FORMULATION AND EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM USING NOVEL ANTI-HYPERTENSIVES FOR THE CHRONOTHERAPY OF ANGINA.

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ABSTRACT

The aim of current investigation was to formulate an effective drug delivery system for patients suffering from cardiovascular problems such as early morning Prinzmetal's angina. To achieve this goal, pulsatile drug delivery was selected because it delivers the drug at right time and at right situation. PTC and PTN drug was taken for getting relief from cardiac problem. The core tablet was prepared using superdisintegrant for instant release. Direct compression technique was used for preparation of core tablet. Core tablet were further compression with HPMC E15 and E50 for lag time. The compressed tablets were evaluated for acceptable physical properties, *in-vitro* drug release and stability study. The result indicated that compressed coated F6 formulation shows rapid and complete drug release of PTC and PTN after 6 hours lag time which is suitable for both drug to achieve time control release, based on chronopharmacutical approach for the treatment of angina.

KEY WORDS: - HPMC E15, HPMC E 50, Pulsatile drug delivery, Prinzmetal's angina.

I. INTRODUCTION

The conventional oral drug delivery is used since decades as most widely used route of administration. It is the most preferred route for the administration of drug and its formulation. As oral dosage form has more advantages as compare to other dosage form such as convenient, patient acceptance, easy to handle, easy to administer, accurate dosage, cost effective, more shelf life etc. (Singhai et al, 2010)

Now a day's various advances in novel drug delivery helps in enhancement of safety and efficacy of the drug and its formulation. As oral drug delivery is still preferred route for drug administration. The dissolution rate is often the rate determining step in drug absorbance; solubility and dissolution is the most important key for examination of oral bioavailability.

One of the most important type of oral drug delivery system is oral controlled drug delivery system. Which represent the popular and convenient form of drug delivery system for most convenient oral advantageous oral dosage form, these oral controlled drug delivery system releases the drug in constant or with random release rate as per the demand or need of the drug. (Nayak et al, 2015)

This dosage form mainly gives a best and various advantages such as constant drug deliveries, loss of drug, reduction in drug dose level and time improve patient compliances. The main aim of this drug is to release a drug after a lag time. This pattern of drug release is called as pulsatile drug release or controlled drug release system. (Shivakumar et al, 2014) Pulsatile drug delivery system aims is to release drug at specific time at specific quantity in an appropriate site if action.

Pulsatile system is designed in such a manner that at the site of action the availability of drug is in right amount and in right time (Sokart et al, 2013). The model drug selected for the present work is PTC and PTN. This shows action on beta blocker and calcium channel blocker receptor and hence acts as pulsatile drug delivery system as anti-angina drug.

II. MATERIALS AND METHODS

PTC, PTN, Hydroxyl propyl methyl cellulose E5 and E 50, Micro crystalline cellulose (MCC), Cross carmellose sodium, Magnesium Stearate, Talc, Sodium Starch Glycolate, Polyvinyl pyrrolidone K 30.

Preparation of PTC and PTN core tablets.

The formulation of PTC and PTN core tablets was shown in Table 1. All ingredients used were passed through sieve no. 40 separately. PTC, PTN, Cross carmellose sodium, Micro crystalline cellulose, Sodium starch glycolate and polyvinyl pyrrolidone K30 were mixed in motor and pestle. Talc and magnesium stearate were then added to above mixed powder. Finally, 100 mg of the blend was weighed accurately and compressed by 8 station tablet press machine (Hanna Instruments, India), equipped with 6 mm flat-faced punches and die (Jitendra et al, 2014).

Preparation of core-in-cup tablets.

The different grade of polymer was used for core coating by direct compressed method. The HPMC E15 and E50 were used in various concentrations shown in Table 2. In this technique die is fill with half coating material and then core is kept in center, after it the reaming half coating material has been poured in it and compressed by 8 station tablet press machine, equipped with 10 mm flat-faced punched and die (Patel et al, 2016).

Calibration curve for PTC and PTN in 0.1 N HCl: -

10 mg of drug were weight accurately and dissolved in 100 ml of 0.1 n HCl in volumetric flask. The concentration was 100 µg/ml after dissolution. From the dilution various stock solutions was prepared to get concentration of 5-25 µg/ml. The working standard was scanned for λmax using UV-Spectrophotometer. Both the drug separately analyzed by same procedure.

Calibration curve for PTC and PTN in 6.8 pH Phosphate buffer: -

10 mg of drug were weight accurately and dissolved in 100 ml of 6.8 pH Phosphate Buffer in volumetric flask. The concentration was 100 µg/ml after dissolution. From the dilution various stock solutions was prepared to get concentration of 5-25 µg/ml. The working standard was scanned for λmax using UV-Spectrophotometer. Both the drug separately analyzed by same procedure (Movva et al, 2013).

FTIR: -

FTIR analysis was carried out to find out the drug-drug and drug-excipients. The sample of both drug and excipients were mixed with KI for analysis. The spectra obtained was compared and interpreted for their functional group (Domala et al, 2014).

