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FORMULATION AND EVALUATION OF CONTROLLED RELEASE TABLETS OF NICORANDIL

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ABSTARCT

In the present work, an attempt has been made to develop Controlled release tablets of Nicorandil by selecting different Types of polymers Guar gum, Sodium CMC, Xanthan Gum. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.49 % in 12 hours hence it is considered as optimized formulation F5 which contains Sodium CMC (20mg).

KEYWORDS: Nicorandil, Guar gum, Sodium CMC, Xanthan Gum, contolled release tablets.

INTRODUCTION

Oral route has been the commonly adapted and most convient route for drug delivery because of more flexibility in the formulation, patient compliance and convient for a physician during dosage adjustment. The drugs are generally formulated in the conventional manner in immediate –release dosage forms. When conventional dosage forms are taken on schedule and more than once daily, leads to fluctuations in plasma drug concentration and doses may be missed. To overcome this, controlled release formulations have been designed. These have advantages such as reduced blood level fluctuations, reduction in dosing frequency, enhanced patient compliance, reduction in dosing frequency, enhanced patient compliance and reduction in adverse effects. The common way of controlling delivering is by incorporating drug into a polymer. Controlled release tablets can be formulated by using hydrophilic and

hydrophobic polymers. Some of Matrix polymers are HPMC, Sodium alginate, Carrageenan, Xanthan gum and Guargum etc.

N-(2-hydroxyethyl)-nicotinamide nitrate (ester) (Nicorandil) is a potassium channel opener in cardiovascular disease. Nicorandil is readily absorbed from gastrointestinal tract .The objective of the study is to formulate and evaluate Nicorandil controlled release tablets using different polymers such as Guar gum, Sodium CMC, Xanthan gum and HPMC K100 to reduce dosing frequency.

METHODOLOGY

Analytical method development

Preparation calibration curve

100mg of Nicorandil pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 10,20,30,40 and 50 µg/ml of Nicorandil per ml of solution. The absorbance of the above dilutions was measured at 262nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Agilent spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 500 cm^{1}. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal

plane.If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The end was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula.

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table 1.1: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo was read.

The bulk density was calculated using the formula.

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding

measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula.

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density, Tap = Tapped Density.

Table 1.2: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
21 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Formulation development of Tablets

All the formulations were prepared by direct compression. The tablets were prepared as per the procedure given below and aim is to prolong the release of Nicorandil.Total weight of the tablet was considered as 150 mg.

Procedure

1) Nicorandil and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.

3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1.3: Formulation composition for tablet.

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicorandil	20	20	20	20	20	20	20	20	20
Guar gum	15	20	25	-	-	-	-	-	-
Sodium CMC	-	-	-	15	20	25	-	-	-
Xanthan Gum	-	-	-	-	-	-	15	20	25
HPMC K 100 M	5	5	5	5	5	5	5	5	5
Aerosil 200	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Sodium Stearyl Fumerate	3	3	3	3	3	3	3	3	3
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL TABLET WEIGHT	150	150	150	150	150	150	150	150	150

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100.

Table 1.4: Pharmacopoeial specifications for tablet weight variation.

Average weight of tablet (mg) (I.P)	Average weight of tablet (mg) (U.S.P)	Maximum percentage difference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition

of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability

It is measured of mechanical strength of the tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL, pH 6.8 Phophate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c $\pm$ 0.5°c

Procedure

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added process was continued from upto 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 262 and 264 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$F = K_o t$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

Log (100-F) = kt.

A plot of log cumulative percent of drug remaining to be released vs time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where,'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the

mechanism of drug release calculated through the slope of the straight Line.

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

Where, M_t/ M_∞ is fraction of drug released at time't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model

$(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

RESULTS AND DISCUSSION

Standard Calibration curve of Nicorandil

Concentration and absorbance obtained for calibration curve of Nicorandil in 0.1 N hydrochloric acid buffer (pH 1.2**).**

It was found that the estimation of Nicorandil by UV spectrophotometric method at λ_{max} 262.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.

