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NEW HOPE IN HYPERTENSION

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ABSTRACT

Formulation and evaluation of floating pulsatile drug delivery system for chronotherapy of hypertension. It is aimed to modulate the pulsatile release profile from time lagged coating using single or a combination of rupturable and erodible polymer. To prepare enalapril maleate core tablets by wet granulation method. To prepare press coated pulsatile tablets by direct compression method.

KEYWORDS: Enalapril Maleate angiotensin I–converting enzyme.

INTRODUCTION

Several controlled release preparations present numerous problems such as resistance drug tolerance and activation of the physiological system due to long term constant drug concentrations in the blood and tissues. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs.

Recent studies also reveal that the body's biological rhythm may affect biological functions such as heart rate, blood pressure, body temperature, blood plasma concentration, intraocular pressure, stroke volume. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm. which require different amounts of drug at expected times within the circadian cycle. Pulsatile drug delivery system has fulfilled this requirement.

Pulsatile Drug Delivery System can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance. Heart rate and blood pressure both exhibit a strong circadian pattern with values for blood pressure, double product typically peaking in the early morning period compare with till late afternoon, and then drops off during night (hypertension).

MATERIALS AND METHODS

The combination of floating and pulsatile principle are very well suitable for site and time specific oral drug delivery have recently been of greater interest in pharmaceutical field to achieve improved therapeutic efficacy. The floating pulsatile delivery provides various advantages such as nearly constant drug level at the site of action, avoidance of undesirable side effects, reduce dose, increased gastric residence of the dosage form.

After review of patents we can concluded that pulsatile drug delivery systems offer the delivery of drugs exhibiting chronopharmacological behavior, necessity of night time dosing, etc. There is a need for new delivery systems that can provide increased therapeutic benefits to the patients to match with circadian rhythm of body. This technique overcomes first pass metabolism and proves most beneficial when taken at bedtime.

Thus it concluded that the pulsatile delivery system release the drug at specific time and at specific site to improves the bioavailability, reduce dosing frequency and hence increase patient compliance and this correlates well with the rational for selection of project.

4.3.5. Drug excipient compatibility study

Compatibility of Enalapril maleate with respective polymes that is HPMC E5, E15 and E50, individual excipients was established by infrared absorption spectral analysis (FTIR). Any changes in the chemical composition after combination with the excipients were investigated with IR spectral analysis.

4.3.5.1. Differential scanning calorimetry

The DSC thermogram were recorded using a differential scanning calorimetry (DSC 60, Shimadzu). Approximately 2-5 mg of each sample was heated in a piece red aluminium pan from 50-300 °C at a heating rate of 10°C/min. under a stream of nitrogen at rate 10

ml/min.

4.4. Formulation Of Pulsatile Tablet[19]

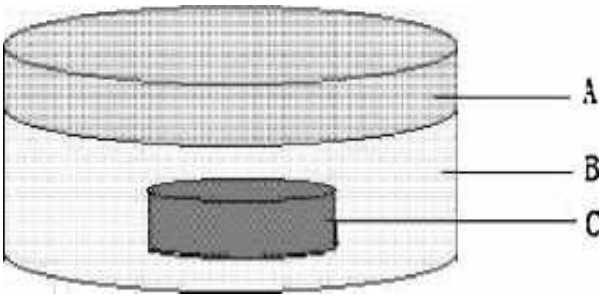

Figure 4.1: Schematic diagram of the floating pulsatile release (FPRT) delivery system.

A:- Buoyancy layer.(Sodium Bicarbonate)
B:- Pulsatile release layer.(HPMC Polymer)
C:- Rapid-release core tablet.(Drug and excipients)

Method using: wet granulation method for core tablet and direct compression for coating.

4.4.1. Rapid-Release Core Tablet Preparation (RRCT)

Rapid Release Core Tablets were prepared by wet granulation method.

- All the ingredients were passed through 60 # mesh sieve separately and collected.
- The ingredients and drug were weighed and mixed in a geometrical order.
- Then the mixture was wetted with solution of PVP K-30 (10% w/v in Iso propyl alcohol).
- The wetted mass was again passed through 22# sieve. The granules were dried.
- These granules were lubricated with magnesium stearate and talc.
- Then the mixture of drug and excipients was compressed by using 6 mm size punch to get a tablet using single punch tablet machine.

The composition of core tablets is given in following table-

Table 4.4: Formulation of core tablet.

Ingredients	Qty. per tablet(mg)
Enalapril Maleate	10
Micro crystalline cellulose (MCC)	75
Sodium starch glycolate (SSG)	2
Silica gel	10
Mg. stearate	1
Talc	2
Total weight	100

4.4.2. Pulsatile Release Tablet Preparation (PRT)

Pulsatile Release Tablet was prepared by taking core tablet respectively and 240 mg of Methocel were used by two steps. In first method taken half quantity of coatings were filled into the die cavity, followed by core tablet placed in the center of die, and and then the rest of the coating materials were filled. So Pulsatile tablet dry-coated with Methocel was prepared in 12 mm diameter and buoyancy layer placed on it and finally compressed by using single punch tablet machine.

