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FORMULATION DEVELOPMENT AND EVALUATION OF NIFEDIPINE SUSTAINED RELEASE MATRIX TABLET

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ABSTRACT
Angina pectoris and hypertension the common cardiovascular diseases, require constant monitoring. Calcium channel inhibitors are presently considered an important class of drug for angina pectoris and hypertension. Nifedifine is one of the molecules widely used for the successful treatment of angina pectoris and blood pressure. Nifedifine has a short half life and the usual oral dosage regimen is 10mg-40mg taken to 3-4 times a day. To reduce the frequency of administration and to improve patient compliance, twice daily sustained release formulations of nifedifine is desirable. In the present study attempt has been made to develop twice daily sustained release matrix tablets of Nifedipine using HPMC achieve better therapeutic success compared to conventional dosage form of Nifedipine.

KEYWORDS: Angina pectoris, sustain release, Nifedipine, HPMC.

INTRODUCTION
Angina is chest pain or discomfort that occurs when an area of a heart muscle doesn't get enough oxygen-rich blood. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time if this system provides some control whether spatial or both drug releases in the body, it is considered controlled release. One of the least complicated approaches to the manufacture of sustained release dosage form involvers the direct compression of blends of drug retardant materials and additives to form a tablet in which drug is embedded in a matrix core of the retardant. Alternately, retardant drug blends may be granulated prior to compression. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism. Upon immersion in water, the hydrophilic matrix quickly forms a gel around the tablet. Drug release is controlled buy a gel diffusional barrier that is formed and / or tablet erosion.

In the present study attempt has been made to develop twice daily sustained release matrix tablets of Nifedipine using HPMC achieve better therapeutic success compared to conventional dosage form of Nifedipine.

MATERIALS AND METHOD
Nifedipine was provided by SaiMirra Pharmaceuticals, Chennai, India. HPMC K15M and HPMC E10 PCR, were received as gift sample from colorcon Asia (Pvt) Ltd, Mumbai, India. Microcrystallinecellulose and Magnesium stearate was purchased from S.D Fine Chemicals, Mumbai, India. Sodium Alginate was purchased from Kemphasol, Mumbai. Aerosil and otheradditives were used as AR grade purchased from S.D Fine Chemicals and Himedia Chemie, India.

PREFORMULATION STUDIES
Drug-Excipients Compatibility Studies
The drug Nifedipine and the excipients were taken in the ratio 1:5 and these mixtures were taken in 2 ml glass vials and sealed. These glass vials were kept at 40^0C/75% RH and 60^0C/90%RH for about one month. At the interval of 2 weeks and 4 weeks, the samples were withdrawn and analyzed for any color change.

Infrared Spectroscopy
Infrared Spectroscopy was conducted using a Shimadzu IR Spectrophotometer and the spectrum was recorded in the region of 2000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (drug and the resulting formulation) in KBr (200-400 mg) and compressing into discs by applying a pressure of 5 tons for 5 mins in a hydraulic press. The pellet was placed in the light path

and the spectrum was obtained. Spectra were recorded for each of the samples.[42]

PREPARATION AND EVALUATION OF NIFEDIFINE SR MATRIX TABLETS

Nifedifine matrix tablets were prepared by wet Granulation method by incorporating matrix formers such as HPMC, PVP and Lactose. Preparation of Nifedifine SR matrix tablets by wet granulation involves **Sieving**(all ingredients passed through the sieve no 30.), Nifedifine is dissolved in sufficient qty of Methylene Chloride and PVP were mixed as per the formula given in Table No.1 matrix formers were incorporated in a powder mix. And finally Diluents Lactose, magnesium stearate and Aerosil were added as lubricant. The magnesium stearate and Aerosil were passed through the sieve No 30 # and mixed together with dried powder in a poly bag for 5 minutes to get a uniform blend. The mixed granules were compressed in to tablets using 8mm round shape punches.

Table No. 1 Composition of Nifedipine Sustained Release Matrix Tablets.

S. No.	Ingredients	Qty./tab(mg)					
		F1	F2	F3	F4	F5	F6
1	Nifedifine	20	20	20	20	20	20
2	HPMC 15LV	40	60	-	-	-	-
3	HPMC k100			40	60	60	60
4	PVPk30	20	20	20	20	20	20
5	Lactose	100	80	100	90	90	90
6	Magnesium stearate	2	2	5	5	5	5
7	Aerosil	-	-	5	5	5	5

EVALUATION OF GRANULES

Angle of repose

Angle of repose was determined by using funnel method. The accurately weighed blend was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touché the apex of the heap of blend. The drug-excipient blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ = h/r

Where, h and r are the height and radius of the powder cone

Bulk Density

Apparent bulk density was determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight.

