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Research Article

FORMULATION, OPTIMIZATION AND IN-VITRO CHARCTERIZATION OF THE SUSTAINED RELEASE MATRIX TABLETS OF NICORANDIL

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Abstract

Conventional drug delivery system for treating the anginal are not much effective as the drug do not reach the site of action in appropriate concentration. Thus an effective and safe therapy of this anginal disorder using specific drug delivery system is a challenging task to the pharmaceutical technologists. Most commonly used method of modulating the drug release is to include it in a matrix system. Because of their flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost-effectiveness, and broad regulatory acceptance. Formulation of Nicorandil matrix tablet was prepared by the polymers blend with to get desirable release profile. Formulated tablets were also characterized by parameters like thickness, weight variation test, drug content uniformity, hardness, friability, swelling index, stability studies and the in-vitro release rate profile was compared with the marketed product's release profile with the help of similarity factor (f2) value.Formulations NIC 4(HPMC and POLYOX,5:1) has shown better drug release over 24 hours of time and it released 98.48% of drug out of 6 formulations. The drug release mainly by diffusion controlled mechanism and coupled with erosion.

Keywords: drug delivery system, anginal disorder, Nicorandil matrix, swelling index, stability studies.

Introduction

Introduction to Drug Delivery[1,2]

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration as well as the traditional belief that by oral administration the drug is as well absorbed as the food stuffs that are ingested daily. In fact, the development of a pharmaceutical product for oral delivery, irrespective of its physical form involves varying extents of optimization of dosage form characteristics within the inherent constraints of GI physiology. Therefore a fundamental understanding of various disciplines, including GI physiology, pharmacokinetics, pharmacodynamic and formulation design are essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form. The more sophisticated a delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

A.Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.

B. The anatomic and physiologic characteristics of the GIT,

C. Physicochemical characteristics and the drug delivery mode of the dosage form to be designed

1.Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for sustained-release systems, the oral route of administration has by far received the most attention with respect to research on physiological and drug constraints as well as design and testing of products. This is because there is more flexibility in dosage form design for the oral route than there is for the parenteral route 2. Over the past 30 years, as the expense and complications involved in marketing new drugs entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems. There are several reasons for the attractiveness of these dosage forms. The goal in designing sustained or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery 3. The enormous problem of patient compliance as well as the therapeutic desirability of controlled tissue drug levels over the time course of therapy is sufficiently compelling reasons to warrant placement of drugs in a sustained form of drug delivery 4. In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner 4. Sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot, and repository dosage forms are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose .

Various Terminologies for controlled drug delivery[4,7,9]

The conventional dosage forms are immediate release type. Non-immediate release delivery systems may be divided conveniently into three categories:

Delayed Release
Sustained Release

a. Controlled Release
b. Prolonged Release

Site-specific and Receptor release

a. Organ targeting
b. Cellular targeting
c. Sub cellular targeting

1. Delayed Release Delayed release systems are those systems that use repetitive, intermittent dosing of a drug from one or more immediate release units incorporated into a single dosage form. Examples of delayed release system include repeat action tablets and capsules. A delayed release dosage form does not produce or maintain uniform drug blood levels within the therapeutic range.

2. **Sustained Release System**

It includes any drug delivery system that achieves slow release of drug over an extended period of time.

Controlled Release System

If the system is successful at maintaining constant drug level in the blood or target tissues, it is considered as a controlled release system.

Prolonged Release System

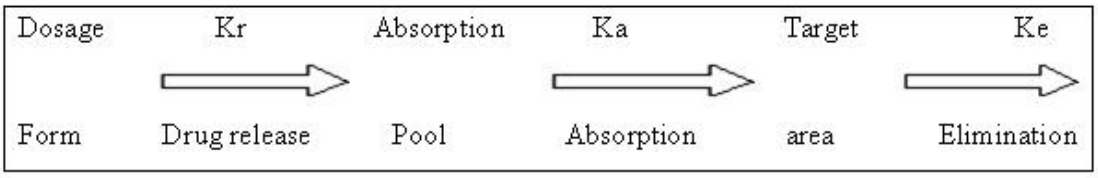
If without maintaining constant level, the duration of action is extended over that achieved by conventional delivery; it is considered as a prolonged release system.

3. Site-Specific and Receptor Release

It refers to targeting of a drug directly to a certain biological location. In the case of site-specific release, the target is a certain organ or tissue, while for receptor release; the target is the particular receptor for a drug within an organ or tissue. Both of these systems satisfy the spatial aspects of drug delivery.

Principle of Sustained Release Drug Delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.



The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka.

Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non immediate release delivery system must be directed primarily at altering the release rate. The main objective in designing a sustained release delivery system is to deliver drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be analogous to that achieved by continuous intravenous infusion where a drug is provided to the patient at a constant rate. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time. It means that the drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:

Kr° = Rate In = Rate Out = Ke Cd Vd

Where, Kr°: Zero-order rate constant for drug release-Amount/time

Ke: First-order rate constant for overall drug elimination-time-1

Cd: Desired drug level in the body – Amount/volume, and

Vd: Volume space in which the drug is distributed-Liters

Classification of Sustained/Controlled Release Systems

Table 1: Various Types of Sustained Release System

Type of system	Rate-control mechanism
Diffusion controlled Reservoir system Monolithic system	Diffusion through membrane
Water penetration controlled Osmotic system Swelling system	Transport of water through semi permeable membrane Water penetration into glossy polymer
Chemical controlled Monolithic system Pendant system Ion exchange resins	Surface erosion or bulk erosion Hydrolysis of pendent group and diffusion from bulk polymer Exchange of acidic or basic drugs with the ions present on resins.
Regulated system Magnetic, Ultrasound	External application of magnetic field or ultrasound to device

The value of Ke, Cd and Vd are obtained from appropriately designed single dose pharmacokinetic study. The equation can be used to calculate the zero order release rate constant. For many drugs, however, more complex elimination kinetics and other factors affecting their disposition are involved. This in turn affects the nature of the release kinetics necessary to maintain a constant drug blood level.

It is important to recognize that while zero-order release may be desirable theoretically, non zero-order release may be equivalent clinically to constant release in many cases. Sustained-release systems include any drug-delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is intermittent dosage regimen . Sustained release dosage forms are designed to of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells, it is considered a controlled-release system.

Sustained Release Preparations

These preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional

complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action .

Nicorandil may be considered as a safe additional drug to beta-blockers for angina relief in patients with stable angina pectoris. Weather, it may be an alternative to beta blockers in post myocardial infarction patients remains to be established. The action of Nicorandil was impressive in the level of risk reduction for cardiac death and all-cause mortality, especially in haemodialysis patients without evidence of significant coronary artery lesions.

Aim and objectives

The aim of the present study is to design and characterize the sustained release tablets of Nicorandil.

The main objectives of the work is,

- To develop a stable, pharmaceutically equivalent formulation.
- To compare the developed formulation with that of reference formulation.
- To study drug and polymer interactions.
- To reduce the dosing frequency of the drug by sustaining its release.
- To perform stability study of the optimized formulation according to ICH guidelines.

Materials and Methods

PREFORMULATION STUDIES:

Before formulation of drug substances into a dosage form, it is essential that drug & polymer should be chemically and physically characterized. Preformulation studies gives the information needed to define the nature of the drug substance and provide a framework for the drug combination with pharmaceutical excipients in the fabrication of a dosage form.

Compatibility studies by IR:

One of the requirements for the selection of suitable excipients or carriers for pharmaceutical formulation is its compatibility. Therefore in the present work a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction of Nicorandil drug with Polyethylene oxide WSR 301NF, HPMC K200M and other excipients used for the study.

Procedure:

Weighed amount of drug (1mg) was mixed with 99mg of potassium bromide (dried at 40-50ºC). The mixture was taken and compressed under 7-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned in IR spectrophotometer.

