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Formulation and Optimization of Press Coated Pulsatile Tablet of Felodipine by Chronopharmaceutical Approach in Treatment of Hypertension

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ABSTRACT

Felodipine is a long-acting 1, 4-dihydropyridine calcium channel blocker (CCB) is mainly used in treatment of hypertension because it inhibits the influx of calcium in smooth muscle cells. The present investigation is aimed to formulate a pulsatile drug delivery system with a lag time of about 6 hr. Core tablet was prepared by direct compression method and sodium starch glycolate used as superdisintegrant. The core tablet was compression coated with different ratio of HPC-EXF and EC N20. 3^2 Full factorial design was used for optimization of barrier layer. Total amount of polymer (X_1) and % of HPC-EXF (X_2) were selected as independent variables. The lag time (t_{10}) and time require for release 90% of drug were selected as dependent variables. Formulation F2 containing 6% sodium starch glycolate coated with 50% of HPC-EXF with 200 mg coat weight was considered optimum because it showed desired lag time of 6 hour.

INTRODUCTION

Over recent years, controlled drug delivery systems have acquired very important role in pharmaceutical Research and Development (R&D) business, because these dosage forms offer many advantages over the conventional drug delivery systems; such as nearly constant level of drug at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency (1). However, there are certain disease conditions for which such a release pattern is not suitable. These conditions demand release of drug as a "pulse" after a predetermined lag time that ideally matches the biological requirement of given disease therapy. Such a release system is known as pulsatile drug delivery systems (2). Nowadays, pulsatile system is gaining a lot of interest as it is increasing patient compliance by means of providing time- and site-specific drug delivery system, thus providing better and temporal delivery of drugs (3).

Through a number of clinical trials and epidemiological studies, it is well documented that the levels of disease activity of number of clinical disorders have a pattern associated with the circadian rhythm of the body. Circadian rhythm regulates many functions in human body like metabolism, physiology, behaviour, sleep pattern, hormone production. There are number of disease conditions which show circadian pattern and advantage of these conditions could be taken by timing and adjusting the administration of drugs according to the circadian rhythm of the disease. Diseases such as cardiovascular, asthma, peptic ulcer, arthritis etc. follow the body's circadian rhythm (4).

All these acted as push for the development of pulsatile drug delivery which release the drug after a predetermined lag time means during certain period of time there is no release of drug after that rapid and complete release of drug that ideally match the circadian pathophysiology of particular disease (5).

Morning hypertension is a condition in which blood pressure is specifically higher in the morning than at other times of day. As the criterion of hypertension based on home blood pressure is 135/85 mm Hg, an average blood pressure early in the morning of ≥135/85 mm Hg is defined as morning hypertension in a broad sense. Cardiovascular events frequently occur early in the morning, and blood pressure increases from the night-time to early in the morning due to

diurnal changes. As early morning blood pressure is significantly associated with the risk of brain, heart and kidney damage and all cardiovascular risks, morning hypertension, in which the blood pressure is increased in the time of the highest cardiovascular risk, is important (6).

Thus present study attempts to design & evaluate a chronomodulated drug delivery system of Felodipine used for treatment of early morning hypertension. It was aimed to have a lag time of 6 hour means if the system is taken at the bed time around 11 am then it expected to release the drug after a period of 6 hour, at the 5 am when early morning hypertension more exacerbates. Such time controlled pulsatile system can be formulated mainly with drug containing cores coated with various erodible polymers. Because coating of polymer to the core, it protects the core from the environment e.g. water, acidic pH and enzymes until the drug is released after a predetermined lag phase. The coatings can erode/dissolve rupture or alter their permeability at the required time (7).

Felodipine is a long-acting 1, 4-dihydropyridine calcium channel blocker (CCB). 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, Felodipine prevents calcium-dependent myocyte contraction and vasoconstriction. Felodipine is the most potent calcium channel blocker in use and is unique in that it exhibits fluorescent activity.

Thus, this study focuses on the development of press coated pulsatile tablet of Felodipine for providing the relief from hypertension. For optimization of the formulation 3^2 full factorial design were employed to investigate the effect of two factors which is total amount of coating and % of HPC-EXF because they affect the lag time and cumulative release of pulsatile drug delivery system.

