Optimized gastroretentive pulsatile drug delivery system of propranolol hydrochloride using full factorial design.

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Abstract

Purpose of this research was to optimize compression coated gastroretentive pulsatile release tablet of propranolol hydrochloride for chronotherapy of hypertension. The tablets were prepared using hydroxypropyl methyl cellulose K100 M and carbopol 934 P as matrix forming polymers and polyvinyl pyrrolidone K30 as channeling agent. Prepared tablets were evaluated for floating lag time, total floating time and lag time before drug release. Optimization of formulation was done by using 32 full factorial designs. The concentrations of matrix forming polymers were selected as independent variables whereas lag time before drug release, drug release at 8, 12 and 20 h were selected as response variables. Tablets of optimized batch F5 containing 25% hydroxypropyl methyl cellulose K100 M and 9% polyvinyl pyrrolidone K30 exhibited the maximum similarity with theoretical profile with similarity factor of 80.69. The lag time before drug release (5 h), drug release at 8 h (27.39%), 12 h (49.48%) and 20 h (86.69%) of optimized batch were close to theoretical release profile. The mechanism of drug release of optimized batch was found to be super case II transport and followed zero order kinetics. Drug-excipient compatibility study showed no interaction between drug and excipients. Stability study of optimized formulation showed that tablets were stable for 1 at environmental conditions of 40 ± 2°C temperature and 75 ± 5% relative humidity. Prepared tablet of propranolol hydrochloride can be useful to provide sustained drug release for 24 h at the site of absorption according to the pathophysiological need of disease.

Keywords: Propranolol hydrochloride, Gastroretentive pulsatile drug delivery, Chronotherapy, Full factorial design.

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Introduction

Various diseases like asthma, hypertension, ischemic heart disease and arthritis show circadian variation that demand time-scheduled drug release for effective drug action. Such diseases like inflammations associated with morning stiffness, asthma and heart attack are prevalent in early hours of the day. Treating these diseases with immediate release dosage forms may be impractical if the symptoms of the disease are pronounced during the night or early morning. Therapy with modified release dosage forms with zero order drug release theoretically leads to controlled and constant levels of drug in plasma throughout the day. In order to optimize therapy in terms of safety, patient compliance, and efficacy, chon pharmaceutical formulations based upon time-controlled drug delivery systems are considered to be potential therapeutic options [1]. Epidemiological studies document that the frequency of many cardiovascular diseases, including myocardial infarction and stroke, varies predictably in time over 24 h as the circadian period. Congestive heart failure and myocardial infarction are manifested more frequently during the night or early in the morning. Blood pressure which arises notably just waking up is usually responsible for such attack. However, for such diseases, conventional drug delivery systems are inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened, because during this time, the patients are asleep [2].

Conventional pulsatile release dosage forms following oral administration are meant to release drug after a lag period of 5-6 h usually in the large intestine. However, the viscous contents of lower part of Gastro Intestinal Tract (GIT) cause hindrance to the drug diffusion and also enzymatic degradation of some drugs makes it an unfavorable site for drug release. Further, highly variable nature of Gastric Emptying (GE) process may result in *in vivo* variability and bioavailability problems. In contrary, gastro-retentive dosage forms reside in stomach only and are not affected by variability of pH, local environment or GE rate [3]. These dosage forms are also specifically advantageous for chon modulated delivery of drugs either absorbed from the stomach, having solubility in acidic pH, requiring local delivery in stomach or degraded in colonic pH. These considerations led to the development of pulsatile release dosage forms possessing gastric retention capabilities.

Many researchers have reported floating pulsatile drug delivery systems for various drugs. Literature survey revealed research articles on gastro retentive drug delivery systems for propranolol using different polymers and approaches. However, no research is reported on Gastro Retentive Pulsatile Drug Delivery System (GRPDDS) for Propranolol Hydrochloride (PH) [4].

PH is a sympathomimetic agent selectively acting on the β 2-adrenergic receptor. It is used as a bronchodilator in the management of hypertension and angina pectoris. It decomposes rapidly at alkaline pH of intestine. The maximum

plasma concentration occurs within 2.5 h and the plasma half-life ranges from 3 to 4 h. It is given orally at a dose of 40-80 mg, twice a day. The oral bioavailability of PH is ~ 20% because of extensive first pass metabolism. Thus PH has all the requisite characteristics for developing into GRPDDS.