Drug Excipients Compatibility studies by forced degradation studies:

The Binary mixtures of drug and excipients (1:1) were prepared and packed in both closed vials and kept in both long term and accelerated environmental conditions (25ºC/60% RH and 40ºC/75% RH) for 1 month. At the end of 1 month period all samples were observed physically.

Construction of calibration curve

An accurately weighed 100 mg of Nicorandil was dissolved in 0.1N HCl & phosphate buffer of pH 6.8 separately and volume was made up to 100 ml in a volumetric flask (Stock Solution: I, 1000 µg/ml). From this 10 ml of solution were pipette out and volume was made up to 100 ml (Stock Solution: II, 100µg/ml). Then the aliquots were prepared, whose concentration ranging from 0 to 33 µg/ml and the absorbance was measured at 262 nm by using UV Spectrophotometer (Shimadzu, Model No: 2450) against the blank. (Wagner G, et al., 1992)

Preparation of Sustained release tablets:

Design of formula and composition:

The design of tablets involved various compromises on the part of the formulator, to produce desired product properties. It involves the correct selection and balance of excipients materials for active ingredients to achieve the desired response.

Based on primary information collected from market samples and previous experience with the manufacturing of various products, the following tentative product specifications were proposed before starting the formulation trials.

Type of Sustained Release system proposed:

Matrix with SR controlling tablets.

Justification for the design of the formula composition:

In addition to the active, Nicorandil 20mg SR tablets contained a number of inert materials as diluents, binders and lubricants, compression and release characteristics to the formulation. The justification for the inclusion of these functional additives is briefly described below:

Diluents:

They are inert materials added to increase the bulk in order to make the tablet with a desired particle size for compression.

MCC pH 102 was used in the present development as directly compressible materials and improves the flow properties of the blend.

Binders:

Materials used to impart cohesive quality to the powdered materials are referred to as binders. They impart cohesiveness to the tablet formulation which insures the tablet remaining intact after compression as well as improving the free flowing qualities by the formulation of granules of desired hardness and size. In the present study Povidone K90F was selected as binder.

Lubricants:

They prevent the adhesion of the tablet material to the surface of the dies and punches reduces inter-particle friction, facilitate the ejection of the tablet from the die cavity and improve the rate of flow of the tablet granulation.

In the present study, Sodium stearyl fumarate was used as lubricant. It is hydrophobic in nature. It was a proper choice as the tablet did not show any tendency to stick to the side of the die. The tablets were found to be satisfactory and the dissolution profiles of the drug substance were satisfactory with the use of Sodium stearyl fumarate.

Dispensing of materials:

All the solid raw materials are dispensed, packed in individual cleaned Poly ethylene bags and labeled.

Actual quantity of API will vary depending on actual potency and LOD

Preparation of Tablets:

Sifting:

Separately sift the Nicorandil drug through 100 mesh, Poly ethylene oxide WSR 301, HPMC K200M, Stearic acid, Povidone K90F, MCC pH 102, Hydrogenated Castor oil (It should be solid at room temperature), Colloidal anhydrous silica through 30 mesh and Sodium stearyl fumarate through 60 mesh.

Collect all the above sifted materials individually into a double lined polyethylene bag.

Pre Mixing:

Load the sifted Nicorandil and Colloidal anhydrous silica into octagonal blender and mix for 10 minutes.

Mixing:

To the premixed blend add MCC pH 102, Polyethylene oxide WSR 301 Stearic acid, Povidone K 90F, Hydrogenated Castor oil and mix for 15 minutes.

Pre-Lubrication and Lubrication:

To the above blend, add HPMC K200M and pre-lubricate for 10 minutes.

Lubricate the above blend with Sodium Stearyl Fumarate in the Octagonal Blender for 5 minutes.

Compression:

Compress the lubricated blend using punches mentioned in Tables and the tablet parameters are given in Tables.

Table No 8 : Punches Specification

Punch dimension	8.00 mm
Punch shape	Circular, Standard concave punches
Upper punch	Plain
Lower punch	Plain

EVALUATION OF TABLETS

Pre compression parameters:

Determination of bulk density and tapped density:

A quantity of 10g of the powder (W) from each formula was introduced into a 50 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall

under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. (Shah D, et al., 1997)

The bulk density and tapped density were calculated using the following formulas Bulk density = W / V_O

Tapped density = W / V_f

Where, W = weight of the powder, V_O = initial volume V_f = final volume.

Angle of repose:

In order to determine the flow property, the Angle of repose was determined. It is the maximum angle that can be obtained between the free standing surface of the powder heap and the horizontal plane.

$$\theta = \tan^{-1} (h/r)$$

Where,

h = height

r = radius

θ = angle of repose

Procedure:

- An accurately weighed sample was taken.
- A funnel was fixed in the stand in such a way that the tip of the funnel was at the height of 6 cm from the surface.
- The sample was passed through the funnel slowly to form a heap.
- The height and the circumference of the powder heap formed were measured.
- The radius was measured and the angle of repose was determined using the above formula. This was repeated three times for a sample. (P.Khemariya, et al., 2010)

Compressibility index (Carr's index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, less the compressibility of a material, it is more flowable. A material having values of less than 20 to 30% is defined as the free flowing material. (P.Khemariya, et al., 2010)

$$C_I = 100 (V_O - V_f)/V_0$$

Hausner's Ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density. (Shah D, et al., 1997)

Drug Content:

The formulated Nicorandil SR tablets were assayed for drug content.

Hausner's Ratio = Tapped density/Bulk density

Post compression parameters:

General Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

Thickness:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by Vernier caliper or by other device. Tablet thickness should be controlled within a ± 7.5% variation of standard value.

Hardness:

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. (S.J. Daharwal, et al., 2007)

Friability:

Friability of a tablet can determine in laboratory by Roche friabilator. This consist of a plastic chamber that revolves at 25 rpm, nearer to 6.5 grams of tablets are dropping through a distance of Six inches in the friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compress tablet that lose less than 0.1 to 0.5% of the tablet weigh are consider acceptable.

The percentage friability was measured by using the following formula

$$\%F = \{W_0 - W_f / W_0\} \times 100$$ Where,

%F = Friability in percentage

W_o = Initial weight of tablet

W_f = Weight of tablets after revolution.

Weight Variation test:

Take 20 tablets and weighed individually. Calculate average weight and compare the individual tablet weight to the average. The tablet passes the U.S.P tests if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. (S.J. Daharwal, et al., 2007)

Method:

From each batch of prepared tablets, ten tablets were collected randomly and

powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 20 ml of methanol was added and then dissolve the substance and then sonicate for 15min to get a clear solution, then volume was made up to 100ml with Phosphate Buffer pH 6.8 separately and then filter the solution through 0.45µm filter and suitable dilutions were prepared with phosphate buffer pH 6.8 separately. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 262 nm by using UV-Visible spectrophotometer. Results were tabulated in table No 17. (Arun kumar.N, et al., 2008)

Dissolution (By UV Method)

Sample preparation:

Transfer one tablet into each dissolution bowels and run the dissolution apparatus as per dissolution parameters. Withdraw 10 ml of sample solution through auto sampler containing free flow filter, at the sampling time. Replace aliquots withdrawn for analysis with equal volumes of dissolution medium which is maintained at 37 ± 0.5°C.

Standard solution:

Dissolve an accurately weighed quantity of Nicorandil 100 mg in 100 ml of 0.1N HCl and Phosphate Buffer pH 6.8 (standard stock solution) separately, from this 10ml of solution were pipette out and volume was made up to 100 ml with 0.1N HCl and Phosphate buffer pH 6.8 separately and the aliquot of concentration of 22µg/ml was prepared and measured the absorbance at 262nm by using UV visible spectrophotometer. (Wagner G, et al., 1992)

Dissolution Medium:

900 ml of 0.1N HCl for first 2hours and then transfer the tablets to Phosphate Buffer pH 6.8 for next proceeding hours.

Buffer Preparation:

0.1N HCl:

Transfer 8.5 ml of concentrated HCl to 1000ml volumetric flask and volume was made up to 1000ml with Distilled water.

