WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 9, 321-341. Review Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF FLOATING-PULSATILE DRUG DELIVERY SYSTEM OF NIFEDIPINE

Anamika Kol*, Dr. Brajesh Kumar Arjariya[2], Sheenam Mansuri[3], Dr. Mohd Jalaluddin[4], Rahim Khan[5] and Rahul Dubey[6]

[1]Scholar, Malhotra College.

[2,4]Associate Professor, Malhotra College.

[3,5,6]Assistant Professor, Malhotra College.

Article Received on
14 May 2022,

Revised on 04 June 2022,
Accepted on 24 June 2022

DOI: 10.20959/wjpr20229-24634

***Corresponding Author**
Anamika Kol
Scholar, Malhotra College.

ABSTRACT

The goal in drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions. Up to late 1980`s design of drug delivery systems governed by the homeostatic theory. Variations in physiological and pathophysiological functions in time, also need for variations of drug plasma concentration has brought a new approach to the development of drug delivery systems, chronopharmaceutical drug delivery. The human body has many built-in rhythms known as biological clocks. Broadly, these can be classified as Ultradian, Circadian, Infradian and Seasonal. Ultradian cycles are shorter than a day, e.g., time taken for a nerve impulse to be transmitted. To develop and evaluate floating-pulsatile System for a cardiovascular drug, Nifedipine; with a four-five-hour delay in release after oral administration. So that the dose administered at bedtime, drug is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is most at risk. The inner core tablets were prepared by using direct compression method. Different preliminary batches of core tablets were taken in to fix concentration of superdisintegrant in tablet. Total 10 tablet were weighed and powder equivalent to 25 mg of Nifidepine was weighed and dissolved in methanol then filtered through Whatman filter paper. The developed system offers a simple and novel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4±0.2h with the relatively low variability. The drug release profile of optimized batch K6+F4 was found to be follow korsmeyer and peppas model. So, it is concluded that formulation release the drug by diffusion and erosion method.

KEYWORDS: Nifedipine, Chronopharmaceutics, Chronotherapy, Pulsatile release tablet.

1. INTRODUCTION (Chronopharmaceutics and Chronotherapy)

The goal in drug delivery research is to develop formulations that meet therapeutic needs relating to particular pathological conditions. Up to late 1980`s design of drug delivery systems governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. Another point raised by circadian variation of physiological function is that drug pharmacokinetics can be time-dependent. Variations in physiological and pathophysiological functions in time, also need for variations of drug plasma concentration has brought a new approach to the development of drug delivery systems, chronopharmaceutical drug delivery.[1-2]

The human body has many built-in rhythms known as biological clocks. Broadly, these can be classified as Ultradian, Circadian, Infradian and Seasonal. Ultradian cycles are shorter than a day, e.g., time taken for a nerve impulse to be transmitted. Circadian cycles last about 24 hours, e.g., sleeping and waking patterns. Infradian cycles are longer than a day, e.g., menstrual cycle. Recently, the role of these rhythms in fighting disease and responding to medication has come under study by researchers and scientists. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed Chronotherapy.[3]

Based on the previous definitions "*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*".[2]

1.1 Floating pulsatile drug delivery system

There are numerous approaches to prolong gastric retention, floating drug delivery system is the most widely used technique and offers a simple practical approach to increased gastric residency through inherent buoyancy. Floating has been achieved with the preparation of low density dry solid systems (e.g., inclusion of sponges, highly porous systems) or with systems, which decrease in density upon contact with gastric fluids based on the expansion of swelling agents or CO2 generation. Pulsatile drug delivery systems are characterized by two releasephases, a first phase with no or little drug being released, followed by a second phase,

during which the drug is released completely within a short period of time after the lag time. The release can be either time or site controlled. The release from the first group is essentially determined by the system, while the release from the second group is primarily controlled by the biological environment in the gastrointestinal tract Most pulsatile delivery systems are reservoir devices covered with a barrier coating, which dissolves erodes or ruptures after a certain time period, followed by rapid drug release from the reservoir. Reservoir type delivery systems based on the expansion of the core have been evaluated for both floating delivery systems having a lower density than gastrointestinal fluids, and for pulsatile systems in which the core expansion causes rupturing of the coating to allow rapid drug release.[4]

To develop and evaluate floating-pulsatile System for a cardiovascular drug, Nifedipine; with a four-five-hour delay in release after oral administration. So that the dose administered at bedtime, drug is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is most at risk.

2. MATERIALS AND METHODS

Drug used for the study "Nifedipine"

2.1 Preparation of the Rapid Release Tablet (RRT)

The inner core tablets were prepared by using direct compression method. Different preliminary batches of core tablets were taken in to fix concentration of superdisintegrant in tablet. Concentration of super disintegrants varies from 1 to 4 mg/tablet. Powder mixtures of nifidepine, crosscarmellose sodium (Ac-Di-Sol), KYRON T314, lactose and ingredients were dry blended for 20 min. followed by addition of magnesium stearate. The mixtures were then further blended for 10 min, 60 mg of resultant powder blend (theoretically equivalent to 20 mg of nifidepine) was compressed using rotary tabletting machine (Cadmach Machinery, Ahmedabad, India) with a 6mm punch and die to obtain the core tablet.[5]

Table 2.1: Formulations of core tablet.

Ingredients(mg)	I	II	III	IV	V	VI	VII	VIII
Nifidepine (mg)	20	20	20	20	20	20	20	20
CCS (mg)	1	2	3	4	-	-	-	-
KYRON T 314(mg)	-	-	-	-	1	2	3	4
Mg-Stearate(mg)	8	8	8	8	8	8	8	8
Lactose(mg)	31	30	29	28	31	30	29	28
Total (mg)	60	60	60	60	60	60	60	60

2.2 Evaluation of the Rapid Release Tablet (RRT)Determination of Drug Content

Total 10 tablet were weighed and powder equivalent to 25 mg of Nifidepine was weighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for content by UV-Spectrophotometer at 236 nm using methanol as blank.

