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FORMULATION AND EVALUATION OF CHRONOMODULATED DRUG DELIVERY OF NISOLDIPINE

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ABSTRACT

The aim of present study was to formulate and evaluate oral multiparticulate pulsatile release of nisoldipine based on chronophamaceutical approach for the treatment of hypertension. In the present study the immediate release tablets were prepared by direct compression by using various proportions of different superdisintegrants. The optimized core tablets were then coated with pH sensitive polymer Eudragit- L100. To achieve the desired dissolution profile, the coated tablets were evaluated for hardness, thickness, friability, weight variation, drug content, and disintegration time and in-vitro drug release. 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.

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INTRODUCTION

Controlled drug delivery systems [1] have acquired a centre stage in the area of pharmaceutical R &D sector. Such systems offer temporal &/or spatial control over the release of drug and grant a new lease of life to a drug molecule in terms of controlled drug delivery systems for obvious advantages of oral route of drug administration. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance. 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 is known as pulsatile release [2, 3, 4, 5.]. The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify ChrDDS compared to the conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, diabetes, cardiovascular diseases, hypercholesterolemia, ulcer and neurological diseases [6, 7.].

Circadian rhythm regulates many body functions in humans, such as metabolism, behavior, sleep patterns, and hormone production. Blood pressure also shows circadian rhythm variation and exhibits 2 times peaks of 7 pm in the evening, and 4 am in the morning. [8]

The conventional drug delivery systems releases drug immediately and requires to be taken during the peak hours of disease attack and hence it is not feasible to use such systems targeting diseases with the symptoms prevailing during early morning hours. In such cases release of drug is preferred in pulses and these systems are termed as chronomodulated pulsatile drug delivery system. [9]

The pulsatile effect, which shows the release of drug as a "pulse" after a predetermined lag time should be designed in such a way that a complete and rapid drug release should follow the lag time. [10]

Hypertension is a disease which shows circadian rhythm in the pattern of two peaks, one in the evening at about 7pm and other in the early morning between 4 am to 8 am. Conventional therapies are incapable to target those time points when actually the symptoms get worsened. To achieve drug release at two time points, chronomodulated delivery system may offer greater benefits.

Nisoldipine is a 1,4-dihydropyridine calcium channel blocker. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, Nisoldipine prevents calcium-dependent smooth muscle contraction and subsequent vasoconstriction. Nisoldipine may be used in alone or in combination with other agents in the management of hypertension.

The aim of the present investigation was to develop and evaluate an alternative, simple, orally applicable one pulse drug delivery system based on a press-coated tablet preparation.

MATERIALS AND METHODS

Materials Nisoldipine was chosen as a model drug and obtained from Chandra labs as a gift sample. Crospovidone, Croscarmellose Sodium, Microcrystalline cellulose used as superdisintegrants , magnesium stearate, talc obtained from Vijlak Pharma Limited, and obtained from Hetero Drugs , Eudragit L 100, used as pH sensitive polymers and obtained from Chandra labs.

Compatibility studies:

Compatibility of drug Nisoldipine with excipients was established by IR absorption spectral analysis. Its spectral analysis of pure Nisoldipine, 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.

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.

Melting point determination:

Melting point determination of the obtained drug sample was done by using capillary method. It is good first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by lowering as well as widening melting point range. Melting point is the temperature at which the material changes from a solid to liquid state. Pure crystalline substances have a clear, sharply defined melting point. Melting point of drug was determined by capillary tube method by using melting point apparatus.

Method:

In this methodology, a thin glass capillary tube containing a compact column of the substance to be determined is introduced into a heated stand (liquid bath or metal block) in close proximity to a high accuracy thermometer. The temperature in the heating stand is ramped at a user-programmable fixed rate until the sample in the tube transition into the liquid state. While determining a melting point, several observations and the temperatures are recorded. The accuracy of a melting point record is assured by: (a) careful sample preparation, (b) proper instrument setup, and (c) routine calibration of the instrument's temperature scale against certified melting point standards.

