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Formulation and *in vivo* Evaluation of Chronomodulated Drug Delivery of Nimodipine

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ABSTRACT

Chronotherapy has been emerging as a novel technology in the field of pharmaceutical research. Delivery of drugs with respect to the circadian rhythm has gained greater importance in the diseases such as diabetes, asthma and hypertension in producing maximum therapeutic action. Present study focus on the formulation and evaluation of Nimodipine pulsatile release tablets with the incorporation of Eudragit pH sensitive polymers used for the chronotherapy of hypertension. Pharmacologically Nimodipine is an anti-hypertensive agent that acts by blocking the L and N-type calcium channels. Evaluation parameters for Nimodipine tablets included friability, drug content, bulk and tapped density, angle of repose and Carr's index and drug release *in vitro* and *in vivo*.

Keywords: Chronotherapy, circadian variation, hypertension, press coated tablets, pulsatile.

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INTRODUCTION

Development of chronotherapy as a novel strategy in drug delivery systems altered the therapeutic approach for various serious diseases such as hypertension, congestive heart failure, stroke, cancer, type-2 diabetes, ulcer, asthma, arthritis and hypercholesterolemia. The onset of symptoms for these diseases alters with the day & night cycle which is considered as a major cause for the evolution of chronopharmacology. Chronopharmacotherapy is based on the circadian rhythms involved in the body through which the drug is released at a pre-determined time that facilitates a beneficial therapeutic effect. [1-3] Drugs with higher first pass effect and drugs that require dosing during the night can be modulated as chronotherapeutic agents which deliver complete release of drug after a delayed time. [4] Chrono modulating system is otherwise called pulsatile or sigmoidal release system which is analogous to biological rhythm. [5] These systems release the drug at the required time and at required concentration at the site of action. [6] Pulsatile systems are beneficial in treating diseases which require a patterned release of drug. [7]

Nimodipine a specific calcium channel blocker at L & N-type calcium channels is used as an anti-hypertensive agent that causes arteriolar and venal dilatation leading to a fall in the pressure of capillary bed. [8-10]

Table 1: formulation of Pulsatile Release Tablet of Nimodipine

Formulation ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nimodipine	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Croscarmellose sodium	2	4	6	8	10	12	-	-	-	-	-	-	-	-	-	-	-	-
PVP k30	-	-	-	-	-	-	1	2	4	5	6	7	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	2	4	6	8	10	12
MCC	84	82	80	78	76	74	85	84	82	81	80	79	84	82	80	78	76	74
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120	120

Usually, between 4:00 am to noon human body releases certain hormones which not only enhances the energy and morning alertness but also raises the blood pressure which is considered as a cause for stroke. [11] This condition can be treated by employing pulsatile release systems that releases a higher concentration of drug in the morning and less amounts during the night which is why the primary aim of the present work is the in vivo evaluation of chronomodulated drug delivery of Nimodipine.

MATERIALS AND METHODS

Nimodipine was received as a gift sample from Chandra labs Hyderabad. Super disintegrants such as PVP k30, Croscarmellose sodium and MCC, magnesium stearate talc were procured from Vijlak Pharma Ltd. and Hetero drugs. pH sensitive polymer Eudragit S 100 were received from Chandra labs.

Preparation of Nimodipine core tablet by direct compression method

Nimodipine along with all other excipients were triturated in mortar and pestle and sieved with sieve #60. They were weighed for the preparation of 50 tablets which are blended followed by the final addition of magnesium stearate (lubricant) and talc (glidant). This mixture was placed in cemach rotary tablet punching machine and compressed into 30 mg tablets with 5 mm flat surface punches using direct compression where the total weight of the tablet was maintained at 120 mg.

Eudragit L-100 weighed at 6.5, 12.5 and 24.5 g was placed into 100 ml beaker to which 50 ml of acetone was added and mixed for 10 minutes followed by the addition of remaining 50 ml acetone. This produces a Eudragit S100 coating solution of 12.5% (w/v) which would release the drug at acidic pH 6-7.

Coating was done by using the standard coating pan, by atomizing the polymeric coating solution through the means of spray gun. The scale-up variables including pan loading, pan speed, number of spray guns, spray rate, and inlet airflow etc. were considered during the preparation process. Nimodipine tablet of approximately 50 were taken and placed in pan coater at 30 rpm at 50°C temperature and coating was carried out with spraying method and dried with same.