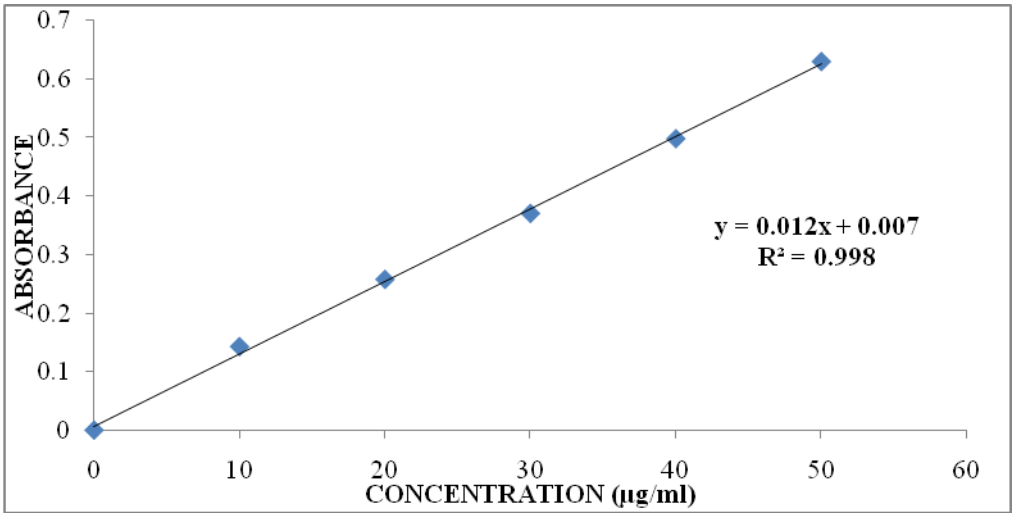

Fig 1: Standard graph of Nicorandil in 0.1 N HCl.

Table 2.1: Concentration and absorbance obtained for calibration curve of Nicorandil in pH 6.8 Phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance* (at 264 nm)
1	0	0
2	5	0.129
3	10	0.218
4	15	0.355
5	20	0.466
6	25	0.561

It was found that the estimation of Nicorandil by UV spectrophotometric method at λ_{max} 264.0 nm in pH 6.8 Phosphate buffer. It had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2-10µg/ml.

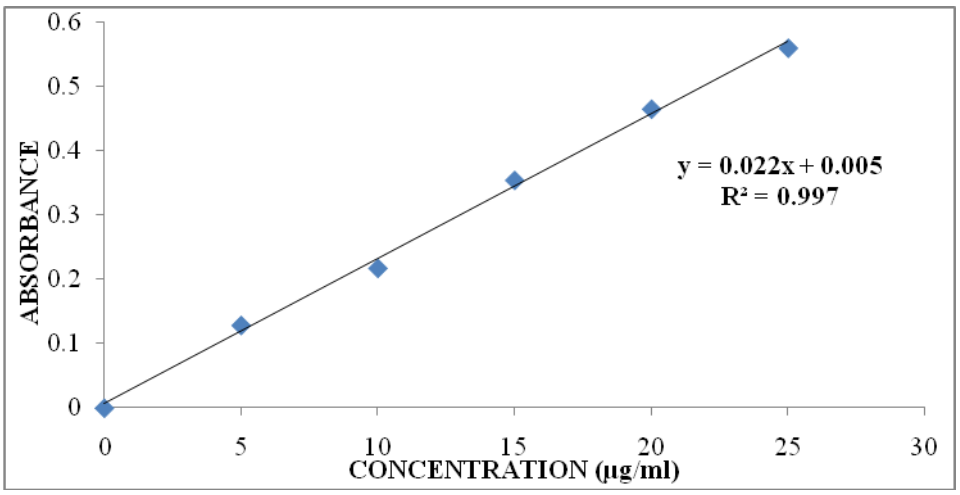

Fig 2: Standard graph of Nicorandil in pH 6.8 Phosphate buffer.