III. PRE COMPRESSION PARAMETERS

1. Angle of repose

The angle of repose of powder was measure using funnel method. In this method funnel is kept in vertical form and fill with the powder. After it has been released which from cone on paper kept bellow. Then measure the height and radius of it. Calculate the angle of repose by following formula, (Jagdale et al, 2014)

$$Tan\theta = \frac{h}{r}$$

Where,

θ is the angle of repose,

h is the height of cone,

r is base radius of cone.

2. Bulk Density

Bulk density can be defined as the ratio of mass to volume of the material. The bulk density of a powder mainly depends on particle size distribution. The equation for determining the bulk density is, (Malladi et al, 2016)

$$\rho_b = \frac{M}{V_p}$$

Where,

ρ_b = Bulk density

M = Weight of sample in grams

V_p = Final volumes of powder in cm^3.

3. Tapped Density: -

Tapped density of given powder was measure using measuring cylinder which was filled with quantity of the powder. The measure cylinder was then placed on tapper apparatus, which taps the powder approximately 100 taps. Within this tap powder totally reached its minimum level. The tapped density was calculated using following formula, (Hasan et al, 2017)

$$\rho_t = \frac{M}{V_T}$$

Where,

ρ_t = Tap density

M = Weight of powder in grams

V_T = Tapped volume of powder in cm.

4. Compressibility Index: -

Carr's index is used for the determination of powder compressibility index. Carr's index formula given bellow, (Gifty et al, 2015)

$$\text{Carr's Index}(\%) = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}}$$

5. Hausner's Ratio: -

It has been used to get information regarding flow property of powder. It has been determined by following formula, (Sandhya et al, 2015)

$$Hausner's\ Ratio = \frac{Tapped\ Density}{Bulk\ Density}$$

Table No. 1:- Composition of core tablet.

Sr. No.	Ingredients	Quantity (Mg)
1.	PTC	25
2.	PTN	05
3.	Cross Carmellose Sodium	02
4.	Micro Crystalline Cellulose (MCC)	02
5.	Sodium Starch Glycol ate	60
6.	Polyvinyl pyrrolidone K30	03
7.	Magnesium Stearate	02
8.	Talc	01
Total		100

Table No 2:-Composition of core-in-cup tablet (F_1-F_4)

Formulation		Coating material (HPMC E 15)		
Batch Code	**Core tablet weight(mg)**	**Coating material in upper layer**	**Coating material in lower layer**	**Total**
F_1	100	90	90	280
F_2	100	100	100	300
F_3	100	110	110	320
F_4	100	120	120	340

Table No. 3:-Composition of core-in-cup tablet (F_5-F_8)

Formulation		Coating material (HPMC E 50)		
Batch Code	**Core tablet weight(mg)**	**Coating material in upper layer**	**Coating material in lower layer**	**Total**
F_5	100	90	90	280
F_6	100	100	100	300
F_7	100	110	110	320
F_8	100	120	120	340

IV. EVOLUTIONS OF CORE-CUP TABLET

1. Diameter

Tablet diameter was measured using Digital vernier caliper. It is expressed in millimeter. (Zay et al, 2017)

2. **Hardness**

The hardness of core tablet and coated tablet was measured using Monsanto tester (Akila et al, 2013).

3. **Friability**

The tablets were weight and placed in plastic chamber of Roche friabilator and rotated at 25 rpm for 4 min. All the tablets were removed, dedusted and reweighted reading note down for calculation. The friability was calculated as per follow, (Chemate et al, 2016)

$$\%\ Friablity = \frac{Final\ weight}{Initial\ weight}\ X\ 100$$

4. **Uniformity of content**

The tablets were randomly selected from the batch and powder them individually. From that powder 40 mg was taken and dissolved in 6.8 pH phosphate buffer. After mixing the different concentration solution was prepared and analyzed by UV spectrophotometrically at ʎmax of the both drug separately. (Garg et al, 2017)

5. Disintegration Study

The disintegration test of both core and coating was done as per procedure given in Indian pharmacopeia. The test was carryout in disintegration apparatus, which conations six tube in basket of 3 inch long. They are open at top and 10 mesh screen at bottom. One tablet was placed in each tube, which was deep in 1 liter water and temperature at 37 ± 0.4 ^{o}C. The test was perform tell all the tablets get disintegrate. (Sharma et al, 2017)

6. In-Vitro Drug Release Study

In-vitro drug release study was performing using two type of buffer solution in USP dissolution testing apparatus type 2 (paddle method). The tablet initially put in 900ml 0.1 n HCl for two hours in 37 ± 0.5 were at 50 rpm. After it dissolution media was changed by 6.8 pH phosphate buffer for further 6 hrs. At fixed time interval 2 ml sample was removed and replaced with fresh buffer solution. The removed sample was diluted till 10 ml. The samples were analyzed using UV- Spectroscope. (Shinde et al, 2012)

7. Stability Studies

The selected formulation was tested for stability study. One month accelerated stability study was performing in condition of relative humidity and temperature (40± 2^{0}C and 75% ± 5% RH). After the one month the tablet were checked for drug release. (Herifindal et al, 2010)

V. RESULT AND DISSECTION

Figure No. 1: - UV absorbance spectrum of PTC in 0.1 N HCL.

