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FORMULATION AND OPTIMIZATION OF SUSTAINED RELEASE MATRIX TABLET OF NIFEDIPINE USING DIFFERENT GRADES OF HPMC

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Abstract:

In the present study nine formulations with variable concentration of polymers (HPMC-K100, HPMC-K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag time, total floating time, and in-vitro drug release. The results indicated that optimized formulation F 6 on immersion in 0.1N HCl solution at pH 1.2 & 6.8 pH phosphate Buffer at 37±0.50C tablets immediately and remain buoyant up to 12 hrs without disintegration. These two factors are essential for the tablet to acquire bulk densit y < 1, so that it remains buoyant on the gastric fluid. The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Higuchi was maximum i.e 0.978 hence indicating drug release from formulations was found to follow Higuchi kinetics. In vitro data obtained for matrix tablet of Nifedipine showed prolonged drug release. Tablets of different release kinetics could be obtained by varying the formulation variables. Thus, Nifedipine is most suitable drug candidate for the Antihypertension. Based on the above considerations, formulation F6 was selected as optimized formula, a perusal of table indicated that the parameters of Matrix Tablet were satisfactory for the intended use.

Key words: Nifedipine, HPMC, Matrix, Sustained Release

INTRODUCTION

Present peroral sustained release drug delivery systems are for a maximum of 24 hours clinical effectiveness. Such systems are primarily for the drugs of short elimination half life[1]. However, also drugs with long half-life qualify if a reduction in steady state fluctuation is desired.

With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxic for an extended period of time. To achieve better therapeutic action various type of drug delivery systems are available, out of which sustained release systems are gaining much importance because of their wide advantages over others like ease of administration, convenience and non-invasiveness.

Oral route is the most commonly employed route of drug administration. Although different route of administration are used for the delivery of drugs, oral route remain the preferred mode. Even for sustained release system the oral route of administration has been investigated the most because of flexibility in dosage forms design that the oral route offers.

Hypertension and angina pectoris, the most common cardiovascular diseases, require constant monitoring. Calcium channel blockers are presently considered an important class of drugs for hypertension and angina pectoris. Successful treatment of these diseases means maintenance of blood pressure at a normal physiological level, for which a Constant and uniform supply of drug is desired. Hence in present study work an attempt has been made to develop sustained release matrix tablet of anti-hypertension drug by using a hydrophilic matrix polymers. The treatment of acute disease or chronic illness has been achieved by delivery of drugs to the patient for many years. these drugs delivery systems include tablet, injectables, suspensions, cream, ointment, liquids, aerosols etc. Today these conventional drug delivery systems are widely used.

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies to an agent such asgene therapy that will induce in vivo production of the active therapeutic agent. Drug delivery system is an interface between the

patient and the drug. It may be a formulation of the drug to administer it for a therapeutic purpose or a device used to deliver the drug. This distinction between the drug and the device is important, as it is the criterion for regulatory control of the delivery system by the drug or medicine control agency. If a device is introduced into the human body for purposes other than drug administration, such as therapeutic effect by a physical modality or a drug may be incorporated into the device for preventing complications resulting from the device, it is regulated strictly as a device. There is a wide spectrum between drugs and devices, and the allocation to one or the other category is decided on a case by case basis. Sustained release (SR) preparations are not new but several new modifications are being introduced. They are also referred to as "long acting" or "delayed release" when compared to "rapid" or "conventional" release preparations. The term sometimes overlaps with "controlled release," which implies more sophisticated control of release and not just confined to the time dimension.

The following are the rationale of developing SR

1. To extend the duration of action of the drug
2. To reduce the frequency of dosing
3. To minimize the fluctuations in plasma level
4. Improved drug utilization
5. Less adverse effects

Advantages of sustained release dosage forms:

1. The frequency of drug administration is reduced.
2. Patient compliance can be improved.
3. Drug administration can be made more convenient as well.
4. The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
5. Better control of drug absorption can be attained, since the high blood level peaks that way be observed after administration of a dose of a high availability drug can be reduced.
6. The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.

7. The total amount of drug administered can be reduced, thus:
   - Maximizing availability with minimum dose;
   - Minimize or eliminate local side effects;
   - Minimize or eliminate systemic side effects;
   - Minimize drug accumulation with chronic dosing.
8. Safety margins of high potency drugs can be increased and the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
9. Improve efficiency in treatment.
   - Cure or control condition more promptly
   - Improve control of condition
   - Improve bioavailability of some drugs
   - Make use of special effects; e.g. sustain release aspirin for morning relief of arthritis by dosing before bed-time.
10. Economies.

SUSTAINED RELEASE

In practice, very few of the applied systems embrace all of these actions. In most cases, the release systems create constant concentration of drug within the body over an extended period of time. The assumption is that there is steady state drug levels in plasma and in target tissue or cells are correlated. Ideally, it is desirable to place the drug at the target, be it a tissue, a population of cells or receptors, leaving the rest of body drug free. Obviously this would be quite difficult, especially if the target is sheltered from systemic circulation by various barriers. For example, drug targeting to the brain via systemic administration is severely limited by selectivity of the blood-brain barrier. Figure 1 and 2 shows comparative blood level profiles obtained from administration of conventional, controlled, and sustained release dosage forms. The conventional tablet or capsule provides only a single and transient burst of drug. A pharmacological effect is seen as long as the amount of drug within the therapeutic range. Problems occur when the peak concentration is above or below this range, especially for drugs with narrow therapeutic windows. Indeed, prolonged release dosage forms reduce fluctuations in plasma drug levels by slowing down the absorption rate due to slower drug release rate.

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

Rationale of study

- The basic rationale for controlled drug delivery is to alter pharmacokinetic and pharmacodynamic of pharmacologically active moieties by using novel drug delivery systems or by modified the molecular structure and /or physiological parameters inherent in a selected route of administration.
- These cover a wide range of prolonged action formulation which provide continuous release of their active ingredient at a pre determined rate and predetermine time, reduced side effects, etc.
- Drug having a short elimination half life, less frequent administration and better patient compliance may be obtained with sustained release preparation as compared to conventional dosage form.

For Hypertension and angina pectoris successful treatment of this disease means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is desired. It can be achieved by preparation of sustained release formulation

EXPERIMENTAL AND RESULTS

Materials and Equipments

Table No. 6.1 List of drug and Excipients used

S. No.	Materials Used	Grade	Gift sample
1.	Nifedipine	Pharma	Alembic Pharma Vadodra.
2.	Ethyl Cellulose	Pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun.
3.	H.P.M.C. K 100	Pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun.
4	H.P.M.C. K4	Pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun.

4.	Talc	Pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun.
5.	Magnesium Sterate	Pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun.
6.	Aerosil	pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun
7.	Avicel	pharma	Mapromax, Life sciences Pvt. Ltd., Dehradun

The following materials that were Pharma grade or the best possible Laboratory Reagent were used as supplied by the manufacturer without further purification or investigation.

Preformulation study

Dose Selection: Matrix release: 30 mg of Nifedipine

Physical appearance

The drug Nifedipine powder was examined for its organoleptic properties like colour and odour

Table No. 6.3 Physical appearance of Drug

Color	: White to off white powder
Odor	: Odor less
form	: powder

Solubility

Solubility study of Nifedipine has been done in various solvent such as water, Phosphate buffer pH 6.8, Phosphate buffer pH 7.6 and 0.1N HCL solution. We were found that a solubility of Nifedipine is good in a 0.1 N HCL solution.

Table No. 6.4 Solubility of Nifedipine

S.No.	Solvent	Solubility
1	Water	+++++
2	Ethanol	+++
3	Methanol	+++
5	Acetone	+++
6	0.1 N HCL	++++++
7	6.8 pH Buffer	+++

Melting Point:

It is one of the parameters to judge the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Since the drugs contain the mixed chemicals, they are described with certain range of melting point.

Procedure for determine melting point:

A small quantity of powder was placed into a fusion tube. That tube is placed in the melting point determining apparatus containing castor oil. The temperature of the castor oil was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted.

Table No. 6.5 melting point of drug

S.No	Method	Literature Melting Point	Practically Melting Point
1	Capillary fusion method	172-174°c	174-175°c

Drug Partition Studies

Partition coefficient is defined as the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium.

$$P_{O/W} = \frac{C_O}{C_W}$$

- Where Co= Concentration of drug in n-octanol phase
- C_w = Concentration of drug in water
- $P_{o/w}$ = Partition coefficient

Partition coefficient is a measure of drug lipophilicity and an indication of its ability to cross biomembrane. For drug delivery, hydrophilic lipophilic balance (HLB) is an important factor. It is also useful in screening of some biologic properties.

Partition coefficient of Nifedipine was determined in octanol:water. Accurately weighed amount of drug (10mg) was taken in a glass stoppered test tube containing 10ml of n-octanol and 10 ml of water. The mixture was shaken on a wrist action shaker for 24hr. Both the phases were

separated using separating funnel and the drug concentration in aqueous and octanol phase was determined by spectrophotometrically at 276 nm.

The partition coefficient of drug found to be in n-octanol: water by using following equation:

$$\text{The partition coefficient, } K = \frac{\text{Amount of drug in organic layer}}{\text{Amount of drug in aqueous layer}}$$

Table No. 6.6 Partition Coefficient Values of Drug

S. No	Medium	Partition Coefficient (Log P)
1	n – octanol : Water	0.426

UV Estimation curve of Nifedipine

The absorption maxima of Nifedipine were determined by running the spectrum of drug solution in double beam ultraviolet spectrophotometer.

Procedure:

100mg equivalent weight of Nifedipine drug sample was dissolved in 100 ml of Distilled water in a volumetric flask. 5 ml of this solution was taken and diluted to 50 ml. The resulting solution was serially diluted to obtain drug concentrations of 5-25 µg/ml. The absorbance of the solutions were measured against in Distilled water as blank at 276nm using the UV spectrophotometer. The plot of absorbance vs. concentration was plotted and the Beer's range was determined.