Evaluation Parameters for sustained release tablets of Nicorandil

Pre-compression parameters

.The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.50±0.02 to 0.56±0.08 (gm/cc) and 0.63±0.12 to 0.68±0.11 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.1±1.25 % to 15.9±1.23 %. The Hausner ration fall in range of 1.14±0.25 to 22.6±2.5. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 2.2: Pre-compression parameters					
Formulations	**Bulk Density(gm/cm^2)**	**Tap Density (gm/cm^2)**	**Carr's Index (%)**	**Hausner ratio**	**Angle Of Repose(Ɵ)**
F_1	0.56±0.08	0.68±0.11	13.2±1.12	1.17±0.17	22.6±2.5
F_2	0.52±0.06	0.69±0.16	14.1±1.3	1.18±0.23	20.7±1.9
F_3	0.51±0.03	0.67±0.13	14.2±1.24	1.25±0.19	20.8±1.8
F_4	0.53±0.04	0.64±0.09	15.9±1.23	1.15±0.18	20.7±2.3
F_5	0.50±0.02	0.67±0.17	15.1±1.24	1.23±0.22	20.8±1.7
F_6	0.54±0.04	0.63±0.12	13.2±1.12	1.16±0.11	20.6±2.1
F_7	0.54±0.06	0.64±0.15	15.1±.2.31	1.21±0.18	22.3±2.4
F_8	0.54±0.06	0.65±0.17	14.1±1.19	1.17±0.16	19.6±1.7
F_9	0.55±0.08	0.65±0.17	13.1±1.25	1.14±0.25	23.4±2.9

Post compression Parameters

Average weight test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 2.3. The average weight of the tablet is approximately in range of 148.69 to 152.98 mg, so the permissible limit is ±5% (.220 mg).

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 2.3. The results showed that the hardness of the tablets is in range of 5.4 to 5.9 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in the result showed that thickness of the tablet is raging from 3.4 to 3.7 mm.

Friability: Table 2.3.

FD	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	149.36	5.6	3.5	0.15	95.32
F_2	148.91	5.9	3.7	0.63	98.12
F_3	147.32	5.7	3.6	0.25	99.60
F_4	148.69	5.9	3.4	0.36	100.2
F_5	150.03	5.8	3.6	0.45	98.45
F_6	152.98	5.9	3.6	0.52	99.91
F_7	140.92	5.6	3.5	0.20	98.64
F_8	148.26	5.8	3.4	0.34	97.39
F_9	150.10	5.4	3.5	0.42	98.69

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 2.3. The average friability of all the formulations lies in the range of 0.15 to 0.63% which was less than 1% as per official requirement of IP.

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 95.32 -100.2 %.

Post compression parameters

***In Vitro* Dissolution studies:** *In-Vitro* dissolution studies were carried out by using 900ml of 0.1 N HCL in USP dissolution apparatus by using paddle method for about 2 hours. After 2 hours the dissolution medium was withdrawn keeping the tablet in the dissolution basket. Then pH 6.8 phosphate buffer was added to the dissolution medium (900ml) and the dissolution was carried out for about 12 hours.The samples were withdrawn at regular time intervals of 30 min,1 hour,2 hr,3,5,5,6,7,8,9, 10,11 and 12 hours respectively. The results were displayed in table 2.4.

Table 2.4: *In vitro* dissolution data.

Time(Hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	13.29	10.33	8.22	11.96	18.69	9.90	18.31	10.96	7.11
1	20.74	18.51	16.13	25.15	23.86	12.68	24.96	21.54	12.88
2	27.88	24.46	25.80	29.42	30.15	20.41	30.45	26.36	22.10
3	36.35	30.14	37.13	33.98	37.25	28.91	36.55	32.64	35.17
4	41.89	35.21	43.64	36.82	42.38	35.28	40.98	40.29	49.89
5	47.91	40.87	55.43	41.99	49.55	42.88	48.71	48.91	55.30
6	51.87	46.88	61.26	54.90	56.97	51.25	59.22	56.33	60.12
7	56.19	52.94	71.90	59.78	60.78	60.11	68.20	60.15	64.59
8	68.22	64.58	85.13	62.99	67.90	66.98	77.61	69.91	72.15
9	75.84	71.20	89.99	69.87	75.81	74.90	84.90	78.29	79.88
10	81.69	79.52		76.10	85.14	82.77	91.19	82.31	86.59
11	90.57	86.41		85.90	92.30	95.12		89.61	90.41
12	94.66	90.89			98.49			95.10	97.25

