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Research Article

FORMULATION AND EVALUATION OF CHRONOMODULATED DRUG DELIVERY OF NIMODIPINE

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ABSTRACT

The objective of this study was to design and developed a rupturable coating type of pulsatile press coated tablet, which releases drug early in the morning hours. This delivery system was helpful to control an early morning surge in Blood Pressure because cardiovascular events occur more frequently in the morning. This delivery system would be useful for the prevention of cardiovascular events in hypertensive patients. Initially core tablet was prepared by using Nimodipine as a drug, and different concentration of cross carmellose sodium, Poly vinyl pyrrolidone k30 as a superdisintegrant by the direct compression method. Core tablet was press coated by using Eudragit S-100 ratios as a press coating polymers. In-vitro drug release was found to be 98 % from coated tablets in 15 min after 7 hrs lag time. FT-IR spectra revealed that there is no chemical incompatibility between the drug and other excipients. Scanning electron micrograph of optimized tablet shown that the thickness level in the coating. The results concluded the programmable pulsatile release has been achieved from coated tablets after a lag time of 5 hrs, which is consistent with the demands of the chronotherapeutic drug delivery and increasing bioavailability.

KEYWORDS: *Nimodipine, Carmellose Sodium, Poly Vinyl Pyrrolidone k30, Eudragit S-100.*

INTRODUCTION

Oral route of drug delivery is typically considered the favored and the most preferable having the highest degree of patient compliance. There are many conditions and diseases where sustained release formulations do not show good efficiency such conditions demand the release of drug after a lag time i. e form of pulse. If the timing of dosage regimen is adjusted according to cyclic rhythm of diseases effective management can be achieved [1, 2]. The rationale of the present study is to develop a drug delivery system which provides required dose at the required time without any failure. Pulsatile drug delivery system solves this problem, a single capsule ingested at the bedtime releases drug early in the morning which gives protection from cardiovascular events. High blood pressure or hypertension as a disease is known medically most common chronic illness [3-6].

Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount [7]. The concept of chronotherapeutics originates from the finding of the major disease conditions such as asthma, cardiac disorders, allergic rhinitis, and arthritis following circadian example of symptom outburst. Nimodipine is a calcium channel blocker originally developed for the treatment of high blood pressure. It is not frequently used for this indication, but has shown good results in preventing a major complication of subarachnoid hemorrhage (a form of cerebral hemorrhage) termed vasospasm; this is now the main use of Nimodipine.

MATERIALS AND METHODS

Materials: Nimodipine was chosen as a model drug and obtained from Chandra labs as a gift sample. Poly vinyl pyrrolidone k30, Croscarmellose Sodium, Microcrystalline cellulose used as super disintegrants , magnesium stearate, talc obtained from Vijlak Pharma Limited, and obtained from Hetero Drugs , Eudragit S 100, used as P^H sensitive polymers and obtained from Chandra labs.

Pre-Formulation Studies:

Compatibility studies:

Compatibility of drug Nimodipine with excipients was established by IR absorption spectral analysis. Its spectral analysis of pure Nimodipine, pure excipients and combination of the drug with excipients carried out to investigate any change in chemical composition of the drug after combining with excipients.

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Method:

The spectrum analysis of pure drug and physical mixture of drug and different excipients which are used for preparation of granules were studied by FTIR. FTIR spectra were recorded by preparing potassium bromide (KBr) disks using a shimadzu corporation (japan) facility (model-8400S). Potassium bromide (KBr) disks were prepared by mixing few mg of sample with potassium bromide by compacting in a hydrostatic press under vacuum at 6-8 tons pressure. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000cm^{-1} to 500cm^{-1} in a scan time of 12 minutes. The resultant spectrum was compared for any spectral for any spectral changes. They were observed for the presence of characteristics peaks for the respective functional group in the compound.

