International Journal of Applied Pharmaceutics

Vol 2, Issue 3, 2010

Research Article

DEVELOPMENT OF PULSATILE RELEASE TABLETS OF ATENOLOL WITH SWELLING AND RUPTURABLE LAYERS

SWATI JAGDALE*, MONALI SALI, AJAY BARHATE, JANARDAN LOHARKAR[2], BHANUDAS KUCHEKAR, ANURUDDHA CHABUKSWAR

MAEER'S Maharashtra Institute of Pharma, MIT Campus, Paud Road, Kothrud, Pune-411038, MS, India, [2]Jalgaon Chemical Private Limited, Jalgaon, MS, India Email: jagdaleswati@rediffmail.com

Received: 07 April 2010, Revised and Accepted: 06 May 2010

ABSTRACT

A tablet system consisting of cores coated with two layers of swelling and rupturable coatings was prepared and evaluated as pulsatile drug delivery system. Cores containing Atenolol as model drug were prepared by direct compression of different ratios of lactose and microcrystalline cellulose and were then coated sequentially with an inner swelling layer containing a superdisintegrants KYRON T 314 and an outer rupturable layer of ethyl cellulose. The effect of level of swelling layer and rupturable coating, was investigated. Rupture and dissolution tests were performed using the USP Type II paddle method at 50 rpm in 0.1 N HCl. The lag time of the pulsatile release tablets decreased with increasing amount of microcrystalline cellulose in the cores and increased with increasing levels of both swelling layer and rupturable ethyl cellulose coating. Increasing levels of the ethyl cellulose coating retarded the water uptake and thus prolonged the lag time.

Keywords: Pulsatile, KYRON T 314, Ethyl cellulose, Atenolol.

INTRODUCTION

Conventional controlled release drug delivery systems are based on single- or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time[1,2]. However, pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, e.g. β- blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special pharmacokinetic features designed according to the circadian rhythm of human [3, 7].

A pulsatile release profile is characterized by a lag time followed by rapid and complete drug release. Pulsatile drug delivery systems are generally classified into time-controlled and site-specific delivery systems. The release from the first group is primarily controlled by the system, while the release from the second group is primarily controlled by the biological environment in the gastro-intestinal tract such as pH or enzymes. Most pulsatile drug delivery systems are reservoir devices covered with a barrier coating .[8,10] 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 be administered so as to maintain a therapeutic blood level only at the required time, 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.

In the present investigation, the barrier can dissolve, erode [11-16] or rupture [10, 17–19] during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core. The rupturing of the barriers are induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipients or swelling agents. [20–26] This study focused on the development of pulsatile release tablets as a per oral, time-controlled, single-unit dosage form. The proposed system consists of a core tablet coated with two layers, an inner swelling layer and an outer rupturable coating. The swelling layer is composed of KYRON T 314, a superdisintegrants, and polyvinyl pyrrolidone (PVP) as a binder, while the rupturable coating is an ethyl cellulose film. KYRON T 314 is derived from cross linked polymer of polycarboxylic acid as per USP/NF and has a K^+ ionic form. It is a very high purity polymer used in pharmaceutical formulation as a super fast disintegrant as well as dissolution improver in solid dosage form like tablet, Capsule, Pellets etc.

MATERIALS AND METHODS

Material

Atenolol was obtained as gift sample from Ajanta Pharma Ltd, Aurangabad, India. KYRON T314 was obtained from Corel Pharma Chem, Ahmedabad. Ethyl cellulose was obtained from Western Pharma, Mumbai. All other chemicals were of pharmaceutical grade.

Preparation of Pulsatile release tablets

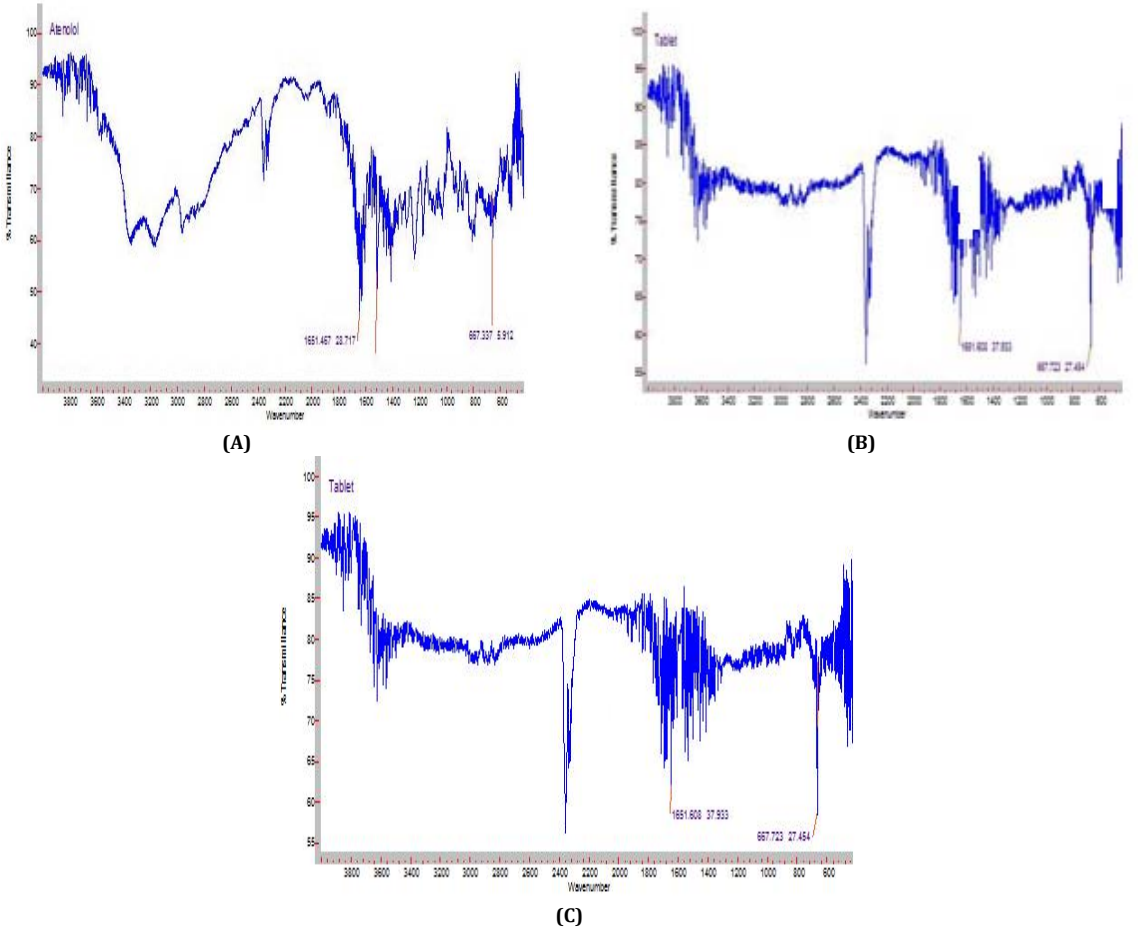
Formulation of core tablets by direct compression

