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Pharmaceutical Sciences **Research Article……!!!**

FORMULATION AND EVALUATION OF NEFIDIPINE NANOPARTICLES FOR TREATMENT OF HYPERTENSION

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KEYWORDS:

Nifedipine, Nanoparticle, Eudragit RS100, Eudragit RSPO.

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ABSTRACT

The present study describes Formulation and Evaluation of nanoparticulate systems containing Nefidipine by using synthetic polymers Eudragit RS 100 and Eudragit RSPO for the treatment of hypertension by sonication method. The FTIR Spectra's of Nanoparticles formulation are compared with the spectra of pure drug of Nifedipine and there is no much deviation in the spectra's and not observed any drug and polymer interactions. The average particle size of the nanoparticles was found in the range of 436 nm to 917 nm. The drug encapsulation efficiency (EE) of the Nifedipine nanoparticles were found in the range of 68.92% to 93.31. The *in-vitro* drug release data of all the formulations were follows control release mechanism over a period of 24 h and the optimized Formulation NF9 shows good results for the drug release kinetics. The short term stability study of optimized formulation has done and subjected to drug encapsulation efficiency and *in-vitro* drug release studies, where results shown that there is no significant change in the formula.

INTRODUCTION:

The oral route is the most convenient in term of delivery and patient compliance.[1]Novel drug delivery system (NDDS) of existing drug molecule to maximize their effectiveness in term of therapeutic action and patient protection.[2] A pharmaceutical compound in the body as needed to safety achieve its desired therapeutic effect.[3] Nanotechnology and Nano science studies have emerged rapidly during the past year in broad range of product domains.[4]As well as Nanoparticle have already been applied as drug delivery system with great success.[5]Nanoparticle can defined as the colloidal particle having size ranging from 10 to1000nm.[6] These have the potential to increase the bioavilability of drug, they have longer clearance time.[7]At present 95% of all new potential therapeutics have poor pharmacokinetic and biopharmaceutical properties therefore ,there is need to develop suitable drug delivery system that distribute the therapeutically active drug molecule only to site of action, increasing the therapeutics indices and safety profiles of new therapeutics.[8] Nanoparticle enhance the aqueous solubility of poorly soluble drug, which improve bioavilability of drug[9-10]. Nefidipine is widely used in the treatment of angina pectoris and systemic hypertension, it is a poorly soluble drug, nefidipine has been used in emergency hypertension.[11] Hence the present work is to formulation and evalution of nefidipine nanoparticle for treatment of hypertension.

MATERIALS AND METHODS

Materials:

Nefidipine was gifted sample from Arathi phramceutical Mumbai. EUDRAGIT® RS 100, EUDRAGIT® RSPO were purchased from yarrow chemicals Pvt. Ltd and all other chemicals and reagent used were of analytical reagent grade.

Method Preparation of Nanoparticles:

Solution of polymer Eudragit RSPO/Eudargit RS100 in methanol was mixed with 0.3%W/V of polyvinyl alcohol by using controlled flow rate syringe pump at the rate of 3ml/min. During this mixing the aqueous phase was sonicated by using a probe sonicator set at 10 KHZ of energy output to produce oil in water type of emulsion .The organic phase was evaporated under reduce pressure. The obtained nanoparticles were recovered by centrifugation at 10,000 rpm for 15min and washed thrice with distilled water. Further centrifugation and nanoparticles were dried.

Table no 1: Formulation table for preparation of nanoparticles by sonication technique

Formulation Code	Nefidipine (mg)	Eudargit RSPO(w/v)	Eudargit Rs100(w/v)	Polyvinyl alcohol(w/v)	Methanol (ml)
NF1	100	0.5	-	0.5	30
NF2	100	1	-	0.5	30
NF3	100	1.5	-	0.5	30
NF4	100	2	-	0.5	30
NF5	100	-	0.5	0.5	30
NF6	100	-	1	0.5	30
NF7	100	-	1.5	0.5	30
NF8	100	-	2	0.5	30
NF9	100	1	1	0.5	30

Characterization of nanoparticle of nifedipine

The compatibility of polymer and drug evaluated by FT-IR, particle size, zeta potential and SEM study, invitro dissolution study.