Spectroscopic studies:

Preparation of standard stock solution:

Standard drug solution of Nimodipine was prepared by dissolving 10 mg of Nimodipine in 10ml of pH 6.8 Phosphate buffer containing 0.05 % w/v of SLS in volumetric flask to give stock solution of 1000 µg/ml. 1ml of stock solution was withdrawn and further diluted with pH 6.8 Phosphate buffer containing 0.05 % w/v of SLS solution to give stock solution of 100 µg/ml concentration.

Preparation of calibration curve:

Calibration curve was prepared in pH 6.8 Phosphate buffer containing 0.05 % w/v of SLS solution at λmax of 238.5 nm by using Jasko UV-Visible spectrophotometer. For this stock solution of 100µg/ml was prepared. Serial dilutions of 5, 10, 15, 20, 25 and 30 µg/ml were prepared and absorbance was taken at 238.5 nm. The solutions were scanned in the range of 200-400 nm against blank. The calibration curve was plotted.

Formulation development:

1. Preparation of Nimodipine core tablet by direct compression method.
2. Coating for core tablet.

Preparation of Nimodipine core tablet by direct compression method:

All the ingredients (Nimodipine, Poly vinyl pyrrolidone k30, Croscarmellose Sodium, Microcrystalline cellulose) were triturated individually in a mortar and passed through #60sieve. Then required of all ingredients were weighted for a batch size of 50 tablets and mixed Uniformly in a mortar except talc and magnesium stearate. Finally magnesium stearate and talc were added as lubricant and glident. This uniformly mixed blend was compressed in to tablets containing 30 mg drug using 5mm flat face surface punches on a cemach rotary tablet machine by direct compression method total weight of tablet was kept 100mg.

Three different weights 6.5gms, 12.5gms and 24.5grms of Eudragit L-100 was weighed and transferred into 100mL beaker to it 50mL of acetone was added and it was thoroughly mixed for 10min then add remaining amount 50mL of acetone to it then it forms 12.5%(w/v) of Eudragit S100 coating solution. This coating will be dissolved in acidic pH and releases the drug at pH 6-7.

It was done by using the standard coating pan, where fixed numbers of tablets were coated each time 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. About 50 tablets of Nimodipine tablet were taken and allow to coatings in pan coater at 30 rpm and 50oC temperature. Coating was carried out with praying method and dried with same.

Table No. 1: Formulation of Pulsatile Release Tablet of Nimodipine

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	-	-	-	-	-	-	-	-	-	-	-	-
Poly vinyl pyrrolidone k30	-	-	-	-	-	-	1	2	4	5	6	7	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	-	-	-	2	4	6	8	10	12
Micro crystalline cellulose	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

Coating Solution:

Table No. 2: Coating solution (Trail 1)

S.NO	INGREDIENTS	QUENTITY
1	Eudragit S-100	3.5g
2	Acetone	100Ml

Table No. 3: Coating solution (Trail 2)

S.NO	INGREDIENTS	QUENTITY
1	Eudragit S-100	12.5g
2	Acetone	100Ml

Table No. 4: Coating solution (Trail 3)

S.NO	INGREDIENTS	QUENTITY
1	Eudragit S-100	24.5g
2	Acetone	100Ml

Evaluation for formulation:

Pre formulations like Bulk density, Tapped density, Angle of repose were studied and post formulation: Weight variation, Thickness, Hardness, Friability, Content uniformity, *In-vitro* Disintegration time, *In-vitro* dissolution studies, Accelerated stability studies were studied.

***In-vitro* Disintegration time:**

The USP device to rest disintegration was six glass tubes that are"3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in one liter beaker of buffer at 37 ± 2^{0}C, such that the tablets remain below the surface of the liquid on their upward Movement and descend not closer than 2.5 cm from the bottom of the beaker.

