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Design and Development of Press Coated Prasugrel Hydrochloride Tablets for Pulsatile Drug Delivery System.

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ABSTRACT

The main aim of the present work was to develop and evaluate Prasugrel hydrochloride press coated pulsatile tablets which releases the total amount of drug at early morning to prevent heart attacks in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) given in combination with Aspirin.This press-coated tablets containing Prasugrel hydrochloride in the inner core was formulated with an outer barrier layer by HPMC K100 / HPMC K4M / Hydroxy propyl cellulose+Hydroxy ethyl cellulose/ Eudragit. The inner core tablet was prepared by the direct compression. technique and outer barrier layer was applied by press coating technique.The effect of polymer on the lag time of drug release was investigated. Prepared Press Coated Tablets was evaluated for all physical tests. Among all the polymers HPMC K100 showed best lag time time for a period of 5 hours and the drug release was prolonged for a period of 12 hours. Compatibility studies carried out by FTIR and DSC studies revealed that all the excipients and polymers were compatible with drug. Accelerated stability study was carried out for the optimized formulation which indicated insignificant difference between before and after storage of formulation.

Keywords: Pulsatile tablets, press coated tablet, prasugrel, lag time

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INTRODUCTION

Pulsatile drug delivery systems are designed according to the circadian rhythm of the body. Disease conditions where constant drug levels are not preferred but need a pulse of therapeutic concentration in a periodic manner acts as a push for the development of pulsatile drug delivery system. These systems have a peculiar mechanism of delivering drug rapidly and completely after a "lag time" i.e. a period of no drug release, characterized by a programmed drug release [1]. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon and cases where night time dosing is required. [2-3].

Prasugrel HCL, thienopyridine derivative is a platelet activation & aggregation inhibitor. For patients with acute coronary syndrome, prasugrel has been shown to decrease the rate of a combined end pointof cardiovascular death, myocardial infarction, or stroke as well as the rate of a combined end point of cardiovascular death, myocardial infarction , stroke, or refractory ischemia.Onset of myocardial infarction has been shown to be more frequent in the morning.Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in the morning. The cause for the findings have been suggested to release of catecholamine , cortisol increase in the platelet aggregation and vascular tone[4]. Antiplatelets are more effective when administered during night..Press coated system can be helpful in this case as they are easy to manufacture and cost effectivethan other system and also promising one. So the main aim of the present study is to develop andevaluate press-coated pulsatile tablets providingmaximum drug plasma concentration fora period of 12 hours after a lag time of 5 hours for those who takes evening dose at approximately 22:00.

MATERIALS AND METHODS

Materials

Prasugrel hydrochloride is a gift of sample from Lara Drugs(Hyderabad,India).HPMC K100M, K4M is a gift of sample from Hetero labs,Hyderabad.Hydroxy Ethyl Cellulose(HEC) from Yucca Enterprises, Mumbai .Hydroxy propyl cellulose (HPC), Eudragit-s 100, are gift of sample from Lara Drugs Hyderabad. Microcrystalline cellulose (MCC) Avicel pH102, from LOBA chemicals, Mumbai.Crosscaramellose is a gift of sample from CiplaLtd,Mumbai. Sodium CMC from Qualigens Fine Chemicals, Mumbai. Talc from Moly Chem.Products, Mumbai. Magnesium stearate from SD fine chemicals, Mumbai. All ingredients were of pharmaceutical and analytical grade.

TABLE 1: Formulation of core tablet

S.No	Name of the ingredient	Quantity (mg/tablet)
1	PrasugrelHCl	10
2	Microcrystalline cellulose	60
3	Lactose	23
4	Crosscaramellose	5
5	Magnesium stearate	2

Preparation of inner core tablets

The mixtures of PrasugrelHcl,Microcrystalline cellulose (MCC, Avicel pH102) , Cross-caramellose Sodium (Ac-Di-sol) and Lactose were dry blended for 5 min followed by addition of Magnesium stearate .These mixtures were further blended for 5 min. Finally 100mg of the powder mixture were weighed and fed manually into the die of a single punch tabletting machine (Cadmach,Ahmedabad , India) , equipped with 6mm round concave punch to produce the desired core tablets . The hardness of the tablets was adjusted at 1- 2 Kg/cm^2 using Monsanto hardness tester[5].