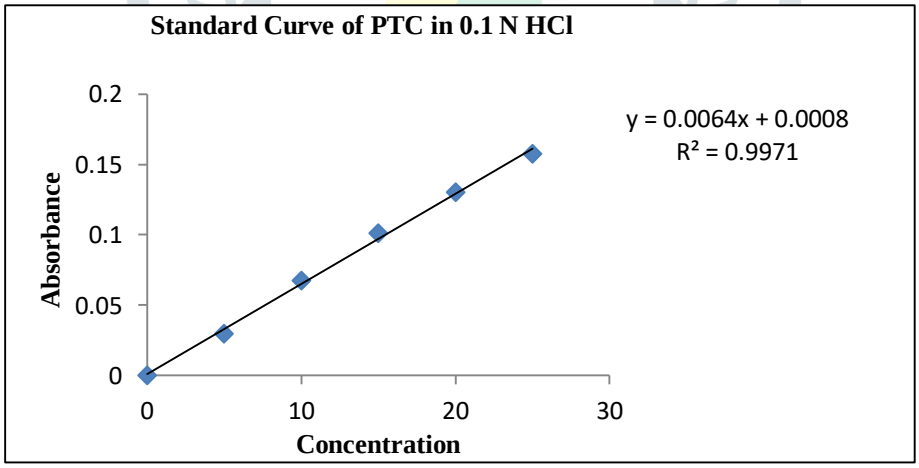


Figure No. 2: - UV absorbance spectrum of PTC in 6.8 pH Buffer.

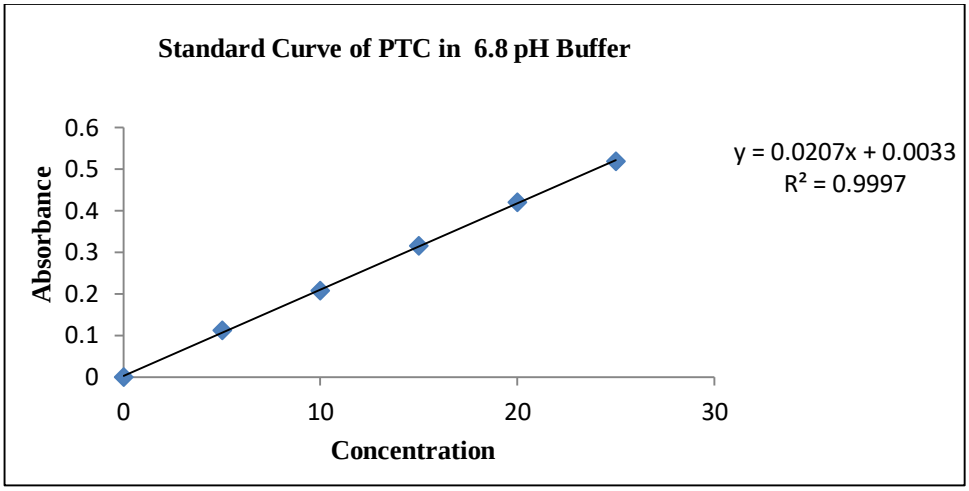


Figure No. 3: - UV absorbance spectrum of PTN in 0.1 N HCL.