Table 4.5: Composition of polymer coating.

Polymer	T1	T2	T3	T4	T5	T6
HPMC E5(mg)	240	-	-	120	120	-
HPMC E15(mg)	-	240	-	120	-	120
HPMC E50(mg)	-	-	240	-	120	120
Total	240	240	240	240	240	240

4.4.3. Floating Pulsatile Release Tablet Preparation (FPRT)

The buoyant layer was prepared by adding gelling agent such as carbopol 934, and sodium bicarbonate which upon contact with gastric fluid formed a gelling mass, sufficient for cohesively binding with the pulsatile release layer. Sodium bicarbonate, which is upon contact with gastric acid in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gelling mass. This produces an upward motion of pulsatile tablet and maintains its buoyancy.

Table 4.6: Composition of buoyancy layer.

Ingredients	Qty. per tablet (mg)
Carbopol 934	90
NaHCO3	10
Total weight	100

4.5. Evaluation Parameters.[19,26,27,43]

4.5.1. Evaluation of powder blend

4.5.1.1. Angle of repose

It is used to estimate the flow property of material. The angle of repose less than 30º indicates good flow property of material. The angle of repose of powder blend was determined by funnel method. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the granules. The powder was allowed to flow through funnel to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation ($\tan \theta = h/r$) where, h=height and r=radius of powder cone.

4.5.1.2 Bulk density

Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder was determined.
Bulk density = weight / bulk volume

4.5.1.3. Tapped density

The measuring cylinder containing a known mass of

powder blend was tapped for a fixed number of times as per USP apparatus-11. The minimum volume occupied by the powder after tapping was measured.
Tapped density = weight/tapped volume

4.5.1.4. Compressibility index: Compressibility index is calculated as follows Tapped density- Bulk density/ Tapped density*100.

The value below 16% indicates a powder with good flow characteristics where as above 25% indicates poor flowability.

Table 4.7 Carr's index.

S.N.	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor

4.5.1.5. Hausner's Ratio
It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. it is the determined by the ratio of tapped density and bulk density.

Hausner's ratio: Vb /Vt
Where Vt = Tapped volume, Vb = untapped volume

S.N.	Hausner's ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

4.5.2. Evaluation of RRCT
4.5.2.1 Weight variation test
Weight variation was carried out by taking 20 tablets and weighed and the average weight was taken. Then the tablets were weighed individually. The percentage weight variation of each tablet from average weight was calculated using the following formula
%Deviation=Individual weight-Average weight/ Individual weight * 100

Table 4.8: Weight variation criteria for tablet.

Average weight of tablet deviation	Percent
130 mg or less	10
>130 mg and <324 mg	7.5
324 mg or more	5

The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet deviated beyond the percentage limit given in table.

4.5.2.2. Tablet dosage form assay (Drug Content)
Twenty tablets were powdered, and 10 mg equivalent weight of Enalapril maleate tablet powder was accurately weighed and transferred into a 100 ml volumetric flask and dissolved with buffer solution. The solution in the volumetric flask was filtered and Pipette out 0.5 ml from above solution into 10 ml volumetric flask and make up with 1 ml FeCl3, 1 ml potassium ferricyanide, kept aside for 10 min. and 1 ml conc. HCl and mark with distilled water. Then, analyzed spectrophotometrically at 778 nm.

4.5.2.3. Hardness test
The hardness of the tablet was measured using a Pfizer hardness tester. It is expressed in Kg/cm^3.

4.5.2.4. Friability test
The friability of the tablet was measured using Roche friabilator. It is expressed in percentage (%). 5 tablets were weighed and transferred to the Friabilator. The friabilator was operated at 25 rpm for 4 min. The tablets were weighed again. The % friability was then calculated by.
% Friability= Initial weight – Final weight / Initial weight * 100.

4.5.2.5. In vitro disintegration test
In vitro disintegration time of tablets from each formulation was determined by using digital tablet disintegration apparatus. In vitro disintegration test was carried out at 37 ±2 in 900 ml. Acid buffer pH 1.2.

4.5.3. Evaluation of Floating Pulsatile Tablet
4.5.3.1. Buoyancy determination
The buoyancy test of floating pulsatile release tablet was studied by placing them in 900 ml beaker containing Buffer pH 1.2, then tablet from same batches were placed in dissolution test apparatus containing buffer pH 1.2, maintained at 37±0.1 ºC and agitated at 50 rpm. The floating onset time (time period between placing tablet in the medium and buoyancy beginning) and floating duration of tablet was determined by visual observation.

4.5.3.2. Drug release lag time
The lag time is the time interval between the dosage forms is placed into the aqueous environment and drug get to release from its dosage form after rupturing or eroding outer layer. It should be determined during the invitro drug release study.