The objective of the present research was to formulate and optimize GRPDDS of PH using full factorial design and to find out the best possible formulation intended for bed time dosing to deliver the drug after a lag time of about 5-6 h, at absorption site in stomach with sustained drug release for 18 h after a lag time [5].

Materials and Methods

Propranolol Hydrochloride (PH) was procured from Yarrow Chem Products, Mumbai, India. Hydroxypropyl methyl cellulose K100 M (HPMC K100 M), Carbopol 934 P, polyvinylpyrrolidone K30 (PVP K30), Microcrystalline Cellulose (MCC), lactose and talc were of Indian Pharmacopoeial grade and purchased from SD Fine Chem. Ltd., Mumbai, India. Methanol, hydrochloric acid (HCL) and other reagents used were of analytical grade [6].

Drug analysis

Accurately weighed 100 mg of PH was transferred in to 100 ml volumetric flask. It was dissolved in 0.1 N HCL and the volume was made up to 100 ml with 0.1 N HCL to get the stock solution of 1000 µg/ml. The stock solution was diluted with 0.1 N HCL and was scanned for UV spectrum by using Shimadzu 1800 UV-Visible double beam spectrophotometer. The solution exhibited maximum absorption at a wavelength of 289 nm [7]. From stock solution, serial dilutions in the range of 5-40 µg/ml in 0.1 N HCL was prepared and absorbance of each solution was measured using 0.1 N HCL as a blank. The standard curve was generated for entire range of concentrations. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated. The calibration curve equation obtained was: Absorbance (Y)=0.020 Concentration(X)-0.000 with correlation coefficient of 0.999. This equation was used to calculate concentration of unknown solution based on absorbance.

Drug-excipient compatibility study

The drug-excipient compatibility study was carried out by using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy. DSC of pure PH and composite mixture of PH with other excipients were carried out using DSC instrument. In this process, samples (5 mg) were weighed into aluminum pans and heated under nitrogen from 5 to 250°C. FTTR spectra were recorded using KBr mixing method on FTTR instrument available at central instrument laboratory of the institute [8].

Calculation for the dose of drug in the sustained release tablets

The total dose of PH for GRPDDS was calculated using available pharmacokinetic data from a design of one compartment model with simultaneous release of loading dose and a zero order release maintenance dose, as described [9]. Required dose calculation revealed that the extended release tablet should contain a total dose of 120 mg and it should release 40 mg (33.33%) drug like conventional dosage form at 8 h after pre-determined lag time of 7 h and 5 mg (4.167%) per h up to 24 h. Hence the theoretical drug release profile generated using above values is shown in (Figure 1).

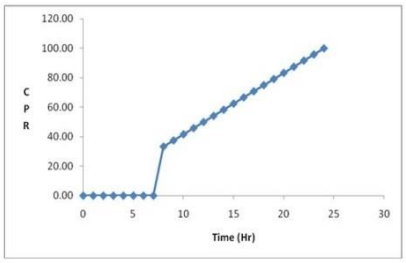

Figure 1. *Theoretical drug release profile from tablet.*

Preparation of core tablets

Core tablets were prepared by direct compression technique. All the ingredients as per formula shown in Table 1 were accurately weighed, passed through 60 # sieve and mixed well using cone blender for 5 min. Then the powder was compressed directly in to tablets using 8 mm diameter die on rotary tablet compression machine to produce final tablet weighing 150 mg (Table 1) [10].

Table 1. *Composition of core tablets.*

Ingredients	Quantity per tablet (mg)	Purpose of ingredient
Propranolol hydrochloride	120	Drug
Lactose	25	Diluent
Magnesium stearate	2	Lubricant
Talc	3	Glidant
Total weight of tablet was 150 mg		

Evaluation of core tablets

The prepared core tablets were evaluated for diameter, thickness, hardness, weight variation, content uniformity and disintegration test. Average thickness and diameter were measured by taking 10 tablets using micrometer screw gauge [11]. Hardness test was conducted for 5 tablets using Monsanto hardness tester and average values were calculated. For friability determination, pre weighed tablet sample (20 tablets) were placed in the friabilator which is then operated for 100 revolutions. The tablets were de-dusted and reweighed. For weight variation test twenty tablets were selected at random, weighed and the average weight was calculated. Not more than

two of the individual weights should deviate from the average weight by more than 7.5%.