2.2.1 Disintegration test

The tablet was put into 100 ml distilled water at 37 ± 2oC. Time required for complete dispersion of a tablet was measured with the help of a digital tablet disintegration test apparatus.

2.2.2 Hardness test

Pfizer hardness tester was used 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.

2.2.3 Friability test

The friability of all the tablets studied was determined using a Roche friabilator. In the disinteration time study, from above study two batches II and VI were selected as optimized batches.

2.3 Preparation of the Floating and Pulsatile Release Tablet (FPRT)

FPRT was designed to comprise PRT and top cover buoyant layer. PRT was taken as the layer for pulsatile release.

2.3.1 Preparation of the Pulsatile Release Tablet (PRT)

Each powder used as erodible outer shell i.e., HPMC K4, HPMC E15 LV, carboxy methylcellulose sodium (NaCMC) was passed through a 500µm. RRT was taken as core. Studies were carried out on different combination of polymers, which were considered as preliminary batches. Dissolution study was carried out for above batches and by observing result it was necessary to carry out experiment on individual polymers.

Table 2.2: Addition of polymer for pulsatile release tablet containing crosscarmellose sodium.

S. No.	Ingredients	Formulation Codes								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1	HPMC K4 M	140	160	180	-	-	-	-	-	-
2	NaCMC	-	-	-	140	160	180	-	-	-
3	HPMCE15 LV	-	-	-	-	-	-	230	260	290

Table 2.4 Addition of polymer for pulsatile release tablet containing KYRON T314.

S.	Ingredients	Formulation Codes					
		K1	K2	K3	K4	K5	K6
1	HPMC K4 M	140	160	180	-	-	-
2	HPMCE15 LV	-	-	-	230	260	290

2.3.2 Compositions of the Buoyant Layers

The compositions of the buoyant layer of the FPRT for floating testing were shown in Table 6.8. All powdered excipients were mixed for 5 min using a mortar and pestle to form a homogenous directly compressible powder mix. Different fillers were used to adjust the tabletweight and effect of fillers on floating time was observed. For the preparation of FPRT tablet, batch K3 and K6 were used in compression with buoyant layer.[5]

Table 2.5 Compositions of the buoyant layers.

Sr No.	Ingredients	Formulation codes				
		F1	F2	F3	F4	F5
1	HPMC K 100M	150	150	150	150	150
2	Sodium bicarbonate	20	40	80	40	20
3	Citric acid	20	40	80	40	20
4	Dicalcium phosphate	20	-	-	-	-
5	Microcrystallinecellulose	-	20	-	-	-
6	Lactose	-	-	20	20	20

2.4 Evaluation of Floating and Pulsatile Release Tablet[6-7]

2.4.1 Physical evaluation

2.4.1.1 Friability test

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

2.4.1.2 Hardness test

Pfizer hardness tester was used 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.

2.4.1.3 Determination of drug content

Total 10 tablet were weighed and powder equivalent to 20 mg of nifidepine was weighed and dissolved in methanol then filtered through Whatman filter paper. Solution was analysed for nifidepine content by UV Spectrophotometer at 236 nm using methanol as blank.

2.4.1.4 In vitro buoyancy determination

Floating behaviour of the tablet is determined by using USP dissolution apparatus II in 500 ml of 0.1 N HCl which is maintained at 37±0.5°C, rotated at 50 rpm. The floating lag time as well as total floating time is observed.

2.4.1.5 Swelling Index determination

Tablets were weighed individually (designated as W1) and placed separately in glass beaker containing 200 ml of 0.1 N HCl and incubated at 37°C±1°C. At regular 1-h time intervals until 24 h, the tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula:

$$SI = \frac{W2-W1}{W1} X\ 100 \quad \text{---------- (6.1)}$$

2.5 Stability testing of the optimized formulation

Temperature dependent stability studies were carried out on the optimized batch. 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.[8,9]

(I) 30 + 2 o C and RH 65 % + 5%

(II) 40 + 2 o 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.

3.1 Evaluation of rapid release tablet (rrt)

Table 3.1: Evaluation of RRT.

Formulation	Hardness Kg/cm^2	Friability (%)	Drug Content (mg%)	Disintegration Time(S)
I	3.8	0.62±0.12	99.22	45
II	3.4	0.69±0.14	98.92	11
III	3.7	0.65±0.11	99.85	30
IV	3.8	0.62±0.11	99.72	28
V	3.6	0.60±0.14	99.35	24
VI	3.2	0.67±0.13	99.97	11
VII	3.9	0.63±0.16	99.65	49
VIII	3.6	0.60±0.11	99.78	10.4

In all formulation, the hardness test indicated good mechanical strength, whereas friability is less than 1% which indicated that tablet had good mechanical resistance. Drug content was found to be high (>99.20) and uniform in all tablet formulations. It was ranged from 98.92 to 99.85 and uniform in all tablet formulations. Absorption maxima was determined by scanning different concentration of solution of drug Nifedipine. Absorption maxima was 236 nm and method obey Beer's law in concentration range 0 to 50 µg/ml, with good correlation coefficient (0.9997). When a standard drug solution was assayed repeatedly (n=6), relative error (accuracy) and relative standard deviation (precision) were found to be 0.72 and 0.93% respectively. The tablets were subjected for evaluation of the in-vitro disintegration time and it was observed that the time for formulation varied from 10 to 52 second. It was observed that the time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrated within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore havingless hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which was confirmed by dissolution study.[11,12]

3.2 Evaluation of the Floating and Pulsatile release Tablet(FPRT)

It was observed that the disintegration time for formulation varied from 10 to 52 second. It was observed that when KYRON T314 was used as disintegrant, tablet was disintegrated within short time due to easy and high swelling ability of KYRON T314 as compared to CCS. It is observed that disintegration time of tablet decreased with increased in concentration of CCS and KYRON T-314. But by disintegration study it was observed that hardness plays important role. For development of pulsatile release study disintegration time must be short to obtain burst effect therefore having less hardness. Hence by observing results it was concluded that batches II and VI were optimized batches which were confirmed by dissolution study.