4.5.3.3 In vitro dissolution studies
The in vitro dissolution studies were carried out in acid buffer pH 1.2.(900 ml) at 37 ± 0.5 C using USP dissolution apparatus type II. The speed of rotation was maintained at 50rpm. Aliquots of dissolution medium were withdrawn at predetermined time interval and content of Enalapril Maleate was determined by using UV Spectrophotometer.

4.6. Optimization by using 3^2 full factorial Experimental Design
It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man, hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time by trial and error

method which is time consuming in nature and requires a lot of imaginative efforts. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interaction. The number of experiments required for these studies is dependent on the number of independent variables selected.

3^k factorial design

Consider a simple example of a 3^k factorial design. Each of the k factors is assigned three levels. The levels are usually High = 1, Medium=0 Low = -1. Such a scheme is useful as a preliminary experimental program before a more ambitious study is undertaken. The outcome of the 3^k factorial experiment will help identify the relative importance of factors and also will offer some knowledge about the interaction effects. Let us take a simple case where the number of factors is 2. Let these factors be X_1 and X_2. The number of experiments that may be performed is 9 corresponding to the following combinations:

Table 4.9: Full factorial design matrix layout.

Experiment Trials.	X1	X2
1	-1	-1
2	0	-1
3	+1	-1
4	-1	0
5	0	0
6	+1	0
7	-1	+1
8	0	+1
9	+1	+1

Table 4.10: Selection of independent and dependent variables.

Translation of coded value in actual units			
Independent Variables	**Levels**		
	Low (-1)	**Medium (0)**	**High (+1)**
Weight ratio of HPMC E5:HPMC E15 (X1)	2:1	1.5:1	1:1
Concentration of SSG (%) (X2)		4	6
Dependent Variables			
1	Drug release lag time		
2	% Drug release		

The response (Y) is measured for each trial.

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

Where,

Y is the dependent variable,

b_0 is the arithmetic mean response of the total runs,

b_1 is the estimated coefficient for factor **X_1**,

b_2 is the estimated coefficient for factor **X_2**,

The main effect (**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, **X_{11}** and **X_{22}** are included to investigate non linearity.

In the present study, a 3^2 full factorial design was employed to study the effect of independent variables, i.e. weight ratio of HPMC E5 and HPMC E15 **(X1)** and concentration of SSG **(X2)** on dependent variable i.e. Drug release lag time (**Y1**) and % drug release at 8 hr.**(Y2)**.

Table 4.11: Formulation of factorial batches.

Ingredient (mg)	Factorial Batches								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Enalapril maleate	10	10	10	10	10	10	10	10	10
SSG %	2	2	2	4	4	4	6	6	6
Silica gel	10	10	10	10	10	10	10	10	10
MCC	75	75	75	73	73	73	71	71	71
Mg.Stearate	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2
Coating layer									
HPMC E5	160	144	120	160	144	120	160	144	120
HPMC E15	80	96	120	80	96	120	80	96	120
Buoyancy layer									
Carbopol 934	90	90	90	90	90	90	90	90	90
NaHCO3	10	10	10	10	10	10	10	10	10
Total	440	440	440	440	440	440	440	440	440

4.7. Stability study of floating pulsatile tablet

The optimized formulation was subjected for accelerated stability studies as per ICH guidelines Q1A (R2) by keeping sample in stability chamber. The formulation was stored at different storage conditions like 40±2 ºC / 75±5 % RH for 30 days.

The formulation was subjected to different tests such as drug release lag time and in vitro drug release study.

5.1. Analysis of drug candidate

5.1.1. Drug characterization

5.1.1.1. UV Characterization

Enalapril maleate shows maximum absorbance at wavelength maxima at 760 nm by uv- visible method.

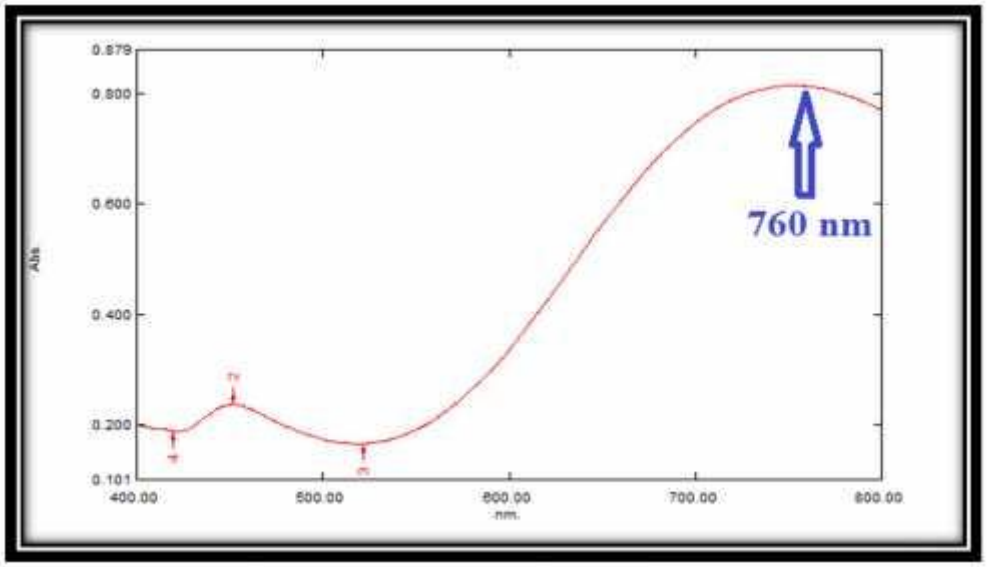

Figure 5.1: Wavelength maxima of enalapril maleate.