The core tablets containing of lactose monohydrate and microcrystalline cellulose (Avicel R PH102) were prepared by direct compression. The drug-containing core tablets were prepared in a similar manner by replacing lactose monohydrate with Atenolol (25 mg per tablet). The core tablet excipients were blended for 10 min in a Turbula R-blender, followed by the addition of magnesium stearate (0.5% w/w) and Aerosil®200 (0.5% w/w). The powder mixture was further blended for 5 min. The core tablets (diameter, 9 mm; biconvex; hardness, 3-6 Kg/cm^2; average tablet weight, 258 mg) were compressed using a rotary tableting machine (Cadmach Machinery, Ahmedabad, India). Optimized batch were selected after selecting optimized batch of swelling layer.

Coating of core tablets

The core tablets were coated with two consecutive layers; KYRON T 314 as an inner swelling layer and ethyl cellulose as an outer rupturable coating. KYRON T 314 was layered onto the core tablets using PVP K 30 as a binder. PVP K 30 was dissolved in 96% v/v ethanol by stirring overnight until a clear solution was obtained. For coating, batch size of 30 tablets was selected. KYRON T 314 was dispersed into the PVP K 30 solution and agitated for at least 30 min to obtain a homogeneous dispersion prior to coating. The coating dispersion was then layered onto the core tablets in a Glatt drum-coater (GC 300, Glatt GmbH, Pratteln, Switzerland) to obtain swelling layer levels of 15%, 20% and 25%. The process conditions were as follows; inlet temperature: 35–37^{0}C; product temperature: 20–22^{0}C; air flow: 110 m^3/h; pan speed: 30 rpm; nozzle diameter: 1.2 mm; atomizing air pressure: 1.1 bar; spray rate: 15 g/min. The coated tablets were further dried in the coating pan for 15 min at 40^{0}C after the coating process was finished. The tablets were then placed in the oven at 40^{0}C for 2 h to remove the residual solvent. For

every batch % weight gain was calculated to get desired pulsatile effect. Polymer was used to increase the binding efficiency of active pharmaceutical ingredients PVP-K30 was used as a coating polymer. Along with titanium dioxide as a opacifier. Talc used as glidants and antiadherants; talc was beneficial as glidants, anti adherents, retardant and filler also.



(A) **(B)**

(C)

Fig. 1: IR Spectrum of (A) Atenolol Drug, (B) Batch B1 tablet, (C) Batch B2 tablet

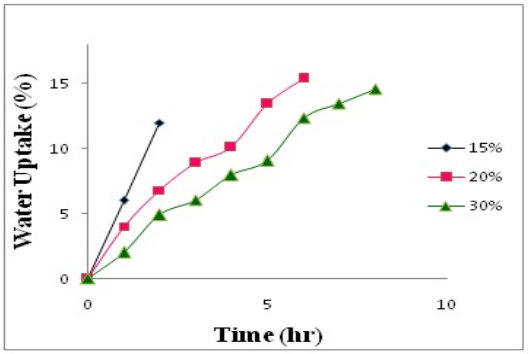


Fig. 2: Effect of ethyl cellulose coating level on % water uptake of pulsatile release tablet.

