# FORMULATION & EVALUATION DELAYED RELEASE DRUG DELIVERY SYSTEM OF NIFEDIPINE USING VARIOUS POLYMERS

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## ABSTRACT

*In the present study an attempt was made to formulate and evaluate Nifedipine delayed release tablet using direct compression technique incorporating Natural and synthetic polymers like Tragacanth and HPMC K 100.Powder blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like thickness, uniformity of weight, hardness, friability, and drug content. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 12 hours using type II dissolution apparatus. Among all the formulation, N5 shows 99.38% of drug release at the end of 12 hours. This finding reveals that above a particular concentration of HPMC K 100 are capable of providing delayed drug release.*

***Keywords:*** *Nifedipine, Tragacanth and HPMC K 100, direct compression method and delayed release Tablets.*

## INTRODUCTION

Historically, oral drug administration has been the predominant route for drug delivery. It is known to be the most popular route of drug administration due to the fact the gastrointestinal physiology offers more flexibility in dosage form design than most other routes. A major challenge for the pharmaceutical industry in drug development is to produce safe and efficient drugs, therefore properties of drugs and the way in which they are delivered must be optimized.

A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time. The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterized and reproducible dosage forms. Oral route still remains the most popular for drug administration by virtue of its convenience to the patient. A sizable portion of orally administered dosage forms, so called conventional, are designed to achieve maximal drug bioavailability by maximizing the rate and extent of absorption. While such dosage forms have been useful, frequent daily administration is necessary, particularly when the drug has a short biological half life. This may result in wide fluctuation in peak and trough steady-state drug levels, which is undesirable for drugs with marginal therapeutic indices. Moreover, patient compliance is likely to be poor when patients need to take their medication three to four times daily on chronic basis. Fortunately, these short comings have been circumvented with the introduction of controlled release dosage forms. These dosage forms are capable of controlling the rate of drug delivery, leading to more sustained drug levels and hence therapeutic action. Hydrophilic matrix

systems are among the most commonly used means for oral controlled drug delivery as they can reproduce a desirable drug profile and are cost effective. The primary mechanism of drug release from hydrophilic matrices occurs when the polymer swells on contact with the aqueous medium to form a gel layer on the surface of the system. The drug then releases by dissolution, diffusion and/or erosion.

**Materials**

Nifidipine, Micro crystralline cellulose, Tragacanth, HPMC K 100, PVP K30, MCC Magnesium stearate, Talc

**Methods:**

**Preformulation parameters**

**Angle of repose:** The angle of repose was calculated using the following formula: Tan θ = h / r Where, Tan θ = Angle of repose, h = Height of the cone , r = Radius of the cone base

**Bulk density: It** is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density was calculated using the formula: Bulk Density = M / Vo Where, M = weight of sample Vo = apparent volume of powder

**Tapped density:** The tapped density was calculated, in gm per L, using the formula: Tap = M / V Where, Tap= Tapped Density

**The Compressibility Index (Carr's Index**): It is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. Carr's Index = [(tap - b) / tap] × 100 Where, b = Bulk Density Tap = Tapped Density

**Drug – Excipient compatibility studies:** Fourier Transform Infrared (FTIR) spectroscopy: The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of ZnSe. The spectra were recorded over the wave number of 4000 cm-1 to 400cm-

**Determination of Wavelength:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

**Determination of Calibration Curve:**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared and those concentrations absorbance were found out at required wavelength.

**Analytical Method** Graphs of Nifedipine were taken in 0.1N HCl and in pH 6.8 phosphate buffer at 245 nm and 250 4respectively.

**Formulation development of Tablets:** All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Nifedipine. Total weight of the tablet was considered as 250mg.Nifedipine and all other ingredients were individually passed through sieve no. All the ingredients were mixed thoroughly by triturating up to 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

**Evaluation of post compression parameters for prepared Tablets:**

**Weight variation test:** 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. The mean and deviation were determined. The percent deviation was calculated using the following formula. % Deviation = (Individual weight – Average weight / Average weight) × 100

**Hardness:** Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. 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. Tablet thickness is an important characteristic in reproducing appearance.

**Friability:** 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 lx 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 Phosphate buffer RPM -- 50 Sampling intervals (hrs) -- 0.5,1,2,3,4,5,6,7,8,10,11,12 Temperature -- 37°c + 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 were removed and pH 6.8 phosphate buffer was added process was continued up to 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 required wavelength 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 are fitted to the following equation. F = Ko t Where, 'F' is the drug release at time't', and 'Ko' 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. Mt/ M∞ = K tn Where, Mt/ 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 (Mt/ M∞) versus log (time) is linear.