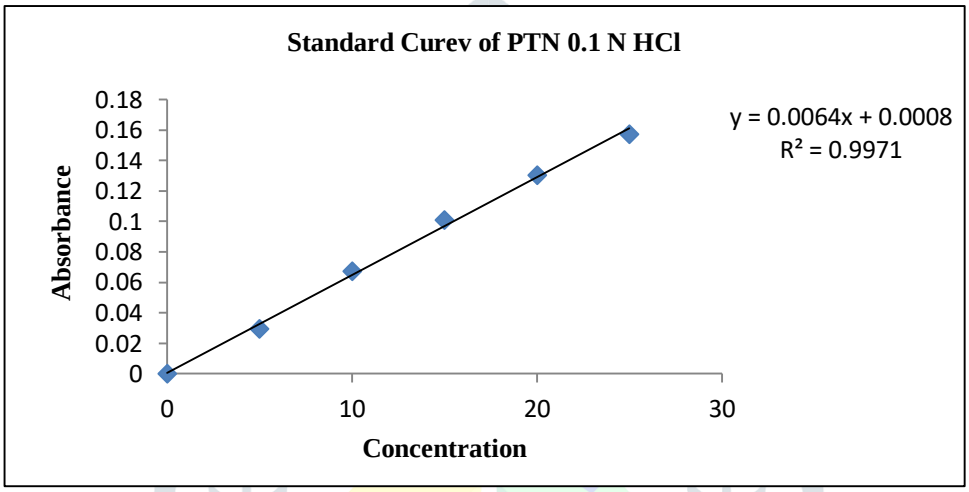
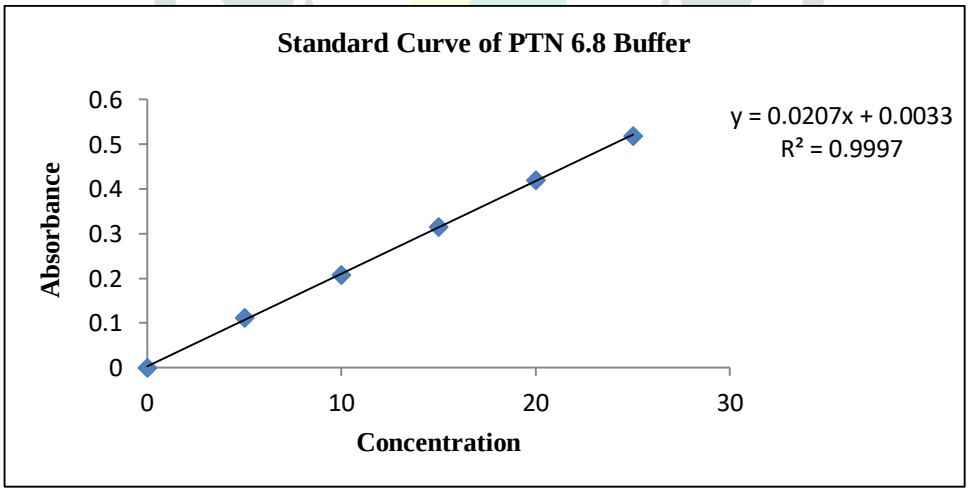


Figure No. 4: - UV absorbance spectrum of PTN in 6.8 pH Buffer.



Compatibility study

By the help of FTIR study we came to know that both the drug don't have any type of interaction and also the both drug don't have any interaction with excipients.

Figure No. 5:- IR spectrum of PTC.

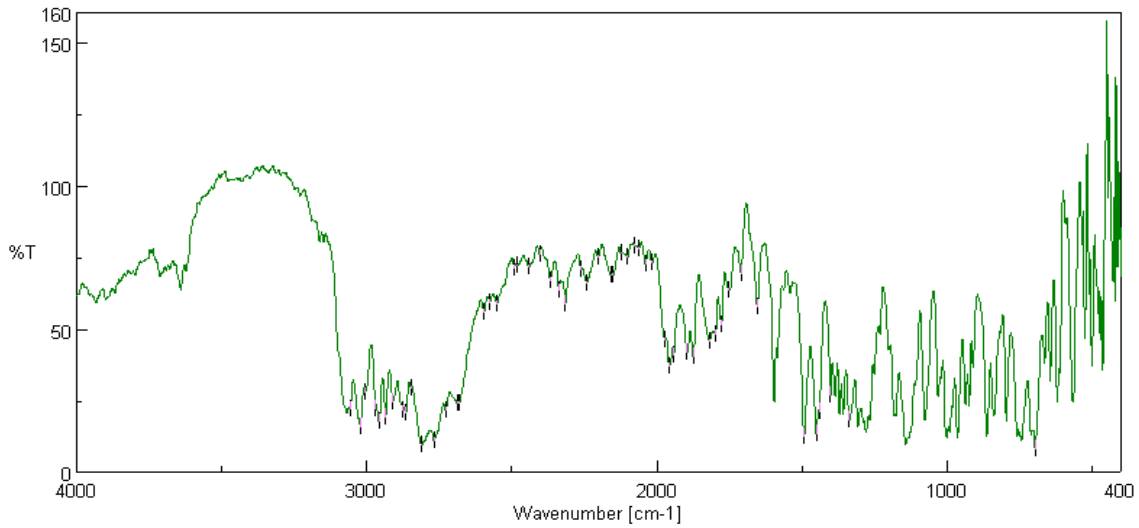


Table No. 4:- Characteristic frequencies in IR spectrum of PTC.

Sr. No.	Inference	Wave Number (cm^{-1})
1.	Aromatic Ring	3021.91
2.	C-H Stretching	2811.7
3.	C=C Stretching	2768.31
4.	C-N Group	1135.99

Figure No. 6:-IR spectrum of PTN.