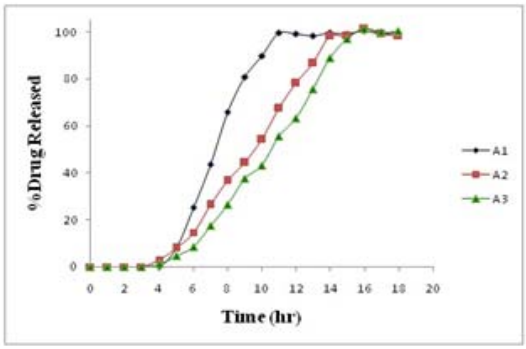


Fig. 3: Dissolution profile for batches A1-A3

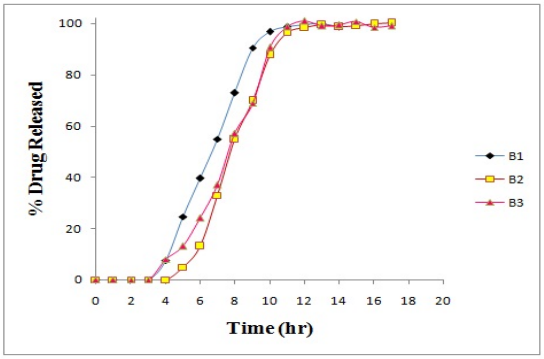


Fig. 4: Dissolution profile for batches B1-B3

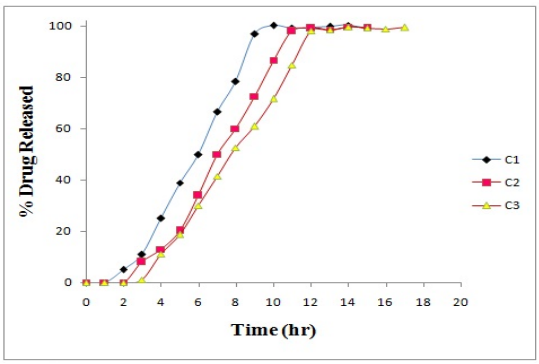


Fig. 5: Dissolution profile for batches C1-C3

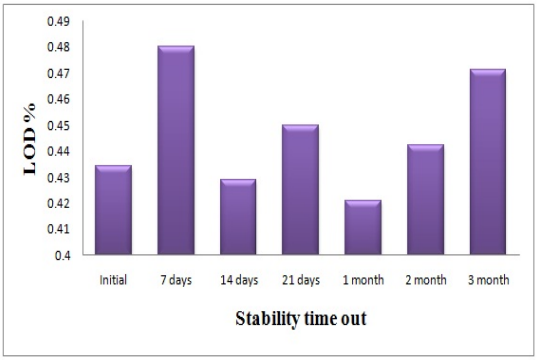


Fig. 6: LOD of stability batch B1, Sample at 30^{0}C (+/-2 C) and 65% RH (+/-5%) condition

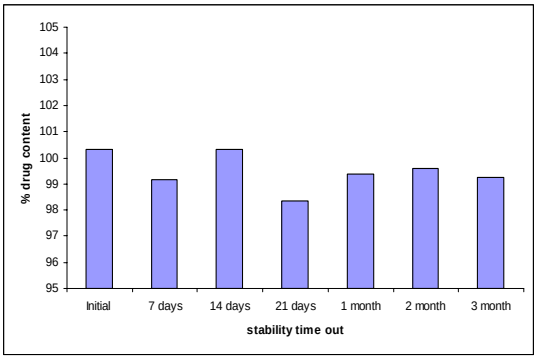


Fig. 7: % drug content of stability batch B1, Sample at 30^{0}C (+/-2 C) and 65% RH (+/-5%) condition

Tablets coated with the swelling layer were then coated with ethyl cellulose solution (Ethocel), in Methylene chloride/ Isopropyl alcohol (65:35 w/w) with 5% (w/w) solids content and plasticized with 20% (w/w) dibutyl sebacetate by stirring for 30 min. Optionally 10% talc was added. Plasticizers and talc amount is based on total solids content of the dispersion. Coating was performed in Glatt drum-coater to achieve required weight gain. The homogeneous dispersion was gently stirred throughout the coating process. The polymer solution was sprayed onto the tablets in a Glatt drum-coater (inlet temperature: 33–35^{0}C; product temperature: 20–22^{0}C; air flow: 110 m^3/h; pan speed: 30 rpm; nozzle diameter: 1.2 mm; atomizing air pressure: 1.1 bar; spray rate: 10 g/min) to obtain desired coating level of ethyl cellulose. The tablets were further dried in the coating pan for15 min at 40^{0}C after the coating process was finished and then placed in the oven at 40^{0}C for 2 h to remove the residual solvent. The coated tablets were equilibrated at room temperature overnight and stored in a closed container prior to further experiments.

Evaluation of pulsatile release tablets

Drug-excipient interactions

The physicochemical compatibilities of the drug and the used excipients were tested by FTIR. FTIR spectra were obtained by using an FTIR spectrometer- 430 (Jasco, Japan). As B1 and B2 formulation was best among the formulation, it was taken into consideration for FTIR study. The drug Atenolol and Formulation B1 and B2 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. Scans were obtained at a resolution of 4 cm−1, from 4,000 to 600 cm−1.

Rupture test

The lag time of pulsatile release tablets is defined as the time when the outer ethylcellulose coating starts to rupture. It was determined visually by using the USP II paddle dissolution apparatus (900 ml of 0.1 N HCl, 37.5^{0}C, 50 rpm, n = 3).

Water uptake study

The %water uptake of pulsatile release tablets was determined in medium-filled containers placed in a horizontal shaker (100 ml of 0.1 N HCl, 37^{0}C, 74 rpm, n = 3). At predetermined time points, the tablets were removed from the dissolution medium, carefully blotted with tissue paper to remove surface water, weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The %water uptake was calculated as follows:

$$\%\text{Water uptake} = \frac{Wt - W0}{W0} \times 100$$

Where,

Wt is weight of wet tablet at time t and W0 is weight of dry tablet.

