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DESIGN & EVALUATION OF PULSATILE DRUG DELIVERY SYSTEM OF ATENOLOL FOR CHRONOMODULATED THERAPY

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ABSTRACT

The present work deals with the study and development of an oral dosage form devised to release drug following a programmed time period after administration. Pulsatile release tablet comprises of a drug containing core and pH sensitive polymeric coating capable of delaying drug release and providing gastric resistance to overcome gastric emptying variability, thus allowing colon delivery to be pursued according to the time-dependent approach. The aim of this work is to evaluate different pH sensitive polymers (Eudragit S-100, ethyl Cellulose, sodium alginate) at different ratio in developing a suitable dosage form, exhibiting a no drug release in upper regions of gastrointestinal tract (GIT) in order to provide site specificity as well as time controlled formulation. Prepared tablets are characterized for physical parameters, drug content, *in vitro* drug release, lag time, stability studies.

KEY WORD: Pulsatile drug delivery, Chronotherapeutics, lag time, Hypertension, Atenolol

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INTRODUCTION

Atenolol, a β-blocker, is prescribed widely in diverse cardiovascular diseases, eg. Hypertension, angina pectoris, arrhythmias, and myocardial infarction. The drug indicates prophylactic treatment of migraine. 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[1]. Hence it is always effective to have absorption of Atenolol at Colon site. Among modified-release oral dosage forms, increasing interest has currently turned to system designed to achieve time specific (delay, pulsatile) and site specific delivery of drugs. In particular, system for delayed release is meant to deliver the active principle after a programmed time period following administration. These systems constitute a relatively new class of device, the importance of which is especially connected with the recent advances in chronopharmacology. In the last decades numerous studies in animals as well as clinical studies have provided convincing evidence, that the pharmacokinetic and/or the timing of drug application within 24 h of a day. A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Time controlled drug delivery system based on chronotherapy or chronopharmacology have been investigated together with release rate controlled system for the treatment of diseases such as ischemic heart disease, asthma and arthritis. Drug for treatment of such diseases should administered so as to maintain a therapeutic blood level only at the required time, and hence the drug release behavior should be controlled by rate. For this purpose, various system and sigmoidal release system have been developed using various techniques and functional polymers or additives. 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 at 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. So by developing the pulsatile device for colonic delivery, plasma peak is obtained at an optimal time, number of doses per day can be reduced[2]. The combination of pH-dependent polymers with time based polymers could offer a means for achieving pulsatile release of drug from the coated system. Furthermore, pH based polymers in combination with biodegradable xanthum gum and starch have also been attempted and proven as better triggers by microbial degradation for colon specific release[3].

MATERIAL AND METHOD

Material

Atenolol was obtained as gift sample from Kopran Ltd, Mumbai, India. Sodium alginate was purchased from Signet Chem Mumbai, India. Eudragit S-100 polymers were obtained from Corel Pharma, Gujarat. All other chemicals and reagents used were either of analytical or pharmaceutical grades.

Tablet Manufacturing Method

Formulation of core tablets by direct compression

Tablets of Atenolol were made by direct compression method. All ingredients were weighed accurately and blended homogeneously for 15 minutes by trituration using glass mortar and pestle. Microcrystalline cellulose was used as direct compressing agent. Crospovidone were used as disintegrating agents. Magnesium stearate and

Talc were used as lubricants. Tablets were compressed in Minipress Tablet Compression Machine using 10 mm round concave punches. (Proton Engineer, Ltd., Ahmedabad, India). The composition of core tablets is given in Table No.1.

Table 1
Composition of Atenolol Core Tablet

Ingredients (mg/tablet)	QUANTITY (mg)
Atenolol	50
Microcrystalline cellulose	90
Lactose	33
Crospovidone	2
Talc	2
Magnesium stearate	3
Total	**180**

PREPARATION OF COATED TABLET

Preparation of Coating:

Coating was made using different pH sensitive polymers like eudragit S-100, ethyl cellulose, sodium alginate.

Table 2
Composition of Coating

INGREDIENT	FC 1	FC 2	FC 3	FC 4	FC 5
Ethyl Cellulose	70	110	150	190	230
Sodium alginate	230	190	150	110	70
Eudragit S-100	30	30	30	30	30

EVALUATION OF CORE TABLETS

Precompressional Studies [4, 5]:

Angle of repose

The angle of repose of blend was determined by the funnel method. The accurately weight blend was taken in the funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the blend. The blend was allowed to flow through the funnel freely on 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 and r are the height and radius of the powder cone.