λ Max. of Nifedipine

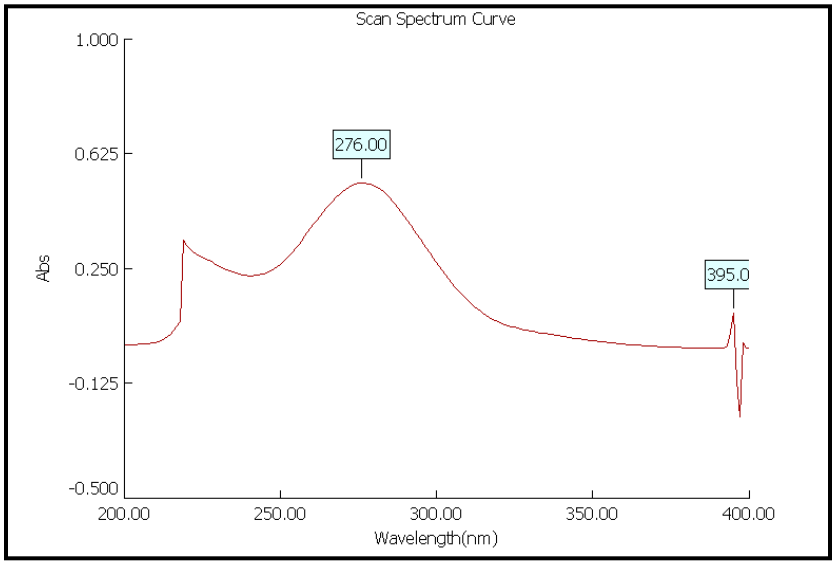
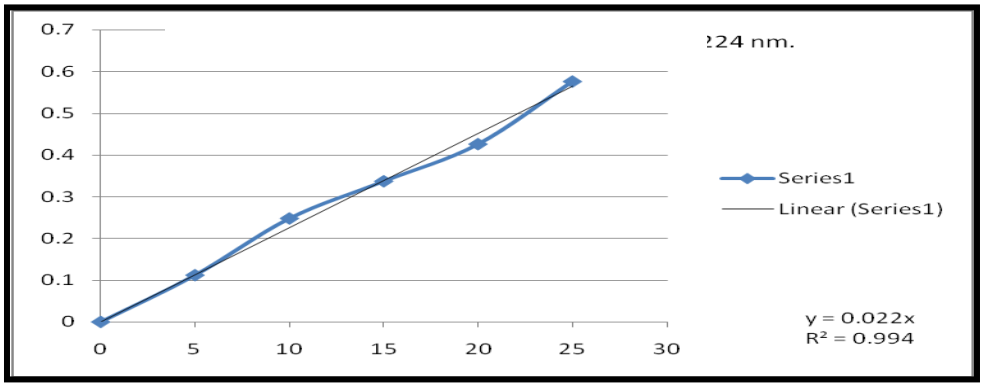


Fig No..6.1 : λ Max. of Nifedipine

Table No..6.7 Calibration Observation table of Nifedipine at 276 nm:-

S. No.	Conc. µg/ml	Absorbance			
		I	II	III	Average
1	5	0.111	0.114	0.111	0.112
2	10	0.246	0.247	0.247	0.248
3	15	0.335	0.340	0.333	0.337
4	20	0.423	0.427	0.432	0.426
5	25	0.572	0.579	0.576	0.576

Calibration curve of Nifedipine at 276 nm



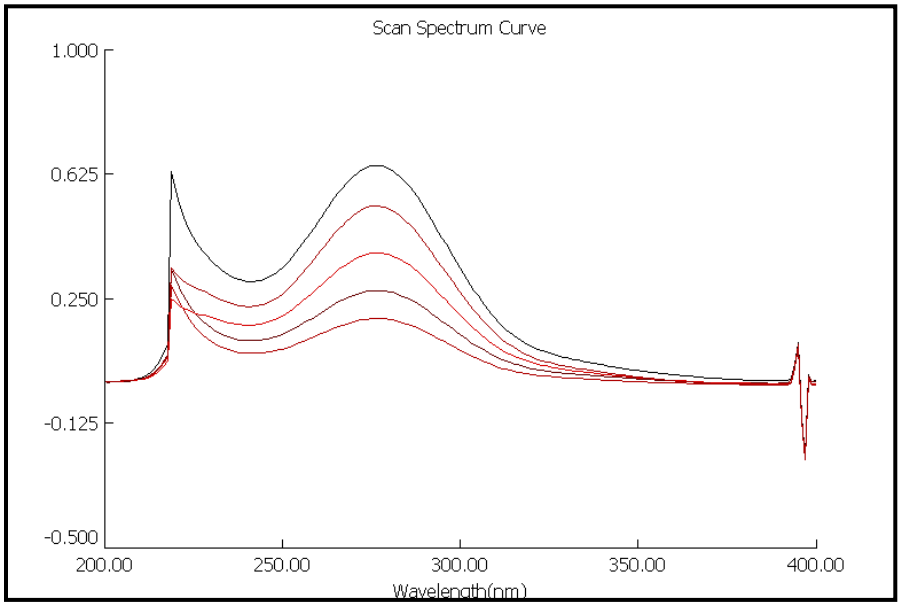


Fig No. 6.2 - calibration curve of Nifedipine HCL

The linear regression analysis for standard curve

The linear regression analysis was done on Absorbance data points. The results are follows:

Table No. 6.8 for standard curve in Distilled water

The intercept	0.000
The correlation coefficient (R^2)	0.994

FTIR Spectroscopy:

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound.

The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region.

Identification of Nifedipine by FTIR Spectroscopy with respect to marker compound. Nifedipine was obtained as White or almost white crystalline powder. It was identified from the result of IR spectrum as per specification.

Sample of pure Nifedipine

The IR spectrum of sample drug shows the peak values which are characteristics of the drug and the graph were shown in figure.

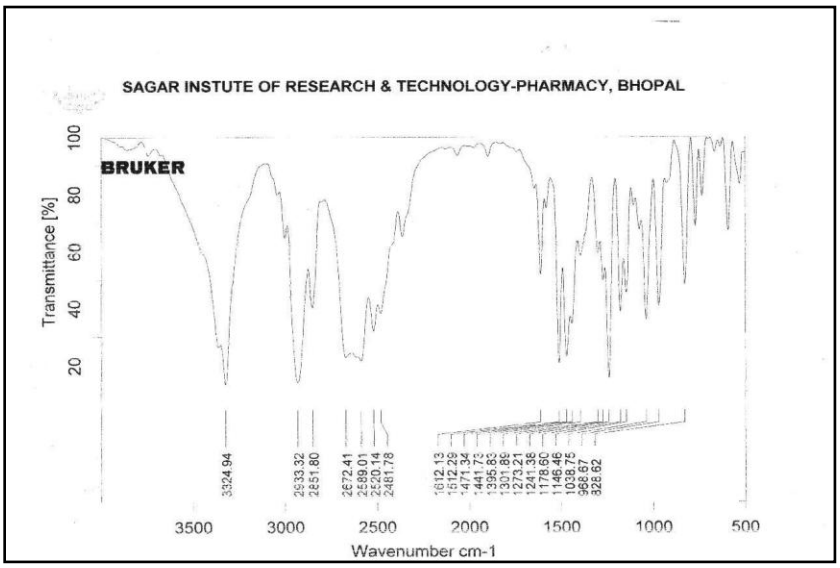


Figure No. 6.3 - FT-IR Spectrum of Pure Drug (Nifedipinee Hydrochloride)