3.3 Pulsatile release tablet (PRT)

For this study, the core tablets containing nifedipine (RRT) were compression coated with different powder such as HPMC K4, HPMC E15LV, sodium carboxymethylcellulose, used as outer erodible shell. Dissolution studies were carried out on combination of polymers as well as on individual polymers. Dissolution studies resulted that batches prepared with combined

polymers formed too sticky mass to release the drug when polymers came into contact with dissolution medium. From this it was resulted that combined polymers are not suitable for pulsatile drug delivery system Core tablet containing crosscarmellose sodium was compression- coated with HPMC K4, HPMC E15LV, sodium carboxymethylcellulose and these batches were taken as preliminary batches for the study of individual polymers. The in vitro release profiles of nifedipine from different-coated systems in 0.1 M HCl solution was provided in Figure Below.

Table 3.2: Dissolution Testing of batch C1-C3.

Time (hrs)	% Drug Released		
	C1	C2	C3
0	0	0	0
1	0	0	0
2	5	3	0
3	10.95	5.67	0
4	25.4	7.45	0
5	38.81	24.87	0
6	49.86	39.66	8.01
7	66.54	50.32	25.03
8	78.24	67.53	43.56
9	96.9	88.27	65.75
10	99.61	94.93	80.55
11		98.88	89.6
12		99.97	95.38
13			98.3
14			99.57
15			99.15
16			99.56

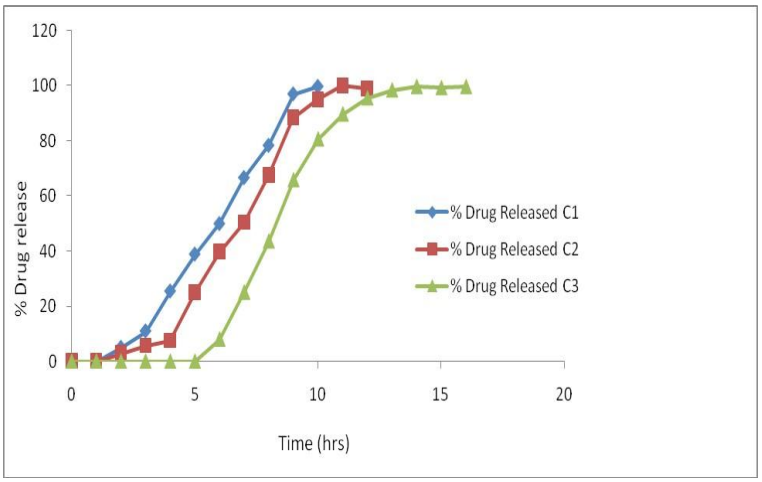

Fig 3.1: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC K4M.

Table 3.3: Dissolution Testing of batch C4-C6.

Time (hrs.)	% Drug Released		
	C4	C5	C6
0	0	0	0
1	0	0	0
2	27.91	0	0
3	52.39	30.87	24.97
4	64.98	51.9	41.74
5	78.49	68.76	65.89
6	90.72	80.95	79.8
7	95.69	91.69	90.98
8	98.19	96.98	96.5
9	99.85	99.81	99.78

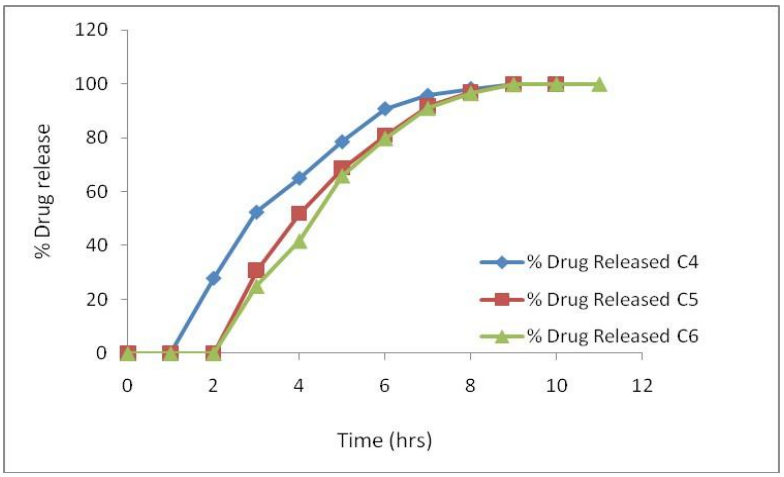

Fig 3.3: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of NaCMC in 0.1 M HCl.

Table 3.4: Dissolution Testing of batch C7-C9.