Sample preparation:

Careless preparation of a sample is the leading cause of inaccurate and irreproducible results in melting point determinations. Any substance being loaded into a melting capillary must be:

1. Fully dry
2. Homogeneous
3. in powdered form

The primary requirement for the good melting point determination is that the sample in a fine powder form. This makes the heat transfer into the sample more efficient and reproducible, and enhances the overall reflectivity of the sample for easier automated detection of melt. Coarse crystalline and non homogeneous samples must be crushed into a fine powder in a mortar.

To fill a capillary tube with a sample, the open end of capillary is pressed gently into the substance several times. The powder is then pushed into the bottom of the tube by repeatedly pounding the bottom of capillary against a hard surface (preferred method). Alternatively, the capillary tube can be dropped on to a table through a glass tube of ≈1 m in length. A sample packing wire can be used at the end to further compact the sample and improve the reproducibility of the measurements.

The temperature at which the materials changes from a solid to a liquid state was recorded. Melting point was determined in triplet and average and standard derivation of the values were noted.

Preparation of Nisoldipine core tablet by direct compression method:

All the ingredients (Nisoldipine, Crospovidone, Croscarmellose Sodium, Microcrystalline cellulose) were triturated individually in a mortar and passed through #60 sieve. 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 8.5 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 L100 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 Nisoldipine tablet were taken and allow to coatings in pan coater at 30 rpm and 50^{o}C temperature. Coating was carried out with praying method and dried with same.

FORMULATION TABLE:

Table 1: Pulsatile Release Tablet of Nisoldipine.

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Nisoldipine	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Croscarmellose sodium	2	4	6	8	10	12	-	-	-	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	-	-	-	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	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

COATING SOLUTION:

Table 2: Coating solution (Trail 1).

S.NO	INGREDIENTS	QUENTITY
1	Eudragit L-100	6.5g
2	Acetone	100Ml

Table 3: Coating solution (Trail 2).

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

Table 4: Coating solution (Trail 3).

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

Evaluation for formulation:

Pre formulation studies were performed like Bulk density, Tapped density, Total porosity, Angle of repose and Evaluation of pulsatile release tablets were performed like Weight variation, Thickness, Hardness, Friability, Content uniformity. [11, 12 13]

***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^{O}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 237nm for Nisoldipine 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) (electro lab TDT- 08L).

Dissolution media:

0.1N HCl for 2 hrs, pH 6.8 phosphate buffer for 4 hr, pH 7.4 phosphate buffer for 1 hr.

Volume of dissolution media:

900mL.

Aliquot withdrawn: 5mL. **Revolutions for minute (speed):** 50. **Bath temperature:** 37 ± 0.5^{O}C.

Accelerated stability studies:

Stability studies Optimized formulation was subjected to stability studies as per ICH guidelines at 30°C/65% RH and 40°C/75% RH for 3 months. Sample were taken and analyzed at time interval. Selected formulation were subjected to stability studies as per ICH guidelines sample were taken and analyzed at time interval of 15 days for 2 months [14,15]

RESULTS AND DISCUSSION

PRE-FORMULATION STUDIES

Determination of melting point:

Melting point of Nisoldipine was determined by capillary tube method and found to be 147.5^{O}C which correlates with that of standard melting point value nisoldipine.

Table 5: Melting point of Nisoldipine.

S. No	Trials	Melting Point(^{o}C)	Mean	Reference Standard(^{o}C)
1	1	147		
2	2	148	147.5^{o}c	
3	3	147		147-148

Compatibility study:

IR interpretation of Nisoldipine PR tablet:

Spectrum of prepared nisoldipine 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 6 and figure 1, 2, 3.

Table 6: Determination of FTIR Functional groups of nisoldipine.