5.1.1.2. FTIR Spectra.[25,26]

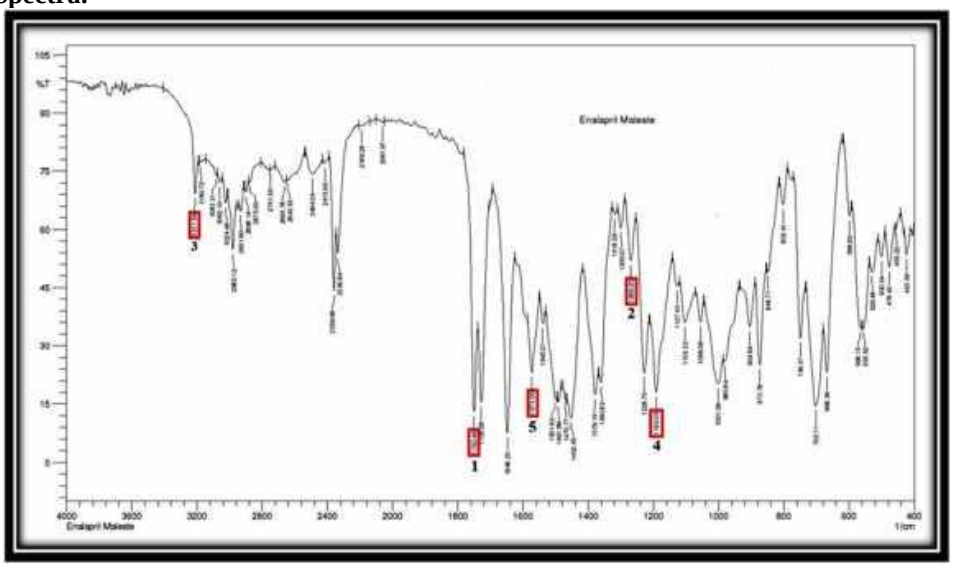

Figure 5.2: FTIR spectra of enalapril maleate.

The IR spectrum of pure drug was having the same peak as of pure drug spectra in standard.

Table 5.1: FTIR peak assign group of enalapril maleate.

No	Group	Reported peak of Enalapril Maleate Wave number (cm-1)	Obtained peak of Enalapril Maleate Wave number (cm-1)
1	C=O(carbonyl)	1670-1820	1750.46
2	C-N(aromatic)	1250-1350	1269.20
3	N-H(amine)	3100-3500	3211.59
4	C-O(ester)	1000-1300	1192.05
5	Aromatic	1400-1600	1573

5.1.2. Calibration curve of enalapril maleate

A representative spectrum of enalapril maleate showing wavelength maxima at 760 nm for concentration of 5 µ g/ml are shown in figure.

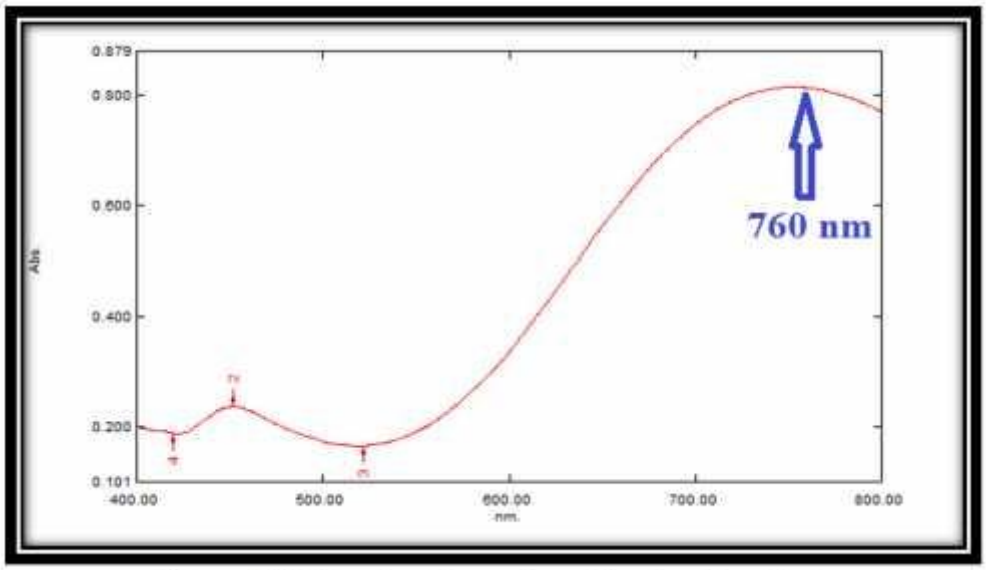

Figure 5.3: Wavelength maxima of enalapril maleate.