A standard coating pan was used where, about 50 tablets of Nimodipine tablets were taken and coated with coating solution by using spray gun atomizer at 30 rpm and 50°C temperature. The scale-up variables such as pan loading, pan speed, number of spray guns, spray rate, and inlet airflow etc. were taken into consideration.

In-vitro release studies

USP dissolution apparatus II (paddle type) is used to measure the in-vitro drug release of pulsatile release capsules. The dissolution studies were carried out in 0.1N HCl for 2 hours, then 4 hrs in phosphate buffer of pH 6.8 and finally 1 hour in phosphate buffer of pH 7.4, at speed of 50 rpm which is maintained at 37 ± 0.5°C. 5 ml samples of were withdrawn at regular intervals and the same amount is replaced with buffer for every withdrawal. Samples were analyzed at 255 nm for Nimodipine by using UV-spectrophotometer and the amount of drug present in the sample was calculated by constructing a calibration curve.

In vivo study Pulsatile tablets of Nimodipine

Twelve New Zealand white healthy rabbits of either sex (2-3 Kg) were selected and maintained at room temperature 25°C, RH 45% and 12 h alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. This protocol was approved by the institutional animal ethics committee **(IAEC NO: P38/VCP/2017/24/Rabbits).**

In vivo Study design [12]

Rabbits were randomly divided into two groups of 6 animals. Pulsatile Nimodipine tablets (optimized formulation F10) were administered to one group (Group A) and pure drug was administered to the other group (Group B) with an equivalent dose to animal body weight. Approximately 0.5 ml of blood samples were withdrawn from marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24 h after dosing. Blood samples should be mixed with heparin and centrifuged at 5000 rpm in cooling centrifuge for 5 minutes and the plasma was separated and stored at -20°C for further analysis.

Preparation of Plasma Samples for HPLC Analysis

Plasma samples (0.5 mL) were treated with 2.5 ml of ice-cold absolute ethanol to precipitate the proteins and ethanol was transferred into a clean tube after centrifugation. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation at 5000-6000 rpm for 10 min, acetonitrile was added to the ethanol and the organic mixture was slightly dried by a steam of nitrogen at room temperature. Then, samples were reconstituted in

200µ1 of 70% of acetonitrile and 30% water for HPLC analysis.

Determination of Nimodipine in Rabbit plasma by HPLC method

In this HPLC method, samples were analyzed using Phenomenex C_{18} (250 mm × 4.6 mm, 5.0µm) column and mobile phase composed of acetonitrile: methanol in the ratio of 50:50 (v/v) at a flow rate of 1 mL/min and detected by UV detector at 237 nm. The retention time Nimodipine (internal standard) was found to be 7.50 min respectively.

Pharmacokinetic Analysis

Various pharmacokinetic parameters such as area under the curve [AUC], elimination half-life ($t_{½}$), Volume of distribution (V_d), total clearance (Cl_T) and mean residence time were performed by a non-compartmental analysis and the values were expressed as the mean ± SD. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test with $p<0.05$.

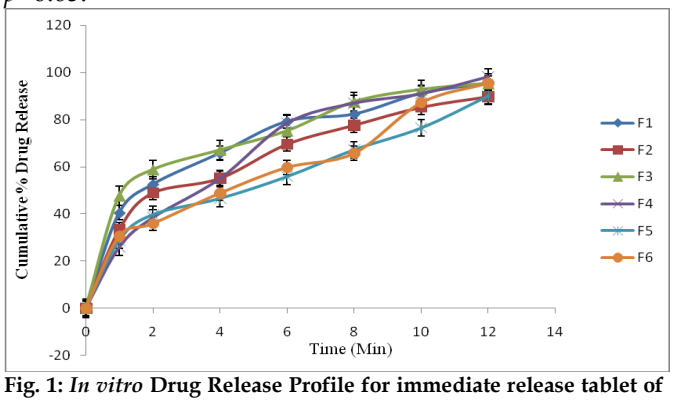

Fig. 1: *In vitro* Drug Release Profile for immediate release tablet of Nimodipine F1-F6