S. No	Functional Groups	Reference Peaks Cm^{-1}	Observed Peaks Cm^{-1}
1	N-H 1^{o} stretching vibration	3382-3389	3387
2	N-H 1^{o} stretching vibration	3143-3150	3148
3	C=N stretching	1621-1629	1624

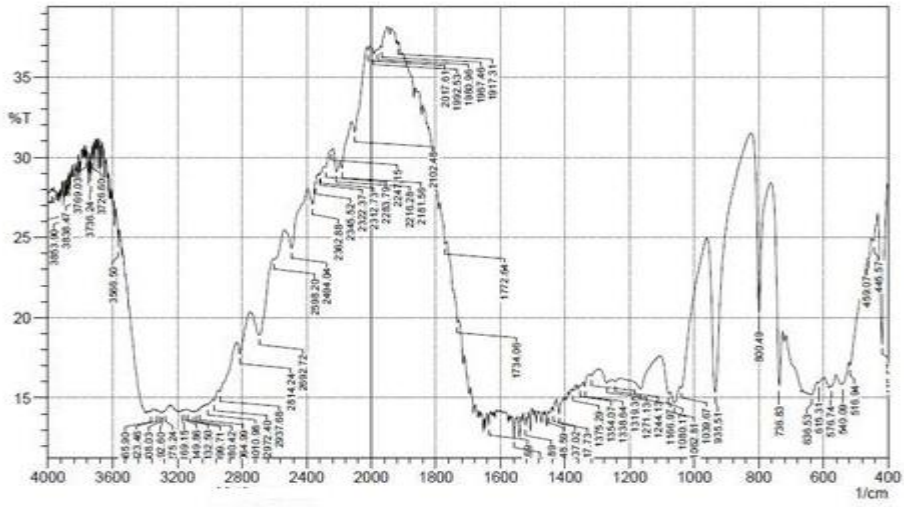


Figure 1: FTIR spectrum of pure drug.

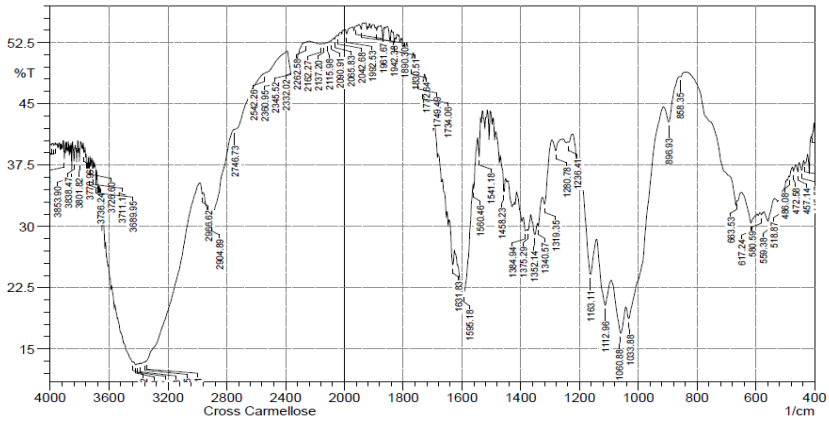
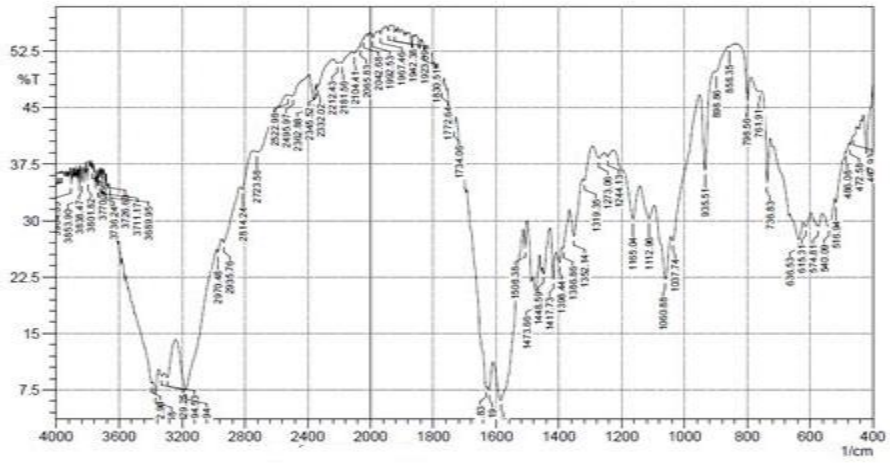


Figure 2: FTIR spectrum of pure drug + Crospovidone.