Phosphate buffer pH 6.8: 6.8 Grams of Potassium dihydrogen ortho phosphate and 0.8 Grams of sodium hydroxide pellets were added to 1000ml of distilled water and adjust the pH with sodium hydroxide pellets.

TREATMENT OF DISSOLUTION DATA WITH DIFFERENT MODELS

The results of *in vitro* release profiles obtained for all formulations were fitted into three kinetic models of data treatment as follows:

1. Cumulative percentage drug released versus time (zero-order kinetic model).
2. Cumulative percentage drug released versus square root of time (Higuchi's model).
3. Log cumulative percentage drug released versus log time (Korsmeyer-Peppas equation).

Zero Order Kinetics: A zero-order release would be predicted by the following equation.

$$A_t = A_0 - K_0 t \quad \ldots 1$$

Where,

A_t = Drug release at time't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr^{-1}).

When the data is plotted as cumulative percentage drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

Higuchi's Model: Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = [D\varepsilon/\tau(2A - \varepsilon C_s) C_S t]^{½} \quad \ldots 2$$

Where,

Q = Amount of drug released at time 't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix

τ = Tortuosity

t = Time (hrs) at which 'Q' amount of drug is released.

Equation-2 may be simplified if one assumes that D, C_S and A are constant. Then equation-2 becomes:

$$Q = Kt^{½} \quad \ldots 3$$

When the data is plotted according to equation-3 i.e., cumulative percentage drug released versus square root of time, yields a straight line, indicating that the

drug was released by diffusion mechanism. The slope is equal to 'K'.

5.3 Korsmeyer and Peppas Model: The release rates from sustained release polymeric matrices can be described by the equation (4) proposed by Korsmeyer et al.

$$Q = K_1 t^n \quad \ldots . 4$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism. For Fickian release, n=0.45 while for anomalous (Non-Fickian) transport, n ranges between 0.45 and 0.89 and for zero order release, n = 0.89. (Peppas, NA, et al., 1985)

Swelling studies:

Nicorandil SR tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing phosphate buffer pH 6.8. At regular intervals (1, 2, 3, 4, 5 and 6hr), the SR tablets were removed from the Petri dishes and excess surface water was removed carefully by using the filter paper. The swollen tablets were then reweighed (designated as W_2**)**. This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Equation**. (**Arun kumar.N, et al. 2008**).** Results were tabulated in Table No: 19

$$\text{Swelling index} = W_2 - W_1/W_1 \times 100$$

Where, W_1 = Initial weight of tablet; W_2 = Swollen tablet

***IN-VITRO* DRUG RELEASE STUDIES FOR REFERENCE PRODUCT**

The *In-Vitro* drug release studies were performed for reference product (NICORAN OD 20mg, Mfg by Torrent Pharmaceuticals, Ahmadabad) using 0.1N HCl for first 2 hours and further proceeding hours by using 6.8 pH Phosphate buffer and then differential and similarity factor were calculated by using following formulas. (Vinod P. Shah, et al., 1988)

$$f1 = \{ [\textstyle\sum_{t=1}^{n} R_t - T_t] / [\sum_{t=1}^{n} R_t] \} . 100$$

$$f2 = 50. \log \{ 1 + (1/n) \textstyle\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} . 100\}$$

Where 'R_t & T_t' are the cumulative percentage drug released at each of the release study. All the parameters have not shown any much variation when compared to the initial data. The *In vitro* dissolution was carried out for three months at the interval of one month.

selected n time point of the reference & test product respectively.

Release kinetics and mechanism

To know the release mechanism and kinetics of Nicorandil, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, Higuchi and Peppa's model. The Peppa's model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation shown as equation. (Peppa's, NA, et al., 1985)

$$Mt/M\infty = kt^n$$

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 II transport), n = 1; and for super case II transport, n > 1. Observation of all the r^2 values indicated that the highest r^2 (0.9984) value was found for Zero order release. According to 'n' value it is 0.82, so it follows non-Fickian diffusion with zero order release.

STABILITY STUDIES

Method

Accelerated stability study was carried out as per ICH guideline 'Q1E Evaluation for stability Data' (Q1E, ICH, 2004) using Neutronic stability chamber for NIC4. This formulation was selected as an optimum formulation and the stability study was carried out at different conditions such as Refrigerator condition, Long term condition and accelerated temperature and humidity conditions for a period of three months. The conditions were modified as 5°C±3°C, 25°C/60%RH and 40°C/75%RH for every one month i.e. 1st, 2nd and 3rd month respectively.

Fifteen tablets were packed in Alu-Alu Blisters and kept at above specified conditions in stability chamber for three months. Tablet samples were evaluated after 1st, 2nd and 3rd month for drug content as well as subjected for the *In vitro* drug

The method adopted and remaining parameters were same as described in dissolution study. The dissolution profiles were analyzed with the aid of dissolution similarity factor f2 and

time point analysis. The drug release profiles were not affected by exposing to different temperature with specified humidity conditions.

The stability data were analyzed using software “Stab for R”. The observed and calculated values are given in Table 36, 37 and 38. The residuals obtained from the calculated values are shown in Figure 31, 33 and 35. The predicted shelf lifes for NIC4 are shown in Figure 32, 34 and 36. The data of time versus cumulative percentage drug release profile are given in Table 33, 34 and 35 and release pattern were shown in Figure 28, 29 and 30.

Results and Discussion

PREFORMULATION STUDIES

Nicorandil is nicotinamide derivative, efficacious in the treatment of angina pectoris and hypertension. It is potassium channel opener providing vasodilatation of arteries and large coronary arteries. In case of cardio vascular diseases, successful treatment can be achieved only by maintaining blood pressure at a normal physiological level and for constant and uniform supply of drug is desired.

Multiple dose administration at intervals of 6 to 8 hours is discomfort to a patient with angina or a hypertensive. This can lead to patient non compliance.

Nicorandil with all evident advantages proved to be a suitable candidate for development of a sustained release dosage form. In the present study, HPMC K200M, Poly ethylene oxide WSR 301 and hydrogenated castor oil which are commonly used in hydrophilic matrix drug delivery systems have been employed to formulate sustained release tablets of Nicorandil.

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy).

Table No 1 : Drug excipients compatibility studies by forced degradation

Drug + Excipient	Initial	First month Observation		Compatible
		25ºC/60% RH	40ºC/75% RH	
Drug	White Powder	No change	No change	Yes
Drug + HPMC K200M	Creamy White Fibrous Powder	No change	No change	Yes
Drug + Polyox WSR 301	White Powder	No change	No change	Yes
Drug + H. Castor oil	White Powder	No change	No change	Yes
Drug + MCC pH 102	White Powder	No change	No change	Yes
Drug + Stearic acid	White Powder	No change	No change	Yes
Drug + Povidone K90F	White Powder	No change	No change	Yes
Drug + Colloidal Anhydrous Silica	White Powder	No change	No change	Yes
Drug + Sodium Stearyl Fumarate	White Powder	No change	No change	Yes

Observation: Compatibility studies at different temperature and relative humidity showed that drug itself was stable at higher temperature and relative humidity as well as compatible with all above used excipients.

