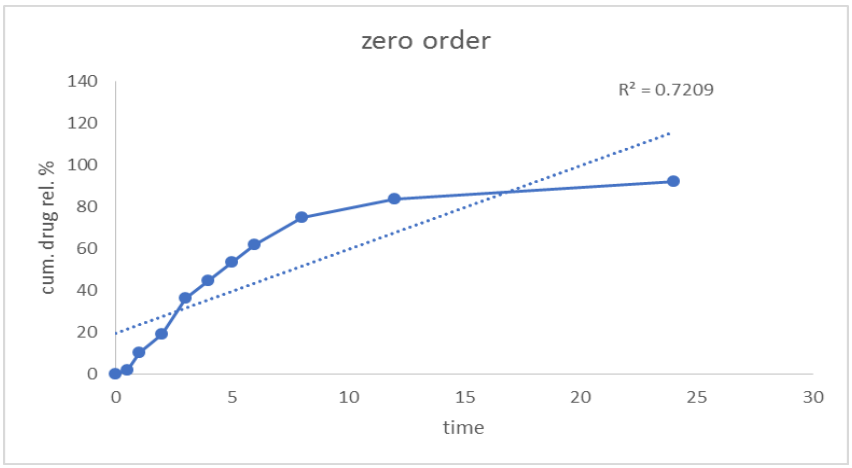


Fig.No.18: Zero order Drug Release kinetics

b. First order Drug Release Kinetics

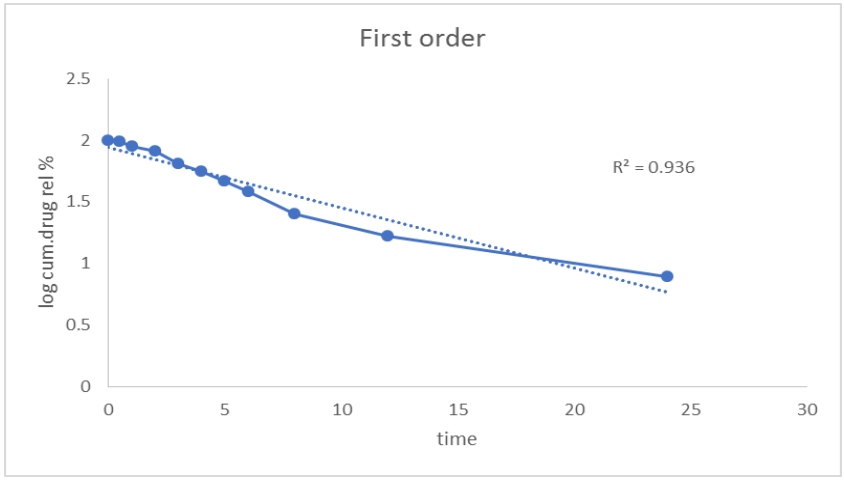


Fig.No.19: First order Drug Release Kinetics.

c. Higuchi's Drug Release Kinetics

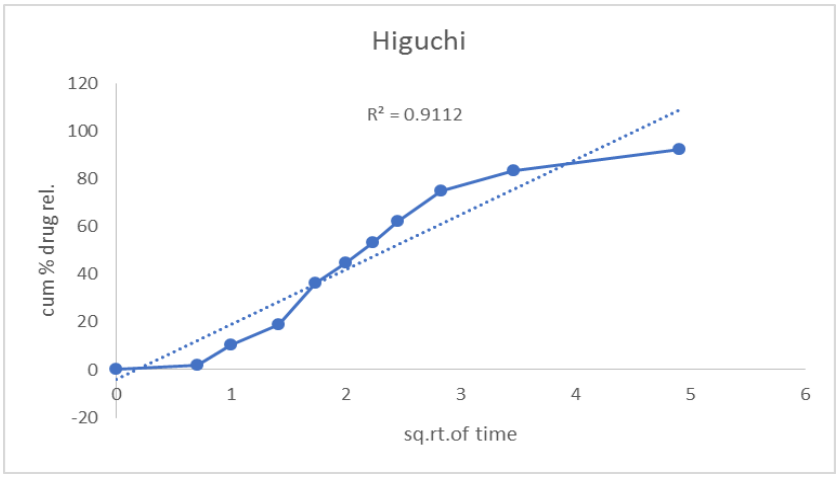


Fig.No.20: Higuchi's Drug Release Kinetics.