Time (hrs.)	% Drug Released		
	C7	C8	C9
0	0	0	0
1	0	0	0
2	20	0	0
3	27.98	5.98	0
4	51.54	15.9	5.98
5	65.89	29.87	30.98
6	77.97	45.76	50.39
7	83.78	53.21	67.29
8	90.98	68.98	80.96
9	99.55	77.98	86.19
10		85.82	93.98
11		90.89	98.42
12		95.97	99.88
13		99.2	99.96

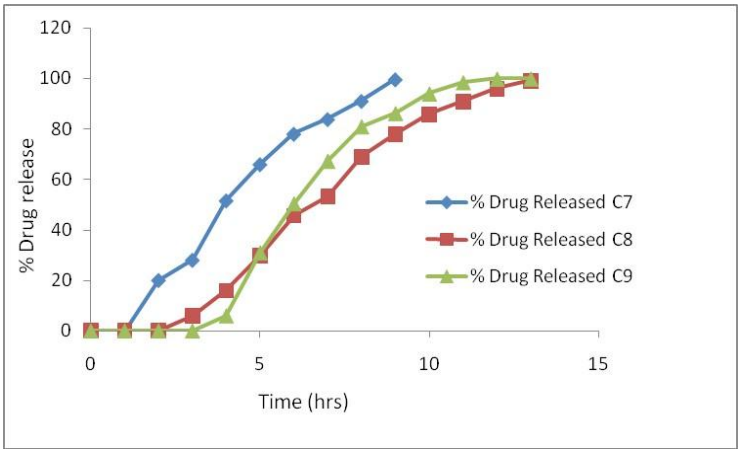

Fig. 3.4: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC E15LV.

Fig 3.4 shows that HPMC K4M gives the lag time of 4 hours then follow the sigmoidal release pattern with 100% drug release at 10th hour. As the concentration of the HPMC K4 coating increases from 140 to 180 mg the lag time extended to 5 hours and then follow the delayed release profile with the 100% drug release at the 17th to 18th hour From Fig 7.19, it was observed that carboxymethylcellulose sodium (NaCMC) shows the lag time of 2 hours, resulting in rapid and complete drug release at 10th hour. But these tablets did not maintain its shape throughout dissolution process which might be concluded that such tablet cannot be floated for longer period of the time. Due to this reason tablet (PRT) of Carboxymethylcellulose sodium (NaCMC) was not studied further. From From fig 7.20 it was observed that HPMC E15LV shows the lag time of 3 hours then follow the sigmoidal release pattern with 100% drug release at 9th hour. As the concentration of the HPMC E15LV coating increases from 240 to 290 mg the lag time extended to 4.5 hours and then follow the delayed release profile with the 100% drug release at the 12th to 14th hour. From above discussion it was cleared that carboxymethylcellulose sodium (NaCMC) cannot be used to develop a successful pulsatile drug delivery system as it cannot give sufficient lag time and is unable to maintain its shape. Other two polymers can be used to develop effective pulsatile drug delivery system. But thesetwo polymers were giving delayed release pattern after sufficient lag time instead of giving pulsatile release pattern (complete and rapid drug release at once). This may be due to the effectof super disintegrants (crosscarmellose sodium). Due to the insufficient swelling of crosscarmellose sodium, it could not give burst release required for complete drug release. Hence these two polymers were further studied by using KYRON T 314 as superdisintegrant in core tablet. Different batches of pulsatile release tablet of HPMC K4M and HPMC E15LV were prepared using KYRON T 314 in core tablet. Fig 3.3, 3.4 shows drug release pattern of

batches K1-K6. By studying dissolution profile, it was observed that batch K6(290mg) was optimized batch. As the coated tablet was placed in the aqueous medium, it was observed that the hydrophilic polymeric layer started erosion, which underwent progressive modification in terms of thickness and consistency. In the second phase of the dissolution procedure, the coating layer gradually starts to erode up to a limiting thickness. After this stage, a rupture of the shell was observed under the pressure applied by the swelling of the core tablet and Nifedipine released. This pressure was high due to high swelling property of KYRON T314 and which resulted in burst effect along with complete and rapid drug release. In case of other batches i.e K1, K2, K4 and K5 amount of coating polymer was too less to achieve desired lag time. Due to high swelling of inner core tablet coating of K1, K2, K4 and K5 formulations could not maintain too long and result in complete drug release within short time. All of this process corresponded to a lag time capable of exhibiting a pulsatile release of the drug. The profiles relevant to the coated tablet showed that a lag phase was followed by the quickly delivery of the active principle. The delay duration clearly depended on the kind and amount of hydrophilic polymer as which was applied on the core. Invitro the lag time of the tablet coated with 290-mg HPMC E15LV was 4.1±0.2 h and given burst with 96.88% and after this the % drug release remains constant due to non-maintenance of sink condition.[13,14]

Table 3.5: Dissolution Testing of batch K1-K3.

Time (hrs.)	% Drug Released		
	K1	K2	K3
0	0	0	0
1	0	0	0
2	20	0	0
3	27.98	5.98	0
4	51.54	15.9	5.98
5	65.89	29.87	30.98
6	77.97	45.76	50.39
7	83.78	53.21	67.29
8	90.98	68.98	80.96
9	99.55	77.98	86.19
10		85.82	93.98
11		90.89	98.42
12		95.97	99.88
13		99.2	99.96

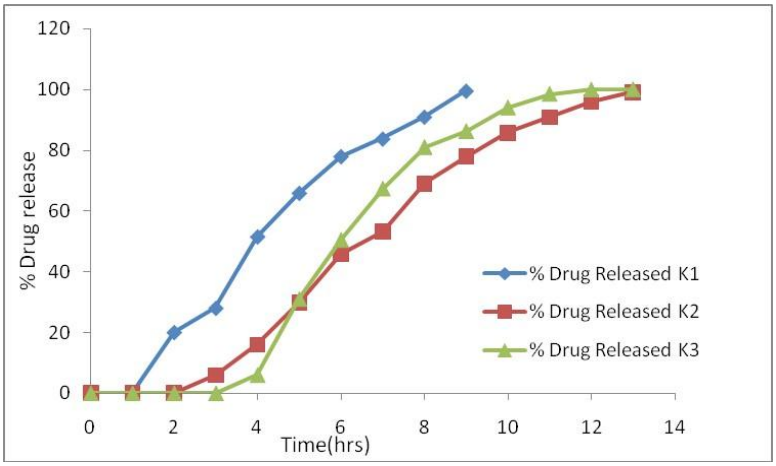

Fig. 3.5: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC K4M+Core tablet containing KYRON T 314.