5.1.2.1. Preparation of calibration curve

Enalapril maleate exhibits maximum absorbance at 760 nm and obeyed beer's law in range of 1-5 µ g/ml. The result of calibration curve preparation are shown below.

Table 5.2 Calibration curve data of pure drug.

Sr. No.	Concentration (µg/ml)	Absorbance			Average absorbance (n=3, Mean±SD)
1	1	0.151	0.155	0.158	0.154±0.003
2	2	0.318	0.323	0.328	0.323±0.005
3	3	0.503	0.497	0.508	0.502±0.005
4	4	0.653	0.649	0.661	0.654±0.006
5	5	0.813	0.810	0.806	0.809±0.003

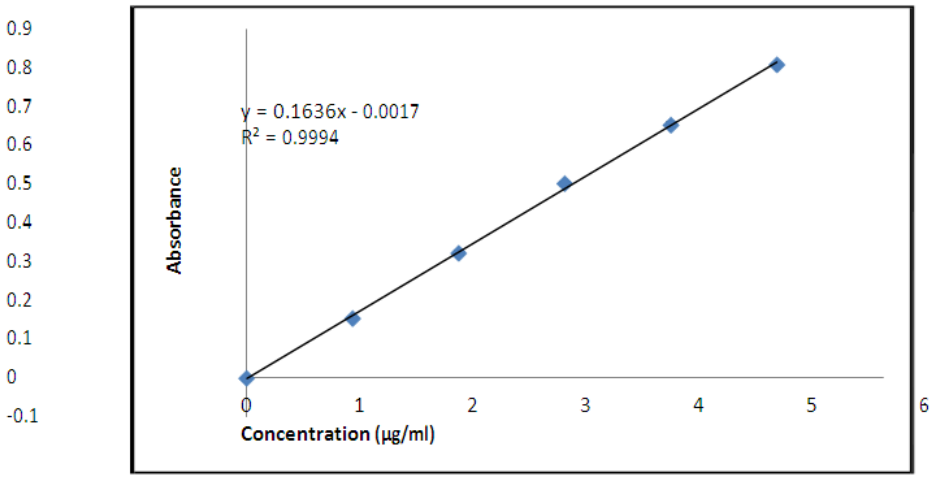

Figure 5.4: Calibration curve of enalapril maleate.

5.2. Formulation and Evaluation Enalapril maleate floating pulsatile tablet

5.2.1. Evaluation of rapid release core tablet

5.2.1.1. Evaluation of preliminary trial batch

5.2.1.1.1. Evaluation of pre compressional parameter

Table 5.8: pre compressional study of powder blend.

Sr. No.	Parameters	Results n=3±SD
1	Bulk Density	0.23±0.02
2	Tapped Density	0.26±0.02
3	Compressibility Index	11.29±0.8
4	Hausner's ratio	1.13±0.06
5	Angle of Repose	24.70º±0.6

5.2.1.1.2. Evaluation of post compressional parameter
Table 5.9 Post compressional study of core tablet.

Sr.No.	Parameters	Results n=3±SD
1	Average Weight(mg)	101.33±0.57
2	Hardness(kg/cm3)	3.36±0.15
3	Friability(%)	0.58±0.13
4	Disintegration Time(sec.)	50±1
5	Drug Content	98.21±0.71
6	Thickness	2.71±0.005
7	Diameter	5.99±0.005

DISCUSSION

From this preliminary test, it should concluded that core tablet have ability to disintegrate rapidly which fulfill the requirement for pulsatile drug delivery. so this formulation can be used for development of floating pulsatile tablet.

5.2.1.2. Evaluation of factorial batches
5.2.1.2.1. Evaluation of pre compressional parameter
Table 5.10: Pre compressional study of powder blend.

S.N.	Parameters	Results n=3±SD		
		RRC 1	RRC 2	RRC 3
1	Bulk Density	0.23±0.02	0.24±0.015	0.25±0.005
2	Tapped Density	0.26±0.02	0.3±0.02	0.30±0.005
3	Compressibility Index	11.29±0.8	17.75±1.04	16.48±0.31
4	Hausner's ratio	1.13±0.06	1.19±0.035	1.19±0.005
5	Angle of Repose	24.70º±0.6	30.22 º ±0.54	26.86 º ±0.52

Angle of repose less than 30 º indicates good flow property. Compressibility index up to 16% indicates good compressibility and value obtained showed satisfied flow property.