Evaluation of prepared powder mixture for core tablets

Prepared powder mixtures for core tablets were evaluated for flow properties such as angle of repose, Bulk Density, Tapped density, Carr's Index and Hausner's Ratio.

Preparation of press coatedtablets

As shown in the Table 2 , various formulation compositions containing Hydroxy Ethyl Cellulose (HEC) and Hydroxy Propyl Cellulose(HPC) , Eudragit-S, HPMC K100, HPMCK4M, were weighed, dry blended up to about 10 minutes and used as press–coating material to prepare press coated pulsatile tablets by Direct compression method. Half of the powder mass for one tablet coat was weighed into a die (10mm in diameter). A lower coating layer was consolidated and the core centered on an even bed. The remaining powder was then added to the die and the final compression was done by 10mm round concave punch on a single punch tabletting machine (Cadmach ,Ahmedabad ,India) to produce press coated tablets . The hardness of the tablets was adjusted at 5- 6 Kg/cm^2 using Monsanto hardness tester[6].

TABLE 2: Formulation of coating compositions.

INGREDIENTS	F1	F2	F3	F4
HEC	75			
HPMCK100M			150	
HPC	75			
EUDRAGIT-S		150		
HPMC K4				150
MCC	380	380	380	380
LACTOSE	50	50	50	50
TALC	10	10	10	10
MAGNESIUM STEARATE	10	10	10	10

Evaluation of core tablets and final press coated tablets:

The press coated tablets of each formulation batch were then evaluated for tablet characteristicssuch as thickness, hardness, weight variation, friability, drug content and in vitro dissolution test.

Drug content:

Twenty tablets were weighed, finally powdered and powder equivalent to 10mg of drug was transferred into the 100ml volumetric flask and add 5 ml of methanol and make up to the 100ml with 6.8 Phosphate buffer and subject it for sonication for 15 min and filtered through0.42 nm of whatmann filter paper and analysed through UV Spectrophotometrically at 254nm.

Lag time of coated tablets:

Coated tablets were evaluated for lag time in 1.2 pH hydrochloric acid ,7.4 phosphate buffer and 6.8 phosphate buffer respectively. Coated tablets were placed in 900 ml of above mentioned dissolution media , agitated at 75 rpm and maintained at 37±0.5^{0}C. The time taken for outer coating to rupture was monitored and reported as lag time[7].

DISSOLUTION STUDIES OF THE COATED TABLETS

Drug release studies of coated tablets were carried out using USP II dissolution test apparatus. In order to simulate the pH changes along the GI tract, three dissolution media with pH 1.2, 7.4 and 6.8 were sequentially used referred to as sequential pH change method. When performing experiments, the pH 1.2 medium was first used for 2 hours (since the average gastric emptying time is 2 hrs.), then removed and the fresh pH 7.4 phosphate buffer. After 3 hours (average small intestinal transit time is 3 hrs.), then the medium was removed and colonic fluid pH 6.8 buffer was added for subsequent hours [8]. Nine hundred milliliters of the dissolution medium was used at each time. Rotation speed was 75 rpm and temperature was maintained at 37±0.5^{o}C. Five milliliters of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed at 254 nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

Compatibility studies

Compatibility of Prasugrel Hydrochloride with the excipients was investigated by Infrared Absorption Spectral Analysis (FTIR)[9].

Accelerated stability study

The accelerated stability studies were carried out for optimized formulation. The formulationwas stored at25±5^{o}C/60% RH and at 40 ± 2^{0}C/75 ± 5 % RH for three months (90 days). At the regular interval of every30 days, samples werewithdrawn and retested for *in-vitro* dissolution test[10].

RESULTS AND DISCUSSION

As per results shown in Table 3, the obtained values of bulk density 0.271±0.021± 0.001 g/cm3 and0.319±0.005 g/cm3 were found within the acceptable range. The percent

compressibility values were within the range of 11.87±0.017-14.240±0.019 indicates acceptable flow property. Hausner's ratio was found to be within the range of1.130±0.024-1.166±0.019, which shown acceptable flow property and good packing ability. Angle of repose was found to be within the range of 25.6±0.031-26.85±0.024, indicated good flow property of the prepared powder mixture for core tablet.