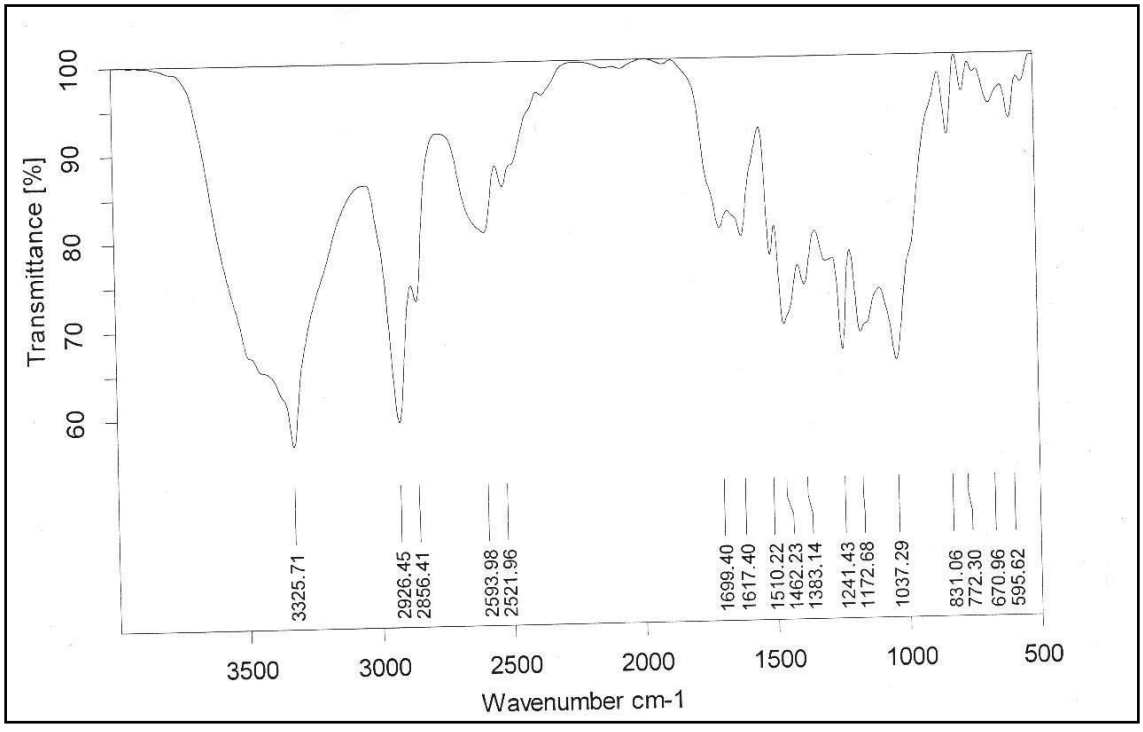


Figure No. 6.4 - FTIR Spectrum of HPMC- K100

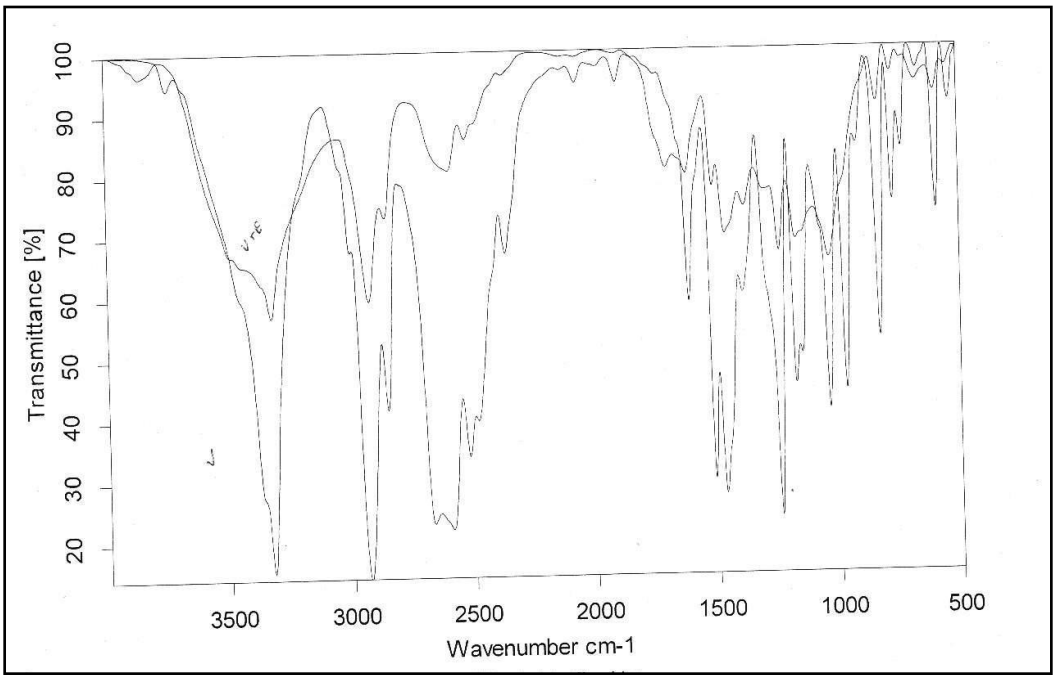


Figure No. 6.5– Overlain FT IR Spectrum of Nifedipine&HPMC-K100.

Loss on Drying (LOD):

Procedure: Loss on drying directly measuring by IR moisture balance. Firstly calibrate the instrument by knob then take 5.000 gm sample (powder) and set the temp at 100°C to 105°C for 5 minutes and constant reading set the knob and check % moisture.

Result: The percentage of loss on drying was **0.0167 %w/w**.

Determination of pH (1% w/v solution in water):

Procedure

1gm of the Powder was taken and dissolved in 100ml of distilled water with sonication and filtered, pH of the filtrate was checked with standard glass electrode.

The pH determination of Nifedipine was done by Digital pH meter and found to be **6.7.**

FLOW PROPERTY OF NIFEDIPINE POWDER:

A. Bulk properties

Bulk density is defined as the mass of powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particles become more spherical in shape, bulk density is increase. In addition as granules size increase, bulk density decrease. Bulk properties such as particle size, bulk density etc. of a solid form, are likely to change during process development. Therefore, comprehensive characterization of all preformulation lots is necessary to avoid misleading predictions.

Bulk density is determined by measuring the volume of a known mass of powder sample that has been passed through a screen into a graduated cylinder or through a volumetric measuring apparatus into a cup.

Procedure:

A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml gm/cc, by the formula

$$\text{Bulk Density} = \frac{\text{Bulk Mass}}{\text{Bulk Volume}}$$

Table No. 6.9 -Bulk Density of Nifedipine

S.NO.	DENSITY	RESULT
1	Untapped Density	**0.242 g/cc**
2	Tapped Density (after 50 tapping)	**0.342 g/cc**

B. **Compressibility index (Carr's index) :**

Compressibility index (C.I.) is an important measure that can be obtained from the bulk and tapped densities. Carr's index a material having values of less than 20% to 30% is defined as the free flowing material.

It can be calculated as per given formula:

$$C.I. = \frac{100\,(V0-Vf)}{V0} \quad OR \quad C.I. = \frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Table 6.10- Carr's index range

S.No.	% Comp. Index	Properties
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair – passable
4	23-25	Poor
5	33-38	Very Poor
6	>40	Extremely poor

Result: The compressibility index of Nifedipine is **29.36%.**

C. Hausner ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

$$\textbf{Hausner ratio} = \frac{\textbf{Tapped density}}{\textbf{Bulk Density}}$$

Table No. 6.11 Hausner ratio and flow property characteristics

S.No..	Hausner ratio	Property
1.	0.0 - 1.2	Free flowing
2.	1.2 - 1.6	Cohesive powder

Standard value of hausner ratio is 1.25

D. Angle of Repose

Flow properties determination of powder or granules is the unique tools to avoid the weight variation of tablet Angle of repose, Carrs index, Hausner ratio are some technique by which we can estimate the flow properties of powder.

- The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated.

$$\mathbf{Tan\ \theta = h/r}$$

Where h, r is the relatively height and radius of the powder cone.

For most pharmaceutical powders, the angle of repose values range from 25 to 45, with lower values indicating better flow characteristics. Values of angle of repose ≤ 30 usually indicate a free flowing material and angle ≥40 suggest a poorly flowing material.

Table No.. 6.11 - Angle of repose (θ) and flow property characteristics

S.N.	Angle of repose (θ)	Flow Property
1.	25-45	Better flow
2.	≤ 30	Free flow
3.	≥40	Poorly flow

Procedure: The angle of repose is a relatively simple technique for estimating the flowability of a powder through a funnel and fall freely onto a surface. The height and diameter of the resulting cone is measured and using the following equation, the angle of repose can be calculated. Weigh 10 gm of Nifedipine powder accurately, and pass through the fennel height up to10 cm from surface and measure the height and diameter by scale.

Tan θ = h/r

Where h, r is the relatively height and radius of the powder cone.

Results: 1. The Angle of repose of Nifedipine is **30** degree.

2. Partical size pass through 40# is **100 (%w/w).**

Moisture by Karl-Fischer Apparatus (KF)
The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulphur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

In the original titrimetric solution, known as Karl Fisher Reagents, the sulfur dioxide and iodine was dissolved in pyridine and methanol. The test specimen may be titrated with the reagent directly, or the analysis may be carried out by a residual titration procedure. The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentration of the reagent ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however other suitable solvents may be used for special or unusual test specimens. (Note: Now-a-days pyridine free KF reagents are coming in which pyridine is replaced by the imidazole, because pyridine has carcinogenic effects).

Preparation of Buffers:

Preparation of acidic buffers:

Preparation of 0.2 M hydrochloric acid:

HCL diluted with water to contain 7.292 gm of HCl in 1000ml.

Preparation of 0.2 M potassium chloride:

Dissolve 14.911gm of potassium Chloride in water and diluted with water to 1000ml.

Preparation of acidic buffer pH 1.2:

Place 50m.l. of the 0.2 M potassium chloride in a 200ml volumetric flask, add the specified volume 85ml. of 0.2 M HCL and then add water to volume.

Preparation of phosphate buffer:

Preparation of 0.2 M sodium hydroxide solution:

Dissolve 8.0 g of sodium hydroxide pallets in 1000 ml of distilled water

Preparation of phosphate buffer pH 6.8:

Place 50 ml of 0.2 M potassium dihydrogen phosphate and add 22.4 ml of 0.2 M of sodium hydroxide. Dilute with distilled water to make up the volume up to 200ml.

Result: The Moisture content of Nifedipine is **0.964 %.**

6.3 FORMULATION DEVELOPMENT

Preparation of Nifedipine Matrix Tablet:-

Direct compression was followed to manufacture the matrix tablets of Nifedipinee Hydrochloride. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation.

Polymers selected for tablets are

HPMC K100

HPMC K4

Excipients like Talc, Magnesium Stearate were selected for the study.

Steps involved in the manufacture of tablets.

First the drug, polymer and other excipients selected were passed through 40- mesh sieve. Required quantity of drug, polymer and excipients were weighed properly and transferred into polyethylene bag and the blend was mixed for at least 15 min. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5 min.

Table No..6.12 Various formulation of Nifedipine matrix tablet (Weights in mg)

A.

Excipients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Nifedipine Hydrochloride	30	30	30	30	30	30	30	30	30
HPMC K 4	80	90	100	-	-	-	40	45	50
HPMC K 100	-	-	-	80	90	100	40	45	50
Lactose	43	33	23	43	33	23	43	33	23
Talc	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Total Weight	160	160	160	160	160	160	160	160	160

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

B. General Appearance

Five tablets from different batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually.

Very good (+++), good (++), fair (+) poor (-), very poor (- -).

C. Thickness and diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

D. Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester .

E. Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).

Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

F. Uniformity of weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

G. Drug content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCL and made up to volume with of 0.1 N HCL. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 276.0 nm using of 0.1 N HCL as blank.

I. Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50c and rpm of 75. One Nifedipine Control layer tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 12 hours. Sample measuring 10 ml were withdrawn after 30 min., 1.0 hr, 1.30 hr, 2.0 hr, 4.0 hr, 6.0 hr, 8.0, 10.0 hr, 12 hour using 10 ml pipette. The fresh dissolution medium was replaced every time with the same quantity of the sample.

Table No. 6.13 Result of Pre Compression Properties of Nifedipine Matrix Tablets

Material	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner ratio
F1	32.24	0.381±0.003	0.809±0.004	33.840 ±0.012	0.472±0.54
F2	29.26	0.382±0.004	0.822±0.007	35.717±0.014	0.468±0.58
F3	30.15	0.385±0.002	0.799±0.008	32.221±0.015	0.483±0.52
F4	29.26	0.380±0.006	0.844±0.004	40.715±0.010	0.452±0.56
F5	29.48	0.388±0.004	0.851±0.005	41.444±0.014	0.456±0.54
F6	31.56	0.354±0.007	0.822±0.006	41.411±0.015	0.430±0.45
F7	30.49	0.375±0.005	0.812±0.003	37.451±0.017	0.464±0.52
F8	30.56	0.387±0.004	0.809±0.007	35.548±0.011	0.478±0.56
F9	31.14	0.354±0.006	0.822±0.008	42.758±0.012	0.429±0.47

Table No. 6.14 Results of Post Compression Properties of NifedipineMatrix Tablets

Formulation code	Thickness (mm)	Hardness (kg/cm2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.90 ±0.06	6.13 ± 0.21	Passes	0.5214± 0.04	99.23±0.48
F2	3.89 ±0.08	6.70 ± 0.30	Passes	0.6325 ±0.04	90.56±0.57
F3	3.90 ±0.03	6.51 ± 0.50	Passes	0.5215 ±0.08	99.77±0.67
F4	3.89 ±0.06	6.73 ± 0.29	Passes	0.6534 ±0.10	99.27±0.23
F5	3.87 ±0.03	6.82 ± 0.51	Passes	0.6485 ±0.04	98.42±0.61
F6	3.89 ±0.05	6.78 ± 0.51	Passes	0.5489 ±0.08	99.54±0.34
F7	3.88 ±0.04	6.80 ± 0.47	Passes	0.5320 ±0.10	99.77±0.56
F8	3.86± 0.04	6.83 ± 0.49	Passes	0.5364 ±0.05	97.37±0.60
F9	3.89± 0.02	6.81 ± 0.50	Passes	0.5422 ±0.15	98.50±0.61

Table No. 6.15 In vitro drug release study of Matrix tablet

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	08.23	07.14	07.24	08.23	07.23	07.45	08.32	07.26	07.28
1	12.32	10.23	11.45	10.45	10.45	11.23	12.23	11.87	12.56
1.5	26.23	22.42	24.23	23.76	31.23	38.23	32.13	26.28	18.58
2	42.45	40.32	45.23	44.23	48.23	46.32	47.14	38.21	40.28
3	76.34	66.11	67.21	65.71	50.56	67.02	71.13	68.24	56.98
4	82.23	77.33	75.11	82.34	55.00	88.13	91.23	89.12	73.98
6	82.55	97.13	87.13	83.00	56.00	99.13	92.00	99.25	84.16
8	83.00	97.10	94.23	83.21	57.25	99.99	93.00	99.56	89.26
12	84.21	97.23	99.26	83.50	57.85	99.87	94.56	99.76	94.56

RELEASE KINETICS OF NIFEDIPINE MATRIX TABLET

Table No. 6.16 Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

S.No.	Time in minutes	% Cum. drug release		
		F1	F2	F3
1.	0	0	0	0
2.	0.5	08.22	07.15	07.22
3.	1	12.32	10.23	11.45
4.	1.5	26.22	22.41	24.22
5.	2	42.44	40.32	45.22
6.	3	76.35	66.12	67.20
7.	4	82.23	77.32	75.11
8.	6	82.53	97.12	87.12
9.	8	83.00	97.10	94.23
10.	12	84.22	97.24	99.25

Figure No. 6.6 : Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

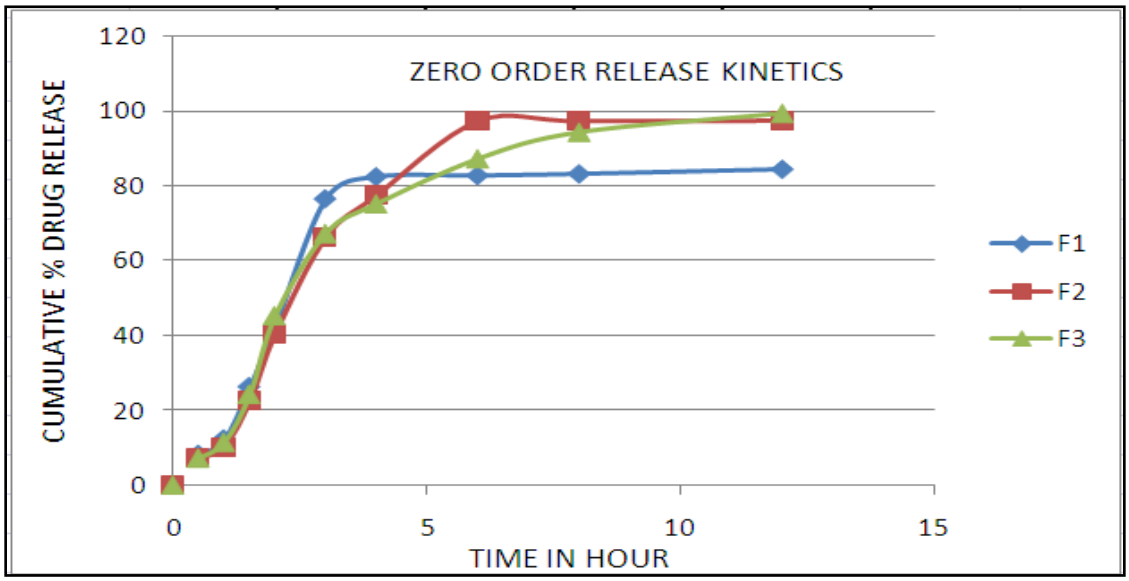


Table No. 6.17: Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

S.No.	Time in minutes	% Cum. drug release		
		F4	F5	F6
1.	0	0	0	0
2.	0.5	08.21	07.22	07.43
3.	1	10.41	10.44	11.23
4.	1.5	23.75	31.25	38.22
5.	2	44.22	48.23	46.31
6.	3	65.72	50.54	67.01
7.	4	82.34	55.00	88.13
8.	6	83.01	56.01	99.12
9.	8	83.22	57.24	99.98
10.	12	83.5	57.84	99.86

Figure No. 6.7: Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

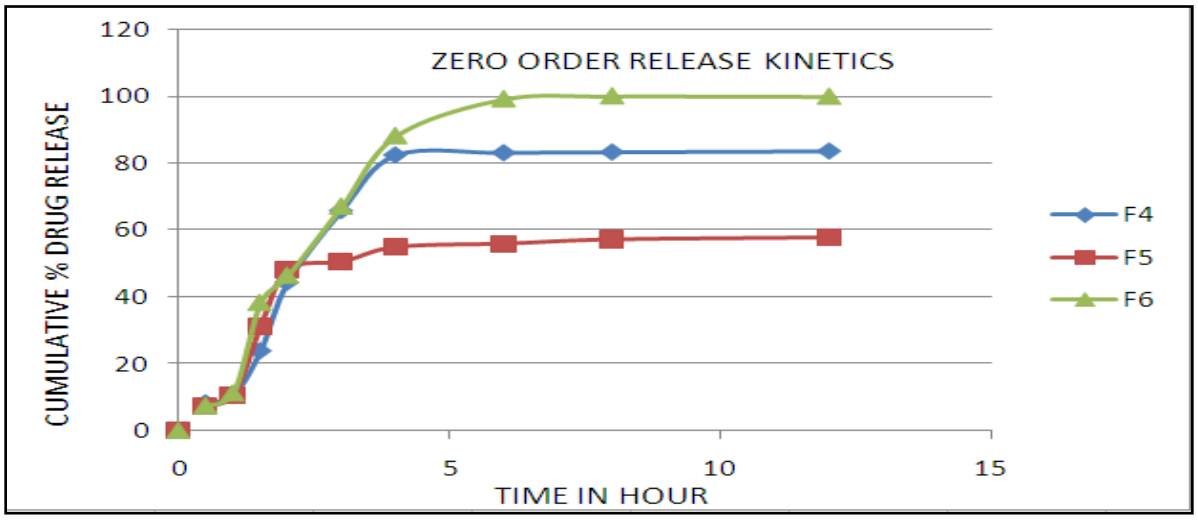


Table No. 6.18: Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-4+ HPMC K-100 as Binder

S.No.	Time in minutes	% Cum. drug release		
		F7	F8	F9
1.	0	0	0	0
2.	0.5	08.33	07.25	07.27
3.	1	12.22	11.86	12.55
4.	1.5	32.12	26.27	18.59
5.	2	47.13	38.22	40.29
6.	3	71.12	68.23	56.98
7.	4	91.23	89.11	73.98
8.	6	92.00	99.25	84.16
9.	8	93.00	99.57	89.26
10.	12	94.56	99.7	94.56

Figure No. 6.8 : Zero order release kinetics data Nifedipine Matrix tablet with HPMC K-4+ HPMC K-100 as Binder