BD = Weight of the powder / Volume of the packing

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2- second intervals. The tapping was continued until no further change in volume was noted.

TBD = weight of the powder / volume of the tapped packing

Compressibility index

The compressibility index of the blends was determined by Carr's compressibility index.

Carr's compressibility index (%) = [(TBD-LBD) x 100] / TBD

A similar index has been defined by Hausne

$$\textbf{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

COATING OF TABLETS

Procedure

Load tablets into pan and turn on heat drying air exhaust and automizingair. when exhaust temperature recheas 30^0 cto 40^0 c start spraying and the color solution was applied at 5 mg build up then allow to dry in fan with air and heat on for 10min.[9] Thecomposition of coating materials were given in the Table No. 2.

Table No. 2 Composition of Coating Materials

Coating Materials	Qty(gm)
FCM Brown	6.25
Propylene glycol	0.7
Methyleness chloride	115.0
Isopropyl alcohol	29.0

EVALUATION OF TABLETS

1. Weight variation

The U.S.P. weight variation test was run by weighing 20 tablets and then the average weight was determined. All the 20 tablets were weighed individually. Find out the tablets having the highest weight and the tablets having the lowest weight, in the above 20 tablets.

2. Thickness
The thickness of the tablets was determined using a thickness gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated.

3. Drug content
Five tablets were selected from each batch. The tablets were assayed individually by extracting the drug from the tablets using acetonirile and methanol (1:1) solution. The drug samples were analyzed by measuring the absorption at 265nm by using HPLC.

4. Friability
The friability test was performed for all the formulated Nifedipine tablets. Ten tablets were taken and their weight was determined. Then they were placed in the friabilator and allowed to make 100 revolutions. The tablets were then deducted and reweighed.

5. Hardness
Pfizer hardness tester was used for measuring the hardness of the formulated Nifedipine SR tablets. From each five tablets were taken and subjected to test. The mean of the five tablets were calculated.

6. In-vitro dissolution studies
Drug release study was carried out in USP II basket-type dissolution test apparatus. Dissolution medium was Phosphate buffer (pH 6.8) Volume of dissolution medium was 900 ml and bath temperature was maintained at 37^0C throughout the study. Basket speed was adjusted to 50 rpm. After 3,6 & 12 hour, 5 ml of sample was withdrawn and analyzed for content by HPLC at 350 nm. Using Chemstation software (Agilent Technologies, New Delhi, India). It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate (6 tablets in each set) and the mean values were plotted versus time with RSDs of less than 3, indicating the reproducibility of the results.[39]

HPLC studies
Liquid chromatographic conditions
Stationary phase : HYPERSIL BDS C18, 250 × 4.6 mm
Mobile phase : ACETONITRILE: WATER (70:30)
Elution mode : 70:30 (V/V) Flow rate 1.5ml/minute
Injection volume : 20µl
Detection : Nifedifine 350 nm
Temperature : Ambient

The mobile phase was filtered through a 0.22µ membrane and degassed using ultra sonicator. The experiments were carried out at 37^oC.

The percentages of the labled around of Nifedifine dissolved at the times specified conform to acceptance. The dissolution limits as per USP is given in the Table No. 3.

Table No. 3 Dissolution limits as per USP

Time (Hours)	Amount Dissolved
3	Between 10%and 30%
6	Between 40%and 65%
12	Not less than 80%

7. Stability studies of the tablets
The selected blister packed formulations stored at 25^0C/ 60%RH and 40^0C/75% RH for 12 weeks and evaluated for their physical appearance and drug content. The formulations were further scanned to observe any possible spectral changes and also performed *in-vitro* dissolution studies.

8. Drug Release Kinetics[46-51]
To study the release kinetics, data obtained from in vitro drug release studies were plotted in various kinetic models: zero order (Equation 1) as cumulative amount of drug released vs time, first order (Equation 2) as log cumulative percentage of drug remaining vs time and Higuchi's model (Equation3) as cumulative percentage of drug released vs square root of time.

$$C = K_0 t \quad \ldots\ldots\ldots (1)$$

Where, K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

$$Log\ C = Log\ C_o - k\ t / 2.303 \ldots\ldots (2)$$

Where, C_0 is the initial concentration of drug, k is the first order constant and t is the time.

$$Q = K\ t\ 1 / 2 \quad \ldots\ldots\ldots\ldots (3)$$

Where, K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time. To evaluate the drug release with changes in the surface area and the diameter of the particles/tablets, the data were also plotted using the Hixson-Crowell cube root law:

$$Q\ 0\ 3 - Q\ t\ 3 = k\ H\ C \times t \quad \ldots\ldots\ldots\ldots (4)$$

Where, Q_t is the amount of drug released in time t, Q_0 is the initial amount of the drug in the tablet and K_{HC} is the rate constant for the Hixson-Crowell rate equation, as the cube root of the percentage of drug remaining in the matrix vs time.