5.2.1.2.2. Evaluation of post compressional parameter
Table 5.11 Post compressional study of core tablet.

S.N.	Parameters	Results n=3±SD		
		RRC 1	RRC 2	RRC 3
1	Weight variation	Pass	Pass	Pass
2	Hardness(kg/cm3)	3.36±0.15	3.41±0.10	3.40±0.01
3	Friability (%)	0.58±0.13	0.56±0.085	0.62±0.06
4	Disintegration Time(sec.)	50±1	35.33±1.154	22±1
5	Drug Content	98.21±0.71	98.74±0.62	98.37±1.09
6	Thickness	2.71±0.005	2.72±0.005	2.71±0.005
7	Diameter	5.99±0.005	5.95±0.06	5.99±0.005

The hardness value of formulation were within the range 3-5 kg/cm^3 Friability values of all formulation less than 1%. According to USP, less than 10 % weight variation is acceptable in the tablet formulation having avg. weight less than 130 mg.

5.2.2. Evaluation of pulsatile release tablet
5.2.2.1. Evaluation of preliminary trial batches
Table 5.12: Evaluation for pulsatile tablet.

Formulation	Thickness (mm) n=3±SD	Hardness (kg/cm^3) n=3±SD	Diameter (mm) n=3±SD	Floating lag time (sec.) n=3±SD	Float- ing time (hr.)	Drug release lag time (min.) n=3±SD
T1	4.83±0.05	5.13±0.05	12.12±0.05	52.33±0.57	>12	96.33±4.01
T2	4.85±0.05	5.3±0.1	12.11±0.05	52.0±1.0	>12	330.66±3.51
T3	4.96±0.05	5.6±0.11	12.11±0.05	51.66±0.57	>12	495.33±5.13
T4	4.9±0.1	5.4±0.05	12.12±0.05	51.33±1.1	>12	455.66±4.50
T5	4.93±0.11	5.5±0.1	12.12±0.05	54.0±1.0	>12	500.66±5.13
T6	4.83±0.05	5.2±0.05	12.11±0.05	54.33±1.1	>12	566±5.56

DISCUSSION

Drug release lag time is most important parameter in pulsatile drug delivery system. Drug release lag time more than 6 hrs is requirement or criteria for pulsatile delivery. So from this batches of floating pulsatile tablet it should concluded that if only HPMC E5 or HPMC E15 are used for pulsatile release coating layer give drug release lag time 96 min. and 331 min. which can not fulfill criteria for pulsatile. And HPMC E50 give lag time more than expected outcome which can not able to give suitable drug release at specific time. But when combination of HPMC E5 and HPMC E15 can be used than it will give drug release lag time 456 min. which fulfill criteria of pulsatile delivery. So weight ratio of HPMC E5 and HPMC E15 are used for development of floating pulsatile tablet.

Table 5.13 Invitro drug release for pulsatile tablet.

Time (hr.)	Cumulative % Drug Release (n=3±SD)					
	T1	**T2**	**T3**	**T4**	**T5**	**T6**
0	0	0	0	0	0	0
1	0	0	0	0	0	0
2	80.72±2.91	0	0	0	0	0
3	97.44±1.26	0	0	0	0	0
4	98.46±0.12	2.64±0.33	0	0	0	0
5	-	5.58±0.44	2.86±0.40	3.13±0.78	1.87±1.66	0
6	-	84.86±1.77	5.80±0.50	5.7±1.95	5.06±1.48	2.83±0.62
7	-	97.67±0.68	8.30±0.49	10.99±1.47	8.55±0.36	4.33±0.78
8	-	-	11.16±0.56	82.38±3.06	12.97±2.46	8.17±0.54
9	-	-	81.61±1.38	97.57±0.80	85.13±1.51	11.97±0.53
10	-	-	96.68±0.59	-	96.68±1.31	79.89±1.58
11	-	-	-	-	-	95.94±1.92

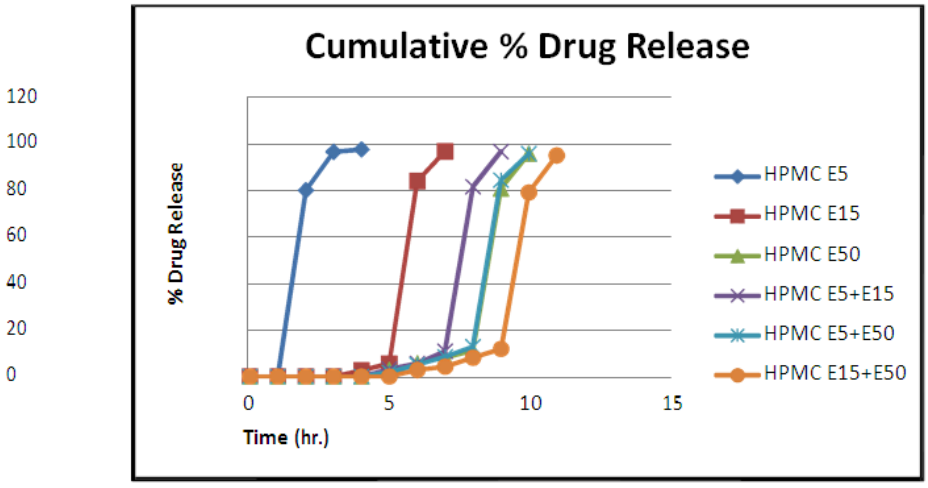

Figure 5.13: Drug release profile for pulsatile tablet.