d. Korsmeyer-Peppas Drug Release kinetics

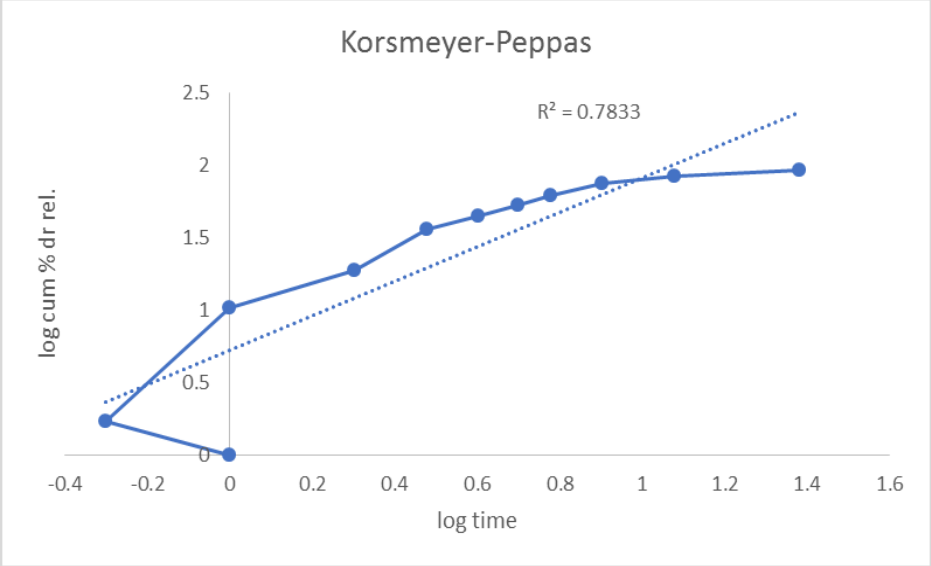


Fig.No.21: Korsmeyer-Peppas Drug Release kinetics.

Optimization and Data analysis (by Design Expert Software)

- **Data analysis (by Design Expert Software)**

A 3^2 Central Composite design was selected and the 2 factors were evaluated at 3 levels. The amount of Ethyl cellulose (X1) and PVA (X2) were selected as independent variables and the dependent variables were % Drug Release and Entrapment efficiency.

The 3^2 Central Composite design was applied to optimize Nanosponges of Nifedipine. The response surface methodology analyzed data clearly indicate that % Drug release and Entrapment efficiency values were mainly depending upon the selected independent variables. The regression equation for the responses fitted in linear model were generated ANOVA was used to identify the significant effect obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability (0.0026) and (0.0114).

Table.No.12: Result of ANOVA.

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Model significant/Not Significant
% Drug release	96.79	**2**	48.40	18.76	0.0026	0.8621	Significant
Entrapment efficiency	102.79	2	51.39	10.32	0.0114	0.7748	Significant

Graphical Representation

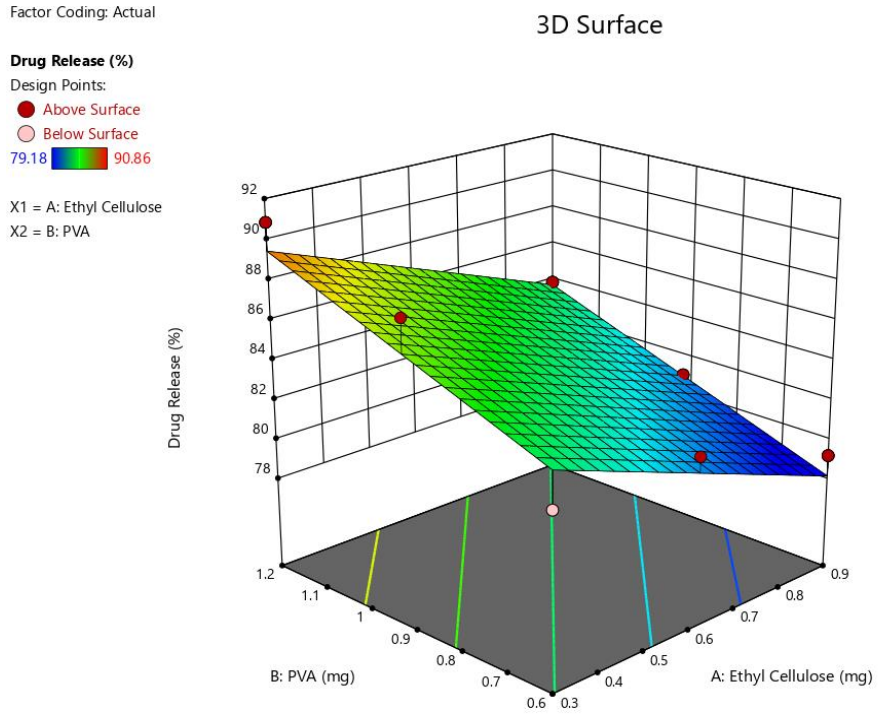


Fig.No.22: A response surface plot showing the effect of concentration of independent variables on the % drug release