Table 3.6: Dissolution testing of batch K4-K6.

Time (hrs.)	% Drug Released		
	K4	K5	K6
0	0	0	0
1	0	0	0
2	15.98	3.98	0
3	43.78	39.98	0
4	54.89	59.79	0
5	63.79	71.98	54.98
6	76.89	80.98	74.89
7	87.99	88.93	87.89
8	95.92	94.99	94.98
9	99.89	99.99	98.99
10		100.09	99.98
11		99.89	100.04
12		100.05	99.97
13		100.03	100.06
14		99.99	100.09

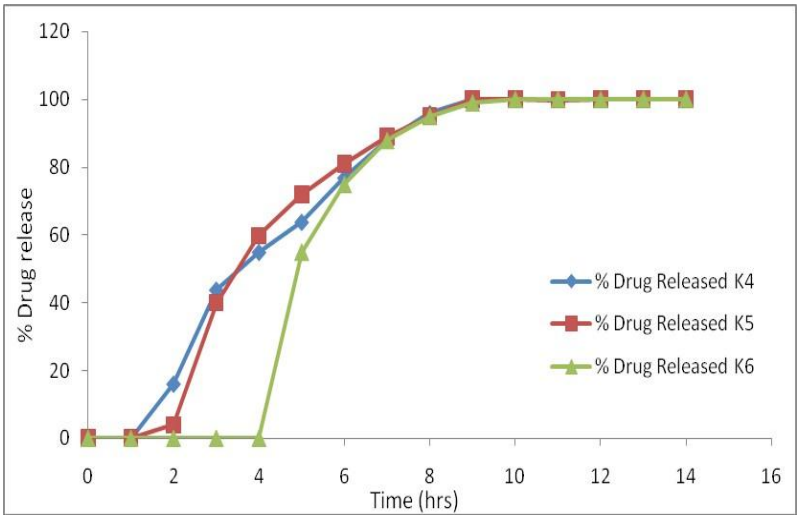

Fig. 3.6: In vitro release profiles of Nifedipine from the pulsatile release tablet (PRT) coated with different amount of HPMC E15LV+Core tablet containing KYRON T 314

3.4 In Vitro buoyancy determination

Table no. 3.7: Onset of time for floating of various formulations.

Formulation	Onset of time for floating
F1	Greater than 1 hr.
F2	Formulation showed no floating
F3	Remaining floating was no more than 3 h
F4	Float completely within 1 min and remained floating over aperiod of 12 h
F5	Greater than 15 min

Floating behavior of tablet depends on added fillers in buoyant layer. Tablets containing lactose floated earlier than tablets prepared with the inorganic filler dibasic calcium phosphate. This could be explained by the different densities, lactose containing tablet had the lowest density (1.0 g/cm3at a hardness of 4.3 Kg/cm2), whereas the dibasic calcium phosphate tablet had a much higher density (1.9 g/cm3 at a hardness of 5.2 Kg/cm2). In addition, lactose has a higher water solubility, resulting in faster water uptake of medium into tablet. Microcrystalline cellulose, an insoluble filler with high water uptake and disintegration capability, resulted in disintegration of tablet.CO2 did not accumulate in buoyant layer of tablet and escaped through the disintegrated tablet, floating was therefore not achieved. Based on these results, lactose was identified as the filler of choice and used for further investigation.

F4 formulation was used for further investigation.

3.4 Swelling index determination

Tablet containing HPMC K4M showed high swelling index as compared to HPMC E15LV and

NaCMC which might be due to hydration property of HPMC K4M. NaCMC showed swelling property but after some time tablet could not maintain its shape and integrity (Eq 6.1) HPMC K4M and HPMC E15LV showed constant increase in swelling index up to 10 h. (Fig 7.23).

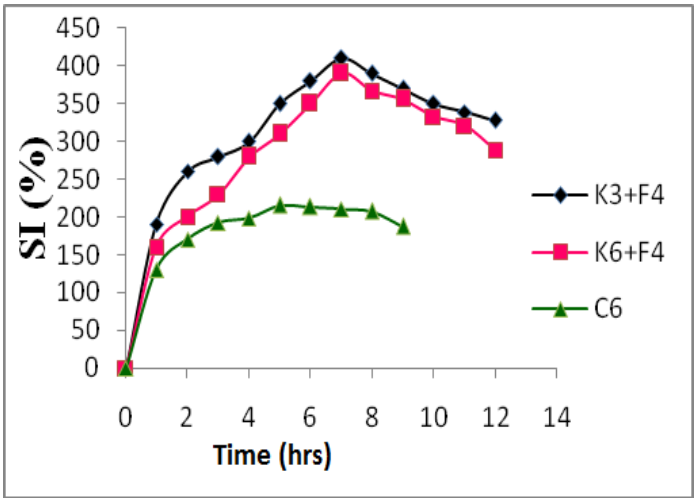

Fig. 3.7: Swelling index of tablets of K3+F4, K6+F4 and C6.

3.5 Floating and Pulsatile Release Tablet (FPRT)

The FPRT was manufactured as described above and consisted of the buoyant layer F4 (Table 6.8) combined with a PRT containing 20 mg Nifedipine core tablet compression- coated with 290 mg of HPMC E15LV (Formulation K6).