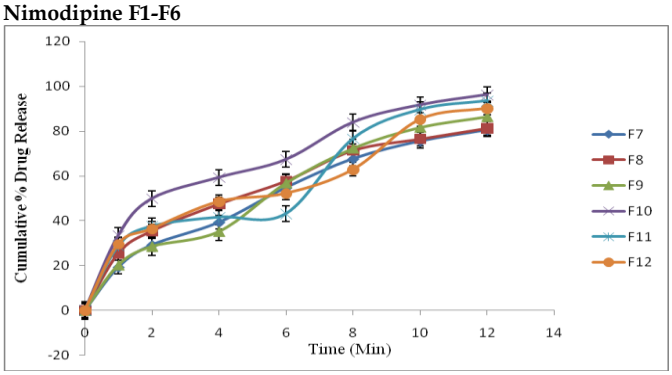

Fig. 2: *In vitro* Drug Release Profile for immediate release tablet of Nimodipine F7-F12

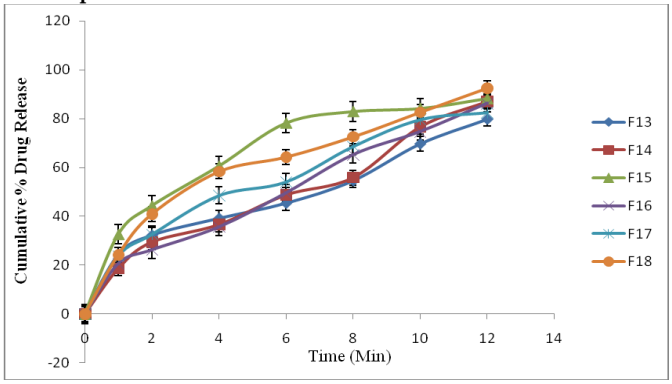

Fig 3: *In vitro* Drug Release Profile for immediate release tablet of Nimodipine F13-F18

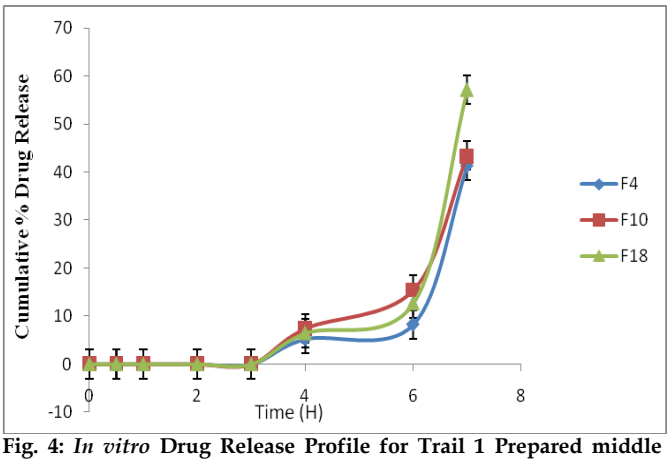

Fig. 4: *In vitro* Drug Release Profile for Trail 1 Prepared middle active layer of Nimodipine tablets F4, F10, F18

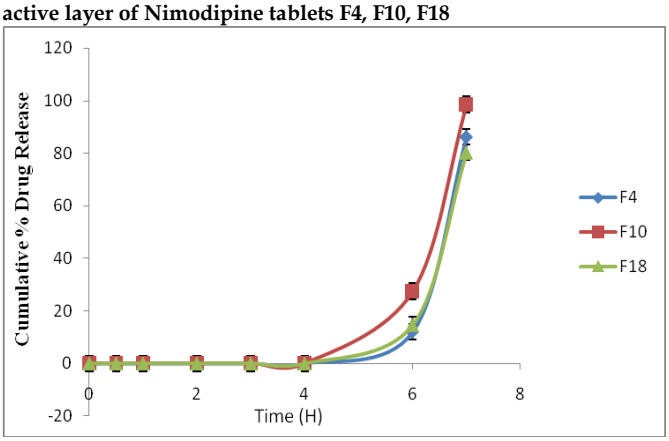

Fig. 5: *In vitro* Drug Release Profile for Trail 2 Prepared middle active layer of Nimodipine tablets F4, F10, F18