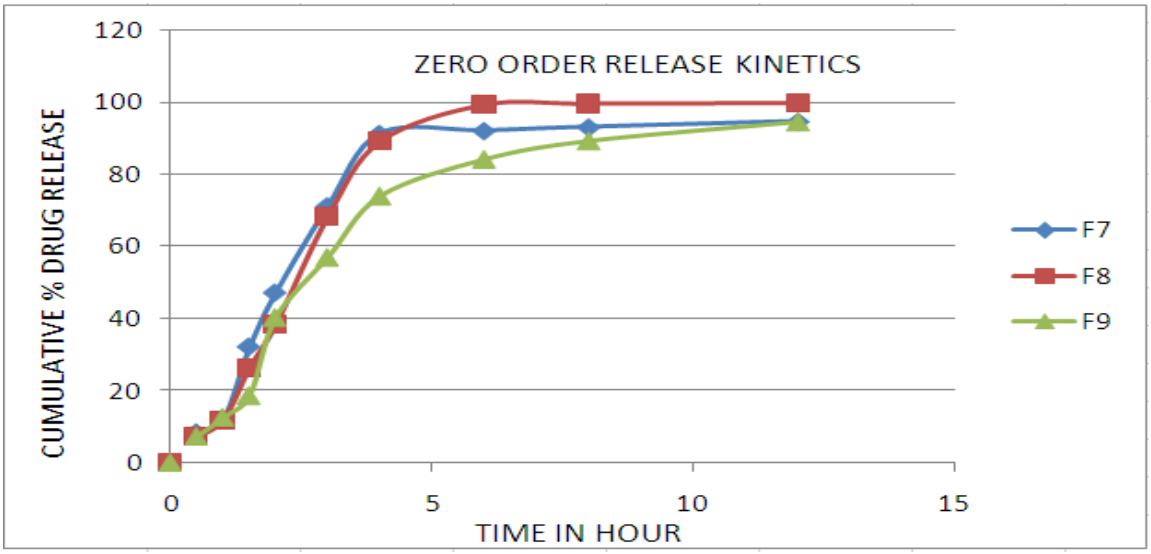


Table No 6.19: first order release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

S.No.	Time in minutes	Log % Cum. drug remain to be release		
		F1	F2	F3
1.	0	0	0	0
2.	0.5	1.966	1.967	1.967
3.	1	1.941	1.952	1.946
4.	1.5	1.911	1.889	1.878
5.	2	1.776	1.775	1.738
6.	3	1.632	1.530	1.515
7.	4	1.415	1.354	1.395
8.	6	1.198	0.456	1.109
9.	8	1.031	0.461	0.761
10.	12	0.735	0.442	-0.13

Figure No. 6.9: first order release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

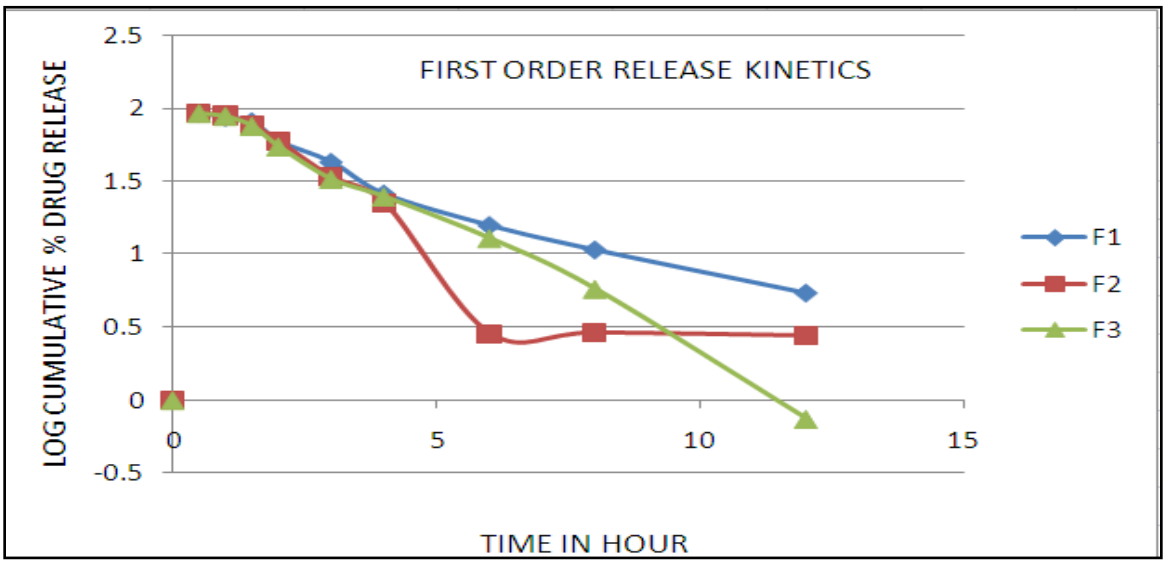


Table No. 6.20: First order release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

S.No.	Time in minutes	Log % Cum. drug remain to be release		
		F4	F5	F6
1.	0	0	0	0
2.	0.5	1.9626	1.96740	1.9663761
3.	1	1.95205	1.95207	1.9482661
4.	1.5	1.88217	1.8373	1.7907778
5.	2	1.7463	1.71407	1.7298124
6.	3	1.53516	1.694056	1.5182507
7.	4	1.24698	1.65321	1.0744505
8.	6	1.23045	1.64344	1.02563
9.	8	1.22504	1.63093	1.0265477
10.	12	1.21746	1.6247	1.0364

Figure No. 6.10: First order release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

Table No. 6.21: First order release kinetics data Nifedipine Matrix tablet with HPMC K-4 + HPMC K-100 as Binder

S.No.	Time in minutes	Log % Cum. drug remain to be release		
		F7	F8	F9
1.	0	0	0	0
2.	0.5	0.2938045	1.967	1.9671733
3.	1	0.2889195	1.945	1.9417101
4.	1.5	0.2711443	1.866	1.9107311
5.	2	0.252849	1.79	1.7761196
6.	3	0.1763807	1.501	1.6336703
7.	4	0.0153597	1.035	1.4153072
8.	6	-0.9065781	0.124	1.1997551
9.	8	-0.44854	0.356	1.0310042
10.	12	-0.2083093	0.619	0.7355987

Figure No. 6.11: First order release kinetics data Nifedipine Matrix tablet with HPMC K-4 + HPMC K-15 as Binder

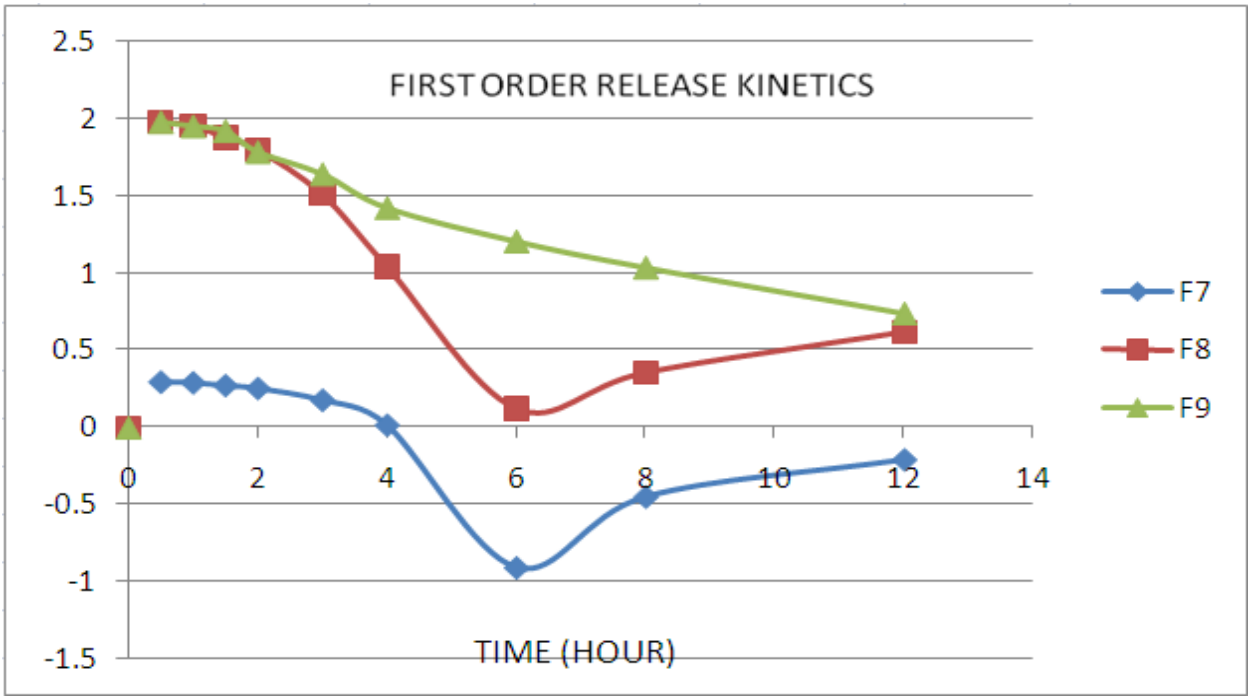


Table No 6.22: Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

S.No..	Root Time	% Cum. drug remain to be release		
		F1	F2	F3
1.	0	0	0	0
2.	0.70710	8.22	7.14	7.23
3.	1	12.32	10.22	11.45
4.	1.27673	26.22	22.41	24.24
5.	1.41422	42.44	40.31	45.23
6.	1.73204	76.33	66.12	67.24
7.	2	82.22	77.32	75.11
8.	2.44948	82.54	97.12	87.14
9.	2.82844	82	97.1	94.24
10.	3.4643	84.20	97.22	99.26

Figure No. 6.12: Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K-4 as Binder