For content uniformity determination, twenty tablets were weighed and powdered in a glass mortar. Quantity of powder equivalent to 120 mg of propranolol hydrochloride was accurately weighed and transferred in a 100 ml volumetric flask containing 20 ml of distilled water. The flask was shaken for 10 min and 50 ml of methanol was added. The flask was shaken for an additional 10 min and the final volume was made up to 100 ml with methanol add the resulting solution was filtered through Whattman filter paper. The filtrate was collected and suitably diluted with methanol to produce final solution of 40 mcg/ml concentration and the absorbance of the solution was measured by UV-Visible Spectrophotometer at the maximum at about 290 nm. The content of PH was calculated taking 206 as a specific absorbance at 290 nm.

Disintegration test was carried out for 6 tablets using USP disintegration test apparatus. The medium used was 0.1 N HCL maintained at 37°C. The time taken for complete disintegration was noted and average disintegration time was calculated [12].

Preparation of granules for outer coating layer

All the ingredients as per the formula shown in Table 2 were accurately weighed and passed through 60 # sieve. Then it was mixed properly by using cone blender for 5 min. The resultant powder was granulated by using isopropyl alcohol (IPA) and passed through 40 sieves. The prepared granules were dried in pre-heated oven at 50°C for 10 min [13]. The granules were mixed with the ingredients to be added extra granularly such as talc and magnesium stearate. The prepared granules were stored in zip lock plastic bag away from moisture till further use (Table 2).

Table 2. *Selection of plomer concentration and coating level.*

Ingredients	**Quantity per tablet (%)**											
	P1	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	**P10**	**P11**	**P12**
HPMC K100M	30	30	35	35	40	40	20	20	25	25	30	30
Carbopol 934P	5	5	5	5	5	5	5	5	5	5	5	5
Sodium bicarbonate	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	52	52	52	52	52	52	52	52	52	52	52	52
Talc*	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate*	1	1	1	1	1	1	1	1	1	1	1	1
Coating level in mg/tablet	400	450	400	450	400	450	300	350	300	350	300	350

Evaluation of granules for outer coating layer

The prepared granules were evaluated for preformulation parameters like Bulk Density (BD), Tapped Density (TD), Carr's Index (CI), Hausner's Ratio (HR) and Angle of Repose (AOR). Accurately weighed 25 g of granules, which were previously passed through 20 # sieve were transferred in 100 ml graduated cylinder. Granules were carefully leveled without compacting, and unsettled apparent volume (Vb) was noted. The apparent BD in g/ml was calculated by the following formula: Bulk density=Weight of powder/Bulk volume (Vb). The cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per min. The cylinder was tapped for 500 times and measured the tapped volume (Vt) to the nearest graduated units. The tapped BD in g/ml was calculated by the following formula: Tapped Density=Weight of powder/Tapped volume (Vt). The CI of the granules blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a granules and the rate at which it packed down. The formula used for calculating Carr's index was: Carr's Index (%)=[(TD-BD) × 100]/TD. The HR is a number that is correlated to the flow ability of a granular material. HR=TD/BD. The AOR of granules was determined by the funnel method [14]. The accurately weighed granules were 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 granules were allowed to flow though the funnel freely on to the surface. The diameter of the granules cone was measured and the AOR was calculated using an equation: $\tan \theta = h/r$, where, h and r are the height and radius of the granules cone, respectively.

Preparation of compression coated tablets

The quantity of granules required for outer coating was accurately weighed. Half of the granules were filled in the die cavity manually and leveled it properly. Then the core tablet was placed on granule bed exactly in the center and the remaining half of the granules were filled in the die cavity. After proper leveling the granules were compressed using Rotary tablet compression machine 12 mm flat punch to produce compression coated tablets.

Evaluation of compression coated tablets

The prepared compression coated tablets were evaluated for diameter, thickness, hardness, friability, weight variation and content uniformity as per the procedure described earlier. The tablets were evaluated for *in vitro* floating studies. *In vitro* floating studies were determined by Floating Lag Time (FLT), Total Floating Time (TFT) and matrix integrity. Floating lag time test was performed to check the floating behaviour. The tablets were dropped in the dissolution medium, i.e., 0.1 N HCL maintained at 37°C and stirred at 50 rpm. The time taken by the tablet to come to the surface of the dissolution medium was reported as FLT. Matrix integrity was observed throughout *in vitro* dissolution studies. The swollen mass of the tablets remained intact or not was checked. The TFT was determined by visual inspection of the tablets placed in the dissolution medium maintained at 37°C and stirred at 50 rpm.