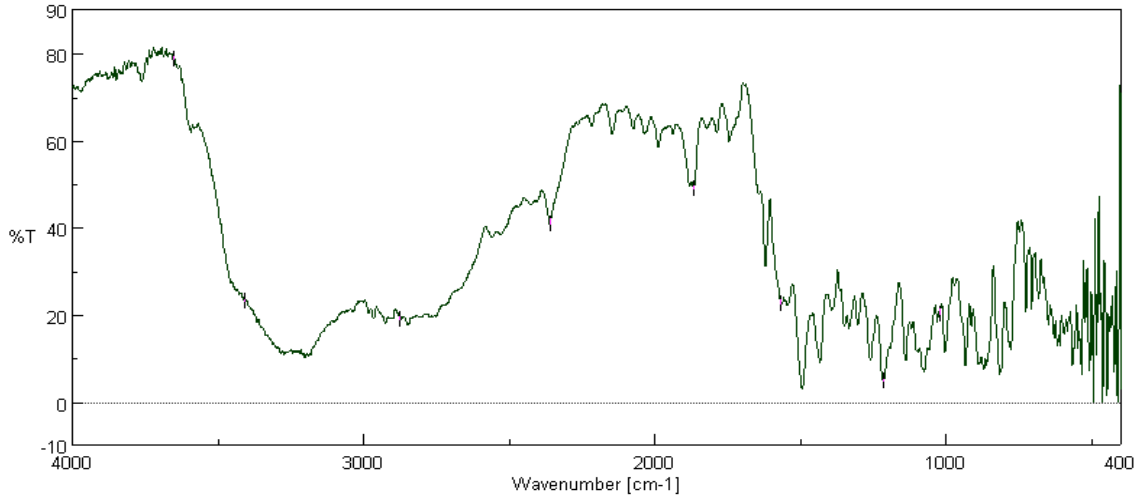


Table No. 5:- Characteristic frequencies in IR spectrum of PTN.

Sr. No.	Inference	Wave Number (cm^{-1})
1.	O-H Stretching for Alcohol & Phenol	3653.48
2.	N-H Stretching for amide	3407.6
3.	C-H- Stretching	2874.38
4.	N-H Stretching for hydrochloride Salts of amino acids	2361.41
5.	C=O-(aromatic) Stretching	1866.76

6.	-N-H- Bending	1566.88
7.	-C=O- Stretching	1214.93
8.	-C-O-(ester) Stretching	1022.09

Pre-compression evaluation study:

In pre compression study all the results are found in the standard limits and have good flow property. Parameters show in table no.6.

Table No. 6:- Evaluation of core tablet powder.

Batch code	Loose Bulk Density (LBD) g/ml	Tapped Bulk Density (TBD) g/ml	Carr's Compressibility Index (%)	Angle of Repose (Degree)
CN_1	0.66 ± 0.01	0.75 ± 0.05	13.43	21.20

Post-compression evaluation study:

In post compression different type of parameter has been study like, weight variation, diameter, thickness, hardness, friability, drug content.

In formulation the friability was found less than 1%, which states that it's mechanically stable. All other parameters has found in its limits. Parameters show in table no.

Table No. 7:-Characterization of Core Tablet

Batch Code	CN_1
Weight Variation (mg)	99.89 ± 0.15
Diameter (mm)	5.02 ± 0.007
Thickness (mm)	4.24 ± 0.005
Hardness (kg/cm^2)	6.50 ± 0.40
Friability (%)	0.343 ± 0.050
Drug Content (%)	99.41 ± 0.68
Disintegration time (sec)	104

Table No. 8:- Evaluation of press coated tablets.

Formulation	Weight Variation (mg)	Diameter (mm)	Hardness (kg/cm2)	Friability	% Drug Content PTC	% Drug Content PTN
F1	189.58 ±0.35	10.25±0.04	6.8 ± 0.55	0.32 ±0.14	99.08±0.47	98.02±0.21
F2	199.98 ±036	10.24±0.01	6.5±0.5	0.15±0.11	99.04±0.50	97.20±0.18
F3	209.47 ±0.31	10.26±0.07	6.4±0.40	0.33 ±0.10	99.02±0.53	98.41±1.01
F4	218.90 ±0.91	10.24±0.04	6.5±0.65	0.49 ±0.12	98.02±0.57	99.25±0.06
F5	189.70 ±0.21	10.26±0.09	6.7±0.60	0.37 ±0.11	99.15±0.19	98.32±0.9
F6	199.42 ±0.31	10.25±0.02	6.5±0.45	0.50 ±0.10	98.18±0.17	97.02±1.41
F7	209.30 ±0.51	10.24±0.05	6.4±0.50	0.24 ±0.13	99.13±0.41	98.22±0.54
F8	219.80 ±0.21	10.26±0.06	6.4±0.40	0.45 ±0.12	98.18±0.07	97.12±1.01

Table No. 9:- Percentage drug release from core tablet.

