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Formulation and Evaluation of Chronomodulated Pulsincap Drug Delivery System of Nitrendipine

M. Vanditha* and K. Sudhamani

Department of Pharmaceutics, Mallareddy Institute of Pharmaceutical sciences, JNTU Hyderabad, Telangana.

* Corresponding author: M. Vanditha, e-mail: m.vanditha8@gmail.com

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ABSTRACT

Nitrendipine modulates NMDA receptor channel function in mammalian neurons. Nitrendipine has been shown to inhibit neutrophil adhesion to vascular endothelium. It is mainly used for its antiarrhythmic, antianginal and antihypertensive activity. It is used as the prototype drug and the drug works by slowing down the rate at which calcium moves to heart and walls of blood vessels allowing better blood flow. In the present study, attempt was made to target the drug to the colon and intentionally delaying the drug absorption from the therapeutic point of view in the treatment of hypertension. Prior to formulation, Preformulation studies were carried out in order to establish compatibility between Nitrendipine and polymers like ethyl cellulose, guar gum, and HPMC K15M by FTIR spectroscopy. The results revealed that the drug and polymers were satisfactorily compatible, without any significant changes in the chemical nature of Nitrendipine. The prepared pulsincaps were evaluated for drug content, weight variation and Invitro release studies. FTIR studies confirmed that there was no interaction between drug and polymers and Invitro release studies of pulsatile device revealed that increasing hydrophillic polymer content resulted in delayed release of Nitrendipine from the pulsincap after a predetermined lag time of 6hrs. Based on invitro studies performed, F6was found to be optimized formulation.

Keywords: Pulsatile system; colon specific; pH and time dependent delivery; Nitrendipine; Chronopharmaceutics; *In vitro* release studies.

1. INTRODUCTION

Controlled drug delivery systems have acquired a centre stage in the arena of pharmaceutical research and development sector. Such systems offer temporal and /or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of patentability. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for obvious advantages of oral route of drug administration. . In such systems the drug release commences as soon as the dosage form is administered as in the case of conventional dosage forms. However, there are certain conditions, which demand release of drug after a lag time. Such a release pattern known as "pulsatile release"[1].

A pulsatile dosage form, taken at bed time with a programmed start of drug release in the early morning hours, can prevent this. By timing drug administration, plasma peak is obtained, at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need of drugs. Saturable first pass metabolism and tolerance development can also be avoided[2].

Drug targeting to colon would prove useful where intentional delayed drug absorption is desired from therapeutic point of view in the treatment of disease that have peak symptoms in the early morning such as nocturnal asthma, angina, arthritis [3,4]. Some orally administered drugs (eg. Metaprolol, Theophiline, Nifedipine, Isosorbide) may exhibit poor uptake in the upper regions of GIT or degrade in the presence of GIT enzymes[5]. Better bioavailability can be achieved through colon-specific drug delivery. Colon targeting is also advantageous where delay in systemic absorption is therapeutically desirable[6].

Cardiovascular diseases such as hypertension and angina, or chest pain, also follow a definite circadian rhythm. Hypertension is increased in the early morning

hours. Systolic blood pressure rises approximately 3mm Hg/hr for the first 4-6 hours post-awakening, while the rate of rise of diastolic blood pressure is approximately 2mm Hg/hr. The silent ischemic events showed a circadian pattern with a high density of 34% events occurring between 6 a.m. and noon.

Nitrendipine has been shown to inhibit neutrophil adhesion to vascular endothelium. It is mainly used for its antiarrhythmic, antianginal and antihypertensive activity. It is used as the prototype drug and the drug works by slowing down the rate at which calcium moves to heart and walls of blood vessels allowing better blood flow. Thus the objective of the present study was to prepare a standard pulsatile drug delivery system of Nitrendipine based on chronopharmaceutical approach for the treatment of hypertension.

2. MATERIALS AND METHODS

Materials

Nitrendipine procured by BMR Chemicals, Hyderabad. lycoat, SSG, were purchased from Sd fine chemical Ltd, Mumbai, and other excipients were procured from Rankem-Mumbai, Otto Chemicals, Mumbai, Narmada chemicals, Hyderabad respectively.

PULSINCAP DESINGNING

Designing or preparation of pulsincap capsules involves 3 steps:

A. Preparation of cross-linked gelatin capsule.
B. Preparation of powder blends for filling into capsules.
C. Formulation of pulsincap of Nitrendipine.