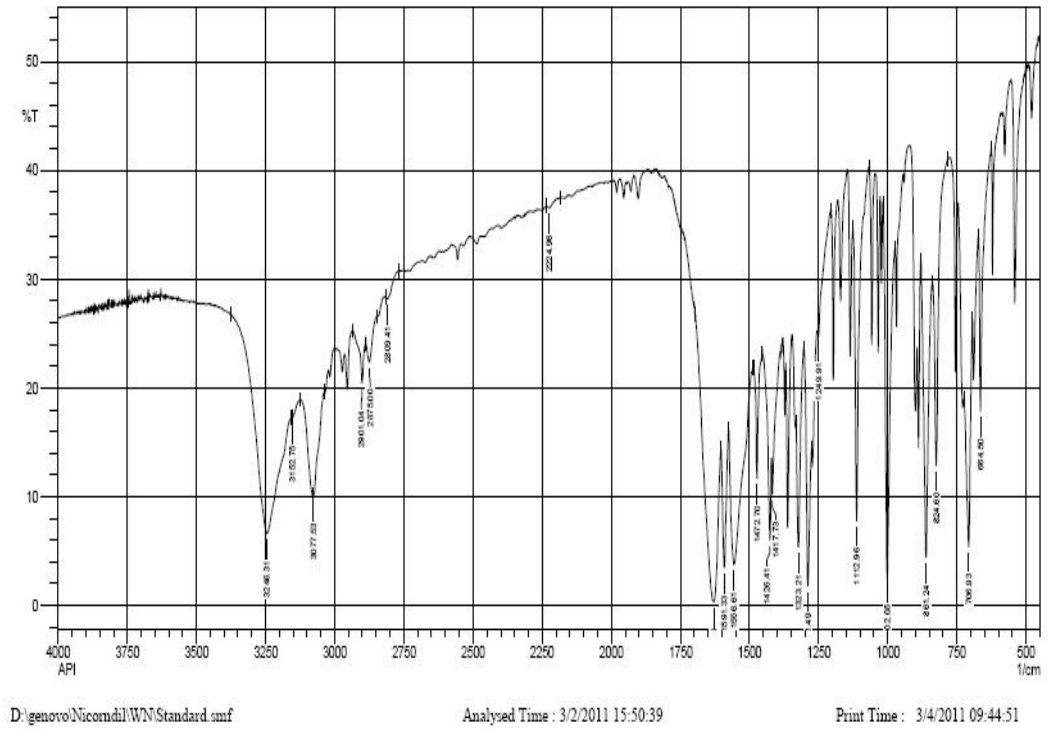


Figure 1 : FTIR Spectra of Nicorandil

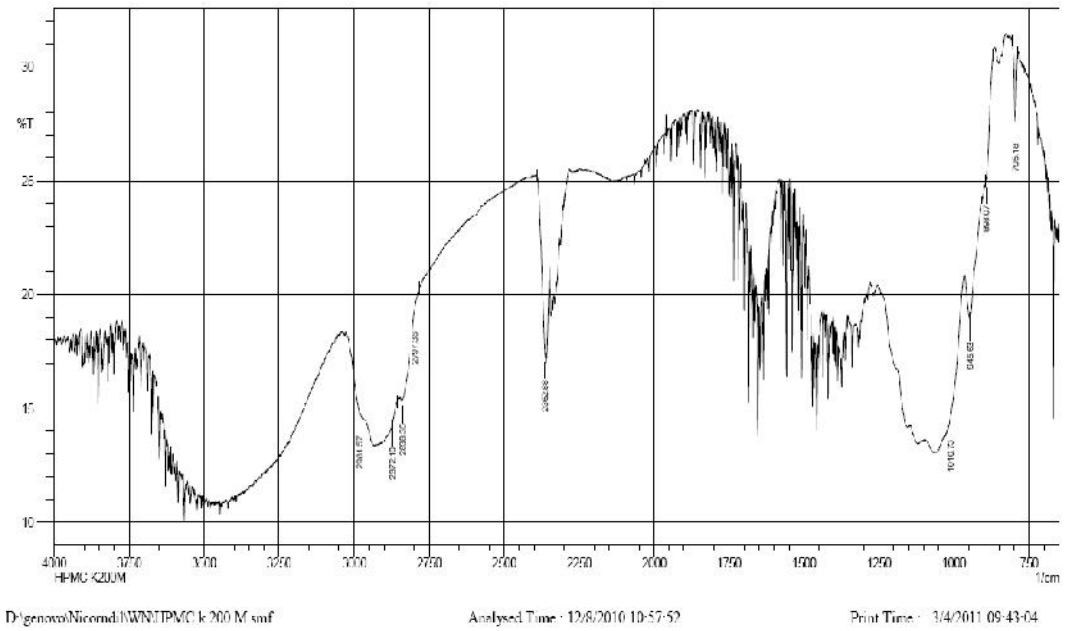


Figure 2 : FTIR Spectra of HPMC K200M

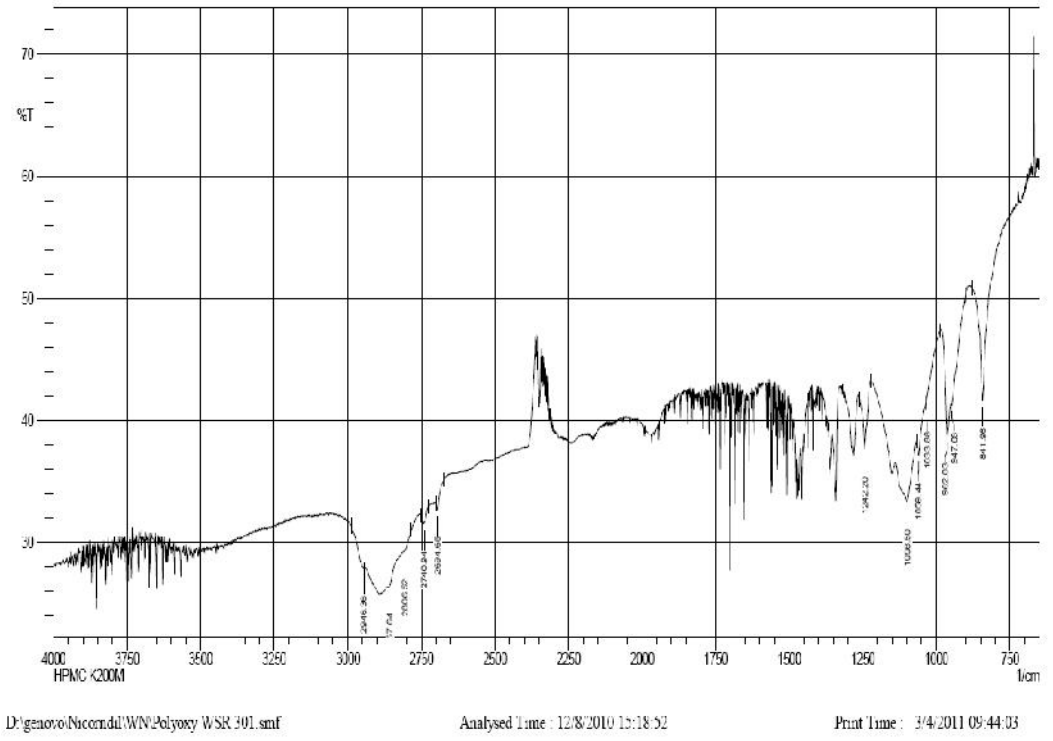


Figure 3 : FTIR Spectra of Poly Ethylene Oxide WSR 301

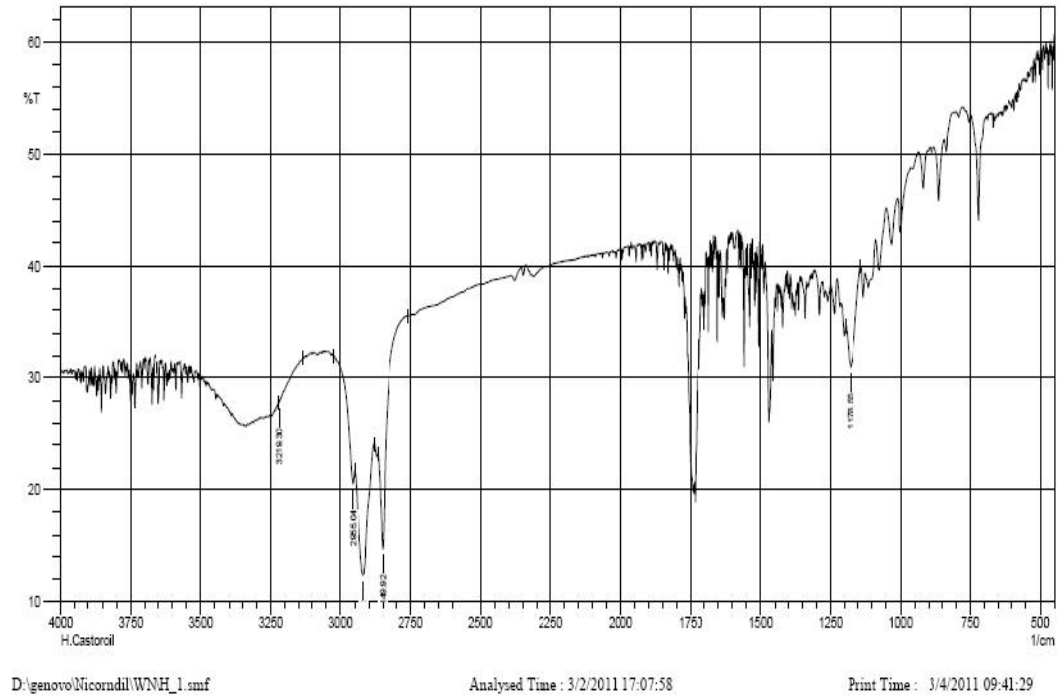


Figure 4 : FTIR Spectra of Hydrogenated Castor Oil

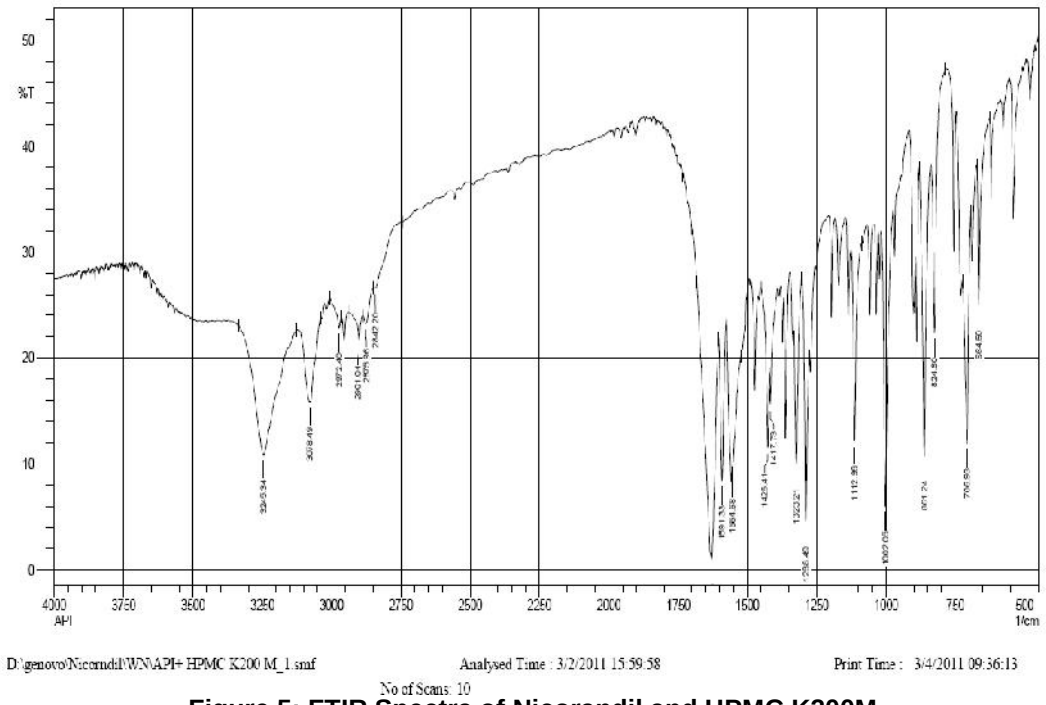


Figure 5: FTIR Spectra of Nicorandil and HPMC K200M

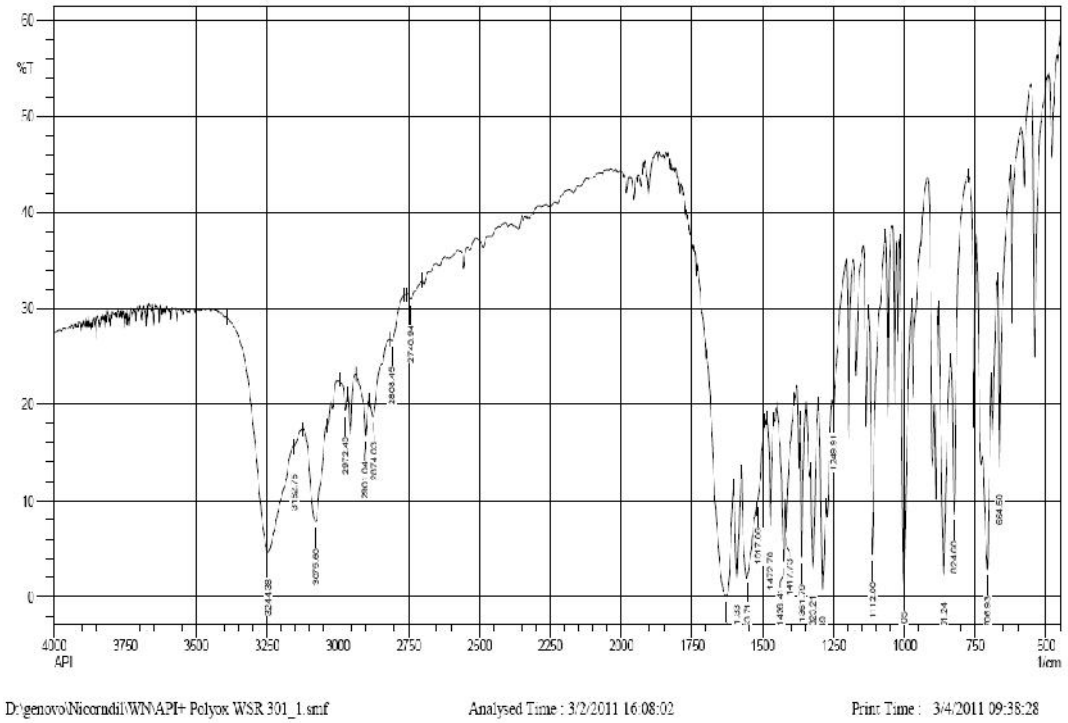


Figure 6 : FTIR Spectra of Nicorandil and Poly ethylene oxide WSR 301

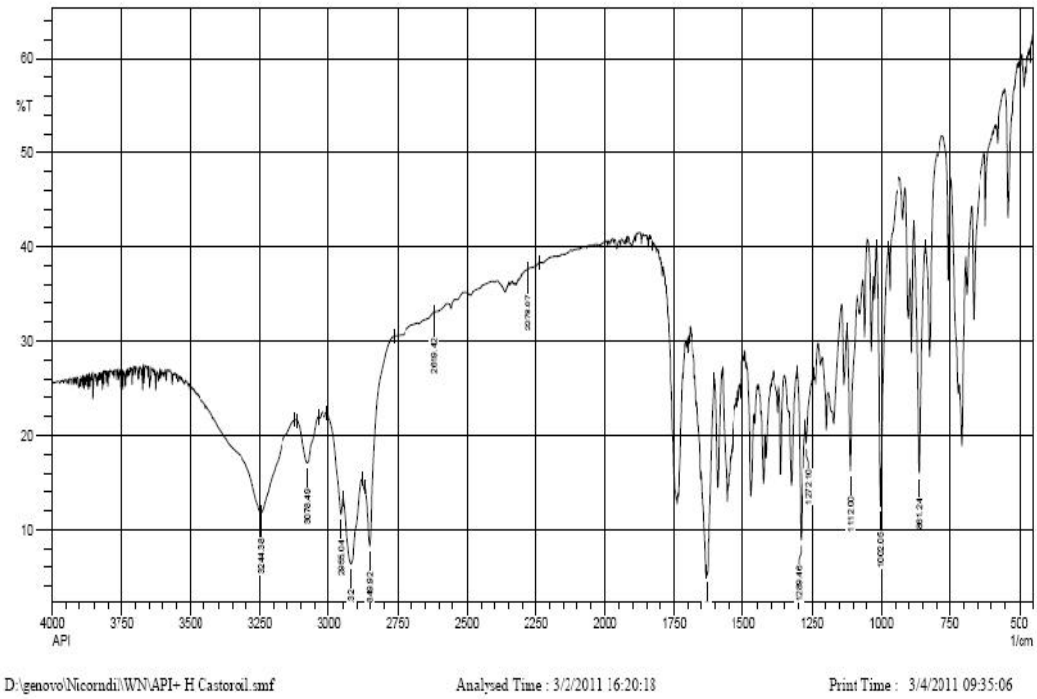


Figure 7 : FTIR Spectra of Nicorandil and Hydrogenated Castor Oil

Table No 2 : FTIR Interpretation data of drug and polymers

Figure No	Name of the compound	Wave number (cm^{-1})	Group Assigned
9	Nicorandil	3246.31, 2901.04, 2875.00, 1591.33, 1556.61, 861.24	N-H Stretching, C-H stretching, CH_2 Asymmetric stretching, N-H bending, C-H bending, NO_2 Asymmetrical stretching
10	HPMC K200M	2981.57, 2872.10,1605.40, 1458.5, 1010.73,	O-H stretching, C-H stretching, C=O stretching, CH_3 bending, C-O-C ring stretching
11	Poly ethylene oxide WSR 301	2946.36, 1242.20, 1033.88, 841.96	C-H stretching, C-O stretching, C-O-C ring stretching, C-H bending
12	Hydrogenated castor oil	3219.30, 2955.04, 1721.05, 1178.55, 711.09	O-H stretching, C-H stretching, C=O stretching, C-O stretching, C-H bending.
13	Nicorandil and HPMC K200M	3245.34, 2901.04, 2875.96, 1591.33, 1554.68, 1323.21, 1112.96, 861.24	N-H Stretching, C-H stretching, CH_2 Asymmetric stretching, N-H bending, C-H bending, NO_2 Asymmetrical stretching
14	Nicorandil and Poly ethylene oxide WSR 301	3244.38, 2901.04, 2874.03, 1591.33, 861.24	N-H Stretching, C-H stretching, CH_2 Asymmetric stretching, C-H bending, NO_2 Asymmetrical stretching
15	Nicorandil and Hydrogenated castor oil	3244.38, 2955.04, 1112.00, 861.24	N-H Stretching, C-H Stretching, C-O stretching C-H bending

Drug –polymer compatibility studies by FTIR

The FTIR spectra of Nicorandil, HPMC K200M, Poly ethylene oxide WSR 301 and waxy substance Hydrogenated Castor oil and the combination of drug and polymers were shown no significant interaction between drug and polymer. The FTIR spectra's of Nicorandil, HPMC K200M, Poly ethylene oxide WSR 301, Hydrogenated Castor oil and mixture of drug along with polymers are shown in figure No: 6 to 12 and interpretation data were given in table No: 06.