5.2.2.2. Evaluation of factorial batches

Table 5.14: Evaluation study of pulsatile tablet for factorial batches.

Formu-lation	Thickness (mm) n=3±SD	Hardness (kg/cm3) n=3±SD	Diameter (mm) n=3±SD	Floating lag time (sec.) n=3±SD	Floating time (hr.)	Drug release lag time (min.) n=3±SD
F1	4.83 ±0.01	5.36 ±0.05	12.10 ±0.005	57.66 ±1.52	>12	345.33 ±4.50
F2	4.86 ±0.005	5.43 ±0.15	12.11 ±0.005	56.66 ±0.57	>12	435.33 ±5.03
F3	4.87 ±0.02	5.43 ±0.11	12.10 ±0.01	56 ±2	>12	468.33 ±3.51
F4	4.88 ±0.01	5.26 ±0.11	12.12 ±0.005	53.33 ±1.52	>12	334.0 ±4.58
F5	4.87 ±0.005	5.36 ±0.05	12.11 ±0.01	55.66 ±2.08	>12	407.66 ±2.51
F6	4.89 ±0.01	5.43 ±0.11	12.10 ±0.005	50 ±2	>12	464.33 ±2.08
F7	4.85 ±0.005	5.33 ±0.05	12.12 ±0.01	58.33 ±1.52	>12	316.33 ±3.21
F8	4.87 ±0.01	5.26 ±0.05	12.12 ±0.005	56.33 ±2.51	>12	401.33 ±1.52
F9	4.85 ±0.01	5.4 ±0.1	12.10 ±0.005	53.33 ±1.52	>12	454.33 ±3.51

Table 5.15: Invitro release study of pulsatile tablets for factorial batches.

Time (hr.)	Factorial batches (% Cumulative drug release) n=3±SD								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0
4	3.23 ±0.38	2.42 ±0.22	0	2.53 ±0.33	3.09 ±0.33	0	2.90 ±0.66	2.75 ±0.44	0
5	7.90 ±0.79	4.47 ±0.33	3.05 ±0.5	6.50 ±0.41	6.51 ±0.71	2.94 ±0.33	7.24 ±0.70	6.28 ±0.89	3.31 ±0.58
6	70.57 ±2.58	7.29 ±1.38	7.24 ±1.36	77.03 ±1.40	10.12 ±0.77	6.43 ±0.79	81.28 ±2.37	9.85 ±0.56	6.69 ±1.45
7	93.46 ±1.69	10.64 ±0.84	11.00 ±1.21	95.19 ±0.53	70.85 ±1.89	9.82 ±1.39	95.54 ±0.57	77.03 ±2.57	9.82 ±0.67
8	96.69 ±0.51	85.21 ±2.68	60.1 ±1.16	97.48 ±0.78	87.6 ±0.83	65.83 ±1.26	97.71 ±0.22	95.78 ±1.46	75.82 ±1.97

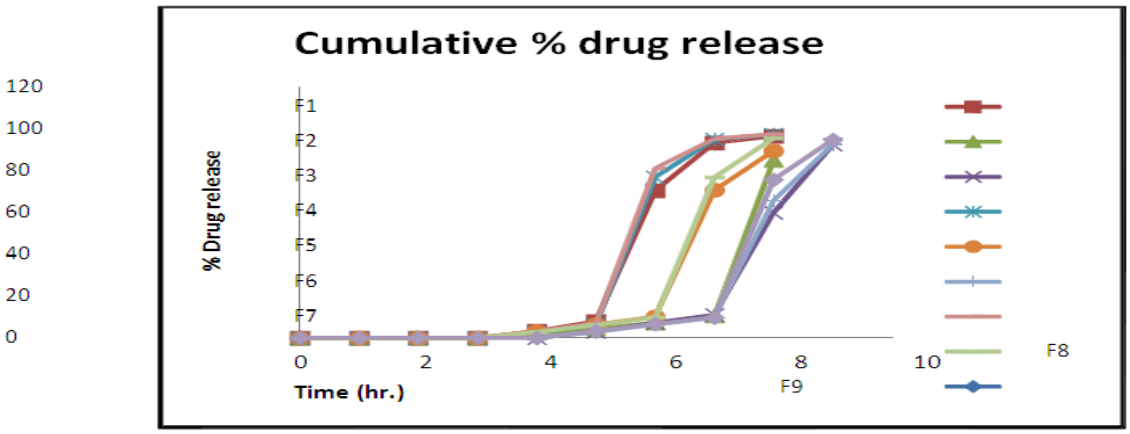

Figure 5.14: Drug release profile for pulsatile tablet of factorial batches.