Bulk density and Tapped Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 gm of blend previously shaken to break any agglomerates formed, then it was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations. LBD= Weight of the Granules/Untapped Volume of the packing

TBD=Weight of the Granules/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below: **Carr's Index (%) = [(TBD-LBD) x100]/TBD**

Hausner's Ratio

Hausner's Ratio was determined by Following Equation:

Hausner's Ratio = Tapped Density / Bulk Density

Post-Compressional Studies [6, 7, 8]:

Uniformity of thickness

Thickness and diameter of both core tablets and coated tablets were measured using a calibrated dial calipers. Three tablets of each formulation were picked randomly and dimensions determined. It is expressed in mm and standard deviation was also calculated.

Weight variation test

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. The specifications for weight variation are mentioned in U.S. Pharmacopoeia.

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of core tablets was determined using a validated dial type hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked from each batch and analyzed for hardness. The mean and standard deviation were also calculated.

Assay of Atenolol [9, 10]

Tablet containing 50 mg of drug was dissolved in 100 ml of phosphate buffer pH 6.8 and 7.4 (simulated intestinal & colonic fluid respectively). The drug was allowed to dissolve in the solvent, the solution was filtered, and 1ml of filtrate was suitably diluted with respective buffer and analyzed spectrophotometrically at 275 nm. The amount of Atenolol was estimated by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each batch of formulation.

Lag time of coated tablets [11, 12]

Coated tablets were evaluated for lag time in pH 6.8 and 7.4 phosphate buffer respectively. Coated tablets were placed in 900 ml of above mentioned buffers, 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.

Dissolution Studies of the Coated Tablets [13,14]

Drug release studies of coated tablets were carried out using USP XXIII dissolution test apparatus I. Initially tablets were placed in 900 ml of 0.1 N HCl for 2 hours maintained at 37±0.5^{0}C, 75 rpm followed by pH 6.8 phosphate buffer for 3 hours and pH 7.4 for 5 hours. Aliquots of predetermined quantity were collected manually at definite time intervals replacing with fresh buffer to maintain sink condition and analysed for drug content using a UV-visible spectrophotometer at λ max of 275 nm.

RESULT AND DISCUSSION

Results of the pre-compression parameters performed on the blend for batch (Table No.3). The result of angle of repose was found to be 24.01±0.85 respectively. Compressibility index was found to be 12.10. The results of Hausner's ratios were found to be 1.14. The results of angle of repose (<30) indicate good flow properties of the powder based on (Table No. 9). This was further supported by lower compressibility index values. Generally, compressibility index values up to 15% results in good to excellent flow properties.

Table 3
Pre-compression evaluation of the blend

Batch	F1
Angle of Repose	24.01 ± 0.85
Bulk Density (gm/cc)	0.650 ± 0.11
Tapped density (gm/cc)	0.750 ± 0.15
Carr's Index	12.10
Hausner's Ratio	1.14

Post-compressional parameters

The results of thickness for tablets are tabulated in (Table No.4). The mean thickness of tablets (n=3) of batches F1 was found to be 3.8±0.1 respectively. The standard deviation values indicated that all the formulations were within the range. The weight variations of all formulations are tabulated in Table No.4. All the tablets passed the weight variation test, i.e., average percentage weight variation was found within the pharmacopoeial limits of ±7.5%.Hardness or crushing strength for batch F1 were found to be 4.5±0.3 which are tabulated in (Table No.4). The low standard deviation values indicated that the hardness of all the formulations was almost uniform and the tablets possess good mechanical strength with sufficient hardness. The formulated tablets were assayed in triplicate. The average value and standard deviations were calculated. The tablets of batch F1 showed 98.77±0.59% drug content respectively. The results are tabulated in (Table No.4)

Table 4
Post-compression evaluation of the prepared Core tablet

Batch	F1
Uniformity of thickness (mm) (n=3)	3.8 ± 0.1
Weight variation (mg) (n=10)	180 ± 2.16
Hardness (kg/cm^2) (n=3)	4.5 ± 0.3
% Drug Content (n=3)	98.77 ± 0.59

In vitro drug release studies

Formulation 1 to 5 (ethyl cellulose, Sodium alginate, Eudragit S-100) as pH sensitive polymer: A Cumulative percent drug released versus time showed in (Table no.5) the dissolution rate was inversely proportional to the coated level applied. (Figure No.1) A lag time of 2 hours, 1 hour, 2 hour, 5 hour and 6 hour was achieved and from the different formulations cumulative % drug release in the

initial 6 hrs of dissolution media pH6.8 was found to be 33.14%, 38.17%, 31.14%, 37.17%, 0%. As the coating ratio was increased there was a significant increase in the lag time upto 6 hrs and inversely the drug release was 0 %. In formulation 5, at 6th hr, burst effect was observed which can be explained on the basis of the fact that as the coating concentration increased the coat became more impermeable and finally retarded the drug release.