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

In-vitro drug release of PDDS capsule was determined using USP dissolution apparatus II (paddle type) (electro lab TDT-08L). The dissolution studies were carried out in 0.1N HCl for 2 hrs, then 4 hrs in pH 6.8 phosphate buffers and finally 1hr in pH 7.4 phosphate buffer at every specific interval 5mL sample were withdrawn and it was replaced by fresh medium with respect to medium at the time to maintain the volume constant. After appropriate dilution, the sample solution was analyzed at 255 nm for Nimodipine by a UV-spectrophotometer. The amount of drug present in the sample was calculated with the appropriated calibration curve. Also the study was carried out in triplicates.

Dissolution apparatus: USP dissolution apparatus II (paddle type) (electrolab TDT- 08L).

Dissolution media: 0.1 N HCl for 2 hrs, pH 6.8 phosphate buffer for 4 hr, pH 6.8 phosphate buffer for 1 hr.

Volume of dissolution media: 900mL.

Aliquot withdrawn: 5mL.

Revolutions for minute (speed): 50.

Bath temperature: 37±0.5^{0}C.

Kinetic Data /Model Fitting of Drug Release from Formulated Matrix Tablets:

Drug release mechanisms and kinetics are two characteristics of the dosage forms which play an important role in describing the drug dissolution profile from a controlled release dosage forms and hence there in vivo performance. The diffusion data obtained is fitted to mathematical models and the best fit is obtained to describe the release mechanism of the drug.

A number of mathematical models have been developed to describe the drug dissolution kinetics from controlled release drug delivery system as follow as,

- Higuchi (cumulative % drug release versus square root of time);
- First order (log cumulative % drug remaining versus time),
- Zero order (cumulative % drug release versus time) and
- Peppas and Korsemeyer model (log cumulative % drug release versus log time).

Accelerated stability studies:

Stability of drug has defined by Lachman L (1987) the ability of particular formulation, in specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug products varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-tested and self-life to be established.

ICH specific the length of study and storage conditions: Accelerated testing 40^{0}C ± 2^{0}C / 75% RH ± 5% for 30 days.

Procedure:

In the present study, stability was carried out at 40^{0}C ± 2^{0}C / 75% RH for a specific time up to 30 days for selected formulation.

RESULTS AND DISCUSSION

Pre-Formulation Studies:

Compatibility study:

IR interpretation of Nimodipine PR tablet: Spectrum of prepared Nimodipine pulsatile release tablets were compared the pure drug IR spectra, showed no significant change in the appearance of characteristics peaks of pure drugs spectra. This indicates that the drug is compatible with formulation components. The spectra are shown below

Table No. 5: Determination of FTIR Functional groups of Nimodipine

S. No	Functional Groups	Reference Peaks (Cm $^{-1}$)	Observed Peaks (Cm $^{-1}$)
1	**N-H 1^0 stretching vibration**	2312-3389	2387
2	**N-H 1^0 stretching vibration**	2143-2150	2148
3	**C=N stretching**	1725-1739	1730