5.3. Statistical Optimization

5.3.1. Fitting of data to the model

A two-factor, three-level full factorial statistical experimental design requires 9 experiments. All the responses observed for 9 formulations prepared were simultaneously fit to quadratic model using Design Expert 9.0.2.0. It was observed that the best fit model was quadratic model and the comparative values of R2, SD, and %CV are given in table along with the regression equation generated for each response as shown in table. A positive value represents an effect that favours the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that both independent variables, viz., Weight ratio of HPMC E5: HPMC E15 (X1) and Conc. of SSG (X2) have positive effects on the responses, viz., Y1 (Drug release lag time) and Y2 (% CDR at 8 h).

The criteria for selection of feasible region of were as shown in table 5.16

Table 5.16: Desirable values of dependent variables for optimization.

Response	Desirable value
Drug release lag time	360-420 min.
Drug release at 8 hr.	80-95 %

Table 5.22: Evaluation parameter of optimised batch.

Evaluation parameters	Results
Thickness	4.87±0.015
Hardness	5.5±0.1
Diameter	12.11±0.005
Buoyancy lag time	51±1.0
Floating time	>12 hr.
Drug release lag time	409.66±3.05 min.

Table 5.23: In vitro drug release of optimised batch.

Time (hr.)	% drug release
0	0
1	0
2	0
3	0
4	2.50±0.31
5	6.76±0.69
6	11.04±0.54
7	75.43±0.59
8	93.89±1.25

Table 5.24: Result of optimised batch for response variables.

Response Variable	Predicted Values	Experimental Values
Y1 (Drug release lag time)	413.47 min.	410 min.
Y2 (% Drug release at 8 hr.)	92.39%	93.89%

5.3.5. Validation of experimental model

For the checkpoint formula, the results of the dependent variables Y1 (Drug release lag time) and Y2 (%Drug Release at 8 h) were found to be within limits. Table 5.25 shows the predicted and experimental values for all the response variables, and the percentage bias. Percentage bias is helpful in establishing the validity of generated equations and to describe the domain of applicability of RSM model.

Table 5.25: Result of checkpoint batch.

Response variable	Predicted Value	Experimental Value	% Bias
Drug release lag time	413.47 min.	410 min.	0.83
% Drug release at 8 hr.	92.39%	93.89%	-1.62

%Bias = (predicted value − experimental value/predicted value) ∗ 100

5.3.6. Stability Study of optimised batch

Table 5.26: Stability data of optimized batch.

Stability study	Drug release lag time	% drug release
Before	410 min.	93.89 %
After	407 min.	95.38 %

After one month stability study of optimized formulation, values of parameters like drug release lag time and % cumulative drug release at 8 hr. were almost similar to the initial values. There was no significant change in any value so formulation is stable.

5.3.7. Comparision with marketed product

Comparision of optimized batch formulation with marketed product of enalapril maleate uncoated tablet.

Table 5.27 Evaluation of marketed product.

Evaluation parameters	Results
Hardness	3.23±0.15
Diameter	7.06±0.05
Disintegration time	29.66±2.51

Table 5.28 In vitro drug release study of marketed product.

Time (min.)	% Drug release
5	34.04±0.95
10	51.83±0.76
15	68.55±0.71
20	79.56±1.44
25	89.91±1.06
30	93.32±0.72

DISCUSSION

From the in-vitro release study of marketed product, it can be concluded that the marketed product released maximum drug within 30 minute and when it compared

with selected formulation of pulsatile tablet, it released maximum drug at 8 hrs. Hence, it can be concluded that marketed product was immediate release tablet and selected formulation was controlled released tablet.

CONCLUSION

The present investigation deals with the formulation and development of floating pulsatile drug delivery system for chronotherapy of hypertension using polymers such as HPMC E5, HPMC E15 and HPMC E50. Combination of HPMC E5 and HPMC E15 were used as release rate controlling polymer for maintaining of drug release lag time. So thus Enalapril maleate could be successfully delivered to provide chronopharmacotherapy if taken at bed time and gives early morning release during that time worsening of condition.

From the evaluation parameter of trial batches it should be concluded that if the concentration of polymer increases or using high viscosity grade polymer than drug release lag time will be increases.

The formulation was optimized using two factor and three level factorial design. The amount of independent variables like weight ratio of polymer HPMC E5: HPMC E15 (X1) and concentration of SSG (X2) showed effect on dependent variables like drug release lag time (Y1) and % drug release (Y2) at 8 hr. Response surface methodology was used to predict levels of factor X1 and X2 to obtain optimization of formulation. From the results of factorial batches, it should be concluded that weight ratio of polymer increase than lag time increase and conc. of SSG increase than % drug release increase. After 1 month stability of optimized batch it should be concluded that there is no significant change in lag time and % drug release.

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