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Chronotherapetically Designed Pulsatile, Colon Targeted Formulation for Atenolol- Design and Characterization

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ABSTRACT

Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of diseases or symptoms. The main objective of the present study is to develop single-unit pulsatile drug delivery system for obtaining no drug release till it reaches in colon followed by pulsed drug release in colon to achieve chronotherapeutic release of atenolol for treatment of hypertension and to improve the patient compliance. In vitro studies revealed that the tablet coated with guar gum and Eudragit S-100 have limited drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Programmable pulsatile, colon-specific release has been achieved from tablet of T7 formulation (50:50) which meet demand of chronotherapeutic drug delivery.

Key Words: pulsatile, chronotherapeutic, hypertension, atenolol

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INTRODUCTION

Assuming that physiological processes and biological functions display constancy over time, much effort had been devoted in the past in developing the drug delivery systems that maintain a flatter plasma level for an extended period of time. However, chronobiological studies believe this concept. Along with many applications in local and systemic delivery of drugs, pulsatile release system would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythm, such as hypertension, nocturnal asthma, angina and rheumatoid arthritis.[1]

The situation is markedly different when oral sustained or delayed release formulations are employed, where the extent of absorption is more susceptible to regional differences in drug absorption and gut transit times.

For most immediate release drug formulations, absorption is complete by the time the swallowed dose has reached the colon and the extent of absorption in the distal gut is of little consequence.[2]

Pulsed or pulsatile drug release is defined as the rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off-release period.[3, 4.] i..e. Pulsatile released the drug rapidly and completely after lag time.[5, 6.]

Pulsatile drug delivery system is a zero order reaction. [7, 8.]

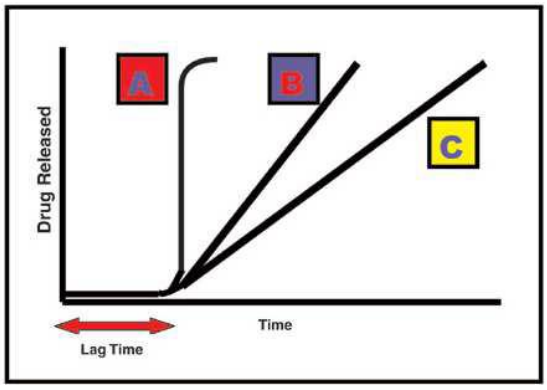

Figure 1 Drug release profiles from pulsatile drug delivery system

A = Release of drug as a "pulse" after a lag time,

B = Delivering the drug rapidly and completely after a "lag time" and

C = Constant drug release over a prolonged period of time after a "lag time". [9,10.]

Pulsatile drug delivery system has gained increasing importance not just for the treatment of diseases that are influenced by the circadian rhythm of the body, but also for the potential it holds to prevent the down regulation of drug receptors and to achieve efficient therapeutic

effects. The time and pH dependant pulsatile drug delivery system is used in treatment of pulmonary disease, cancer, GI ulcer, asthma, angina pectoris, and hypertension. [11,12,13]

Hypertension:-

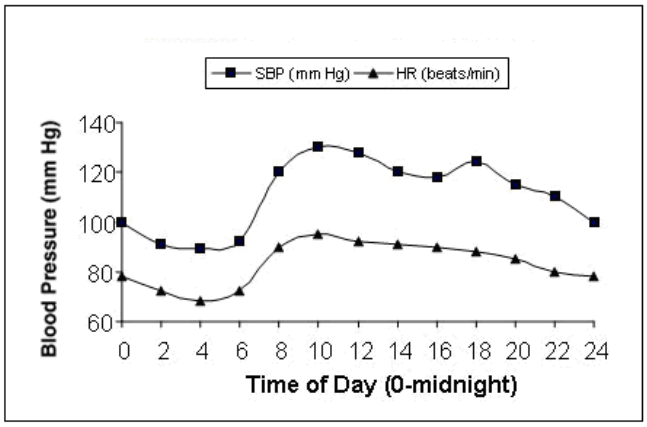

Figure 2 Diagram of circadian variation in systolic blood pressure and heart rate[14]

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, e.g. hypertension, angina pectoris, arrhythmias, and myocardial infarction. Administration of conventional tablet has been reported to exhibit fluctuation in the plasma drug level, resulting either in manifestation of side effect or reduction in drug concentration at the receptor site. Atenolol has strong absorption throughout GIT as well as in colon. But, it causes GI irritation problem. Hence it is always effective to have absorption of Atenolol at colon site.[15, 16, 17]

On the other hand, colon-specific drug delivery system (CDDS) have been developing as one of the site specific drug delivery system .Along with many application in local and systemic delivery of drugs the CDDS would also be advantageous when a delay in absorption is desirable from a therapeutic point of view as for the treatment of diseases that have a peak symptom in the early morning and that exhibit circadian rhythm, such as angina, asthma and rheumatoid arthritis.[19, 20, 22.]