As per results shown in Table 4, hardness of final press coated tablet of the formulation F1 toF4was varied from 5.2±0.81 to 5.5±0.50 Kg/cm2. which indicated good strength of tablet.The average percent weight deviation of all tablets was found to be within the limit and hence allformulation passed the weight variation test as per I.P. Percentage weight loss of tablets of the each formulation was found to be in the range 0.15±0.04 to 0.85±0.01which was less than 1%,indicating good strength of tablet. The drug content was found to be uniform among all formulation and ranged from 96.01±0.04± 0.22to 99.81±0.02. Thickness of the formulation F1 to F4 varied from 4.01±0.18 to 4.23±0.41 which indicated proper relation with coating amount and was maintained properly.

Among all the polymers HPMC K100 showed best lag time for a period of 5 hours and the drug release was prolonged for a period of 12 hours. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. The characteristic absorption peaks of appeared appeared at 688.6, 1279.8 1784.59 & 1680.28 denoting stretching vibration of –CS, -CF, , C=O andC=C, respectively. Form the figures it was observed that same peaks were also reported in the best optimsed formulation (Formulation 3).There was no change or shifting of characteristic peaks in drug in the best formulation (Formulation 3)suggested that there was no significant drug polymer interaction which indicates the stable nature of the drug in the formulation.

The press coated pulsatile tablets were packed in the screw capped bottles and stored at 25 ± 2ºC, 60 ± 5% RH and at 40 ± 2 ºC, 75 ± 5% RH for 3 months. Drug release from press coated pulsatile tablets before and after storage under varying conditions were evaluated periodically at the regular interval of every month. The results indicated that the drug release from the pulsatile press coated tablets was not changed significantly when stored at varying conditions and the release data was given in table. Thus the drug release from press coated tablets was found to be quite stable.

TABLE 3: Evaluation of prepared powder mixture for core tablets:

Formulation	Angle of repose (θ)	Bulk Density (g/cm3)	Tapped density (g/cm3)	Carr's Index (%)	Hausner's Ratio
Core	32.65±0.05	0.35±0.012	0.40±0.022	14.21±0.011	1.15±0.014
F1	26.40±0.07	0.271±0.021	0.316±0.011	14.240±0.019	1.166±0.019
F2	25.76±0.05	0.255±0.025	0.291±0.005	12.37±0.024	1.142±0.014
F3	25.6±0.031	0.350±0.012	0.408±0.011	14.21±0.022	1.161±0.014
F4	26.85±0.024	0.319±0.005	0.362±0.021	11.87±0.017	1.130±0.024

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TABLE 4:Evaluation of core tablets and final press coated tablets.

Batch code	Hardness (Kg / $cm^{2)}$	Thickness (mm)	Friability (%w/w)	Content uniformity(%)	Weight variation (mg)
CORE	1.5 ±0.50	2.77±0.22	0.85±0.01	99.96±0.02	99.75±3.05
F1	5.5±0.50	4.01±0.18	0.29±0.02	96.01±0.04	700.56±2.05
F2	5.2±0.81	4.16±0.22	0.22±0.05	97.40±0.03	700.11±2.11
F3	5.5±0.02	4.15±0.28	0.25±0.05	99.81±0.02	700.31±3.81
F4	5.3±0.50	4.23±0.41	0.15±0.04	96.32±0.05	700.28±2.01

Table 5: Stability studies of best formulation according to ICH guide lines.

S.NO	Time (hrs.)	% drug release (mg)						
		Initial	25±5°C/60% RH			40±5°C/75% RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month
1	1	08.25	08.19	08.14	08.10	08.12	08.07	07.99
2	2	16.61	16.53	16.50	16.46	16.48	16.42	16.38
3	3	25.02	24.90	24.86	24.81	24.84	24.78	24.73
4	4	33.04	32.96	32.91	32.87	32.88	32.85	32.81
5	5	41.94	41.91	41.87	41.84	41.86	41.82	41.77
6	6	49.76	49.67	49.63	49.60	49.61	49.57	49.53
7	7	58.51	58.50	58.45	58.41	58.42	58.39	58.36
8	8	66.82	66.77	66.72	66.69	66.71	66.68	66.63
9	9	74.17	74.12	74.10	74.07	74.09	74.05	73.99
10	10	82.90	82.79	82.75	82.70	82.73	82.69	82.65
11	11	91.07	91.02	91.00	90.96	90.98	90.94	90.91
12	12	99.31	99.24	99.18	99.15	99.16	99.11	99.05

Figure 1 : Schematic representation of a press coated system.