The *in vitro* dissolution study of compression coated tablets was performed using USP apparatus type II fitted with paddle (50 rpm) at 37 ± 0.5°C using 0.1 N HCL (pH 1.2; 900 ml) as a dissolution medium. At the predetermined time intervals, 10 ml samples were withdrawn and replaced with equal volume of fresh dissolution medium maintained at same temperature. The samples were filtered and suitably diluted. Absorbance of these solutions was recorded at 289 nm wavelength using Shimadzu UV-1800 double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a calibration curve. All the studies were carried out in triplicate.

Water permeability test was used to evaluate the extent of water penetration into the tablets. Tablet formulations containing 2 mg of amaranth, the water soluble dye, in the core tablet were prepared and used to aid easy recognition of water penetration. Each tablet was separately immersed in 900 ml 0.1N HCL kept at 37 ± 0.5°C. The tablets were removed from the medium at an interval of 1, 2, 4, 6 and 10 h and observed for color change. The spreading of dye in the swollen mass indicated the time for complete wetting of core tablet by 0.1 N HCL. Visual observation of the color change and the condition of the core were used to evaluate the extent of water penetration.

Preliminary screening for excipients selection for outer coating layer

HPMC K100 M and carbopol 934 P were used to prepare granules for outer coating layer of compression coated tablets. Compression coated tablets were prepared at varying concentration of polymer and varying coating level. The final press coated tablets were subjected to *in vitro* floating studies and *in vitro* dissolution studies. Compression coated tablets were prepared with different types of fillers at same concentration of polymer and coating level to study the effect on drug release and matrix integrity as per Table 3. Tablets were subjected to *in vitro* floating and dissolution studies. Compression coated tablets were formulated using thee different channeling agents to increase drug release rate as per Table 4. The final press coated tablets were subjected to *in vitro* floating and dissolution studies (Tables 3 and 4).

Table 3. *Selection of type of filler.*

Ingredients	Quantity per tablet (%)		
	PF1	**PF2**	**PF3**
HPMC K100M	25	25	25
Carbopol 934P	5	5	5
Sodium bicarbonate	10	10	10
Lactose	57	-	28.5
MCC	-	57	28.5
Talc*	2	2	2
Magnesium stearate*	1	1	1
Coating level in mg/tablet	300	300	300

Table 4. *Selection of channeling agent.*

Ingredients	Quantity per tablet (%)		
	PC1	**PC2**	**PC3**
HPMC K100M	25	25	25
Carbopol 934P	5	5	5
Sodium bicarbonate	10	10	10
Lactose	52	52	52
PVP K30*	5	_	_
NaCl*	_	5	_
PEG 4000*	_	_	5
Talc*	2	2	2
Magnesium stearate*	1	1	1
Coating level in mg/tablet	300	300	300

Optimization of variables using full factorial design

A 32 randomized full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations.

The concentration of polymer HPMC K100 M (X1) and concentration of channeling agent PVP K 30 (X2) was chosen as independent variables. Lag time before drug release, Q8, Q12, Q20 (% drug release at 8, 12, 20 h, respectively) were taken as dependent variables. The formulation layout for the factorial design batches (F1-F9) is shown in (Table 5).

Table 5. *Composition of factorial batches.*

Ingredients	Formulation Code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
HPMC K100M (X1)	0.2	0.2	0.2	0.25	0.25	0.25	0.3	0.3	0.3
Carbopol 934P	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Sodium bicarbonate	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PVP K3O* (X2)	0.06	0.09	0.12	0.06	0.09	0.12	0.06	0.09	0.12
Talc*	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Magnesium stearate*	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Lactose q.s to	1	1	1	1	1	1	1	1	1
Coating level (mg/tablet)	300	300	300	300	300	300	300	300	300
Independent Variables	Coded Values				Actual Values (mg)				
Amount of HPMC K 100M (% w/w)	-1		0	+1	60	75	90	-	-
Amount of PVP K3O (% w/w)	-1		0	+1	18	27	36	-	-

Short term stability study

To determine any change for *in vitro* release profile and percentage drug content on storage, a short term stability study of the optimal batch was performed at 40°C in humidity jar with 75% Relative Humidity (RH). Samples were withdrawn at 1mo interval and evaluated for any change of *in vitro* drug release pattern and percentage drug content.