Time	% Release PTC	% Release of PTN
0	0	0
5	99.557	99.48
10	99.25	98.89
15	97.093	97.42
20	96.738	96.34
25	96.393	95.879
30	95.749	94.24
35	94.504	93.79
40	93.318	93.123
45	92.709	92.145
50	92.306	91.504
60	91.663	90.73

Figure No. 7:- Dissolution profile of core tablet

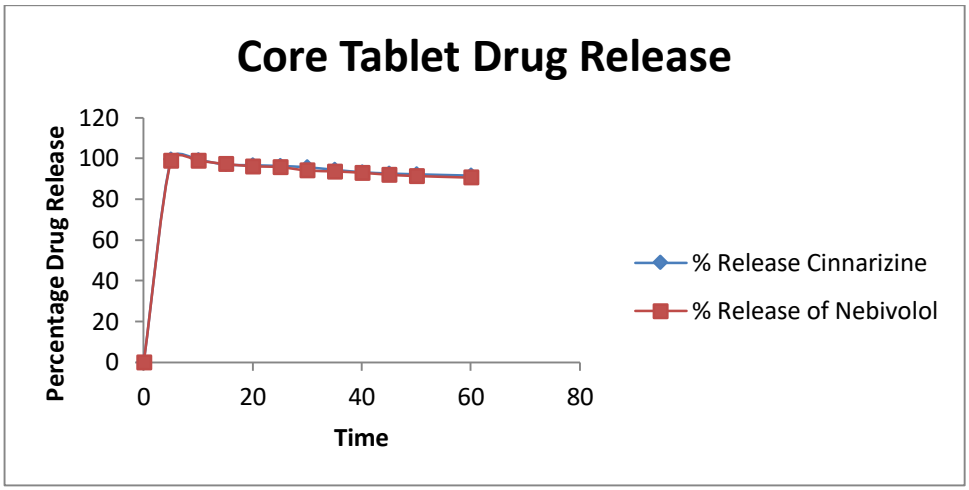


Table No. 10:- Percentage drug release of Batch F1-F4.

Time in Min.	% Release Of Individual Batch PTC			
	F1	F2	F3	F4
00	0	0	0	0
60	0	0	0	0
120	0	0	0	0
180	0	0	0	0
240	0	0	0	0
300	10.89	7.35	4.26	2.01
360	17.61	15.46	9.54	5.14
370	25.62	29.12	18.45	12.48
380	37.54	40.35	27.54	25.73
390	46.78	51.34	40.58	39.98
400	59.89	62.31	53.69	50.45
410	70.12	73.98	67.12	62.47
420	81.25	80.48	78.56	76.23

Figure No. 8:- Dissolution profile of Batch F1-F4.

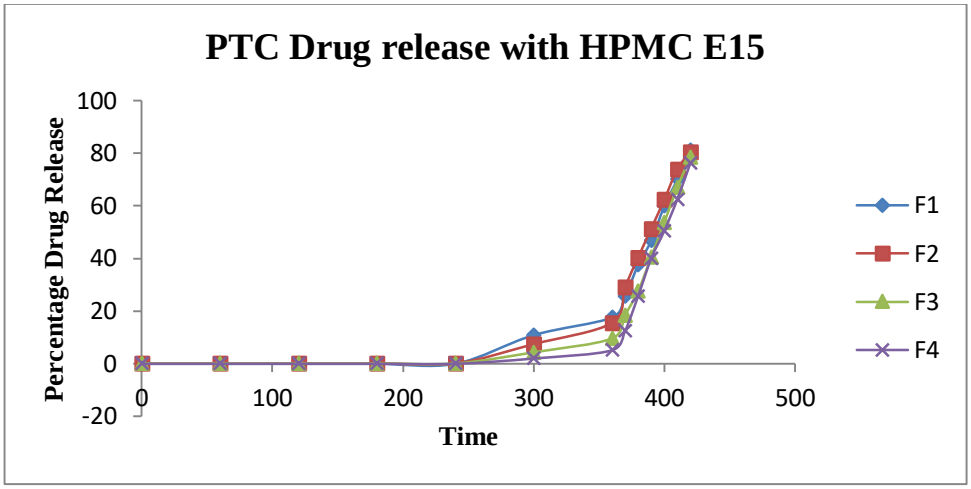


Table No. 11:- Percentage drug release of Batch F1-F4.

Time in Min.	% Release Of Individual Batch PTN			
	F1	F2	F3	F4
00	0	0	0	0
60	0	0	0	0
120	0	0	0	0
180	0	0	0	0
240	0	0	0	0
300	6.001	5.126	3.668	0
360	9.224	8.055	6.885	3.669
370	15.079	11.948	12.151	11.262
380	35.409	35.386	32.891	30.833
390	53.409	53.345	44.633	41.988
400	76.806	76.802	65.154	62.794
410	88.705	88.642	82.802	79.853
420	94.736	94.672	88.82	85.865

Figure No. 9: - Dissolution profile of Batch F1-F4.