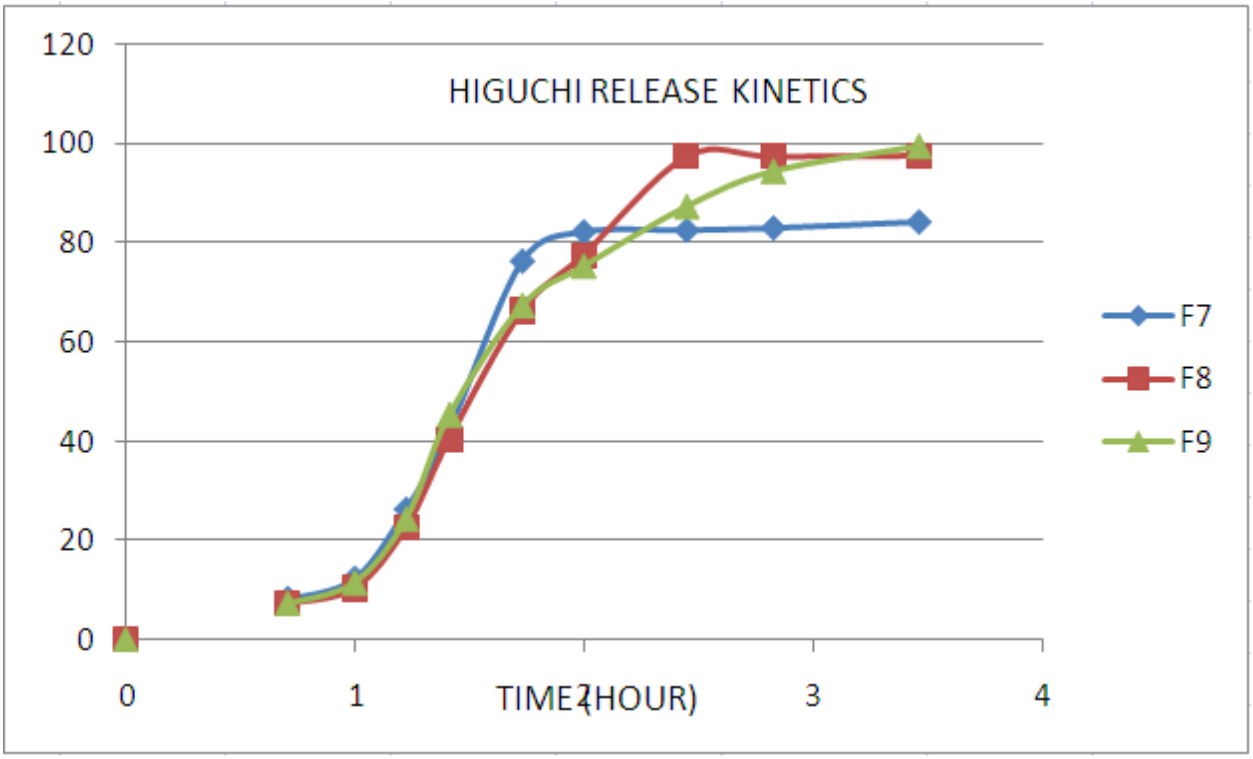


Table No. 6.23: Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

S.No.	Root Time	% Cum. drug remain to be release		
		F4	F5	F6
1.	0	0	0	0
2.	0.70711	8.23	7.22	7.45
3.	1	10.45	10.45	11.21
4.	1.27673	23.76	31.22	38.23
5.	1.41422	44.22	48.23	46.32
6.	1.73205	65.71	50.56	67.01
7.	2	82.34	55	88.13
8.	2.44948	83	56	99.12
9.	2.82843	83.22	57.24	99.99
10.	3.4642	83.5	57.85	99.87

Figure No. 6.13: Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

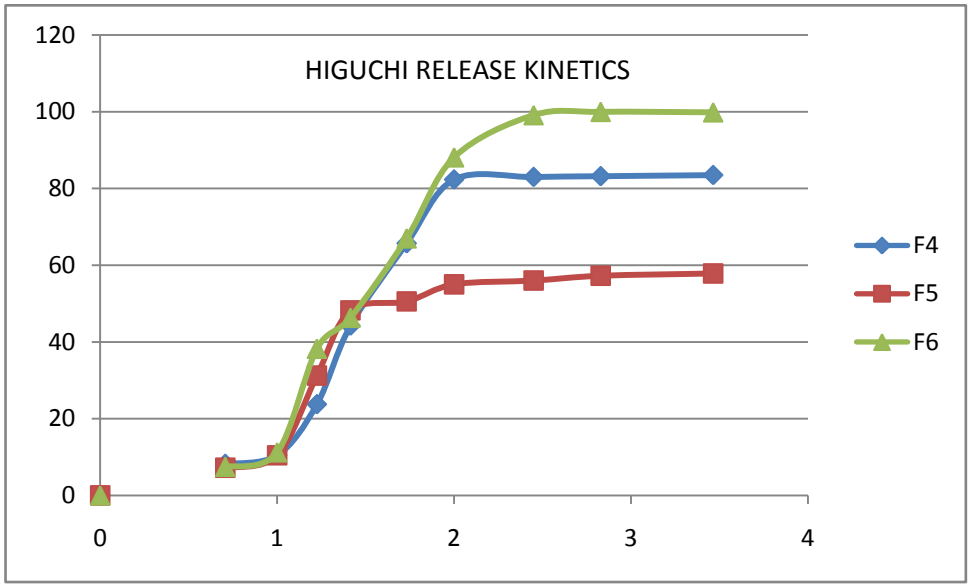


Table No 6.24 : Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K4 + K-100 as Binder

S.No..	Root Time	% Cum. drug remain to be release		
		F7	F8	F9
1.	0	0	0	0
2.	0.70712	8.32	7.26	7.28
3.	1	12.23	11.87	12.56
4.	1.27673	32.13	26.26	18.58
5.	1.41421	47.13	38.21	40.28
6.	1.73204	71.12	68.24	56.97
7.	2	91.23	89.12	73.98
8.	2.44948	92	99.25	84.17
9.	2.82843	93	99.56	89.26
10.	3.4641	94.56	99.76	94.56

Figure No. 6.14 Higuchi release kinetics data Nifedipine Matrix tablet with HPMC K4 + K-100 as Binder

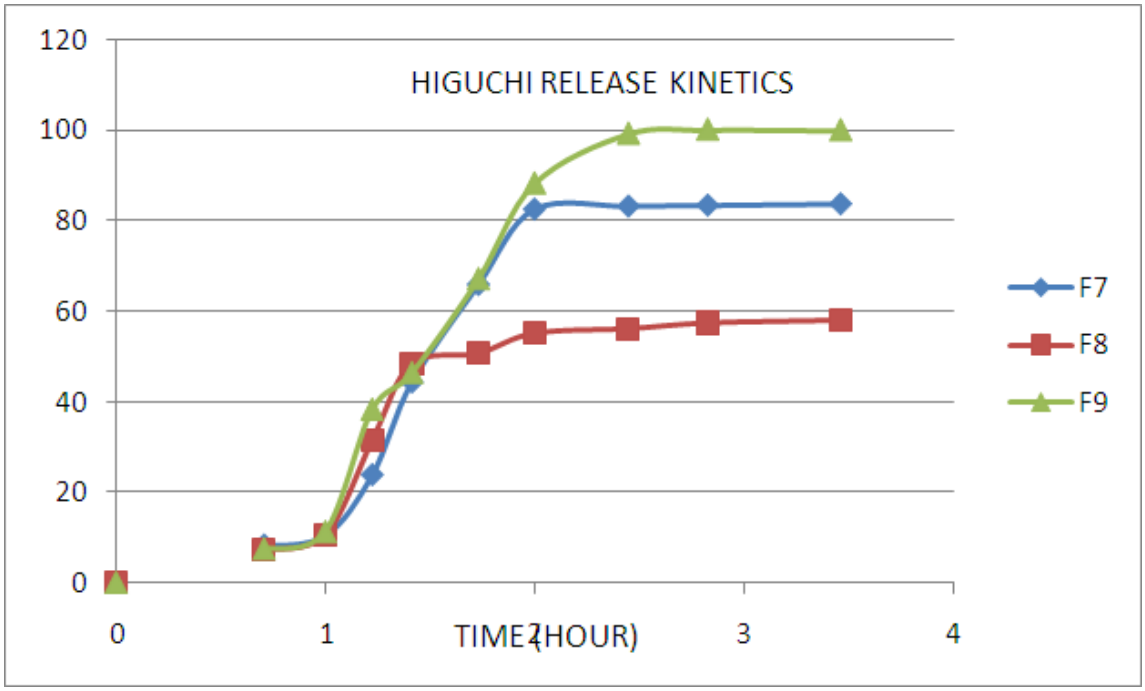


Table No. 6.25: Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K4 as Binder

S.No.	log Time	Log cum % drug release		
		F1	F2	F3
1.	0	0	0	0
2.	-0.30103	0.9154	0.8537	0.85974
3.	0	1.09060	1.00988	1.05881
4.	0.176091	1.4187	1.35063	1.38433
5.	0.30103	1.62786	1.60551	1.65543
6.	0.477121	1.88275	1.82027	1.82743
7.	0.60206	1.91502	1.88834	1.8757
8.	0.778151	1.91671	1.98735	1.94016
9.	0.90309	1.91909	1.98722	1.97417
10.	1.079181	1.92537	1.9879	1.99677

Figure No. 6.15: Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K4 as Binder