5. RESULTS AND DISCUSSION

1. Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as "investigation of physical and chemical properties of the drug substance alone and when combined with excipients." The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced. As a part of preformulation study drug-excipients and the result were given in the Table No 4.

Table No. 4 Pre-formulation study drug-excipients

TESTS	OBSERVATIONS	LIMITS
Identification By IR	Complies	IR Spectrum of sample should be concordant with that of standard.
p^H	9.2	Between 9.00 and 10.00
Loss on drying	0.49 %	Not more than 1.00% w/w
Description	Yellow powder	Yellow powder

Drug – excipient compatibility studies

The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients that are added in the formulation. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious and easy to administer and safe. The excient compatibility studies were show in the Table No. 6.

IR Spectral analysis for drug alone and in combination with other excipients was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interaction. Excipient compatibility for nifedipine given in the Table No. 5.

The principal peaks of pure Nifedipine and Nifedipine – Excipient mixture are shown in Table 5 considerable changes in the IR peaks of the drug were observed when mixed with excipient which indicates the absence of any chemical incompatibility between drug and excipients. The major IR peaks Wave numbers given in the Table No.5 and the peaks given in the figure No. 1 to 3.

Table No. 5Major IR peaks of Nifedipine and Nifedipine- Excipient mixture

Samples	Composition	Major peaks (Wave numbers, cm^{-1})
A	Nifedipine standard	580.59, 752.26, 1230.63, 1290.42, 1315.5, 1350.22, 1379.15, 1440.87, 1465.95, 1492.95, 1529.6, 1572.04, 1602.9 1622.19, 1668.48, 1707.06, 2875.96, 2933.83, 3122.86.
B	Nifedipine SR Tablets	581.79, 755.28, 1232.53, 1289.71 1314.7, 1351.34, 1380.18, 1442.28, 1464.74, 1495.47, 1530.4, 1573.03, 1601.7 1631.23, 1669.15, 1707.09, 2875.37, 2934.92, 3123.79.
C	Nifedipine placebo	580.48, 751.31, 1231.61, 1290.51, 1316.7, 1351.13, 1379.21, 1441.81, 1465.82, 1493.01, 1529.1, 1571.07, 1603.09 1622.24, 1668.48, 1707.01, 2875.31, 2934.74, 3123.86.

Table No. 6 Excipient compatibility for nifedipine

S.No	Drug+Excipients	Parameter	Initial Value of parameter	Conditions			
				RT 40^0C/75% RH		RT 60^0C/90% RH	
				2 week	4 week	2 week	4 week
1.	Nifedipine +HPMC K15LV	Any colour Change	Yellow powder	۞	۞	۞	۞
2	Nifedipine + HPMC 100	Any colour Change	Yellow powder	۞	۞	۞	۞
3.	Nifedipine + Lactose	Any colour Change	Yellow powder	۞	۞	۞	۞
4.	Nifedipine +PVP	Any colour Change	Yellow powder	۞	۞	۞	۞
5	Nifedipine + Aerosil	Any colour Change	Yellow powder	۞	۞	۞	۞
6	Nifedipine + Magnesium stearate	Any colour Change	Yellow powder	۞	۞	۞	۞

- **NO COLOUR CHANGE**

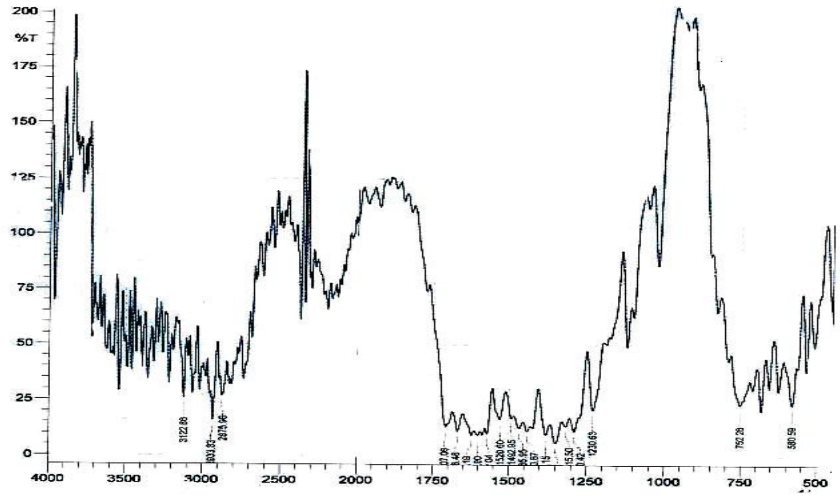


Figure No. 1Excipient compatibility Nifedipine.