The physicochemical compatibility of drug and polymer was established through FTIR studies. IR spectral analysis of Nicorandil showed the peaks at wave numbers of, 3246.31 (N-H Asymmetric stretching), 3077.53 (CH_2 Asymmetric stretching), 1591.33, 1556.61 (N-H bending), 1323.21 (N=O Asymmetric stretching), 861.24 (C-H bending), confirming the purity of drug with standard respectively.

In the physical mixture of Nicorandil with Hydroxy propyl methyl cellulose, Poly ethylene oxide WSR 301 and Hydrogenated castor oil, the major peaks of Nicorandil 3245.34.56 (N-H Asymmetric stretching), 3078.49 (CH_2 Asymmetric stretching), 1591.33, 1554.68 (N-H bending), 1323.21 (N=O Asymmetric stretching), 861.24 (C-H bending), wave numbers. However, additional peaks were absorbed in physical mixtures which could be due to presence of polymers and indicated that there was no chemical interaction between Nicorandil and other excipients.

The flow properties and other derived properties evaluated for all 6 formulations were proved to be within limits showing good flow properties. The physical properties like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio of all formulations were compiled with standard specification and the results were tabulated in table no.13.

Post compression parameters

Thickness and Weight Variation

The tablet thickness were observed by using digital vernier caliper and found to be in the range of 4.07±0.006mm to 4.13±0.006mm. The weight variation of the tablet was found to be in the range of 208.56±1.26mg to 211.53±1.73mg.

Hardness

The difference in the hardness was affect the release of the drug from hydrophilic matrices which is 5.44±0.17 to 7.02±0.17 KP released by diffusion through the gel layer and/or erosion of this layer and is independent of the dry state.

Friability

Tablet strength was tested by Roche Friabilator. The friability of all formulations was observed within the range of 0.252±0.025 to 0.334±0.036.

Drug content:

The Drug content of all formulations were observed within the range of 98.48±0.19 - 99.73±0.99.

Table No 3 : *In-Vitro* dissolution studies for trial batches of F1 to F6

Time in Hours	Cumulative % Drug Release					
	F1	F2	F3	F4	F5	F6
1	25.72	21.42	20.17	20.84	17.41	18.31
2	54.89	50.25	48.24	49.47	42.34	36.74
4	78.21	68.49	62.31	63.45	60.72	53.79
8	92.17	81.57	84.94	81.24	74.84	71.87
10	99.34	92.31	98.47	91.35	88.64	89.36
12	98.75	98.41	98.27	98.94	98.14	97.89

Table No 4 : *In-Vitro* Dissolution Studies for trial batches of F7 to F12

Time in Hours	Cumulative % Drug Release					
	F7	F8	F9	F10	F11	F12

1	29.47	26.79	19.71	26.17	22.18	17.24
2	55.61	51.44	37.81	51.49	43.22	31.28
4	71.49	65.58	51.39	65.74	59.47	49.47