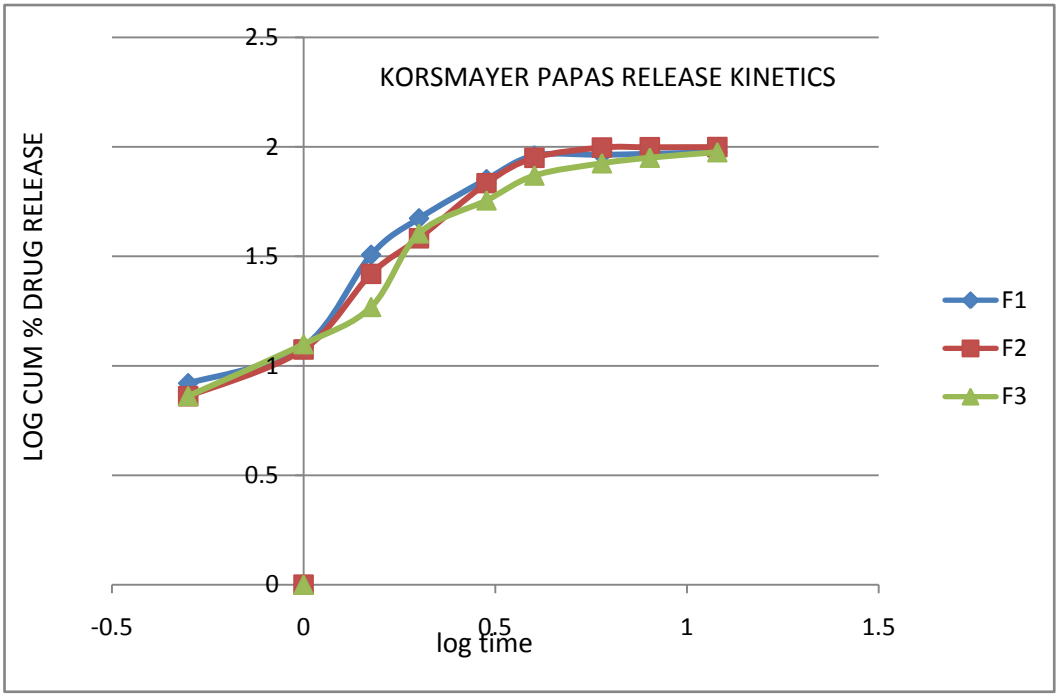


Table No. 6.26 : Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

S.No.	log Time	Log cum % drug release		
		F4	F5	F6
1.	0	0	0	0
2.	-0.30103	0.9154	0.85913	0.87215
3.	0	1.01912	1.01911	1.05038
4.	0.176090	1.37584	1.49456	1.5823
5.	0.30103	1.64572	1.68331	1.66576
6.	0.477121	1.81762	1.70381	1.8262
7.	0.60206	1.91561	1.74036	1.94512
8.	0.778151	1.91907	1.74819	1.99621
9.	0.90309	1.92018	1.75778	1.99996
10.	1.079181	1.92167	1.7623	1.99944

Figure No. 6.16: Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K-100 as Binder

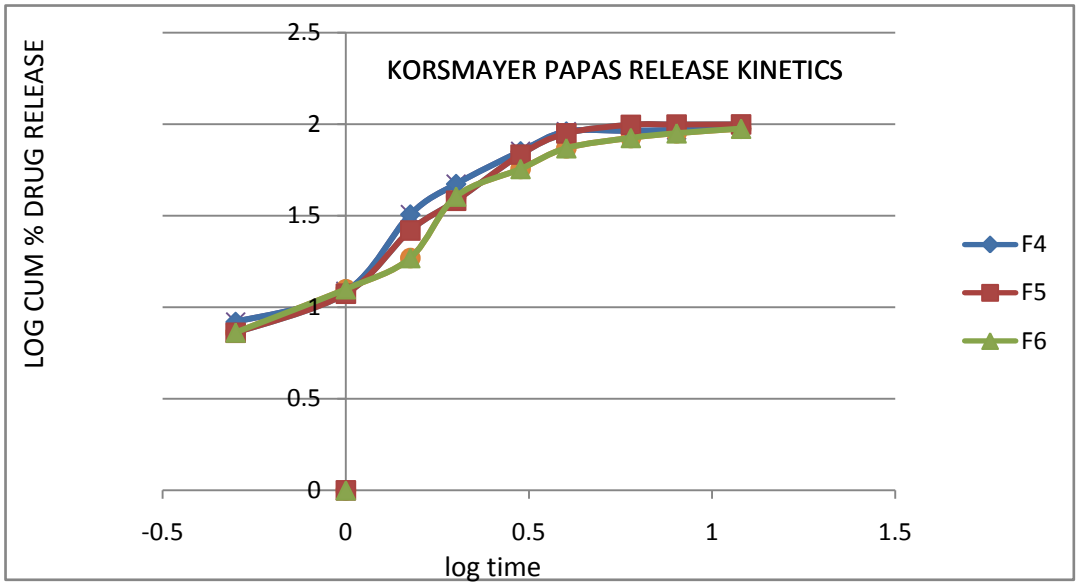


Table No. 6.27: Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K-4 + K-100 as Binder

S.No.	log Time	Log cum % drug release		
		F7	F8	F9
1.	0	0	0	0
2.	-0.30101	0.92002	0.86092	0.86211
3.	0	1.08742	1.07445	1.0988
4.	0.176091	1.50692	1.41963	1.26905
5.	0.30103	1.67339	1.58218	1.60509
6.	0.477121	1.85205	1.83405	1.75572
7.	0.60206	1.96013	1.94998	1.86911
8.	0.778151	1.96379	1.99673	1.92511
9.	0.90309	1.96848	1.99808	1.95066
10.	1.079181	1.97571	1.99895	1.97572

Figure No. 6.17: Korsmayer Papas release kinetics data Nifedipine Matrix tablet with HPMC K4 + K-100 as Binder

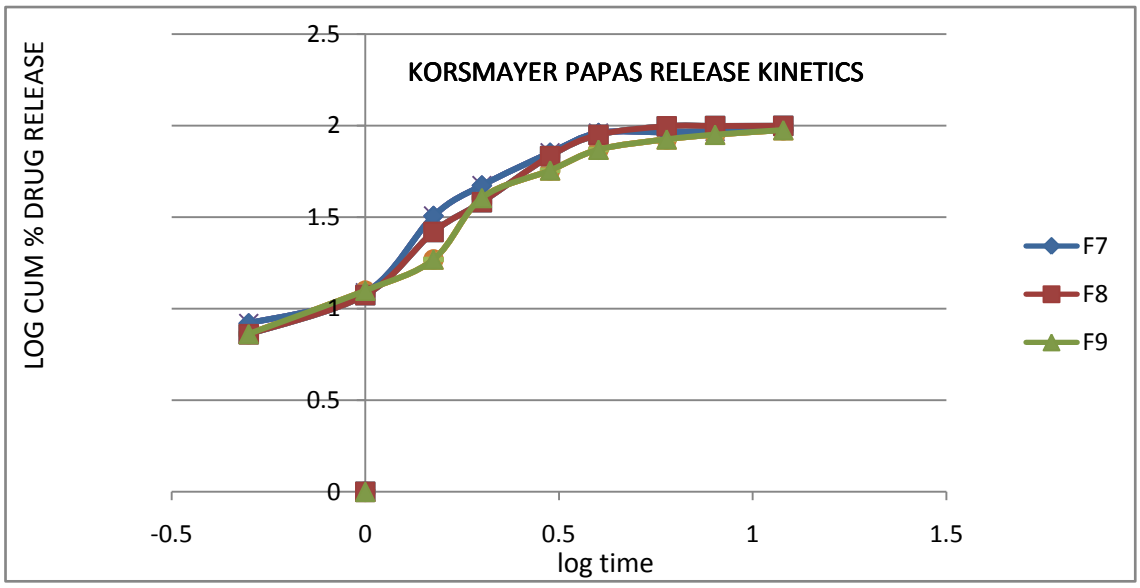


Table No. 6.28: Kinetic data of Nifedipine Matrix Tablet in comparison with All Formulation

FORMULATION		ZERO ORDER	FIRST ORDER	HIGUCHI	KORSMAYER PAPAS	BEST FITTED MODEL
F1	r^2	0.441	0.631	0.810	0.849	Korsmayer Papas
F2	r^2	0.668	0.858	0.868	0.898	Korsmayer Papas
F3	r^2	0.675	0.981	0.896	0.896	First Order
F4	r^2	0.496	0.678	0.828	0.852	Korsmayer Papas
F5	r^2	0.154	0.333	0.762	0.755	Higuchi
F6	r^2	0.581	0.797	0.873	0.861	Higuchi
F7	r^2	0.512	0.793	0.847	0.859	Korsmayer Papas
F8	r^2	0.632	0.909	0.857	0.899	First Order
F9	r^2	0.708	0.969	0.894	0.916	First Order

In the present study nine formulations with variable concentration of polymers (HPMC-K100, HPMC-K4) were prepared by direct compression method and evaluated for physicochemical properties, buoyancy lag time, total floating time, and in-vitro drug release. The results indicated that optimized formulation F 6 on immersion in 0.1N HCl solution at pH 1.2 & 6.8 pH phosphate Buffer at 37±0.5^{0}C tablets immediately and remain buoyant up to 12 hrs without disintegration. These two factors are essential for the tablet to acquire bulk density < 1, so that it remains buoyant on the gastric fluid.

The In vitro drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of Higuchi was maximum i.e 0.978 hence indicating drug release from formulations was found to follow Higuchi kinetics.

SUMMARY

We are thinking of developing matrix drug delivery system of drugs only due to recent advance in technology. In present study matrix tablet of Nifedipine was prepared and evaluated. This tablet contains layer of API which called matrix layer. This tablet may helpful for reducing multi dosing therapy in depressed patients experience difficulty in taking multi dose of drug.

- Suitable analytical method based on UV visible spectrophotometer was developed for Nifedipine. λ max of 276 nm was identifying HCL solution.
- From the FT-IR spectra the interference was verified and found that Nifedipine did not interfere with the polymers and excipients used.
- Direct compression method was established to manufacture matrix tablet of Nifedipine.
- First of all pre and post compression parameter of powder blend of all formulations like bulk density, tap density, Carr,s index , Hausner,s ratio, angle repose.
- Evaluation parameter like weight variation ,hardness, thickness, friability, drug content indicate that value were within permissible limit for All formulations

- In vitro drug release study of all the formulation was carried out and based on the result F6 batch for instant release and matrix release tablet of Nifedipine was identified as the best formulation among all the other formulations.