FTIR Study:

The FTIR spectrum of the nanoparticle formulation was compared with the standard FTIR Spectra of pure drug. The FTIR spectral measurements were taken in ambient temperature using Bruker instrument. Eudargit RSPO, Eudargit RS100, physical mixture of above three was done using Bruker FTIR spectrometer ascertains compatibility.

Surface morphology:

The surface morphology is most commonly measured by scanning electron microscopy. The surface morphology has been studied by using ZEISS scanning electron microscopy (SEM).

Particle size:

The particle size and distribution is measured by Malvern zeta sizer by wet technique. The average particle size of the individual batch of nanoparticles was reported.

Zeta potential:

The zeta potential of nanoparticle is commonly used to characterize the surface charge property of nanoparticle. Zeta potential is measured by malvern zeta analyser**.**

In-vitro drug release studies:

In-vitro drug release studies were performed in USP type II dissolution apparatus at rotation speed of 50 rpm. The prepared nanoparticles were immersed in 900ml of phosphate buffer solution in a vessel, and temperature was maintained at 37±0.20°C. Required quantity 5ml of the medium was withdrawn at specific time periods and same volume of dissolution medium was replaced in flask to maintained a constant volume. The withdrawn samples were analysed using Spectrophotometer.

Drug entrapment efficiency:

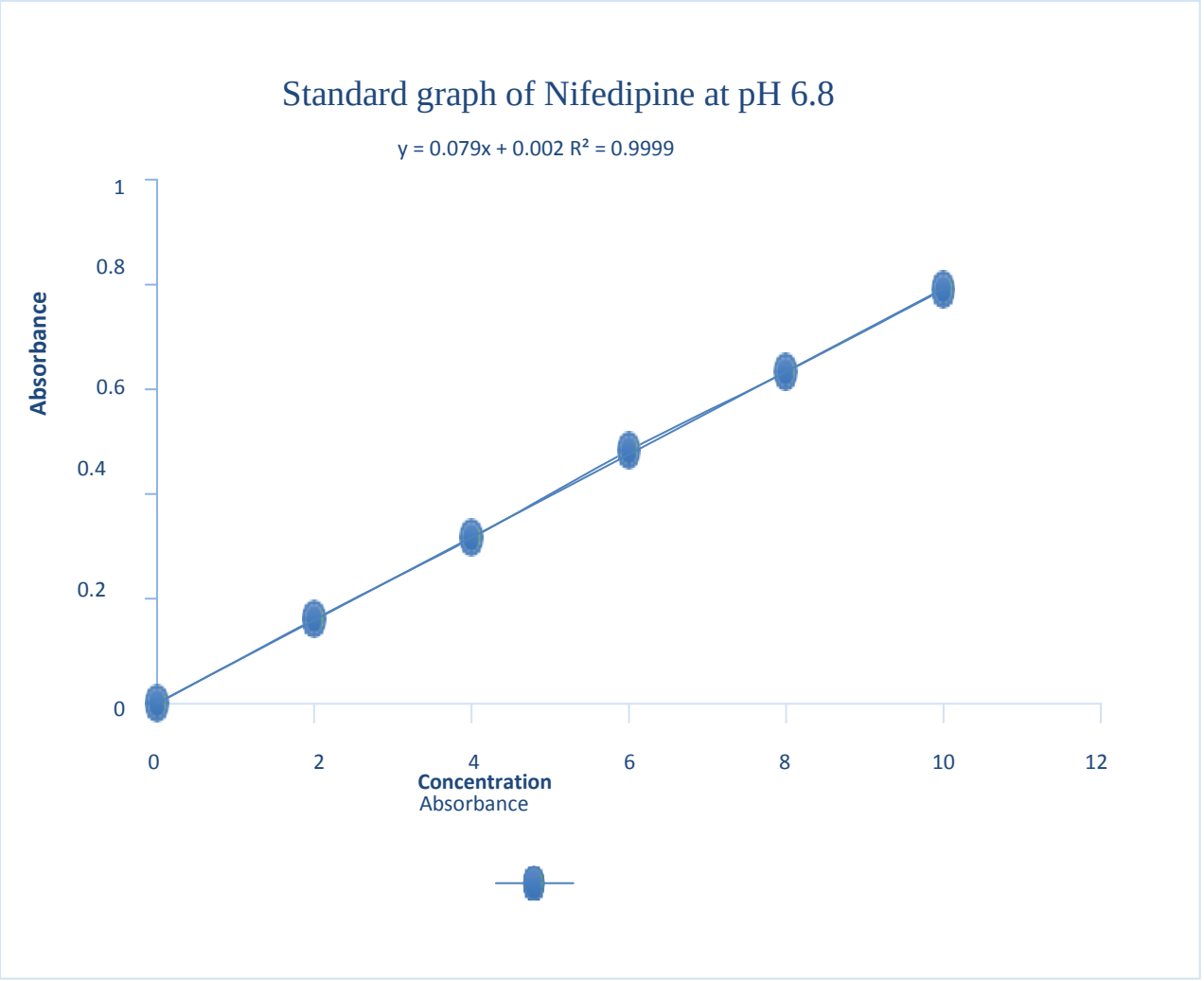
The nanoparticles were separated from the aqueous medium by ultracentrifuge at 10,000RPM for 30min at 50°C. Then the resulting supernatant solution was decanted and dispersed into phosphate