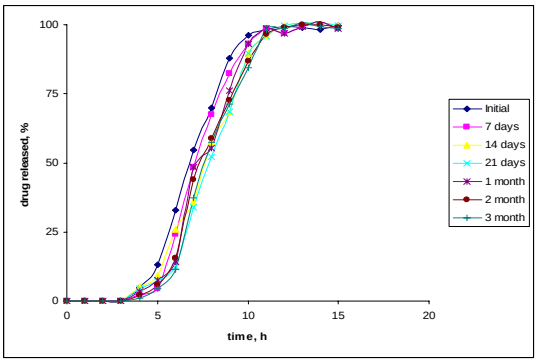


Fig. 8: Dissolution testing of stability batch B1, Sample at 30^{0}C (+/-2 C) and 65% RH (+/-5%) condition

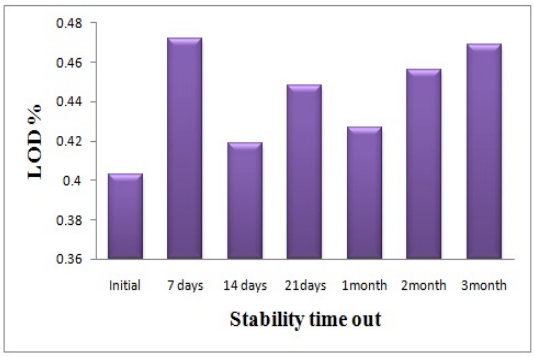


Fig. 9: LOD of stability batch B1, Sample at 40⁰C (+/-2 C) and 75% RH (+/-5%) condition

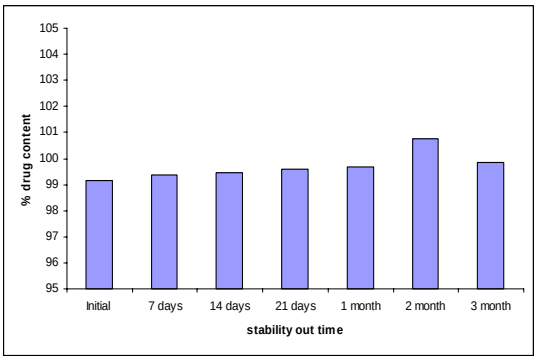


Fig. 10: % drug content of stability batch B1, Sample at 40⁰C (+/-2 C) and 75% RH (+/-5%) condition

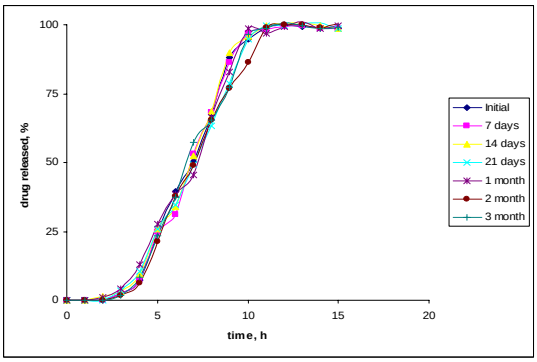


Fig. 11: Dissolution testing of stability batch B1, Sample at 40⁰C (+/-2 C) and 75% RH (+/- 5%) condition

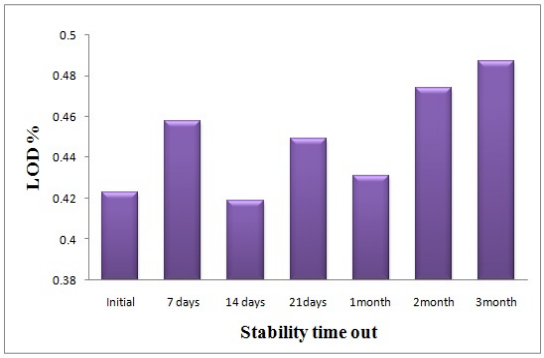


Fig. 12: LOD of stability batch B2, Sample at 30⁰C (+/-2 C) and 65% RH (+/-5%) condition

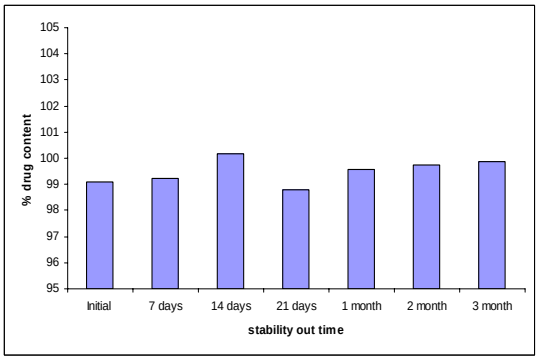


Fig. 13: % drug content of stability batch B2, Sample at 30⁰C (+/-2 C) and 65% RH (+/-5%) condition

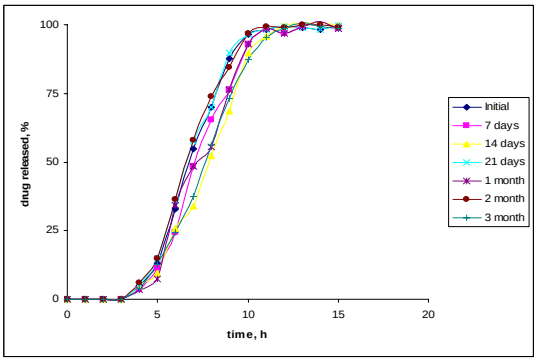


Fig. 14: Dissolution testing of stability batch B2, Sample at 30⁰C (+/-2 C) and 65% RH (+/-5%) condition

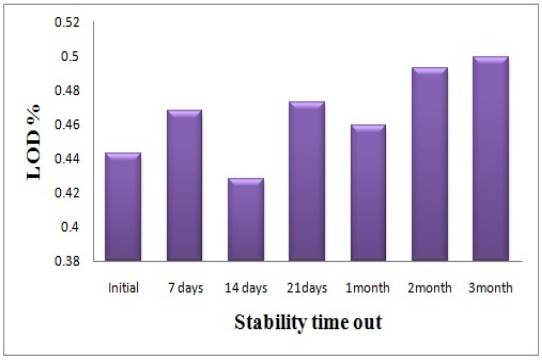


Fig. 15: LOD of stability batch B2, Sample at 40⁰C (+/-2 C) and 75% RH (+/-5%) condition