MATERIALS AND METHODS

Materials

Felodipine was purchased by Nivedita Chemicals Pvt. Ltd. Mumbai. Lactose Monohydrate and Microcrystalline cellulose were gifted by DFE Pharma, Germany and JRS Pharma, Germany respectively. HPC EXF and EC N20 were obtained from Signet Chemical, Mumbai, India and

DOW Chemical, Mumbai, India respectively. Sodium starch glycolate was procured from DFE Pharma.

Methods

Identification of drug

Identification of Felodipine was carried out by Infra-Red absorption spectroscopy (FT-IR).

Preformulation studies

Bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose were performed for core powder blend (8).

Drug – excipients compatibility studies

Compatibility must be established between the active ingredient and other excipients to produce a stable, efficacious, attractive and safe product.

Fourier Transform Infra-red Spectroscopy (FTIR)

FT-IR spectra (400-4000 cm^{-1}) of Felodipine, used in formulations and physical mixture were obtained on a Thermo scientific FT-IR spectrophotometer. Samples were prepared by KBr pellet technique by mixing weighed amount of drug (3 mg) with 100 mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and subjected to compress under 10-ton pressure in a hydraulic press to form a transparent pellet (9).

Formulation of press coated tablet

Formulation of core tablet by direct compression method

Core tablet of Felodipine was prepared by direct compression method using the composition as shown in below Table:

Table 1: Composition of core tablet

Ingredients (mg)	Batch code		
	C1	C2	C3
Felodipine	10	10	10
Sodium starch glycolate (Primojel®)	2	4	6
Lactose monohydrate (Supertab11SD)	52	52	52
Microcrystalline cellulose (Vivapur® 112)	35	33	31
Magnesium stearate	1	1	1
Total	100	100	100

All ingredients used in formulation including Felodipine, Microcrystalline cellulose, Lactose monohydrate and Sodium starch glycoalte were passed through 40 # sieve and dry blended for 10 minutes. Lubricated this blend with pre sifted Magnesium stearate through 60 # sieve and mixed for 3 minutes.

Final lubricated blend was directly compressed using 6.0 mm round standard concave punch plain on both side by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (10,11).

Development of Press-coated tablets

The core tablet was compression coated with different quantities of coating material containing different ratio of HPC-EXF and EC N20. Powder blend for press-coated tablet was prepared by dry blending together different ratio of HPC-EXF and EC N20.

Half the quantity of the coating polymer was placed in the die cavity; the core tablet was carefully placed in the centre of the die cavity and filled with the other half quantity of the coating polymer. The coating material was compressed by using rotary tablet compression machine (Hardik Eng. Pvt. Ltd, Ahmadabad, India) (9, 12, 13).

Formulation optimization

In this study, a 3^2 full factorial design was used for the optimization by using STATISTICA®7 (StatSoft® Inc.) software. In this design 2 factors were evaluated, each at 3 levels, and

experimental trials were performed at all 9 possible combinations (14). Two independent variables i.e. X_1: Total amount of polymer and X_2: % of HPC-EXF were selected against two dependent variable Y_1: Lag time (t_{10}) and Y_2: Times require for 90% drug release for optimization.

Table 2: Formulation Design layout for 3^2 full factorial design

Batch code	Coded value		Actual value	
	X_1	X_2	Total amount of polymer (mg) X_1	% of HPC-EXF X_2
F1	-1	-1	200	25
F2	-1	0	200	50
F3	-1	+1	200	75
F4	0	-1	250	25
F5	0	0	250	50
F6	0	+1	250	75
F7	+1	-1	300	25
F8	+1	0	300	50
F9	+1	+1	300	75

Table 3: Compression coat formula for different tablet batches

Ingredient (mg)	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet	100	100	100	100	100	100	100	100	100
HPC-EXF	50	100	150	62.5	125	187.5	75	150	225
EC N20	150	100	50	187.5	125	62.5	225	150	75
Total wt	300	300	300	350	350	350	400	400	400

Evaluation of compress coated tablets

Core and compress-coated tablets were evaluated for post-compression parameters such as weight variation, thickness, hardness, friability test, content uniformity test and *in vitro* drug release study (15, 16).

Weight variation

Weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP-XXIX test if no tablet differs by more than two times of percentage deviation.