Figurec3: FTIR spectrum of pure drug + Croscarmellose Sodium.

Standard calibration curve of Nisoldipine:

Linearity of prepared solution was found in the range of 4 to 24µg/mL. From regression analysis value of co-efficient of regression (R^2) was 0.998 (Figure 4). This confers the range selection was satisfactory and follows Beer-Lambert's law.

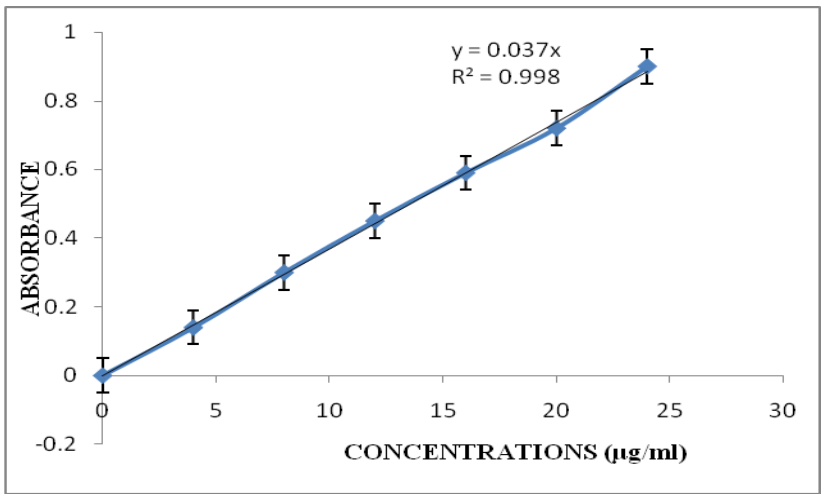


Figure 4: Standard graph of nisoldipine in 7.4 phosphate buffer.

Evaluation tests

Table 7: Bulk density, Tapped density, Carr's index, Hausner ratio, Angle of repose, %drug content.

F code	Bulk density (mg/ml)	Tapped density (mg/ml)	Angle of repose	Carr's index	Hausners ratio	%Drug content
F1	0.54±0.19	0.52±0.15	24.34±0.44	09.23±1.12	1.13±0.24	97.23±1.23
F2	0.57±0.16	0.58±0.17	22.67±0.31	08.23±1.42	1.11±0.10	98.04±1.03
F3	0.57±0.17	0.64±0.21	26.54±0.41	10.12±0.8	1.13±0.20	96.56±0.94
F4	0.59±0.25	0.68±0.25	25.89±0.55	11.34±0.6	1.14±0.24	98.11±0.63
F5	0.57±0.18	0.59±0.18	22.56±0.0.57	12.23±0.12	1.11±0.32	95.23±0.81
F6	0.58±0.20	0.66±0.20	25.30±0.30	11.23±0.25	1.12±0.30	96.45±0.32
F7	0.51±0.14	0.64±0.16	22.56±0.57	10.34±0.31	1.14±0.20	95.11±1.17
F8	0.54±0.16	0.68±0.17	23.67±0.60	09.11±0.24	1.12±0.25	98.23±0.45
F9	0.65±0.18	0.61±0.19	25.56±0.44	09.45±1.15	1.13±0.70	97.13±1.17
F10	0.66±0.25	0.67±0.18	21.06±0.31	13.45±1.3	1.09±0.20	96.23±0.49
F11	0.51±0.17	0.68±0.16	22.34±0.37	14.23±1.5	1.13±0.16	98.97±0.95
F12	0.55±0.16	0.64±0.20	25.99±0.70	11.34±1.25	1.12±0.12	98.45±0.35
F13	0.56±0.19	0.66±0.18	23.14±0.50	09.67±1.55	1.09±0.14	99.85±0.24
F14	0.52±0.13	0.66±0.17	22.09±0.57	10.23±1.55	1.14±0.15	99.18±0.13
F15	0.51±0.18	0.63±0.16	24.78±0.77	10.45±1.5	1.15±0.15	99.25±1.21
F16	0.52±0.13	0.61±0.15	23.45±0.80	09.68±1.3	1.18±0.18	97.45±1.30
F17	0.58±0.13	0.68±0.19	21.89±0.86	09.47±1.09	1.12±0.15	99.94±1.31
F17	0.56±0.16	0.67±0.20	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**