So by developing the pulsatile device for colonic specificity, plasma peak is obtained at an optimal time, number of doses per day can be reduced. The combination of pH-dependent polymers with time based polymers could offer a means for achieving pulsatile release of drug from the coated system.[15,16.]

MATERIAL AND METHOD:

Material

Atenolol was obtained as gift sample from Glaxo Pharma Ltd, Goa, India. Guar gum was purchased from Signet Chem., Mumbai, India. Eudragit L-100 polymers were obtained from

Evonik Pharma, Germany. All other chemicals and reagents used were either of analytical or pharmaceutical grades as supplied by the manufacturer.

Preformulation Studies:-

Atenolol was observed for its color and nature. Melting point, solubility, Spectroscopic Characteristics such λ_{max} and standard graph of Atenolol were carried out.

Drug-Excipients Interactions

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. FTIR spectra were obtained by using an FTIR spectrometer. As Atenolol, Atenolol + Gaur gum, Atenolol + Eudragit S-100, was meeting pharmacopoeia's specification, it was taken into consideration for FTIR study (IR200 spectrometer JASCO). The drug Atenolol and physical mixture of drug and polymer were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press.

Tablet Manufacturing Method

Formulation of core tablets by granulation

The inner core tablets were prepared by using direct compression method. As shown in Table 1 powder mixtures of Atenolol, Colloidal silicon dioxide, Sodium starch glycolate and Lactose were dry blended for 20 min. Starch solution was added as binder and prepared the dump mass. Resulting dump mass was passed through the sieve no.22 so as to get the granules. Allow the granules to air dry. Finally addition of Magnesium stearate was done. All the contents were well mixed for 10 min., 70 mg of owder blend was compressed using rotary tabletting machine (Karnavati Rimek mini press) punch size 6.5mm and die size 6.5mm.

Evaluations of Granules

Evaluation of granules was performed such as bulk density, tapped density, carr's index, Hausner ratio, and angle of repose.

Evaluation of core tablets

Tablets were evaluated for friability test, hardness test, disintegration and drug content. These parameters were referring to as post-compression parameter.

Friability test

The friability of all the tablets studied was determined using a Roche friabilator.

Hardness tester

The hardness test was carried by using Monsanto hardness test apparatus for the determination of hardness of tablets. The tablet was placed in contact between the plungers and handle was

pressed. The force of fractured was recorded.

Disintegration test

Thermoni tablet disintegration test machine IP (Campbellelectronics Bombay 400025 was used for disintegration test. One tablet was placed in each of the six tubes of the basket with a disk. The apparatus, was operated using 0.1 N HCl medium as the immersion fluid, maintained at 37 ± 2C°. At the end of the time limit specified in the monograph, basket from the fluid was lifted , and the tablets were observed. All of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, the test on 12 additional tablets was repeated. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Drug content

For the determination of the drug content, total 10 tablet were weighed and powder equivalent to 50 mg of Atenolol was weighed and dissolved in 0.1N HCl then filtered through Whatman filter paper. Solution was analyzed for Atenolol content by UV-Spectrophotometer at 275 nm using reference as blank 0.1N HCl.

Formulation of mixed blend for barrier layer

As given in the Table 2 the various formulation compositions containing Eudragit S-100 and Guar Gum. T1 to T7 different compositions were weighed and dry blended at about 10 min. and used as press-coating material to prepare press-coated pulsatile tablets (T1-T7) respectively by direct compression method.

Each blend was evaluated for its Angle of repose and refers to as pre-compression parameter. Static angle of repose was determined according to the fixed funnel and freestanding cone method, whereby accurately weighed polymer (3 g) were carefully poured through the funnel with its tip at 2-cm height (H), until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter, 2R, of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation. The results are shown in table.