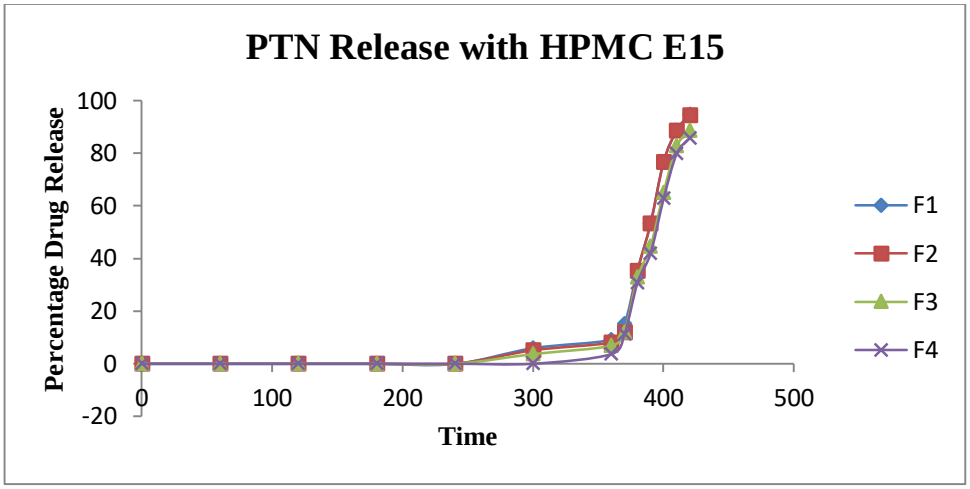


Table No. 12:- Percentage drug release of Batch F5-F8 .

Time in Min.	% Release Of Individual Batch of PTC			
	F5	F6	F7	F8
00	0	0	0	0
60	0	0	0	0
120	0	0	0	0
180	0	0	0	0
240	0	0	0	0
300	26.74	0	0	0
360	42.840	43.182	36.174	31.569
370	51.987	50.747	48.95	43.78
380	63.964	61.165	57.36	52.654
390	77.89	76.007	64.21	69.31
400	86.147	86.134	72.84	74.15
410	95.67	92.287	85.31	86.124
420	99.989	99.979	97.10	95.124

Figure No. 10:- Dissolution profile of Batch F5-F8.

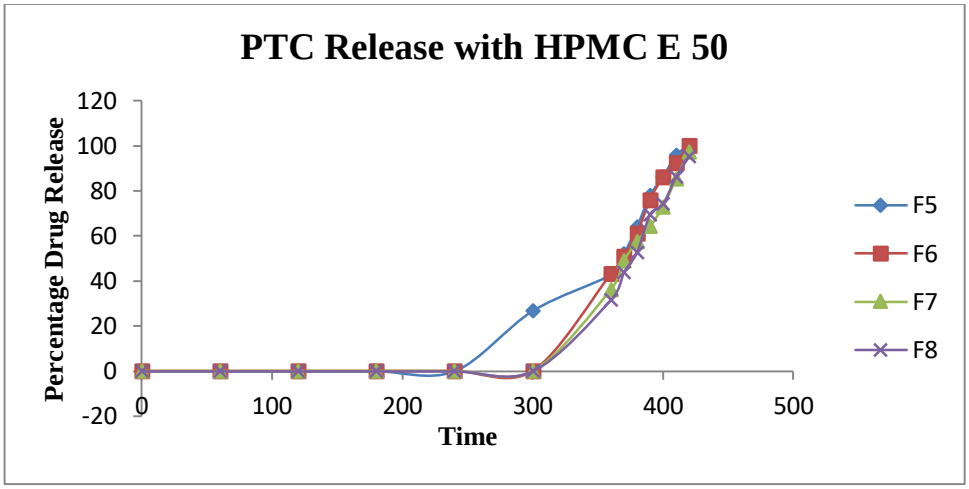
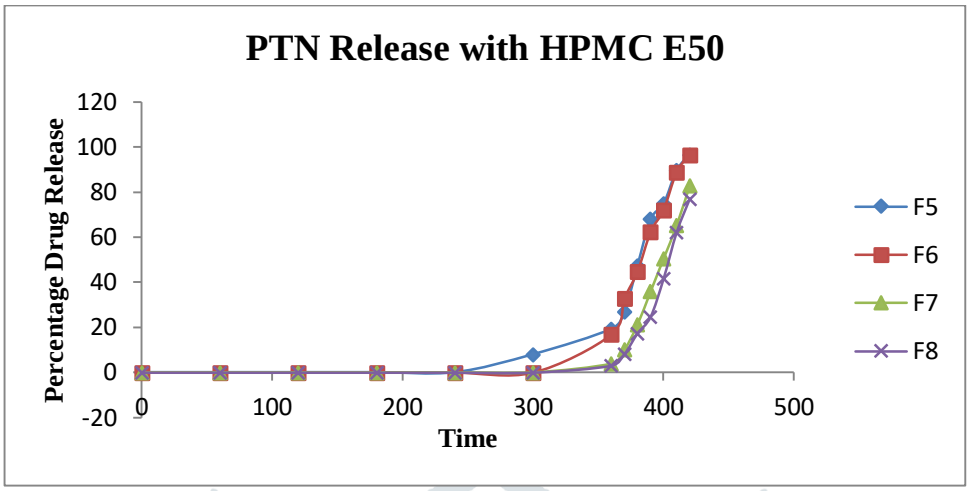


Table No. 13:- Percentage drug release of Batch F1-F4

Time in Min.	% Release Of Individual Batch of PTN			
	F5	F6	F7	F8
00	0	0	0	0
60	0	0	0	0
120	0	0	0	0
180	0	0	0	0
240	0	0	0	0
300	8.012	0	0	0
360	19.33	16.87	3.95	3.084
370	27.025	32.93	10.095	8.258
380	47.506	44.67	21.203	17.394
390	68.033	62.28	35.88	24.712
400	74.89	72.046	50.502	41.687
410	83.81	88.83	65.201	62.201
420	96.57	96.39	82.849	76.925

Figure No. 11:- Dissolution profile of Batch F5-F8.