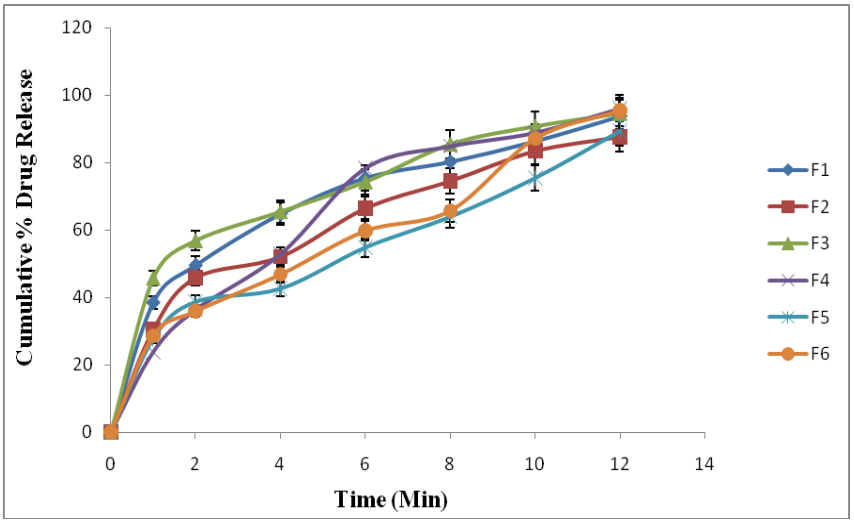


Figure 5: in *vitro* Drug Release Profile for immediate release tablet of Nisoldipine F1-F6.

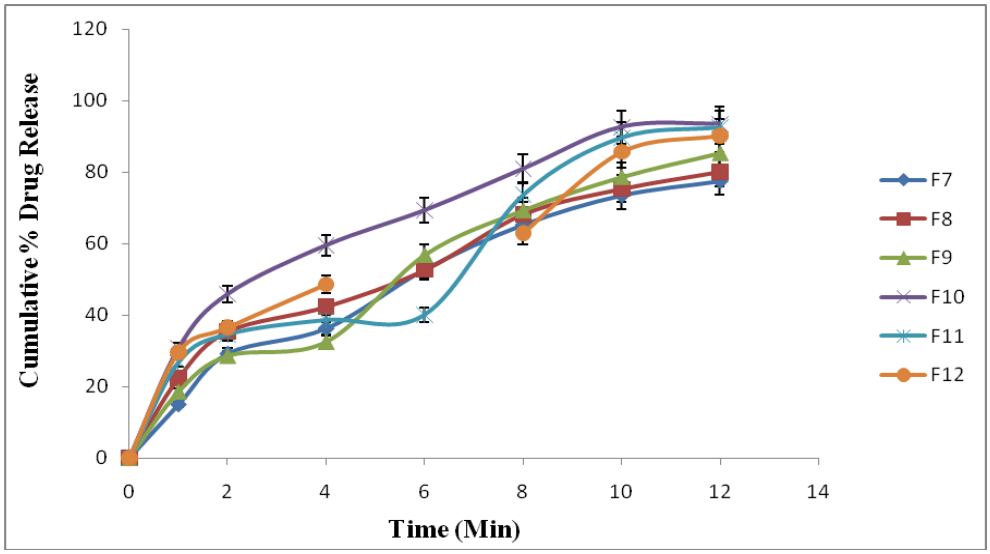


Figure 6: in *vitro* Drug Release Profile for immediate release tablet of Nisoldipine F7-F12.