$\tan \theta = (H/R)$

Preparation of press-coated tablets:

Tablet prepared with 125mg was found to be ideal in term of all desire product characteristics, so optimize formulation where prepared by taking coat layer of 125mg. (Table. 2) 125mg of barrier layer material was weighed and transferred into a 10mm die then the core tablet was placed manually at the center. The remaining 125mg of the barrier layer material was added into the die and compressed using rotary tabletting machine (Karnavati Rimek mini press). Weight of each tablet was adjusted up to 320 mg having mean thickness 3±0.2 mm.

Evaluation of press-coated tablets: -

Tablets were evaluated for friability test, hardness test and drug content. These parameters were referring to as post-compression parameter.

Table. 1 Formulation of core tablet

Sr.No.	Ingredients'	Quantity	Category
1	Atenolol	50mg	Antihypertensive
2	Colloidal Silicon dioxide	1mg	Super disintegrating
3	Sodium starch glycolate	2.5mg	Super disintegrating
4	Lactose	12mg	Diluents
5	Starch binder solution	3.5mg	Binder solution
6	Magnesium stearate	1mg	Lubricant
7	**Total**	**70 mg**	

Table.2 Formulation of barrier layer in different concentrations

Sr. No.	Polymer	T1	T2	T3	T4	T5	T6	T7
1	Eudragit S-100	100mg	125mg	150mg				62.5mg
3	Gaur gum				100mg	125mg	150mg	62.5mg
4	**Total**	**100mg**	**125mg**	**150mg**	**100mg**	**125mg**	**150mg**	**125mg**

Composition of each layer

To get maximum target ability of drug to the colon barrier layer coat was given. The appropriate concentration of barrier layer was given. The appropriate concentration of barrier layer was justified on the basis of final quality of press coated tablet with respect t its various pre compression and post compression parameter. By performing these study the optimum concentration of coating material was justified

Tablet prepared with coat layer of 100mg shown poor tablet strength, when subjected to friability and hardness study Tablet prepared with coat layer of 150mg shown much thickness and hardness and these tablet where shown more problem as capping and chipping.

Tablet prepared with 125mg was found to be ideal in term of all desire product characteristics, so consider above optimize formulation where prepared by taking coat layer of 125mg. By considering these finding further evaluation parameter like in-vitro drug release and kinetic study were performed only on the formulation were prepared with coating material 125mg.

In vitro drug release study of press-coated tablets: -

In vitro dissolution studies were carried out using USP Type II (paddle method) 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. When performing the experiment, pH 1.2 medium was used for 2 h (since the average gastric emptying time is 2h), Then removed and fresh pH 7.4 phosphate buffer saline (PBS) was added. After 3 h (average small intestinal transit time is 3h), the medium was removed and fresh pH 6.8 dissolution medium was added for subsequent hours. 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. 10ml of dissolution media was withdrawn at predetermined time interval (15, 30, 45, 60, 120) and fresh dissolution media was replaced. The withdrawn samples were analyzed at 275nm, by UV absorption spectroscopy and the cumulative percentage release was calculated over the sampling times.

RESULT AND DISCUSSION:-

Atenolol was white or almost white odourless amorphous powder. Melting point of Atenolol was found to be 153^{0}C. Solubility of Atenolol was found to be freely soluble in acetic acid, DMSO, ethanol, methanol and sparingly soluble in water, slightly soluble in dichloromethane, practically insoluble in ether. Various type of evolution test for drug were performed given Table 3

Table 3 Evaluation of pure Atenolol drug

Sr. No.	Bulk Density	Tapped density	Carr's index	Hausner ratio	Angle of repose
1	0.57	0.58	1.72	1.02	25.78
2	0.56	0.57	1.75	1.01	23.51
3	0.57	0.58	1.72	1.05	26.16
4	0.58	0.59	1.69	1.01	24.75
5	0.57	0.58	1.72	1.03	25.8
6	0.57	0.58	1.72	1.02	23.54
Mean	0.57± 0.006325	0.58± 0.006325	1.72± 0.018974	1.02± 0.015055	24.92± 1.180926

λ_{max} of Atenolol found to be 275nm by using uv spectroscopic method. Calibration curve of Atenolol was constructed in 1.2, 7.4 and 6.8 phosphate buffer solution separately.