Hardness and Thickness

For each formulation, the hardness of 10 tablets was determined using Monsanto hardness tester and Thickness of 5 tablets was determined using Vernier caliper.

Friability

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X } 100$$

Drug content

10 tablets of Felodipine were taken and crushed. Amount of the powder equivalent to 10 mg of Felodipine was dissolved in 100 ml of distilled water, filtered, diluted suitably and analysed for drug content at 363 nm using UV-spectrophotometer (17).

***In vitro* dissolution study**

In-vitro dissolution study was performed using USP Type I dissolution apparatus (Basket type) at speed of 100 rpm.0.1 N HCl of pH 1.2 was first used for 2 hr, which was then replaced with phosphate buffer pH 6.8 and kept up to 12 hr. Aliquot of dissolution medium (5 ml) were withdrawn at specific time intervals of 1 hr and filtered each with Whatman filter paper. Equal amount of fresh dissolution medium was replaced immediately after each withdrawal. The amount of drug present in each sample was determined by UV-spectrophotometer at 363 nm.

RESULTS AND DISCUSSION

An absorption maximum was determined by scanning different concentration of solution of Felodipine. It was found to be 363 nm and method obeys Beer's law in concentration range 10 to 50 µg/ml, R^2 was found to be 0.998.

Pre-compression evaluation like angle of repose, bulk density, tapped density, % compressibility and Hausner's ratio of core powder blend are shown in below Table:

Table 4: Pre-compression parameters of core powder blend

Parameters	Observation (n = 3)
Angle of repose (radian)	39.34±0.32
Bulk density (gm/ml)	0.39±0.02
Tapped density (gm/ml)	0.6±0.01
Carr's index	35.0±0.50
Hausner's ratio	1.53±0.03

The values of pre-compression parameters of core powder blend indicate the poor flow properties.

FT-IR spectra of Felodipine is shown in below Figure 1.

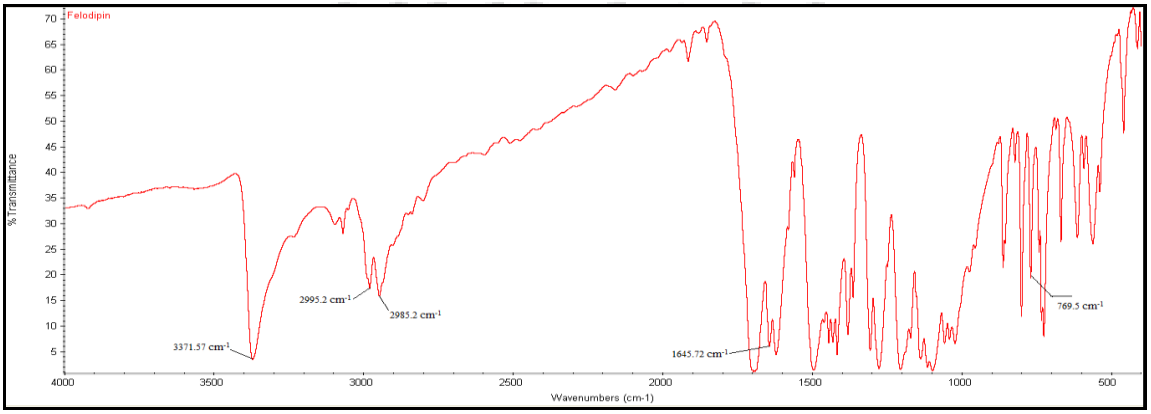

Figure 1: FT-IR spectra of (A) Felodipine and (B) final formulation

In the FT-IR spectrum of Felodipine the characteristic peaks corresponding to C=O stretching, N-H stretching, C-Cl stretching were identified.

Core tablet (C1- C3) was characterized for post-compression parameters like weight variation, thickness, hardness, friability, drug content and disintegration time.