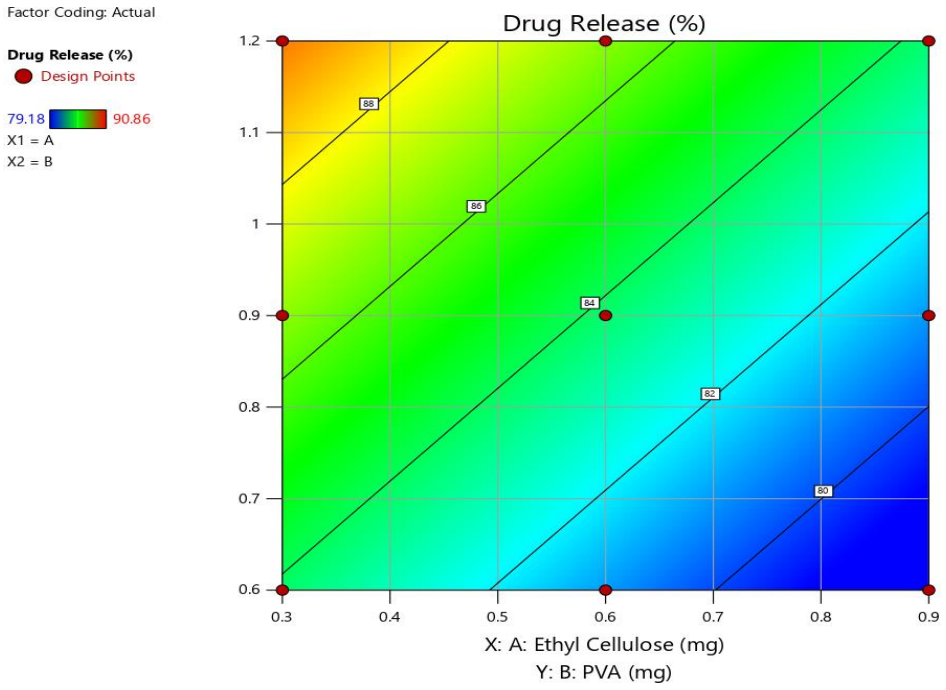


Fig.No.23: A counterplot of showing the relationship between various levels of independent variables to gain fixed value of % drug release.