Table 3.8: Dissolution testing of batch K6+F4.

Time (hrs.)	% Drug Released
0	0
1	0
2	0
3	0
4	11.09
5	54.98
6	74.89
7	87.89
8	94.98
9	98.99
10	99.98
11	100.04
12	99.97
13	100.06
14	100.09

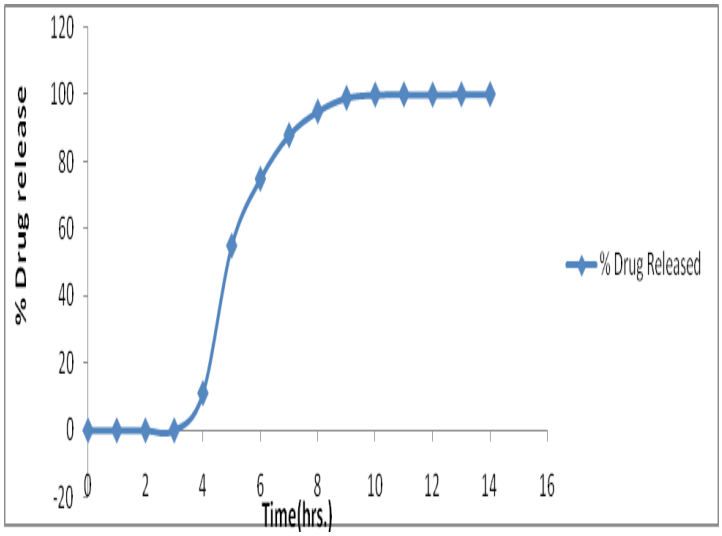

Fig. 3.8: In vitro release profiles of Nifedipine from the floating–pulsatile release tablet (FPRT) of batch K6+F4.

3.7 Evaluation of floating and pulsatile release tablet

Only FPRT tablets of optimized batch (K6+F4) were evaluated for friability test, hardness test and drug content. In formulation, the hardness test indicated good mechanical strength. Hardness was ranged from 3.8 to 4.0 Kg/cm2. Friability was ranged from 0.5 to 0.56. Friability is less than 1% which indicated that tablets had good mechanical resistance. Drug content was found to be high (>99.23). It was ranged from 99.32 to 99.45 and uniform in all tablet formulations. An ultraviolet (UV) spectrophotometric method was given at 236 nm and method obeys Beer's law in concentration range 5 to 50 µg/ml, with good correlation coefficient (0.9997).

Table 3.8: Evaluation of Floating and Pulsatile Release Tablet.

Srno.	Formulations	Hardness (Kg/cm^2) Friability (%)	Drug content (%)	
1	K6+ F4	3.8	0.43±0.11	99.45

3.8 Stability testing of the best formulation

According to the result of dissolution testing, the two batches were selected for the stability studies K6+F4 out of the total formulation batches. Studies were carried out as ICH guidelines.

3.9 Results of stability studies for batch no. K6+F4

Sample at 30 C (+/-2 C) and 65% RH (+/-5%) condition

Table 3.9: Results of stability studies for batch no. K6+F4.Sample at 30 C (+/-2) and 65% RH (+/-5%) condition.

Tests	Initial	7 days	14 days	21 days	1 month	2 months	3 months
Stabilityout date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Appearance	white colour	White Colour	white colour	white colour	white colour	white colour	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 months	3 months
Stabilityout date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
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

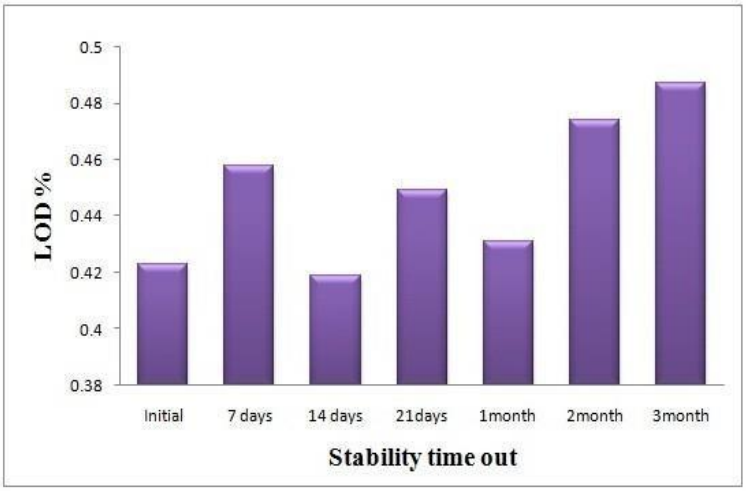

Fig. 3.9: LOD of stability batch K6+ F4, 300C±2 and 65% RH ±5%.

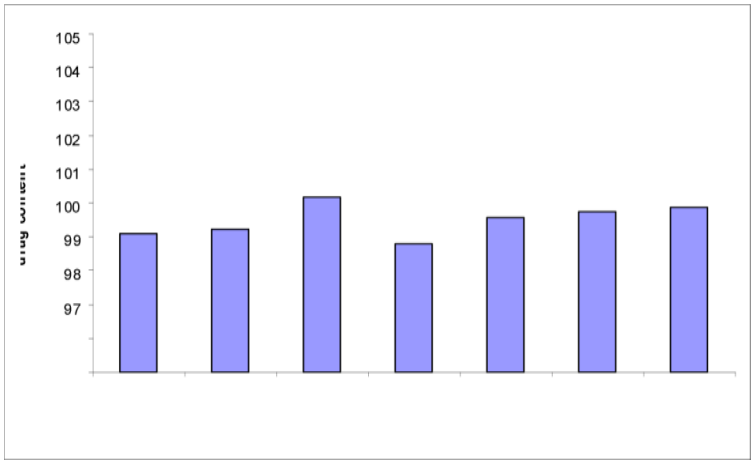

Fig. 3.10: % drug content of stability batch K6+F4, 300C±2 and 65% RH±5%.