A. Preparation of cross-linked gelatin capsule:

Formaldehyde treatment:

About 100 hard gelatin capsules size '0' were taken. Their bodies were separated from the caps and placed on a wire mesh. The bodies which were placed on a wire mesh were spread as a single layer. 25 ml of 15% v/v of formaldehyde solution was prepared and placed in a desiccators. To this a pinch of potassium permanganate was added. The wire mesh containing the bodies of the capsules was kept on the top of desiccators' containing formaldehyde liquid at the bottom in equilibrium with its vapor and immediately the desiccators' was tightly closed and sealed. The bodies of capsules were made to react with formaldehyde vapors by exposing them for varying periods of time viz., 3, 6, 9 and 12 hrs. Then they were removed and kept on a filter paper and dried for 24 hrs to ensure completion of reaction between gelatin and formaldehyde vapors, afterwards the capsules were kept in an open atmosphere, to facilitate removal of residual formaldehyde. These capsule bodies were capped with untreated cap and stored in a polythene bag.

Optimization of formaldehyde treated capsule bodies exposed at various time intervals viz., 3, 6, 9, 12hrs:-

Formaldehyde treated capsule bodies which were exposed at various time intervals viz., 3, 6, 9 and 12hrs were optimized by conducting Disintegration test. The test was performed on both untreated and treated capsules. Formaldehyde treated bodies joined with untreated caps and was tested for disintegration. Disintegration test was carried out by using Electrolab disintegration test apparatus. pH 1.2, pH 6.8, pH 7.4 buffers were used as medium and maintained at 37°C throughout the experiment. The time at which the capsules disintegrate are noted.

B. Preparation of powder blend for filling into capsules:

Different blend formulations of drug, sodium starch glycolate, Lycoat, MCC,Mg.stearate and talc were prepared for filling into capsules.In each formulation, accurately weighed quantity of the drug and excipients were passed through the mesh No.60. The excipients along with super disintegrants were taken in different proportions for formulating blend for filling into capsules.

Each formulation of blend was punched as a tablet and disintegration test was conducted and the time at which the tablets disintegrate was noted. The tablet which disintegrates in short time was selected and that particular formulation in the form of powder blend was chosen for preparation of pulsincap.

C. FORMULATION OF PULSINCAP OF NITRENDIPINE:

The modified release pulsincaps containing 20mg of Nitrendipine were prepared by using different excipients in varying ratios as shown in the Table 5.5. The formaldehyde treated capsule bodies which were exposed to 6 hrs was optimized and chosen for the pulsincap formulation based on disintegration time. For drug formulation, the powder blend F6 formulation containing drug-20mg and excipients like,Lycoat talc-and MCC-q.s was optimized based on the disintegration studies and used for filling into the capsules. For hydrogel plug formulation, the plug was prepared by using the combination of hydrophobic polymer like Ethyl cellulose and natural & semi synthetic hydrophilic polymers like Gaur gum, HPMC K15M in varying ratios. Initially the total weight of the plug was taken as 30 mg and the ratio of hydrophobic & hydrophilic polymer as 1:1. Then further formulations were designed by increasing the weight of the plug to 45mg and the ratios of hydrophobic & hydrophilic polymer combination as 1:1, 1:1.5, 1:2.

Preparation of immediate release tablets of Nitrendipine

Hard gelatin capsules of 'size 0' which were hardened with formaldehyde treatment for 6hrs were chosen for the formulation. The bodies and caps separated manually.The drug Nitrendipine (100mg) along with the excipients like Lycoat (super disintegrant), MCC (diluent) and Talc(Glidant, Mg.stearate(lubricant) were accurately weighed and passed through mesh no.60.All the ingredients were mixed together in a mortar to

obtain a homogeneous mixture by using geometric dilution technique, and then punched in tablet punching machine.

I. Preparation of Hydrogel plug:

Plug was prepared as a compressed tablet and placed at the opening of capsule body. The capsule body was closed by a cap.Hydrogel plug was prepared by using different polymers like Ethyl cellulose, Gaur gum, and HPMC K15M at different concentrations.A combination of hydrophobic and hydrophilic polymers were used viz., Ethyl cellulose: Gaur gum, Ethyl cellulose: HPMC K15M; in different ratios like 1:1, 1:1.5, and 1:2.

A tight fit between the plug and impermeable capsule shell is essential to regulate water penetration into the capsule content and the drug release prior to complete erosion of plug material. Ideally plug should erode only from the surface exposed to the release medium. Plug ejection can be done by swelling on contact with aqueous fluids (or) pushing out by increased internal pressure (or) erosion (or) by enzyme degradation.