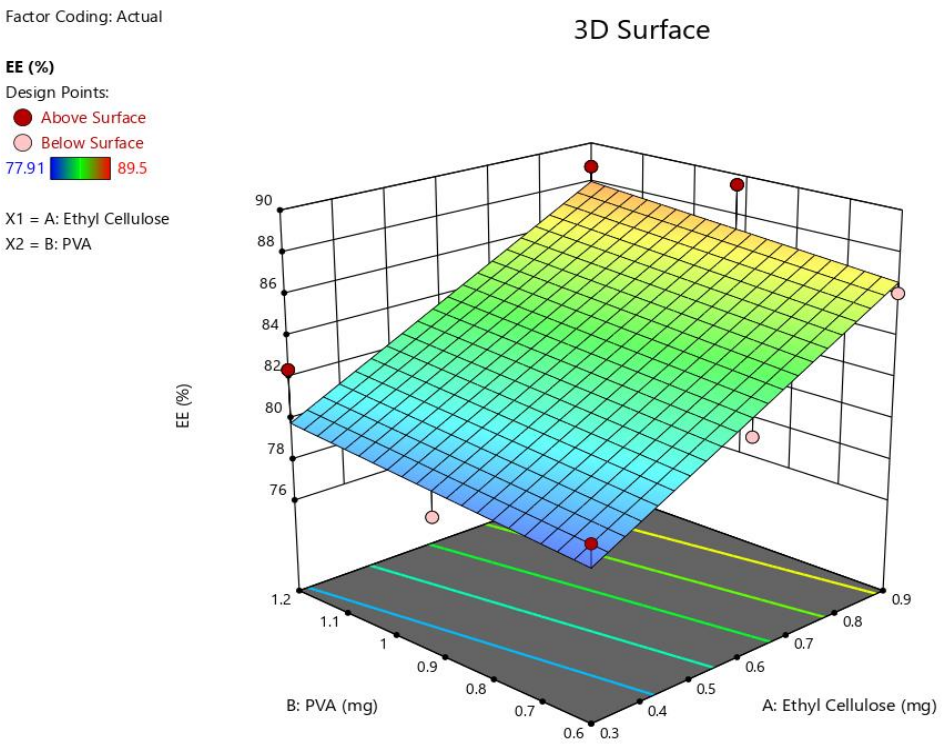


Fig.No.: 24 response surface plot showing an effect of concentration of independent variables on the Entrapment efficiency.

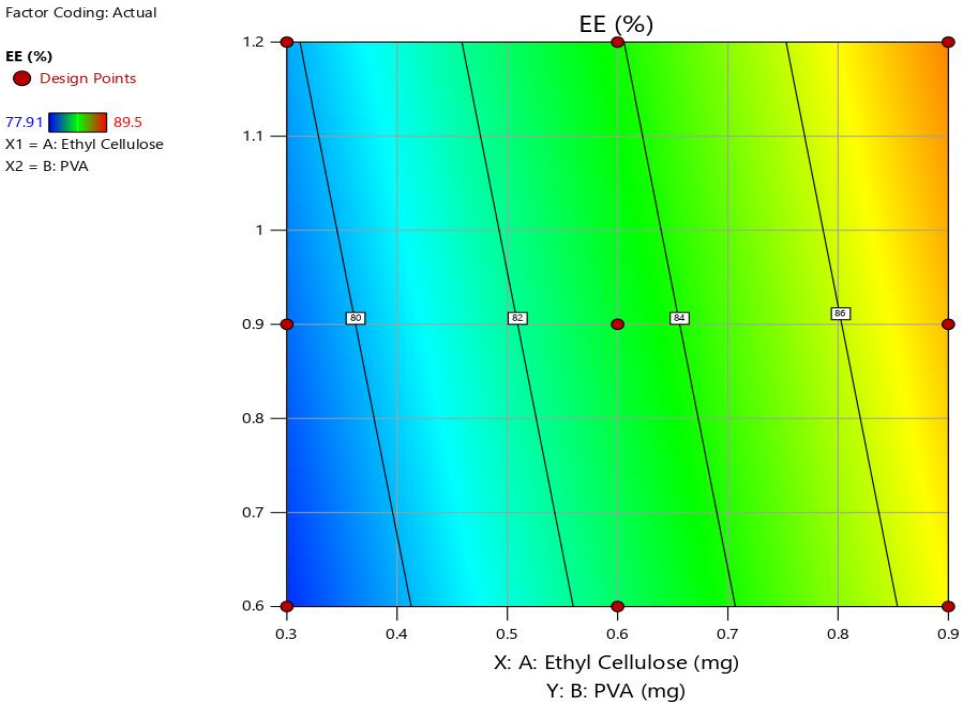


Fig.No.25: A counter plot showing the relationship between various levels of independent variables to gain fixed value of Entrapment efficiency.

Stability studies

A stability study was performed for a batch of the optimized formulation (F2) according to the guidelines of the International Conference on Harmonization. The NS were placed in glass vials and stored at 40±2°/75± 5 % RH atmospheric conditions in a stability chamber for a period of 3 months. Samples were analysed for Drug Content (%) and Drug Release (%).

The stability study was conducted for three months and analyzed for any changes in Physical appearance, Drug Content (%), Drug Release (%), and Drug Entrapment Efficiency (%) and was evaluated at the end of the study as shown in Table no 13. It was found that there were no significant changes in the formulation with respect to the evaluation parameters performed and thus it could be concluded that the formulation was stable after the 3-month stability study at accelerated conditions 40±2°/75± 5 % RH.

Table No.13: Stability study of Optimized batch F2 at 40°C ± 2°C /75% RH ± 5% RH.