8	90.74	83.27	70.31	81.29	71.21	71.35
10	99.10	97.81	83.47	90.07	87.26	84.37
12	98.42	97.36	99.38	99.17	98.47	98.94

***In-vitro* drug release studies:**

Batches of Nicorandil were prepared with HPMC K200M, Ploy ethylene Oxide WSR 301 and Hydrogenated castor oil by direct compression and wet granulation technique. *In-vitro* dissolution profile of batches F1 to F12 were prepared with two different concentrations of polymers (1:3 and 1:4) and the drug release was shown to 97.36 to 99.38% at the end of 12 hours by both direct compression and wet granulation techniques.

Then batches of Nicorandil were prepared with HPMC K200M, Poly ethylene oxide WSR 301 and Hydrogenated castor oil combinations with different concentrations by direct compression technique.

The formulation of NIC 5 and 6 showed comparatively high hardness value of 6KP. This could be a presence of more concentration of Ploy Ethylene Oxide WSR 301, which is responsible for more hardness of the tablet. The low hardness value observed with formulation NIC 4 due to the presence of less concentration of poly ethylene oxide WSR 301, which is generally decreases the hardness of tablet. Tablet hardness is not an absolute indicator of strength. Another measure of tablet strength is friability. All formulations showed less than 1% W/W friability that indicates the ability of tablets to withstand shocks which may encountered during transport. All the tablet formulations showed acceptable physicochemical properties and compiled with In house specification for weight variation, assay, hardness and friability.

The *in vitro* drug release characteristics were studied in simulated gastric and intestinal fluid for a period of 24 hours using USP II dissolution apparatus. Initially tablets were prepared with a drug-polymer ratio of 1:1. But the tablets released 98% ethylene oxide WSR 301. The formulation NIC4 was showed that it releases the 98.79% of Nicorandil at the end of 24 hours and the blend of these formulation showed good compressibility and flow properties. The formulation NIC 5 & 6 showed 95.34% and 96.47% of drug release at the end of 24 hours, this is due of nicorandil at the end of 3 hours. In an attempt to prolong the drug release, the concentration of polymer was increased. The tablets were prepared with the ratio of 1:3 and 1:4. The drug releases 97.36 to 99.38% at the end of 12 hours by both direct compression and wet granulation technique. Based on the results of *in vitro* dissolution, the tablets were prepared with combination of polymers.