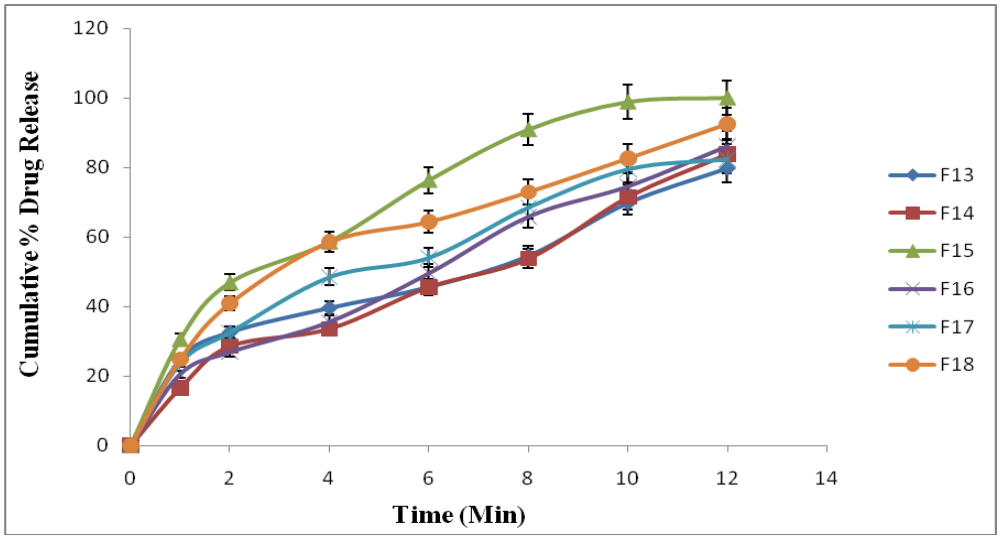


Figure 7: *In vitro* Drug Release Profile for immediate release tablet of Nisoldipine F13-F18.

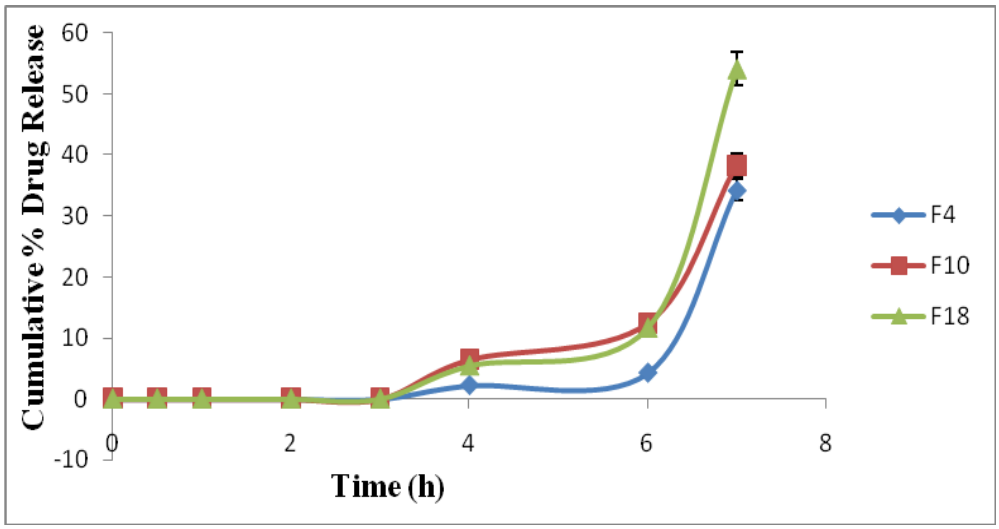


Figure 8: *In vitro* Drug Release Profile for Trail 1 Prepared middle active layer of Nisoldipine tablets F4, F10, F18.

