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Formulation and evaluation of sustained release matrix tablets of nifedipine

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ABSTRACT

Nifedipine is a calcium channel blocker, which has short half-life, makes the development of sustained release (SR) dosage form. The present work was to formulate a sustained release matrix dosage form of Nifedipine by using hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) to achieve better bioavailability and also to reduce dosing frequency and side-effects. Nifedipine matrix tablets were prepared by direct compression method. Formulated tablets were also characterized by parameters like thickness, weight variation test, drug content uniformity, hardness, friability and the in-vitro release rate profile was compared with the marketed product's release profile. FT-IR spectra revealed that there was no interaction between drug and polymers. Tablets were subjected to In-Vitro drug release in 0.1 N HCl (pH 1.2) for first 2 hours followed by phosphate buffer (pH 6.8) for remaining 10 hours. From among all the developed formulations, NF2 formulation sustained the drug release for longer period of time as compared to other formulations. So, NF2 was selected as the best formulation. To know the drug release kinetics Zero order, First order, Higuchi plot, Korsmeyer Peppa's plot were constructed. For optimized formulations zero order plot showed linearity with high regression coefficient values than the first order. According to 'n' values obtained from the Korsmeyer peppa's plot it may be concluded that the drug release is by fickian transport and drug release was controlled by diffusion mechanism.

Key Words: Nifedipine, Sustained release matrix, HPMC, EC, Direct compression.

INTRODUCTION

Matrix tablets type of controlled drug delivery systems, which release the drug in continuous manner. These release the drug by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid nonswellable hydrophobic materials or plastic materials.

FORMULATION DEVELOPMENT

PROCEDURE

The method of development of Nifedipine matrix tablets is Direct Compression method.Direct compression is a popular choice. The prime advantage of direct compression over wet granulation is economic since the direct compression requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labor leading to reduced production cost of tablets. Direct compression is more suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental

effects. Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution.

PREPARATION OF NIFEDIPINE MATRIX TABLETS[2]

Nifedipine matrix tablets were prepared by direct compression method. Matrix tablets each containing 30mg of Nifedipine were prepared with matrix former such as HPMC K 100M, Ethylcellulose, HPMC E5, Eudragit RL, magnesium stearate and Sodium starch glycolate in different ratio by direct compression technique. The ingredients previously sieved (#60mesh) are mixed in a mixer for 15 min and the tablets were punched using 6mm punches in high speed 8 station rotary tablet machine.

FORMULATIONS OF NIFEDIPINE

Ingredients	NF1(mg)	NF2(mg)	NF3(mg)	NF4(mg)	NF5(mg)
Nifedipine	30	30	30	30	30
HPMC-K100M	200	195	190	185	180
Ethyl cellulose	25	30	35	40	45
HPMC E5	2.2	2.2	2.2	2.2	2.2
Eudragit RL	5	5	5	5	5
Sodium starch glycollate	10	10	10	10	10
Magnesium Stearate	2.8	2.8	2.8	2.8	2.8
Talc	5	5	5	5	5
Iron oxide red	qs	qs	qs	qs	qs
Average weight (mg)	280	280	280	285	285

PREFORMULATION STUDIES

A preformulation activity ranges from supporting discovery's identification of new active agents to characterizing physical properties necessary for the design of dosage form. Critical information provided during Preformulation can enhance the rapid and successful introduction of new therapeutics entities for humans. Preformulation testing is an investigation of physical and chemical properties of a drug substance.

PHYSICAL APPEARANCE

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour, embossing, debossing.

HARDNESS TEST

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

FRIABILITY TEST

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets were determined by using Veego Friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions.

The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

% Friability of tablets less than 1% is considered acceptable.

UNIFORMITY OF THICKNESS

The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using screw gauge.

WEIGHT VARIATION TEST

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed.

PERCENTAGE DEVIATION IN WEIGHT VARIATION

Average weight of tablets (mg)	% **Percentage deviation**
130 or less	10%
130 to 324	7.5%
>324	5%

DRUG CONTENT UNIFORMITY

Five tablets from each batch were finely powdered and the powder equivalent to 30mg of

Nifedipine was weighed and dissolved in suitable quantity of methanol. The solution was

filtered, suitably diluted and the drug content was analyzed spectrophotometrically at 235nm.