The drug was mixed with different proportions of HPMC K200M and Poly Ethylene Oxide WSR 301. The 1:4 and 1:5 concentration of HPMC K200M was mixed with 1:1, 1:1.5 and 1:2 concentration of Poly Ethylene oxide WSR 301. When the concentration of Poly ethylene oxide increases it retards the drug release. But equal proportions of HPMC K200M and poly ethylene oxide WSR 301, it releases the drug immediately. The formulations were prepared with high concentration of HPMC K200M and low concentration of Poly ethylene oxide WSR 301 only retards the drug release. The formulation NIC1 was prepared with 1:4 & 1:1 concentration of HPMC K200M and Poly ethylene oxide WSR 301, the tablets shown 96.54% of drug release at the end of 18hours. This is due to the less concentration of HPMC K200M. The formulation NIC2 was prepared with 1:4 & 1:1.5 concentration of HPMC K200M and Poly ethylene oxide WSR 301, same like first formulation these tablets also showed drug release 97.32% at the end of 18 hours. The formulation NIC3 was prepared with 1:4 & 1:2 concentration of HPMC K200M and Poly ethylene oxide WSR 301, the tablets showed 98.47% of drug release at the end of 21 hours due to high concentration of Polyethylene oxide. Next further 3 batches were prepared with high concentration(1:5) of HPMC K200M and 1:1, 1:1.5 and 1:2 concentration of Poly to increased concentration of Poly ethylene oxide and increased hardness of tablets.

The NIC1 to NIC3 showed burst release of Nicorandil in the initial hours, which is probably due to faster dissolution of highly water soluble drug from core and its diffusion out of matrix forming the pores

for the entry of solvent molecules. Among all these formulation, the NIC4 showing 15-20% of drug release within 2 hours and 98.79% of drug release at the end of 24 hours. This formulation can be considered as a successful formulation since they showed little deviation from the theoretical release pattern throughout the dissolution period.

The optimized formulation NIC4 was compared with reference product i.e. NICORAN OD20mg and cumulative % drug release, Differential factor f1 and Similarity factor f2 were calculated and tabulated in table No: 30.

Table No 5 : *In-Vitro* Dissolution data for final batches of NIC 1 to NIC 6

Time in Hours	Cumulative % Drug Release					
	NIC 1	NIC 2	NIC 3	NIC 4	NIC 5	NIC 6
1	11.85	10.79	10.35	08.34	08.21	07.98
2	23.24	21.56	20.75	15.26	16.39	15.46
4	35.68	33.87	32.79	27.78	28.84	26.84
8	53.79	52.61	49.68	48.56	47.24	46.57
12	71.99	71.24	68.47	65.41	62.13	64.52
18	98.14	98.53	85.26	83.24	80.58	82.19
21	97.21	97.98	99.08	91.03	88.26	87.46
24	96.54	97.32	98.47	98.79	95.34	96.47

Table No 6 : *In-Vitro* Drug Release Data of Formulation Nic 1

***In-vitro* drug release data**		**Higuchi's data**		**Peppa's data**	
Time in h	**Cu. % drug release**	**Sqrt of time**	**Cu.% drug release**	**log time**	**log cu. % drug release**
0	0	0	0		
1	11.85	1.00	11.85	0	1.07371835
2	23.24	1.414213562	23.24	0.30102999	1.366236124
4	35.68	2.00	35.68	0.60205999	1.552424846
8	53.79	2.83	53.79	0.90308998	1.730701544
12	71.99	3.464101615	71.99	1.07918124	1.857272174
18	98.14	4.24	98.14	1.25527250	1.991846054
21	97.21	4.58	97.21	1.32221929	1.987710943
24	96.54	4.90	96.54	1.38021124	1.984707294

Table No 7 : *In-Vitro* Drug Release Data of Formulation: Nic 2

In-vitro drug release data		Higuchi's data		Peppa's data	
Time in h	**Cu. % drug release**	**Sqrt of time**	**Cu.% drug release**	**log time**	**log cu. % drug release**
0	0	0	0		
1	10.79	1.00	10.79	0	1.033021445
2	21.56	1.414213562	21.56	0.30102999	1.333648757
4	33.87	2.00	33.87	0.60205999	1.529815197
8	52.61	2.83	52.61	0.90308998	1.721068302
12	71.24	3.464101615	71.24	1.07918124	1.852723911
18	98.53	4.24	98.53	1.25527250	1.993568483
21	97.98	4.58	97.98	1.32221929	1.991137435
24	97.32	4.90	97.32	1.38021124	1.9882021

Table No 8 : *In-Vitro* Drug Release Data of Formulation: Nic 3

In-vitro drug release data		Higuchi's data		Peppa's data	
Time in h	**Cu. % drug release**	**Sqrt of time**	**Cu.% drug release**	**log time**	**log cu. % drug release**
‘0	0	0	0		
‘‘‘‘‘‘‘‘‘‘‘‘‘‘ ‘‘‘‘‘‘‘‘‘‘‘‘1	10.35	1.00	10.35	0	1.01494035
2‘	20.75	1.414213562	20.75	0.301029996	1.317018101
4	32.79	2.00	32.79	0.602059991	1.515741417
8	49.68	2.83	49.68	0.903089987	1.696181587
12	68.47	3.464101615	68.47	1.079181246	1.835500328
18	85.26	4.24	85.26	1.255272505	1.930745328
21	99.08	4.58	99.08	1.322219295	1.995985998
24	98.47	4.90	98.47	1.380211242	1.993303938

Table No 9 : *In-Vitro* Drug Release Data of Formulation: Nic 4

In-vitro drug release data		Higuchi's data		Peppa's data	
Time in h‘‘‘‘‘‘‘‘‘‘‘ ‘‘	**Cu. % drug release**	**Sqrt of time**	**Cu.% drug release**	**log time**	**log cu. % drug release**
0	0	0	0		
1‘	8.34	1.00	8.34	0	0.92116605
2‘	15.26	1.414213562	15.26	0.30102999	1.18355453
4	27.78	2.00	27.78	0.60205999	1.44373224
8	47.43	2.83	47.43	0.90308998	1.67605312
12‘	63.14	3.464101615	63.14	1.07918124	1.80030457
18	83.24	4.24	83.24	1.25527250	1.92033207
21	91.03	4.58	91.03	1.32221929	1.95918454
24	98.79	4.90	98.79	1.38021124	1.99471298

In-Vitro Release kinetics

Data of *in-vitro* drug release were fit into different equations and kinetic models to explain the release kinetics of Nicorandil from the sustained release tablet. The kinetic models used were a Zero-order equation, Higuchi's model and Peppa's models. The obtained results in these formulations were plotted in various model treatment are as follows. I.e. Cumulative percentage drug release Vs Square root of time (Higuchi's) and Log cumulative percentage release Vs Log time (Peppa's). To know the mechanism of drug release from sustained release tablet, the drug release data was fit into Higuchi's models. The correlation

coefficient values (R) indicate the kinetic of drug release was zero order and the mechanism of drug release by Peppa's model indicates the non fickian evidenced with diffusion exponent values (n) and the values were tabulated in Table No: 31.