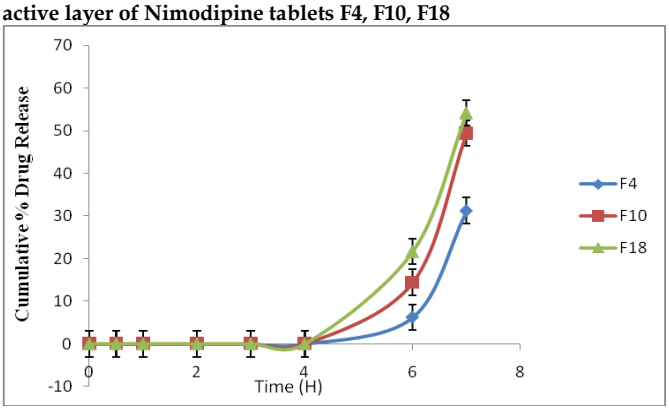

Fig. 6: *In vitro* Drug Release Profile for Trail 3 Prepared middle active layer of Nimodipine tablets F4, F10, F18

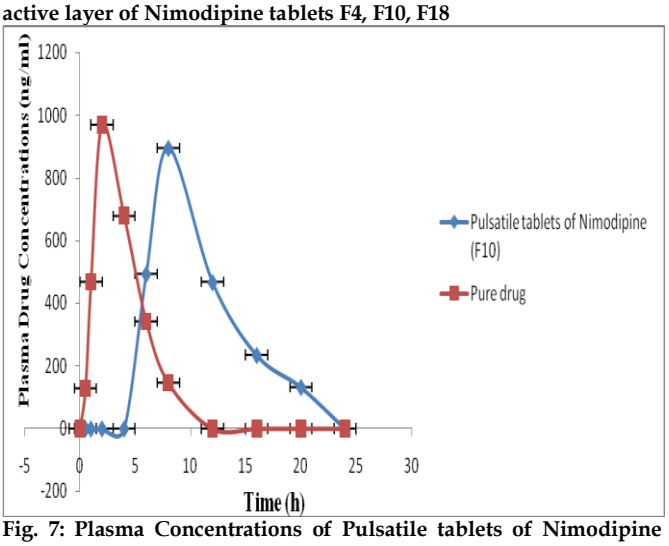

Fig. 7: Plasma Concentrations of Pulsatile tablets of Nimodipine (F10) and active drug at different time intervals (Mean ± SD, n = 6)

Table 2: Bulk density, Tapped density, Carr's index, Hausner's ratio, Angle of repose, % drug content

Formulation code	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose	Carr's index	Hausner's ratio	% Drug content
F1	0.66 ± 0.05	0.67 ± 0.08	24.34 ± 0.44	09.23 ± 1.12	1.13 ± 0.24	97.23 ± 1.23
F2	0.51 ± 0.07	0.68 ± 0.06	22.67 ± 0.31	08.23 ± 1.42	1.11 ± 0.10	98.04 ± 1.03
F3	0.55 ± 0.06	0.64 ± 0.00	26.54 ± 0.41	10.12 ± 0.8	1.13 ± 0.20	96.56 ± 0.94
F4	0.56 ± 0.09	0.66 ± 0.08	25.89 ± 0.55	11.34 ± 0.6	1.14 ± 0.24	98.11 ± 0.63
F5	0.52 ± 0.03	0.66 ± 0.07	22.56 ± 0.0.57	12.23 ± 0.12	1.11 ± 0.32	95.23 ± 0.81
F6	0.51 ± 0.08	0.63 ± 0.06	25.30 ± 0.30	11.23 ± 0.25	1.12 ± 0.30	96.45 ± 0.32
F7	0.52 ± 0.03	0.61 ± 0.05	22.56 ± 0.57	10.34 ± 0.31	1.14 ± 0.20	95.11 ± 1.17
F8	0.58 ± 0.03	0.68 ± 0.09	23.67 ± 0.60	09.11 ± 0.24	1.12 ± 0.25	98.23 ± 0.45
F9	0.56 ± 0.06	0.67 ± 0.03	25.56 ± 0.44	09.45 ± 1.15	1.13 ± 0.70	97.13 ± 1.17
F10	0.66 ± 0.05	0.52 ± 0.05	21.06 ± 0.31	13.45 ± 1.3	1.09 ± 0.20	96.23 ± 0.49
F11	0.54 ± 0.09	0.58 ± 0.07	22.34 ± 0.37	14.23 ± 1.5	1.13 ± 0.16	98.97 ± 0.95
F12	0.57 ± 0.06	0.64 ± 0.01	25.99 ± 0.70	11.34 ± 1.25	1.12 ± 0.12	98.45 ± 0.35
F13	0.57 ± 0.07	0.68 ± 0.05	23.14 ± 0.50	09.67 ± 1.55	1.09 ± 0.14	99.85 ± 0.24
F14	0.59 ± 0.05	0.59 ± 0.08	22.09 ± 0.57	10.23 ± 1.55	1.14 ± 0.15	99.18 ± 0.13
F15	0.57 ± 0.08	0.66 ± 0.04	24.78 ± 0.77	10.45 ± 1.5	1.15 ± 0.15	99.25 ± 1.21
F16	0.58 ± 0.00	0.64 ± 0.06	23.45 ± 0.80	09.68 ± 1.3	1.18 ± 0.18	97.45 ± 1.30
F17	0.51 ± 0.04	0.68 ± 0.07	21.89 ± 0.86	09.47 ± 1.09	1.12 ± 0.15	99.94 ± 1.31
F18	0.54 ± 0.06	0.61 ± 0.09	23.05 ± 0.75	14.99 ± 1.20	1.14 ± 0.15	98.56 ± 1.36