**Hixson-Crowell release model:** (100-Qt) 1/3 = 1001/3 – KHC.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).

**Table - Results Of Preformulation Parameters**

| Formulation Code | Angle of Repose | Bulk density (gm/ml) | Tapped density (gm/ml) | Carr's index (%) | Hausner's Ratio |
|---|---|---|---|---|---|
| N1 | 25.83±0.0094 | 0.57 ± 0.99 | 0.68 ± 0.54 | 15.1 | 1.25 ± 0.12 |
| N2 | 24.64±0.0087 | 0.51 ± 0.89 | 0.62 ± 0.68 | 14.6 | 1.24 ± 0.32 |

| | | | | | |
|---|---|---|---|---|---|
| N3 | 22.32±0.0039 | 0.52 ± 0.72 | 0.66 ± 0.74 | 13.3 | 1.21 ± 0.42 |
| N4 | 22.61±0.0041 | 0.56 ± 0.53 | 0.61 ± 0.87 | 12.3 | 1.22 ± 0.56 |
| N5 | 20.76±0.0058 | 0.52 ± 0.64 | 0.62 ± 0.91 | 14.7 | 1.21 ± 0.57 |
| N6 | 20.89±0.0049 | 0.51 ± 0.97 | 0.67 ± 0.21 | 14.6 | 1.24 ± 0.48 |
| N7 | 20.72±0.0056 | 0.53 ± 0.78 | 0.64 ± 0.32 | 13.4 | 1.23 ± 0.43 |
| N8 | 20.82±0.0041 | 0.50 ± 0.84 | 0.64 ± 0.45 | 12.3 | 1.22 ± 0.59 |

**_In-vitro_ quality control parameters for tablets**

| Formulation codes | Weight variation(mg) | Hardness ($kg/cm^2$) | Friability (%loss) | Thickness (mm) | Drug content (%) |
|---|---|---|---|---|---|
| N1 | 248.47 | 5.9 | 0.63 | 3.69 | 96.52 |
| N2 | 249.53 | 5.7 | 0.52 | 3.12 | 99.34 |
| N3 | 249.72 | 5.3 | 0.74 | 3.79 | 97.82 |
| N4 | 248.60 | 6.0 | 0.82 | 3.35 | 99.15 |
| N5 | 247.29 | 5.4 | 0.60 | 3.92 | 98.51 |
| N6 | 249.53 | 6.2 | 0.71 | 3.78 | 99.40 |
| N7 | 250.10 | 5.5 | 0.86 | 3.23 | 97.61 |
| N8 | 250.01 | 5.9 | 0.56 | 3.41 | 98.76 |