Table No 10 : Release kinetics and mechanism of all formulations

Formulation code	Mathematical models			
	Zero order	Higuchi's	Peppa's Model	
	R^2	R^2	R^2	N
NIC 1	0.941	0.982	0.987	0.660
NIC 2	0.945	0.982	0.988	0.694
NIC 3	0.971	0.994	0.992	0.696
NIC 4	0.979	0.998	0.997	0.775
NIC 5	0.978	0.999	0.993	0.754
NIC 6	0.976	0.997	0.995	0.777

Swelling studies:

Table No 11 : Swelling index profile of all formulations

Time (hr)	NIC1 (%)	NIC2 (%)	NIC3 (%)	NIC4 (%)	NIC5 (%)	NIC6 (%)
0	0	0	0	0	0	0
1	50.26	55.15	58.33	48.28	48.62	52.34
2	88.31	91.75	105.90	87.85	89.26	94.85
3	123.00	127.15	139.42	135.19	132.56	136.66
4	168.73	167.35	182.47	178.28	183.54	196.54
5	201.42	197.80	206.14	199.00	201.20	210.65
6	210.21	208.95	226.42	216.09	223.79	238.28

***IN-VITRO* DRUG RELEASE STUDIES FOR REFERENCE PRODUCT**

Table No 12: f1 and f2 calculations

Time in h	Reference product (NICORAN OD 20mg)	Test Product (NIC 4)	/r-t/	$/r-t/^2$	f1	f2
0	0	0	0	0	0	0
1	9.83	8.34	1.49	2.22	15.15	90.00
2	18.26	15.26	3.00	9.00	16.42	74.50
4	28.64	27.78	0.86	0.73	03.00	102.14
8	50.65	47.43	3.22	10.36	06.75	73.36
12	66.28	63.14	3.14	9.85	4.73	73.94
18	85.67	83.24	2.43	5.90	2.83	79.50
21	91.45	91.03	0.42	0.17	0.45	117.63
24	98.14	98.79	-0.65	0.42	-0.66	-----
SUM	448.92	435.01	14.91	38.65	f_1= 6.08	f_2= 87.29

‘‘

STABILITY STUDIES

Stability Compilation Data for Nicorandil SR Tablets

Table No 13 : Stability results of SR tablets at Refrigerator condition

S.No	Test	Initial		5 ± 3ºC		
				1 month	2 month	3 month
1	Description	White to off white color		No change	No change	No change
2	Assay	99.47 ± 0.25		99.41 ± 0.10	99.27 ± 0.15	98.79 ± 0.12
3	Dissolution	Time in H	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)
		1	08.34	08.22	08.35	08.19
		2	15.26	14.22	14.20	14.74
		4	27.78	27.94	27.34	28.22
		8	47.24	46.95	44.62	44.64
		12	63.14	64.67	64.08	63.31

		18	83.24	81.86	80.94	80.59
		21	91.03	91.42	90.15	89.45
		24	98.79	98.81	98.78	98.52

Table No 14 : Stability results of SR tablets at Long term condition

S.No	Test	Initial		25ºC ± 2ºC/60% ± 5% RH		
				1 month	2 month	3 month
1	Description	White to off white color		No change	No change	No change
2	Assay	99.47 ± 0.25		99.35 ± 0.12	98.18 ± 0.29	97.45 ± 0.15
3	Dissolution	Time in H	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)
		1	08.34	08.59	08.67	08.47
		2	15.26	15.42	21.06	21.17
		4	27.78	25.95	27.25	27.73
		8	47.24	47.13	44.55	44.02
		12	63.14	65.09	65.34	66.15
		18	83.24	83.19	81.00	77.05
		21	91.03	89.86	89.73	88.62
		24	98.79	98.68	97.85	97.41

Table No 15 : Stability results of SR tablets at Accelerated condition

S.No	Test	Initial		40ºC ± 2ºC/75% ± 5% RH		
				1 month	2 month	3 month
1	Description	White to off white color		No change	No change	No change
2	Assay	99.47 ± 0.25		95.89 ± 0.27	89.64 ± 0.66	78.29 ± 0.60
3	Dissolution	Time in H	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)	% CDR (Avg)
		1	08.34	09.47	07.58	09.12
		2	15.26	17.59	14.66	19.45
		4	27.78	24.08	26.63	28.44
		8	47.24	41.41	46.21	42.93
		12	63.14	56.76	65.90	57.42
		18	83.24	77.32	76.61	72.01
		21	91.03	88.96	83.78	78.43
		24	98.79	94.90	89.69	78.71

Stability data for calculation of Shelf life:

Table No 16 : Calculated assay for Refrigerator condition

S.No	Batch No	Time in Months	Observed Assay in %	Calculated Assay in %
1	1	0	99.47	99.54
2	1	1	99.41	99.31
3	1	2	99.27	99.07
4	1	3	98.79	98.83
5	2	0	99.47	99.54
6	2	1	99.35	99.31
7	2	2	99.25	99.07
8	2	3	98.64	98.83
9	3	0	99.47	99.54
10	3	1	99.29	99.31
11	3	2	99.16	99.07
12	3	3	98.74	98.83

Table No 17 : Calculated assay for Long term condition

S.No	Batch No	Time in Months	Observed Assay in %	Calculated Assay in %
1	1	0	99.47	99.67
2	1	1	99.35	98.97
3	1	2	98.18	98.28
4	1	3	97.45	97.58
5	2	0	99.47	99.67
6	2	1	99.28	98.97
7	2	2	98.29	98.28
8	2	3	97.64	97.58
9	3	0	99.47	99.67
10	3	1	99.18	98.97
11	3	2	98.49	98.28
12	3	3	97.31	97.58

Table No 18 : Calculated assay for Accelerated condition

S.No	Batch No	Time in Months	Observed Assay in %	Calculated Assay in %
1	1	0	99.47	101.11
2	1	1	95.89	94.38
3	1	2	89.64	87.66
4	1	3	78.29	80.93
5	2	0	99.47	101.11
6	2	1	96.13	94.38
7	2	2	90.75	87.66
8	2	3	79.96	80.93
9	3	0	99.47	101.11
10	3	1	95.64	94.38
11	3	2	88.42	87.66
12	3	3	79.17	80.93

Discussion

The stability studies were carried out according to ICH guidelines for optimized formulation i.e. NIC 4. The formulations of all batches were prepared with a waxy material Hydrogenated castor oil, which is a solid at room temperature, which is used to coat the drug molecules and increase the stability of product or reduce the compressibility force on the tablets and saturated higher aliphatic acids such as Stearic acid Which is used to reduce the moisture content of the drug.

The stability studies were carried out under 3 conditions i.e. Refrigerator stability (5±3°C), Long term stability (25±2°C/60±5% RH) and Accelerated stability studies (40±2°C/75±5% RH). The tablets were packed in Alu-Alu blister packing. Then tablets were stored under 3 conditions and the tablets were withdrawn at every one month and evaluate the tablet parameters like description, assay and dissolution. After first month the tablets showed the same results as that of initial result at all three conditions. After second month the tablets showed the same results as that of initial result at Refrigerator and Long term stability conditions, but at accelerated stability condition a slight variation in assay and dissolution i.e. ±2%. After third month the tablets showed the same results as that of initial result at Refrigerator and Long term condition but in accelerated condition the assay and dissolution results are deviating ±15% of the initial result.

According to 3 months stability data, the shelf life at three conditions i.e. Refrigerator condition, Long term condition and Accelerated condition was found to be 47, 17 and 2 months. The Residuals were shown in tables.

Conclusion

The hydrophilic matrices of HPMC K200M, Poly ethylene oxide WSR 301 and waxy material Hydrogenated castor oil alone could not control the Nicorandil release effectively for 24hours but a combination of hydrophilic polymers HPMC K200M and Poly ethylene oxide WSR 301 at different concentrations release the drug effectively over a prolonged period of 24 hours and it is better system for once a day administration.

Formulations NIC 4 has shown better drug release over 24 hours of time and it released 98.48% of drug out of 6 formulations. The drug release mainly by diffusion controlled mechanism and coupled with erosion.

Stability studies were conducted according to ICH guidelines, carried out for optimized formulation NIC 4 for a period of 3 months and the obtained results were within the specification at both Refrigerator and Long term conditions and out of specification at accelerated condition. Among all formulations, the optimized formulation NIC4 fulfills over objective.

Future aspects:

Further studies are needed to investigate this formulation such as,

- To perform *In-Vivo* studies
- To perform a clinical studies
- To perform a Bioavailability and Bioequivalence studies

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