***IN- VITRO* DRUG RELEASE STUDY**

Dissolution rate of Nifedipine was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm using 900mL of 0.1N HCL (1.2 pH buffer) for first 2 hrs. and remaining 10 hrs. in phosphate buffer pH (6.8) as dissolution medium. Temperature of the dissolution medium was maintained at 37 ± 0.5°C, aliquot of dissolution medium was withdrawn at regular intervals and replaced with the same volume of fresh dissolution medium. The samples were analyzed at 235nm by UV spectrophotometer and the results were reported. The absorbances were recorded and percentage drug release was calculated.

***IN VITRO* DRUG RELEASE STUDIES DETAILS**

Apparatus used	:	USP XXIII dissolution test apparatus
Dissolution medium	:	1.2 pH acidic and6.8 pH phosphate buffer solution.
Dissolution medium volume	:	900 mL
Temperature	:	37 ± 0.5°C
Speed of basket paddle	:	50 rpm
Sampling intervals	:	10 and 30mins
Sample withdraw	:	5 mL
Absorbance measured	:	237nm, 235nm

DRUG RELEASE ANALYSIS

To analysis the mechanism for the release and release rate kinetics of the formulated dosage form, the data obtained from conducted studies was fitted into Zero order, First order, Higuchi matrix, korsmeyer- Peppas constant. In this by comparing the r-values obtained, the best-fit model was selected.

ZERO ORDER KINETICS

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation.

$Q_t = Q_0 + K_0 t$

Where, Q_t = amount of drug dissolved in time t,

Q_0 = initial amount of drug in the solution,

K_0 = Zero order release constant.

FIRST ORDER KINETICS

To study the first order release rate kinetics the release rate data were fitted to the following equation.

$\text{Log } Q_t = \log Q_0 + K_1 t / 2.303$

Where, Q_t = amount of drug released in time t,

Q_0 = initial amount of drug in the solution,

K_1 = first order release rate constant

HIGUCHI MODEL

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs in corporate in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media.

$Q_t = K_H . t^{1/2}$

Where Q_t = amount of drug released in time t,

K_H = Higuchi dissolution constant.

KROSMEYER AND PEPPAS RELEASE MODEL

To study this model the release rate data are fitted to the following equation

$M_t / M_\infty = K . t^n$

Where, M_t / M_∞ = fraction of drug release,

K = release constant,

t = release time,

n = Diffusional exponent for the drug release that is dependent on the slope of the matrix dosage forms.

STABILITY STUDIES

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity an light and enables recommended storage conditions, re-test periods and shelf lives to be established.

ICH SPECIFIES THE LENGTH OF STUDY AND STORAGE CONDITIONS

Accelerated testing $40^0C \pm 2^0C$ / 75 ± 5 % RH for 30 days.

In the present study, stability studies were carried out at 40^0C / 75 % RH for a specific time period up to 30 days for the selected formulations.

RESULTS AND DISCUSSION

COMPATIBILITY STUDIES

Compatability studies were performed using ir interpretation for pure drug and for pure drug and excipients and it was found that there were no interactions between the pure drug and the excipients so the further formulation was carried out.