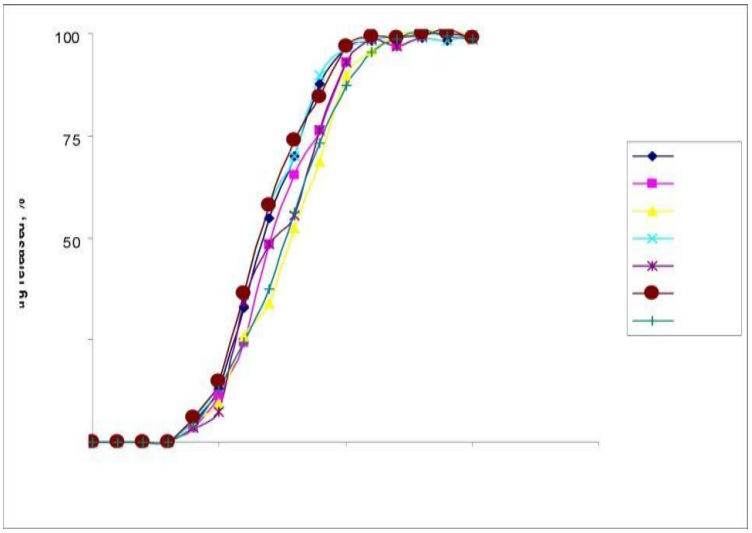

Fig. 3.11: Dissolution testing of stability batch K6+F4, Sample at 300C ±2 and 65% RH ±5%.

Table 17: Hardness, Friability, Disintegration Time of batch K6+F4 at 300C±2 /65%RH ±5%.

Days	Hardness Kg/cm^2	Friability (%)	Disintegration Time(S)
Initial	3.5	0.65±0.12	33
7 days	3.4	0.66±0.14	19
14 days	3.6	0.64±0.11	30
21 days	3.7	0.63±0.11	23
1 month	3.6	0.63±0.14	35
2 month	3.5	0.67±0.13	19
3 month	3.4	0.68±0.16	48

Table no. 3.11: Results of stability studies for batch no. K6+F4.Sample at 400C (+/-2 C) and 75% RH (+/-5%) condition.

Tests	Initial	7 days	14 days	21 days	1 month	2 month	3 month
Stability out date	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
Appearance	white colour	white colour	white colour	white colour	white colour	white colour	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	2/10/11	9/10/11	16/10/11	23/10/11	30/10/11	30/11/11	30/12/11
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

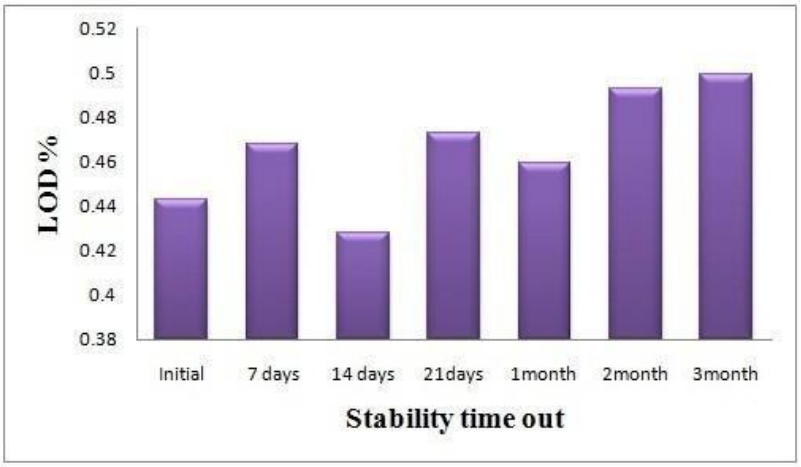

Fig. 3.12: LOD of stability batch K6+F4, Sample at 400C (+/-2 C) and 75% RH(+/-5%)

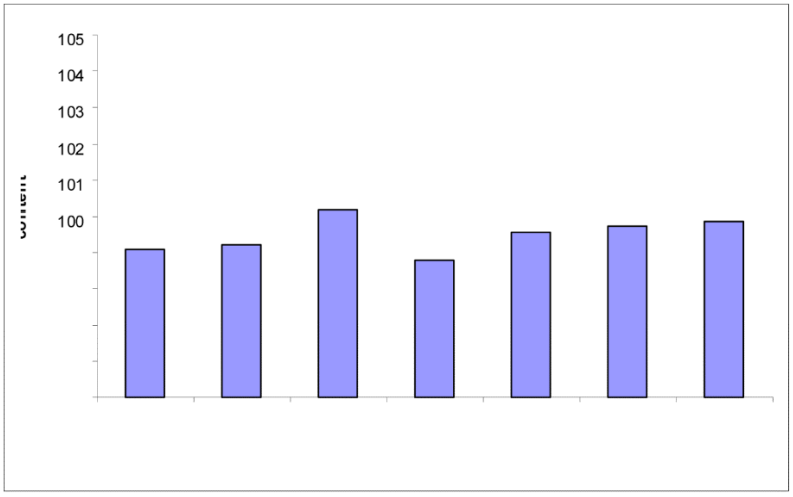

Fig. 3.13: % drug content of stability batch K6+F4, Sample at 400C (+/-2 C) and 75% RH (+/-5%) condition.