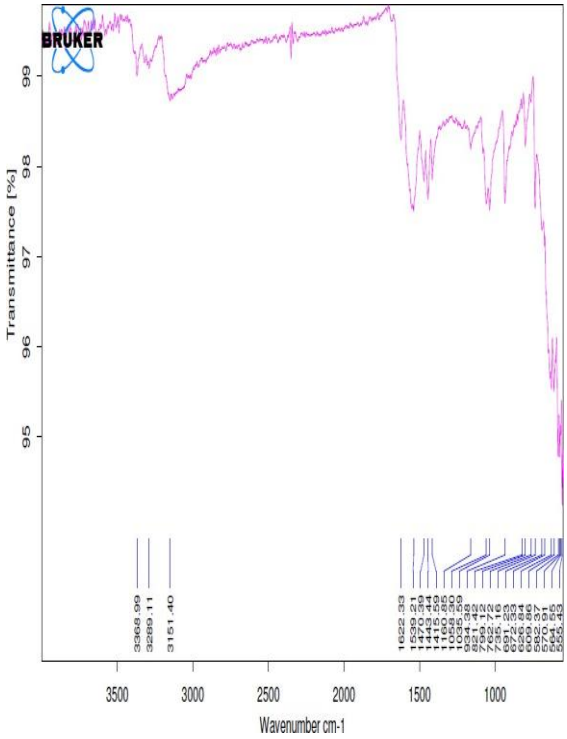


**Fig 1 - Drug –Excipient compatibility**

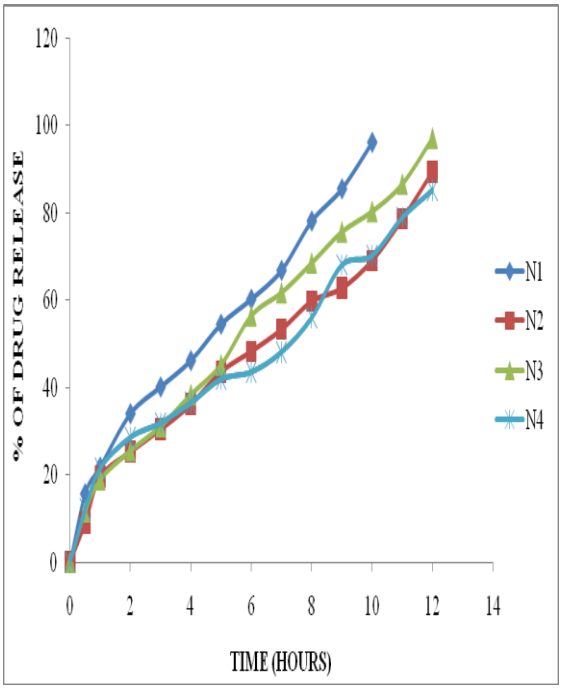


**Fig 2 - Dissolution profile of Nifedipine (N1, N2, N3 and N4 formulations)**

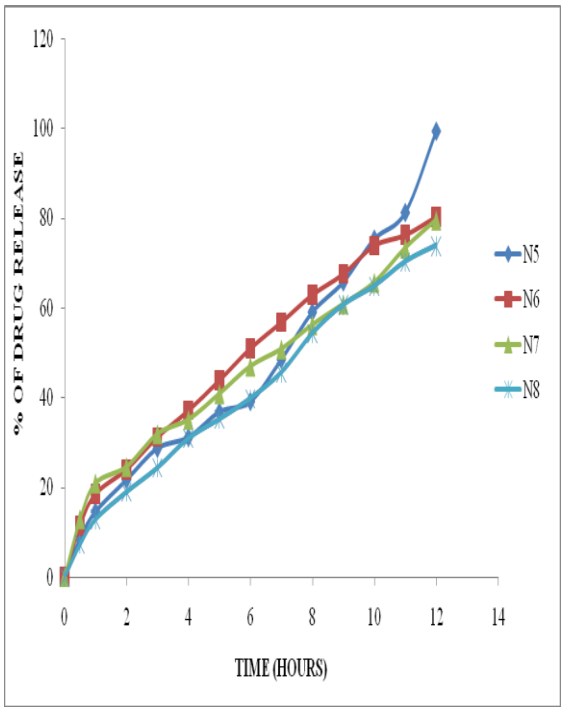


**Fig 3 - Dissolution profile of Nifedipine (N5, N6, N7 and N8 formulations)**

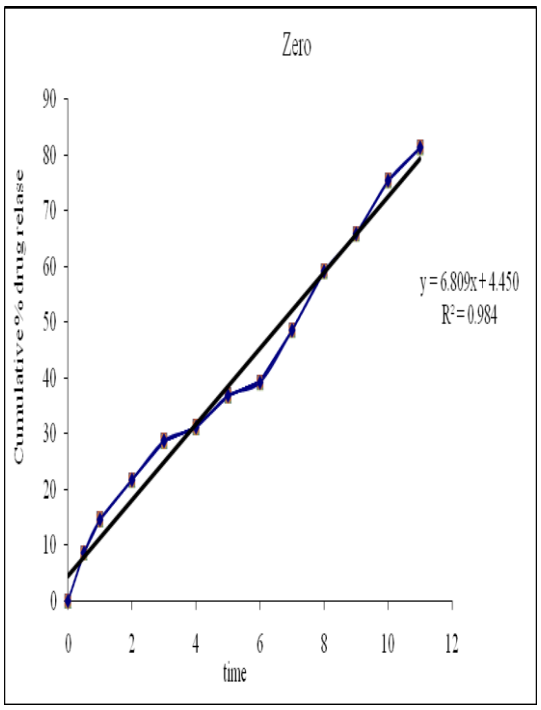


**Fig 4 - Zero order release kinetics graph**

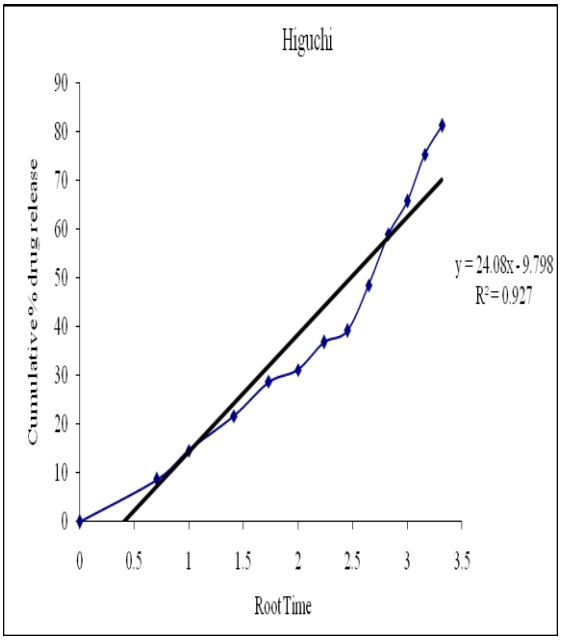


**Fig 5 - Higuchi release kinetics graph**

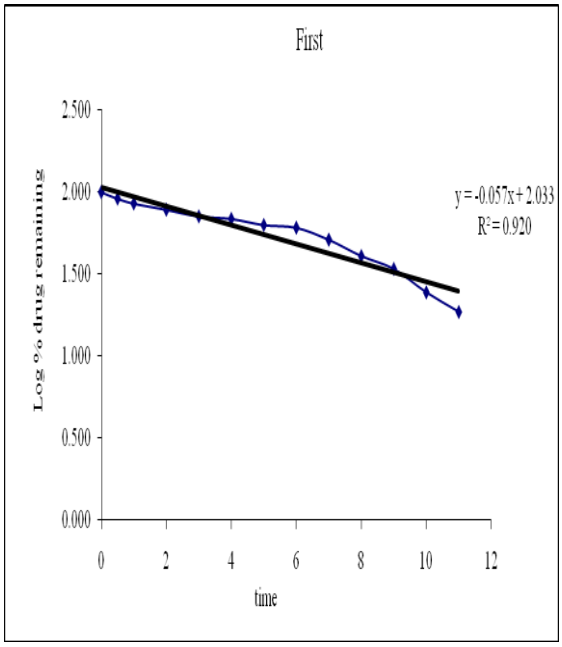


**Fig 7 - First order release kinetics graph**

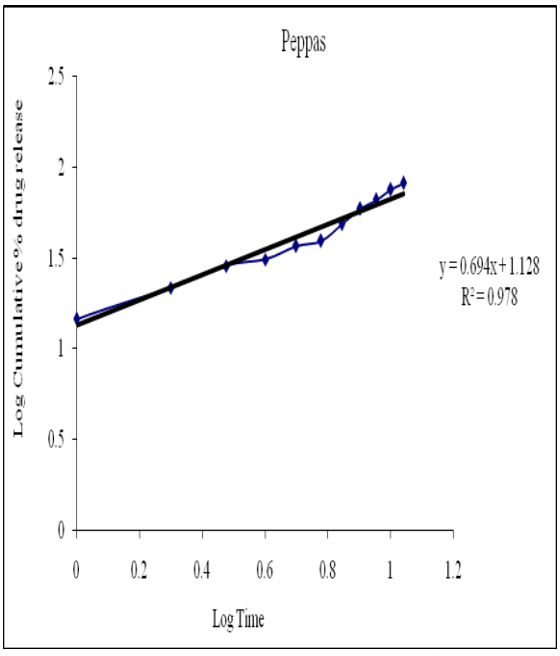


**Fig 6 - Kars mayer peppas graph**

## CONCLUSION

In present work attempt was made to formulate and evaluate delayed release tablets of Nifedipine. Attempts were made to achieve delayed drug release from the dosage form. Prepared eight formulations of Nifedipine by direct compression method. FTIR studies revealed that there was no incompatibility between drug and excipients. Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose, bulk density, tapped density, compressibility index and hausner ratio powder has good flow properties. Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined within IP limits. Among all the formulations N5 with 25mg polymer content (HPMC K 100) showed the drug release of 99.38 % in 12 h and was selected as the ideal formulation. Finally concluded release kinetics to optimised

formulation (N5) has followed Zero order release kinetics. The method of direct compression utilizes minimum machinery and man power. From the economical point of view, it may be beneficial for the local pharmaceutical firms to adopt such simple technologies for the preparation of delayed release product**.**

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