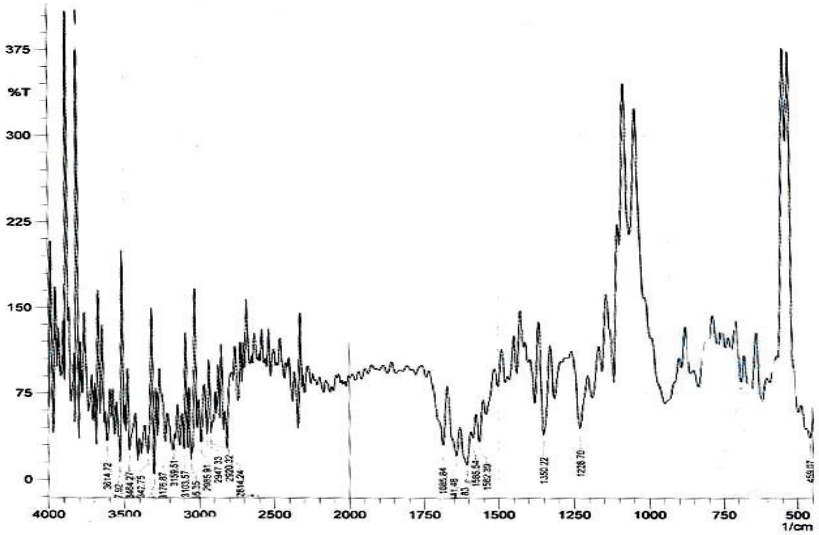


Figure No. 2 Excipient compatibility Nifedipine + KMCP 100.

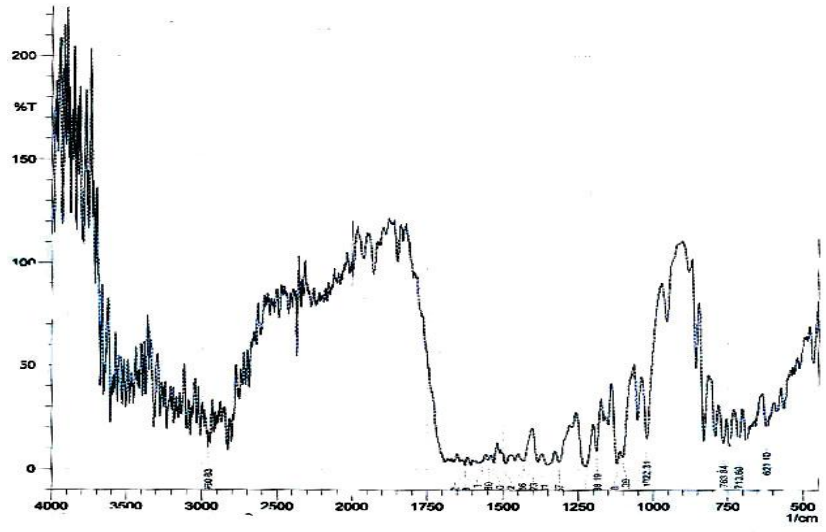


Figure No. 3 Excipient compatibility Nifedipine + Excipient.

Micromeritics properties

Table No. 7 Angle of Repose, Bulk Density, Tapped Density, Carrs Compressibility Index and Hausner's Compressibility.

Property	F1	F2	F3	F4	F5	F6
Angle of Repose (^{o})	$33^0$59`	$33^0$05`	$33^0$69`	$34^0$02`	$33^0$31`	$33^0$13`
Bulk Density (gm/cm^3)	0.476	0.455	0.466	0.488	0.466	0.476
Tapped Density(gm/cm^3)	0.572	0.556	0.557	0.556	0.542	0.541
Carr's Compressibility Ratio	16.6	15.5	19.7	13.9	16.2	13.50
Hausner's Ratio	1.20	1.22	1.19	1.135	1.16	1.13
Flow Property	Good	Good	Good	Good	Good	Good

Bulk Density

The results of bulk density are depicted in Table No. The density was ranged from 0.455 to 0.488. The bulk density depends on particle size, shape and cohesiveness of the particles.

Angle of Repose

The angle of repose values was ranged from $33^0$13` to $34^0$02. Generally a flow characteristic is measured by angle of repose. Improper flow of powder is due to the frictional forces between the particles. These frictional forces are quantified by angle of repose. The lower the angle of repose the better is the flow property. Formulations shows good flow property. The values were given in the Table No. 7.