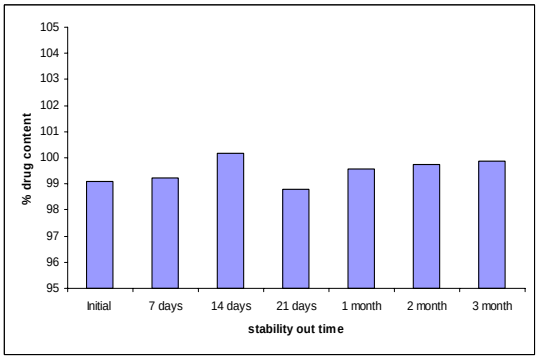


Fig. 16: % drug content of stability batch B2, Sample at 40⁰C (+/-2 C) and 75% RH (+/-5%) condition

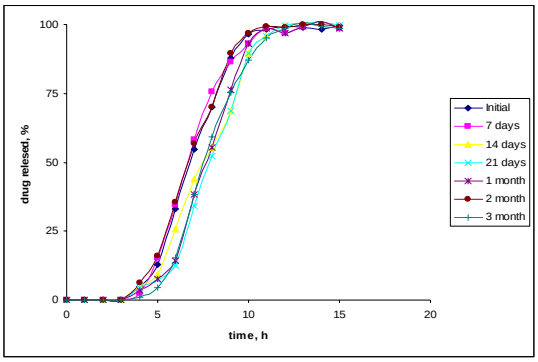


Fig. 17: Dissolution testing of stability batch B2, Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%) condition

Dissolution study

The USP II rotating paddle method (37.5 ^{0}C, 50 rpm, 900 ml of 0.1 N HCl, n=3) was used to study the drug release from the pulsatile release tablets. Samples were withdrawn after predetermined time intervals and the amount of Atenolol released was assayed with a spectrophotometer (UB Varian Cary 100 scan) at a wavelength of 275nm.

Stability testing of the best formulation

Stability studies are an integral part of the drug development program and are one of the most important areas in the registration of Pharma products. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established. Stability assessment started with studies on the substance to determine degradation products and degradation pathway.

Temperature dependent stability studies were carried out on the optimized batches. They were packed in Low Density Polyethylene (LDPE) bags enclose in High Density Polyethylene (HDPE) container.

And stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(I) 30 ± 1 ◦C and RH 65 % ± 5%

(II) 40 ± 1 ◦C and RH 75 % ± 5%

Tablets were withdrawn after a period of 7, 14 days, 1, 2, 3 months and analyzed for physical characterization (appearance, moisture content), dissolution study and percentage assay.

Determination of moisture content (Loss on drying)

The tablets were crushed with the help of mortar and pestle. Take crucible and keep in drying oven at 105°C for half an hour. Cool at room temperature in desiccators for 30 minutes. Weigh accurately empty bottle, add 2 g of powder into it and weigh. Distribute the sample as evenly as practicable by gentle sidewise shaking to a depth not exceeding 10 mm. Place the LOD bottle in the drying oven at 105°C by for four hours. After drying is completed, open the drying oven, close the crucible carefully and allow it to cool at room temperature in desiccator for 30 minutes. Weigh the crucible and calculate the percentage LOD.

Calculation

Wt. of empty crucible (W1):

Wt. of crucible + sample (W2):

Wt. of sample (W2-W1):

Wt. of crucible + sample after drying (W3):

Loss in wt. of sample after drying (W2-W3):

LOD (% w/w) **=** (W2 - W3)/ (W2 - W1) **x** 100

Table 1: Formula for batch no. A1 to A3:

Stage No.	Formula (mg)	A1	A2	A3
I	**Core tablet preparation**			
	Weight of tablet	**258**	**258**	**258**
II	**Coating of swellable Layer**			
1	KYRON 314	10	10	10
2	Starch	10	10	10
3	PVP K 30	10	10	10
4	Talcum	4.5	4.5	4.5
5	Titanium Dioxide	4.5	4.5	4.5
		297	**297**	**297**
	Weight gain on tablet	**15%**	**15%**	**15%**
III	**Coating of rupturable layer**			
1	Ethyl cellulose	20.5	35.5	45.5
2	dibutyl sebacetate	8	11	12.5
3	Talcum	9	10	12.5
4	Titanium Dioxide	5.5	6.5	7.5
		340	**360**	**375**
	Weight gain on tablet	**15%**	**20%**	**25%**

Table 2: Formula for batch no. B1 to B3

Stage No.	Formula (mg)	B1	B2	B3
I	**Core tablet preparation**			
	Weight of tablet	**258**	**258**	**258**
II	**Coating of Swellable Layer**			
1	KYRON 314	20.0	20.0	20.0
2	Starch	10	10	10
3	PVP K 30	10	10	10
4	Talcum	6	6	6
5	Titanium Dioxide	6	6	6
		310	**310**	**310**
	Weight gain on tablet	**20%**	**20%**	**20%**
III	**Coating of Rupturable layer**			
1	Ethylcellulose	20.5	35.5	45.5
2	Dibutyl sebacetate	8	11	12.5
3	Talcum	9	10	12.5
4	Titanium Dioxide	5.5	6.5	7.5
		353	373	388
	Weight gain on tablet	**15%**	**20%**	**25%**

Table 3: Formula for Batch no.C1 To C3

Stage No.	Formula (mg)	C1	C2	C3
I	**Core tablet preparation**			
	Weight of tablet	**258**	**258**	**258**
II	**Coating of Swellable Layer**			
1	KYRON 314	30.0	30.0	30.0
2	Starch	16	10	15
3	PVP K 30	10	10	15
4	Talcum	6	6	3
5	Titanium Dioxide	6	6	3
		320	**320**	**320**
	Weight gain on tablet	**25%**	**25%**	**25%**
III	**Coating of Rupturable layer**			
1	Ethyl cellulose	20.5	35.5	45.5
2	Dibutyl sebacetate	8	11	12.5
3	Talcum	9	10	12.5
4	Titanium Dioxide	5.5	6.5	7.5
		363	**383**	**398**
	Weight gain on tablet	**15%**	**20%**	**25%**

RESULTS AND DISCUSSION

Design of the Pulsatile release tablets

The pulsatile release tablet system developed in the present study was a reservoir devices, where the tablet cores were surrounded by two consecutive layers, a swelling layer and a rupturable layer, respectively. The swelling layer consisted of KYRON T 314 as the swelling agent because of its superior swelling behavior and PVP K 30 as the binder. The rupturable coating consisted of a plasticized ethyl cellulose film. Ethyl cellulose was chosen because it formed a mechanically weak (low puncture strength and low elongation) and semipermeable film, which could rupture easily upon exposure to the dissolution medium and the resultant internal pressure developed within the tablet cores.