CONCLUSION

- In vitro data obtained for matrix tablet of Nifedipine showed prolonged drug release. Tablets of different release kinetics could be obtained by varying the formulation variables. Thus, Nifedipine is most suitable drug candidate for the Antihypertension. Based on the above considerations, formulation F6 was selected as optimized formula, a perusal of table indicated that the parameters of Matrix Tablet were satisfactory for the intended use.

REFERENCES

1. LECKMAN L, LIBERMAN HA, KANIG JL., THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY, 3RD ED., VARGHESE PUBLISHING HOUSE, BOMBAY ,1987:430-453
2. ROBINSON JR, LEE HL, CONTROLLED DRUG DELIVERY : FUNDAMENTALS AND APPLICATION, 2RD EDITION, MARCEL DEKKAR INC., NEW YORK , 1987:4-36
3. NOTARI. R., BIOPHARMACEUTICS AND CLINICAL PHARMACOKINETICS, AN INTRODUCTION, 3RD, MARCELDEKKER INC. NEW YORK , 1980:152-154.
4. BROWN MJ, PALMER CR, CASTAIGNE A, ET AL. (2000). "MORBIDITY AND MORTALITY IN PATIENTS RANDOMISED TO DOUBLE-BLIND TREATMENT WITH A LONG-ACTING CALCIUM-CHANNEL BLOCKER OR DIURETIC IN THE INTERNATIONAL NIFEDIPINE GITS INTRSTUDY: INTERVENTION AS A GOAL IN HYPERTENSION TREATMENT (INSIGHT)". LANCET 356 (9227): 366–72. DOI:10.1016/S0140-6736(00)02527-7. PMID 10972368.
5. POOLE-WILSON PA, KIRWAN BA, VOKÓ Z, DE BROUWER S, VAN DALEN FJ, LUBSEN J (2006). "SAFETY OF NIFEDIPINE GITS IN STABLE ANGINA: THE ACTION TRIAL". CARDIOVAS DRUGS THER 20 (1): 45–54. DOI:10.1007/S10557-006-6312-4. PMID 16552473.
6. ODOU P, FERRARI N, BARTHÉLÉMY C, ET AL. (2005). "GRAPEFRUIT JUICE-NIFEDIPINE INTERACTION: POSSIBLE INVOLVEMENT OF SEVERAL MECHANISMS". JOURNAL CLINICAL PHARM THER 30 (2): 153–8. DOI:10.1111/J.1365-2710.2004.00618.X. PMID 15811168.

7. HYPERTENSION: MANAGEMENT OF HYPERTENSION IN ADULTS IN PRIMARY CARE. CLINICAL GUIDELINE CG34. NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (NICE), JUNE 2006. FULLTEXT INDEX. ISBN 1-86016-285-1.
8. GROSSMAN E, MESSERLI FH, GRODZICKI T, KOWEY P (1996). "SHOULD A MORATORIUM BE PLACED ON SUBLINGUAL NIFEDIPINE CAPSULES GIVEN FOR HYPERTENSIVE EMERGENCIES AND PSEUDOEMERGENCIES?". JAMA 276 (16): 1328–31. DOI:10.1001/JAMA.276.16.1328. PMID 8861992.
9. VARON J, MARIK PE (2003). "CLINICAL REVIEW: THE MANAGEMENT OF HYPERTENSIVE CRISES". CRITICAL CARE (LONDON, ENGLAND) 7 (5): 374–84. DOI:10.1186/CC2351. PMC 270718. PMID 12974970.
10. CAMPAGNOLO, DI. "AUTONOMIC DYSREFLEXIA IN SPINAL CORD INJURY". EMEDICINE. RETRIEVED 2011-07-14.
11. KING JF, FLENADY VJ, PAPATSONIS DN, DEKKER GA, CARBONNE B (2003). "CALCIUM CHANNEL BLOCKERS FOR INHIBITING PRETERM LABOUR". IN FLENADY, VICKI. COCHRANE DATABASE OF SYSTEMATIC
12. Y. RAJAJAYARAO, P. DIVYA, K. DIVYASREE, S. MANOHAR BABU FORMULATION AND EVALUATION OF MATRIX TYPE SUSTAINED RELEASE NIFEDIPINE TABLETS INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY 2013, 4(1), 34-45
13. DEWAN T AKHTER, RIAZ UDDIN, NAZ H HUDA, KUMAR B SUTRADHAR DESIGN AND FORMULATION OF TWICE DAILY NIFEDIPINE SUSTAINED RELEASE TABLET USING METHOCEL K15M CR AND METHOCEL K100LV CR INTERNATIONAL JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES 2012 VOL 4, ISSUE 1,
14. PRABAKARAN L, VISHALINI M HYDROPHILIC POLYMERS MATRIX SYSTEMS OF NIFEDIPINE SUSTAINED RELEASE MATRIX TABLETS: FORMULATION OPTIMIZATION BY RESPONSE SURFACE METHOD PELAGIA RESEARCH LIBRARY 2010, 1 (1): 147-165
15. PASUPATHI A, PALANISAMY P, B JAYKAR, R MARGRET CHANDIRA, B.S. VENKATESWARLU FORMULATION, OPTIMIZATION AND *IN-VITRO* EVALUATION OF NIFEDIPINE SUSTAINED RELEASE TABLET INDIAN JOURNAL OF RESEARCH IN PHARMACY AND

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16. BERTIL ABRAHAMSSONA, MAGNE ALPSTEN, BJORN BAKEC, ULF E. JONSSON, MARIA ERIKSSON-LEPKOWSKA, ANNHILD LARSSON DRUG ABSORPTION FROM NIFEDIPINE HYDROPHILIC MATRIX EXTENDEDRELEASE (ER) TABLET-COMPARISON WITH AN OSMOTIC PUMP TABLET AND EFFECT OF FOOD JOURNAL OF CONTROLLED RELEASE 1998 52 PAGE NO. 301–310
17. KIBBE AH., HANDBOOK OF PHARMACEUTICAL EXCIPIENTS; AMERICAN PHARMACEUTICAL ASSOCIATION AND PHARMACEUTICAL PRESS, WASHINGTON LONDON; 2000; 3RD ED; 102-106.
18. CHOWHAN ZT. ROLE OF BINDERS IN MOISTURE-INDUCED HARDNESS INCREASE IN COMPRESSED TABLETS AND ITS EFFECT ON IN VITRO DISINTEGRATION AND DISSOLUTION. J PHARM SCI 1980; 69: 1–4.
19. ROWE RC. THE ADHESION OF FILM COATINGS TO TABLET SURFACES – THE EFFECT OF SOME DIRECT COMPRESSION EXCIPIENTS AND LUBRICANTS. J PHARM PHARMACOL 1977; 29: 723–726.
20. BANKER G, PECK G, JAN S, PIRAKITIKULR P. EVALUATION OF HYDROXYPROPYL CELLULOSE AND HYDROXYPROPYL METHYL CELLULOSE AS AQUEOUS BASED FILM COATINGS. DRUG DEV IND PHARM 1981; 7: 693–716.
21. OKHAMAFE AO, YORK P. MOISTURE PERMEATION MECHANISM OF SOME AQUEOUS-BASED FILM COATS. J PHARM PHARMACOL 1982; 34 (SUPPL.): 53P.
22. ALDERMAN DA, SCHULZ GJ. METHOD OF MAKING A GRANULAR, COLD WATER DISPERSIBLE COATING COMPOSITION FOR TABLETS. UNITED STATES PATENT NO. 4,816,298; 1989.
23. PATELL MK. TASTE MASKING PHARMACEUTICAL AGENTS. UNITED STATES PATENT NO. 4,916,161; 1990.
24. HARDY JG, KENNERLEY JW, TAYLOR MJ, ET AL. RELEASE RATES FROM SUSTAINED-RELEASE BUCCAL TABLETS IN MAN. J PHARM PHARMACOL 1982; 34 (SUPPL.): 91P.
25. HOGAN JE. HYDROXYPROPYLMETHYLCELLULOSE SUSTAINED RELEASE TECHNOLOGY.

DRUG DEV IND PHARM 1989; 15: 975–999.

26. SHAH AC, BRITTEN NJ, OLANOFF LS, BADALAMENTI JN. GEL-MATRIX SYSTEMS EXHIBITING BIMODAL CONTROLLED RELEASE FOR ORAL DELIVERY. J CONTROL RELEASE 1989; 9: 169–175.
27. WILSON HC, CUFF GW. SUSTAINED RELEASE OF ISOMAZOLE FROM MATRIX TABLETS ADMINISTERED TO DOGS. J PHARM SCI 1989; 78: 582–584.
28. DAHL TC, CALDERWOOD T, BORMETH A, ET AL. INFLUENCE OF PHYSICOCHEMICAL PROPERTIES OF HYDROXYPROPYL METHYLCELLULOSE ON NAPROXEN RELEASE FROM SUSTAINED RELEASE MATRIX TABLETS. J CONTROL RELEASE 1990; 14: 1–10.
29. VILA JL, REMUNAN C, BRETAL MJ,NUNEZ A. ACCELERATED STABILITY STUDY OF SUSTAINED RELEASE NIFEDIPINE TABLET PREPARE WITH GELUCIRE. INTERNATIONAL JOURNAL OF PHARMACEUTICS VOLUME 80, ISSUES 1–3 PAGES 151-159.
30. HASIGAVA A,NAKAGAWA H,SUGIMOTO I. APPLICATION OF SOLID DISPERSIONS OF NIFEDIPINE WITH ENTERIC COATING AGENT TO PREPARE A SUSTAIN-RELEASEDOSAGE FORM. CHEMICAL AND CHEMICAL AND PHARMACEUTICAL BULLETIN VOL. 33 (1985) NO. 4 P 1615-1619.