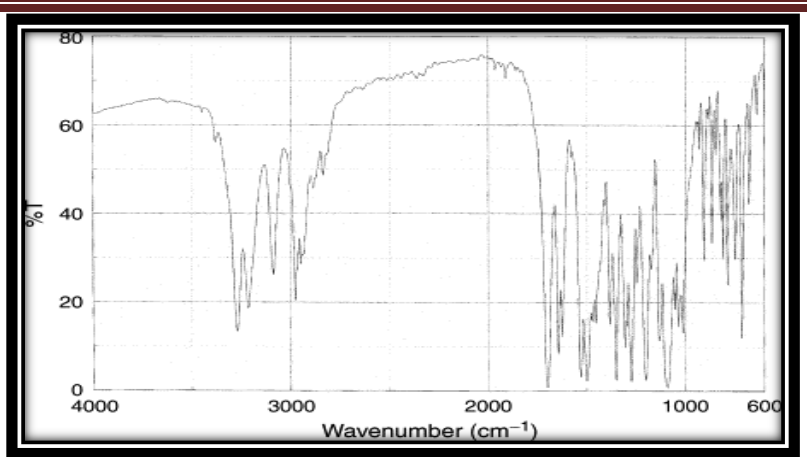

Fig. 1: FTIR spectrum of pure drug

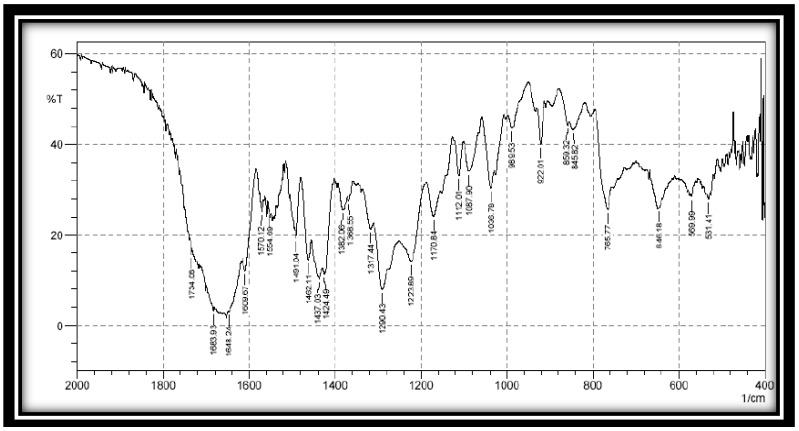

Fig. 2: FTIR spectrum of pure drug + Poly vinyl pyrrolidone k30

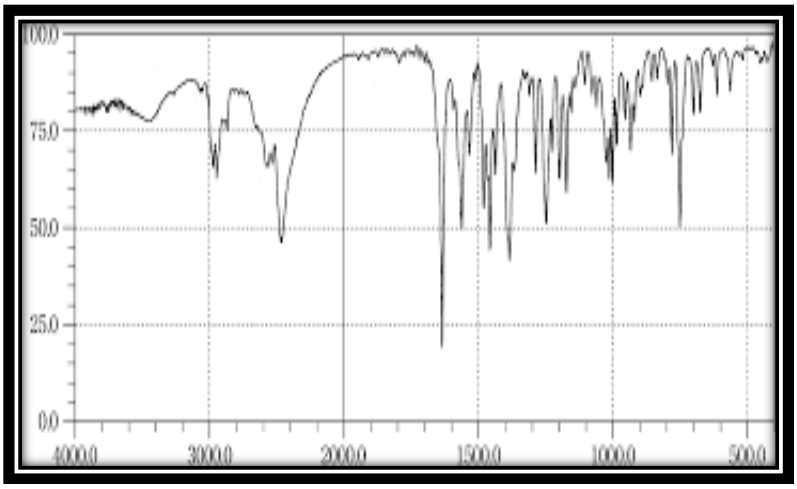

Fig. 3: FTIR spectrum of pure drug + Croscarmellose Sodium

DSC:

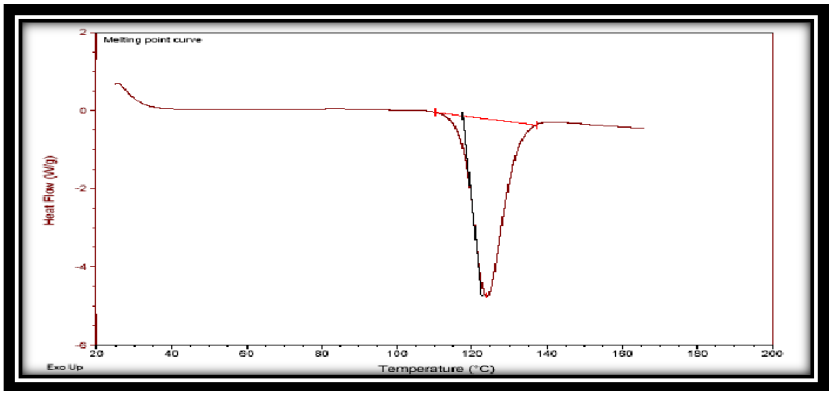

Fig. 4: DSC of Nimodipine Pure drug

The thermal behavior of Nimodipine was studied using DSC Thermogram. The DSC Thermogram of Nimodipine exhibited an endothermic peak at 125.5 ^{o}C.