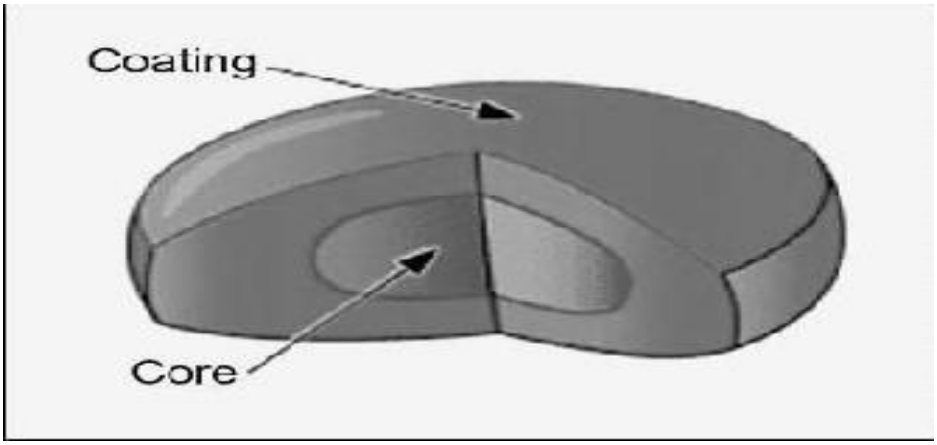

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Figure 2: Steps involve in the manufacturing of press coated tablet.