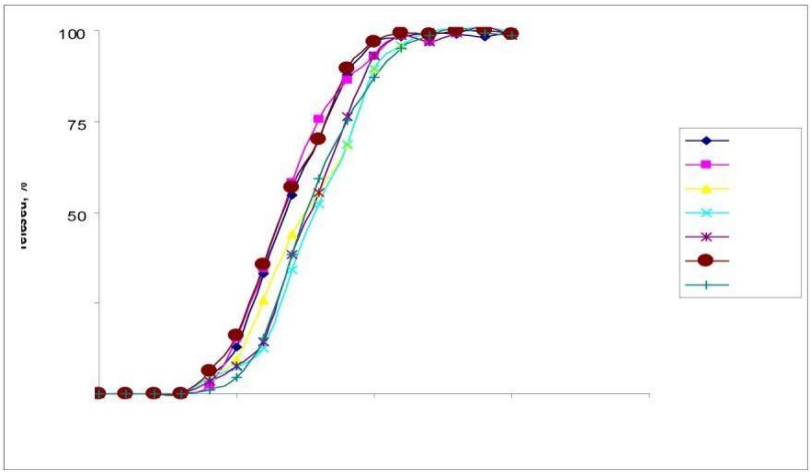

Fig. 3.14: Dissolution testing of stability batch K6+F4, Sample at 400C (+/- 2 C) and 75%RH (+/-5%) condition.

Table no. 3.12: Hardness, Friability, Disintegration Time(S) of batch K6+F4 at 400C±2/75%RH ±5%.

Days	Hardness Kg/cm^2	Friability (%)	Disintegration Time(S)
Initial	3.70.61±0.11	35	
7 days	3.6	0.67±0.15	21
14 days	3.7	0.65±0.11	34
21 days	3.5	0.63±0.14	26
1 month	3.6	0.60±0.15	30
2 month	3.6	0.66±0.13	17
3 month	3.8	0.61±0.16	45

For Floating pulsatile release tablet of nifedipine optimized batch K6+F4, it was seen that there are no significant changes in drug release profile for the batches stored at 300C (+/-2 C)

and 65% RH (+/-5%) and 400 C (+/-2 C) and 75% RH (+/-5%) when compared with initial batch. From the stability data it can be concluded that there were no changes in any parameter testedin formulation, so the optimized batch K6+F4 are said to be stable.

CONCLUSION

The core containing KYRON T-314 disintegrate the tablet within short time due to easy and high swelling ability of KYRON T-314 as compared to CCS The PRT containing the buoyant material, such as HPMC K100M, NaHCO3, and citric acid achieved a satisfactory buoyant force in vitro, whereas the floating onset time was less than 1 min. The pulsatile releasing mechanism of PRT is based on the exploitation of the peculiar interaction between hydrophilic polymeric coating and the aqueous gastrointestinal fluids.

The in vitro release profiles of Nifedipine from PRT prepared using HPMC E15LV as retarding polymer are characterized by a predetermined lag time (4.1±0.2 h for K6+F4), the duration of which depends on the kind and amount of the polymeric layer applied on the cores as well as type of superdisintegrant in core tablet. The developed system offers a simple and novel technique for pulse release of drugs. From the results it is concluded that the PRT we prepared could achieve a rapid release after lag time of 4±0.2h with the relatively low variability. The drug release profile of optimized batch K6+F4 was found to be follow korsmeyer and peppas model. So, it is concluded that formulation release the drug by diffusion and erosion method.

REFERENCES

1. Jha N, Bapat S; Chronobiology and chronotherapeutics, Kathmandu University Medical Journal, 2004; 2(8): 384-388.
2. http;//www.pharmatutor.org/articles/pulsatile-drug-delivery-system-a-review
3. Gajbhiye N, Dr. Kadam V, Jadhav K, Patel J, Pulsatile drug delivery system, Journal of Pharmacy Research, 2010; 3(1): 120-123.
4. Rajput M, Sharma S, Sissodia N, Sharma S, Pulsatile Drug Delivery System; A Review, International Journal of Research in Pharmaceutical and Biomedical Sciences, Jan – Mar, 2012; 3(1): 118-124.
5. Salunkhe A, Mali K, Mahajan N , Ghorpade V, Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate, Scholars Research Library, 2011; 3(3): 147-160.
6. T Akelesh, Sravan Perla, R Venkatnarayanan Formulation and evaluation of Nifedipine

sustained release pellets. International research journal of pharmacy Pagenu, 2011; 2(8): 177-180.

7. Sreekanth S, Palanichamy S. Formulation and evaluation studies of floating matrix tablets of nifedipine. International Journal of Pharma and Bio Sciences, 2010; 2: 1-8.
8. Sharma S, Dutt S, Saharawat R, Pulsatile Drug Delivery System; A Review An Advanced Approach, International Journal Of Pharmacy & Technology, June, 2011; 3: 1179-1188.
9. Roy P, Shahiwala A, Multiparticulate formulation approach to pulsatile drug delivery, Current perspectives Journal of Controlled Release, 2009; 74-80.
10. Yoshio ueda, Kobe, Takehisha Hata, Time controlled explosion systems and processes for preparing the same, US Patent no. 4871549.
11. Ubaldo Conte, Busto Arsizio Tablet for pharmaceutical use able to release active substances at successive times US Patent no.4865849.
12. Paul R. Mgruder, Palo Alto Composition comprising sulbutamol US Patent no.4751071.
13. Stephen M, James B. Pike Osmotically driven delivery devices with pulsatile effect US Patent no.5209746.
14. Salunkhe A, Mali K, Mahajan N, Ghorpade V, Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate, Scholars Research Library, 2011; 3(3): 147-160.