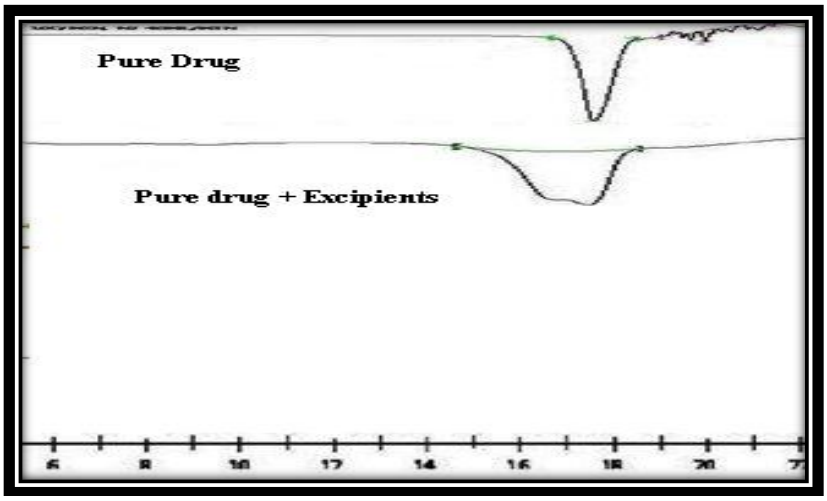

Fig. 5: DSC of Nimodipine + Excipient mixture

The thermal behavior of drug and physical mixture of drug and polymer was studied by using DSC Thermogram. DSC thermogram of drug exhibited characteristic peak at 125.5^{o}C.

Analytical method development:

Determination of λ_{max} of drug solution:

λ_{max} of Nimodipine was determined using UV spectrophotometer against pH 6.8 phosphate buffer as blank. Maximum absorbance was observed at 238.5 nm (λ_{max}) of prepared sample. This was considered as λ_{max} of solution and absence of any impurity must be ensured.

Preparation of standard stock solution of Nimodipine drug:

Working standard stock solution of Nimodipine was prepared as discussed in Methodology. From working standard stock solution of the drug, working standard stock solution was prepared from which working dilutions of 5, 10, 15, 20, 25, 30 µ g/mL were prepared and analyzed for absorbencies at 238.5 nm against pH 6.8 phosphate buffer as blank.

Standard calibration curve of Nimodipine:

Linearity of prepared solution was found in the range of 5 to 30µg/mL. From regression analysis value of co-efficient of regression (R^2) was 0.9998. This confers the range selection was satisfactory and follows Beer-Lambert's law.

Kinetic Analysis of Dissolution Data:

The release rate kinetic data of optimized formulation PR8 of matrix tablets are shown in **Table 7.**

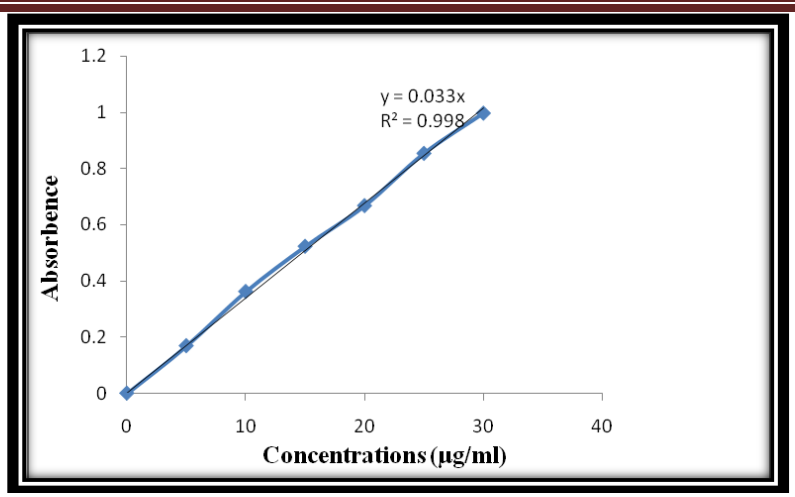

Fig. 6: Standard graph of Nimodipine 6.8 phosphate buffer

Table No. 6: Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose, %drug content