II. Capsule filling:

Immediate release tablet was filled into the 6th hr formaldehyde treated capsule body manually by filling method. Then, hydrogel plug in the form of a tablet is placed above the mixture i.e., at the opening of capsule body. The capsule body was closed by a cap.

III. Capsule sealing:

The joint of the treated capsule body and untreated cap of the capsules was sealed with a small amount of 5% ethyl cellulose ethanolic solution.

Evaluation of Pulsatile Drug Delivery Systems:

The prepared Pulsincaps were evaluated for the following tests:

1. Weight variation:

10 capsules were selected randomly from each batch and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than or more than 110% of the average.

2. Estimation of drug content:

From each batch of the prepared pulsincaps of Nitrendipine ten pulsincaps were randomly selected and the contents were removed and powdered. From this sample 20 mg powder was accurately transferred into a 100 ml volumetric flask. Then 10 ml of methanol was added to dissolve Nitrendipine. The solution is made up to volume with pH 7.4 phosphate buffer. The resulted solution was filtered through 0.45µm filter paper and suitably diluted and the drug content was estimated spectrophotometrically by measuring the absorbance at 236 nm.

3. Evaluation of swelling index of hydrogel plug:

Swelling index was studied by measuring the percentage water uptake by the hydrogel plug. The prepared hydrogel plugs were accurately weighed and placed in 100 ml pH 1.2 buffer for 2 hrs then in 100ml of pH 6.8 buffer for next 3hrs and 100ml of pH 7.4 buffer for the remaining time. The plugs were removed at definite time intervals from their respective swelling media and weighed after drying the surface water by using filter paper.

***In vitro* release studies:**

Dissolution study was carried out to measure the release rate of drug from prepared pulsincap formulation using USP I dissolution apparatus at 37^{0}C using 3 different dissolution media of pH 1.2, pH 6.8 and pH 7.4 phosphate buffers in order to mimic in vivo GIT conditions. Initially first 2hrs of dissolution was conducted in pH 1.2 buffer, followed by 3hrs of dissolution study in pH 7.4 phosphate buffer as the small intestinal transit time is 3hrs then later study was carried out in pH 6.8 phosphate buffer. 5 ml samples of dissolution fluid were withdrawn at predetermined time intervals with the help of a syringe. The volume withdrawn at each time interval was replaced with 5ml of fresh dissolution medium maintained at same temperature. The filtered samples were suitably diluted whenever necessary and assayed for Nitrendipine by measuring absorbance at 236nm, by UV absorption spectroscopy. %CDR was calculated over the sampling times.

3. RESULTS AND DISCUSSION

Determination of Nitrendipine λ-max:

Determination of Nitrendipine λ-max was done in 6.8 ph buffer for accurate quantitative assessment of drug dissolution rate. The Nitrendipine peak value is 236. The linearity was found to be in the range of 2-12 µg/ml in 6.8 ph buffer. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law. The solubility studies were conducted in various buffers we can say that 6.8 pH buffer has more solubility when compared to other buffer solutions.

FTIR STUDIES:

It indicates that the drug was intact and has not reacted with the excipients used in the formulation and hence they are compatible. Hence, it can be concluded that the drug is in free-state and can release easily from the polymeric network in the free form.

Evaluation of Physical Parameters of compressed tablets of Nitrendipine:

The pulsincap dosage form was evaluated for weight variation, drug content estimation.It complies with official specifications. All the 6 formulations of Nitrendipine pulsincaps were subjected to dissolution studies.

Formulations F1, F2, F3 contain the hydrogel plug with combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: HPMC K15M in the ratio of 1:1-1:2 of total 45mg weight of the plug. In pH 1.2 after the initial 2 hours of dissolution study the drug release for formulations F1, F2 and F3 was 12.08, 12.63, 5.73 respectively. In pH 7.4, F1, F2 and F3 showed release rates of 90.12, 86.48, 64.58 by the end of 5th hour respectively. In pH 6.8buffer, F1, F2 and F3 showed

release rates of 97.58, 99.83, 75.25 by the end of 6th hour respectively. In formulations F1, F2 and F3 the drug was released prior to predetermine lag time. so further works was done with increase in the polymer ratio.