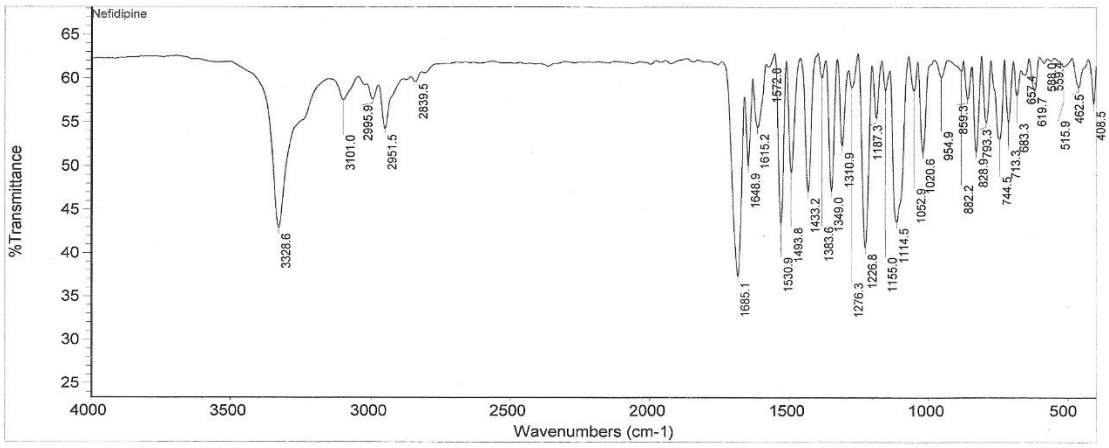


Figure 4: FT-IR SPECTRA OF PURE DRUG NIFEDIPINE

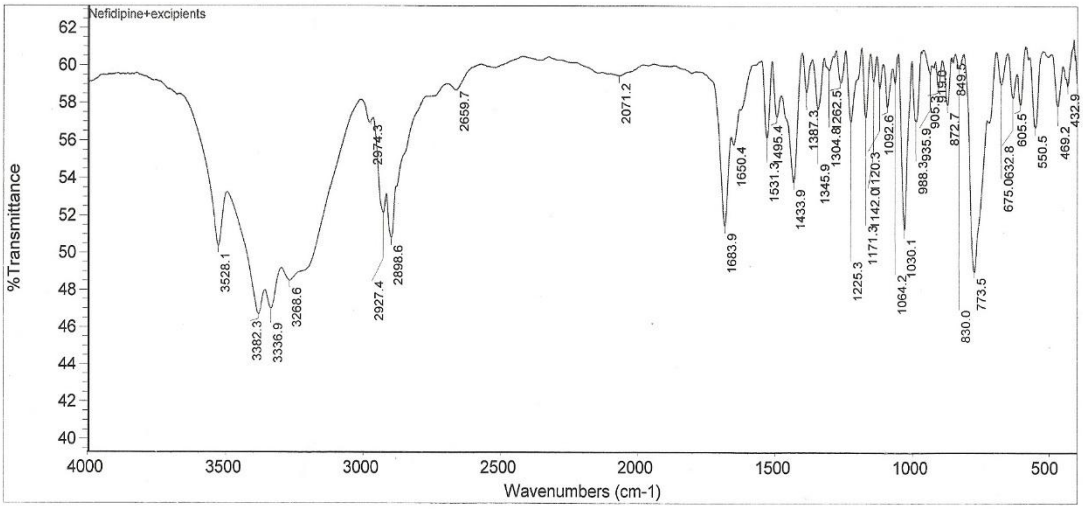


Figure 5: FT-IR SPECTRA OF NIFEDIPINE AND EXCEPIENTS

FT-IR Spectrum values of Nifedipine

Group	cm^{-1}
N-H stretching	3328.6
C-H aromatic	3101
C-H aliphatic	2951.5
C=O stretching	1685.1
C-O ester stretching	1227.47
NO2 stretching	1530.9

PREFORMULATION STUDIES

Preformulation studies were conducted for the following parameters for the 5 formulations and it was found that all the parameters measured are within limits.

PREFORMULATION STUDIES OF DIFFERENT NIFEDIPINE FORMULATIONS

S.no.	Parameteres	NF1	NF2	NF3	NF4	NF5	Mean
1	Angle of repose(^{0})	25.31	23.95	26.25	27.45	29.3	26.45
2	Bulk density(g/cm^3)	0.657	0.6520	0.6488	0.6516	0.6568	0.6528
3	Tap density(g/cm^3)	0.7108	0.8110	0.6677	0.6832	0.7164	0.7146
4	Hausner ratio	1.06	1.01	1.04	1.08	1.09	1.06
5	Carr's index(%)	12.02	11.02	12.09	13.4	14.4	12.58

STANDARD CALIBRATION CURVE

The wavelength of pure Nifedipine in 235 nm was scanned from the concentration range of 10 to 50 µg/mL. standard calibration graph of pure Nifedipine was plotted by taking concentration vs absorbance and a good correlation was obtained with R^2 value of 0.09992.

Table no.12: Data for standard plot of Nifedipine

Sl. No.	**Concentration (µg / mL)**	*** Absorbance at 235 nm AM ± SD**
1	0	0.00 ± 0.000
2	10	0.125 ± 0.13
3	20	0.256 ± 0.090
4	30	0.382 ± 0.10
5	40	0.508 ± 0.10
6	50	0.642 ± 0.12

EVALUATION TESTS OF TABLETS

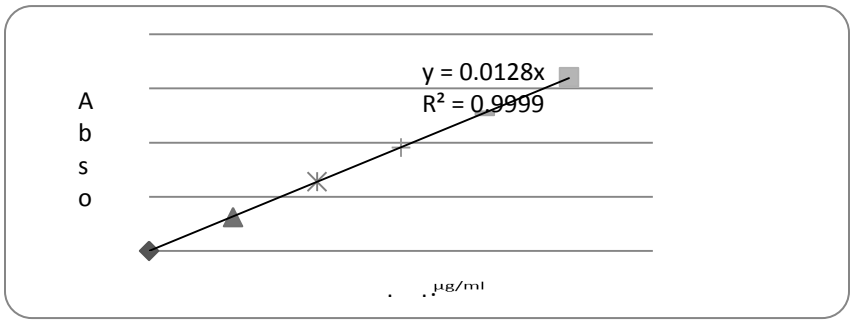


Figure 6: Calibration curve of Nifedipine

EVALUATION STUDIES OF TABLETS

The evaluations of tablets were performed for the following parameters and the 5 formulations prepared fall within the limits.