buffer PH 6.8. Thus the procedure was repeated twice to remove the unentrapped drug molecule completely. The amount of drug entrapped in the nanoparticle was determined as the difference between the total amount of drug used to prepare the nanoparticle and the amount of drug present in the aqueous medium.

Stability studies:

The prepared Nifedipine nanoparticles were packed in a screw caped bottle and were stored at 40 ± 2^{O}C and 75% RH for 45 days. After storage of 45 days, the products were tested for drug entrapment efficiency and drug release study as per the ICH Guideline.

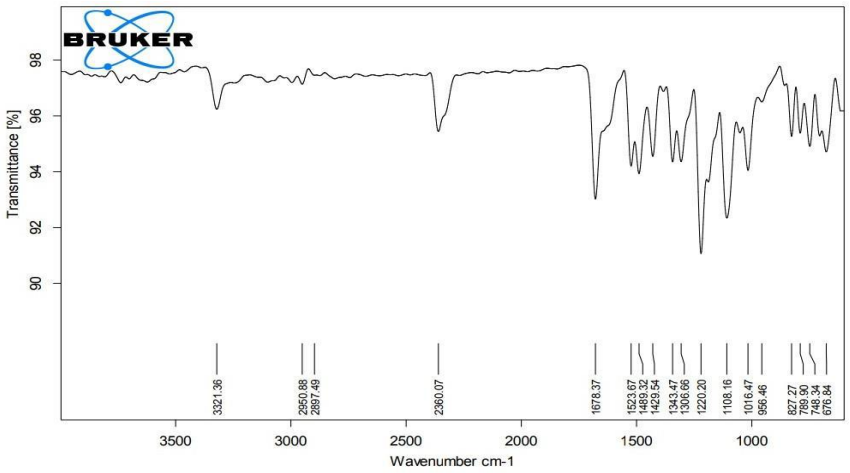
Result and Discussion



Calibration curve of nefidipine Fig no: 1

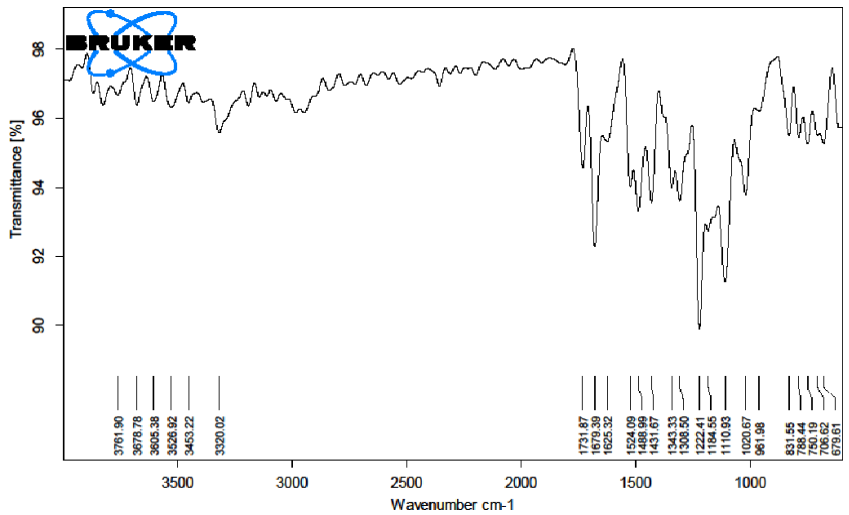
Results R2 value of standard graph of drug not more than 0.9999 i.e. it obeys beer's law.

Study of Compatibility By FTIR:

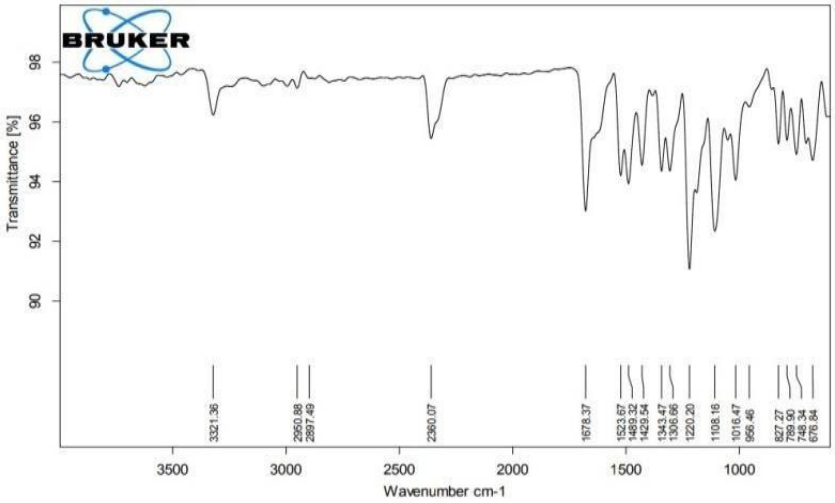


From the FTIR spectra of the pure drug and the combination of drug with polymer was observed that all the characteristics peaks of nefidipine is present in combined spectra as well thus indicating the compatibility of the drug with the polymer the individual FTIR spectra of pure drug nefidipine, Eudragit RSPO and Eudargit RS100 as well as combination spectra of the drug and polymer (formulation F9) are shown in the fig no 2, 3. It was found that the drug was compatible with polymer in physicalmixture.