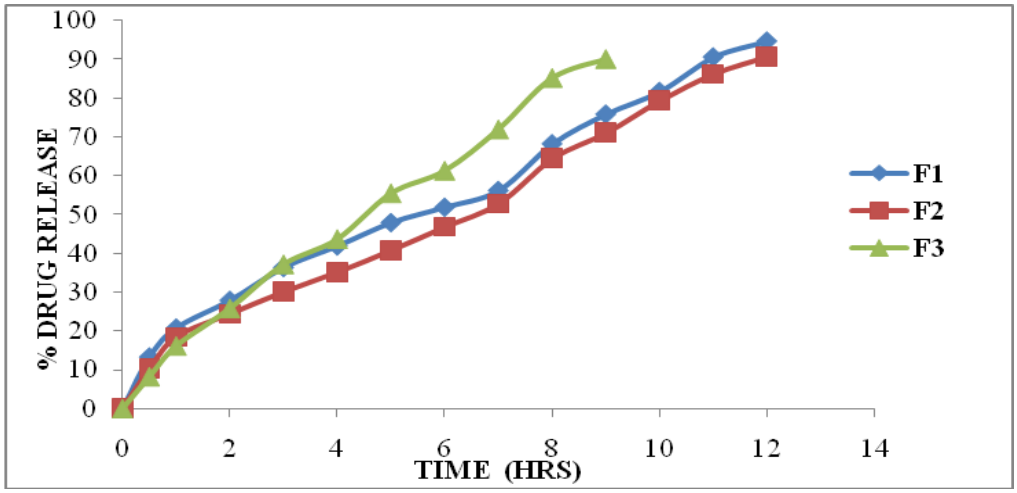

Fig 4: Dissolution profile of formulations prepared with Guar gum polymer

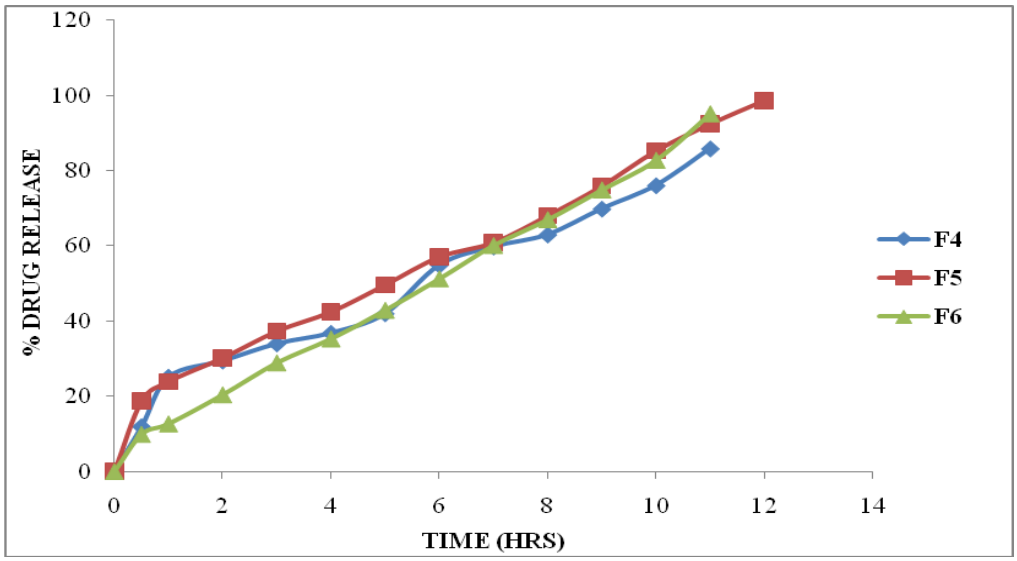

Fig 5: Dissolution profile of formulations prepared with Sodium CMC polymer.

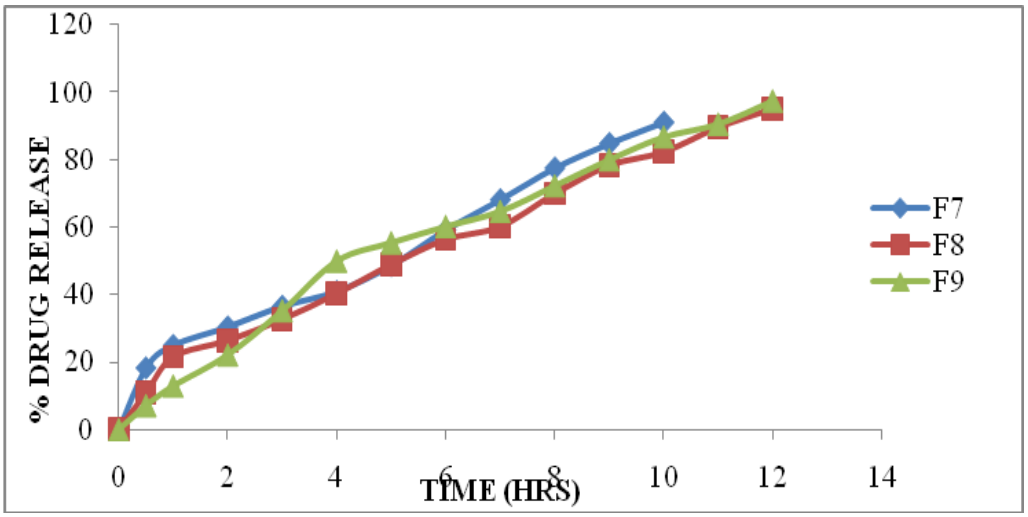

Fig 6: Dissolution profile of formulations prepared with Xanthan Gum as polymer.