From standards the graph we get following equation

For 0.1N HCl (1.2 pH phosphate buffer): - Y= 0.003x+0.001 andR^2=0.996

For 7.4 Phosphate buffer: - Y=0.040x-0.029 and R^2=0.994

For 6.8 Phosphate buffer: - Y=0.016x-0.007 and R^2=0.997,

Table . 4 Authentication of Pure drug by FTIR spectra

Groups	Peaks (cm^{-1})
N-H stretching	3358.07
CH (in aromatic)	2922
C=O (ketone group)	2868
C-H stretching	6796

Drug-Excipients Interactions:

The IR spectra of Formulation T2, T5, T7, were compared with the standard spectrum of Atenolol (Figure.5). IR spectrum of Atenolol is characterized by the absorption of-COOH group at 1612.49 cm−1 (Figure.6).In spectra of Formulation T7, this band was same absorption pattern as that of pure drug (Figure.7). Mentioned evidences thus lead to the conclusion that changes are

not seen as there is no physical interaction between the drug and polymers.

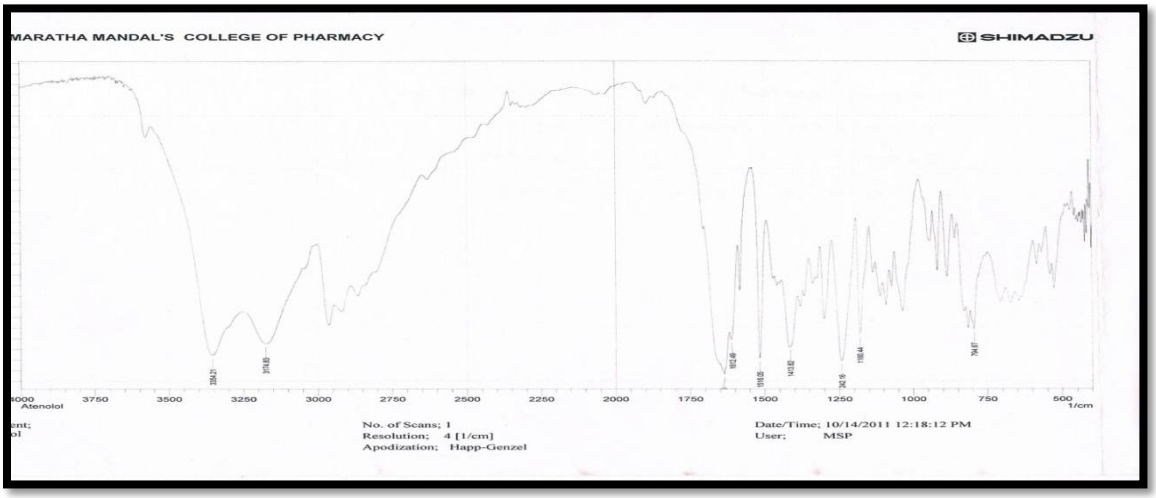

Figure 5 FTIR Spectra of-Atenolol

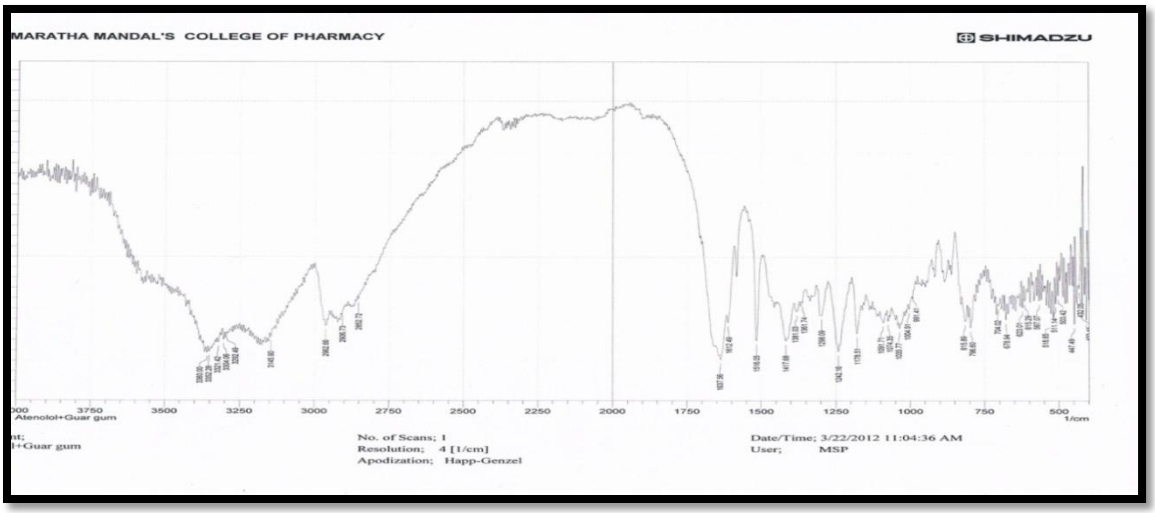

Figure 6 FTIR Spectra of-Formulation T5

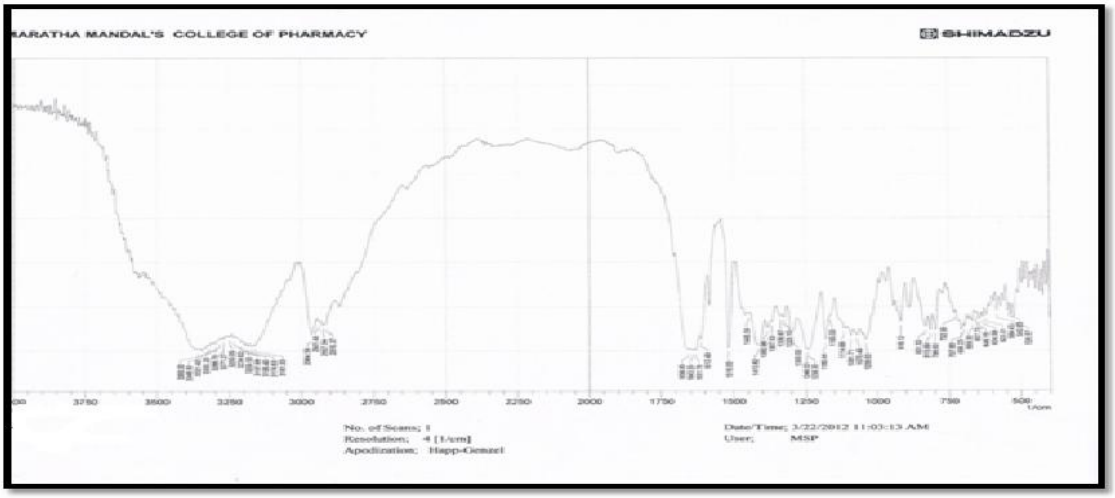

Figure 7 FTIR Spectra of-Formulation T2

Evaluation of Granules:

Evaluation of granules were performed and the result of evaluations parameter are given in table.5

Table. 5 Evaluations of Granules

Sr. No.	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
1	0.54	0.55	1.81	1.01	28.78
2	0.53	0.54	1.85	1.01	24.51
3	0.55	0.57	3.50	1.03	26.09
4	0.54	0.55	1.81	1.01	23.57
5	0.54	0.55	1.81	1.01	26.17
6	0.55	0.56	1.78	1.01	25.77