IR spectrum of pure drug fig no2



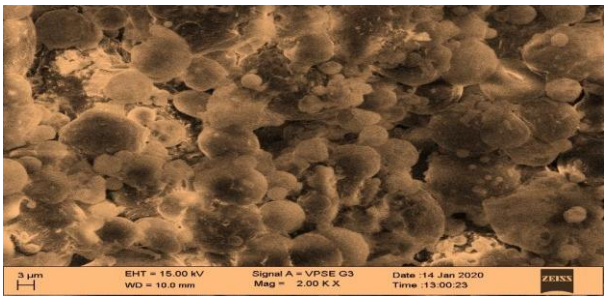
IR spectrum of Nefidipine NF4 Fig no3



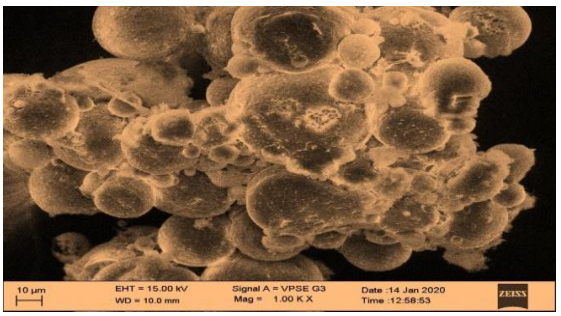
IR spectrum of Nefidipine NF9

Figno4 Surface morphology:

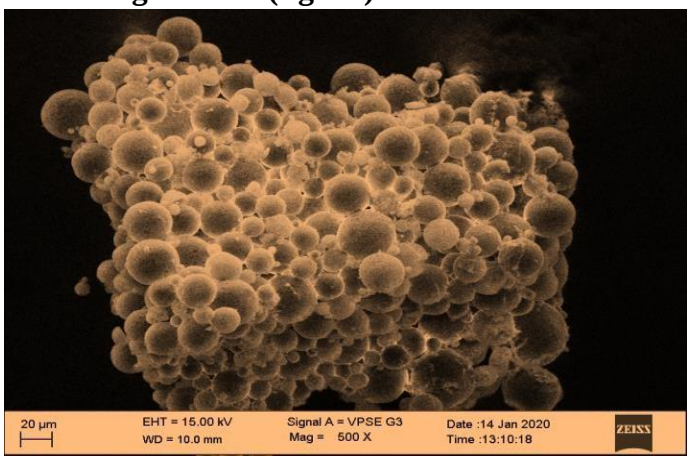
The surface morphology of the nanoparticles was characterized by SEM studies. Fig no 5,6,7show the SEM images of polymeric nanoparticle containing the drug nefidipine



SEM images ofNF1(figno5)



SEM images of NF4(figno6)



SEM Image of NF9 (figno7)

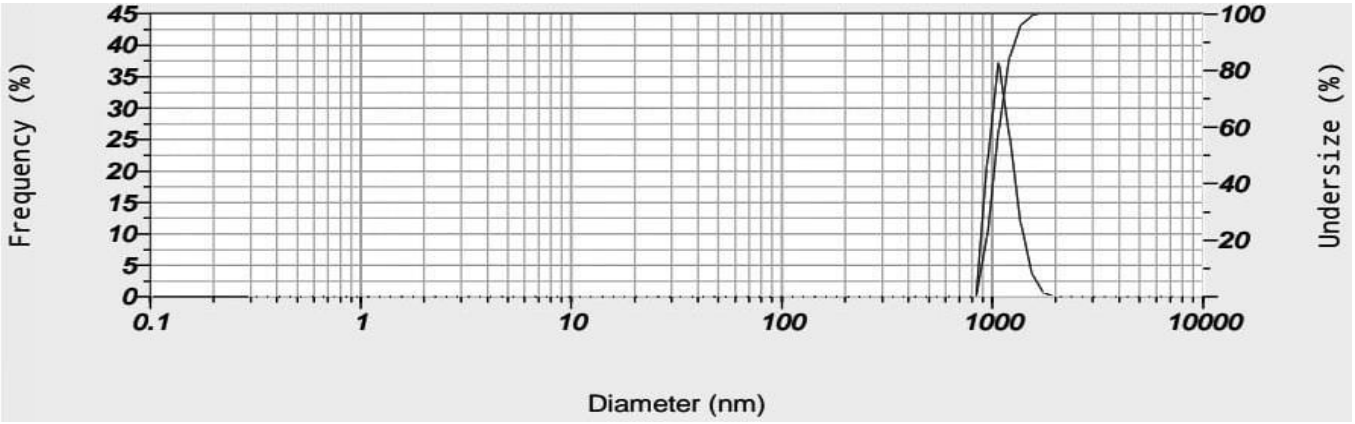
Table no2: Particle size and Drug Entrapment Efficiency of prepared nanoparticle formulations