Table 5: Post-compression parameters of core tablet

Batch code	Weight variation (mg)	Thickness	Hardness (Kg/cm^2)	Friability	*In vitro* disintegration time (sec)
C1	103 ± 2.15	3.29 ±0.24	3.3±0.67	0.45±0.07	30±2.98
C2	105 ± 2.47	3.31± 0.15	3.4±0.84	0.47±0.05	24±2.87
C3	106 ± 2.34	3.35±0.25	3.1±0.42	0.49±0.04	18±2.94

From the result of post-compression parameters of core tablet, deviation in weight is less than 10% indicated that there was no significant weight variation in the core tablets. Hence, all the tablet formulations passed the USP-XXIX weight variation test. The hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be uniform in all formulations. From the result of disintegration time of core tablet it was found that minimum disintegration time was observed with formulation C3 containing 6% Sodium Starch glycolate. So the formulation C3 containing 6% Sodium Starch glycolate is selected as optimized core tablet for further preparation of compress coated tablet.

In-vitro drug release profile of all nine formulations was found typical sigmoidal curves with a distinct lag time. It showed that lag time increased with decreasing concentration of HPC-EXF.

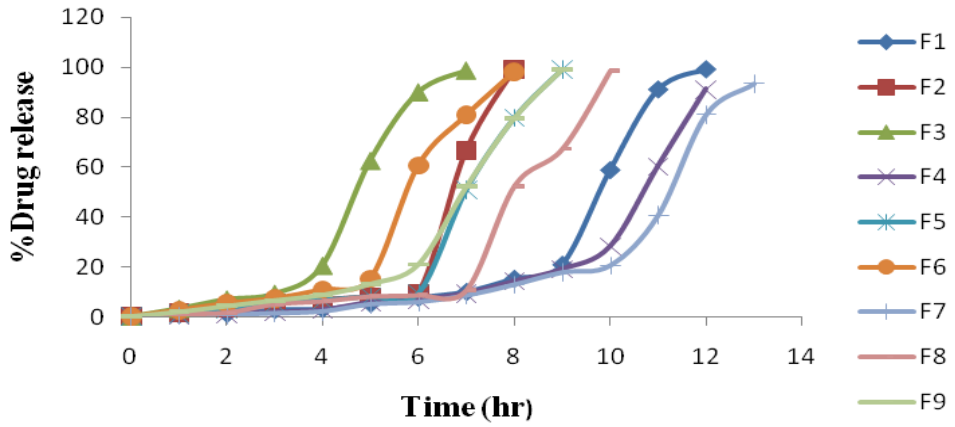

Figure 2: Dissolution profiles of final batches (F1-F9)

From release profile of all nine batches it was observed that drug release from tablet was inversely proportional to concentration of HPC-EXF. Formulation F3, F6 and F9 show >10% of drug released before the lag time of 6 hours while significant retardation was observed from the batches F1, F4 and F7 containing higher amount of EC N20 in the outer shell.

Formulation F2 and F5 show less lag time of 6 hours (<10% drug release) and nearer 99% of drug release at the end of 7 to 9 hours

Result of dependent variable of 3^2 full factorial design (Table 7) showed that batch F2 and F5 have lag time of 6 hours and time requires for release 90% of drug is 7.72 hr and 8.54 hr respectively. But batch F2 showed drug release at 7^{th} hour: 66.59% and batch F5 showed drug release at 7^{th} hour 50.78%. So, based on the all dependant variables batch F2 was selected as optimized batch.

Table 6: Results of dependent variables

Batch code	Coded value		Response	
	X_1	X_2	Y_1	Y_2
F1	-1	-1	7.02	10.97
F2	-1	0	6.00	7.72
F3	-1	1	3.07	6.00
F4	0	-1	7.14	11.96
F5	0	0	6.02	8.54
F6	0	1	3.77	7.53
F7	1	-1	7.37	12.75
F8	1	0	6.75	9.72
F9	1	1	4.33	8.54

A three factor and two level (3^2) full factorial design was applied in this study to optimize the formulations. Total amount of coating and % of HPC-EXF were chosen as the independent variables while lag time (t_{10}) and time require for release 90% of drug were taken as dependent variable.

The polynomial equation for 3^2 full factorial design is described as follows:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

Where, Y is the dependent variables, β_0 is the arithmetic mean response of the nine runs, and β_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_{11} and X_{22}) are included to investigate non-linearity.