Stability study:-

Figure No. 12: - Percentage drug release before & after stability study of PTC.

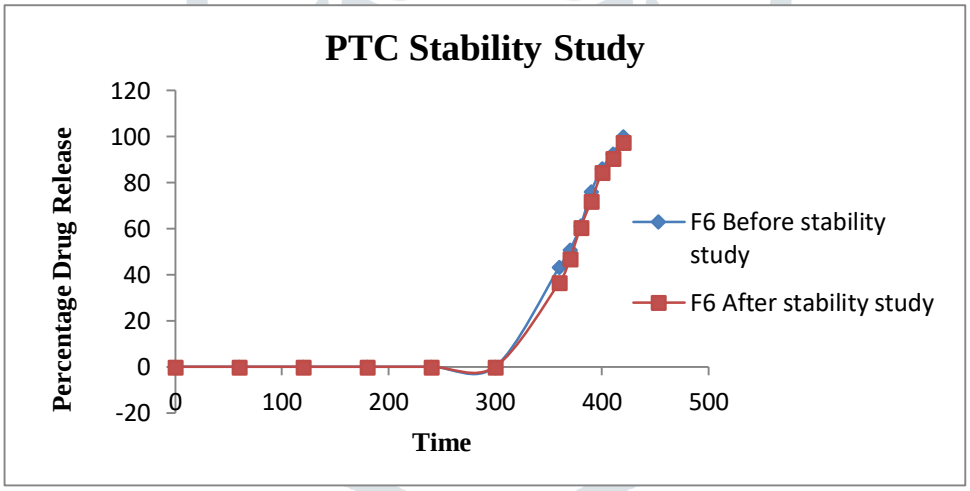
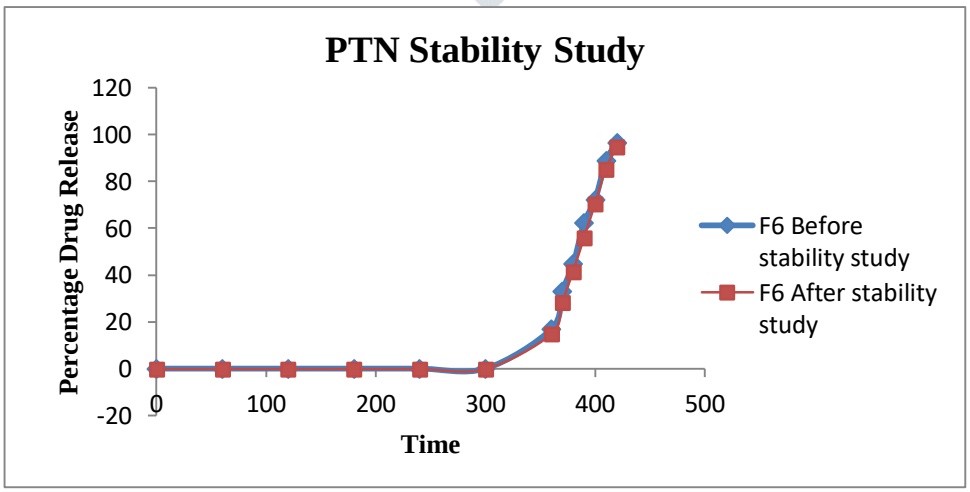


Figure No. 13: - Percentage drug release before & after stability study of PTN.



VI. SUMMARY AND CONCLUSION:

An adequate attempt was completed to develop pulsatile drug delivery system of PTC and PTN to treat Angina. Tablets were prepared using different grade of polymers like HPMC E15 and HPMC E50. Tablet was also evaluated for *In vitro* studies.

From the results found in the current study, we can concluded that-

- From the IR study we observed that there were no Drug- Drug interaction and Drug-Excipient interaction.
- To get lag time of 6 hrs. we have coated tablets with different grade of HPMC and evaluated with *in vitro* dissolution study.
- From the study we can say that lag time is indirectly proportional to the amount of polymer used for coating.
- The release profiles of drug from all formulations followed first order kinetics.
- Between different grades HPMC E 50 F6 shows most suitable result for pulsatile drug delivery.
- Pulsatile tablet F6 shows 99.97 % of PTC drug and 96.83 % of PTN drug release after 6 hrs.
- The stability study of F6 was carried out as per the standard protocol.
- From study we can conclude that pulsatile tablet of F6 PTC and PTN has 6 hrs. lag time. Tablet taken at 9 pm and can release drug at 3 am when symptoms of angina occurs.

VII. REFERENCE

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