SI No.	Formulation	Particle size(nm)	Drug Entrapment Efficieny(%)
1	NF1	436.7	68.92
2	NF2	572.9	87.16
3	NF3	649.1	90.24
4	NF4	752.7	92.13
5	NF5	891.2	78.16
6	NF6	735.3	87.24
7	NF7	917.4	88.12
8	NF8	845.1	91.24
9	NF9	504.7	93.31

Particle size analysis:

The mean particle size of the nanoparticle was found to be 436nm. Fig no7, 8, shows the result of particle size distribution of nefidipine of nanoparticle.

Surface charge: The zeta potential was found to be -917 nm.



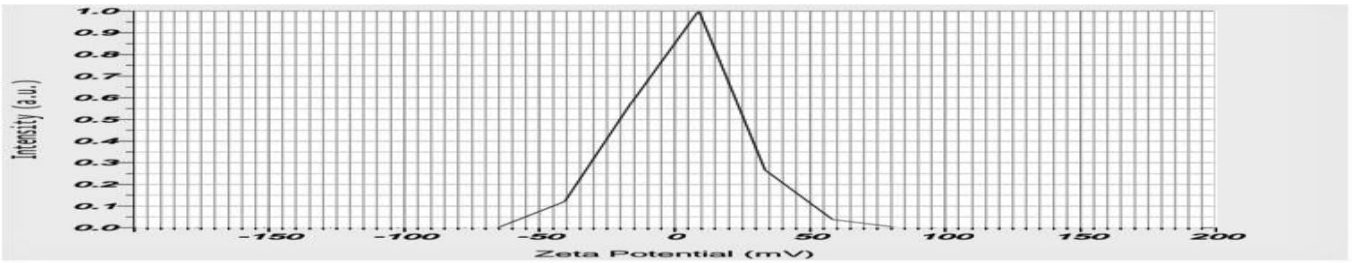


Fig No:-08, 09 Particle size distribution and Zeta potential of prepared nanoparticle formulation of NF9 In vitro dissolution studies:

The results of invitro dissolution studies of prepared nanoparticle are show in fig no9.The cumulative percentage of drug dissolution fromNF1to NF9 range from 84.89% to 94.44%, but NF9shows the drug release in control manner Compare to other formulation. Because combination of Eudragit RSPO and

Eudragit RS100 retard the release rate of drug. Hence the formulation shows better retard than all other formulation.