Mean	**0.54 ±** 0.007528	**0.55 ±** 0.010328	**1.79±** 0.689483	**1.01±** 0.008165	**25.81±** 1.774145

Evaluation of Core tablet

Evaluation of tablets were performed and the result of evaluation parameters are given in table 6

Table 6 Evaluation of core tablet

Sr. No.	Hardness Kg/cm	Friability %	Disintegration time in sec.	Drug content %
1	4.7	0.53	125	99.88
2	4.9	0.53	117	99.71
3	4.3	0.52	143	99.95
4	4.7	0.50	123	99.77
5	4.3	0.49	127	99.47
6	5.0	0.47	129	99.57
Mean	**4.65±** 0.294958	**0.5±** 0.024221	**127.3±** 8.710147	**99.72±** 0.182181

Weight variation was found to be in standard range as established by official compendia.

Evaluation of Polymeric blend

Polymeric blend was evaluated for angle of repose. The angle of repose of polymeric blend was found to be from 19.77 to 23.99. The values of pre-compression parameters evaluated were within prescribed limit and indicated a good free flowing property.

Evaluation of Press coating tablet:

The data obtained from post-compression parameter such as weight variation, hardness, friability, and drug content are shown in Table 7. In all formulation, the hardness test indicated good mechanical strength. Hardness was ranged from 3 to 4.3 Kg/cm^2. Friability was ranged from 0.47 to 0.53. Friability is less than 1% which indicated that tablets had good mechanical resistance. Drug content was found to be high (99.47). It was ranged from 99.47 to 99.95 and uniform in all tablet formulations. An ultraviolet (UV) spectrophotometric method was used for the determination of drug content.