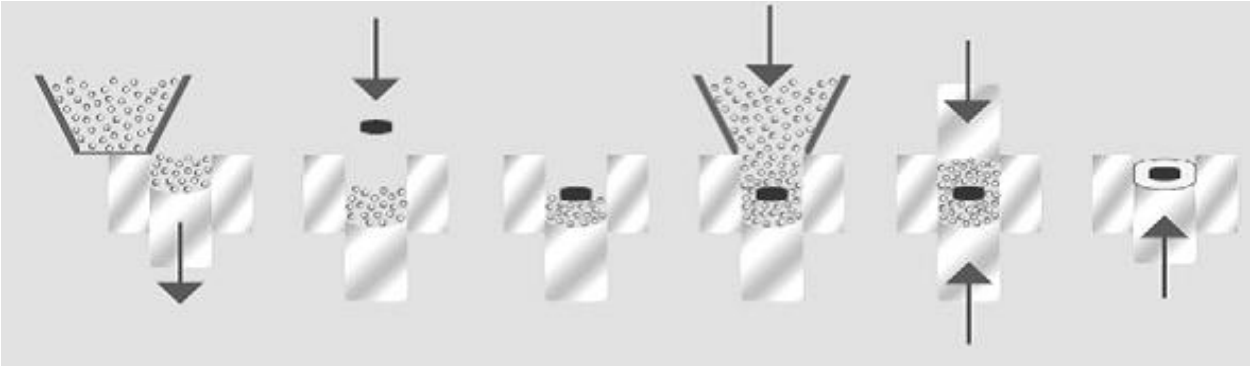

Figure 3: Dissolution profiles of press coated tablets

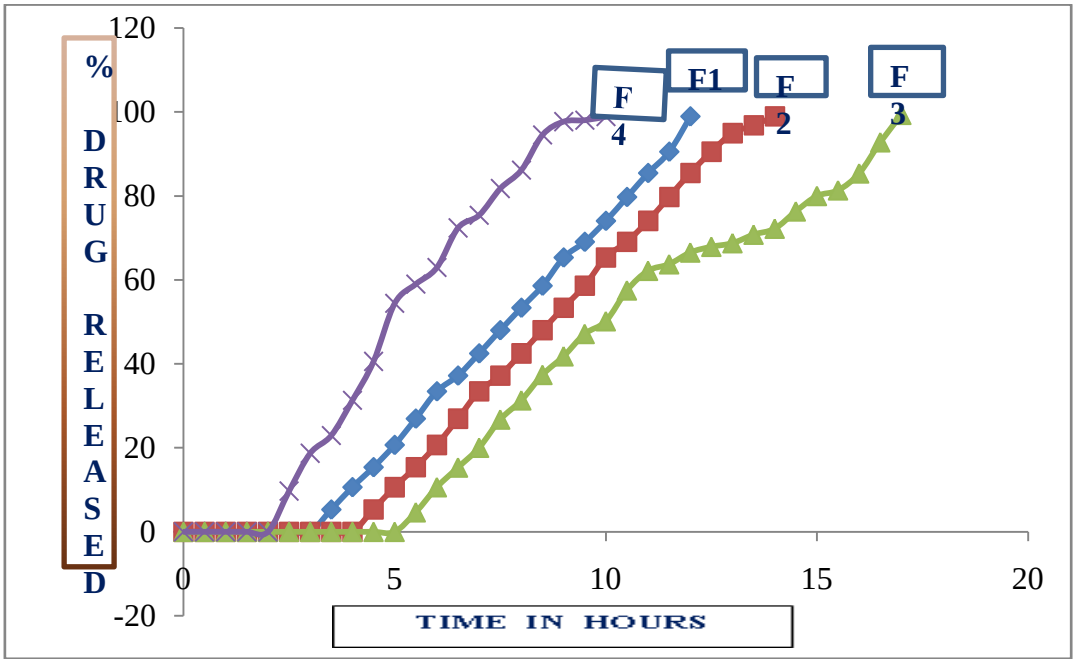

Figure 4: Lag time profiles of press coated tablets

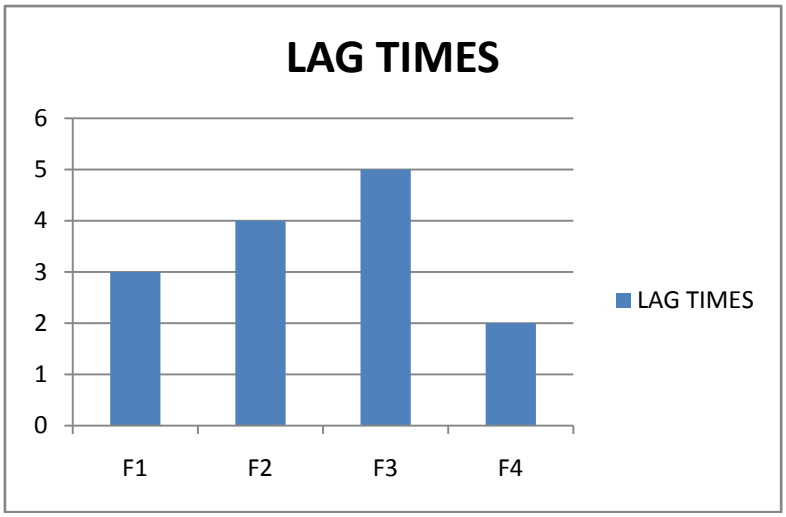

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Figure 5: FTIR Graph of Prasugrel HCL