Compressibility Index (CI)

The result of the compressibility Index values were ranged from13.50 to19.7 CI is indirectly related to the relative flow rate, cohesiveness and particle size. All the Formulations show good flow property. The results were given in the Table No.

Hausner's Ratio

The results of Hausner's ratio of formulations are depicted in the Table No. 7. The values of Hausner's ratio of all the formulations were in the ideal range. So all these formulations show good flow property.

Post Compression Paramater

Table No. 8Post Compression Paramater of F1 to F6

Parameter	Formulations					
	F1	F2	F3	F4	F5	F6
Hardness kg/cm^2	5.2	5.7	7.2	6.8	7.2	7
Friability(%)	0.24	0.22	0.26	0.28	0.25	0.26
Thickness(mm)	3.46	3.55	3.8	3.9	3.8	3.9
Drug Content (%)	98.73	99.02	98.9	99.1	99.08	99.04
Weight Variation	Weight of all the tablets was found between the ranges of 199.8 mg to 200.3 mg which is well within the USP limits (7.5%).					

Hardness

The hardness of the tablets of all batches was ranged from 3.5 to 6 kg/cm^2. The results of hardness tests are given in the Table No. 8. The hardness of tablets of all formulations is within the limit which was sufficient to maintain the mechanical strength.

Friability

The results of friability test, the percentage friability was ranged from 0.22 to 0.28 (NMT 0.8%). In the present study, the percentage friability for all the formulations was found below 0.8% indicating that % friability is within the limit. The results were given in the Table No. 8.

Thickness (mm)

The results of thickness test are depicted in Table No. 8. The thickness was ranged from 3.46 to 3.9. In the present study, thethickness for all the formulations was found indicating that thickness is within the limit.

Drug Content (%)

The drugs content of all the tablets was found between the ranges of 98.7% to 99.1% which is well within the USP limits. The results were given in the Table No. 8.

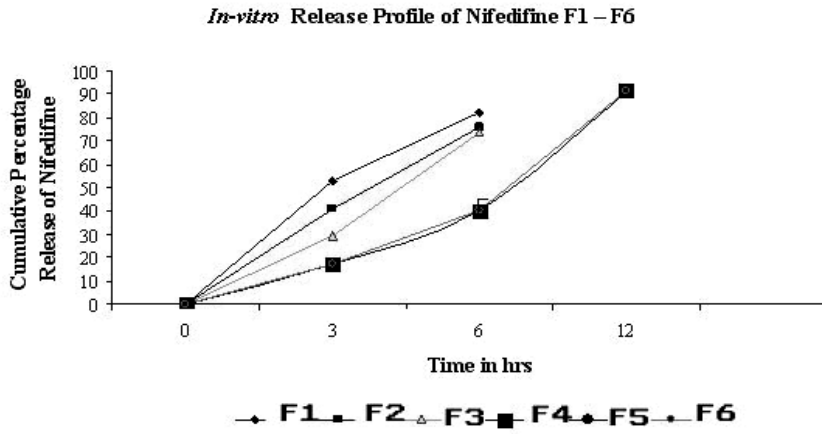
Weight Variation

The weight variation for the various tablet formulation is depicted in the Table No. 8. The values of the weight variation showed that it is within the acceptable limit as per In house specification (± 7.5 from the average weight).

In-vitro release profile of Nifedifine

Table No. 9 In-vitro Release Profile of NifedifineF1 – F6 SR Tablets.

D	Cumulative Percentage Release of Nifedifine					
	F1	F2	F3	F4	F5	F6
3	53	41	29.16	17.19	17.22	17.16
6	82	76	73.46	40.24	40.19	40.23
12	_	_	_	91.12	91.08	91.10



FigureNo. 4 In-vitro Release Profile of Nifedifine F1 – F6 SR Tablets

The Formulation N1, N2, containing HPMC E15 LV concentration has shown more drug release and are not able to maintain matrix integrity. formulations N3,N4,N5 and N6 were prepared using HPMC K100LV. The formulation N4,N5,N6 shows a good dissolution with in the limit. The results were show in the Table No. 9 and figure No. 4.