Evaluation Parameters	Observation			
	Initial	After 1 Month	After 2 Month	After 3 Month
Drug Content (%)	92.20	92.01	91.78	91.11
Drug Release (%)	90.86	90.35	89.91	89.57

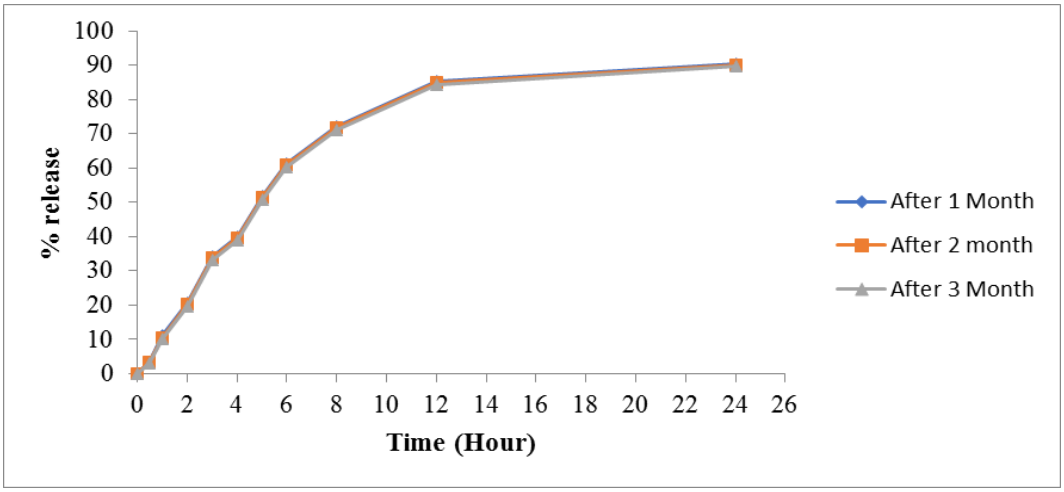


Fig. No. 26: Graph of In Vitro Drug Release After Stability Study (Batch F2).

CONCLUSION

- The aim of the study was to formulate, optimize and evaluate Nifedipine Nanosponges for solubility enhancement and Polymeric Nanosponges delivery system was to deliver Nifedipine in a controlled manner.
- In the present study, an attempt has been done to successfully developed a Nifedipine Nanosponges by emulsion solvent diffusion method, using polymer such as ethyl

cellulose and PVA. This method of manufacturing was found to be simple did not require specialized equipment and has scale up feasibility and cost-effective method.

- From the result of experiment, it can be concluded that:
- Preformulation parameter for identification of drug such as UV spectrophotometry, melting point, solubility was evaluated and the result found to be satisfactory and all the values obtained to be satisfactory and all the values obtained comply pharmacopoeial limits
- FTIR Spectrum of drug was carried out, in that all the characteristic's peaks of Nifedipine were present at their respective wavelength.
- Compatibility studies were performed using FT-IR and DSC, it can be concluded that there is no significant Drug-Excipient interaction. The drug and excipients are therefore compatible with each other. The drug and excipients are therefore compatible with each other.
- 3^2 Central Composite design and Optimization technique successfully used in the Formulation of Nifedipine Nanosponges by using Ethyl cellulose and Polyvinyl alcohol and %Drug release and entrapment efficiency are dependent on the selected independent variables.
- In 3^2 Central Composite design After analyzed the responses then optimization was carried out, after analyzing the responses, optimization was performed, revealing that the F9 Batch is the optimized batch according to the 3^2 Central Composite design.
- Saturation Solubility study was carried out, the result showed that the Nifedipine Nanosponges led to a significant increase in solubility of Nifedipine compare to the pure drug in distilled water and the main objective was successfully achieved, to enhance the solubility of the drug.
- Nifedipine Nanosponges were evaluated for Particle size, Poly Dispersity Index, Production yield, Drug content, Drug entrapment efficiency, In Vitro Drug release studies, Drug release kinetics and Stability study. And results found to be satisfactory
- Batch no 2 was selected as optimized batch because it has highest drug release of 90. 86% for further studies like kinetic study and stability study and Kinetics study was appeared to occur in Fickian diffusion.
- Optimized Batch F2 formulation was then subjected to stability studies for 3 months, it could be concluded that formulation was stable after 3-months stability study.

ACKNOWLEDGEMENT

The author is thankful to JIIU's Ali-Allana College of Pharmacy, Akkalkuwa, for providing Excipients, Chemicals, Equipment, Glassware, and a helpful environment for study; the author is also grateful to Dr. G. J. Khan Principal, Ali-Allana College of Pharmacy and Dr. Mohd. Rehan Deshmukh for their valuable guidance.

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