Formulations F4, F5, F6 contain the hydrogel plug with combination of hydrophobic polymer and Hydrophilic polymer i.e., Ethyl cellulose: Gaur gum, in the ratio of 1:1-1:2 of total 45mg weight of the plug. In pH 1.2 after the initial 2 hours of dissolution study, the drug release for formulations F4, F5 and F6 was 10.50, 5.33, 1.4 respectively. In pH 7.4, F4, F5 and F6 showed release rates of 26.47, 18.32, 9.08 by the end of 5th hour respectively. In pH 6.8, F4, F5 and F6 showed release rates of 92.99, 92.54 by the end of 8th hour respectively,whereas F6 shows 99.52% of drug release at the end of 8th hour, which have maintained a lag phase of about 6hours as per our study. So F6 formulation was considered as the optimized formulation.

As the polymer ratio was increased it was observed that the rate of drug release in pH 1.2 buffer and pH 6.8 phosphate buffer was decreased which is one of the important parameter for designing colon targeted drug delivery system, to have minimum drug release in upper GIT. As F6 showed the drug release of 99.52% at the end of 8th hour and maintained the required lag time of 6hours. There was minimum drug release during the lag time and the burst release occurred after predetermined lag time i.e., during 7th hour, therefore formulation F6 was considered as best formulation.

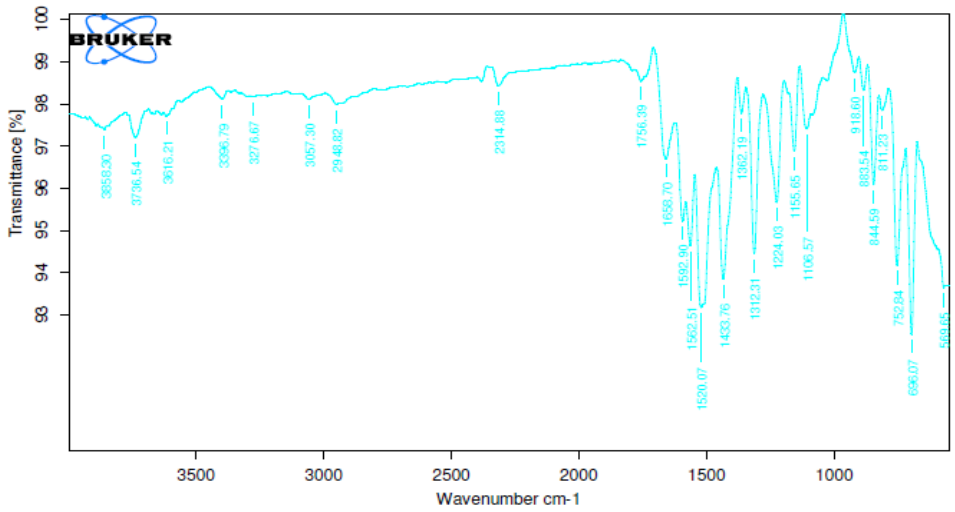
It was observed that a proper lag time of 6 hours was maintained with minimal upper GIT drug release for the combination of Ethyl cellulose and Guar gum hydrogel plug in the 1:2. It was observed that as the concentration of Hydrophilic polymer was increased the release rate of drug was delayed and finally burst release of drug from the formulation occurred after lag time. So basing on these observations, of all the 6 pulsincap formulations, F6 formulation containing hydrogel plug of ethyl cellulose & Guar gum in 1:2 ratio was selected as optimized pulsincap formulation for colon targeting to treat rheumatoid arthritis.

Table 1: Formulation of Hydrogel Plugs

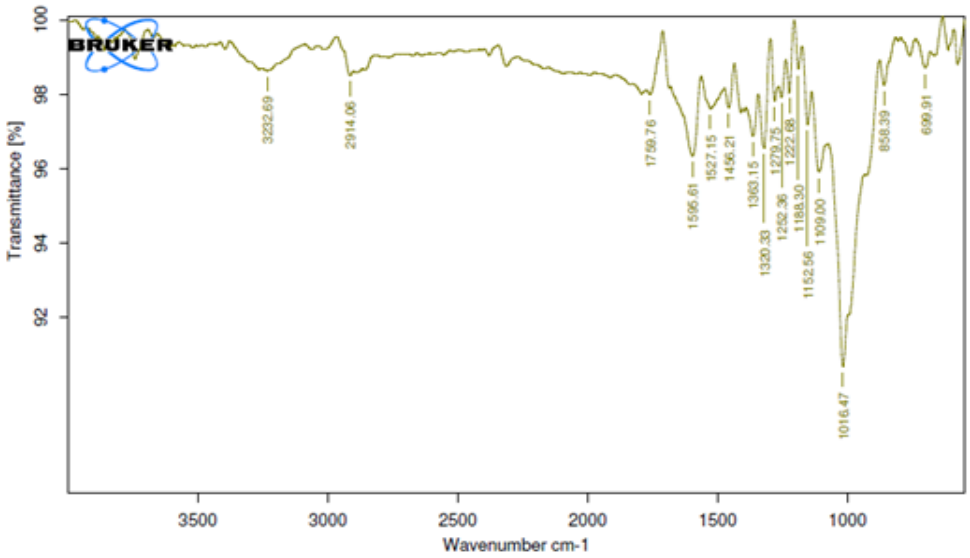
Polymers	F1	F2	F3	F4	F5	F6
Ethyl cellulose	15	15	15	15	15	15
HPMC K15M	15	22.5	30			
Gaur gum				15	22.5	30
Total weight	30	37.5	45	30	37.5	45