To develop the pulsatile release tablet based on swelling and rupturable coatings, several studies were necessary to identify formulation variables, which provided the desired system properties, namely a rapid drug release after a certain lag time. The influence of core composition, level of swelling layer and rupturable coating, and magnesium stearate in rupturable layer was investigated.

Drug-excipient interactions

From the spectrum (Fig.1), it was seen that the major peaks of drug has not changed, so this indicate there are no interactions between drug and excipients for batches B1 and B2.

Effect of the amount of swelling layer and Rupturable Coating

The amount of swelling layer was important variable influencing the rupturing. Unexpectedly, the lag time of tablets with a higher level of swelling layer increased at all ethyl cellulose coating levels. The hardness of the core tablets coated with KYRON T 314 (25%) was 5.8 Kg/cm^2 respectively. Core tablets coated with higher levels of KYRON T 314 (without rupturable membrane) had a higher hardness, which might retard the water penetration through this layer. KYRON T 314 swelled when in contact with medium and therefore probably retarded the further water penetration into the core, which by itself had a high disintegration force resulting in short lag times.

The KYRON T 314 layer was also more porous than the core, thus resulting in a lower swelling pressure. In contrast, a decrease in lag time with increasing amount of swelling layer was seen with pulsatile hard gelatin capsules of similar design. With the hard gelatin capsules, only the swelling layer and not the capsule content contributed to the rupturing process, while with the pulsatile

release tablets of this study, both the tablet core and the swelling layer influenced the rupturing process.[27] As expected, higher levels of the rupturable ethyl cellulose layer increased the lag time. The drug release (Fig. 3,4,5) and the water uptake prior to rupture (Fig. 2) were investigated as function of the amount of rupturable ethyl cellulose layer. The lag time increased with increasing ethyl cellulose level, the drug was released rapidly and completely at ethyl cellulose levels of 15% and 20%. At the higher ethyl cellulose level of 25%, the drug was released slower after the lag time; this was again caused by the lower degree of rupturing of the thicker coating. Higher ethyl cellulose levels retarded the water uptake (Fig. 2). Interestingly, all curves showed an almost linear water uptake with time until critical water level, where the ethyl cellulose coating ruptured. The critical water uptake level was slightly higher at higher level of ethyl cellulose. This could be explained by the higher mechanical strength of the thicker coating, requiring a higher degree of swelling (water uptake) for rupturing.

Dissolution Study

Atenolol release from batches A1 to A4 has been shown in Fig. 3. Atenolol release from tablet, layered with 15% (w/w) KYRON 314 and coated with 15-25% (w/w) Ethocel shows the lag time of 4 hours then follow the sigmoidal release pattern with 100% drug release at 10 th hour. As the concentration of the ethyl cellulose coating increases from 15 to 25 % (w/w) the lag time extended to 5 hours and then follow the delayed release profile with the 100 % drug release at the 17 to 18 hour.

Atenolol release from batches B1 to B4 shown in Fig. 4. Atenolol release from tablet layered with 20% (w/w) KYRON 314 and coated with 15-25 % (w/w) Ethocel shows the lag time of 4 hours then follows the sigmoidal release pattern with 100% drug release at 8th hour. As the concentration of the ethyl cellulose coating increases from 15 to 25 % (w/w) shows no significant changes in the lag time and the further release profile. Slightly delayed release after initial lag time of 4 hour with the 100% drug release at the 12th hour observed as the coating level of ethyl cellulose increases upto 25 % (w/w).

Atenolol release from batches C1 to C4 shown in Fig. 5. Atenolol release from tablet layered with 25% (w/w) KYRON 314 and coated with 15-25% (w/w) Ethocel shows the lag time of 2 hours with 100% drug release at 8th hour. As the concentration of the ethyl cellulose coating increases from 20 to 25 % (w/w) shows delayed release after initial lag time of 3 hour with the 100% drug release at the 10th hour. Slightly delayed release after initial lag time of 3 hours with the 100% drug release at the 12th hour observed as the coating level of ethyl cellulose increases upto 25 % (w/w).

Stability testing of the best formulation

According to the result of dissolution testing, the two batches were selected for the stability studies B1 and B2 out of the total formulation batches.

Selected batches of the swellable and rupturable Pulsatile Drug Delivery of Atenolol, B1 and B2 were analysed for the appearance, loss on drying, assay, dissolution testing.

Result of stability studies for batch no. B1

For Swellable and rupturable Pulsatile Drug Delivery System of Atenolol optimized batch B1 and B2 from Table 4-7, Figure 6 to 17 it was seen that there are no significant changes in drug release profile for the batches stored at 30^{0}C (+/-2 C) and 65% RH (+/-5%) and 40^0 C (+/-2 C) and 75% RH (+/-5%) when compared with initial batch.

From the stability data (Table No. 4-7, Figure 6 to 17) for Swellable and rupturable Pulsatile Drug Delivery System of Atenolol it can be concluded that there were no changes in any parameter tested in formulations, so the optimized batches B1 and B2 are said to be stable.