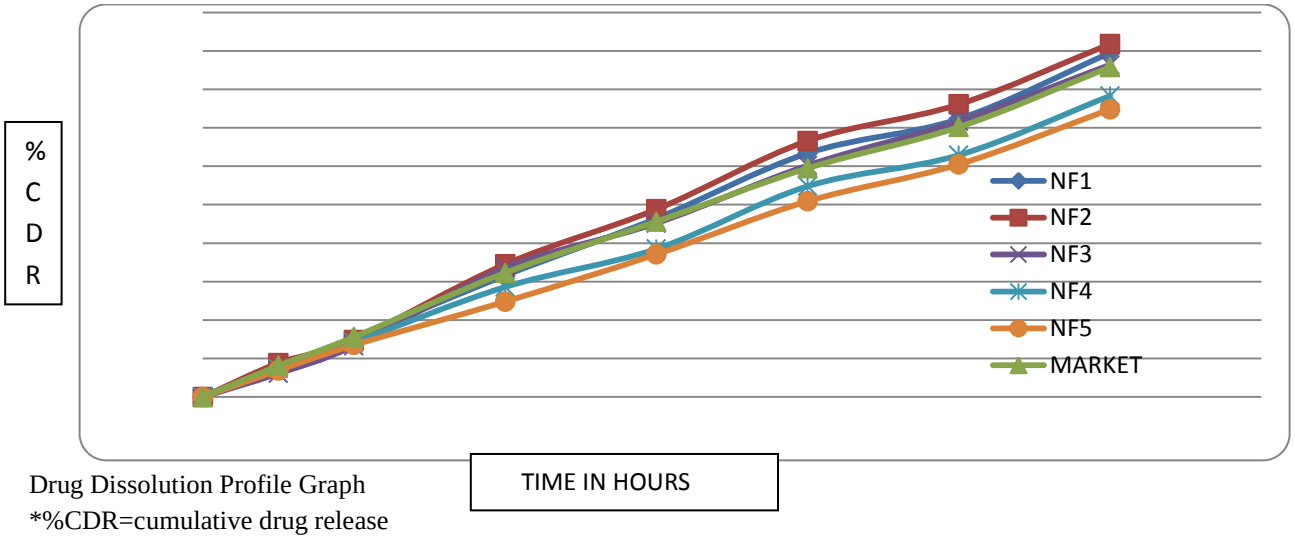
Formulations	Hard ness (kg/cm^3)	Friability (%)	Thickness(mm)	Deviation in weight variation(mg)
NF1	3.68±0.28	0.35±0.021	2.58 ± 0.13	278±3.36
NF2	3.62 ±0.29	0.15±0.011	2.52 ± 0.052	280±2.32
NF3	3.7 ±0.28	0.22±0.02	2.60 ± 0.11	282±3.54
NF4	3.84 ±0.28	0.18±0.02	2.64 ± 0.15	279±2.26
NF5	4.02 ±0.29	0.29±0.01	2.62 ± 0.1	281±3.16

DRUG RELEASE PROFILE

Among all developed formulations of Nifedipine, NF2 shown good dissolution profile and drug release sustained over the period of 12 hrs.

Table no.14:*In-vitro* release of Nifedipine from different formulations

Time(hr)	NF1	NF2	NF3	NF4	NF5	Market
0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
1	7.20%	8.80%	6.10%	7.40%	6.90%	8.10%
2	15.30%	14.80%	13.30%	14.20%	13.50%	15.60%
4	31.60%	34.50%	33.50%	28.60%	24.80%	32.30%
6	46.40%	48.80%	45.20%	38.50%	37.10%	45.60%
8	63.40%	66.60%	60.20%	54.80%	50.90%	59.50%
10	72.30%	76.10%	71.70%	62.90%	60.50%	70.20%
12	89.50%	91.80%	86.40%	78.30%	74.80%	85.80%