Coating concentration and drug release are inversely related, but in case of ethyl cellulose, sodium alginate, eudragit S-100 there was considerable decrease in the drug release because the dissolution medium of pH 6.8 phosphate buffer is well above the pH of eudragit S-100 solubilization. Eudragit S-100 get solubilised at pH 7.0. All the coated tablets showed a nearby complete drug release in 24 hrs. The lag time and *in vitro* drug release profiles for all polymer at different concentration and variable ratio indicate that lag time is directly proportional and dissolution rate is inversely proportional to the ratio of polymer applied. FC 5 are proved to be the most appropriate pH sensitive polymers for pulsatile drug delivery. FC 5, was considered as optimum formulation as it showed the desirable lag time in fig no 1.

Table 5

In-vitro drug release study of tablets coated with Ethyl cellulose, Sodium alginate, and Eudragit S 100 (F1-F5)

Dissolution medium	Time(Hrs)	% Cumulative Drug Release				
		FC 1	FC 2	FC 3	FC 4	FC 5
0.1 N HCl	0	0	0	0	0	0
	0.5	0	0	0	0	0
	1	0	0	0	0	0
	2	0	4.01±4.58	0	0	0
6.8 pH buffer	3	11.03±4.57	11.02±1.75	11.01±3.46	0	0
	4	15.06±3.02	22.06±6.23	16.06±6.25	0	0
	5	26.08±4.59	31.12±1.74	26.08±1.70	0	0
	6	33.14±3.02	38.17±3.47	31.14±3.47	37.17±4.60	0
7.4 pH buffer	7	41.18±4.59	47.21±3.48	40.17±6.26	43.19±6.02	47.20±3.00
	8	47.22±1.75	56.26±7.56	52.22±4.59	54.23±7.96	56.25±1.74
	9	56.26±6.25	68.31±4.61	65.28±9.66	62.30±10.57	65.31±6.25
	10	65.31±1.74	71.37±4.60	74.36±9.69	66.34±7.99	69.36±6.03
	12	79.39±3.40	85.33±7.96	86.47±6.29	85.36±6.28	86.38±7.96
	18	81.37±1.75	87.36±7.97	89.45±9.67	88.29±4.61	89.41±4.62
	24	83.39±4.59	89.45±4.62	91.46±3.51	90.42±6.00	92.42±4.56

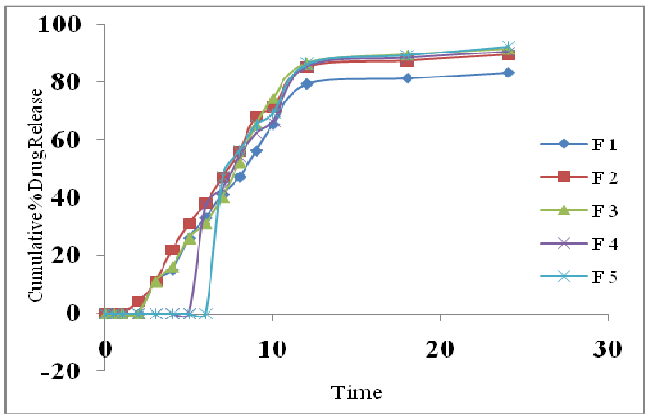

Figure 1
In-vitro drug release profile of tablets coated with Ethyl cellulose, Sodium alginate, eudragit S 100 of formulation 1 to 5

Stability studies[15, 16]

The stability study was carried out at 40°C/75% RH for formulation FC 4, FC 5 up to 30 days. At every 1 month time interval, the coated tablets were analyzed for drug content uniformity and *In-vitro* drug release. The results of accelerated stability study are tabulated in (Table No.6).

Table No.6

FORMULATION	TIME	30 Days	60 Days	90 Days
FC 4	24 Hr	90.37	91.22	89.66
FC 5	24 Hr	91.78	91.33	92.67

The results of accelerated stability study showed that there was no change in the formulation after one month. *In vitro* drug release study showed that after 1, 2, and 3 months values obtained were, The drug release throughout 24 hours obtained within range of targeted release profile. After 3 month stability study the assay result was stable.

CONCLUSION

The aim of this study was to explore the feasibility of time and pH dependent colon specific, pulsatile drug delivery system of Atenolol to treat Hypertension. A satisfactory attempt was made to develop pulsatile release tablets using pH sensitive polymers (ethyl cellulose, sodium alginate, eudragit S-100)

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