Table no: 3 invitro dissolution studies

Time (hr)	% Drug Release								
	$\bar{x}$SD								
	NF1	NF2	NF3	NF4	NF5	NF6	NF7	NF8	NF9
0	0	0	0	0	0	0	0	0	0
0.5	5.9 ±0.7	4.9 ±0.2	5.0 ±0.5	5.9 ±0.7	4.9 ±0.2	4.98 ±0.5	5.9 ±0.5	5.4 ±0.5	4.9 ±0.4
1	13.6 ±0.4	10.68 ±0.8	12.09 ±0.1	13.56 ±0.4	10.68 ±0.8	12.09 ±0.1	11.67 ±0.5	11.98 ±0.6	11.9 ±0.3
1.5	22.36 ±0.2	18.46 ±0.8	19.67 ±0.2	22.36 ±0.2	18.46 ±0.8	19.67 ±0.17	18.89 ±0.5	19.09 ±0.4	19.67 ±0.2
2	35.16 ±0.7	30.89 ±0.2	28.08 ±0.2	35.16 ±0.7	30.89 ±0.2	28.08 ±0.16	27.98 ±0.7	29.8 ±0.6	30.87 ±0.9
3	38.67 ±0.9	36.42 ±0.2	44.87 ±0.3	38.67 ±0.9	36.42 ±0.2	44.87 ±0.3	45.87 ±0.15	40.56 ±0.1	41.89 ±0.4
4	49.75 ±0.5	44.09 ±0.6	49.98 ±0.3	49.75 ±0.6	44.09 ±0.6	49.98 ±0.35	48.79 ±0.1	49.98 ±0.5	50.08 ±0.02
5	49.8 ±0.6	49.87 ±0.9	54.89 ±0.1	49.8 ±0.6	49.87 ±0.9	54.89 ±0.17	55.89 ±0.4	58.6 ±0.2	59.3± 0.965
6	59.2 ±0.2	56.77± 0.2	56.87± 0.7	59.2 ±0.2	56.77 ±0.2	56.87 ±0.65	57.07 ±0.9	61.2 ±0.4	66.6 ±0.2
7	64.89 ±0.1	58.65 ±0.3	62.56 ±0.2	64.89 ±0.1	58.65 ±0.3	62.56 ±0.24	64.6 ±0.45	67.5 ±0.7	69.4± 0.8
8	70.0 ±0.3	63.14 ±0.1	68.05 ±0.6	70.0 ±0.4	63.14 ±0.2	68.05 ±0.55	70.67 ±0.1	72.4 ±0.6	74.25 ± 0.9
9	76.4 ±0.4	66.29± 0.6	79.45± 0.6	76.45 ±0.4	66.29 ±0.5	79.45 ±0.5	78.56 ±0.1	76.5 ±0.4	79.4 ± 0.1
10	79.4 ±0.4	71.42 ±0.4	80.56 ±0.8	79.4 ±0.4	71.42 ±0.5	80.56 ±0.9	80.76 ±0.9	81.2 ±0.9	84.2± 0.982
11	85.64 ±0.6	73.26± 0.1	84.67 ±0.4	85.64 ±0.6	73.26 ±0.2	84.67 ±0.5	83.98 ±0.5	84.9 ±0.6	89.5± 0.482
12	88.25 ±0.99	75.16 ±0.18	86.79 ±0.99	88.25 ±0.99	75.16 ±0.18	86.79 ±0.99	85.67 ±0.4	88.4 ±0.74	91.4 ±0.46
18	91.67 ±0.2	77.66 ±0.963	87.98 ±0.32	91.67 ±0.15	77.66 ±0.963	87.98 ±0.32	87.09 ±0.5	90.46 ±0.38	93.2± 0.17
24	94.46 ±0.453	79.28 ±0.147	88.89 ±0.623	94.46 ±0.43	79.28 ±0.147	88.89 ±0.623	89.24 ±0.756	92.56 ±0.374	95.16 ±0.636