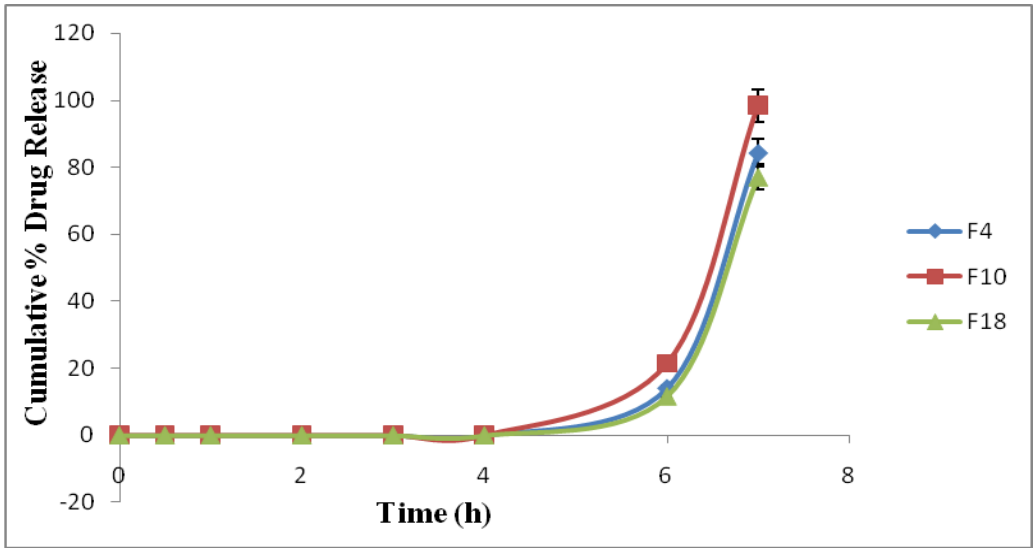


Figure 9: *In vitro* Drug Release Profile for Trail 2 Prepared middle active layer of Nisoldipine tablets F4, F10, F18.

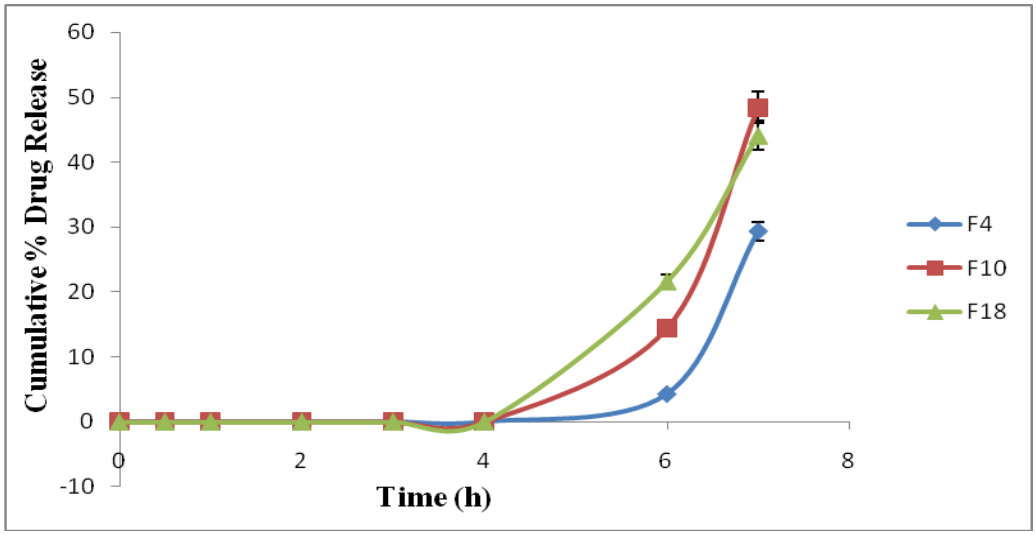


Figure 10: in *vitro* Drug Release Profile for Trail 3 Prepared middle active layer of Nisoldipine tablets F4, F10, F18.