From the tabular column 2.4 it was evident that the formulations prepared with Guar gum as retarding polymer in low concentrations produce the required retarding action to the tablets. As the concentration of polymer increases the retarding nature was decreased.Guar gum in the concentration of 15 mg showed good % drug release i.e., 94.66% in 12 hours.

Where as in case of formulations prepared with Sodium CMC as retarding polymer, the formulations with 20 mg concentration of polymer showed complete drug release in 12 hours. whereas the concentration of polymer increases the retarding nature also increased. The Formulations Containing Sodium CMC in 20 mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.49%.

Where as in case formulations prepared with Xanthan Gum as retarding polymer,as the concentration of polymer increases the retarding nature was also increased. When compared with Sodium CMC polymers it was failed to produce desired drug release pattern.

From the above results it was evident that the formulation F5 is best formulation with desired drug release (98.49%) pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the smechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release mode

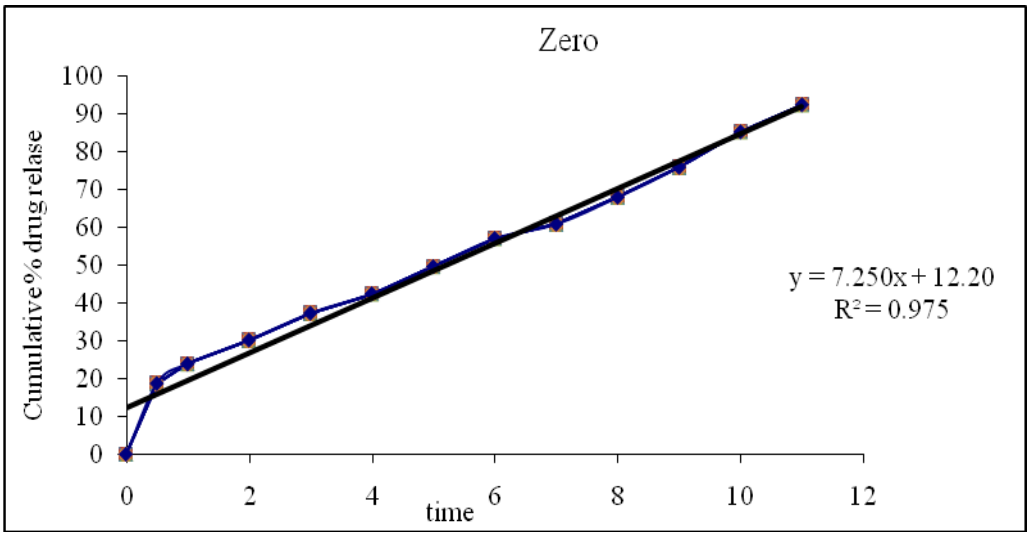

Fig 7 : Zero order release kinetics graph.