Formulation Code	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose	Carr's index	Hausners 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	09.681.3	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)

***In vitro* dissolution study:**

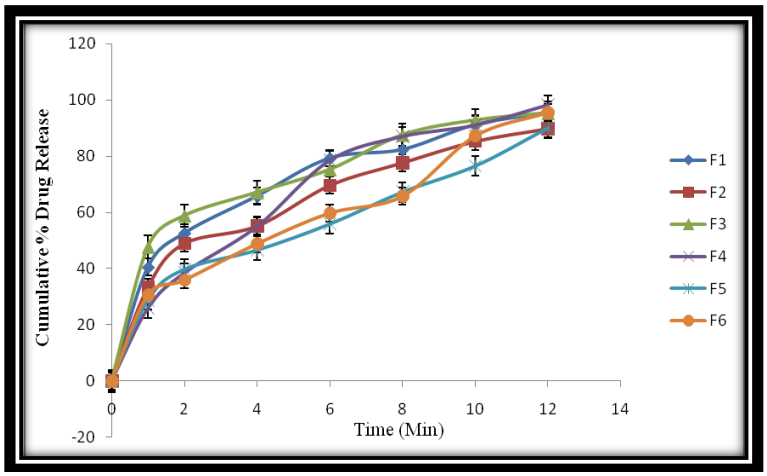

Fig. 7: in *vitro* Drug Release Profile for immediate release tablet of Nimodipine F1-F6

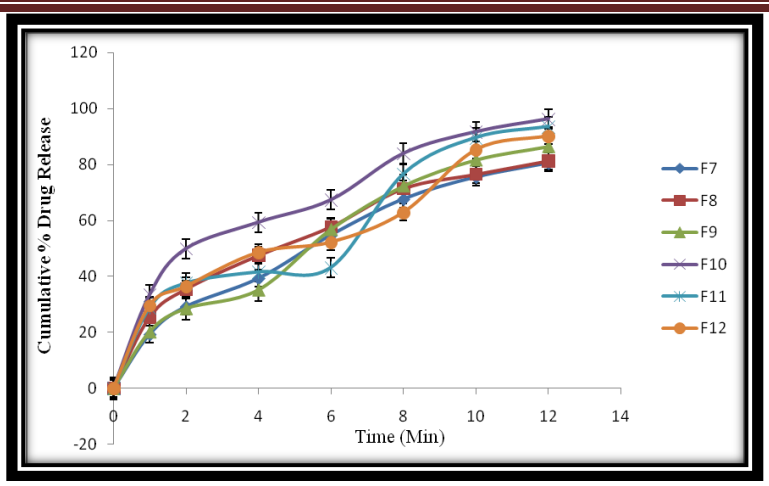

Fig. 8: *in vitro* Drug Release Profile for immediate release tablet of Nimodipine F7-F12