In-vitro Release kinetics of F4

Table No. 10 In vitro release kinetics of Nifedipine-USP phosphate buffer pH - 6.8

Time in hrs	√t	log t	Amount released (mg)	% drug released	% drug to be released	Log % drug released	Log % drug to be released	$(D)^{1/3}$
3	1.732	0.4771	3.12	17.19	82.81	1.23527	1.91808	4.35874
6	2.449	0.7781	8.05	40.24	59.76	1.60465	1.77641	3.90964
12	3.464	1.0791	18.32	91.12	8.8	1.95961	0.94841	2.07079

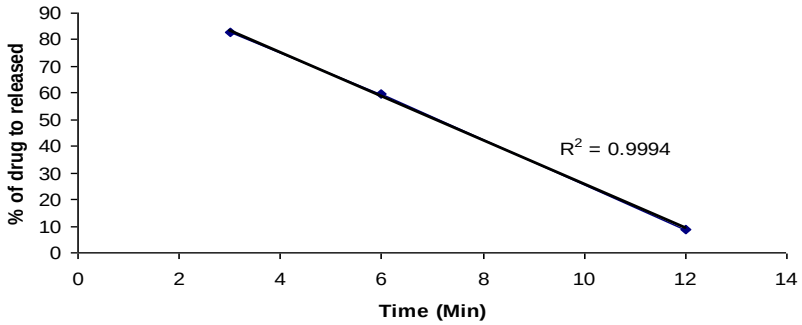


Figure No. 5Kinetic Release of Nifedipine (pH 6.8) Zero order.

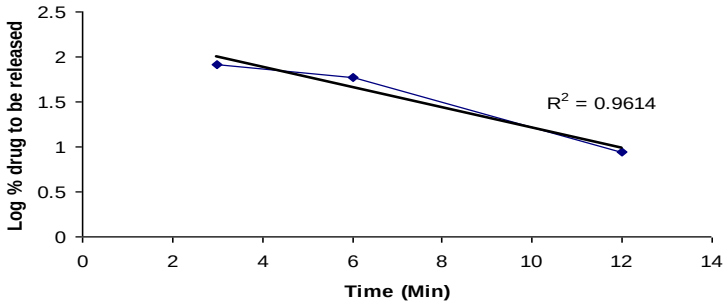


Figure No. 6 Kinetic Release of Nifedipine (pH 6.8) first order.

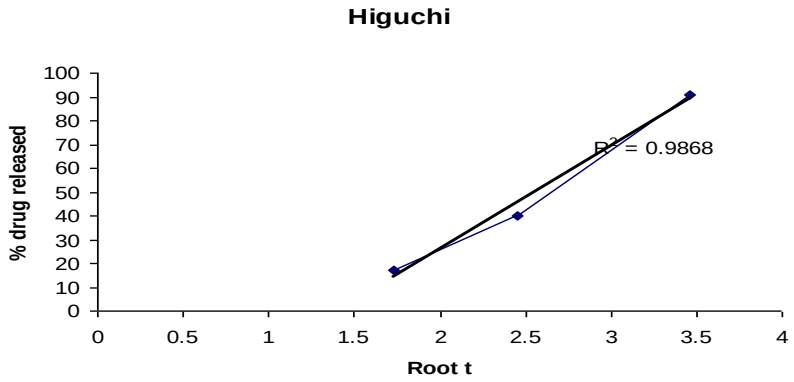


Figure No. 7 Kinetic Release of Nifedipine (pH 6.8) Higuchi

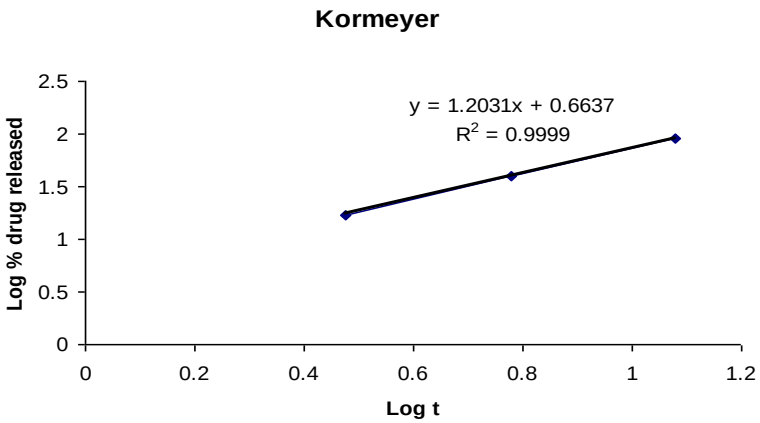


Figure No. 8 Kinetic Release of Nifedipine (pH 6.8) Kormeyer.