Table 2: Formulation of immediate release tablets of Nitrendipine

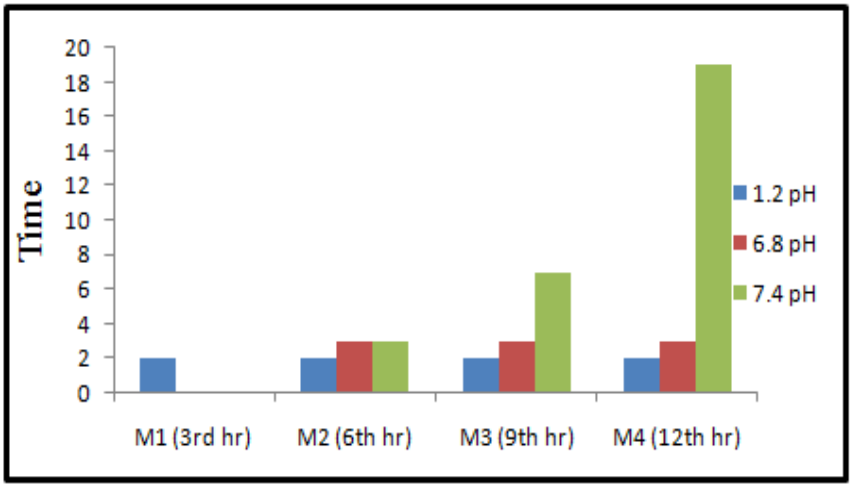
INGREDIENTS	N1	N2	N3	N4	N5	N6
Nitrendipine (mg)	20	20	20	20	20	20
Sodium Starch Glycolate	3	6	9	-	-	-
Lycoat	-	-	-	3	6	9
Talc	3	3	3	3	3	3
Mg stearate	3	3	3	3	3	3
MCC	q.s	q.s	q.s	q.s	q.s	q.s
Total wt (mg)	100	100	100	100	100	100



FTIR spectrum of Nitrendipine



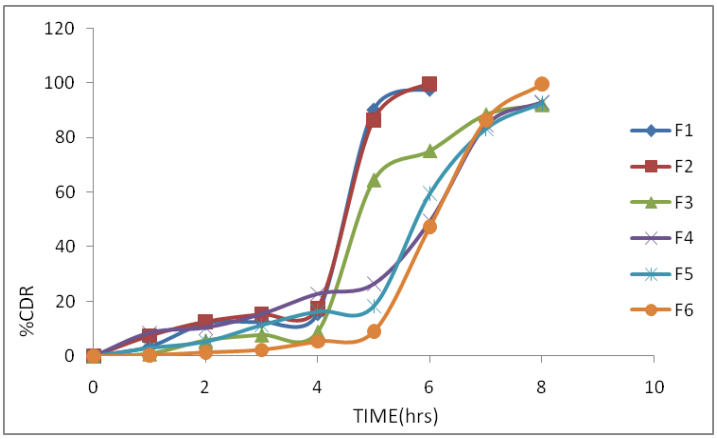
FTIR Spectrum of drug and polymers



Graph representing disintegration time for treated capsules

Table 3: Disintegration time of Nitrendipine IR Tablets

Formulation code	Disintegration time (minutes)±SD
N1	1.38±11
N2	1.22±15
N3	0.50±12
N4	1.54±17
N5	0.55±12
N6	0.41±15



In Vitro Drug Release Profiles of F1-F6

4. CONCLUSION

This system can be considered as one of the promising formulation technique for preparing colon specific drug delivery systems and in Chronotherapeutic management of hypertension. From the evaluation studies it was concluded that it is possible to formulate Nitrendipine colon targeted drug delivery system by the design of time and pH dependent modified chronopharmaceutical formulation.

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