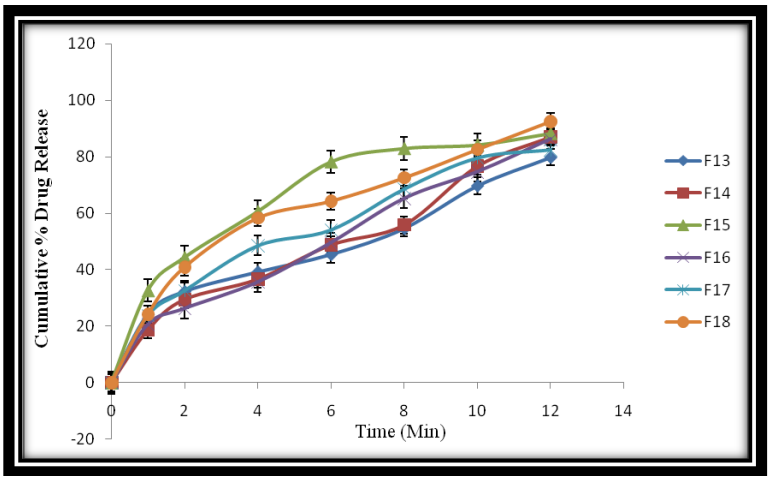

Fig. 9: *in vitro* Drug Release Profile for immediate release tablet of Nimodipine F13-F18

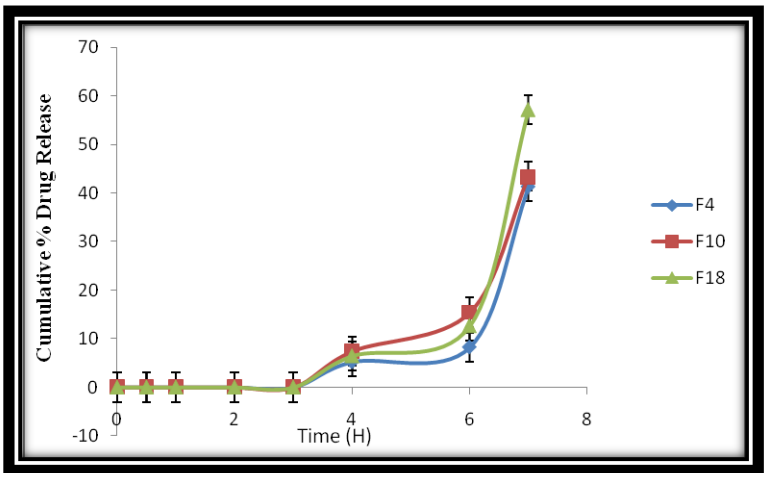

Fig. 10: *in vitro* Drug Release Profile for Trail 1 Prepared middle active layer of Nimodipine tablets F4, F10, F18

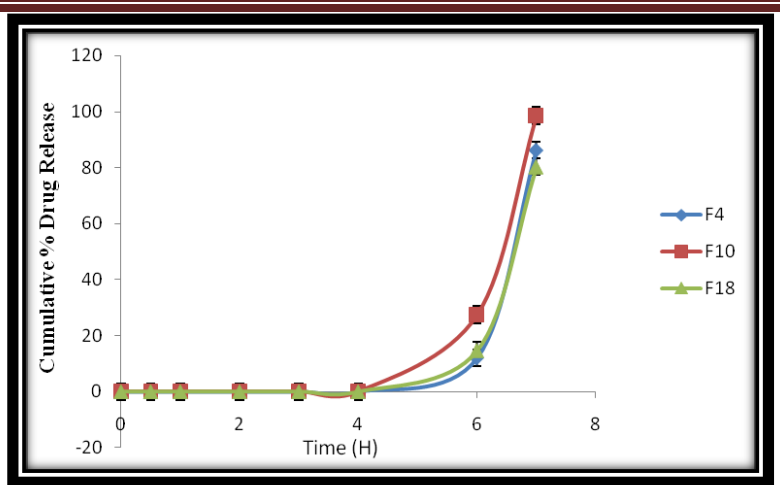

Fig. 11: *in vitro* Drug Release Profile for Trail 2 Prepared middle active layer of Nimodipine tablets F4, F10, F18