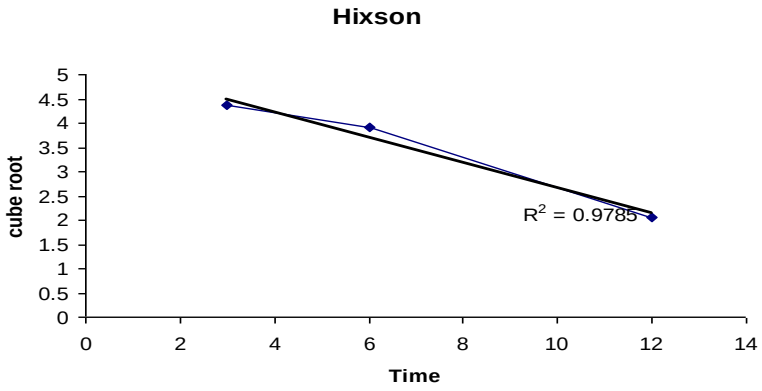


Figure No. 9 Kinetic Release of Nifedipine (pH 6.8) Hixson.

Table No. 11 Consolidation data governing the following equations from F4.

	Equations				
	Zero-rate equation %remaining vs t	**First-rate equation %log remaining vs**	**Higuchi (Q = $Kt^{½}$)**	**Peppas exponential equation**	**Hixson crowell Cube root equation**
r^2	0.9994	0.9614	0.9868	0.9999	0.9785

So only for final formulation (F4) the data could be graphed according to different modes of data treatment. There are shown in figure;

Figure No.5 - according to zero order kinetics
Figure No.6 - according to first order kinetics,
Figure No.7 - according to Higuchi Square root dependent equation ($Q = K^{t½}$).
Figure No.8 - according to peppas exponential equation ($Q = K^n$),
Figure No.9 - Hixson crowell cube root equation respectively.

From these graphs the kinetic values were calculated by linear regression (r^2) analysis and least square techniques. These values were shown in the Table No. 10 and 11.

The data was plotted as % drug released (Vs) time has indicated that the release rate is almost linear. The linear regression value was found to be 0.9994, which indicates that the release rate is satisfying the zero order kinetics. The graph is shown in figure No 5.

The data was also drawn according to first order rate kinetics and the plot is shown in figure No. 6. The linear regression value was found to be 0.9614. The data has satisfied zero order release of the drug than first order rate of release.

Higuchi's square root dependent diffusion equation in which the % drug release was plotted against time and plot is shown in figure No. 7. The plot is linear. This indicates that the diffusion mechanism is operative. The linear regression value 0.9868. So the drug release obeys diffusion mechanism, with zero order rate.

Peppas exponential equation in which the log % drugs release was plotted against log time. The plot was found to be the linear regression value was 0.999. This indicates that there is significant swelling in the matrix during dissolution time and the mechanism of drug release is anomalous diffusion. The plot is shown in figure No. 8.

The data was also plotted accordingly to the Hicksoncrowell cube root equation the plot was found to be linear by the obtained values of r2 = 0.9785. This result indicated that there is a considerable erosion of the tablet has taken place during dissolution. The plots were given in the figure No. 9.

ACCELERATED STABILITY STUDIES

Based on the finalized formula and manufacturing process, a lab scale batch was taken and the formulated tablets were packed in Blisters and loaded in stability chambers for accelerated stability studies at 40^0C/75%RH and 30^0C/65%RH. The required quantity of tablets in 40^0 C/75%RH were analyzed at the end of 1^{st},2^{nd} and 3^{rd} month and for tablets in 30^0C/65%RH were analyzed at the end of 3^{rd} for its physical appearance, Hardness, Average weight, disintegration time, dissolution and Assay. The values were given in the Table No. 12 and 13.

Table No. 12 Stability Data of Nifedipine F4 SR Matrix Tablets stored at 24^0C ±2 at 60%±5%RH

S. No.	Tests	0 month	1st month	2ndmonth	3rd month
1.	Description	Complies	Complies	Complies	Complies
2.	Average Weight 198 - 200.1 mg	200.08 mg	200.07 mg	200.06 mg	200.07 mg
3.	Average Thickness 3.5 mm -4 mm	3.9 mm	3.9 mm	3.9 mm	3.9 mm
4.	Average Hardness	6.8 kg/cm^2	6.8 kg/cm^2	6.8 kg/cm^2	6.8 kg/cm^2
5.	Friability NMT 1.0 %	0.24%	0.24%	0.25%	0.26%
6.	Dissolution Profile (Cumulative % drug release)	3hr-17.7 6hr-40.27 12hr-91.46	1hr-17.9 4hr-40.28 8hr-91.52	1hr- 17.6 4hr-40.54 8hr91.48	1hr- 17.8 4hr-40.41 8hr-91.43
7.	Assay of Nifedipine	91.18%	91.12%	91.15%	91.17%
8.	Related Substances Total Impurities	0.77%	0.79%	0.82%	0.84%

Storage conditions: 24^0C ±2 at 60% ±5%RH
Description: Coated Brown color, round shaped tablets.