Results and Discussion

Drug-excipient compatibility study

DSC thermograms of PH and the composite mixture of PH with other excipients respectively. It is evident from the DSC thermo grams that the sharp endothermic peak obtained in pure PH was retained without any shift in the composite mixture indicating absence of any physical incompatibility of PH with the excipients used in the tablet formulation (Figures 2 and 3).

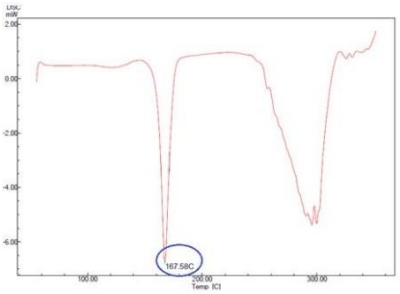

Figure 2. *DSC thermogram of propranolol HCL.*

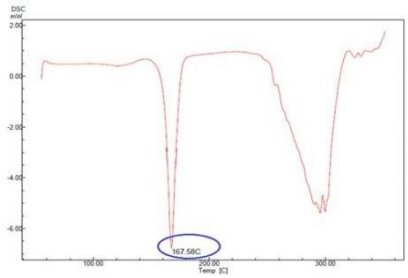

Figure 3. *DSC thermogram of drug with other excipients.*

FTTR spectra of PH and composite mixture of PH with other excipients are respectively. The prominent peaks observed for different functional groups in FTIR spectra for pure PH and the composite mixture are shown in the Table 6. There was not a major change in the peaks corresponding to the functional groups indicating absence of any chemical interaction of PH with the excipients used in the tablet formulation (Table 6) (Figures 4 and 5).

Table 6. *Ftir data for drug and physical mixture.*

Ingredients	Drug Peak (cm-1)	Physical Mixture Peak (cm-1)
Functional group	3282.62	3286.47
-NH stretch	2954.74	2977.89
C-H stretch	1581.52	1581.52
Aryl C=C stretch	1242.07	1265.22
Aryl -O–CH2	1022.2	1033.77
Aryl-O–CH2 symmetric	794.62	771.47
Peak due to alpha- substituted naphthalene		

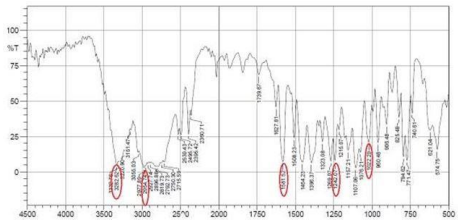

Figure 4. *FTIR spectra of propranolol HCL.*

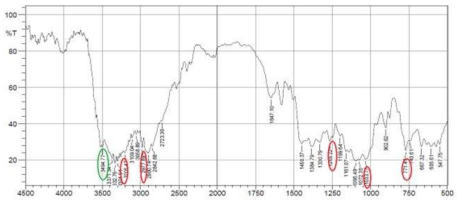

Figure 5. *FTIR spectra of propranolol HCL with other excipients.*

Evaluation of core tablets

The prepared core tablets were evaluated for diameter, thickness, hardness, weight variation, content uniformity and disintegration test. The granules for outer coating layer were evaluated for micromeritic properties and preformulation parameters. That the granules had accepted flowability and compressibility.

Evaluation of compression coated tablets

The compression coated tablets were evaluated for hardness, weight variation test *in vitro* floating studies and *in vitro* drug release studies. The results are as shown in. In water permeability test, the spreading of dye in batch containing 30% HPMC K100 M was slower as compared to batch containing 25% HPMC K100 M due to higher diffusional resistance to water penetration offered by high concentration of polymer. From this study, it can be concluded that tablets with higher polymer concentration has longer time for water penetration in comparison to tablets with lower polymer concentration. The results are in accordance with lesser drug release observed when using higher concentration of polymer.

Optimization of variables using full factorial design

Tablets of factorial batches were evaluated for physicomechanical properties, *in vitro* floating and dissolution studies. The results are summarized. The comparative *in vitro* dissolution profiles of factorial batches are shown in Figure 6. From the results of *in vitro* drug release study it was concluded that as the concentration of polymer increases the drug release decrease due to increased diffusional resistance at higher concentration of polymer. Addition of channeling agent increases the drug release but higher concentration of channeling agent cause rupture of tablet matrix and such effect is typically observed at lower concentration of polymer. Drug release increases proportionately with increase in concentration of channeling agent (Figure 6).