The polynomial equations (equations 1-2) relating the response lag time (Y_1) and time require for release 90% of drug (Y_2) with the independent variables are given below.

$$Y_1 = 6.18+0.39X_1-1.73X_2+0.23X_1X_2+0.11X_1X_1-0.81X_2X_2 \ (r^2 = 0.996) \quad \_\_\_\_ (1)$$

$$Y_2= 8.7+1.05X_1-2.27X_2+0.19X_1X_2-0.06X_1X_1+0.97X_2X_2 \ (r^2 = 0.995) \quad \_\_\_\_ (2)$$

When amount of total polymer was increased (X_1), lag time (Y_1) and time require for 90% drug release (Y_2) was increased and when % of HPC-EXF was increased (X_2), lag time (Y_1) and time require for 90% drug release (Y_2) was decreased.

The relationship between the dependent and independent variables was further elucidated using surface plot and contour plot as shown in Figure 4.

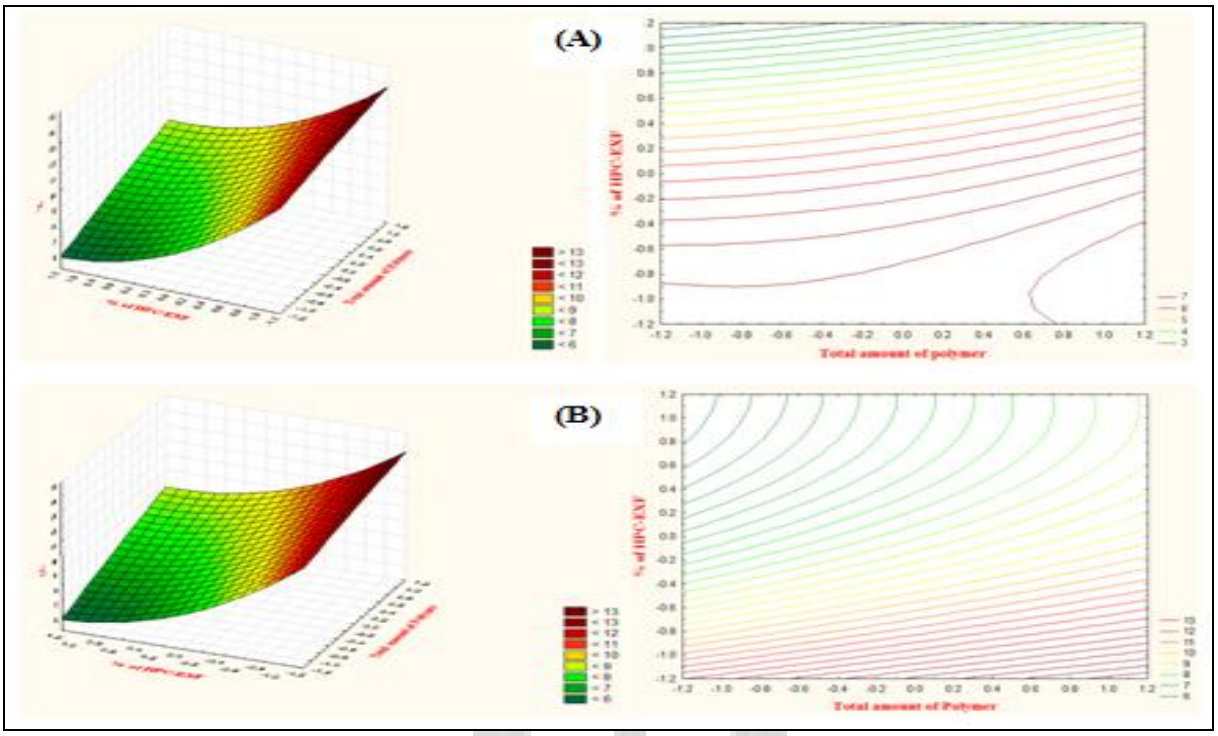

Figure 3: Surface and Contour plot of (A) lag time (Y_1), (B) time require for 90% of drug release (Y_2)

CONCLUSION

A press coated pulsatile drug delivery system for Felodipine to mimic the circadian rhythm of the disease by releasing the drug at appropriate time (At the time of symptoms exacerbates). The formulation consisted of a core tablet containing a drug Felodipine and outer layer of combination of hydrophilic and hydrophobic polymer of HPC-EXF and EC N20. From all the batches it was concluded that Formulation F2 was the ideal formulation with lag time of 6 hrs followed by burst release of drug and also meeting all specifications of pre-compression and post-compression parameters and stability studies. Thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms.

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