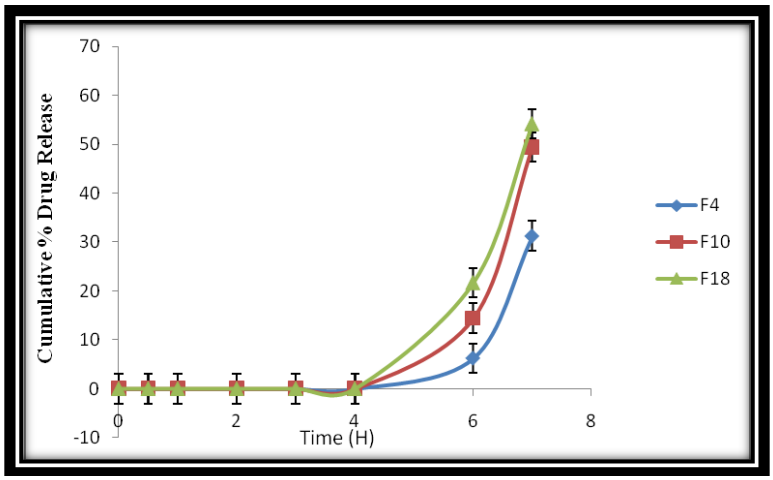

Fig. 12: *in vitro* Drug Release Profile for Trail 3 Prepared middle active layer of Nimodipine tablets F4, F10, F18

Table No. 7: Comparison of Kinetic Data of Optimized Formulation F10

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	n	R^2	n	R^2	n	R^2	N
F4	0.919	8.689	0.994	0.140	0.937	29.01	0.709	2.475

Table No. 8: Stability studies

Parameters	Time (Months)			
	0 Initial	1st month	2nd month	3rd month
Strength	No Change	No Change	No Change	No Change
Color	No Change	No Change	No Change	No Change
Drug Content (%)	98.23 ± 1.40	99.23 ± 2.98	98.23 ± 1.48	97.94 ± 2.54
***In-vitro* drug release**	99.24	99.54	99.23	99.42

DISCUSSION

The immediate release tablets were prepared by using different types and different concentration of superdisintegrating agents like Croscarmellose, Poly vinyl pyrrolidone k30 and sodium starch glycolate. For immediate release tablets dissolution studies were performed in that three best formulations were selected (F4, F10, F18) for pulsatile release formulation. Selected three formulations were coated with three trails were of different weights of coating material used for trail 1 6.5gm of coating material was used, trail 2 12.5gm of coating material was used and trial 3 24.5gm of coating material was used. Trial 2 was showed good release pattern. The polymer Poly vinyl pyrrolidone k30 shows good drug release profile than Croscarmellose and sodium starch glycolate. The 5% Poly vinyl pyrrolidone k30 shows better results. Formulations prepared by using Croscarmellose 8 % showed the maximum amount of drug release 84.24%after 7th hour in pulsatile release formulations. Formulations prepared by using Poly vinyl pyrrolidone k30 5% showed the maximum amount of drug release 98.42% after 7th hour in pulsatile

release formulations. The coating polymer Eudragit S-100(50% weight gain) produces the lag time of 6hrs. From the above drug release profile the F10 was selected as best formulation. The corresponding plot (Log Cumulative Drug Release Vs Log time) for Korsmeyer – Peppas equation indicated a good linearity (r2=0.709). The diffusional exponent "n" was 2.475, which appears to indicating the release of drug polymer matrix formulations was found to be super case-II transport, i.e., drug release by more than one mechanism. Super case II transport generally refers to erosion of polymeric chain and anomalous transport. Drug- excipient interactions play a crucial role with respect to the stability and potency of the drug. FT-IR techniques have been used to study the physical and chemical interaction between drug and excipients used. There was no significance difference between the absorption peaks of pure drug and optimized formulation. The results concluded that there was no interaction between pure drug and excipients. The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation. The formulation was found to be stable, with no change in the weight variation, thickness, and friability, hardness, drug content and *In vitro* drug release pattern.

CONCLUSION

A chronotherapy based pulsatile release tablets of Nimodipine was successfully developed, Taking into consideration the chronotherapy of hypertension, pulsatile release tablet with 120mg tablet. Formulation F10 gave satisfactory release lag time of 7 drug release within 15min. Hence this formulation can be helpful for the patients with morning surge.

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