Table 4: Results of stability studies for batch no. B1, Sample at 30^{0}C (+/-2 C) and 65% RH (+/-5%) condition

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Appearance	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour
LOD (%)	0.435	0.480	0.429	0.45	0.421	0.442	0.471
Assay (%)	100.33	99.18	100.27	98.36	99.39	99.59	99.27

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	2.22	1.52	0	0	0	0
3	2.34	9.33	3.32	1.68	2.50	3.33	1.73
4	7.45	22.86	9.43	8.45	7.45	9.49	6.34
5	24.87	37.65	25.86	23.47	24.93	25.89	21.45
6	39.66	58.3	34.06	37.38	31.18	34.63	37.78
7	50.32	65.52	52.32	57.32	53.13	52.32	48.96
8	67.53	76.28	68.53	65.27	68.22	63.34	65.55
9	88.27	92.92	89.70	77.26	86.34	89.77	76.98
10	94.93	98.59	95.93	96.44	96.77	94.61	86.42
11	98.83	96.96	99.80	98.76	98.34	99.75	98.79
12	99.97	99.18	100.19	100.07	99.45	99.67	99.88
13	99.17	100.89	100.54	99.50	99.76	100.43	99.86
14	98.88	98.57	99.78	98.56	98.39	100.67	98.98
15	98.54	99.67	98.44	98.98	98.48	98.69	100.39

Table 5: Results of stability studies for batch no. B1 Sample at 40⁰ C (+/-2 C) and 75% RH (+/-5%) condition:

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Appearance	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour
LOD (%)	0.403	0.472	0.419	0.448	0.427	0.456	0.469
Assay (%)	98.15	99.36	99.47	99.58	99.69	100.77	99.85

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	0	1.52	0	2.22	0	0
3	2.34	2.45	3.32	3.33	9.33	1.73	1.67
4	7.45	7.46	9.43	10.49	22.86	6.34	8.44
5	24.87	24.98	25.86	25.89	37.65	21.45	23.48
6	39.66	31.18	34.06	34.63	58.3	37.78	37.37
7	50.32	53.19	52.32	49.32	65.52	48.96	57.36
8	67.53	68.29	68.53	63.34	76.28	65.55	65.29
9	88.27	86.37	89.70	78.77	92.92	76.98	77.26
10	94.93	96.75	95.93	94.61	98.59	86.42	96.44
11	98.83	98.37	99.80	99.75	96.96	98.79	98.76
12	99.97	99.46	100.19	99.67	99.18	99.88	100.66
13	99.17	99.79	100.54	100.43	100.89	99.86	99.51
14	98.88	98.55	99.78	100.67	98.57	98.98	98.57
15	98.54	98.47	98.44	98.69	99.67	100.39	98.99

Table 6: Results of stability studies for batch no. B2.Sample at 30 C (+/-2 C) and 65% RH (+/-5%) condition

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Appearance	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour
LOD (%)	0.423	0.458	0.419	0.449	0.431	0.474	0.487
Assay (%)	99.73	99.65	99.57	98.48	99.33	99.26	99.14

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	5.24	7.54	5.89	4.66	4.36	7.32	5.89
5	13.86	14.24	12.54	11.35	14.38	12.54	13.33
6	33.67	48.3	37.78	37.37	58.3	34.06	37.38
7	54.73	55.52	48.96	57.36	65.52	52.32	57.32
8	69.99	76.28	65.55	65.29	76.28	68.53	65.27
9	87.77	92.92	76.98	77.26	92.92	89.70	77.26
10	96.35	98.59	86.42	85.24	98.59	95.93	96.44
11	98.25	96.96	98.79	98.76	96.96	99.80	98.76
12	99.38	99.18	99.88	100.66	99.18	100.19	100.07
13	98.99	100.89	99.86	99.41	100.89	100.54	99.50
14	98.35	98.57	98.98	98.57	98.57	99.78	98.56

15	99.57	99.67	100.39	98.99	99.67	98.44	98.98

Table 7: Results of stability studies for batch no. B2.Sample at 40^{0}C (+/-2 C) and 75% RH (+/-5%) condition

Tests	**Initial**	**7 days**	**14 days**	**21 days**	**1 month**	**2 month**	**3 month**
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Appearance	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour	white to off white colour
LOD (%)	0.443	0.468	0.428	0.473	0.459	0.493	0.499
Assay (%)	99.11	99.23	100.17	98.28	99.56	99.72	99.86

Tests	**Initial**	**7 days**	**14 days**	**21 days**	**1 month**	**2 month**	**3 month**
Stability out date	2/03/10	9/03/10	16/03/10	23/03/10	30/03/10	30/04/10	30/05/10
Dissolution study Time (hr)	**% Drug Release**						
0	0	0	0	0	0	0	0
1	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	5	2.37	5.12	4.56	3.46	2.14	1.03
5	13	4.36	9.43	7.32	7.54	5.89	4.66
6	33	14.38	25.86	12.54	14.24	12.54	11.35
7	54.73	58.3	34.06	34.06	48.3	37.78	37.37
8	69.99	65.52	52.32	52.32	55.52	48.96	57.36
9	87.77	76.28	68.53	68.53	76.28	65.55	65.29
10	96.35	92.92	89.70	89.70	92.92	76.98	77.26
11	98.25	98.59	95.93	95.93	98.59	86.42	85.24
12	99.38	96.96	99.80	99.80	96.96	98.79	98.76
13	98.99	99.18	100.19	100.19	99.18	99.88	100.66
14	98.35	100.89	100.54	100.54	100.89	99.86	99.41
15	99.57	98.57	99.78	99.78	98.57	98.98	98.57

CONCLUSION

Atenolol release from batches *B1 to B4***,** Atenolol release from tablet, layered with 20% (w/w) KYRON 314 and coated with 15-20 % (w/w) Ethocel shows the lag time of 4 hours then follows the sigmoidal release pattern with 100% drug release at 8th hour. Slightly delayed release after initial lag time of 4 hour with the 100% drug release at the 12th hour observed as the coating level of ethyl cellulose increases upto 25% (w/w).