Above parameters are communicated as Average ± Standard Deviation; (n=3)

Table 3: Comparison of PK parameters of pulsatile tablets of Nimodipine (F10) and Pure Drug

Parameters	Pulsatile tablets of Nimodipine (F10)	Pure Drug
C_{max} (ng/ml)	895.20 ± 7.05	968.75 ± 8.78
AUC $_{0\text{-}t}$ (ng h/ml)	3940.30 ± 4.11	3240.52 ± 4.01
$AUC_{0\text{-}\infty}$ (ng h/ml)	4412.97 ± 5.14	3842.78 ± 2.02
T_{max} (h)	7.99 ± 0.12	2.01 ± 0.14
$t_{1/2}$ (h)	10.15 ± 0.05	4.50 ± 0.014
MRT (h)	10.28 ± 4.85	4.014 ± 2.34

RESULTS AND DISCUSSION

Nimodipine pulsatile release tablets were made by incorporating various types of super disintegrants such as PVP k30, sodium starch glycolate and croscarmellose at varying concentrations. Ideal formulations (F4, F10 and F18) were selected for evaluating drug dissolution studies. The three formulations were coated with 6.5, 12.5 and 24.5 g coating solutions in trail 1, 2 and 3 respectively where trail 2 presented satisfactory release. 5% PVP k30 polymer showed better drug release when compared to Croscarmellose and sodium starch glycolate. Formulations that contained 8% croscarmellose presented a maximum drug release of 84.24% after seventh hour where formulations with 5% PVP presented 98.42% drug release. A lag time of 6 hrs was achieved with Eudragit S-100. F10 was chosen as the best formulation based on the drug release pattern. Dissolution profiles were showed in Figure 1-6.

The pulsatile release of formulated Nimodipine tablets was studied in rabbits after oral administration. *In-vivo* evaluation studies were performed based on the uniform and reliable results of *in-vitro* drug release studies. Various pharmacokinetic parameters were compared to obtain mean plasma drug concentration curve versus time. From each animal's drug plasma profile C_{max} and T_{max} of the three formulations (Table 3) were obtained. Animals that received Nimodipine pulsatile tablets have a $AUC_{0\text{-}t}$ of 3940.30 ± 4.12 ng/ml/hr and those which received pure drug has an $AUC_{0\text{-}24}$ of 3240.52 ± 4.02 ng/ml/hr. *In vivo* release of pulsatile tablets was based on the mean residence time where an increase in the MRT from 4.014 to 10.28 h was a result of alteration in drug release and elimination. The average T_{max} for pure drug Nimodipine was found to be 2.00 ± 0.14 h and that of pulsatile drug was 8.00 ± 0.12 h. Pure drug presented a low T_{max} than pulsatile formulation indicating a rapid absorption. Table 3 reveals a lag time of 3 hrs for pure and pulsatile Nimodipine before finally showing maximum concentration (C_{max}) at 8 hours that correlated with the *in-vitro* drug release of 8 hours and the statistically difference between the groups was significant at $p \leq 0.05$.

Nimodipine pulsatile release tablets were prepared based on the chronopharmacology of hypertension as 120 mg tablet. From the formulations prepared, F10 showed a beneficial lag time of 7 hours and drug release within 15 minutes which was found to be used in treating morning stroke in hypertensive patients.

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