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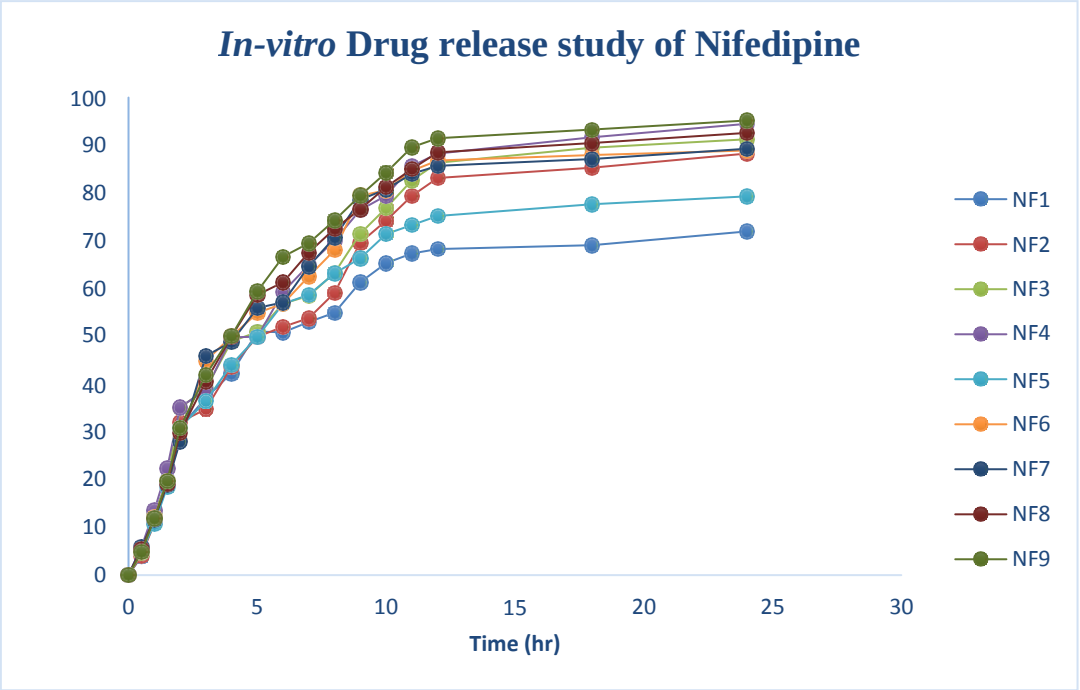

Graph of in-vitro drug release of Nifedipine Nanoparticles from NF1 to NF9 Fig no10

Release kinetics:

The in- vitro release data obtained from all the formulation was subjected to various kinetic release models. Data revealed that release kinetics follows first order drug release kinetics and 'n' values of first order shows in ranges so it indicates that the release kinetics in anomalous (non- fickian) transport date shown in table no 4.

Table No: 4 Regression co-efficient value (R2) and n values of Nifedipine nanoparticle according to different kinetics models.

Formulation	Zero order		First order		Higuchi	Peppas	
	R^2	N	R^2	N	R^2	R^2	N
F_1	0.788	4.123	0.876	0.075	0.941	0.887	0.733
F_2	0.873	5.230	0.950	0.120	0.965	0.929	0.803
F_3	0.865	5.392	0.963	0.136	0.967	0.927	0.778
F_4	0.862	5.579	0.971	0.152	0.969	0.944	0.744
F_5	0.822	4.763	0.923	0.096	0.955	0.929	0.765
F_6	0.837	5.523	0.934	0.139	0.954	0.938	0.794
F_7	0.828	5.480	0.932	0.136	0.951	0.944	0.775
F_8	0.840	5.657	0.961	0.150	0.959	0.946	0.795
F_9	0.847	5.201	0.946	0.119	0.963	0.936	0.775

Stability report study:

The prepared nifedipine nanoparticles were packed in screw caped bottle and were stored at 40±2^{o}C and 75% RH for 45 days.

Formulation	Drug Entrapment Efficiency	
NF9	Before stability test	After stability test
	95.16	94.64

In vitro dissolution studies

Formulation	Percentage of Drug Release	
NF9	Before stability test	After stability test
	93.31	92.72

CONCLUSION:

It can be concluded from the experimental study carried out that the formulation of Nifedipine Nanoparticles yields a formulation with spherical and smooth surface, Nano size range, good percentage entrapment efficiency and practical yield. The particle size analysis indicated that the particles were in the size range of 436.7nm-917.4 nm. The formulated Nanoparticles show good Entrapment Efficiency, *In-vitro* drug release showed that release from the Nanoparticles successfully retarded for over 24h. The formulations were found to be stable in Short term stability studies. From the above results, we have selected NF9 has an optimized formulation which shown good morphological features, drug entrapment efficiency and maximum drug release.

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