The following conclusions can be drawn on the basis of the results of the studies. To achieve pulsatile drug release profile Atenolol core tablet was layered with KYRON 314. Minimum layering amount 15-20% (w/w) was needed for Atenolol tablet to achieve desired lag time and further coated with ethyl cellulose (Ethocel) an insoluble, water-permeable polymeric coating with layering amount from 15-25% (w/w). The lag time was controlled by coating level. Addition of the talc is very advantageous due to reduced sensitivity of lag time to the variations in the coating level.

Thus it is possible to obtain a time-lags of 4 to 5 hrs with different core composition with different release kinetics. This can be used a platform technology for swellable and rupturable Pulsatile Drug Delivery System.

REFERENCES

1. Daumesnil R. Marketing considerations for multiparticulate drug delivery systems. In: Ghebre-Sellassie, editors. Multiparticulate Oral Drug Deliver, Marcel Dekker, New York, 1994.pp 457– 474.
2. Qiu Y, Zhang G. Research and development aspects of oral controlled-release dosage forms. Wise DL, editor. In: Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker, New York, 2000.pp 465–504.
3. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int. J. Pharm. 1996; 136: 117– 139.
4. Chang RK, Guo X, Burside BA, Couch RA, Rudnic EM. Formulation approaches for oral pulsatile drug delivery. Am. Pharm. Rev. 1999; 2 (1): 6 – 13.
5. Bussemer T, Bodmeier R. A review of pulsatile drug delivery. Am. Pharm. Rev. 2001; 4: 18– 24.
6. Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. Crit. Rev. Ther. Drug Carrier Syst. 2001; 18: 433–458.
7. Lemmer B. Chronopharmacokinetics: implications for drug treatment. J. Pharm. Pharmacol. 1999; 51: 887–890.
8. Krogel I, Bodmeier R. Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. Pharm. Res. 1999; 16: 1424– 1429.
9. Krogel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. Pharm. Res. 1998; 15: 474– 481.
10. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. Int. J. Pharm. 1999; 187:175– 184.
11. Phuapradit W, Railkar A. Shah NH. Pharmaceutical composition, EP Patent 0,673,645, September 27, 1995.
12. Amer MS, Tawashi R. Drug loaded pollen grains with an outer coating for pulsed delivery, US Patent 5,275,819, January 4, 1994.
13. Ross AC, Macrae RJ, Walther M, Stevens HNE. Chronopharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J. Pharm. Pharmacol. 2000; 52: 903– 909.
14. Gopferich A. Erosion of composite polymer matrices. Biomaterials 1997; 18: 397– 403.
15. Gopferich A. Bioerodible implants with programmable drug release. J. Control. Release 1997; 44: 271– 281.

16. Freichel OL, Lippold BC. A new oral erosion controlled drug delivery system with a late burst in the release profile. Eur. J. Pharm. Biopharm. 2000; 50: 345– 351.
17. Ueda S, Hata T, Asakura S, Yamaguchi H, Kotani M, Ueda Y. Development of a novel drug release system, time-controlled explosion system (TES). I. Concept and design. J. Drug Target. 1994; 2: 35– 44.
18. Ueda S, Yamaguchi H, Kotani M, Kimura S, Tokunaga Y, Kagayama A et al. Development of a novel drug release system, time-controlled explosion system (TES). II. Design of multiparticulate TES and in vitro drug release properties. Chem. Pharm. Bull. 1994; 42: 359– 363.
19. Gazzaniga A, Iamartino P, Maffione G, Sangalli ME. Oral delayed-release system for colonic specific delivery. Int. J. Pharm. 1994;108: 77– 83.
20. Sangalli ME, Maroni A, Zema L, Busetti C, Giordano F, Gazzaniga A. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. J. Control. Release 2001; 73: 103– 110.
21. P.W.S. Heng, L.W. Chan, S.H. Chew, Mechanism of pellet coat rupture and its effect on drug release, Chem. Pharm. Bull. 1999; 47: 939–943.
22. Heng PWS, Chan LW, Chew SH. Mechanism of pellet coat rupture and its effect on drug release.Chem. Pharm. Bull. 1999; 47: 939–943.
23. Hata T, Shimazaki Y, Kagayama A, Tamura S, Ueda S. Development of a novel drug release system, time-controlled explosion system (TES). V. Animal pharmacodynamic study and human bioavailability study. Int. J. Pharm. 1994; 110: 1– 7.
24. Gazzaniga A, Sangalli ME, Giordano F. Oral Chronotopic drug delivery systems: achievement of time and/or site specificity. Eur. J. Pharm. Biopharm. 1994; 40:246–250.
25. Fan TY, Wei SL, Yan WW, Chen DB, Li J. An investigation of pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinylpyrrolidone in the core tablets. J. Control. Release 77; 2001: 245–251.
26. Morita R, Honda R, Takahashi Y. Development of oral controlled release preparations, a PVA swelling controlled release system (SCRS) I. Design of SCRS and its release controlling factor.J. Control. Release 2000; 63: 297– 304.
27. Dashevsky A, Bussemer T, Mohamad A, Bodmeier R. Process and formulation variables affecting the performance of a rupturable capsule-based drug delivery system with pulsatile drug release. Drug Dev. Ind. Pharm.2004;30(2):171-179.