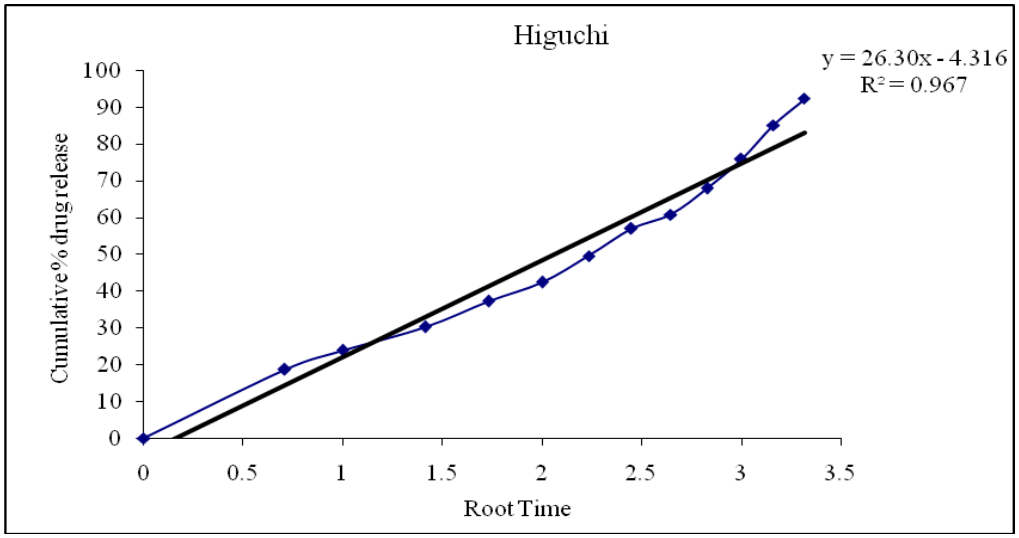

Fig 8: Higuchi release kinetics graph.

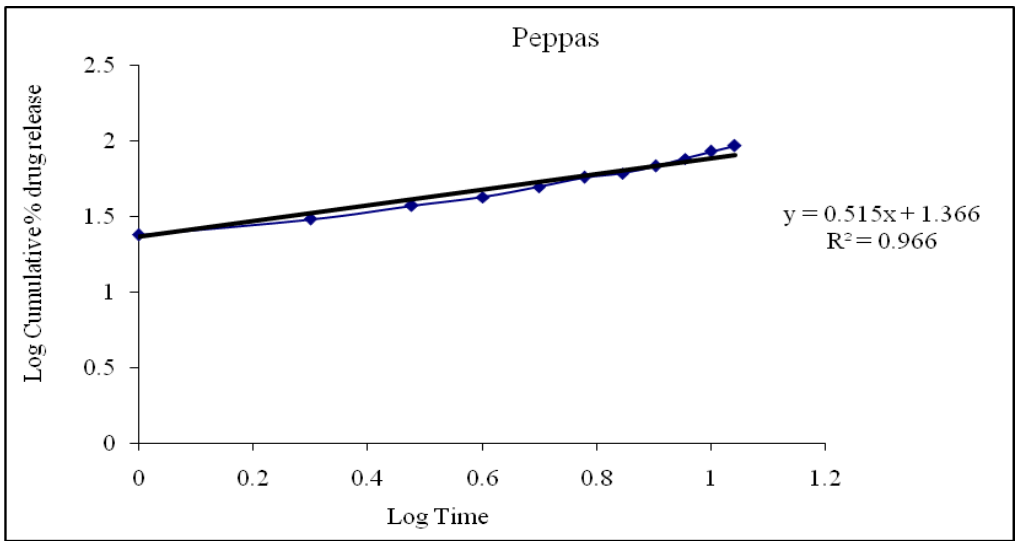

Fig 9: Kars mayer peppas graph.

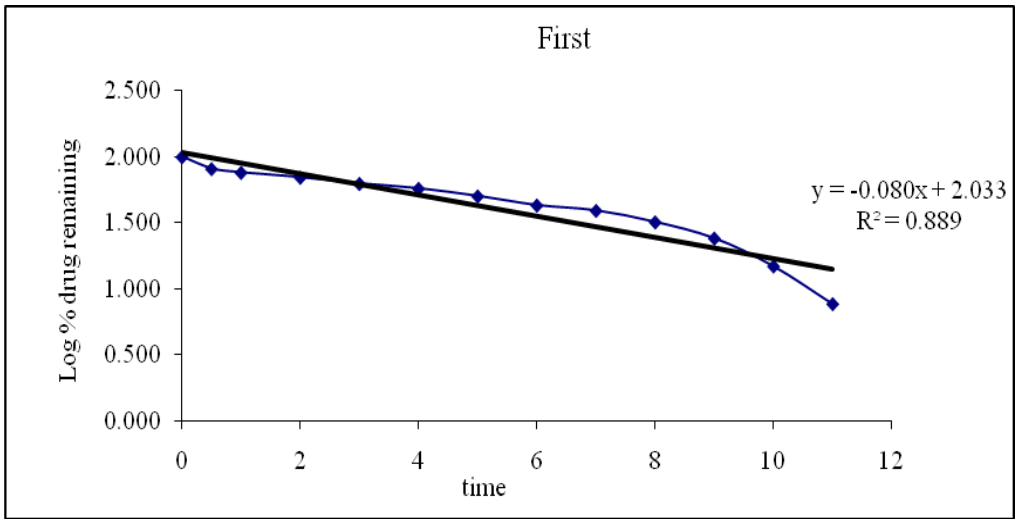

Fig 10: First order release kinetics graph.