Table No. 13Stability Data of Nifedipine F4 SR Matrix Tablets stored at 40^0 C ±2 at 75%±5%RH

S. No.	Tests	0 month	1st month	2ndmonth	3rd month
1.	Description	Complies	Complies	Complies	Complies
2.	Average weight 198 – 200.1 mg	200.08 mg	200.07 mg	200.06 mg	200.07 mg
3.	Average Thickness 3.5 mm - 4 mm	3.9 mm	3.9 mm	3.9 mm	3.9 mm
4.	Average Hardness	6.8 kg/cm^2	6.8 kg/cm^2	6.8 kg/cm^2	6.8 kg/cm^2
5.	Friability NMT 1.0 %	0.24 %	0.24 %	0.25 %	0.27 %
6.	Dissolution Profile (Cumulative % drug release)	3hr-17.9 6hr-40.29 12hr-91.49	1hr-17.8 4hr-40.27 8hr-91.48	1hr- 17.6 4hr-40.28 8hr91.47	1hr- 17.8 4hr-40.29 8hr-91.48
7.	Assay of Felodipine	91.17%	91.15%	91.17%	91.18%

Storage conditions: 40^0C ±2 at 75% ±5%RH
Description: Coated brown colour, round shaped tablets.

The accelerated stability studies were conducted for 3 months. There was no physical change has been observed in the formulations at all three stability conditions and also there was no significant change has been observed in drug content, Hardness and friability of the selected formulations at all three stability conditions. So F4 formulations were found to be stable. The stability data results were given in the table 12 and 13.

CONCULSION

Nifedifine is one of the molecules widely used for the successful treatment of angina pectoris and blood pressure. Nifedifine has a short half life and the usual oral dosage regimen is 10mg-40mg taken to 3-4 times a day. To reduce the frequency of administration and to improve the patient compliance, twice daily sustained release formulations of nifedifine is prepared by using HPMC K 15LV, HPMC K 100, Poly vinyl pyrrolidine, lactose, Aerosil and magnesium stearate.

In the drug-excipient interaction study using IR, it was found that Nifedifine was having compatibility with all the excipients used in the formulation .The compatibility studies were done. The chosen excipients for the formulations were found to be compatible with the active ingredient and having no physical interaction with the active pharmaceutical ingredient. Also there was no change in the physical appearance of the blend.

The micrometric properties such as angle of repose, Hausner's ratio, bulk density, tapped density and carr's index of blend containing drug and excipient were studied. The obtained value angle of repose (θ) ranges between 33^0.05' to 33^0.59.' Hausner's ratio below 1.25 and carr's index below 20 indicating good flow properties.

The tablets of different formulations were subjected to various evaluation tests such as weight variation, friability, thickness, hardness and content-uniformity according to procedure specified in US Pharmacopoeia. The weight variation was less than ±7.5% and friability was 0.2% respectively.

The thickness of tablet was 3.9mm and hardness of tables was 7.2kg/cm^2. Good uniformity of drug content

was found among different batches of the tablets and the drug content was more than 99.1%w/w.

In-vitro dissolution studies were performed for the formulations using USPII tablet dissolution tester employing basket type at 50rpm using 900 ml of Phosphate buffer (6.8) as dissolution medium. The samples withdrawn were analyzed by using HPLC.

The Formulation F1, F2, containing HPMC E15 LV concentration has shown more drug release and are not able to maintain matrix integrity. Formulations F3,F4,F5 and F6 were prepared using HPMC K100LV in increased ratio in order to overcome the drug release rate therefore this formulations were prepared in bulk and subjected to further stability studies.

Order of release was performed on selected F4 formulation. The data was plotted according to the Zero order equation, First order equation, Higuchi equation, Peppas equation and Hicksoncrowell equation. The order of release of the drug was found to be zero order. The formulation was released by diffusion and considerable erosion followed by swelling.

The stability studies were performed on selected formulations i.e. F4 at $25^0C \pm 2^0C$ / 60% ± 5% RH, $35^0C \pm 2^0C$ / 60% ± 5% RH and $40^0C \pm 2^0C$ / 75% ± 5% RH. For 3 months. At the interval of 1month the formulations were checked for physical appearance, drug content, hardness and friability etc. There was no physical change has been observed in the formulations at all three stability conditions and also there was no significant change has been observed in drug content, hardness and friability of the selected formulations at all three stability conditions. So F4 formulations were found to be stable.

The present study demonstrated that polymers (KPMC 100) could be successfully employed for formulating sustained release matrix tablets of Nifedipine. The sustained release tablets can be expected to reduce the frequency of administration and decrease the dose dependent side effects associated with repeated administration of conventional Nifedipine.

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