Table 8: Stability studies.

Parameters	Time (Months)			
	0(Initial)	1st month	2 nd month	3rd month
Strength	No Change	No Change	No Change	No Change
Color	No Change	No Change	No Change	No Change
Drug Content (%)	99 ± 0.40	98 ± 0.98	97.2 ± 0.48	96.9 ± 0.54
In-vitro drug release	98.4	98.4	98.3	98.3

DISCUSSION

The immediate release tablets were prepared by using different types and different concentration of super disintegrating agents like Croscarmellose, Crospovidone 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 Crospovidone shows good drug release profile than Croscarmellose and sodium starch glycolate. The 5% Crospovidone shows better results. Formulations prepared by using Croscarmellose 8 % showed the maximum amount of drug release 84.24%after 7^{th} hour in pulsatile release formulations. Formulations prepared by using Crospovidone 5% showed the maximum amount of drug release 98.42% after 7^{th} hour in pulsatile release formulations. The coating polymer Eudragit L-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=0.9514). The diffusional exponent "n" was 0.9094, 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 results were showed in table 8.

CONCLUSION

Promising Pulsatile release system for Nisoldipine with appropriate amounts of excipients is successfully developed on the lines of novel drug delivery systems. They provided a desirable lag time followed by rapid and complete drug release to meet the challenges of chronotherapeutics of hypertension.

REFERENCES

1. Shangraw RF (1989) Compressed tablets by direct compression. Liebermann HA, et al. B. Pharmaceutical dosage forms, Tablets. (2nd edn). Marcel Dekker, New York, USA, 1: 195-243.
2. Sachin S, Neeraj K (2007) Pulsatile Drug Delivery: Current Scenario. Current Research and Information. Pharm Sci 8(2): 27-33.
3. Ravi KRJ, Veera JM, Mohamed STS, Madhu SCC (2009) Review on: Pulsatile Drug Delivery Systems. J Pharm Sci Res 1(4): 109-115.
4. Veena Belgamwar, Madhuri Gaikwad, Ganesh Patil, Sanjay Surana (2008) Pulsatile drug delivery system. Asian J Pharm 2(3): 141-145.
5. Shweta Arora, Ali J, Alka Ahuja, Sanjula Baboota, Qureshi J (2006) Review of pulsatile drug delivery systems: an approach for controlled drug delivery. Indian J Pharm Sci 68(3): 295-300.].
6. Smolensky MH, Peppas NA (2007) Chronobiology, drug delivery and chronotherapeutics. Adv Drug Deli Rev 59(9-10): 828-851.
7. Jha N, Bapat S (2004) Chronobiology and chronotherapeutics.].
8. Bhalla A, Singh R, Sachdev A, D'Cruz S, Duseja A. Circadian pattern in cerebro vascular disorders. Neurol India. 2002;50:526–7.]
9. Patil AS, Dandagi PM, Masthiholimath VS, Gadad AP, Najwade BK. Development and characterization of chronomodulated drug delivery system of captopril. Int J Pharm Investig.2011;1:227–33.]
10. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carrier Syst. 2001; 18:433–58.]
11. Aulton ME. Pharmaceutics the Science of Dosage Form Design. 2nd ed. Philadelphia: Churchill living stone. 2005. PP. 201-7.
12. Subramanyam CVS. Textbook of Physical Pharmacy.2nd editors, Vallabah prakashan, PP: 180-234.
13. Bentley's, Ea Rawlins. Text book of Pharmaceutics. 2003 Eighth editors. All India traveler book seller, Delhi. PP.270-281.)
14. Shah Punit, Mashru Rajshree, Rane Yogesh Stability testing of pharmaceuticals Journal of pharmaceutical research. 2007; 6, PP: 1-9.
15. White WB, Johnson MF, Black HR, Fakouhi TD Effects of the chronotherapeutic delivery of verapamil on circadian blood pressure in African-American patients with hypertension. Ethn Dis. 1999; 9(3):341-9.

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