From the above graphs it was evident that the formulation F5 was followed zero-order release mechanism.

FTIR

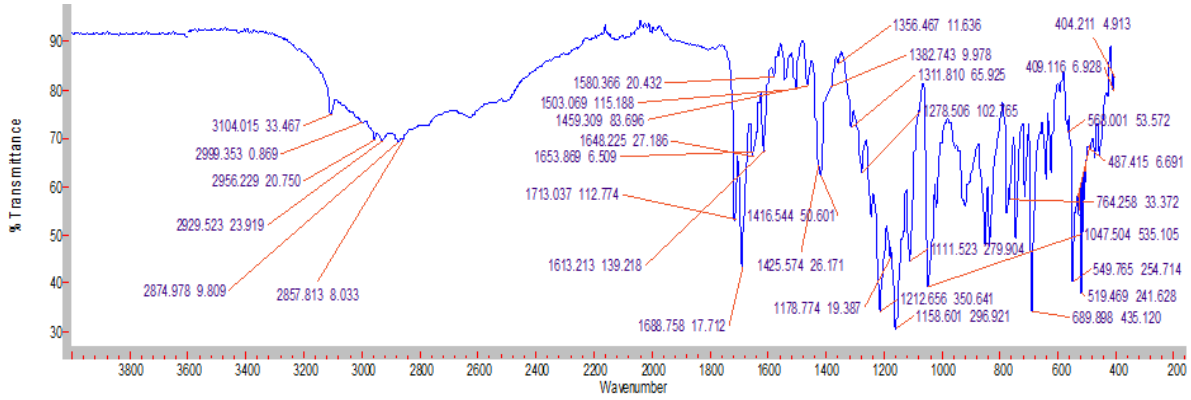

Fig no 11: FT-IR Spectrum of Nicorandil pure drug.

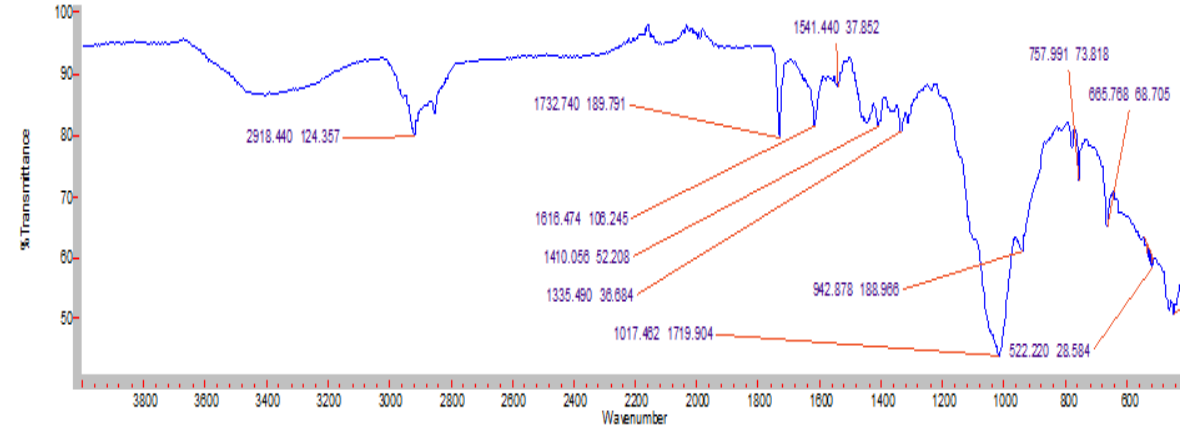

Fig No 12: FT-IR Spectrum of Optimised Formulation.

There is no incompatibility of pure drug and excipients. There is no disappearence of peaks of pure drug and in optimised formulation.

CONCLUSION

In the present work, an attempt has been made to develop Controlled release tablets of Nicorandil by selecting different Types of polymers Guar gum, Sodium CMC, Xanthan Gum as retarding polymer. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F5 formulation showed maximum % drug release i.e., 98.49 % in 12 hours,

hence it is considered as optimized formulation F5 which contains Sodium CMC (20mg). Whereas the formulations with Guar gum showed low retarding with increasing concentration of polymer. The formulations with Xanthan Gum were produce the desired rug release pattern.

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