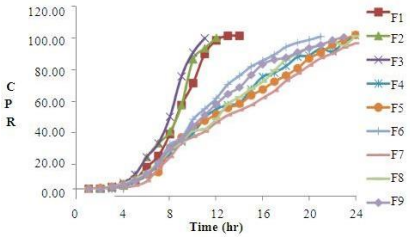

Figure 6. *In vitro dissolution profiles of factorial batches.*

Kinetic modeling of dissolution data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsemeyer-Peppas model as evident from regression coefficients. In case of the controlled or sustained release formulations, diffusion, swelling and erosion are the you most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibition of water, causing the polymer to swell and changing it from a glassy to rubbery state. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. For a sellable cylindrical (tablet) drug delivery system, the n value of 0.45 is indicative of Fickian diffusion controlled drug release, n value between 0.5-0.85 signifies anomalous (non-Fickian) transport, n value of 0.85 indicates case II transport, and n value greater than 0.85 indicates super case II transport. The value of diffusion exponent n for most factorial formulations was>0.85 indicating super case II transport drug release from the formulations [15]. The drug release from optimized batch F5 can be best described by zero order model followed by Higuchi model and the mechanism of drug release is super case II transport as n value is 1.14.

Conclusion

From this research study, it was concluded that development of gastroretentive chronomodulated system provided dual advantage of site specific absorption and pulsatile drug release. In addition, the developed formulations reduced the need of frequent administration and there by enhance patient compliance. A combination of HPMC K100M and carbopol 934 P resulted in sustained release floating pulsatile drug delivery. The prepared tablets provided drug release for 24 h with lag time of 5-6 h before drug release and can be used as once day dosage form for chronotherapy of hypertension.

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References

1. Lemmer B. Chonopharmacokinetics: Implications for drug treatment. J Pharm Pharmacol. 1999;51:887-90.
2. Ghimire M, McInnes FJ, Watson DG, et al. *In-vitro in-vivo* correlation of pulsatile drug release from press coated tablet formulations: A pharmacoscintigraphic study in the beagle dog. Eur J Pharm Biopharm. 2007;67:515-23.
3. Fox KM, Mulcahy DA. Circadian rhythms in cardiovascular diseases. Postgrad Med J. 1991;67:33-6.
4. Millar-Craig MW, Bishop CN, Raftery EB, et al. Circadian variation of blood pressure. Lancet. 1978;1:795-97.
5. Hoffman A, Stepensky D, Lavy E, et al. Pharmacokinetic and pharmacodynamic aspects of gastroretentive dosage forms. Int J Pharm 2004;277:141-53.
6. Badve SS, Sher P, Korde A, et al. Development of hollow porous calcium pectinate beads for floating-pulsatile drug delivery. Eur J Pharm Biopharm. 2007;65:85-93.
7. Krögel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int J Pharm. 1999;187:175-84.
8. Jagdale SC, Sali MS, Barhate AL, et al. Formulation development and evaluation of floating pulsatile drug delivery system of atenolol. J Pharm Sci Technol. 2013;67:214-28.
9. Kshirsagar SJ, Patil SV, Bhalekar MR, et al. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. Int J Pharm Investig. 2011;1:207-13.
10. Roy P, Shahiwala A. Statistical optimization of ranitidine hydrochloride floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. Eur J Pharm Sci. 2009;37:363-69.
11. Hao Z, Xuetao J, Lingshan K, et al. Design and gamma-scintigraphic evaluation of a floating and pulsatile drug delivery system based on an impermeable cylinder. Chem Pharm Bull. 2007;55:580-85.
12. Salunkhe AK, Dias RJ, Mali KK, et al. Formulation and evaluation of floating pulsatile drug delivery system of metoprolol tartrate. Der Pharmacia Letter. 2011;3:147-60.
13. Jagdale SC, Suryawanshi VM, Pandya SV, et al. Development of press-coated, floating-pulsatile drug delivery of lisinopril. Sci Pharm. 2014;82:423-40.
14. Momin S, Khan S, Ghadage DM, et al. Formulation and evaluation of bilayer tablets of propranolol hydrochloride. J Drug Deliv Ther. 2017;7:50-7.
15. Srikanth MV, Uhumwangho MU, Rao NS, et al, Formulation and evaluation of gastro retentive floating drug delivery system for Propranolol HCl. J Pharm Bioall Sci 2011;8:1339-48.

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