Drug Dissolution Profile Graph

*%CDR=cumulative drug release

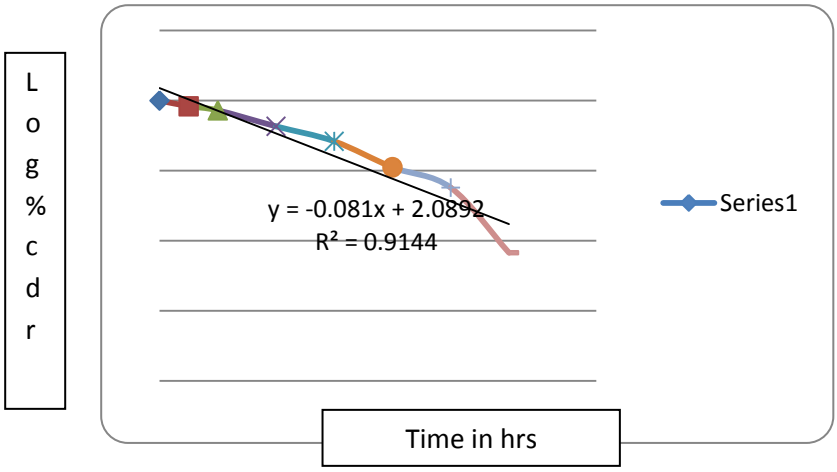
***IN-VITRO* DRUG RELEASE KINETICS**

The *in-vitro* release profiles for all the formulations was applied on various kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppa's equation. Higher correlation was observed in the Higuchi equation. For planer geometry, the value of n<0.5 indicates a Fickian diffusion mechanism, for 0.5<n<1.0, indicates anomalous (non-fickian) transport, and n=1 implies case II (relaxation controlled) transport. In the present systems, the value for n was found to be in the range of 0.3278 to 0.3967 indicating that the release mechanisms followed fickian diffusion transport. The formulation NF2 was having n=0.3833, indicating that the release mechanism followed is fickian diffusion controlled mechanism.

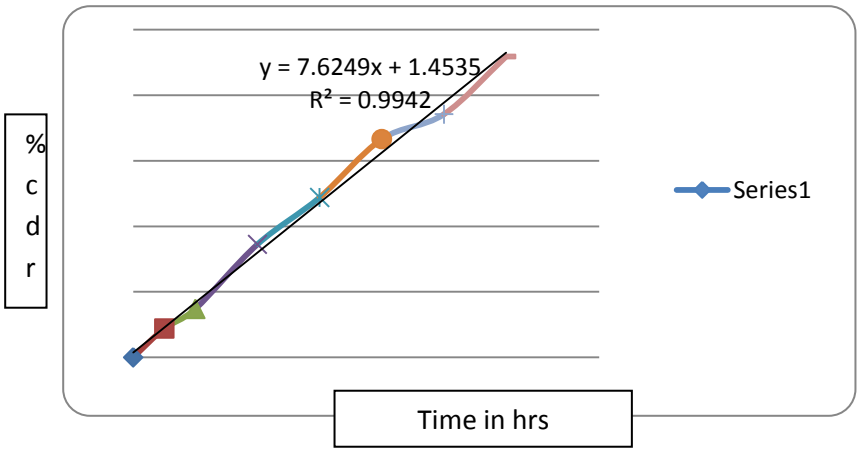
Drug Release Kinetic Studies Based On Different Kinetic Models

Formulation	First order R^2	Zero order R^2	Higuchi R^2	Korsmeyer- Peppa's R^2	Slope n
NF1	0.971	0.978	0.946	0.974	0.3278
NF2	0.954	0.994	0.968	0.972	0.3833

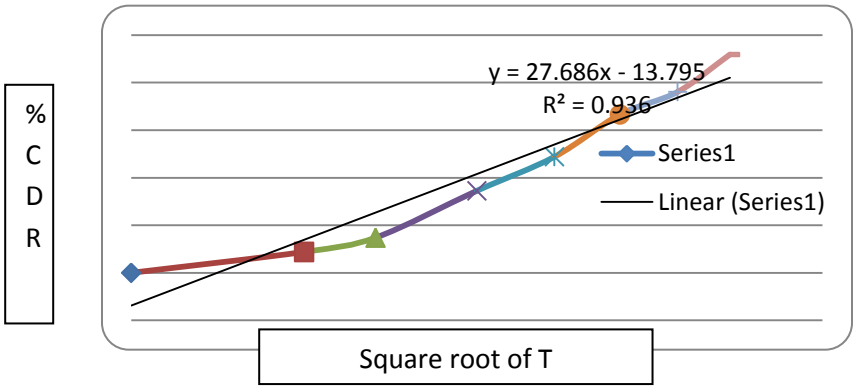
NF3	0.946	0.972	0.942	0.956	0.3675
NF4	0.942	0.967	0.930	0.965	0.3967
NF5	0.938	0.945	0.939	0.962	0.3329