In weight variation test, 20 tablets were selected random and average weight variation was calculated. Then individual tablet were weighed and weight was compared with average weight. It was varied from 317to 323.2 mg.

Table 7: Post-compression parameter For Press coating tablet

Sr. No.	Formulation	Hardness Kg/cm	Friability%	Drug content%
1	T2	3.7±0.089443	0.53±0.014142	99.88±0.055498
2	T5	3.9±0.09143	0.53±0.014172	99.71±0.051390
3	T7	4.3±0.099734	0.52±0.0153021	99.95±0.064468

In Vitro dissolution of press coated tablets:

In vitro drug release profile for individual as well as combination of two polymers were shown in Figure 8. During drug dissolution study, it was observed that, enteric coat of guar gum and Eudragit S100 was intact for 2 hr in pH 1.2, but Eudragit S100 get dissolve in intestinal pH 7.4 and guar gum remained intact. After replacing media with pH 6.8 phosphate buffer, guar gum formed the soft gel which resulted in immediate drug release. On exposure to the dissolution fluids, the gum gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core tablets. The hydration of guar gum seems not to be affected by the pH of the dissolution medium. Thus, guar gum in the form of coat was capable of protecting the drug from being released completely in the physiological environment of stomach and small intestine. Drug release profile varied as concentration ratio of polymers was changed.

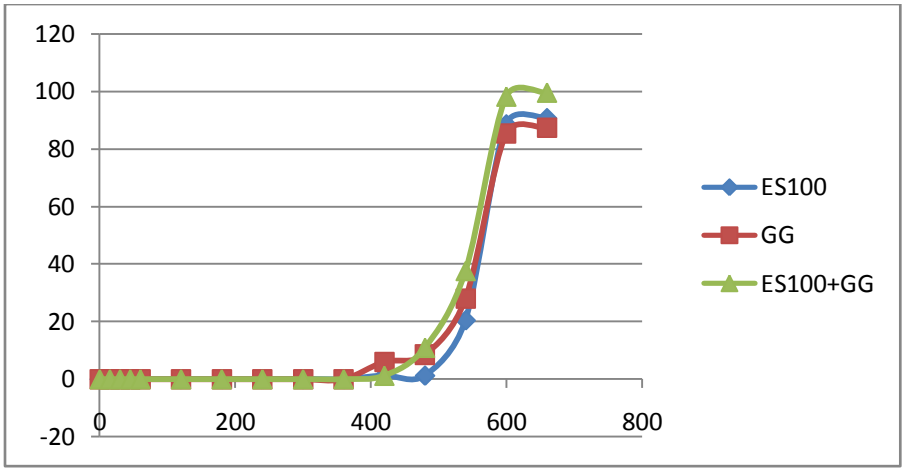

Figure 8 Drug relased profile

Formulation T2 (100:0) showed only insufficient drug release i.e.90.68% over 11 hr. For T5 (0:100) formulation showed only insufficient drug release i.e. 87.30%. The drug release from these formulations was observed to show strong pH dependency in their release profiles. The carboxylic acid group present in EudragitS100 reacts with the phosphate bases (HPO_4^{2-}) in the buffer resulting in increase in EudragitS100 dissolution rate in pH 7.4. But, Formulation

T7(50:50) showed require release rate in comparison with other formulation i.e. 99.5% Thus, this study , clearly indicated that the 50:50 ratio is more suitable among the polymers combinations used in the formulations to design pulsatile release formulations of Atenolol.

In vitro released study data was subjected to various kinetic models namely zero order, first order, Higchi model, Peppaas model and Hixon crowell, so as to check the released mechanism. All prepared formulation shown zero order released profile with highest R^2 value as compared with other models. This indicates the suitability of designed formulation in the chronotherapy.

CONCLUSION

Chronotherapy aims at providing API at the certain level of timing with regard to the diseased condition to be treated. The performance achieve by designing a chronopharmaceutical modulated drug delivery always shows on upper hand in disease treatment compared to conventional therapy. Present study demonstrated that when an antihypertensive drug Atenolol is fabricated with colon targetivity coupled with chronotherapy shows on released of API at time intervals of 15, 30, 45, 60,120 min. which indicate that if prepared formulation is administered at bed time will released the contain in early morning so as to give the highest therapeutic benefit of treatment and ultimately improved patient compliance.

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