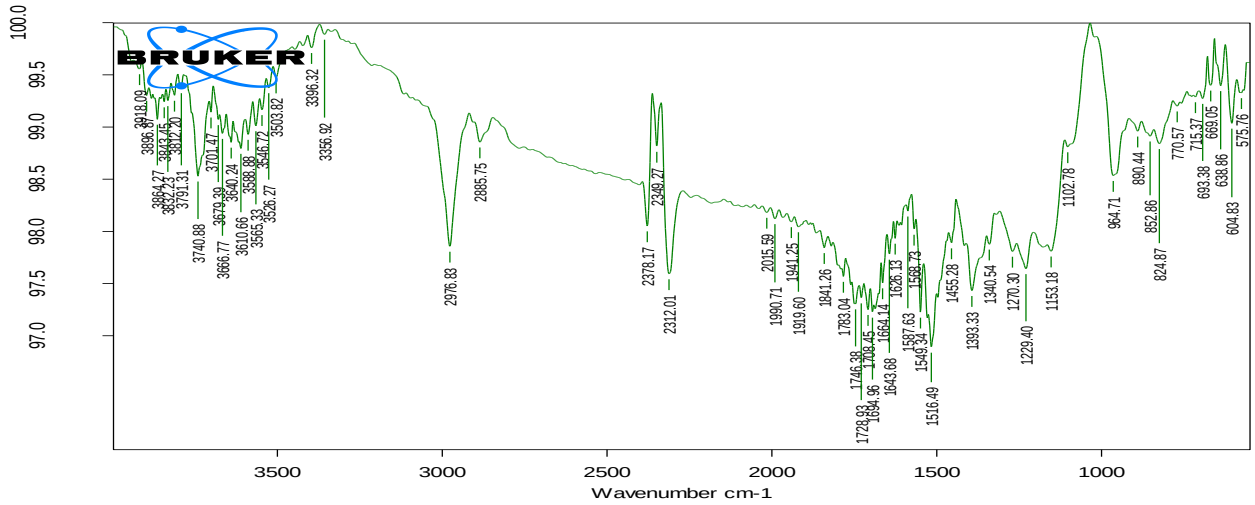
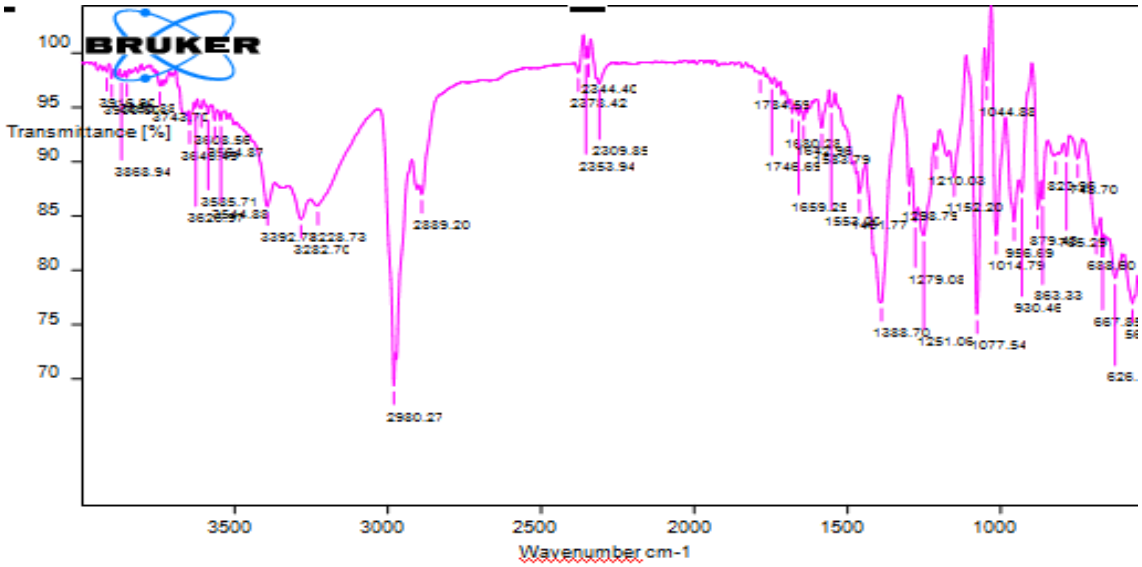


Figure 6: FTIR Graph of Optimised Formulation Containing HPMC K100.



CONCLUSION

Tablets prepared by compressing with HPMC K100 having 5.5kg/cm^2 hardness and 600 mg weight was found to be satisfactory to retard the drug release . A timed delayed press coated pulsatile tablet for chronotherapeutic delivery of Prasugrelhydrochloride was successfully developed. In accordance with the chronomodulated therapy of heart attacks in ACS patients who are undergoing PCI, the lag time criterion of 5 hours and sustained release for a period of 12 hours was satisfied. The dosage form can be taken at bed time and will release the contents in the early morning hours when these symptoms were more prevalent.

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