First order plot of optimized formulation(NF2)
*% cdr=cumulative drug remained

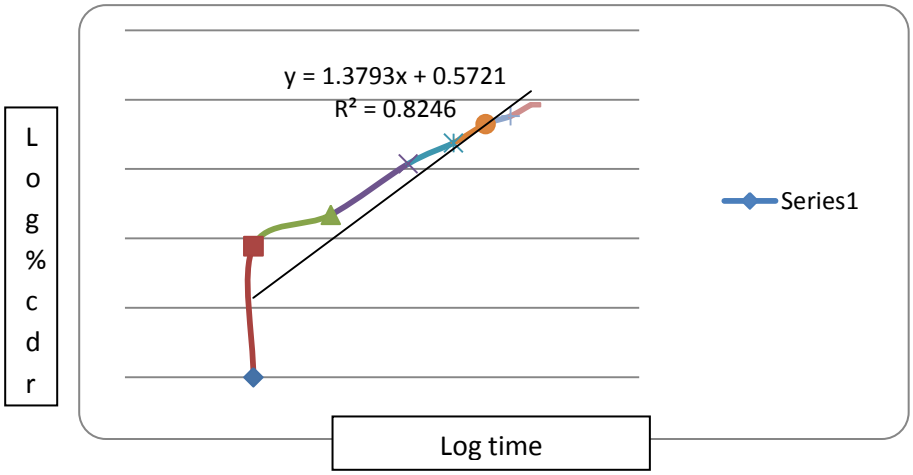


Zero order plot of optimized formulation(NF2)
*% cdr=cumulative drug release



Higuchi plot of optimized formulation(NF2)

*% cdr=cumulative drug release



Korsmeyer- Peppa's plot of optimized formulation(NF2)
*% cdr=cumulative drug release

STABILITY STUDIES

In the present study, stability studies were carried out at 40^0C / 75 % RH for a specific time period up to 30 days for the selected formulation.

Stabilities studies of Nifedipine tablets

Formulation code	Hardness (gm/cm^2)	Friability (%weight loss)	Drug content uniformity%	Weight variation (280±7.5%)	Thickness (mm)	%Drug release
NF2	3.62	0.15	98.91 ± 1.24	280mg	2.52	90.78

Stability studies for the above mentioned parameters are carried out and it was found that the NF2 formulation showed the good shelf life and all the parameters are within the given limits.

CONCLUSION

The main objective of present investigation is to formulate and evaluate Nifedipine matrix tablets. The following conclusion were drawn from these experimental results are IR studies indicated that the drug is compatible with all the excipients, Tablets prepared by direct compression method were found to be good and free from chipping and capping. The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared. The hardness and the friability values, flow properties of the prepared tablets was found to be within the limits for all the five formulations. The dissolution was carried in two different media to mimic the conditions of gastro intestinal tract first 2 hrs. in 1.2 pH. Buffer and the rest 10 hrs. in 6.8pH phosphate buffer.From among all the developed formations, NF2 formulation was shown drug release up to 91.80% at 12 hour was selected as the best formulation. The stability study shown that no significant changes in tablets after 30 days study

SUMMARY AND CONCLUSION

The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body and also to achieve and maintain the desired drug concentration. Nifedipine is an antihypertensive drug used in the treatment of hypertension and angina pectoris. The plasma half-life of Nifedipine is about 2 hours. The literature survey discussed reveals the research work done to develop sustained release drug delivery system containing anti-hypertensive, anti-viral and NSAID's drugs. Polymers used in this study are HPMC and EC.In the present study five formulations were formulated by using HPMC and EC in various proportions. All the formulations were subjected for

evaluation. Results of reformulation studies, evaluation studies, in-vitro dissolution study have shown satisfactory results. On the basis of in-vitro dissolution drug release data and graphical analysis formulation NF2 showed a good controlled release profile .The release kinetics of formulations NF2 showed a good correlation of Krosmeyer-Peppas with good 'n' values. According to 'n' values obtained NF2 follows Fickian diffusion as release mechanism. The formulations were subjected to accelerated stability study. The formulation NF2 was found to be stable as there was no change in the drug content.

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